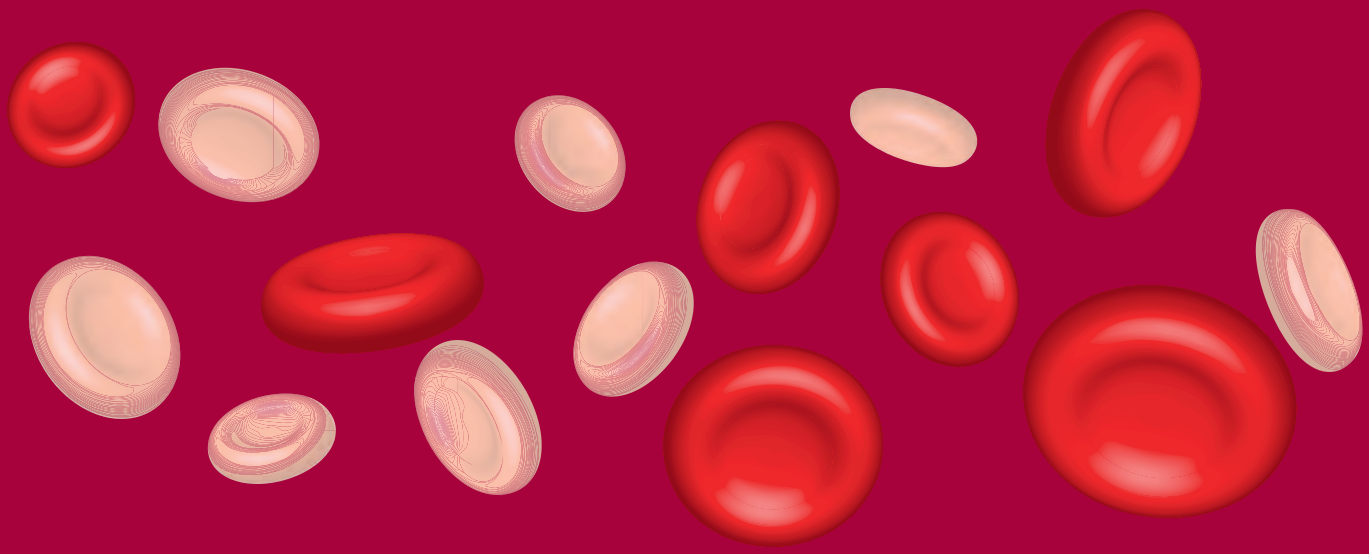
MOSCOW SCHOOL OF HEMATOLOGY

ОНКО клиническая ГЕМАТОЛОГИЯ

IV Московская международная школа молодых ученых по гематологии им. С. П. Боткина 1–2 марта 2024 г.

ТЕЗИСЫ РАБОТ И ДОКЛАДОВ



ПРИЛОЖЕНИЕ К ЖУРНАЛУ
«Клиническая онкогематология. Фундаментальные исследования и клиническая практика»
том 17, № 3, 2024

Уважаемый читатель!

Вы держите в руках номер, в котором представлены тезисы и клинические случаи IV Московской международной школы молодых ученых по гематологии им. С. П. Боткина. Школа прошла 1–2 марта 2024 года в Москве и была организована кафедрой гематологии и трансфузиологии имени академиков И.А. Кассирского и А.И. Воробьева совместно с НИИ детской онкологии, гематологии и трансплантологии им. Р.М. Горбачевой, ПСПбГМУ имени академика И.П. Павлова и АНО «Московская школа гематологии».

В этом году существенно изменился формат школы. Во-первых, большая часть участников (52 %) получили возможность представить данные в виде устных докладов. Во-вторых, к оценке работ был приглашен 21 эксперт, в том числе из-за рубежа. Это привело к расширению географии стран-участниц. Помимо постсоветских стран, мы получили работы от участников из Саудовской Аравии, Иордании, Египта. Наконец, главная перемена состоит в том, что официальным языком конференции стал английский язык. Суммарно на школу было подано 68 работ, из которых 52 работы представляли собой оригинальные исследования, 16 — клинические случаи. Двадцать семь работ были отобраны на устный доклад.

Конференция была посвящена онкогематологии. Оценка проводилась в 5 категориях: трансплантация, лимфопролиферативные и плазмоклеточные болезни, острые лейкозы, миелопролиферативные болезни, биология.

В экспертную комиссию по разделу «Трансплантация» вошли:

профессор Александр Дмитриевич Кулагин, директор НИИ детской онкологии, гематологии и трансплантологии им. Р.М. Горбачевой, Санкт-Петербург, главный внештатный специалист-гематолог по Северо-Западному федеральному округу, Санкт-Петербург;

профессор Иван Сергеевич Моисеев, заместитель директора по научной работе НИИ детской онкологии, гематологии и трансплантологии имени Р.М. Горбачевой, Санкт-Петербург;

Гамалетдин Мохамед Фатхи, консультант и управляющий директор отделения гематологии и трансплантации костного мозга Больницы Института Насера для исследований и лечения, Египет.

Экспертами по разделу «Лимфопролиферативные и плазмоклеточные болезни» были:

Наталья Михайловна Михайлова, руководитель отдела клинической онкологии НИИ детской онкологии, гематологии и трансплантологии имени Р.М. Горбачевой, Санкт-Петербург;

профессор Владислав Олегович Саржевский, заместитель главного врача по онкологии Национального медико-хирургического центра им. Н.И. Пирогова, Москва;

профессор Гаяне Сепуговна Тумян, заведующая отделением противоопухолевой лекарственной терапии и гематологии Национального медицинского исследовательского центра онкологии имени Н.Н. Блохина, Москва;

Джон Апостолидис, консультант-гематолог отделения взрослой гематологии и трансплантации стволовых клеток Специализированной больницы короля Фахада, Даммам, Саудовская Аравия;

профессор Рейяд Дада, консультант по гематологии и онкологии Специализированной больницы и исследовательского центра короля Фейсала, Альрвада, Джидда, Саудовская Аравия;

профессор Мохамед Абдельмути Мохамед Самра, консультант по медицинской онкологии и гематологии отделения гематологии и трансплантации костного мозга, декан Национального института рака, Каирский университет, Египет.

Экспертами в категории «Острые лейкозы» выступили:

профессор Вадим Вадимович Птушкин, руководитель гематологической службы Городской больницы имени С.П. Боткина, Москва. Главный внештатный гематолог Москвы, Москва;

профессор Ахмед Абси, Министерство здравоохранения Национальной гвардии — отдел здравоохранения, Медицинский город короля Абдулазиза, Джидда, Саудовская Аравия;

профессор Сергей Николаевич Бондаренко, заместитель директора НИИ детской онкологии, гематологии и трансплантологии им. Р.М. Горбачевой, Первый Санкт-Петербургский государственный медицинский университет им. академика И.П. Павлова, Санкт-Петербург;

Лариса Леонидовна Гиршова, старший научный сотрудник НИИ иммуноонкологии, ННМЦ «Центр персонализированной медицины», Санкт-Петербург;

Ирина Анатольевна Лукьянова, заведующая поликлиникой онкологии и химиотерапии гемобластозов и депрессий кроветворения Национального медицинского исследовательского центра гематологии, Москва.

Экспертизу работ, поданных в раздел «Миелопролиферативные болезни», проводили:

профессор Ольга Юрьевна Виноградова, ведущий научный сотрудник Московского городского гематологического центра ГКБ им. С.П. Боткина, Москва;

профессор Василий Анатольевич Шуваев, заведующий поликлиническим отделением Российского научно-исследовательского института гематологии и трансфузиологии Федерального медико-биологического агентства России, Санкт-Петербург;

Елена Владиславовна Морозова, руководитель отделения онкологии, гематологии и трансплантологии для подростков и взрослых НИИ детской онкологии, гематологии и трансплантологии имени Р.М. Горбачевой, Санкт-Петербург.

Экспертами в разделе «Биология» выступили:

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Максим Леонидович Филипенко, заведующий лабораторией фармакогеномики Института химической биологии и фундаментальной медицины СО РАН, Новосибирск;

Григорий Анатольевич Цаур, заведующий лабораторией молекулярной биологии, иммунофенотипирования и патоморфологии Областной детской клинической больницы № 1, Екатеринбург, Россия.

В мероприятии участвовали 523 специалиста (270 очно и 253 онлайн) из 7 стран (Российская Федерация, Республика Беларусь, Республика Казахстан, Египет, Германия, Саудовская Аравия, Иордания), из них граждан России 499, иностранных граждан 24. Авторы тезисов, набравших наибольшее число баллов, были признаны лучшими. Победителями школы молодых ученых стали:

Алексина Алексеевна Шатилова, младший научный сотрудник НИО иммуноонкологии НИЦ персонализированной онкологии НЦМУ «Центр персонализированной медицины» ФГБУ «НМИЦ имени В.А.Алмазова», г. Санкт-Петербург;

Туйара Никоновна Александрова, врач-гематолог отделения гематологии, Республиканской больницы № 1 — Национального центра медицины им. М.Е. Николаева, г. Якутск;

Анастасия Германовна Попова, врач-ординатор 2-го года обучения по специальности «гематология» в ФГАОУ ВО «РНИМУ им. Н. И. Пирогова», г. Москва;

Мария Александровна Санникова, врач-гематолог дневного стационара гематологии онкологии и химиотерапии Московского гематологического центра ГБУЗ ГКБ им. С.П. Боткина ДЗМ, Москва;

Полина Вячеславовна Коцелябина, врач-ординатор 2-го года обучения по специальности «гематология» в НИИ детской онкологии, гематологии и трансплантологии имени Р.М. Горбачевой, ПСПБГМУ им. академика Павлова, г. Санкт-Петербург.

Победители награждены премиальной стажировкой в медицинской клинике «Princess Noorah Oncology Center, King Abdulaziz Medical City», в городе Джедда, в Саудовской Аравии.

V Московская международная школа молодых ученых по гематологии им. С. П. Боткина состоится 28 февраля — 1 марта 2025 года. К участию принимаются тезисы оригинальных исследований и описания клинических случаев. Как и в 2024 году, преимущественными темами школы станут трансляционные исследования в области онкогематологии и гематологии. Подробная информация о правилах подачи работ будет опубликована на сайте Московской школы гематологии (https://mshg.ru), на страницах журнала «Клиническая онкогематология».

Ждем новых победителей на школе в 2025 году!

С уважением,
оргкомитет IV Московской международной
школы молодых ученых по гематологии
им. С. П. Боткина

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СЕССИЯ 1
ОСТРЫЕ ЛЕЙКОЗЫ

Experience with midostaurin therapy in adult patients with newly diagnosed FLT3 mutated acute myeloid leukemia

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Introduction. FMS-like tyrosine kinase 3 (FLT3) gene mutations are the most frequently detected genetic aberrations in patients with newly diagnosed acute myeloid leukemia (AML), identified in approximately 30 % of patients. FLT3 mutations are associated with a higher relapse rate and can lead to worse overall (OS) and event-free (EFS) survival. The addition of midostaurin, an FLT3 tyrosine kinase inhibitor, to standard chemotherapy (CT) for FLT3+ AML and after allogeneic hematopoietic stem cell transplantation (allo-HSCT) improves OS and EFS.

Objectives. To evaluate the results of therapy in adult patients with FLT3+ AML, who received midostaurin in combination with standard CT, as well as after allo-HSCT.

Methods. In this study 97 patients were enrolled, all of them received program chemotherapy with midostaurin in induction, consolidation and maintenance therapy. The median age was 46 (18–74) years. Median follow-up was 14.0 (0.1–41.7) months. The FLT3-ITD mutation was detected in 77 (79 %) patients. The favorable prognostic group ELN2022 (Fav-ELN2022) included 5 (5 %) patients, the intermediate prognostic group (Int-ELN2022) — 81 (84 %) patients, and the unfavorable prognostic group (Unfav-ELN2022) — 11 (11 %) patients.

Results. Complete remission (CR) was achieved in 71 (66 %) patients (Fav-ELN2022 — 100 %; Int-ELN2022 — 74 % and Unfav-ELN2022 — 55 %). Early mortality rate was 6.2 % (5 patients — sepsis, 1 — COVID-19). 20 (20.6 %) patients were primary refractory. The rate of primary refractoriness was higher in Unf-ELN2022 — 45 % than in Int-ELN2022 and in Fav-ELN2022 — 18.5 % and 0 % respectively. Allo-HSCT was performed in 38 (39 %) patients, of which 19 (50 %) were in the first CR. Midostaurin was restarted in 17 patients after allo-HSCT, with a median of 72 (26–370) days. The median duration of CR was 8.9 (1.1–40.9) months. OS was 63 % (95 %CI 53–72) (Figure 1) and EFS was 40 % (95 %CI 31–50) (Figure 2). 33 (46 %) patients subsequently developed a relapse with a median of 7.2 (1.3–24.9) months. Therapy with midostaurin was well tolerated; no adverse events requiring discontinuation of treatment were observed.

Conclusions. Midostaurin is effective and safe for use in combination with standard CT and after allo-HSCT in adult patients with FLT3+ AML.

Key words: acute myeloid leukemia, FLT-3, midostaurin.

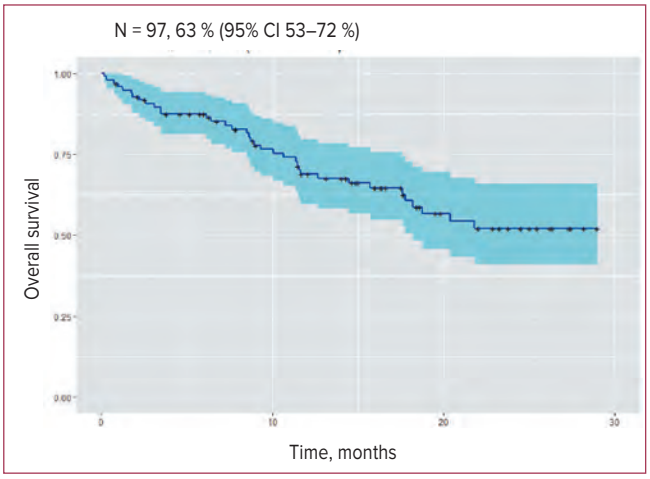

Figure 1. Overall survival

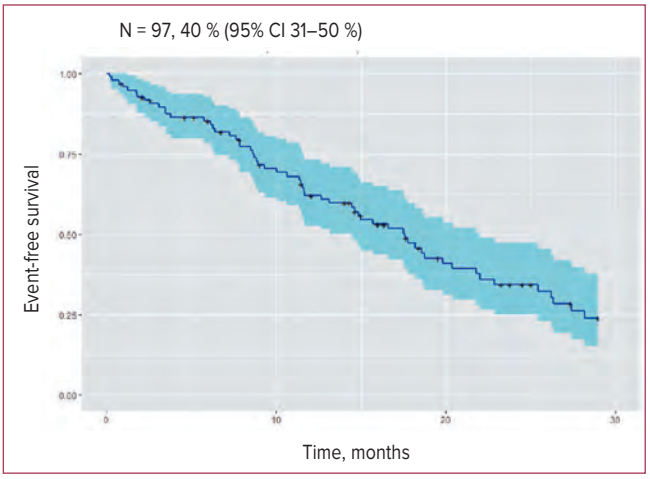

Figure 2. Event-free survival

An effective prognostic model for survival in patients with acute myeloblastic leukemia

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Introduction. Acute myeloid leukemia (AML) is a disease in which malignant transformation and uncontrolled proliferation of myeloid progenitor cells occur. For selection of optimal treatment approaches and prediction of response to therapy patients with AML are divided into groups based on genetic factors and clinical characteristics. Despite this risk stratification, response to therapy and disease outcome for an individual AML patient depend on many factors related to the patient's clinical characteristics and tumor subtype. One important factor is the resistance of leukemic cells to chemotherapeutic agents, which represents one of the main obstacles to improving the survival outcomes of patients with AML. Our study used a new prognostic scale for risk stratification of AML patients, based on identifying the sensitivity or resistance of leukemic cells to chemotherapeutic drugs.

Objectives. The purpose of our study was to develop an effective model for predicting survival in patients with AML.

Methods. The study included 53 patients who received treatment at the State Budgetary Healthcare Institution NSO City Clinical Hospital 2 from January 1, 2014 to December 31, 2018. The median age of the patients was 51.2 ± 14.5 years, there were 25 men (47.2 %), and 28 women (52.8 %). All patients underwent a standard examination, including genetic, molecular cytogenetic examination of the bone marrow, and flow cytometry of the bone marrow. Leukemic cells were isolated from the bone marrow of patients with AML according to standard methods. After isolation they were cultured in IMDM medium supplemented with 10 % fetal bovine serum and a 1 % solution of antibiotics and antimycotics (10,000 μg/ml streptomycin, 10,000 IU/ml penicillin and 25 μg/ml amphotericin) at 37 °C with 5 % CO2. Next, the cells were incubated with various doses of cytostatic drugs for 72 hours, a WST1 solution was added, after which IC50 was assessed using a spectrophotometer. Total RNA was extracted from tumor cells for RNA quantification using real-time qPCR. As part of the study, immunocytochemical determination of P-glycoprotein (P-gp) was performed in bone marrow smears of patients with AML. Univariate and multivariate analyzes were performed to construct an effective model for predicting survival in patients with AML.

Results. The response to antileukemic therapy was assessed in each patient with AML after 1–2 courses of induction chemotherapy. The majority of patients had primary chemo resistance (60.4 %). Remission and relapse were achieved in 30.2 % and 9.4 % of AML patients. In the present study, we compared the influence of established prognostic factors and parameters reflecting the multidrug resistance (MDR) phenotype of tumor cells (drug sensitivity, MDR1/P-gp mRNA expression) on response to therapy and, as a consequence, on the prognosis of patients with AML.

In addition to the standard prognostic factors mentioned above, the analysis included clinical parameters, including hemorrhagic, infectious and hyperplastic manifestations, anemia, intoxication as well as relation to previous therapy (primary or secondary AML).

Patients with AML who received induction therapy with intensive anthracycline-based treatment were analyzed separately. In this group of AML patients, statistically significant ($p < 0.05$) positive correlations of response to therapy were identified according to the following parameters: strong correlations with cell sensitivity to daunorubicin ($r = 0.72$); moderate correlations — with general sensitivity to cytostatic drugs ($r = 0.61$), age ($r = 0.55$), karyotype of leukemic cells ($r = 0.60$), risk stratification by genetics ($r = 0.70$), stratification prognosis based on cytogenetic/molecular markers and clinical characteristics (hereinafter standard prognosis stratification) ($r = 0.55$).

Thus, among the analyzed prognostic factors influencing response to therapy in patients with AML, the sensitivity of tumor cells to chemotherapeutic drugs in vitro and the karyotype of tumor cells may have the greatest prognostic value. Based on the presented data, we developed a prognostic score based on assessing the sensitivity of tumor cells to chemotherapeutic drugs and the expression of MDR1 mRNA in tumor cells, as well as standard prognostic factors (leukemia origin, karyotype, age, presence of aberrant immunophenotype) for risk stratification of AML patients.

All patients were divided into groups according to the sensitivity of leukemic cells to cytotoxic drugs (high, medium, low), the level of MDR1 mRNA expression (weak, moderate, strong), the presence of one or more unfavorable mutations in tumor cells, the age of the patient (< 40 years, 40–60 years, > 60 years) and the presence of one or more markers of aberrant immunophenotype in tumor cells. Based on the sum of scores for all parameters of our prognostic scale, patients can be divided into three risk groups: 0–2 — low-risk group, 3–5 — intermediate-risk group, 6–12 — high-risk group, which allows us to predict the response of a particular patient to the chemotherapy protocol before starting treatment. Among patients with AML, the risk group distribution according to our prognostic score correlated best with response to therapy ($r = 0.84$). On univariate analysis, the risk group defined by genetic risk stratification (RR 1.96, 95 % CI 1.03–3.68, $p = 0.039$) and the risk group defined by our prognostic score (RR 1.17, 95 % CI 1.17–3.93, $p = 0.01$), demonstrated the greatest impact on overall survival of leukemia patients. In a multivariate analysis to predict patient survival, a model was built based on the inclusion of such parameters as the level of white blood cells, risk stratification according to our prognostic scale, the degree of anemia, the presence of infectious complications and intoxication syndrome (model p value = 0.035).

The greatest impact on overall survival of AML patients was exerted by the risk group determined by our prognostic score (HR 2.8, 95 % CI 1.31–6.02, $p = 0.008$). In summary, univariate and multivariate Cox proportional hazards regression analyzes clearly demonstrated that risk stratification according to the prognostic score presented in this work is an independent prognostic factor for overall survival in patients with AML.

Conclusions. Thus, risk stratification of patients with AML according to the developed prognostic scale can be used to predict both response to therapy and overall survival in patients with AML. The level of leukocytosis, the degree of anemia, the presence of infectious complications and intoxication syndrome at the onset also play an important role in survival diseases. The data obtained can be used in clinical practice for effective selection of therapy and prediction of survival in patients with AML.

Combination of BCL2 inhibitor with azacitidine in the treatment of elderly patients with newly diagnosed acute myeloid leukemia

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Introduction. BCL2 inhibitor venetoclax in combination with azacitidine (AzaVen) shows good results in the treatment of newly diagnosed acute myeloid leukemia (AML) in elderly patients not candidates for standard intensive chemotherapy

Objectives. Retrospective analysis of the efficiency and tolerability of AzaVen in primary elderly patients with AML and identification of problems associated with its use in real clinical practice.

Methods. The retrospective study included a cohort of patients (n = 91) observed at the S.P. Botkin City Clinical Hospital in the period from 2017 to 2023 years. Statistical processing was carried out using the GraphPad Prism program, version 8.0.0 for Windows, GraphPad Software

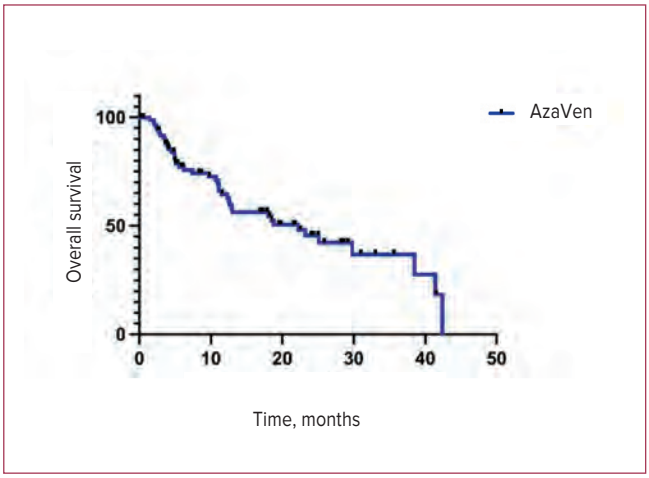

Figure 1. Overall survival

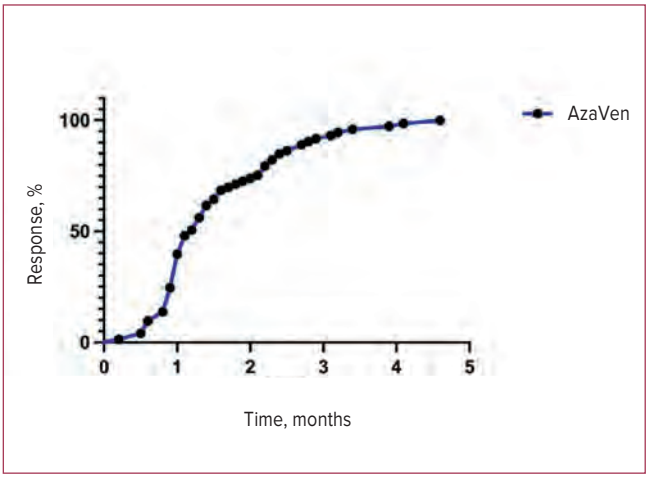

Figure 2. Time to response to therapy

(USA, www.graphpad.com). Survival and cumulative risk curves were constructed using the Kaplan-Meier method, and differences in the study groups were calculated using the log-rank test. Differences were considered significant at $p < 0.05$. The sample was characterized by descriptive statistics methods.

Results. The median age was 70 years (range 55–90 years), 56 % of patients were over 70 years old. The median follow-up period for patients was 9.8 months. Fifty-one percent of patients were males. According to the 2022 ELN risk classification, 79 % of patients had intermediate risk, 8 % had favorable risk, 12 % had unfavorable risk, with no data provided in 1 patient. The median duration of therapy was 4.9 months. (range 0.9–42 months). By the time of the final analysis, 50 patients continue to receive treatment. Forty-one patients had therapy discontinued (25 patients due to relapse of the disease, 10 were found to be primarily refractory to this therapy, 6 died during therapy). Median overall survival was 22.2 months (Figure 1). Among the patients who died (n = 42), the causes of death were: progression of AML (55 %), infectious complications (45 %). Remission was achieved in 74 patients. Complete remission (CR) was achieved in 36 patients (42.9 %). Complete remission with incomplete recovery (CRi) was recorded in 18 patients (21.4 %). Complete remission with partial recovery (CRh) — 8 people (9.5 %) Morphological remission (MLFS), as the maximum response to therapy, was recorded in 12 patients (14.3 %). The median time to response was 1.2 months (range 0.2–4.6 months) (Figure 2). During cycle 1, therapy was suspended in 22 (24 %) patients due to the development of infectious complications. Six people received antifungal therapy during the 1st cycle (3 patients to prevent fungal complications).

Conclusions. The combination of venetoclax and azacitide demonstrates good tolerability, clinically significant benefits in overall survival, remission rates for elderly patients with newly diagnosed acute myeloid leukemia who have not previously received treatment and are not candidates for an intensive course of chemotherapy.

Combination of BCL2 inhibitor and low-dose cytarabine in the treatment of elderly patients with newly diagnosed acute myeloid leukemia

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Introduction. A BCL2 inhibitor in combination with low-dose cytarabine (LDAC-Ven) shows good results in the treatment of newly diagnosed acute myeloid leukemia (AML) in elderly patients who are not candidates for standard intensive chemotherapy [1].

Objectives. Retrospective analysis of the effectiveness and tolerability of LDAC-Ven in primary elderly patients with AML, as well as identification of problems associated with its use in real clinical practice.

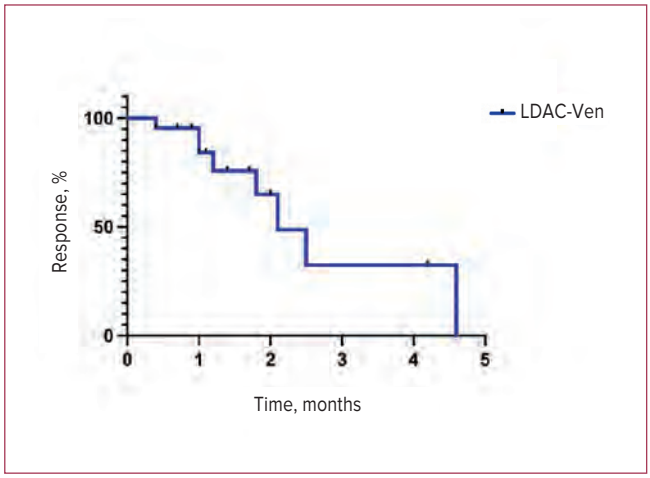

Figure 1. Median duration of response to LDAC-Ven

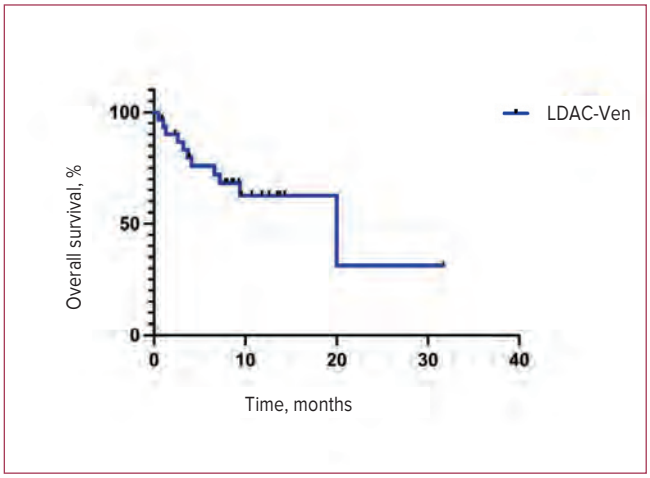

Figure 2. Overall survival of patients treated with LDAC-Ven

Methods. The retrospective study included a cohort of patients (n = 31) observed at the S.P. Botkin City Clinical Hospital, Moscow Healthcare Department in the period from 2021 to 2023 years. The median age was 73 years (range 56–82 years), 51 % of patients were over 70 years old. The median follow-up period for patients was 8.5 months. (range 0.5–31.7 months). Statistical processing was carried out using the GraphPad Prism program, version 8.0.0 for Windows, GraphPad Software (USA, www.graphpad.com). Survival and cumulative risk curves were constructed using the Kaplan-Meier method, and differences in the study groups were calculated using the log-rank test. Differences were considered significant at $p < 0.05$. The sample was characterized by descriptive statistics methods.

Results. The median duration of therapy was 5 months. (range 0.5–12.3 months). At the time of final analysis, 11 patients remained on treatment. In twenty patients, therapy was discontinued (8 were transferred to another line of therapy due to disease progression, 11 died, 1 were transferred to another line due to allergies). The median overall survival was 20 months (Figure 1). Among the patients who died (n = 11), the causes of death were: progression of AML (n = 6), infectious complications not associated with COVID-19 (n = 4), COVID-19 (n = 1). Remission was achieved in 22 patients (71 %). Of these, complete remission (CR) was achieved in 14 patients (63.5 %). Complete remission with incomplete recovery (CRi) was recorded in 5 patients (23 %). Morphological remission (MLFS), as the maximum response to therapy, was recorded in 3 patients (13.5 %). In 9 patients, remission was not achieved (6 patients were primary refractory to therapy, 2 died before response assessment, 1 during the 1st cycle). The median time to remission was 1.1 months (range 0.4–4.6 months). Among the patients who achieved remission, 8 patients had a relapse of the disease. The median response to therapy was 2.1 months (Figure 2). The median until loss of remission is 4.5 months. During the 1st cycle of therapy, the following complications were recorded: neutropenia grade 4 — 25 patients (81 %), anemia grade 3 — 25 patients (81 %), thrombocytopenia grade 4 — 12 patients (38 %), febrile neutropenia — 7 patients (23 %), infections — 3 patients (10 %).

Conclusions. The combination of venetoclax and LDAC demonstrates good tolerability, clinically significant benefits in overall survival, remission rates for elderly patients with newly diagnosed acute myeloid leukemia who have not previously received treatment and are not candidates for an intensive course of chemotherapy.

Experience of treatment acute myeloid leukemia with FLT3 mutations in the Botkin Hospital, Moscow

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Introduction. The FLT3 gene is a crucial prognostic factor in patients with acute myeloid leukemia (AML). Mutations in the FMS-like tyrosine kinase-3 (FLT3) gene occur in approximately 30 % of AML patients. The most common mutations in the FLT3 gene are internal tandem duplications (ITD) in the juxtamembrane domain, detected in approximately 25 % of cases. Point mutations in the tyrosine kinase domain (TKD) are less common, occurring in 7-10 % of patients. According to ELN2022, AML with FLT3 mutations is classified as intermediate risk; however, the presence of this mutation complicates treatment response and correlates with prognosis.

Objectives. To analyze the survival of patients with newly diagnosed AML with FLT3 gene mutations based on the intensity of therapy and inclusion of tyrosine kinase inhibitors (TKIs) in the treatment regimen.

Materials and methods. A retrospective analysis of medical records was conducted for patients from September 1, 2021, to September 1, 2023. The study included individuals with newly diagnosed AML and diagnosed FLT3 mutations. Diagnosis verification used morphological, flowcytometric, cytogenetic, and molecular methods in accordance with the 2020 clinical recommendations for AML treatment. FLT3 gene mutations were determined by polymerase chain reaction (PCR). Survival analysis was conducted based on treatment intensity and inclusion of TKIs using the Kaplan-Meier method. Statistical significance of survival differences in the study groups was assessed using the log-rank test, considering differences significant at $p < 0.05$.

Results. The study included 49 patients, with 61.2 % being female and 38.8 % male. The median age at disease onset was 54.7 years (range 18–79 years). Patient somatic status, evaluated by Karnofsky and ECOG scales, had median values of 70 % and 2, respectively. FLT3-ITD mutation was detected in 85.7 %, FLT3-TKD in 16.3 %, and both mutations in 1 patient. The median overall survival in the study group was 86.43 weeks. Midostaurin was the TKI of choice. The best response in FLT3+ AML treatment was observed in patients receiving intensive chemotherapy with midostaurin ("7+3" induction and consolidating courses with intermediate doses of cytarabine) followed by allogeneic stem cell transplantation (SCT) (n = 7) in the first-line therapy. Median overall survival (OS) in this group was not reached. When using other midostaurin-containing therapy combinations without SCT (n = 17), the median OS was 25 weeks (p = 0.0343) (Figure 1).

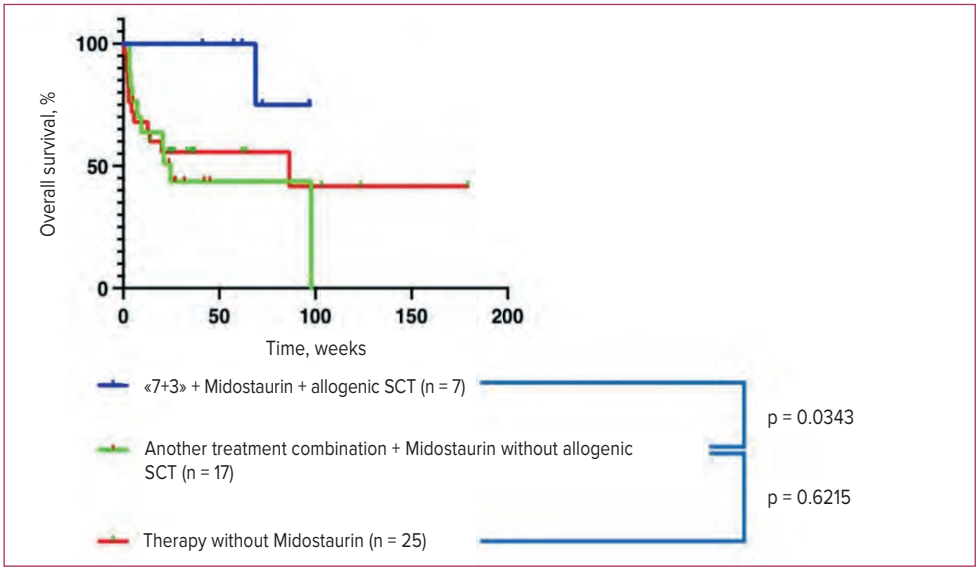

Figure 1. Overall survival

Similar results were obtained in patients on therapy without midostaurin addition (n = 25). Complete response to treatment was achieved in 59.10 % of patients, refractoriness in 22.70 %, and 18.20 % died during myelotoxic aplasia. Causes of mortality were infection (50 %, n = 12), progression (41.6 %, n = 10), stroke (4.2 %, n = 1), and COVID-19 (4.2 %, n = 1).

Conclusions. The detection of FLT3 mutation serves as a predictor of unfavorable prognosis in AML. Identifying this mutation at the disease onset is an integral diagnostic step. Adding TKIs to intensive chemotherapy, particularly "7+3", followed by allogeneic stem cell transplantation, yielded the best results in first-line therapy. Including TKIs in other therapy regimens without stem cell transplantation did not show advantages. Chemotherapy courses without midostaurin for FLT3+ AML in this study demonstrated unsatisfactory results.

Acute myeloid leukemia with mutations in epigenetic modifiers: molecular features and prognosis

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Introduction. Abnormalities in epigenetic regulation due to specific somatic mutations in relevant genes are the important step in leukemia development. The detection frequency of IDH1/2, DNMT3A and ASXL1 mutations among patients with newly diagnosed acute myeloid leukemia (AML) is high. Prognostic value is obvious for mutations in ASXL1, but only for patients without favorable genetic alterations (ELN-2022). Molecular features and impact on prognosis in different cohorts (including favorable risk group) of IDH1/2, DNMT3A and ASXL1 mutations require further investigation.

Objectives. To assess the concomitant genetic abnormalities using next-generation sequencing (NGS) and evaluate the prognosis for newly diagnosed AML with mutations in epigenetic regulators.

Methods. This study included 147 patients with newly diagnosed AML (74 males and 73 females) with median age of 51 years (18-90). Standard ("7+3"), high ("HiDAC", "FLAG±Ida"), and low (HMA or LDAra-C ± venetoclax) intensity chemotherapy regimens were administered to 131 patients. Patients were stratified according to ELN-2022: 24,2 % into favorable, 46,8 % into intermediate and 29 % into adverse risk categories. We have analyzed IDH1 R132, IDH2 R140, DNMT3A R882 and ASXL1 exon 12 mutations using droplet digital PCR and Sanger sequencing. NGS was performed on 18 DNA samples from patients with mutations in epigenetic modifiers. Statistical analysis included the estimation of complete remission rate (CRR), incidence of early (during the first 6 mon.) relapse (ER), overall survival (OS), relapse-free survival (RFS), and cumulative incidence of relapse (CIR).

Results. The frequency of DNMT3A R882 mutation was 17,7 %, IDH mutations — 15,6 % (IDH1 R132 — 6,1 % and IDH2 R140 — 9,5 %), exon 12 ASXL1 mutations — 9,6 %. IDH mutations were closely associated with mutations R882 in DNMT3A (30,8 % vs 12,4 %, p = 0,02). The co-incidence of NPM1 mutation and association of mutations in epigenetic modifiers with patient's karyotype are presented in Table 1. Based on NGS-panel sequencing results, the majority of coexisting mutated genes were involved in RAS signaling (20,3 %), DNA repair (18 %) and receptors/kinases (15,6 %) (Figure 1). Patients with mutations in epigenetic modifiers and concomitant NRAS/KRAS-mutations had inferior OS (median 14 mon. vs 21,2 mon., p = 0,045). When NF1-mutations presented, there were less CRR (40 % vs 87,5 %, p = 0,021). CRR was also fewer in case of 9 or more mutated genes (Figure 2).

R882 mutation in DNMT3A was associated with worse prognosis among following categories:

- Patients with cytogenetically-normal AML: OS 11,3 mon. vs 24,1 mon., p = 0,048;
- NPM1-mutated AML: ER 50 % vs 7,7 %, p = 0,028; OS 10,7 mon. vs 24,1 mon., p = 0,006; RFS 5,5 mon. vs 14,8 mon., p = 0,03; CIR 83,3 % vs 55 %, p = 0,045;
- FLT3-ITD-positive AML: CIR 100 % vs 60,8 %, p = 0,036; ER 100 % vs 29,4 %, p = 0,022;
- Favorable risk group (ELN-2022): median OS wasn't reached vs 11,3 mon., p = 0,027.

Patients with triple-mutated AML (DNMT3A R882 + NPM1 + FLT3-ITD) had worse prognosis than patients with only two mutations (NPM1 + FLT3-ITD): OS 10,7 mon. vs 20,1 mon., p = 0,049; RFS 5,3 mon. vs 19,9 mon., p = 0,04; CIR 100 % vs 50 %, p = 0,037; ER 100 % vs 25 %, p = 0,048.

Table 1. Association of mutations in IDH1/2, DNMT3A and ASXL1 with NPM1 mutation, ELN-2022 risk groups and patient's karyotype

Characteristic	*IDH1/2* WT	*IDH1/2* mut	p	*DNMT3A* WT	*DNMT3A* R882	p	*ASXL1* WT	*ASXL1* mut	p
ELN-2022 prognostic categories									
Favorable, % (n)	70 (21/30)	**30** (9/30)	**0,029**	73,3 (22/30)	26,7 (8/30)	0,308	83,3 (25/30)	16,7 (5/30)	0,286
Intermediate and Adverse, % (n)	87,2 (82/94)	**12,8** (12/94)		81,9 (77/94)	18,1 (17/94)		90,4 (85/94)	9,6 (9/94)	
***NPM1* gene**									
Mutated, % (n)	68,7 (22/32)	**31,3** (10/32)	**0,015**	59,4 (19/32)	**40,6** (13/32)	**0,002**	87,5 (28/32)	12,5 (4/32)	0,749
Wild type, % (n)	88,3 (68/77)	**11,7** (9/77)		87 (67/77)	**13** (10/77)		89,5 (69/77)	10,4 (8/77)	
Cytogenetic									
Normal karyotype, % (n)	73,2 (41/56)	**26,8** (15/56)	**0,009**	73,2 (41/56)	26,8 (15/56)	0,217	94,6 (53/56)	5,4 (3/56)	0,156
Pathologic karyotype, % (n)	92,5 (49/53)	**7,5** (4/53)		83 (44/53)	17 (9/53)		86,8 (46/53)	13,2 (7/53)	
t(8;21) (q22;q22), % (n)	100 (11/11)	0 (0/11)	0,1	90,9 (10/11)	9,1 (1/11)	0,251	**7,5** (7/94)	**36,4** (4/11)	**0,004**

ASXL1 exon 12 mutations were associated with an adverse outcome among favorable genetic risk category: OS 3,5 mon. vs 30,7 mon., p = 0,034; CRR 50 % vs 94,7 %, p = 0,01.

Conclusions. Mutations in epigenetic modifiers don't have an independent prognostic value by themselves, but can predict the negative outcome in certain cohorts of patients. Co-occurring DNMT3A mutation is an adverse factor among cytogenetically-normal AML, NPM1 and FLT3-ITD mutations. Patients with favorable-risk AML have inferior OS when concomitant ASXL1 or DNMT3A mutations are presence. Alterations in NRAS/KRAS or NF1, and high mutational burden (more than 9 mutated genes) can predict worse prognosis in AML-patients with IDH1/2, DNMT3A or ASXL1 mutations.

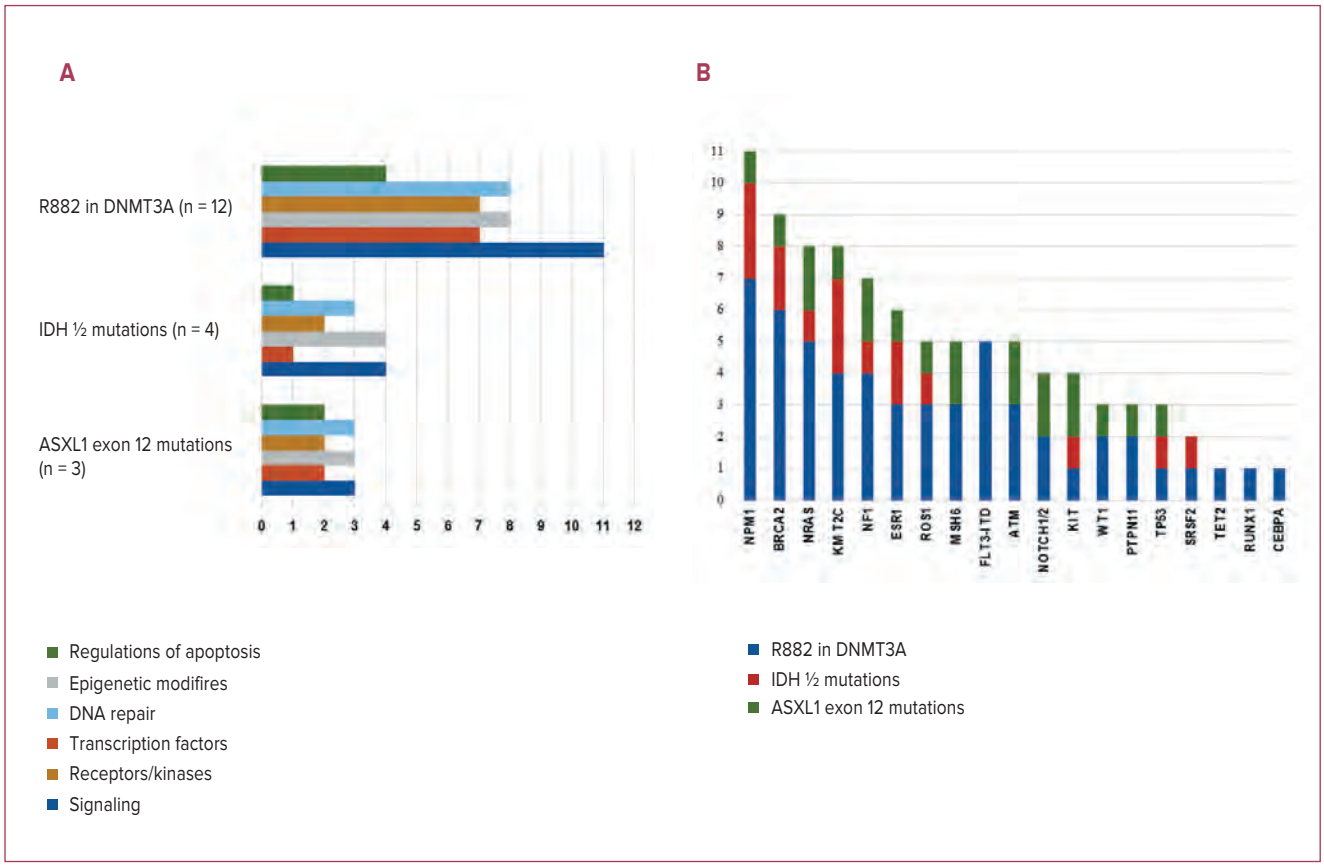

Figure 1. Landscape of coexisting mutated genes in AML with IDH1/2, DNMT3A or ASXL1 mutations: (A) distribution of acquired mutations into functional categories; (B) mutations in different genes

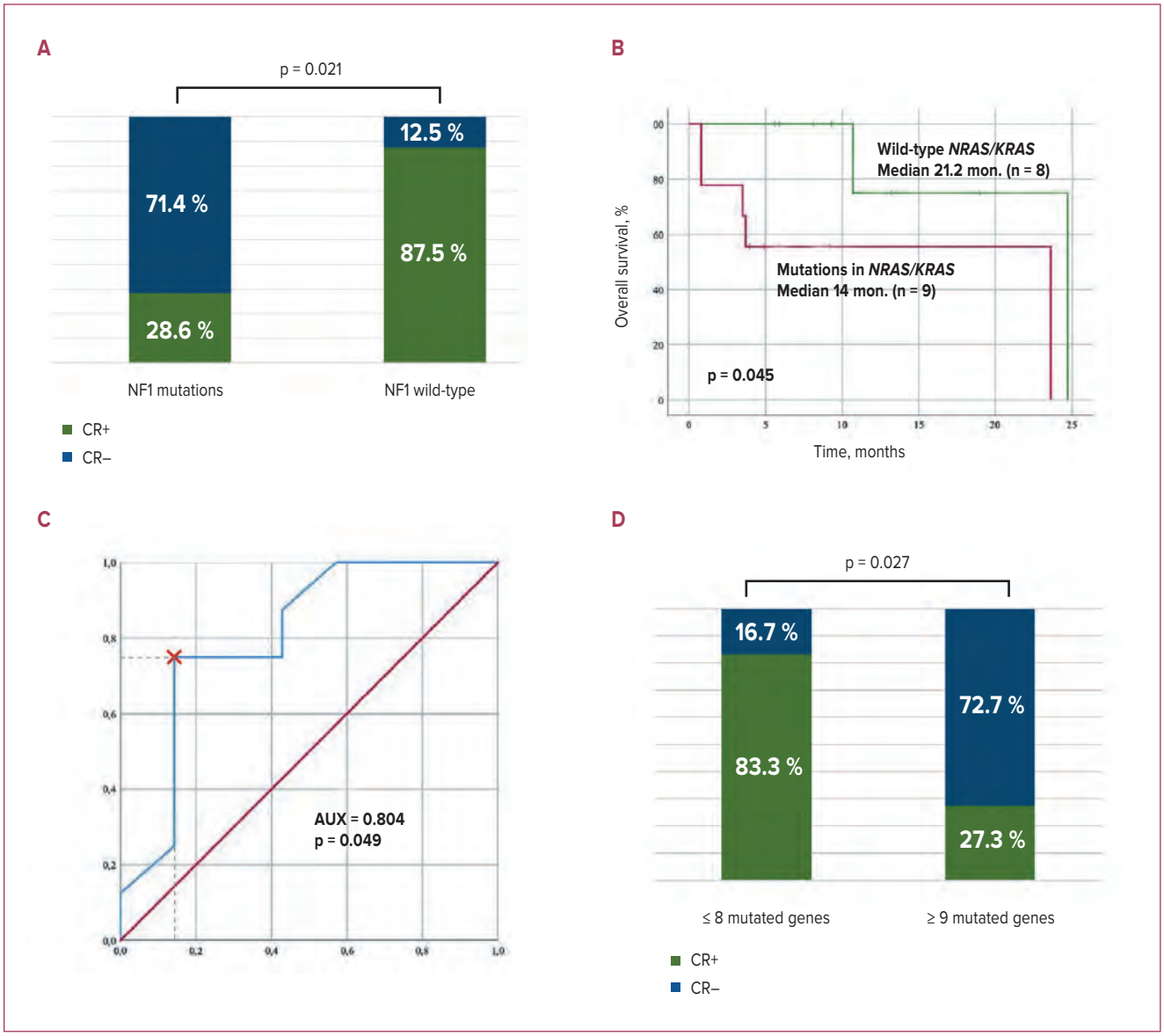

Figure 2. Prognosis depending on the NGS-results: (A) CRR in patients with NF1-mutations and with wild-type NF1; (B) OS depending on the presence of mutations in RAS signaling (*NRAS/KRAS*); (C) ROC-curve which is representing the CRR depending on number of mutations; (D) CRR depending on number of mutated genes

High leukocyte counts, genetic landscape and immunophenotypic maturity of acute myeloid leukemia

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Introduction. High leukocyte counts at the onset of acute myeloid leukemia (AML) are known to be associated with certain genetic abnormalities in tumor cells such as *FLT3-ITD*, inv(16). However, the relationship of molecular genetics, leukocyte counts and immunophenotype of tumor cells have not been extensively characterized.

Objectives. To evaluate the association of certain tumor cell immunophenotypes with leukocyte counts and genetic landscape in patients with AML.

Patients and methods. This multicenter retrospective study included 235 patients with AML, observed from 2010 to 2022. Molecular genetics and cytogenetics data were available for all patients. Immunophenotypic features of blast cells were analyzed for 201 patients. Patients were divided into 4 groups based on mutation landscape: 1) no identified mutations; 2) mutations in the epigenetic regulation genes only (*IDH1/2, DNMT3A*, and *TET)2*; 3) driver mutations only (*NPM1, FLT3, CEBPA)*; 4) a combination of mutations of groups 2 and 3. Patients with t(8;21), inv(16) and *KMT2A*-rearrangements were studied separately. For alternative analysis patients were divided into other 6 groups according to immunophenotype: 1) CD34+CD117+CD13+CD33+MPO-; 2) CD34+CD117+CD13+CD33+MPO+(< 70 %); 3) CD34+CD117+CD13+CD33+MPO+(> 70 %); 4) CD34–CD117+/–CD13+/–CD33+/–MPO+Lys–/^{low}; 5) CD34–CD117+/–CD13+/–CD33+/–MPO+/–Lys^{high}; 6) myelomonocytic immunophenotype — a blast clones combination of groups 4 and 5. Immunophenotypic maturity was determined based on the expression of CD34 and CD117 markers. Multivariate logistic regression with step-by-step selection, Pearson Chi-square, nonparametric Kruskal-Wallis rank criterion and Mann-Whitney U-criterion were used for the statistical analysis.

Results. *FLT3* and inv(16) were significantly associated with leukocyte counts > 30 × 10^9/L (OR = 5.45, p < 0.0001; OR=10.03, p = 0.0009, respectively). t(8;21) as well as adverse cytogenetic lesions like -5/del(5q); -7; -17/abn(17p), inv(3), *KMT2A*-rearrangements, complex or monosomal karyotype were statistically significantly associated with leukocyte counts less than 30 x 10^9/L at the onset of disease (p < 0.0001). Molecular genetic landscape was associated with leukocyte counts elevated in following order: no mutations → only *DNMT3A/TET2/IDH1/2* → only *NPM1/FLT3/CEBPA* → *DNMT3A/TET2/IDH1/2* plus *NPM1/FLT3/CEBPA* (Figure 1). The number of patients with a mature immunophenotype (CD34-CD117+/–) of blast cells increased in the same order (Figure 2). Thus, mature (CD34-CD117+/–) immunophenotype was also significantly associated with the presence of *NPM1/FLT3/CEBPA* gene mutations (p < 0.001). Conversely, t(8;21) and inv(16) were associated with immature CD34+CD117+ immunophenotype (p < 0.001). No statistically significant differences in leukocyte counts were found between the six groups with different immunophenotypes, except difference between group №1 (CD34+CD117+CD13+CD33+MPO–) and № 6 with myelomonocytic immunophenotype. There were significantly higher values of leukocytes in the last group (p = 0.0045).

Conclusions. The genetic profile in AML is significantly associated with a high/low number of leukocytes at the AML onset. We have demonstrated the association between the accumulation of mutational events and the increase in leukocytosis. AML with driver, i.e., later oncogenic mutations (*NPM1/FLT3/CEBPA*) were associated with a more mature immunophenotype of the tumor cells clone (CD34-CD117+/–) and leukocytosis > 30 × 10^9/L.

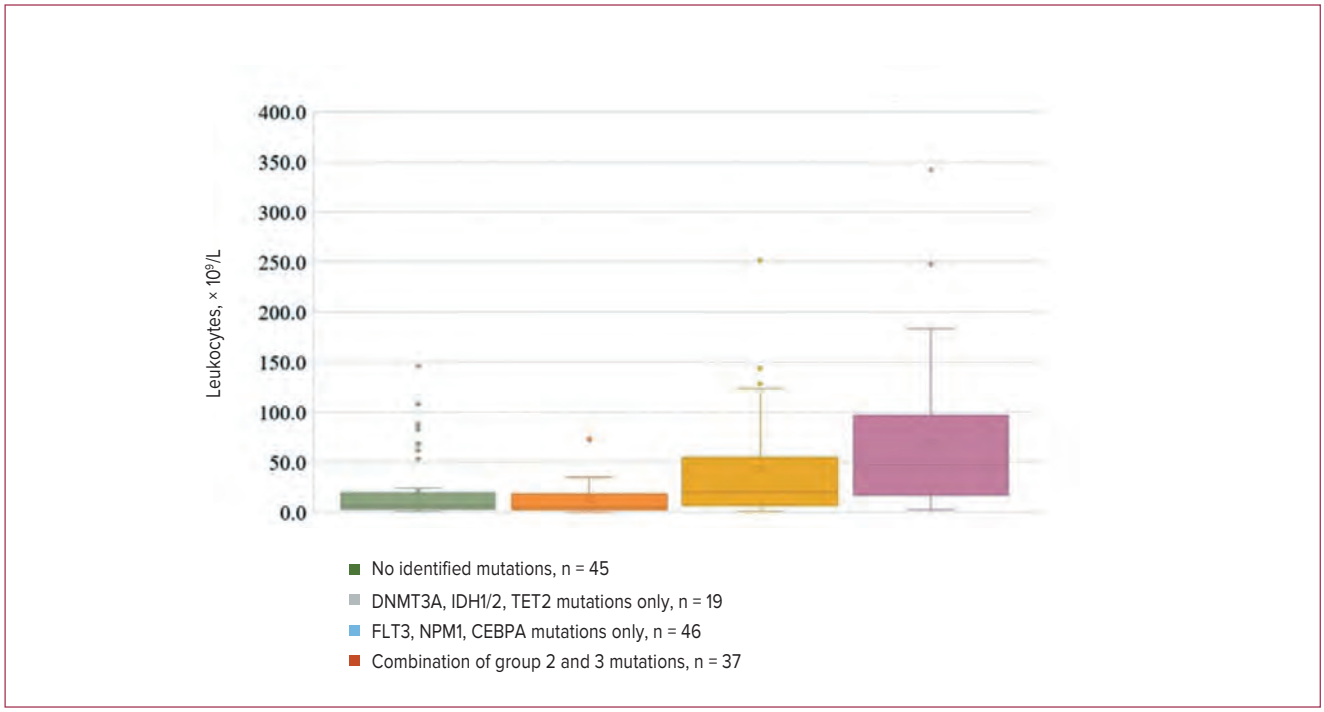

Figure 1. Association of leukocyte count and mutational landscape

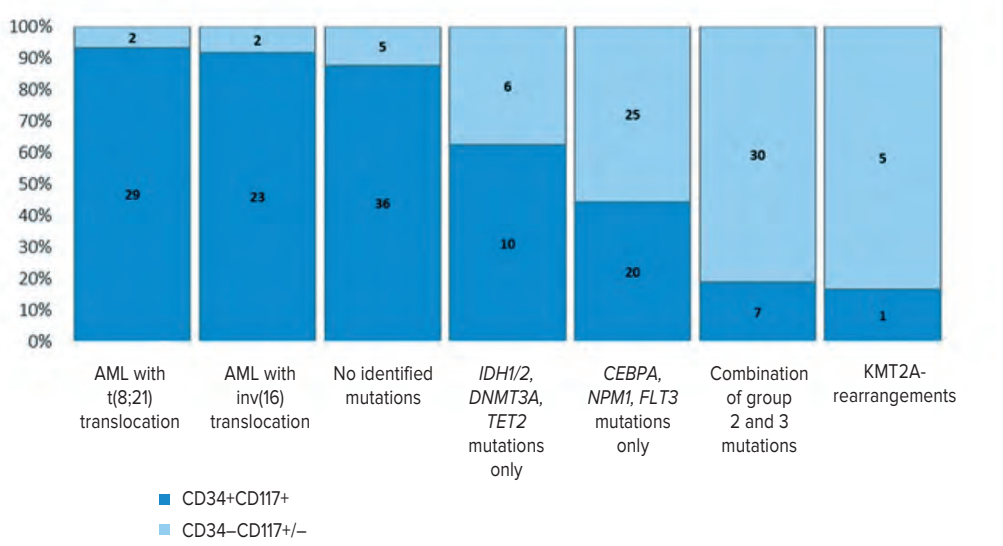

Figure 2. CD34+CD117+ and CD34–CD117+/– blast clones ratio in patients with different mutation landscape (N = 201)

СЕССИЯ 2 ЛИМФОПРОЛИФЕРАТИВНЫЕ ЗАБОЛЕВАНИЯ

Modified follicular lymphoma international prognostic index 2 (FLIPI-2 mod.): development and validation

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Introduction. Current prognostic models for follicular lymphoma (FL) have various limitations because they were developed primarily on data from clinical trials, which do not reflect a representative sample of the target population. In addition, differences in study groups, numbers of patients included, prognostic parameters used, treatments used, and statistical errors make comparisons between different models difficult.

Objectives. Development of a prognostic model for assessing the risk of follicular lymphoma for use in clinical practice.

Methods. The study included 191 patients with FL over 18 years of age from January 2007 to November 2023, with a median follow-up of 3.8 (1.8–4.8) years. All patients were divided into 2 groups (Table 1): the study group consisted of 118 patients observed at the Russian Research Institute of Hematology and Transfusiology (development of a prognostic model), the control group (validation) included 73 patients undergoing treatment at the NMRC of Oncology named after N.N. Petrov.

The obtained data was analyzed using Jamovi 2.4.8.0 (macOS), Microsoft Excel 16.75.2 (for Mac), R version 4.2.2. To predict the value of a binary variable, logistic regression analysis was performed, followed by evaluation of the model using ROC analysis. Survival analysis was performed using the Kaplan-Meier method using the log-rank test to assess the significance of differences. The relationship between survival time and independent variables was assessed using univariate and multivariate Cox regression analyses. Quantitative data are presented in the form of Me (Q3–Q1), frequencies — in the form of eigenvalues with an indication of the 95 % confidence interval (CI).

Results. According to the survey results, the mean value of beta-2-microglobulin (2-MG), equal to 5.54 mg/L, and the median — 5.02 (3.18–7.33) mg/L significantly exceeded the upper value (2.64 mg/L) reference interval. According to the ROC analysis, the prognostically significant level of β2-MG in relation to overall survival (OS) and progression-free survival (PFS) was 4.59 mg/L, sensitivity was 69.2 % and 67.4 %, specificity was 51.1 % and 52.0 % respectively. According to univariate regression analysis (β2 = 4.113, p = 0.043), the relative risk for the found level of β2-MG (≥ 4.59 mg/L) in relation to 5-year PFS was 1.914 (95 % CI 1.011–3.624), p = 0.046.

Considering that the results of stratification into risk groups using the FLIPI-2 index did not reveal differences in survival between the intermediate and high-risk groups of patients, as well as the previously determined threshold value of β2-MG, an attempt was made to modify this prognostic system. Previously, all quantitative variables were dichotomized, but for β2-MG a more differentiated scaling was used: 0–2.64 mg/L — 0 points, 2.65–4.58 mg/L — 0.5 points, ≥ 4.59 mg/L — 1 point. According to the results of ROC analysis in relation to 5-year OS and PFS, coding β2-MG values 0, 0.5 and 1 is characterized by the highest value of the area under the curve (AUC), which was 0.696 (95 % CI 0.599–0.793), p < 0.001 and 0.652 (95 % CI 0.554–0.749), p = 0.002, respectively. The remaining parameters of the FLIPI-2 index and the rules for assigning points were left unchanged. PFS was used as the primary endpoint, as with FLIPI-2. We compared six different models, the quality of which was assessed by AUC value. For the sixth model (stratification of patients into two risk groups, coding β2-MG values as 0, 0.5 and 1), the AUC was 0.695 (95 % CI 0.600–0.790), p < 0.001. In the low-risk group, 5-year PFS was 87.4 % (95 % CI 77.6–98.5), in the high-risk group — 36.2 % (95 % CI 24.5–53.5, median 34.4 months), p < 0.0001. The resulting model (FLIPI-2 mod.) demonstrated stable stratification results (Table 2), including in the analysis of 5-year OS (p < 0.0001), EFS (p = 0.00026) and DFS (p = 0, 0023) (Figure 1).

Table 1. Comparative characteristics of the study groups (n = 191)

Parameter	The study group (n = 118)	Control group (n = 73)	p
Age, years	55,0 (45,0–67,8)	47,0 (37,0–57,0)	**0,0021***
Sex, %			
M F	35,6 (27,0–44,9) 64,4 (55,1–73,0)	32,9 (22,3–44,9) 67,1 (55,1–77,7)	0,7013
GELF, %			
Any node > 7 cm ≥ 3 nodes > 3 cm each Splenomegaly Cytopenia Leukocytosis > 5 × 10^9/L Pleural/peritoneal effusions B-symptoms	38,1 (29,4–47,5) 67,8 (58,6–76,1) 35,6 (27,0–44,9) 2,5 (0,5–7,3) 14,4 (8,6–22,1) 16,1 (10,0–24,0) 50,8 (41,5–60,2)	46,6 (34,8–58,6) 82,2 (71,5–90,2) 31,5 (21,1–43,4) 4,1 (0,9–11,5) 2,7 (0,3–9,6) 8,2 (3,1–17,0) 26,0 (16,5–37,6)	0,2498 **0,0289*** 0,5625 0,5463 **0,0088*** 0,1165 **0,0007***
Grade, %			
1–2 3A 3B	72,0 (63,0–80,0) 20,3 (13,5–28,7) 7,6 (3,6–14,0)	68,5 (56,6–78,9) 27,4 (17,6–39,1) 4,1 (0,9–11,5)	0,4405
Extranodal lesion, %	27,1 (19,4–36,1)	31,5 (21,1–43,4)	0,5152
Bone marrow, %	52,5 (43,2–61,8)	49,3 (37,4–61,3)	0,6646
Stage (Ann Arbor), %			
I–II III–IV	7,6 (3,6–14,0) 92,4 (86,0–96,5)	9,6 (3,9–18,8) 90,4 (81,2–96,1)	0,8820
Complete blood count			
WBC, × 10^9/L Hb, g/L PLT, × 10^9/L LYMPH, × 10^9/L	6,27 (4,66–8,68) 136 (123–143) 211 (175–276) 1,49 (1,12–2,60)	6,00 (4,77–7,51) 132 (121–140) 231 (164–284) 1,33 (0,96–1,68)	0,6082 0,2634 0,7377 **0,0180***
β2-MG, mg/L	5,02 (3,18–7,33)	2,25 (1,62–2,85)	< **0,0001***
LDH, IU/L	220 (174–327)	207 (170–250)	0,1266
t(14;18) [FISH], %	44,0 (33,6–54,8)	41,4 (23,5–61,1)	0,8073
Response rate, %			
PR CR OO	43,2 (31,1–52,7) 65,3 (55,9–73,8) 87,3 (79,9–92,7)	45,2 (33,5–57,3) 69,9 (58,0–80,1) 95,9 (88,5–99,1)	0,7883 0,5103 **0,0480***
Time to response, months			
PR CR OO	3,6 (2,7–4,7) 5,8 (3,6–12,1) 3,9 (2,9–5,8)	4,5 (3,8–5,3) 5,2 (4,3–6,5) 4,6 (4,1–5,7)	**0,0181*** 0,9767 **0,0267***
POD24, %	27,1 (19,4–36,1)	20,5 (12,0–31,6)	0,3056
Time to event, months			
Progression Relapse POD24	11,6 (7,5–19,2) 21,4 (11,9–44,2) 11,3 (8,3–14,4)	22,0 (10,6–27,1) 6,6 (5,2–13,0) 7,4 (5,2–15,8)	0,1522 **0,0185*** 0,3594
Median observation, years	3,1 (1,9–5,0)	3,2 (1,8–4,4)	0,3499

Note: CR — complete response, LDH — lactate dehydrogenase, OO — objective response, POD24 — progression of disease within 2 years, PR — partial response, 2-MG — beta-2-microglobulin.

* Significance level ≤ 0.05.

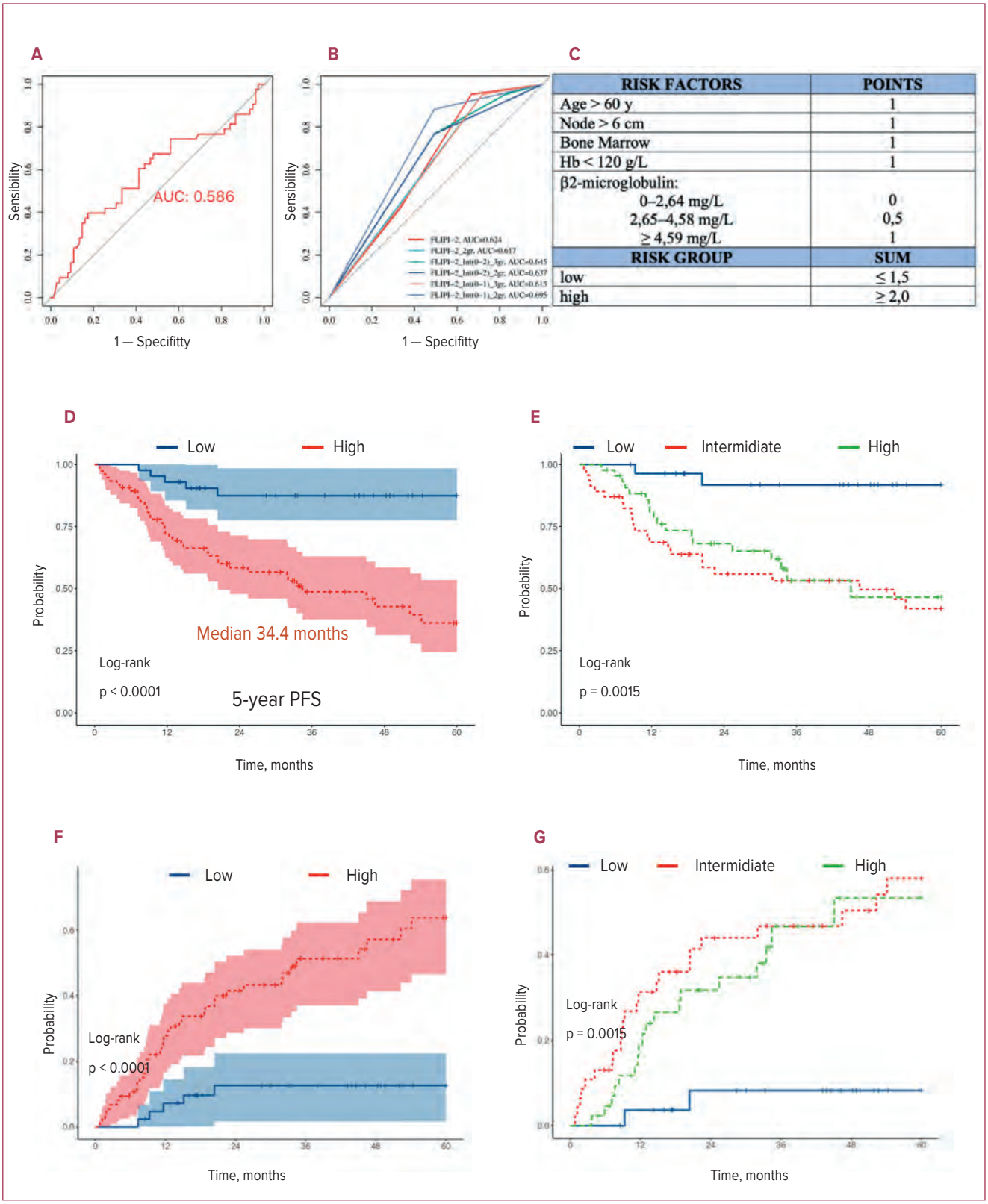

Figure 1. (A) ROC analysis in relation to 5-year PFS to determine the threshold value of β2-MG; (B) ROC curves of six models in relation to 5-year PFS: 1) FLIPI-2, 2) FLIPI-2 with distribution into two groups (FLIPI-2_2gr), 3) FLIPI-2 with interval estimate β2-MG (0, 1, 2 points) and distribution into three groups (FLIPI-2_Int(0-2)_3gr), 4) FLIPI-2 with interval assessment β2-MG (0, 1, 2 points) and distribution into two groups (FLIPI-2_Int(0-2)_2gr), 5) FLIPI-2 with interval assessment β2-MG (0, 0.5, 1 point) and distribution into three groups (FLIPI-2_Int(0-1)_3gr) and 6) FLIPI-2 with an interval assessment of β2-MG (0, 0.5, 1 point) and the distribution of patients into two risk groups (FLIPI-2_Int(0-1)_2gr) — FLIPI-2 mod.; (C) Rules for accruing points for the FLIPI-2 mod. index; (D) Five-year PFS depending on FLIPI-2 mod. risk group (study group); (E) Five-year PFS depending on FLIPI-2 risk group (study group); (F) Five-year risk of progression depending on FLIPI-2 mod. risk group (study group); (G) Five-year risk of progression depending on FLIPI-2 risk group (study group)

Table 2. Survival rates in patients from the study group depending on the risk group of basic FLIPI-2 and FLIPI-2 mod.

Survival rate	FLIPI-2	p	FLIPI-2 mod.	p
5-years OS				
Low Intermediate High	100 % 65,9 % (51,1–84,9) 54,5 % (36,8–88,6 %)	**0,0052***	96,9 % (91,0–100,0) – 53,6 % (40,1–71,6)	**< 0,0001***
5-years PFS				
Low Intermediate High	91,7 % (81,3–100,0) 42,0 % (28,3–62,1) 46,6 % (30,6–70,8)	**0,0015***	87,4 % (77,6–98,5) – 36,2 % (24,5–53,5)	**< 0,0001***
5-years RFS				
Low Intermediate High	90,2 % (78,0–100,0) 29,2 % (13,8–61,9) 37,6 % (17,6–80,3)	**0,0058***	72,4 % (53,1–98,8) – 32,2 % (18,0–57,8)	**0,0023***
5-years EFS				
Low Intermediate High	78,7 % (63,6–97,4) 27,4 % (15,7–47,8) 28,6 % (12,8–64,1)	**0,0019***	67,1 % (51,8–86,7) – 23,9 % (13,2–43,4)	**0,00026***

Note: EFS — event-free survival, OS — overall survival, PFS — progression-free survival, RFS — relapse-free survival.
* Significance level ≤ 0.05.

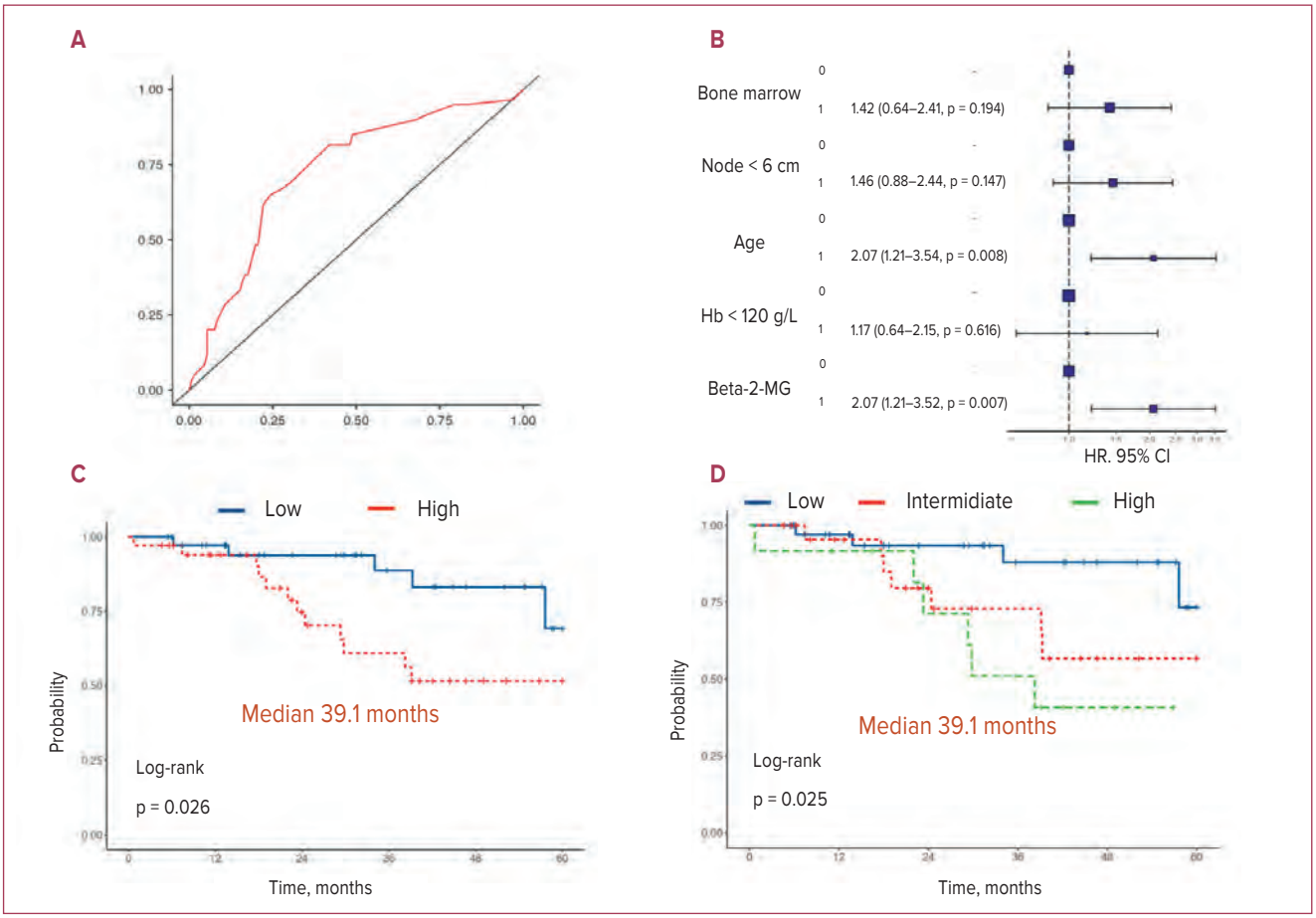

Figure 2. (A) ROC analysis in relation to 5-year PFS for the FLIPI-2 mod. prognostic index; (B) Odds ratio indicating 95 % CI of the five factors included in FLIPI-2 mod., according to the results of Cox regression analysis; (C) Five-year PFS depending on FLIPI-2 mod. risk group (control group); (D) Five-year PFS depending on FLIPI-2 risk group (control group)

The model (FLIPI-2 mod.) was validated on 73 patients from the control group. In the low-risk group, 5-year PFS was 69.3 % (95 % CI 46.2–100.0), in the high-risk group — 51.5 % (95 % CI 34.7–76.5), p = 0.025 (Figure 2). For 5-year OS, there was a similar trend in differences: p = 0.07.

Conclusions. It has been shown that for patients with FL, a β2-MG value of 4.59 mg/l has a greater prognostic role than the upper limit of the reference interval. Based on the results obtained, the prognostic index FLIPI-2 mod. was developed for predicting PFS, stratifying patients into two risk groups (p < 0.0001) and having high predictive value for OS (p < 0.0001), DFS (p = 0.0023) and EFS (p = 0.00026).

Key words: follicular lymphoma, prognosis, survival, prognostic index, beta-2-microglobulin, FLIPI-2.

Comparative characteristic of patients with multiple myeloma with kidney damage and without it

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Introduction. Multiple myeloma is a B-cell malignant tumor, the morphological substrate of which is plasma cells that produce monoclonal non-functional immunoglobulin. The incidence of MM is approximately 1 % among all malignant tumors and up to 10–15 % of all tumors of hematopoietic and lymphoid tissues [1].

Kidney damage in MM may be the first or only manifestation of this disease and serves as the most important negative prognostic factor that reduces patient survival [2, 3]. The main cause of kidney damage in multiple myeloma is damage to nephron structures by monoclonal light chains [2]. Myeloma nephropathy most often develops (33–57 % of all causes of renal failure), less commonly AL amyloidosis (21 %) and light chain deposition disease (22 %) [2, 4]. Kidney failure is the second leading cause of death in multiple myeloma [1, 5].

Objectives. To conduct a comparative analysis of factors influencing kidney damage in multiple myeloma and to evaluate changes in kidney function during chemotherapy.

Materials and methods. Clinical and laboratory parameters of 100 patients who were treated in the hematology department of the Stavropol Regional Clinical Oncology Hospital for 2020–2022 were subjected to retrospective analysis.

These parameters were assessed at the time of diagnosis and after 6–12 months of chemotherapy (CT). The patients were divided into two groups: group I — 50 patients with multiple myeloma complicated by kidney damage; Group II — 50 patients with multiple myeloma without kidney damage. In group I, 21 patients had stages IIA-IIB and 29 patients had stages IIIA-IIIB, according to the classification of myeloma by B. Durie, S. Salmon (1975). In group II there were 23 and 27 patients, respectively.

The following were comparable in both groups: mean age, male/female ratio, body mass index, multiple myeloma treatment regimens. Consequently, demographic, constitutional indicators, and treatment regimens did not affect the results of the study. The following parameters were studied: the duration of the period from the onset of complaints to diagnosis, the specialist who made the preliminary diagnosis, the results of instrumental research methods (computer tomography (CT), X-ray examination, magnetic resonance imaging (MRI)), the percentage of plasma cells, the type of free cells detected light chains (FLC), type of immunoglobulins detected, levels of hemoglobin, calcium, total protein, urea, uric acid, LDH, creatinine, estimated glomerular filtration rate (eGFR) over time.

Results. In group I, from the onset of complaints to diagnosis, an average of 13 months passed, in group II — 7 months. Mostly, patients were consulted by a hematologist after receiving the results of X-ray/CT/MRI diagnostics performed in connection with pain syndrome. Patients were also referred by general practitioners (group I — 24 %, group II — 20 %), nephrologists (10 % and 0 %, respectively) and neurologists (4 % in both groups).

At the initial diagnosis of MM, all patients of both groups had degenerative-destructive changes and pathological fractures in one or more parts of the spine. Commonly, these changes were detected in the lumbosacral region (in 29 patients of group I and 24 patients of group II). In general, the total damage to various parts of the skeletal system in patients in group I was higher than in patients in group II (74 and 67, respectively, t = 1.984, p = 0.05).

When studying the myelogram, the average percentage of plasma cells was 40 % in group I, 27 % in group II ($t = 3$, $p < 0.05$). The percentage of patients with FLC kappa in groups I and II was the same (64 % and 62 %, respectively). In the group of patients with kidney damage, lambda free light chains were slightly more common (32 % vs 24 %). There was no significant difference in the frequency of detected IgA and IgG in both groups. In addition, in our study, in almost every seventh patient with multiple myeloma without signs of kidney damage, free light chains were not detected at all.

13 patients (26 %) with severe renal failure were started on renal replacement therapy (RRT) by hemodialysis. The average age of patients was 59 (45;74) years, men predominated (m:f — 9:4). In this cohort of patients, only IgG was detected; the percentage of detection of kappa or lambda FLC was almost the same (54 % and 46 %, respectively).

68 % of patients in group I and 60 % of patients in group II had anemia at the time of diagnosis (Hb — 94.8 (50;160) g/l and Hb — 106.2 (72;155) g/l, respectively). During dynamic observation, it was revealed that in patients of group II during therapy, the hemoglobin level increased and after a year it was Hb — 126 (95;166) g/l. In group I, this indicator changed in dynamics to a lesser extent (Hb — 109 (53;142) g/l) ($t = 2.8$, $p < 0.05$).

At the time of diagnosis, CKD C3b-5 was diagnosed in 82 % of patients in group I, after 6 months — 64 %, and after 1 year — 56 %. The estimated GFR (eGFR) in patients of group I with impaired renal function was 28.12 (3;69) ml/min/1.73 m^2 at the onset of the disease, in group II — 69.1 (60;104) ml/min/ 1.73 m^2 ($t = 6.1$, $p < 0.05$). During treatment, after 12 months in group I, a partial renal response was obtained with an increase in eGFR to 36.0 (8;62) ml/min/1.73 m^2. In group II, after 1 year, eGFR was 75.6 (61;108) ml/min/1.73 m^2. In 37 (74 %) patients of group I, renal function improved during chemotherapy. However, 13 patients of group I (26 %) required hemodialysis sessions. Moreover, in 9 of them (70 %) dialysis treatment was started at the time of diagnosis. And only in 2 patients, renal function improved during treatment, and it became possible to stop hemodialysis.

Conclusions. 1. Representative factors of kidney damage in multiple myeloma in our study were: the duration of time from the onset of the disease to diagnosis, eGFR at the time of diagnosis and the percentage of plasma cells obtained during the study of the myelogram.

2. Patients with multiple myeloma and kidney damage had (significantly) lower hemoglobin levels and more often destructive skeletal lesions.

3. During chemotherapy, 78 % of patients achieved a partial renal response. More often, renal response was not achieved in male patients already starting RRT at the time of diagnosis.

4. Timely diagnosis of MM will avoid severe kidney damage, promote a better renal response and improve the prognosis of the disease.

Key words: multiple myeloma, kidney damage, factors.

References

1. Клинические рекомендации «Множественная миелома», 2022.

2. Bradwell AR. Serum Free Light Chain Analysis (plus Hevylite). 6th Edition, 2010.

3. Chan DT, Craig K, Donovan K, Phillips A. Myeloma renal disease: Presentation and outcome. Nephron Clin Pract. 2006;104(3): c126–31.

4. Li J, Zhou D Bin, Jiao L, et al. Bortezomib and dexa-methasone therapy for newly diagnosed patients with multiple myeloma complicated by renal impairment. Clin Lymphoma Myeloma. 2009. doi:10.3816/CLM.2009.n.077.

5. Dimopoulos MA, Roussou M, Gavriatopoulou M, et al.Bortezomib-based triplets are associated with a high probability of dialysis independence and rapid renal recovery in newly diagnosed myeloma patients with severe renal failure or those requiring di-alysis. Am J Hematol. 2016;91 (5):499–502. doi: 10.1002/ajh.24335.

Russian experience of combination therapy with venetoclax and obinutuzumab in treatment-naïve chronic lymphocytic leukemia patients — data from multicentre prospective study

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Introduction. Venetoclax is a BCL-2 inhibitor that produces deep responses with high rates of undetectable minimal residual disease (MRD) for patients with chronic lymphocytic leukemia (CLL) (Al-Sawaf et al. 2020). In CLL14 trial, treatment of first line CLL with a combination therapy of venetoclax and obinutuzumab (VenG) has shown perspective efficacy and good tolerability. Meanwhile, CLL14 main inclusion criteria were CIRS>6 and/or creatinine clearance <70ml/min. Prospective real-world data on VenG are limited.

Objectives. We prospectively assessed safety, effectiveness and surrogate marker of effectiveness — MRD in treatment-naïve CLL-patients treated with VenG in 14 centers of 12 regions of Russia (Moscow, Saint-Petersburg, Bryansk, Surgut, Yuzhno-Sakhalinsk, Chita, Krasnoyarsk, Stavropol, Ufa, Krasnodar, Volgograd, Kirov).

Methods. Patients requiring therapy with treatment-naive CLL treated from September 2020 and included in analysis between March 2023 and October 2023 were evaluated. Treatment consisted of 12 months of venetoclax with standard dose ramp up and 6 cycles of obinutuzumab with total of 8 infusions. Response assessment was performed using iwCLL criteria and can be documented every 3 months during therapy and with 3-6 months intervals after end of the planned number of cycles. MRD was assessed by multi-parametric bone marrow flow cytometry with a sensitivity of 10-4. Time-to-event analyses were performed with the Kaplan-Meier method.

Results. Fourty-two patients received at least one dose of venetoclax were enrolled (Table 1). The patients had a median age of 60 years (range; 23–76). Binet stage at time of treatment initiation: A 3 patients (7 %), B — 24 (57 %), C — 8 (19 %). Median observation time was 13,4 months and for 29 patients MRD response has been documented at least once. Patients harboured the following cytogenetic abnormalities: del(13q) 11/22 (50 %); del(11q) 7/22 (32 %); trisomy 12 3/22 (14 %); del(17p) 1/42 (2 %). Seventy-six percent (29/38) of patients harboured an unmutated IGHV status.

The best MRD response for the whole cohort was 100 %. Nineteen patients (65 %) have already achieved undetectable MRD by 3 months of observation. The majority of patients had an undetectable MRD since 3rd month of assessment which lasted till 18th month of observation (Figure 1).

No disease progression was documented so far. The median progression-free survival (PFS) as well as overall survival (OS) have not been reached. At current observation timepoint both PFS and OS are 88,7 % and 100 % with COVID-19 cases of death exclusion (Figure 2).

Laboratory signs of tumor lysis syndrome (TLS) were documented for 2 patients, one of whom was diagnosed with pneumonia at 4th month of treatment with fatal outcome. TLS risk categories were represented as follows: low — 14 patients (35 %), intermediate — 24 (60 %), high — 2 (5 %).

Conclusions. This real-world experience showed well tolerability, high undetectable MRD response rate and high PFS and OS with currently available modest follow-up period. Overall, our results confirm the optimistic results from CLL14 trial and shift our understanding of the group for which venetoclax and obinutuzumab are used in first line towards a younger population.

Key words: chronic lymphocytic keukemia, venetoclax.

Table 1. Patients characteristics

Characteristics	N (%)
Patients, total	42
Median age (range)	60 (23–76)
Male/female	29/13
Binet stage A B C	 3 (7 %) 24 (57 %) 8 (19 %)
ECOG 0 1 2–4	 14 (33 %) 28 (67 %) –
Deletion 13q Deletion 11q Trisomy 12 Deletion 17p	11/22 (50 %) 7/22 (32 %) 3/22 (14 %) 1 (2 %)
Unmutated IGVH	29/38 (76 %)
Median observation time (range)	13 (0,7–33)

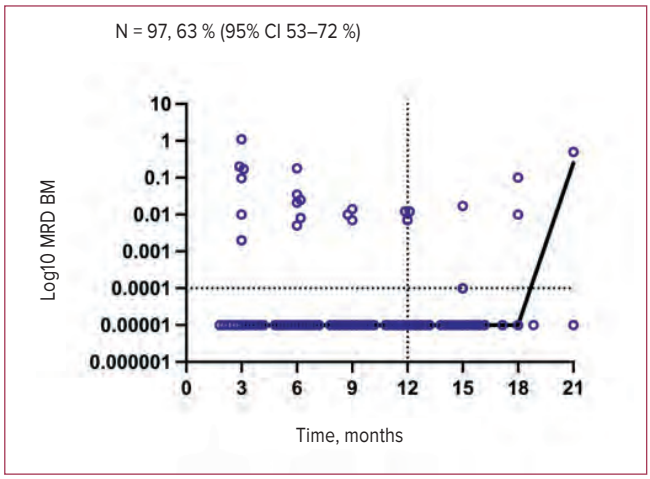

Figure 1. MRD Dynamics

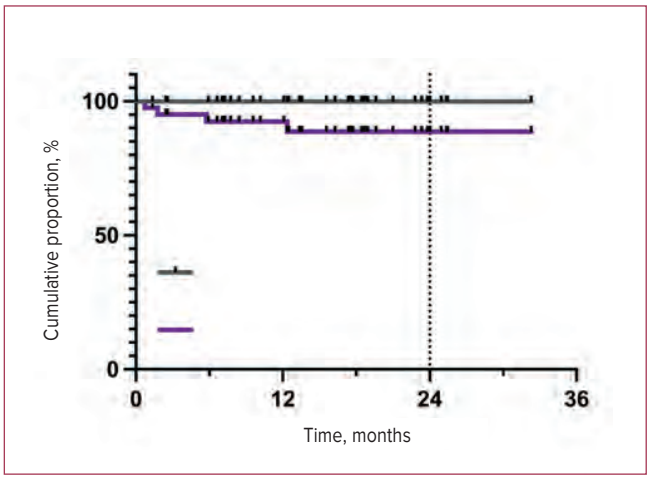

Figure 2. Overall survival and progression free survival

Ibrutinib dose modifications do not have an impact on the rate of progression in relapsed chronic lymphocytic leukemia patients

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Introduction. Ibrutinib is routinely prescribed for indefinite periods of time. Administration of ibrutinib has been associated with several adverse events (AEs) resulting in dose reductions or temporary discontinuation of the drug, giving rise to concerns of sub therapeutic drug levels promoting resistance to ibrutinib. Although data from early clinical trials and clinical practice have suggested that poor dose adherence was associated with adverse outcomes (UK Forum, 2016, Barr PM, 2017), this was not supported by later publications (Mato AR, 2018, Ahn IE, 2019).

Objectives. The aims of the study were to uncover the reasons for ibrutinib dose modifications and the relationship between dose intensity (DI) and progression in a cohort of relapsed and refractory CLL patients.

Methods. The study included 258 patients with available dose information, who used ibrutinib between November 1, 2015 and March 1, 2019. DI was defined as the ratio of the "delivered" to "planned" dose of ibrutinib. DI was calculated until 60, 180, 360, and 720 days, and all patients with events occurred before these points were excluded. Landmark analysis of survival was performed at corresponding points of 2, 6, 12, and 24 months. In time to treatment failure (TTF) analysis, all events other than progression were censored. Dose modifications were performed at the discretion of the treating physician, according to published guidelines. There was no limitation on the term of dose interruption: the patient could restart ibrutinib after the resolution of toxicity, independent of the dose-hold duration. Cases of progressive disease during the dose hold were excluded.

Results. The median age of patients was 65 years (range 32–92), 65 % were males, 36 % of patients had 17p deletion. 212 patients received ibrutinib as monotherapy, 46 (18 %) in combination with monoclonal antibodies. All patients have started ibrutinib at 420 mg, except for the 11 patients in whom the dose was reduced at inception for pharmacokinetic reasons. Fifty-nine (23 %) patients experienced only dose interruptions, 46 (18 %) had dose reductions only, while 48 (19 %) had both dose interruptions and reductions. The median DI in the subgroup of patients who had dose reductions and interruptions was 97.2 % (range, 22.6–99.9 %). In the total sample, a DI < 100 % was observed in 153 (59 %) patients and a DI < 97 % in 76 (29 %) patients. The reasons

Table 1. Reasons for treatment interruptions and reductions

	Number of episodes (%)	Number of patients	Median duration, range (days)
Treatment interruptions			
Surgical operations/biopsies/manipulations	82 (51.25 %)	56	6 (3–48)
Infections	37 (23.1 %)	29	7,5 (2–38)
Atrial fibrillation	9 (5.6 %)	6	5 (1–28)
Other cardio/vascular events	6 (3.7 %)	6	23,5 (10–125)
Compliance	8 (5 %)	8	4 (2–8)
Hemorrhagic complications	6 (3.7 %)	6	5 (3–66)
Myalgia / arthralgia	4 (2.5 %)	3	11 (8–15)
Diarrhea	3 (1.8 %)	3	5 (1–5)
Hepatotoxicity	2 (1.3 %)	2	7, 14
DVT and heparin therapy	1	1	10
Pharmacokinetics (phenobarbital)	1	1	8
Headache	1	1	35
Dose reductions			
Pharmacokinetic considerations	66 (47 %)	51	10 (2–743)
Neutropenia	17 (12.1 %)	15	574 (34–936)
Myalgia/arthralgia	11 (7.8 %)	9	80 (13–598)
Atrial fibrillation	10 (7.1 %)	7	48,5 (7–353)
Hepatoxicity	9 (6.4 %)	9	226 (7–458)
Multiple causes	8 (5.6 %)	8	201 (21–841)
Bleeding in patients with anticoagulants/ antiplatelet drugs	6 (4.3 %)	4	95 (61–110)
Infections	5 (3.5 %)	4	21 (14–363)
Compliance	3 (2.1 %)	3	25 (10–28)
Skin eruptions	3 (2.1 %)	3	547 (91–1049)
Other	3 (2.1 %)	3	*

*Other: 1 — diarrhea (95 days), 1 — headache (207 days), 1 — symptomatic sinus bradycardia (41 days)

for dose interruption or reduction are shown in Table 1, representing recorded modifications of therapy either for 36 months of ibrutinib administration, or for entire period of ibrutinib treatment. Among 74 non-pharmacokinetic episodes of dose reductions, a total of 21 (28 %) were permanent, while in the other 53 cases patients were able to resume the dosing after the resolution of AE. The sample of patients with DI < 97 % significantly differed in older age, ECOG > 2, a history of myocardial infarction, and the presence of HBs antigen. After a median follow-up of 33.8 months (1.23–66 months), a total of 155 patients (60 %) remained under observation. In total, 87 treatment failure events were registered as a first event. Using different DI levels (70–99 %), none of the samples showed statistically significant differences in TTF, although there was a strong trend towards shorter TTF in patients with Dis < 70 % within the first 2 months of treatment (Figure 1, A–C). When performed after exclusion of pharmacokinetic dose modifications, TTF analysis yielded same results (Figure 1, D–F). As opposed to TTF analysis, highly significant differences were found in analysis of OS, performed for the DIs calculated within 2, 12, and 24 months (Figure 1, H–G).

Conclusions. Dose modification does not impact the rate of progression in relapsed chronic lymphocytic leukemia patients. As the cohort of patients with dose modifications was, on average, older than that without modifications, and had higher prevalence of comorbid conditions, significant association of dose reductions/interruptions with poor OS was observed. In clinical practice, modification of ibrutinib dose is justifiable when indicated.

References

1. Woyach JA, Barr PM, Kipps TJ et al. Characteristics and Clinical Outcomes of Patients with Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Receiving Ibrutinib for ≥ 5 Years in the RESONATE-2 Study. Cancers (Basel). 2023 Jan 13;15(2):507

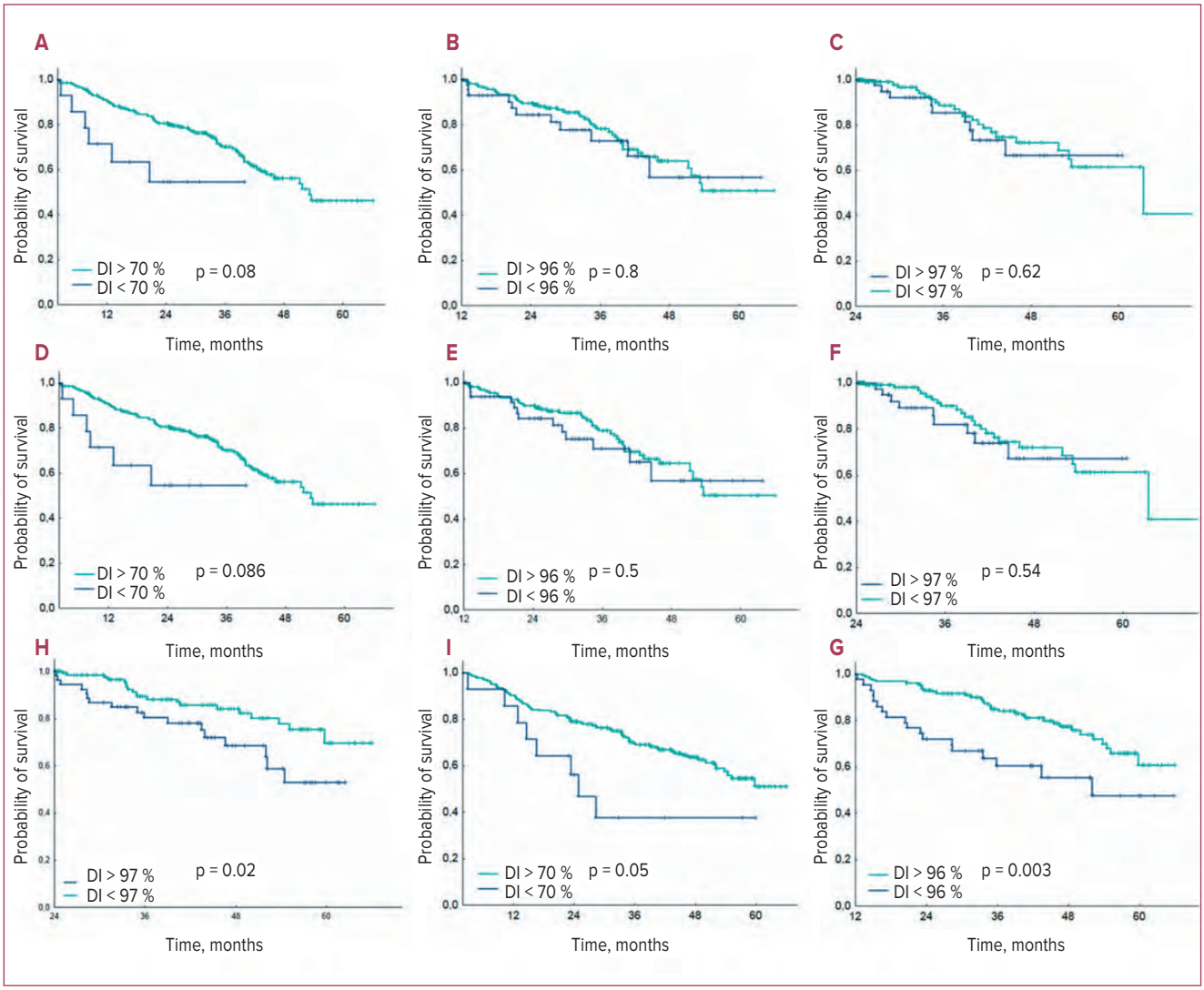

Figure 1. Time to treatment failure and overall survival: (A, D) Landmark analysis of time to treatment failure at 2 months (A — without pharmacokinetic modifications, D — including pharmacokinetic modifications); (B, E) Landmark analysis of time to treatment failure at 12 months (B — without pharmacokinetic modifications, E — including pharmacokinetic modifications); (C, F) Landmark analysis of time to treatment failure at 24 months (C — without pharmacokinetic modifications, F — including pharmacokinetic modifications); (H, I, G) Landmark analysis of overall survival at time points 2, 12 and 24 months

Ibrutinib and venetoclax combination in treatment of CLL with complex karyotype

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Introduction. Studies by Kittai (2021) and Al-Sawaf (2020) showed an adverse impact of karyotypic complexity (CK) on survival of patients with chronic lymphocytic leukemia (CLL) treated with ibrutinib or venetoclax. Optimal treatment choice as well as treatment duration in this high-risk group of patients is unclear. A number of clinical trials, focusing on patients with adverse prognostic factors are currently investigating an MRD-guid-

ed approach using different combinations of venetoclax and BTK inhibitors. Thus, Lydia Scarfo et al. (2023) offered an addition of ibrutinib in case of MRD-positivity by the end of 1-year venetoclax monotherapy. HOVON group promotes MRD-guided end of combinational therapy and re-treatment in case of MRD-positivity (Kater, 2022). FLAIR trial determines the total duration of therapy based on the time required to achieve MRD-negative status (Hillmen, 2022). Meanwhile, achievement of response with undetectable MRD was determined as the goal of therapy since CLARITY trial (Munir, 2022).

Objectives. The aim of our study is to evaluate the effectiveness of combinational therapy with ibrutinib and venetoclax in comparison with sequential therapy with ibrutinib and venetoclax for the patients with CLL and CK.

Methods. This observational study included patients with CLL with high genetic complexity (high-CK), defined as ≥ 5 aberrations or CK (≥ 3 aberrations) in combination with a 17p deletion (CK+del17p). The first retrospective cohort included patients treated with ibrutinib monotherapy (Imono) untill progression with switch to venetoclax (→Ven) starting from May 2015. The second prospective cohort included patients receiving ibrutinib in combination with venetoclax (IVen) from July 2019. Venetoclax therapy was started at the 3rd month of ibrutinib. Combinational therapy was continued until a complete/partial response with MRD-negativity is achieved in 3 sequential measurements 3 months apart. If this MRD-negativity was not achieved at 24th month of therapy, venetoclax was discontinued and ibrutinib continued indefinitely. Since patients were not observed at parallel time intervals survival analyses were performed with and without censoring of cases of death from COVID-19.

Results. Ninety-four patients have been included in the study. There were 50 patients in the first cohort and 44 patients in the second cohort. Thirty-four patients in the 1st cohort have switched to venetoclax. The patient characteristics are presented in Table 1. At the current follow-up time, IVen regimen showed significantly better PFS compared to ibrutinib monotherapy (p = 0,05 and p = 0,0015, Figure 1, A, B). There was no significant difference in OS (p = 0,26). In a subgroup of patient in Imono cohort who have switched to venetoclax time to second progression starting from the beginning of ibrutinib was similar to IVen cohort (p = 0,41), and there was no difference in OS (p = 0,29) (Figure 1, C, D). In the group of patients treated with Imono the majority of patients achieved partial remission or partial remission with lymphocytosis by 12 months, and no patients had MRD-negative response. In the IVen cohort the range of MRD-negativity has been gradually increasing during treatment period (Figure 2). With a median follow-up of 24 months 27 patients from IVen group have achieved a

Table 1. Comparison of characteristics for sequential and combinational therapy with Ibrutinib and venetoclax

Characteristics	Ibrutinib	Ibrutinib + Venetoclax	p
Patients, total	50	44	
Median age (range)	65 (34–83)	63 (30–80)	0.4458
Male/female	28/22	22/22	0.9431
Binet stage at the start of ibrutinib therapy			0.2422
A	–	–	
B	26 (52 %)	30 (68 %)	
C	24 (48 %)	14 (32 %)	
ECOG			0.118
0-1	46 (92 %)	44 (100 %)	
2-4	4 (8 %)	–	
High-CK (^{3}5 aberrations)	42 (84 %)	37 (84 %)	0.2168
CK (^{3}3 aberrations) + deletion 17p	8 (16 %)	7 (16 %)	
Deletion 17p	35 (70 %)	28 (64 %)	0.4696
Unmutated IGVH	45/45 (100 %)	31/36 (86 %)	0.2394
Median previous therapy lines (range)	2 (0–7)	1 (0–5)	0.2502
Richter syndrome	4 (8 %)	0	0.8700

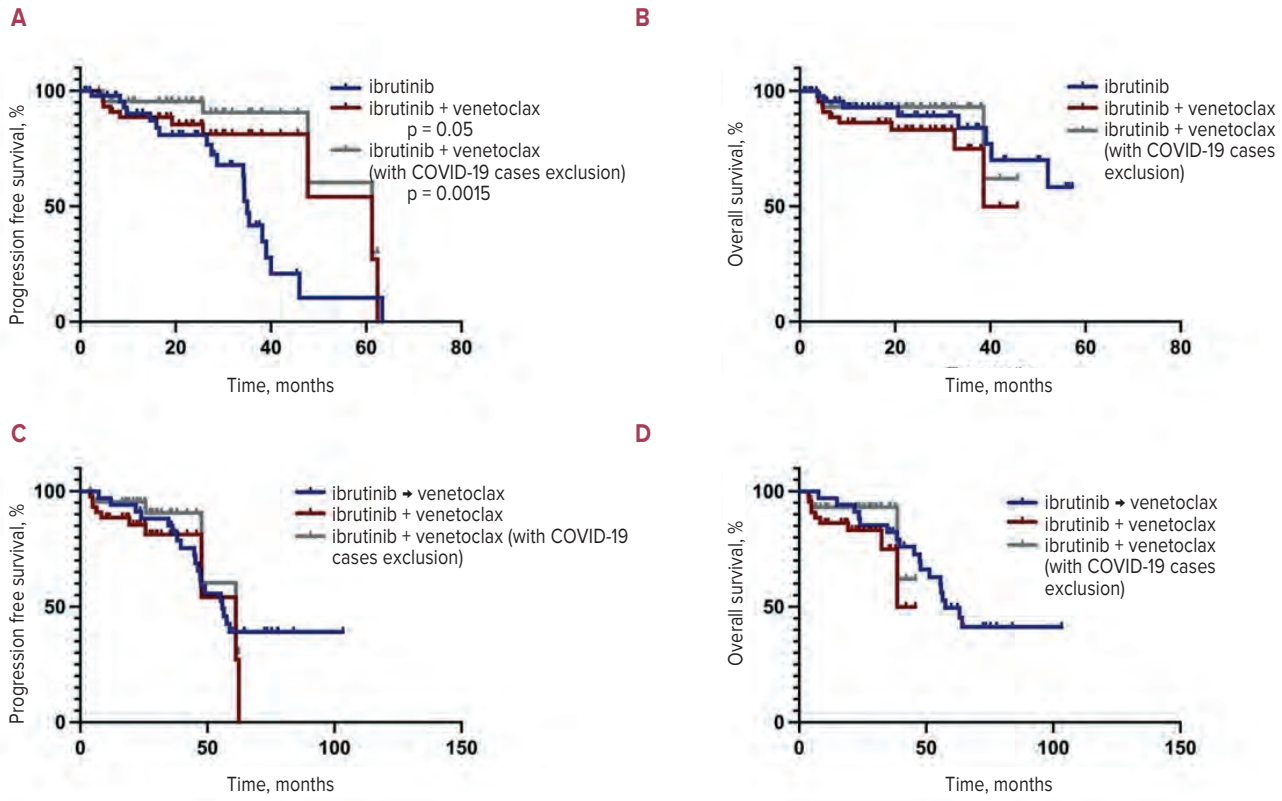
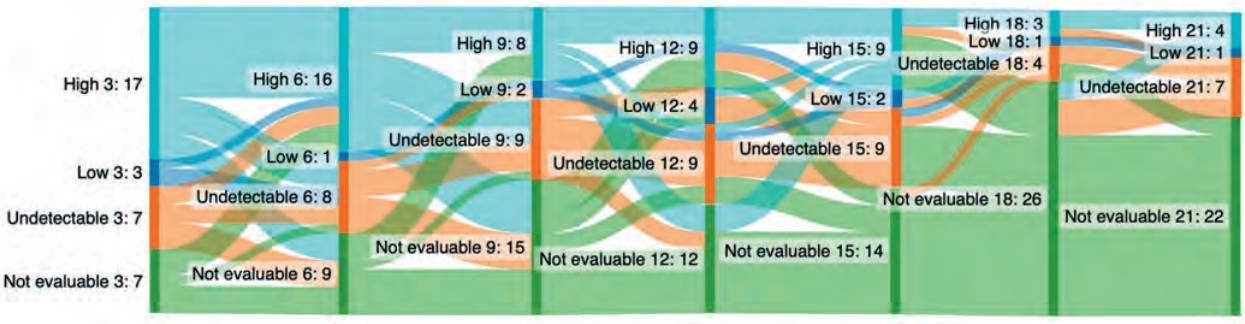


Figure 1. Progression-free and overall survival for combinational and sequential therapy with Ibrutinib and venetoclax



Best response

Complete remission MRD (+) MRD (–)	27 (79 %) 13 (48 %) 14 (51 %)
Partial remission MRD (+) MRD (–)	5 (15 %) 3 (1 %) 2 (6 %)
Progression	2 (6 %)

Figure 2. Dynamics and best response for Ibrutinib and venetoclax combination

complete remission (79 %) and 16 (47 %) had unmeasurable MRD. Eleven patients (25 %) in IVen group were able to stop treatment due to MRD-negativity.

Conclusions. Combinational therapy IVen is clearly superior to ibrutinib monotherapy in high-risk patients with complex karyotype. IVen is an effective oral regimen, allowing to achieve MRD-negativity in most patients. Further observation is required to see whether simultaneous administration of ibrutinib and venetoclax will outperform sequential therapy with regards to rate of resistance to both drugs. Progression-free and overall survival for combinational and sequential therapy with Ibrutinib and venetoclax.

Reproductive technology procedures for preserving fertility of patients with advanced stages of classical Hodgkin's lymphoma and primary mediastinal large B-cell lymphoma

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Introduction. Classical Hodgkin's lymphoma (cHL) and primary mediastinal large B-cell lymphoma (PMBCL), unlike most lymphoproliferative diseases of adults, most often occur at a young age (median 30 years). For this category of patients the most pressing issue is the preservation of reproductive potential during antitumor treatment. Currently, there are no clear criteria to predict the preservation of ovarian reserve after intensive chemotherapy. In the context of preserving reproductive function, gonadotropin-releasing hormone analogues and oral contraceptives are most often discussed in routine practice. However, in the modern practice, these drugs can be used to prevent pregnancy and reduce the amount of menorrhagia during the period of induced thrombocytopenia, but are not an alternative to assisted reproductive technology procedures.

Objectives. Determination of the optimal fertility preservation program before starting intensive therapy regimens for advance stages of cHL and PMBCL.

Methods. A modern approach to preserving reproductive function includes cryopreservation of biological material before the start of antitumor treatment. To assess the possibility of performing this procedure, it is necessary to evaluate the patient's age, the presence of concomitant diseases, and obstetric and gynecological history. All patients undergo an ultrasound examination of the pelvic organs to count the number of antral follicles and evaluate the level of follicle-stimulating (FST) and anti-Mullerian hormones (AMF). There are 22 female patients (pts) with cHL and PMBCL, who underwent ovarian stimulation followed by cryopreservation of the oocytes and/or embryos. All pts received antitumor treatment at the Russian National Medical Research Center of Oncology named after. N.N. Blokhin.

Results. The cryopreservation procedure was performed on 14 pts with advanced stages of cHL aged from 18 to 37 years. In 8 (57 %) pts the disease was diagnosed for the first time and they were scheduled for EACODD-14 regimen; 5 pts with relapse/resistance disease after cryopreservation of reproductive material, received several lines of salvage therapy, including high-dose chemotherapy with auto-HSCT. The number of oocytes obtained ranged from 3 to 31 (average 12), for 1 patient the procedure was considered unsuccessful, 2 were in the process of ovarian stimulation. In case of PMBCL, successful cryopreservation of reproductive material was performed in 5 patients. Subsequently, HDCT with auto-HSCT was performed for one of them. Ineffective collection of oocytes was recorded for one 38 years old pt, who had previously received 6 courses of R-DA-EPOCH with two stages of dose escalation of cyclophosphamide, etoposide and doxorubicin.

Conclusions. Reproductive technology procedures continue to improve and become safer. Before starting intensive chemotherapy, it is necessary to inform patients about risks of antitumor treatment and modern options for preserving fertility.

Venetoclax after progression on ibrutinib in CLL patients: results of a Russian multicenter study

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Introduction. Currently, venetoclax is the therapeutic choice for many patients with chronic lymphocytic leukemia progressed on ibrutinib. The optimal drug combinations with venetoclax, the goals and timing of therapy, as well as predictors of response are not yet clear. Only a few clinical trials have included patients with progression on ibrutinib (Kater AP, et.al., J Clin Oncol 2019). Approach to ibrutinib discontinuation and addition of antibodies to CD20 are still a matter of debates.

Objectives. The aim of this multicenter study was to retrospectively compare outcomes in patients who received venetoclax either alone or in combination with monoclonal antibodies to CD20, as well as outcome of patients who continued ibrutinib after switching to venetoclax.

Methods. The study included 122 patients with disease progression on ibrutinib according to iwCLL2018 criteria. The data were collected by 27 centers from 25 regions of Russia. Fifty four patients (44 %) received venetoclax without monoclonal antibodies, 46 (38 %) in combination with obinutuzumab, 22 (18 %) with rituximab. Nineteen patients stopped ibrutinib before venetoclax with median interval between treatments of 10 days (range 0–91 days). All other patients received venetoclax concomitantly with ibrutinib for some time after progression. Patients who stopped ibrutinib less than 3 months from the date of onset of venetoclax were considered to have discontinued ibrutinib

Results. The median age was 63 years (range 30–82), 76 patients were males (62 %). Median progression free survival (PFS) for all patients was 26.5 months, overall survival (OS) was 35.2 months. Fifteen patients (12 %) had Richter transformation before venetoclax. Overall survival of these patients was significantly worse when compared to other patients, with hazard ratio (HR) 3.46 95 % CI 1,42 - 8,48 ($p < 0.0001$). Twenty two patients stopped therapy before the event of death or progression. Reasons included toxicity (N = 10), three consecutive confirmation of MRD-negative remission 3 months apart (N = 11), and allogeneic stem cell transplantation (N = 1). Patients who died or had progression within 3 months after the onset of venetoclax, as well as patients with Richter syndrome diagnosed before the onset of venetoclax were excluded from survival analysis. On pre-treatment, poor outcome was significantly predicted by time to progression on ibrutinib <24 months (PFS: HR 0.53,95 % CI 0.27–1.06, p = 0,04; OS: HR 0.45, 95 % CI 0,22–0,93, p = 0,01) and ECOG status > 2 (PFS: HR 0.37, 95 % CI 0,1–1,35, p = 0,007; OS: HR 0.32, 95 % CI 0,08–1.27, p = 0,002). There were no differences in baseline characteristics in patients who continued and discontinued ibrutinib, although in the former group more patients have developed Richter syndrome during treatment. Ibrutinib discontinuation was associated with better outcome (PFS: HR 3.72, 95 % CI 1.95–7.09; OS: HR 3.93, 95 % CI 1.96–7.88, Figure 1, A, B). In total 15 deaths occurred before progression (COVID-19 — 11 patients, secondary cancers — 2, sudden death — 1, pneumonia — 1), and the majority (N = 13) in the group of patients who continued ibrutinib. The group of patients who received antibodies to CD20 was younger (63 versus 69 years, p-0.03), while other baseline parameters were similar. No significant differences were found in either PFS (HR 1.38,95 % CI 0.69–2.7) or OS (HR 1.36, 95 % CI 0.67–2.8, Figure 1, C, D). Subgroup analysis of patients who discontinued ibrutinib showed that patients who received venetoclax with monoclonal antibodies had better PFS compared to those on venetoclax alone (HR 6.32, 95 % CI 1.43–27.8, p = 0.045), while OS in the two subgroups did not differ.

Conclusions. Our data do not support the hypothesis that continuing ibrutinib therapy beyond 2–3 months in the context of progression on ibrutinib benefits patients. As evident from increase in PFS, it seems that patients who had discontinued ibrutinib may benefit from adding 0020 antibodies to venetoclax.

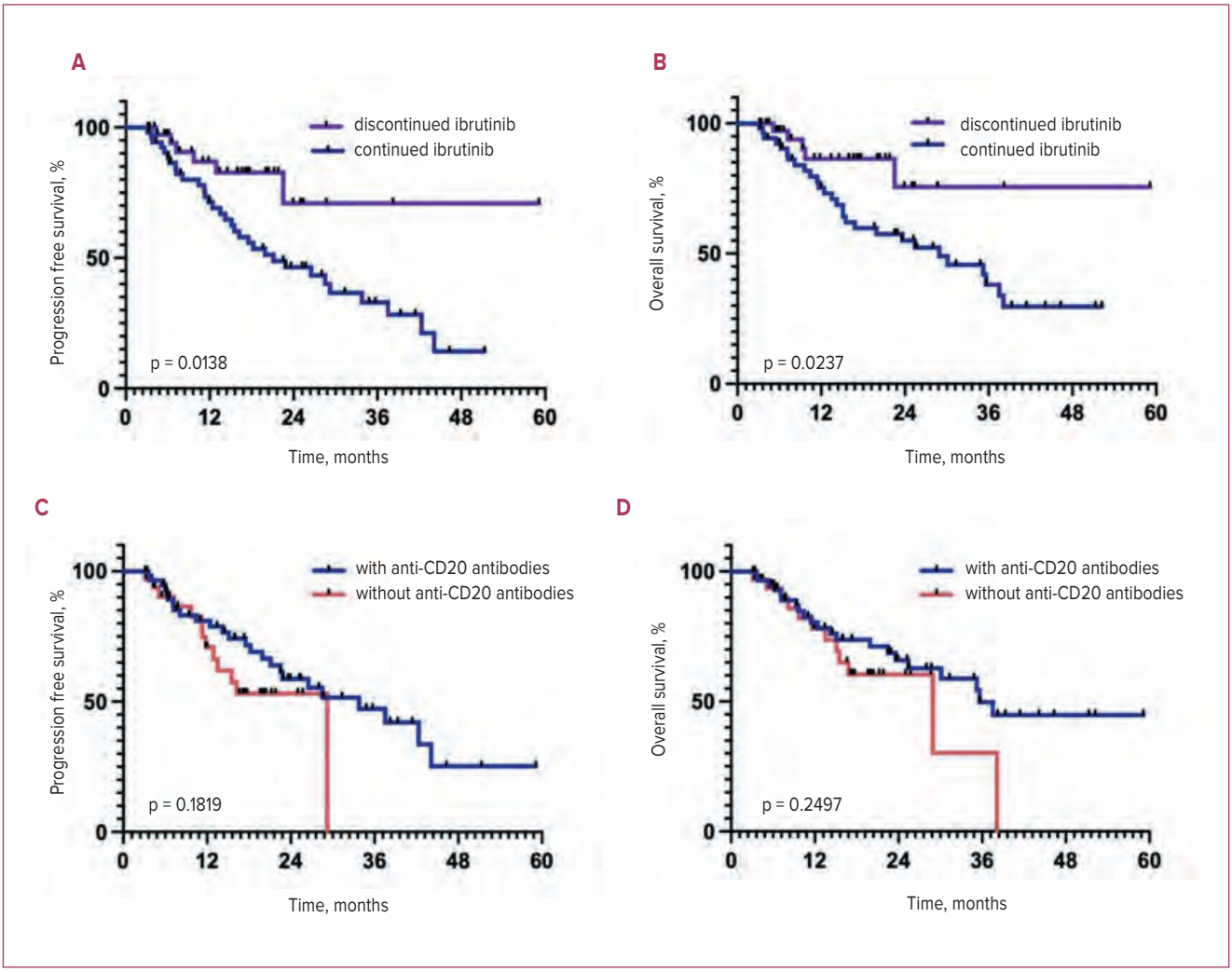

Figure 1. Progression free (A, C) and overall (B, D) survival for patents according to ibrutinib discontinuation (A, B) and anti-CD20 addition (C, D)

Venetoclax after immunochemotherapy in CLL patients: results of the Russian multicenter study

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Introduction. Venetoclax is a highly effective targeted agent for patients with chronic lymphocytic leukemia (CLL), including high-risk CLL and immunochemotherapy-refractory (CIT) patients. The question about which venetoclax-based regimen is optimal for patients with CLL progression after CIT remains unanswered, and the prognostic value of early achievements of negative minimal residual disease (MRD) is still unknown.

Objectives. The aim of this multicenter study was to compare retrospectively the effectiveness of treatment venetoclax-based regimens in patients with CLL progression after CIT and evaluate the prognostic value of MRD during the treatment.

Methods. The study included 164 patients with disease progression after CIT according to iwCLL2018 criteria. The data were collected by 27 centers from 25 regions of Russia. Fifty four patients (33 %) received venetoclax without monoclonal antibodies (VENmono regimen), 63 patients (38 %) — in combination with rituximab (RVen), 47 patients (29 %) — in combination with obinutuzumab (GVen). The median number of prior lines of therapy was two lines (range 1-9) (Table 1). MRD in the bone marrow was determined in 35 patients using flow cytometry with a sensitivity of 10-4. Progression free survival (PFS) and overall survival (OS) were calculated by the Kaplan-Meier method using the log-rank test to assess statistically significant differences, significance level p was set less than 0.05.

Results. The median age was 64 years (range 25–86), 124 patients were males (62 %), 40 patients were females (38 %). There were 9 patients with Binet stage A (5 %), 96 — with Binet stage B (58 %), 56 — with Binet stage C (34 %) in the study. ECOG 2–3 was determined in 29 (18 %) patients. Unmutated IGHV status was detected in 82 %, 17p13 deletion — in 27 % of patients (Table 1). In the overall group of patients the estimated 3-year PFS was 65 %, 3-year OS was 80 %, the median follow-up of patients was 18 months. An unfavorable predictor of time to progression was Binet stage C (PFS: HR 2.67, 95 % CI 1.04–6.91), p = 0.272) (Table 2). The median PFS in the RVen group was 30 months, while it was not reach in the GVen and VENmono groups. However, no statistically significant differences were found between the groups. There was a trend toward improving OS GVen regimen group in comparison with RVen and VENmono groups, but the differences were not statistically significant (Figure 1). MRD of

Table 1. Patients characteristic

Characteristic	Results
All patients	164
G-Ven	47 (29 %)
R-Ven	63 (38 %)
VenMONO	54 (33 %)
Median age (range)	64 (25–86)
Male/female	124/42
Binet stage	
A	9 (5 %)
B	96 (58 %)
C	56 (34 %)
ECOG	
0–1	132 (80 %)
2–4	29 (18 %)
Deletion 17p	31/114 (27 %)
Unmutated IGHV	97/119 (82 %)
Median number of prior lines of therapy (range)	2 (1–9)
Lymph nodes > 5 cm	91 (55 %)

Table 2. The influence of clinical and molecular genetic factors on the effectiveness of therapy

Prediction factor	HR (95 % CI)	p
Unmutated IGHV	0,75 (0,17–3,9)	0,7068
Deletion 17p	0,74 (0,25–2,18)	0,6042
Lymph nodes > 5 cm	1,8 (0,7–4,62)	0,2527
Number of prior lines of therapy >2	0,89 (0,33–2,41)	0,8224
ECOG 3-4	2,02 (0,5–8,18)	0,2016
Binet stage C	2,67 (1,04–6,91)	0,0272

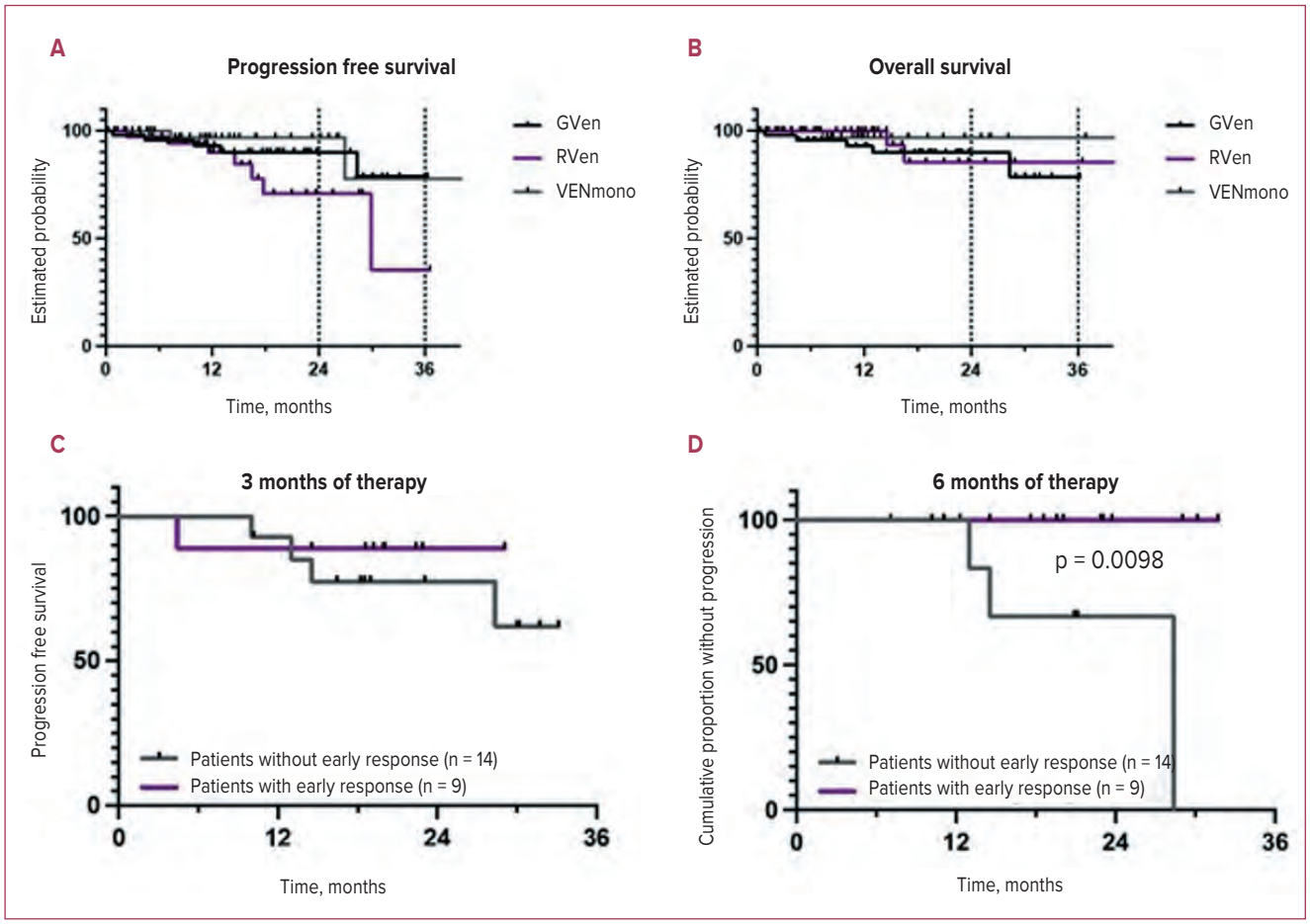

Figure 1. Progression free and overall survival in patients on venetoclax-based regimens

less than 10-4 in the bone marrow was achieved in 21 (60 %) patients after 6 months of therapy and was maintained by 18 months of follow-up. The PFS was higher in this group of patients in comparison with the group of patients who did not achieve a negative MRD ($p < 0.098$).

Conclusions. In the present study there were no statistically significant differences between the GVen, RVen and VENmono regimens. To obtain more accurate data the observation time needs to be increased. MRD status in the bone marrow after 6 months of therapy can be a predictor of long-term response to treatment.

Comparison of the effectiveness of RB and R-CHOP regimens in first-line therapy in 277 patients with grade I-II follicular lymphoma: a retrospective single-center analysis

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Introduction. Chemoimmunotherapy, including cytotoxic drugs and anti-CD20 monoclonal antibodies have significantly improved outcomes in patients with newly diagnosed follicular lymphoma (FL) compared with chemotherapy. A number of clinical studies have compared the effectiveness of the two most popular treatment regimens, rituximab plus bendamustine (RB) and rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP), with conflicting results.

Objectives. The purpose of this study was to conduct a retrospective analysis of the treatment results of a large cohort of patients with grade 1-2 FL who received RB or R-CHOP regimens in the first line of therapy in real-life clinical practice, to analyze the impact of individual prognostic factors, as well as maintenance therapy with rituximab on survival. Secondary endpoints were the incidence of secondary malignancies and causes of mortality

Materials and methods. Data were collected on patients with grade 1–2 FL who were treated at the Botkin Hospital from November 2006 to November 2022. The inclusion criteria for the study were newly diagnosed histologically confirmed FL of cytological grade 1–2; age ≥ 18 years; RB or R-CHOP therapy as first line. No radiation therapy was allowed. Response assessment was performed according to the 2007 International Working Group criteria.

Results. 277 patients met the inclusion criteria for the study. 164 patients received R-CHOP and 113 patients received RB. Patient characteristics are presented in Table 1. Overall response rates were comparable between groups (96 % vs 94 % in the RB and R-CHOP groups, respectively, p = 0.3396). The median follow-up period was 35 (3–117) months in the RB group and 50 (3–200) months in the R-CHOP group. The median progression-free survival (PFS) in the R-CHOP group was 86 months, while the median PFS in the RB group was not reached, the differences did not reach statistical significance (HR 0.65; 95 % CI 0.42–1.004; p = 0.0665) (Figure 1, A).

Three-year PFS was 81 % and 72 %, and five-year PFS was 66 % and 57 % in the RB and R-CHOP groups, respectively. Progression within 24 months of initiation of therapy (POD24) was more common in the R-CHOP group (20 % vs 11 %, p = 0.0466). The median time to next therapy in the R-CHOP group was 90 months and was not reached in the RB group (HR 0.75; 95 % CI 0.48–1.18; p = 0.2277). Analysis of individual prognostic factors showed superior PFS in most subgroups receiving the RB regimen (Figure 2). The R-CHOP regimen tended to improve PFS only in patients with PET SUVmax values greater than 14 (HR 2.46; 95 % CI 0.52–11.62; p = 0.2211).

The use of rituximab maintenance therapy improved PFS in both treatment groups: in the R-CHOP group, the differences reached the level of significance (HR 0.22; 95 % CI 0.05–1.01; p = 0.0001), in the RB group they did not reach the level of significance (HR 0.41; 95 % CI 0.02–8.67; p = 0.3605) (Figure 1, C, D).

There were no significant differences in overall survival (Figure 1, B). The 5-year cumulative incidence of secondary malignancies as well as the incidence of grade 5 infections were comparable between groups.

Conclusions. In summary, our study shows that the RB regimen generally has comparable long-term efficacy to the R-CHOP regimen in first-line therapy in patients with grade 1–2 FL. Analysis of individual prognostic factors showed better PFS in most subgroups using the RB regimen. R-CHOP showed a trend towards improved PFS only in patients with PET SUVmax values greater than 14. POD24 was less common in the RB group. Our study did not find differences in the incidence of secondary malignancies or non-lymphoma-related mortality.

Key words: follicular lymphoma, the first line of therapy, rituximab, bendamustine, CHOP, maintenance therapy with rituximab, POD24, survival, secondary malignancies, infections.

Table 1. Patient characteristics at baseline

Characteristic	RB (n = 113)	RCHOP (n = 164)	P-value
Sex			0,9582
Female, n (%)	72 (64 %)	105 (64 %)	
Age			0,4467
≤ 60 лет > 60 лет	54 (48 %) 59 (52 %)	86 (52 %) 78 (48 %)	
Age at diagnosis, median (range), years	61 (30–84)	59 (26–76)	0,0887
Age at start of therapy, median (range), years	61 (30–86)	60 (26–77)	0,1208
Median time from diagnosis (range), months	2 (0–45)	1 (0–60)	0,2615
Stage			0,1048
I-II, n (%) III-IV, n (%)	14 (12 %) 99 (88 %)	11 (7 %) 153 (93 %)	
FLIPI			0,1795
Low, n (%) Intermediate, n (%) High, n (%) Missing	12 (13 %) 20 (22 %) 59 (65 %) 22	11 (10 %) 19 (17 %) 84 (74 %) 50	
B-symptoms, n (%)			0,0105
Yes Missing	21 (23 %) 23	54 (40 %) 28	
Elevated Hgb, n (%)			0,1034
≤ 120 г/л Missing	14 (15 %) 20	28 (24 %) 48	
Elevated LDH, n (%)			0,2876
> ULN Missing	22 (30 %) 39	31 (38 %) 82	
Nodal sites, n (%)			0,8296
> 4 Missing	83 (78 %) 6	120 (76 %) 7	
Bulky disease > 7 cm, n (%)			0,3303
Yes Missing	45 (45 %) 14	54 (39 %) 26	
Extranodal disease, n (%)			0,1731
Yes Missing	36 (34 %) 8	67 (43 %) 7	
Bone marrow involvement, n (%)			0,6195
Yes Missing	57 (66 %) 26	88 (69 %) 36	
Leukemic phase*, n (%)			0,0514
Yes Missing	4 (5 %) 25	16 (12 %) 34	
Ki-67, n (%)			0,5162
≤ 30 % > 30 % Missing	85 (91 %) 8 (9 %) 20	110 (89 %) 14 (11 %) 40	
SUVmax, n (%)			0,1926
≤ 14, n (%) > 14, n (%) Missing	62 (85 %) 11 (15 %) 10	55 (76 %) 17 (24 %) 10	

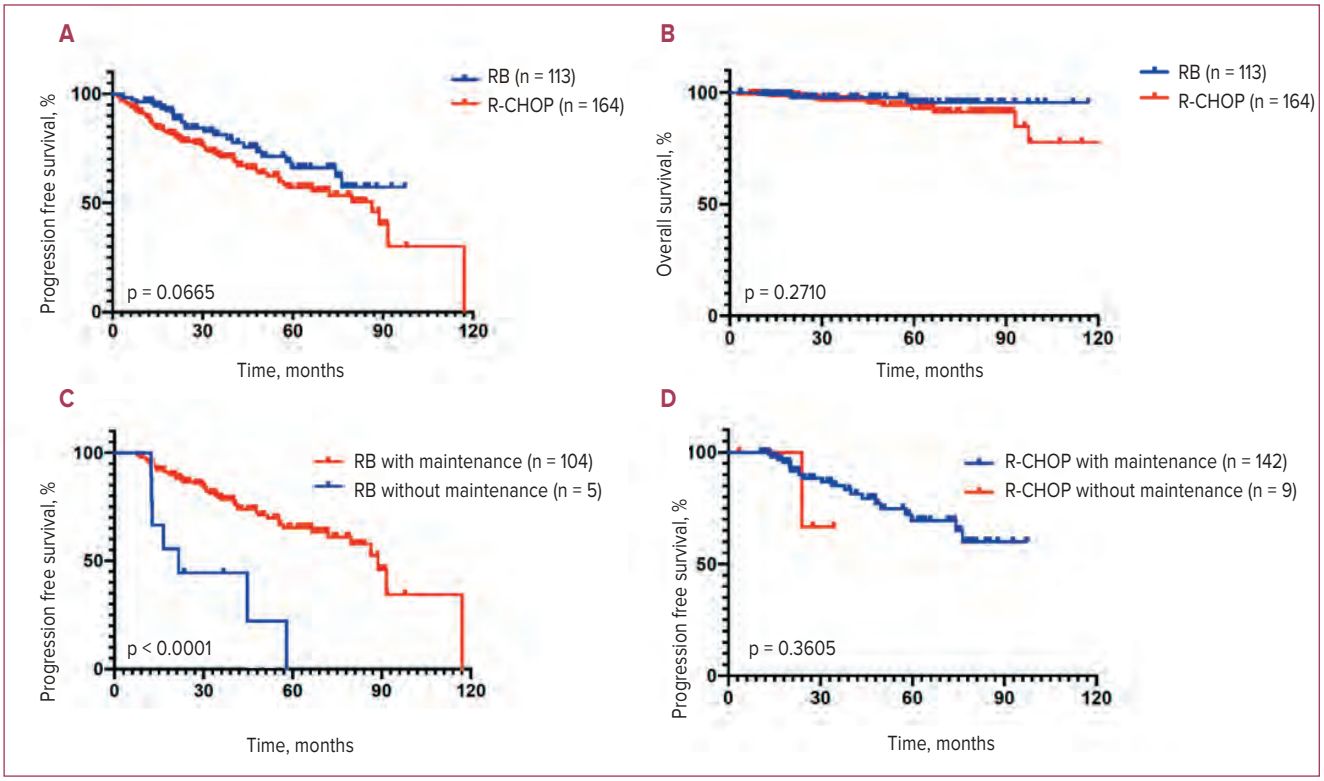

Figure 1. Progression free and overall survival of patients. RB — rituximab plus bendamustine. R-CHOP — rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone

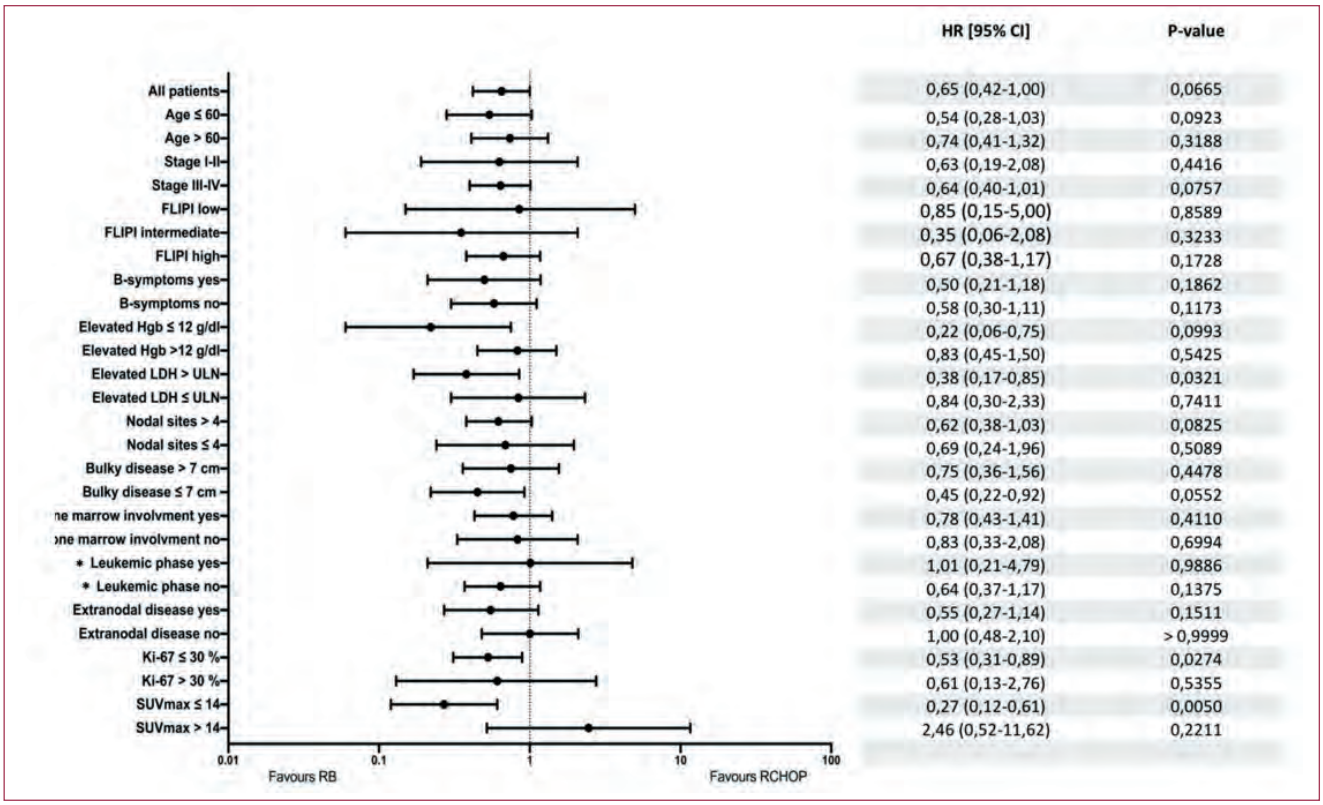

Figure 2. Unifactor analysis of progression free survival by pretreatment prognostic factors for patients, receiving RB or R-CHOP. Hgb — hemoglobin; LDH — lactate dehydrogenase; ULN — upper limit of normal; FLIPI — Follicular Lymphoma International Prognostic Index; SUVmax — maximum standardized uptake value

* Leukemic phase was detected by cytological blood smear analysis and confirmed by flow cytometry at time of diagnosis (a number of circulating lymphoma cells >5 × 10^9/l).

Oral Ist triplet in the treatment of relapsed multiple myeloma: real-world clinical practice experience

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Introduction. Ixazomib, the first oral proteasome inhibitor [PI] [1], approved in combination with lenalidomide-dexamethasone (Rd) for treating patients with multiple myeloma [MM] who have received ≥ 1 course of therapy previously [2]. The TOURMALINE-MM1 trial demonstrated statistically significant improvement in progression-free survival with ixazomib-Rd compared to placebo-Rd in patients with RRMM (median PFS 20.6 vs 14.7 months; hazard ratio [HR] 0.74; 95 % CI 0.59–0.94; P = 0.01), with limited additional toxicity [3]. Since 2020, ixazomib treatment has become available available under government drug programs for outpatient treatment of patients in real clinical practice.

Objectives. Analysis of the results therapy with IRd triplet in patients with relapsed MM in the Nizhny Novgorod region.

Methods. Primary medical documentation of patients with recurrent MM, who received Ird therapy was analyzed.

Results. From 01.2020 to 10.2023, 26 patients with relapsed MM received IRd therapy (males 10 (38 %), females 16 (62 %), aged 40 to 83 years (median age 69 years)), mainly having ECOG scores of 1 and 2: 0 score — 3 (10 %), 1 score — 12 (45 %), 2 score — 9 (34 %), 3 score — 3 (10 %). The number of prior lines of therapy ranged from 2 to 4, with a median of 2. The medicines in previous lines: 26 (100 %) patients previously received bortezomib treatment, 10 (37 %) received lenalidomide. IRd therapy was initiated in 13 (50 %) cases upon early progression, in 5 (19 %) for late progression, in 2 (7.5 %) for early relapse, in 2 (7.5 %) for late relapse, and 4 (16 %) patients switched to IRd after lenalidomide-based therapy. The median number of cycles administered was 11 (range from 2 to 26) with an overall response rate (ORR) of 80 %: 9 (35 %) patients achieved minimal response (MR), 7 (26 %) achieved a partial response (PR), 2 (7 %) achieved very good partial response (VGPR), 3 (13 %) a full response (FR), intolerability was observed in 2 (7 %) patients, and 3 (12 %) patients were refractory to therapy. With prolonged therapy, there was a trend towards increased depth of response. Patients on long-term therapy achieved VGPR and FR. There were no reported severe toxicities leading to therapy discontinuation, lengthening of intervals between cycles, or dose reductions. Currently, 11 patients have completed therapy, out of whom 4 are alive and receiving treatment including monoclonal antibodies, carfilzomib, and pomalidomide. The median progression-free survival (PFS) for patients in the studied group was 18 months, and the median overall survival (OS) was 83 months (Figure 1).

Conclusions. Modern treatment programs for RRMM involve a long-term therapy model aimed at prolonged tumor suppression and transforming MM into a manageable chronic condition. IRd, a completely oral triplet therapy, does not cause significant toxicity and ensures the preservation of the quality of life of MM patients. According to the TOURMALIN MM1 study, the addition of ixazomib to Rd overcomes the low PFS associated with high-risk cytogenetic abnormalities in RRMM patients [4], which is important in real-world clinical practice for patients without an assessment of cytogenetic risk. The therapy results in real-world clinical practice are comparable to those in clinical trials.

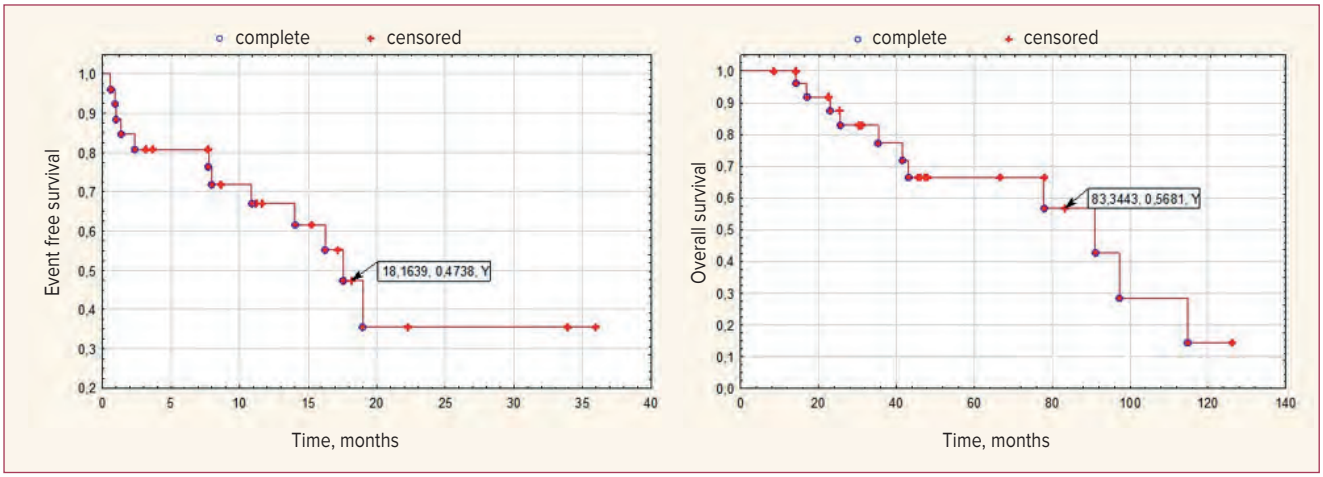

Figure 1. Event free and overall survival in patients with R/R Multiple myeloma, receiving Ird (n = 26)

Combination of venetoclax and standard platinum-containing regimens in the treatment of relapses and resistant course of B-cell lymphomas

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Introduction. Patients with relapse and refractory course (R/R) of B-cell lymphomas have an unfavorable prognosis. Standard second-line chemotherapy for R/R diffuse B-large cell lymphoma (DBCL) based on platinum-containing (cisplatin, carbioplatin, oxaliplatin) therapy courses and autologous hematopoietic stem cell transplantation (auto-HSCT) allows achieving complete remission (CR) in 40 % of patients and 2-year non-progressive survival (PFS) at 25 % (G.W. van Imhoff 2014). The phase I study demonstrated the high efficiency of including the selective BCL-2 inhibitor venetoclax in the R-ICE anti-relapse therapy regimen with the achievement of PR in 78 % of patients (P. Caimi, D. Jagadeesh 2018).

Objectives. To evaluate the efficacy and safety of venetoclax addition to standard salvage therapy of B-cell lymphomas.

Methods. The study included patients over 18 years of age who received one line of therapy with resistance (accumulation of RFP on the Deauville scale of 4 points after 1 line of therapy) or recurrence of DLBCL and primary mediastinal B-large cell lymphoma (PMBCL), as well as patients with early recurrence of follicular lymphoma (FL) during maintenance therapy with rituximab (POD 24). 2–4 courses of PCT were conducted according to the schemes of R-DHAP (rituximab, cisplatin, cytarabine, dexamethasone) or R-GDP (rituximab, gemcitabine, oxaliplatin) (DLBCL/FL) and R-ICE (rituximab, carboplatin, ifosfamide, etoposide) with the addition of venetoclax on 1–10 days of each 21-day cycle at a dose of 400 mg per day. The mobilization and collection of autologous hematopoietic stem cells (auto-HSC) was carried out at the time of restoration of myelopoiesis after 1–3 courses of therapy. The response was evaluated according to the criteria of Lugano (PET/CT). Upon reaching 1-3 points on Deauville, an auto-HSCT was performed with the R-B(Be)EAM conditioning regime (rituximab, bendamustine (karpustine), etoposide, cytarabine, melphalan). The level of BCL-2 expression was assessed in 21/29 patients: hyperexpression was detected in 17/21 (81 %) cases.

Results. From January 2019 to December 2023, 29 patients were included: 14 - DLBCL, 7 — PMBCL, 8 — FL, median age 47 years (21–65), M/W: 20/9. The first line of therapy: R-CHOP-like courses — 25/29, mNHL-BFM-90 — 2/29, R-COP/R-B — 2 (FL). Complete response was achieved in 17/29 (58 %) patients, partial response — 2/29 (7 %), stabilization/progression — 9/29 (31 %), death after the first course of therapy (pneumonia) — 1/29 (3.4 %). In 18/28 patients (64.4 %), a sufficient amount of auto-SCC was harvested (on average 8.7×10^6/kg). Failure of mobilization in 8/28 (28.5 %), refusal of collection in 2/28 (7.1 %). By December 2023, auto-HSCT was performed in 13/18 (72 %) patients. In 5/29 (17 %) cases, allotment was performed (2 due to failure of mobilization and 3 in subsequent lines of therapy). 2 deaths in the state of PR from COVID-19. With a follow-up period of 56 months, the median PFS

was 15 months (FL 8,9 months; DLBCL 25 months; PMBCL 15 months), the median OS was not achieved (in patients with FL, the OS was 20 months, in patients with DLBCL and PMBCL, the OS was not achieved).

Conclusions. In this study, the potentially high efficacy and reasonable safety of venetoclax inclusion in platinum-containing anti-relapse therapy regimens was demonstrated. In subsequent approaches to therapy, the inclusion of polatuzumab vedotin and bispecific antibodies, the mobilization of CCM after the first course and the reduction of the duration of venetoclax administration to 5 days with the preservation of the total dose are planned.

Causes of lymphadenopathy in patients with HIV infection according to results of lymph node biopsies

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Introduction. The syndrome of generalized lymphadenopathy in HIV infection remains insufficiently studied to date, and results of statistical analysis of etiological causes differ among different researchers in many countries around world. The main reasons leading to enlargement of lymph nodes: infectious process (including HIV itself), hemoblastosis, metastatic lesions.

Objectives. To study causes of lymphadenopathy in patients with HIV infection by analyzing results of histological studies of lymph node biopsies.

Methods. We analyzed 145 histological studies of lymph node biopsies in patients with a confirmed diagnosis of HIV infection, performed between 2013 and 2023, in two pathology departments with a hematopathology profile.

Results. The structure of causes of lymphadenopathy in patients with HIV infections is represented by following nosological forms: HIV-associated lymphadenopathy (lymphadenitis) — 50.3 % (n = 73); diffuse large B-cell lymphoma (DLBCL) — 21.4 % (n = 31); polymorphic cell lymphoproliferative disease — 6.2 % (n = 9); classical Hodgkin lymphoma (mixed cell variant) — 4.8 % (n = 7); atypical mycobacteriosis — 4.1 % (n = 6); Kaposi's sarcoma — 3.4 % (n = 5); tuberculosis — 2.8 % (n = 4); follicular lymphoma (Gr 3a) — 2.1 % (n = 3); Burkitt's lymphoma — 1.4 % (n = 2); plasmablastic lymphoma (n = 2) and lymphoma with peripheral T-lymphocyte immunophenotype, unspecified, 2 % each (n = 2); plasma cell variant of Castleman's disease — 0.7 % (n = 1). One patient had a combined lymph node lesion: polymorphic cell lymphoproliferative disease and Kaposi's sarcoma. In most cases of HIV-associated lymphadenitis (n = 70), immunohistochemical examination revealed expression of p24 protein of human immunodeficiency virus in follicular dendritic cells (Figure 1), and detection of Epstein-Barr virus by molecular genetic method using in situ hybridization (detection of small viral RNA) was observed in 69 observations (Figure 2).

Conclusions. The most common cause of lymphadenopathy was viral lymphadenitis (HIV-associated lymphadenopathy) with various morphological changes in lymphoid tissue (previously — patterns A, B, C), which correlate with stages of the disease (acute, subchronic, chronic). The most common lymphoma associated with HIV infection was DLBCL, characterized by an aggressive course. Noteworthy are cases of damage to lymph nodes by polymorphocellular lymphoproliferative disease and Hodgkin's lymphoma, which are often diagnosed untimely. Treatment of polymorphocellular lymphoproliferative disease against background of HIV infection is currently not standardized: most cases describe complete recovery in such patients after start of antiretroviral therapy, and in rarer cases, use of various combinations of antitumor chemotherapy. Among infectious causes, atypical mycobacteriosis and tuberculosis predominated. It is necessary to remember about possibility of damage to lymph nodes during HIV infection by Kaposi's sarcoma, which may be metastatic in nature.

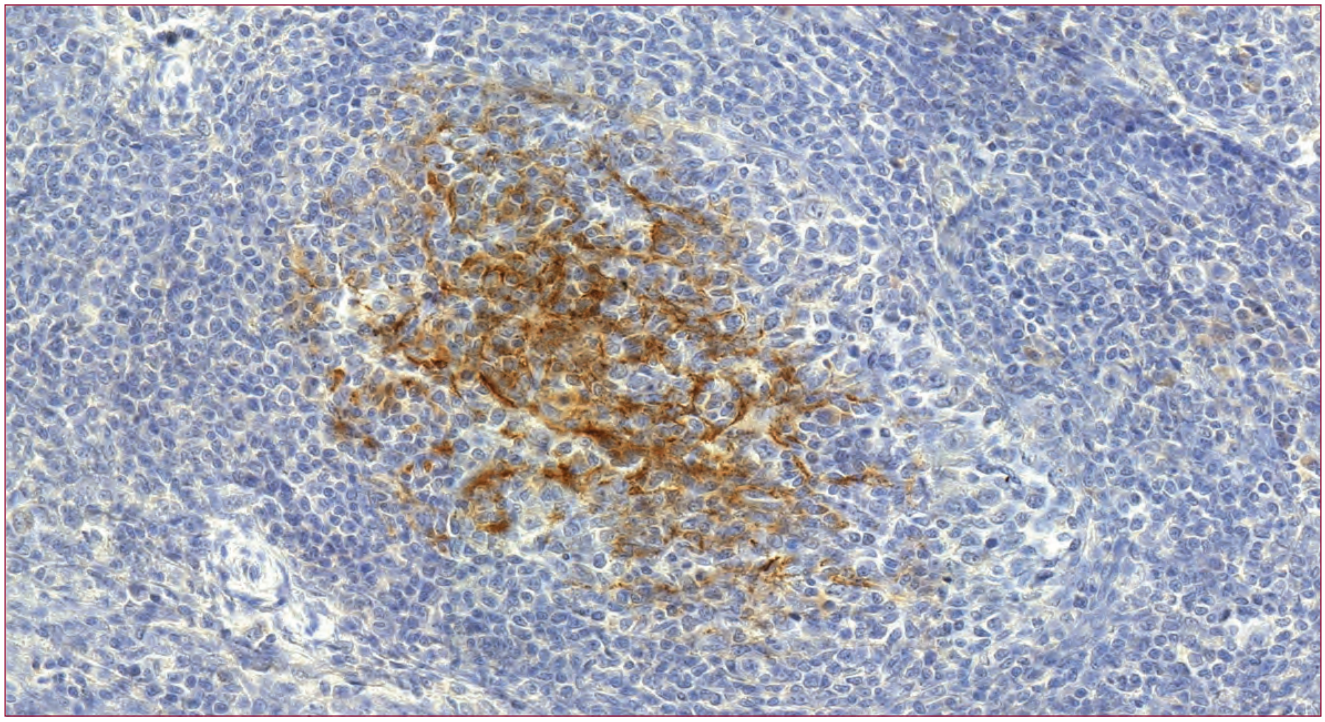

Figure 1. Immunohistochemical reaction to protein p. 24 (HIV)

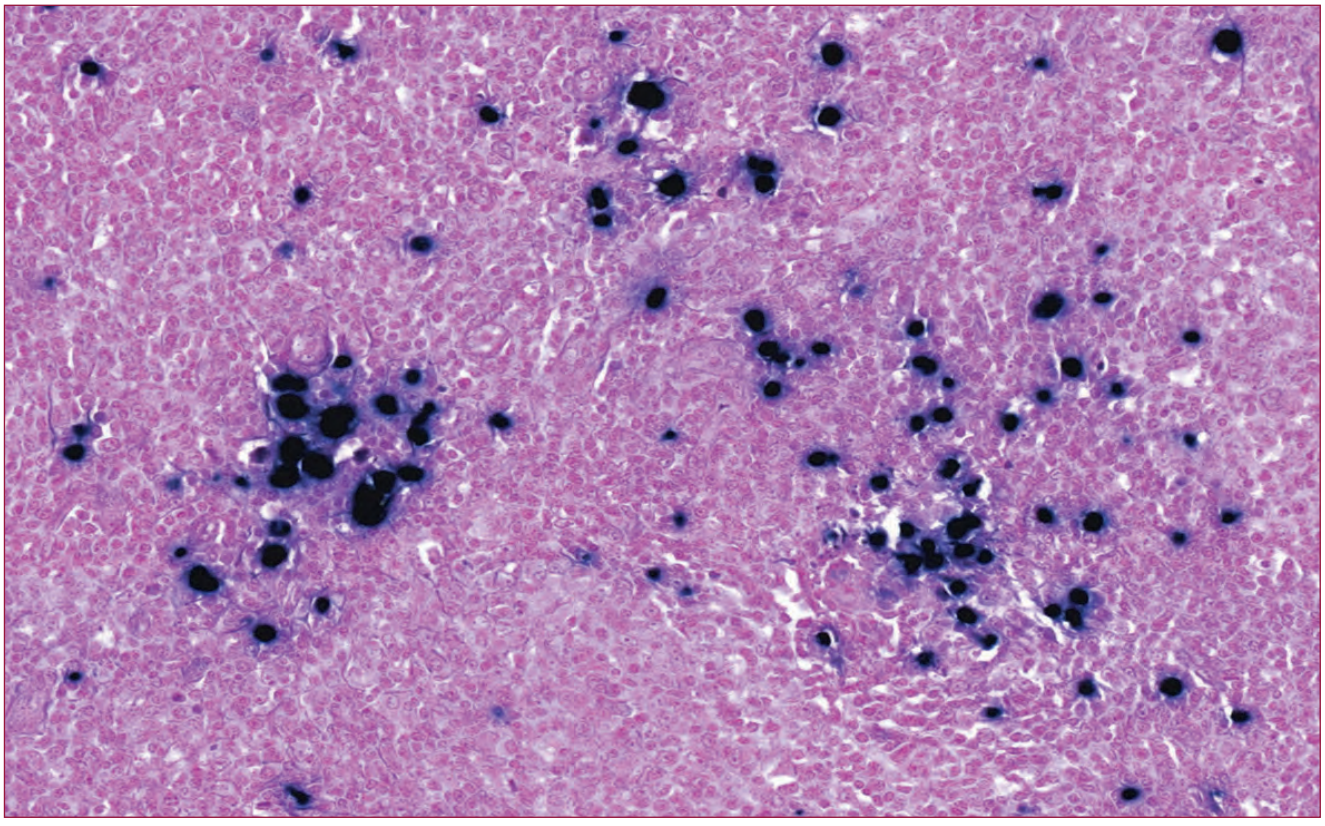

Figure 2. Small viral RNAs of the Epstein-Barr virus mainly in cells located interfollicularly

Nivolumab in the treatment of relapsed/refractory HIV-related Hodgkin lymphoma

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Background. Patients living with HIV (PLWH) are 3-30 times more likely to develop Hodgkin lymphoma (HL) than in the general population, regardless of the use of antiretroviral therapy (ART), and there are currently no standards for the treatment of HIV-related HL. The question of the prognosis of patients with HL and HIV in comparison with the general population also remains open. Immune checkpoint inhibitors (ICIs), particularly nivolumab, have demonstrated high efficacy and safety in the treatment of relapsed/refractory (r/r) HL, but data in the HIV-related r/r HL population are limited to a few case reports.

Objectives. To evaluate the effectiveness and safety of nivolumab (Nivo) in patients with r/r HL and HIV.

Patients and methods. The study included 10 patients with r/r HL and HIV who were treated at the RM Gorbacheva Research Institute of Pediatric Oncology, Hematology and Transplantation from 2017 to 2023. Males accounted for 80 %, median age was 39 years (28–58). The median number of previous lines of therapy was 3 (1–4). The median of CD4+ cell at the start of nivolumab therapy was 402 cells/μl (111–770). All patients were on ART at the start of Nivo. Nivolumab at a fixed dose of 40 mg was received by 4 patients (40 %), combination therapy — 5 patients: bendamustine + gemcitabine — 2 (20 %), bendamustine — 2 (20 %), BeGeV — 1 (10 %). In 4 cases, nivolumab was used as bridge therapy before auto-HSCT. The median of Nivo courses was 21 (12–48). Median follow-up was 27 months (range 7–74).

The primary endpoint was overall response rate (ORR) to Nivo. Secondary endpoints were toxicity, overall survival (OS), and progression-free survival (PFS) within 24 months of Nivo initiation. Common Terminology Criteria for Adverse Events (CTCAE 5.0) were used to evaluate treatment-related adverse events. The LYRIC criteria were used to assess response on PET-CT. Analysis of OS and PFS was performed using the Kaplan-Meier method.

Results. The ORR to the therapy in this cohort was 90 % (complete response — 80 %, partial response — 10 %, indeterminate response — 10 %). Relapse/progression of HL was observed in 7 (70 %) patients who subsequently received various combination therapy: bendamustine — 7 (100 %), gemcitabine — 2 (29 %), brentuximab vedotin — 3 (43 %), vinblastine — 3 (43 %), lenalidomide — 1 (14 %), ICE — 2 (29 %).

OS and PFS at 24 months were 100 % and 64 % (95 % CI 38–100 %), respectively. Treatment-related adverse events were observed in 1 case: autoimmune thyroiditis grade 2 according to CTCAE 5.0, controlled during replacement therapy.

Conclusions. Preliminary results of this study demonstrated the effectiveness and safety of nivolumab in the treatment of r/r HL and HIV. A study on a larger patient population is needed.

Key words: Hodgkin lymphoma, HIV, Nivolumab.

Outcome of relapsed and refractory patients with chronic lymphocytic leukemia, receiving ibrutinib: analysis of 457 patients

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Introduction. A number of salvage treatment options are currently available for relapsed and refractory (R/R) patients with chronic lymphocytic leukemia (CLL), including BTK inhibitors, BCL2 inhibitors, monoclonal antibodies, chemoimmunotherapy. Despite several clinical trials conducted in R/R patients, the optimal treatment options for first and subsequent relapses are unclear [Munir T, 2019, Fraser G, 2020, Kater A, 2020]. Real world data on the safety and efficacy of BTK inhibitors in R/R patients help to better guide treatment decision. Here we present our experience on the use of ibrutinib in R/R patients.

Objectives. To evaluate time on treatment, reasons for discontinuation, overall survival and predictors of response in a cohort of R/R patients with CLL, receiving ibrutinib.

Methods. Patients requiring therapy with R/R CLL who started treatment between July 2015 and July 2022 at Botkin hospital, Moscow, were evaluated. All patients received ibrutinib at dose 420 mg/day with dose modifications according published guidelines. The addition of antibodies to CD20 was permitted, but the combination of ibrutinib with other medications and chemotherapy regimens was an exclusion criterion from the study. The main outcomes of the study were the time on treatment (TOT) and overall survival (OS). Time-to-event analyses were estimated using the Kaplan-Meier method, and differences were evaluated using log rank test.

Results. The study included 457 patients with the median age was 67,7 years (range 30–91). One hundred eight patients were older than 75 years, 60 % were males. In total 58 patients received ibrutinib along with monoclonal antibodies, all other received ibrutinib alone. 135 patients (35 %) out of 385 tested had 17p deletion and 196 (80 %) out of 244 tested had unmutated *IGHV*. The median number of previous therapy lines was 3 (range 1–15). Seventy-nine patients (17 %) had preexisting significant cardiovascular disease (a history of myocardial infarction, heart failure, cardiomyopathy, or atrial fibrillation), 73 (16 %) — diabetes mellitus, 33 (5 %) — HBs-antigen.

The median time on treatment in these heavily pretreated patients was 35,4 months, and overall survival 52,1 months. The reasons for discontinuations are presented in Table 1. The most common reasons were pro-

Table 1. Reasons for therapy discontinuation

	N	%
Progresson	123	45
Death from COVID-19	38	14
Infections	25	9
Toxicity	23	8
Hepatotoxicity	5	2
Arrhythmias	4	1
Hemorrhagic complications	4	1
Death from other causes	17	6
Second tumour	16	6
Thromboembolic events	9	3
Allogeneic stem cell transplantation	5	2
Patient's desire	2	1
Unknown	4	1
	275	

gression of the disease (45 %), death from COVID-19 (14 %) and other causes (6 %). Overall, events attributable to ibrutinib occurred in 21 % of cases, with infections being the most common reason for discontinuation (9 %). Arrhythmias and hemorrhagic complications were the reason for discontinuation in 2 % of cases in total.

Worse TOT was associated with a number of previous therapy lines (HR 0,7, 95 % CI 0,5–0,9, p = 0,002) and 17p deletion (HR 0,71, 95 % CI 0,54–0,94, p = 0,036), while IGHV mutational status and Binet stage before ibrutinib initiation had no impact on TOT. The patients were divided into 4 categories based on the type of relapse: late (> 24 months) relapse after chemoimmunotherapy, early (< 24 months) relapse after chemoimmunotherapy, relapse with 17p deletion relapse with 17p deletion regardless of timing, and Richter syndrome. TOT was significantly worse in patients with 17p deletion compared to late relapse (HR 0,58, 95 % CI 0,39–0,85, p = 0,01) and in patients with early relapse compared to late relapse (HR 0,63, 95 % CI 0,45–0,87, p = 0,01) (Figure 1). Patients with Richter syndrome had the worst prognosis (Figure 1). No differences were noted between patients with early relapse and relapse with 17p deletion. Overall survival was significantly predicted by age (HR 0,58, 95 % CI 0,39–0,84, p = 0,005), diabetes mellitus (HR 0,7, 95 % CI 0,48–1,0, p = 0,047), the presence of HBs-antigen (HR 0,7, 95 % CI 0,48–1,0, p = 0,042). Concomitant cardiovascular disease, deletion 17p, and IGVH mutational status did not impact OS.

Conclusions. In R/R patients progression of the disease is the main reason for treatment discontinuation. Early relapse after chemoimmunotherapy as well as 17p deletion are associated with poor prognosis and probably require an alternative treatment. Infections are the main cause of death and an important reason for discontinuation. Concomitant cardiovascular diseases are not associated with poor outcome and cardiovascular adverse events rarely lead to treatment discontinuation.

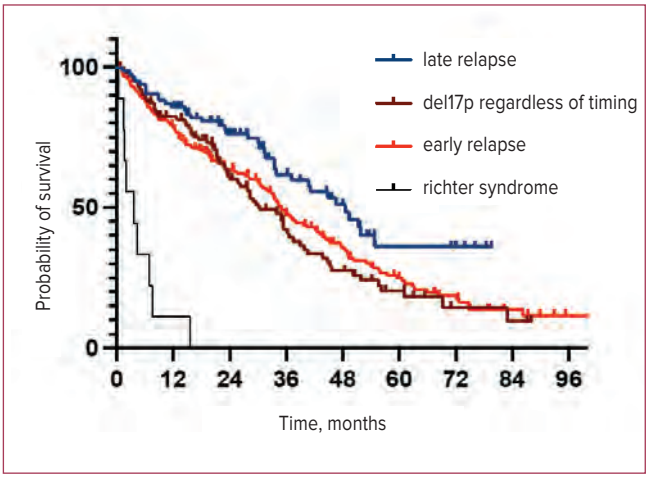

Figure 1. Time on treatment by category

Key words: Chronic lymphocytic leukemia, ibrutinib.

References

1. Munir T, Brown JR, O'Brien S, et.al. Final analysis from RESONATE: Up to six years of follow-up on ibrutinib in patients with previously treated chronic lymphocytic leukemia or small lymphocytic lymphoma. Am J Hematol. 2019 Dec;94(12):1353-1363.

2. Fraser GAM, Chanan-Khan A, Demirkan F, et.al. Final 5-year findings from the phase 3 HELIOS study of ibrutinib plus bendamustine and rituximab in patients with relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma. Leuk Lymphoma. 2020 Dec;61(13):3188-3197.

3. Kater AP, Wu JQ, Kipps T, et.al. Venetoclax Plus Rituximab in Relapsed Chronic Lymphocytic Leukemia: 4-Year Results and Evaluation of Impact of Genomic Complexity and Gene Mutations From the MURANO Phase III Study. J Clin Oncol. 2020 Dec 1;38(34):4042-4054.

Outcome of patients with chronic lymphocytic leukemia with deletion 17p, receiving ibrutinib as a 1st line of therapy

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Introduction. 17p deletion and *TP53* mutations are traditional markers of adverse prognosis in patients receiving chemoimmunotherapy. A number of studies have shown poor prognosis of patients with *TP53* aberrations in relapsed and refractory patients, receiving novel agents, including venetoclax and BTK inhibitors (Huang Q,2022). In the 1st line settings continuous therapy with BTK inhibitors in patients with TP53 aberrations is associated with a better progression-free survival compared to fixed duration therapy (Al-Sawaf O, 2020). Outcome of patients with 17p deletion and *TP53* mutations, receiving BTK inhibitors as a 1st line of therapy in real word practice is currently under investigation. In this study we report data on a cohort of patients observed at Botkin hospital, Moscow.

Objectives. To evaluate effectiveness of first-line ibrutinib in a cohort of patients with CLL carrying 17p deletion.

Methods. Patients requiring therapy with treatment-naive CLL and 17p deletion who started treatment between July 2016 and August 2022 at Botkin hospital were evaluated. All patients received ibrutinib at dose 420 mg/day with dose modifications according published guidelines. The addition of antibodies to CD20 was permitted, but the combination of ibrutinib with other medications was an exclusion criterion from the study. The main outcomes of the study were the time to treatment discontinuation (TTD) and overall survival (OS). Time-to-event analyses were performed with the Kaplan-Meier method.

Results. The study included 44 patients, the median age was 68 years (range 39–86), male to female ratio 1:1. Twelve patients (27 %) had preexisting serious cardiovascular diseases including myocardial infarction, cardiomyopathy and/or atrial fibrillation, 5 patients had diabetes mellitus. Two patients received ibrutinib in combination with monoclonal antibodies, all other patients as a monotherapy. At the median follow up of 22,3 months (range 7–91) 28 (63 %) patients have discontinued treatment. The reasons for discontinuations were progression in 14 patients (50 %), intolerance — 4 patients (9 %), deaths before progression — 4 (1 — second tumour, 3 — cardiovascular causes), COVID-19 — 3 (7 %), allogeneic transplantation — 3 patients (7 %). The median time to treatment discontinuation was 31,5 months, and an estimated treatment persistence probability at 2-years was 63 % (Figure 1). Two patients had confirmed Richter syndrome before initiation of therapy and 2 patients developed RS at progression. Among patients with progression 6 were switched to venetoclax w/o antibodies to CD20, 4 patients received either R/G-CHOP or R-EPOCH, and other patients had a supportive care. The median overall survival was 74,9 months, and OS at 2-years was 80 %. Neither parameters including age, sex, comorbidities, stage, and LDH level were associated with time to discontinuation or overall survival.

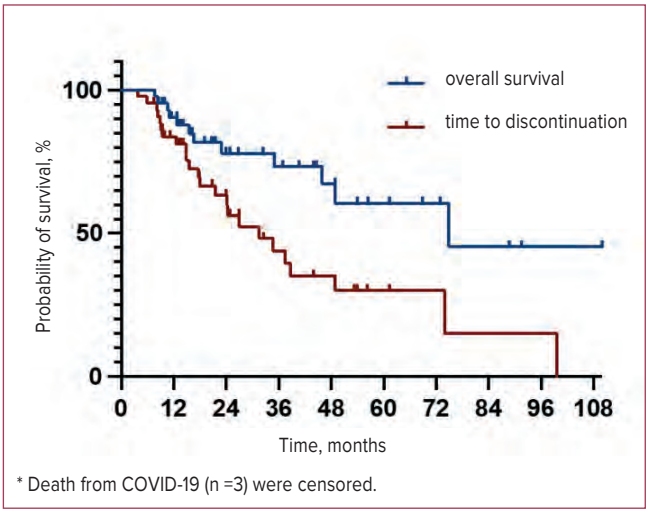

Figure 1. Time to treatment discontinuation and overall survival*

Conclusions. Our data show significant progress in the treatment of patients with CLL carrying 17p deletion and in general, are very similar to the data obtained in a nationwide Italian study, where TTD and OS by 2 years were 63,4 % and 82,6 % (Rigolin GM, 2023). On the other hand, these results remain unsatisfactory as 50 % of patients die from the progression of CLL. Further research exploring combination therapies are warranted in these cohort of patients.

Efficacy of brentuximab vedotin and bendamustine in patients with classic Hodgkin lymphoma: retrospective analysis of Botkin hospital cohort of patients

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Introduction. Hodgkin lymphoma (HL) is an uncommon B-cell malignant neoplasm, with high curable rate for patients with localized disease or advanced. However, up to 30 % of patients with HL are either refractory or relapsed after primary treatment. Combination of Brentuximab vedotin and Bendamustine (BvB) is easy-to-follow regimen with possibility of outpatient treatment. The above-mentioned characteristics determine the place of this regimen as a pre-auto-HSCT in young patients as well as a salvage therapy in relapse after auto-HSCT. For

Table 1. Patients' characteristics

Patient's characteristics	**N = 19**
Age, median (range)	38 (25-75)
Male/Female	9/10
Histology of HL (%)	
Nodular sclerosis	14 (74 %)
Mixed cellularity	2 (11 %)
Lymphocyte rich	2 (11 %)
Lymphocyte depleted	1 (5 %)
Disease stage (%)	
II	6 (32 %)
III	3 (16 %)
IV	10 (53 %)
ECOG (%)	
0-1	15 (79 %)
2	2 (11 %)
3	2 (11 %)
Prior lines of therapy, median (range)	3 (1-5)
Prior radiotherapy (%)	12 (63 %)
Prior Auto-HSCT (%)	4 (21 %)
Prior Nivolumab (%)	1 (5 %)
Primary refractory (%)	7 (37 %)
B-symptoms (%)	14 (74 %)
BvB cycles, median (range)	6 (3-8)
Post Auto-HSCT (%)	5 (26 %)
Post Allo-HSCT (%)	3 (16 %)

elderly patients BvB is an applicable therapeutic option in the impossibility of transplantation. Evidence from retrospective and prospective studies in regards of BvB have shown remarkable progression free survival (PFS) with 2-years PFS ranging 60–90 %, and overall survival (OS) ranging 80–90 %.

Objectives. The objective of this study is to assess patient response to BvB in the treatment of relapsed/refractory classic Hodgkin Lymphoma especially for patients beyond first salvage therapy unlike many other studies.

Methods. We retrospectively analyzed patients with relapse/refractory Hodgkin Lymphoma who received BvB immunochemotherapy between 2017 and 2023 in Moscow city center of hematology of Botkin hospital. Brentuximab vedotin was given 1.8 mg/kg on day 1, and bendamustine was given 90 mg/m^2 day 2, cycles repeated every 21 days. Response assessment was performed using Lugano criteria. PFS and OS analyses were performed with the Kaplan-Meier methods. PFS included cases of disease progression, relapse after therapy completion, death of any case, and next line of therapy.

Results. Nineteen patients received at least one cycle of BvB were enrolled (Table 1). The patient median age was 38 (range 25–75), 9 males (47 %) and 10 females (53 %). Disease stage at time of treatment initiation: II — 6 (32 %), III — 3 (16 %), IV — 10 (53 %). The median of prior lines of therapy was 3 (range 1-5). Twelve patients

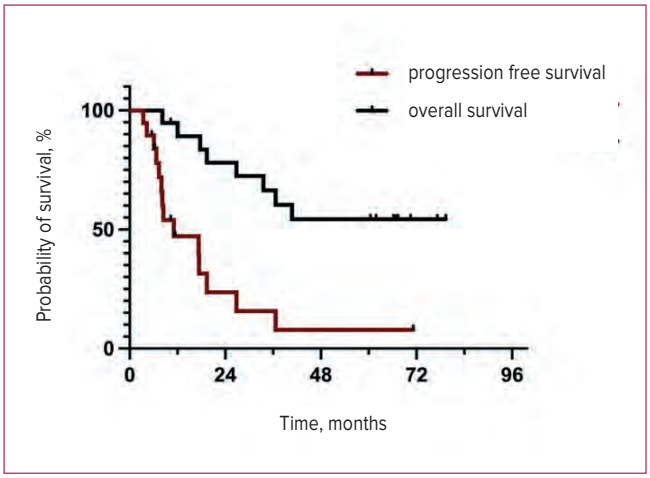

Figure 1. Progression free and overall survival

(63 %) underwent radiotherapy before BvB, and only 1 patient (5 %) was treated with Nivolumab. For 4 patients (21 %) BvB was a salvage therapy in relapse after Auto-HSCT, and for 4 patients (21 %) BvB preceded Auto-HSCT, 1 patient (5 %) had Auto-HSCT after one more line. The overall response rate 68 % (13 patients) and all these patients have achieved complete response. Stable disease was achieved in 5 % (1 patient), and progressive disease — 26 % (5 patients). After median follow up of 40,7 months, the median PFS was 11 months, and the median OS was not reached (Figure 1).

Conclusions. BvB combination is an effective outpatient-based salvage regimen for heavily pretreated patients with multiple lines chemotherapy in relapsed/refractory HL, as majority of patients in our study were beyond first salvage. BvB regimen might be used both in young and elderly patients, as well as in patients preparing for auto-HSCT and not.

Upfront autologous stem cell transplantation for stage IV double-expressor diffuse large B-cell lymphoma

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Introduction. Improving the effectiveness of first-line immunochemotherapy (ICT) for double-expressor (DEL) diffuse large B-cell lymphoma (DLBCL) remains an urgent clinical task in oncohematology. Upfront high-dose chemotherapy (HDCT) with autologous hematopoietic stem cell transplantation (auto-HSCT) still considered a clinical option to increase the survival of these patients [1].

Objectives. To improve the effectiveness of first-line therapy stage IV DEL DLBCL.

Methods. A group of 105 patients(pts): DLBCL NOS, age 18–65, stage IV, IPI ≥ 2, CR/PR after x6 R-CHOP/R-DA-EPOCH from 2010 to 2019 at NMRC of Oncology named after N.N. Petrov of MoH of Russia was retrospectively analyzed. The upfront group included patients with HDCT followed by auto-HSCT as a first-line consolidation therapy (n = 35). The control group included patients with follow-up after induction (n = 70) and CR only. Patients and procedures characteristics are shown below (Table 1).

The primary endpoint was 3-yr progression-free survival (PFS). Secondary endpoints were 3-yr overall survival (OS) and relapse rate. Endpoints were analyzed separately according to DEL status. The Kaplan-Meier method was used to estimate OS and PFS. The log-rank test was used to evaluate differences in survival.

The binomial logistic regression was used to define the statistically significant factors. The primary endpoint was used as a dependent variable. Independent variables were DEL status, sex and pulmonary or gastric involvement. Covariates were age and Ki67 level. The control group was selected as a learning sample and the upfront group as a test sample.

The sample size of the study protocol was estimated to test the difference in 3-yr PFS and relapse rate between selected groups. The closest in design and inclusion criteria RCT with ours reported 13 % relapse rate after upfront auto-HSCT. [1] The medium relapse rate in target population is about 40 % to the world data [2]. A sample of 96 pts (upfront, n = 32; control, n = 64) was required for a power of 80 % and with a one-sided α level of 5 % with enrollment ratio 1:2.

A two-sided p-value of < 0.05 significance level was considered to be statistically significant in all analyses. All statistical analyses were performed using STATISTICA for Windows (ver. 12 License №. BXXR310F-964808FA-V).

Results. In upfront pts with DEL (Figure 1) 3-yr PFS was 100 % [95 % CI 100–100] vs 28.6 % [95 % CI 13–62.7] in control, p < 0.001. The same impact of upfront in pts with DEL was found in 3-yr OS — 100 % [95 % CI 100–100] vs 57.1 % [95 % CI 39,5–82,8] in control, p = 0.002 (Figure 2).

There was no impact of upfront HDCT with auto-HSCT on 3-yr PFS among pts without DEL — 86.4 % [95 % CI 73.2–100] in the upfront vs 83.5 % [95 % CI 71.3–97.8] in the control, p = 0.71 (Figure 3). There was a tendency toward improvement of 3-yr OS in the upfront — 95.5 % [95 % CI 87.1–100] vs 77.4 % [95 % CI 64–93.6] in the control, p = 0.11 (Figure 4).

Two significant independent factors that increased the chance of relapse were found using the logistic regression: DEL and pulmonary involvement (Table 2). According to Z-values and OR, both factors had equal influence on the ER chance.

Table 1. Patient and procedures characteristics

Characteristic	Criteria	Upfront, n = 35		Control, n = 70		p-value
		n	%	n	%	
Sex	Male Female	18 17	51 49	32 38	46 54	0.67
IPI	2 3 > 4	10 19 6	29 54 17	29 25 16	41 36 23	0.28 0.09 0.67
Bulky (≥ 7,5 sm)	**Yes** **No**	**21** **14**	**60** **40**	**24** **46**	**34** **68**	**0.02**
Extranodal > 1 site	Yes No	27 8	77 23	50 20	71 29	0.69
Bone marrow involvement	Yes No	7 28	20 80	17 53	24 76	0.8
Pulmonary involvement	Yes No	7 28	20 80	15 55	21 79	0.86
Gastric involvement	Yes No	13 22	37 63	15 55	21 79	0.13
Cell of origin	GCB Non-GCB No data	16 19 0	46 54 0	21 27 22	30 39 31	1.0
DEL	Yes No No data	13 22 0	37 63 0	21 31 18	30 44 26	0.82
ICT	**R-CHOP** **DA-EPOCH-R**	**16** **19**	**46** **54**	**55** **15**	**79** **21**	**0.004**
Characteristic	Criteria	Upfront, n = 35		Control, n = 70		p-value
Observation period (mon)	Mean±SDev Median (range)	60.6 ± 22.4 68 (19–82)		62.5 ± 41.1 55 (6–143)		0.78
Age (years)	Mean±SDev Median (range)	48.0 ± 11.7 53 (18–63)		48.9 ± 12.5 53 (22–64)		0.53
LDH (U/l)	Mean±SDev Median (range)	385.3 ± 272.9 295 (169–1450)		417.7 ± 240.6 347 (145–1065)		0.42
Ki67 (%)	**Mean±SDev** **Median (range)**	**81.7 ± 13.5** **82.5 (40–100)**		**86.9 ± 14.1** **90 (50–100)**		**0.03**

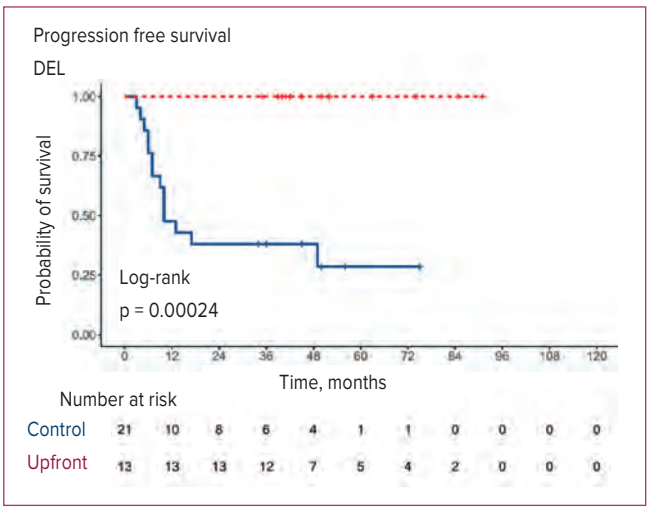

Figure 1. Progression free survival of patients with DEL receiving either HDCT followed by auto-HSCT or chemotherapy

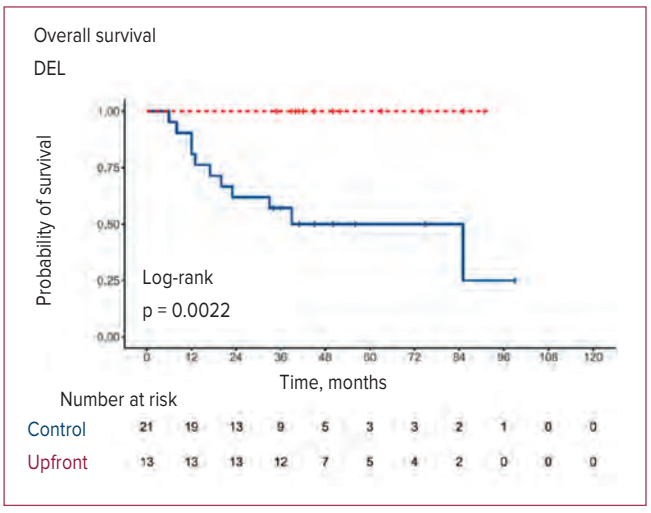

Figure 2. Overall survival of patients with DEL receiving either HDCT followed by auto-HSCT or chemotherapy

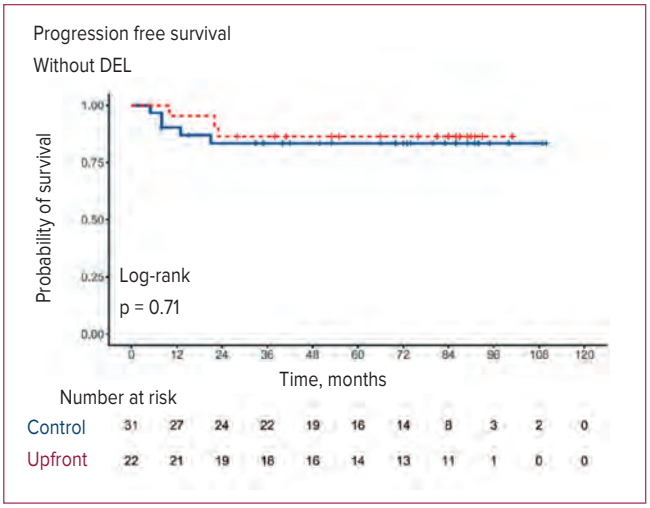

Figure 3. Progression free survival of patients WITHOUT DEL receiving either HDCT followed by auto-HSCT or chemotherapy

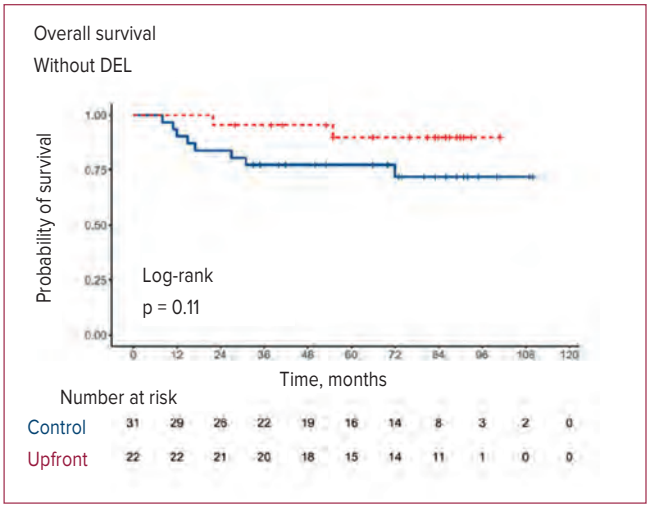

Figure 4. Overall survival of patients WITHOUT DEL receiving either HDCT followed by auto-HSCT or chemotherapy

Table 2. Logistic regression model — learning group (control)

Predictor	Estimate	SE	Z	p	OR	95 % CI OR
B0 — interception	–4,33	3,03	–1,43	0,152	0,01	$3{,}49e^{-5}$–4,91
DEL (Yes/No)	**2,00**	**0,87**	**2,27**	**0,02**	**7,39**	**1,32–41,4**
Lung (Yes/No)	**2,63**	**1,04**	**2,51**	**0,01**	**13,8**	**1,78–107,7**
Gastric (Yes/No)	–2,29	1,25	–1,83	0,06	0,1	0,01–1,18
Sex (Male/Female)	0,32	0,82	0,39	0,69	1,38	0,27–6,93
Age	0,01	0,03	0,54	0,58	1,01	0,95–1,09
Ki67	0,02	0,02	0,73	0,46	1,02	0,96–1,08

Table 3. Logistic regression model — test group (upfront)

Predictor	Estimate	SE	Z	p	OR	95 % CI OR
B0 - interception	–1,66	8,33	–0,2	0,84	0,18	$1{,}5e^{-8}$–$2{,}35e^{6}$
DEL (Yes/No)	–20,5	7424	–0,002	0,99	$1{,}15e^{-9}$	0–∞
Lung (Yes/No)	–21,4	10869	–0,001	0,99	$4{,}71e^{-10}$	0–∞
Gastric (Yes/No)	–21,0	7170	–0,002	0,99	$7e^{-10}$	0–∞
Sex (Male/Female)	0,5	2,21	0,22	0,82	1,65	0,02–127,2
Age	0,07	0,07	0,95	0,34	1,07	0,92–1,26
Ki67	–0,03	0,09	–0,3	0,759	0,97	0,8–1,18

The obtained model has very good quality (AUC = 0.859), and medium predictive power (R_2N = 0.508), medium sensitivity (83.3 %), specificity (85.7 %), and accuracy (84.8 %). Overall model test: p = 0.001. Both predictive values (positive — 78.9 %, negative — 88.8 %) reached good levels. Patients with DEL, treated by standard ICT, have a 78.9 % chance of experiencing relapse. However, the same pts without DEL have an 88.8 % chance of avoiding relapse if treated by standard ICT only.

The regression test confirmed no significant influence of any factors or covariates on the relapse rate in the upfront group (Table 3). Taking into account the equal distribution of clinical and biological characteristics in both groups and the significantly lower relapse rate in the upfront group, combined with the data from survival analysis, we can make the suggestion that the negative prognostic impact of DEL was leveled out by upfront auto-HSCT.

Conclusions. 1. Selected patients with DEL have better 3-yr PFS (p < 0.001) and OS (p < 0.001) if treated by upfront HDCT with auto-HSCT.

2. The choice of upfront auto-HSCT should be based on DEL status — patients with DEL have a high chance (78,9 %) of experiencing relapse. Patients without DEL shouldn't be overtreated and mostly (88,8 %) avoid relapse by standard ICT. If patient has a pulmonary involvement, it can also be considered as a negative prognostic factor, but further evaluation is needed.

3. Upfront HDCT with auto-HSCT can overcome the negative prognostic impact given by DEL on prognosis in DLBCL NOS, age 18-65, stage IV, IPI ≥ 2 with DEL.

References

1. Epperla N, Kumar A, Abutalib S et al. ASTCT Clinical Practice Recommendations for Transplantation and Cellular Therapies in Diffuse Large B Cell Lymphoma. Transplantation and Cellular Therapy 29 (2023) 548-555.

2. Cortelazzo S, Tarella C, Gianni A.M, et al. Randomized Trial Comparing R-CHOP Versus High-Dose Sequential Chemotherapy in High-Risk Patients with Diffuse Large B-Cell Lymphomas. @J. Clin. Oncol. 2016; 34(33):4015–22. DOI: 10.1200/JCO.2016.67.2980.

3. Sehn LH, Salles G. Diffuse Large B-Cell Lymphoma. N Engl J Med. 2021;384(9):842–58. https://doi.org/10.1056/NEJMra2027612

Brentuximab vedotin in combination with BeGeV in patients with relapses and refractory of Hodgkin's lymphoma: 3-year follow-up

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Introduction. Despite the fact that LH is one of the most curable malignant diseases and has no analogues in 5-year survival among all types of cancer over the past 40 years, in real clinical practice up to 30 % of patients have a refractory course or relapse (R/R) of LH and need a second or subsequent lines of therapy. Historically, standard treatment regimens (DHAP/ICE/IGEV/DVD) followed by autologous bone marrow transplantation (autoHSCT) allowed to achieve long-term responses in no more than 40 % of patients. After the appearance in clinical practice of the drugs brentuximab vedotin and checkpoint inhibitors (nivolumab, pembrolizumab), the life time of patients with LH increased. Given the high efficacy of new drugs in the third and subsequent lines of LH therapy, physicians have begun to introduce these drugs into the treatment of LH in the second line of therapy to improve treatment outcomes. We present 3 years of experience in the use of BV + BeGeV therapy regimens in patients with P/R LX.

Objectives. To evaluate the efficacy, toxicity, mobilization ability, and cost-effectiveness of the anti-relapse course of BeGeV + BV therapy in patients with Hodgkin's lymphoma, who are candidates for autoHSCT.

Materials and methods. The study included patients who were candidates for autoHSCT, refractory to previous therapy or who relapsed after it (platinum-containing therapy courses, courses with checkpoint inhibitors). Patients were scheduled to receive 2 courses of BeGeV + BV therapy (bendamustine 90 mg/m^2 on 2–3 days, gemcitabine 800 mg/ m^2 on 1 and 4 days, vinorelbin 20 mg/ m^2 on 1 day, prednisolone 100 mg on 1-4 days, brentuximab vedotin 1.8 mg/kg on 1 day) with the collection of peripheral blood stem cells (PCCs) after the 1st course. After 2 cycles of therapy, the response was evaluated based on PET-CT data. When PET-negative remission (DS 1–3) was achieved, the third course of therapy was carried out and autoHSCT (BEAM + brentuximab vedotin) was performed. When a partial response or stabilization was achieved after 2 cycles of BeGeV + BV, an additional 2 cycles of therapy were conducted with an assessment of the response after 4 cycles. When the CR was reached after 4 cycles, an autoHSCT was performed. In the absence of CR the patient was transferred to other types of treatment. Survival results were evaluated at the last follow-up. The median OS was estimated using the Kaplan-Meyer method.

Results and discussion. The study included 37 patients aged 18 to 60 years (median age — 34 years) who were treated at the Botkin Hospital from 2020 to 2023. There were 20 men and 17 women in the study group. Primary refractory course was detected in 10 patients (27 %), early relapse — in 14 (38 %), late relapse — in 13 (35 %). The median of BeGeV + BV courses was 3. After the 2nd cycle of therapy, ORR was 97 % (36/37), of which a complete metabolic response was achieved in 30/36 (83 %), PR was achieved in 6/36 (17 %). All 6 people with PR after the 2nd cycle of therapy achieved CR after the 4th cycle. AutoHSCT was performed in 35/37 patients. With a median follow-up of 20.5 months, PFS and OS were 84 % and 97 %, respectively. In 36/37 cases, effective mobilization of PCCs (CD34+ more than 2.0 million/kg body weight) was performed. In the future, a patient with an insufficient number of cells for autoHSCT was collected with a stable hematopoiesis. The most common side effects (grade 3–4) were: skin toxicity — 17 patients (46 %); hepatotoxicity — 18 patients (48 %); neutropenia — 27 patients (73 %), of which febrile neutropenia — 16 patients (43 %). Due to the high initial frequency of adverse events, it was decided to reduce the dosage of bendamustine to 70 mg/m^2 (70 mg/m^2 — 26 patients, 90 mg/m^2 — 11). In 4 patients, therapy was de-escalated to combinations of bendamustine with brentuximab due to intolerant toxicity. Of the 37 patients, only 9 needed hospitalization for a bed, all the others received a course as part of a day hospital.

Conclusions. The BeGEV + BV chemotherapy course has a high efficiency and mobilization ability, an acceptable toxicity profile without loss of effectiveness when reducing the dosage of bendamustine to 70 mg/m^2, and is also a cost-effective course for a hospital. Taking into account the presented data, it is possible to consider the possibility of using the BeGeV + BV course as one of the treatment options for patients with P/R HL who are candidates for autoHSCT.

Experience in managing of patients with follicular lymphoma in the Moscow region

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Introduction. Follicular lymphoma is a common lymphoproliferative disease, ranking second in incidence among lymphomas. Therapeutic options for the treatment of FL include immunochemotherapy with anti-CD20 monoclonal antibodies. The disease is usually characterized by a favorable prognosis and a good response to treatment, but relapsed and refractory diseases remain a significant clinical problem. Much attention has been paid to early disease progression at 24 months (POD24), which is a predictor of poor 5-year overall survival.

Materials and methods. A retrospective analysis of 95 records of patients diagnosed with follicular lymphoma who applied to the CDC MONIKI from 06/01/2021 to 06/01/2023 was carried out. Patients with a follow-up period of more than 6 months were included in the study. The diagnosis of follicular lymphoma and response to therapy were assessed according to generally accepted criteria. Descriptive statistics methods were used in the analysis.

Results. The analysis included 76 patients, 23 men (30.3 %), median age 55 years (33–78). Median follow-up was 40 months (7–191). The characteristics of the disease are shown in Table 1. In 77.6 % of patients, the disease was diagnosed in stages III-IV. Bulky lesion was noted in 5 (6.6 %) patients. Extranodal sites included bone marrow, soft tissue, lung, skin, duodenum, and conjunctiva. Transformation to diffuse large B-cell lymphoma (DBCL) was noted in 2 patients (after 3 and 126 months). Four patients (5.3 %) were observed without treatment. In 2 patients therapy was started later, after 5 and 12 months, in 1, transformation to DBCL was recorded, in 1, observation was continued (follow-up duration 58 months). The majority of patients (94.7 %) received first-line therapy. First-line treatment regimens are shown in Table 2. The overall response rate to first-line drug therapy was 87.8 %. Maintenance therapy with rituximab was administered to 56 patients (86.1 %). Among 18 patients with a partial response, 7 patients achieved a complete response during the period of maintenance therapy and follow-up. Relapse of the disease

Table 1. Disease characteristics

Cytological grade	**n (%)**
1–2	48 (63.2)
3	14 (18.4)
No data	14 (18.4)
Stage	**n (%)**
I	6 (7.9)
II	11 (14.5)
III	45 (59.2)
IV	14 (18.4)
bulky	5 (6.6)

Table 2. 1st line treatment regimens for FL

Treatment regimens	n	%
RCHOP	48	64,9
RB	9	12,2
RCOP	5	6,8
CHOP	4	5,4
R-mono	4	5,4
R-mono + radiotherapy	1	1,4
RB + radiotherapy	1	1,4
RFC	1	1,4
CV	1	1,4

RCHOP — rituximab, cyclophosphamide, doxorubicin, vincristin, prednisolone; RB — rituximab, bendamustine; RCOP — rituximab, cyclophosphamide, vincristin, prednisolone; CHOP — cyclophosphamide, doxorubicin, vincristin, prednisolone; R-mono — rituximab monotherapy; RFC — rituximab, fludarabine, cyclophosphamide; CV — cyclophosphamide, vincristin.

Table 3. 2nd line FL therapy

Treatment regimens	n
RB	9
RCHOP	3
RBAC	2
RDHAP	2
RICE	1
RCOEP	1
RFC	1
R-mono	1
G-mono	1
G-Len	1
FC	1
CV	1

RB — rituximab, bendamustine; RCHOP — rituximab, cyclophosphamide, doxorubicin, vincristin, prednisolone; RBAC — rituximab, bendamustine, cytarabine; RDHAP — rituximab, dexamethasone, cisplatine, cytarabine; RICE — rituximab, ifosphamide, carboplatin, etoposide; RCOEP - rituximab, cyclophosphamide, vincristin, etoposide, prednisolone; ; RFC — rituximab, fludarabine, cyclophosphamide; R-mono — monotherapy rituximab; G-mono — obinutuziumab monotherapy; G-Len — obinutuziumab, lenalidomide; FC — fludarabine, cyclophosphamide; CV — cyclophosphamide, vincristin.

was verified in 16 patients (24.6 %). The median duration of the first remission was 21.5 months. Refractoriness to 1st line of therapy was observed in 9 patients. 2nd line treatment regimens included courses of high-dose therapy (RBAC, RDHAP, RICE), obinutuzumab-containing courses (Table 3). An overall response to 2nd line therapy was observed in 16 patients. 9 patients received 3 or more lines of therapy, 6 of them had primary refractory disease or early relapse. The therapeutic options used were RCHOP-like courses (2), bendamustine-containing courses (2), obinutuzumab therapy (3), metronomic therapy, duvelisib (2).

Discussion. The results obtained are comparable with the results of Russian and foreign centers. Most patients responded to 1st line of therapy, but in 30 % of cases relapse or primary refractoriness was noted. In 10 % of cases, third/fourth line therapy was required.

Conclusions. Approaches to the treatment of patients with FL complied with national clinical guidelines. Treatment of refractory and recurrent FL currently remains a pressing issue. The development of new agents in the treatment of FL is a promising area of modern hematology.

Interim MRI-results for prognosis in adults with primary central nervous system lymphoma

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Abstract. Among the extranodal lymphomas, primary central nervous system lymphoma (PCNSL) is mostly associated with the worst prognosis in terms of both morbidity and survival. The prognosis of patients with PCNSL has improved during the last decades. The median overall survival (OS) of patients with PCNSL increased from 12,5 months in the 1970s to 26 months in the 2010s with the introduction of new methods of therapy. Currently, the standard for initial diagnosis and response assessment in PCNSL is based on contrast-enhanced MRI. Interim response assessment of patients with PCNSL is a routine procedure, but the prognostic value of this study is poorly understood.

Objectives. To assess the impact of interim contrast-enhanced brain MRI results after two cycles of chemotherapy on the outcomes of patients with PCNSL.

Materials and methods. The present retrospective study enrolled 60 patients with PCNSL. Median age at the time of diagnosis was 58 years (range 25–74) with 36 patients (60 %) being females. PCNSL was diagnosed by surgical resection in 27 patients (43,6 %) or stereotactic brain biopsy in 35 patients (56,4 %). High-dose methotrexate-based regimens with rituximab was the base of induction therapy. The third component of chemotherapy was cytarabine (R + MA) in 25 % of cases and temozolomide. (R + MT) in 75 % of cases. All patients underwent contrast-enhanced brain MRI after the second cycle of therapy. Patients were divided according to deep of response and intensity of induction therapy. Survival curves are estimated, using the Kaplan-Meier method and compared statistically using the log rank test.

Results. Complete response (CR) after 2 cycles of therapy was achieved in 16 patients (26,7 %), partial response in 20 (33,3 %) patients (median observation period: 9,2 months). Patients with CR to systemic chemotherapy after 2 cycles of therapy had significantly better OS. Median of overall survival was not achieved in all groups. The 2-year overall survival was analyzed. In the group of patients who achieved CR after 2 cycles, the 2-year survival rate was 100 % with R+MA and 81,8 % with R + MT. Among patients who did not achieve a complete response, the 2-year OS was 70 % in R + MA group and in the group of patients who received R + MT 68,9 % (Figure 1). The differences were statistically significant when comparing the depth of response.

Conclusions. Achieving a complete response after the second cycle of therapy can be a predictor of a favorable prognosis in patients with PCNSL. Response assessment with interim MRI can distinguish chemosensitive and chemoresistant patients.

References

1. Hua Yang, Yang Xun, Anping Yang et al. Advances and challenges in the treatment of primary central nervous system lymphoma. Journal of Cellular Physiology. 2020;235:9143–9165.

2. Wieduwilt MJ, Valles F, Issa S et al. Immunochemotherapy with intensive consolidation for primary CNS lymphoma: a pilot study and prognostic assessment by difusion-weighted mri. Clinical Cancer Research. 2012;18(4):1146–1155.

3. Chiavazza C, Pellerino A, Ferrio F et al. Primary CNS Lymphomas: Challenges in Diagnosis and Monitoring. Biomed Res Int. 2018;2018:3606970.

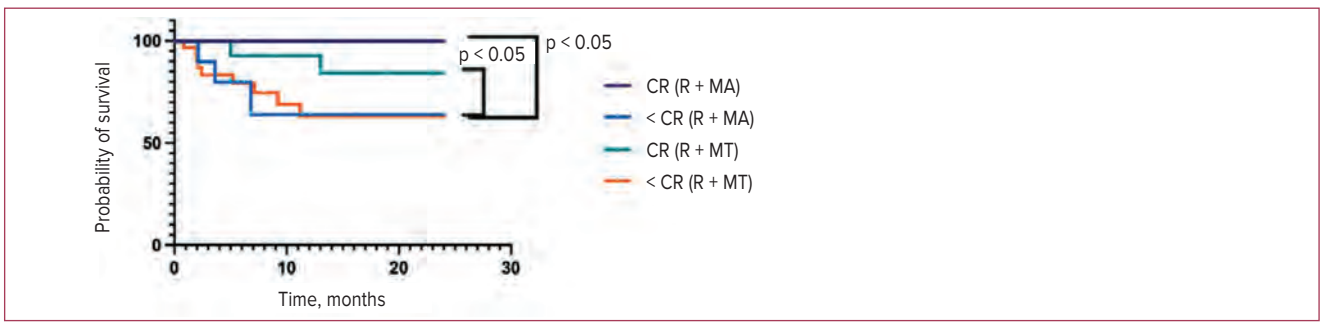

Figure 1. Kaplan-Meier 2-year overall survival curve of patients with PCNSL. CR — complete response; R + MA — rituximab, methotrexate, cytarabine; R + MT — rituximab, methotrexate, temozolomide

The use of the Russian original PD-1 inhibitor (Prolgolimab) in the treatment of patients with relapsed and refractory classical Hodgkin lymphoma

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Introduction. Classic Hodgkin lymphoma (cHL) is a potentially curable disease in approximately 80–85 % of patients. The standard approach for relapsed and refractory patients with cHL is high-dose chemotherapy with autologous HSC transplantation (autoHSCT). After second-line regimens (DHAP, ICE), a complete response can be achieved in 30–40 % of patients. PD-1 inhibitors (nivolumab, pembrolizumab) in combination with chemotherapy significantly improved the antitumor response. Prolgolimab specifically binds to the PD-1 receptor and blocks its interaction with ligands PD-L1 and PD-L2. The drug is registered in the Russian Federation for the treatment of inoperable or metastatic melanoma and is currently being intensively studied for other malignant neoplasms.

Objectives. To evaluate the efficacy and safety of prolgolimab alone and in combination with DHAP chemotherapy.

Methods. Prolgolimab in combination with the DHAP regimen was used in 9 patients (2 men and 7 women) with refractory (n = 5) and relapsed (n = 4) cHL. The median age at onset was 29 years (range, 22–39 years). As first-line therapy, patients received ABVD (3) and BEACOPP-like regimens: BEACOPP-14 (1), EACODD-14 (3), eBEACOPP (2). The median number of previous therapy lines was 2 (range 1–3). 3 patients received brentuximab vedotin therapy, and 4 patients received radiation therapy. The median duration of response to first-line therapy was 29 months (range, 12–47 months).

Results. All 9 patients received 2 administrations of prolgolimab alone with subsequent 2–3 cycles of combination therapy (prolgolimab + DHAP), after which an interim evaluation of the effect was performed using PET/CT. The overall response rate was 89 % (7 CR, 1 PR). One patient was withdrawn from the study due to insufficient effect. Next, 6 patients underwent successful chemomobilization with etoposide at a dose of 375 mg/m^2/day on days 1 and 2 and a sufficient number of BMSCs were collected (median CD34+ 4.18 × 10^6/kg).

No adverse events were registered during prolgolimab monotherapy. When using the combination of prolgolimab and DHAP, 2 patients had an isolated increase in liver transaminases to 3 upper limits of normal (1 of them had proven Gilbert's syndrome). In general, the combination was well tolerated; none of the patients required discontinuation of treatment due to adverse events. Median duration of response was 6 months (range 3–10 months). With a median follow-up of 12 months, all patients maintained the achieved effect.

Conclusions. Prolgolimab in combination with DHAP has shown high efficacy and a low toxicity profile. The combination of prolgolimab + DHAP makes it possible to enhance the antitumor response and perform auto-HSCT in a larger number of patients with relapsed and refractory cHL compared with standard second-line regimens (DHAP, ICE).

VRD protocol in newly diagnosed multiple myeloma: preliminary treatment results

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Background. Over decades multiple myeloma has tendency towards decent treatment outcomes, however remains its position on incurable cancer diseases list. Risk-adapted strategy, optimal regimens of induction, consolidations and supportive care — all of that makes further improving of outcomes.

Objectives. To estimate preliminary results of treatment in newly diagnosed multiple myeloma patient's candidates for a stem cell transplant.

Methods. All patients have been administered with VRD regimen induction therapy along with following

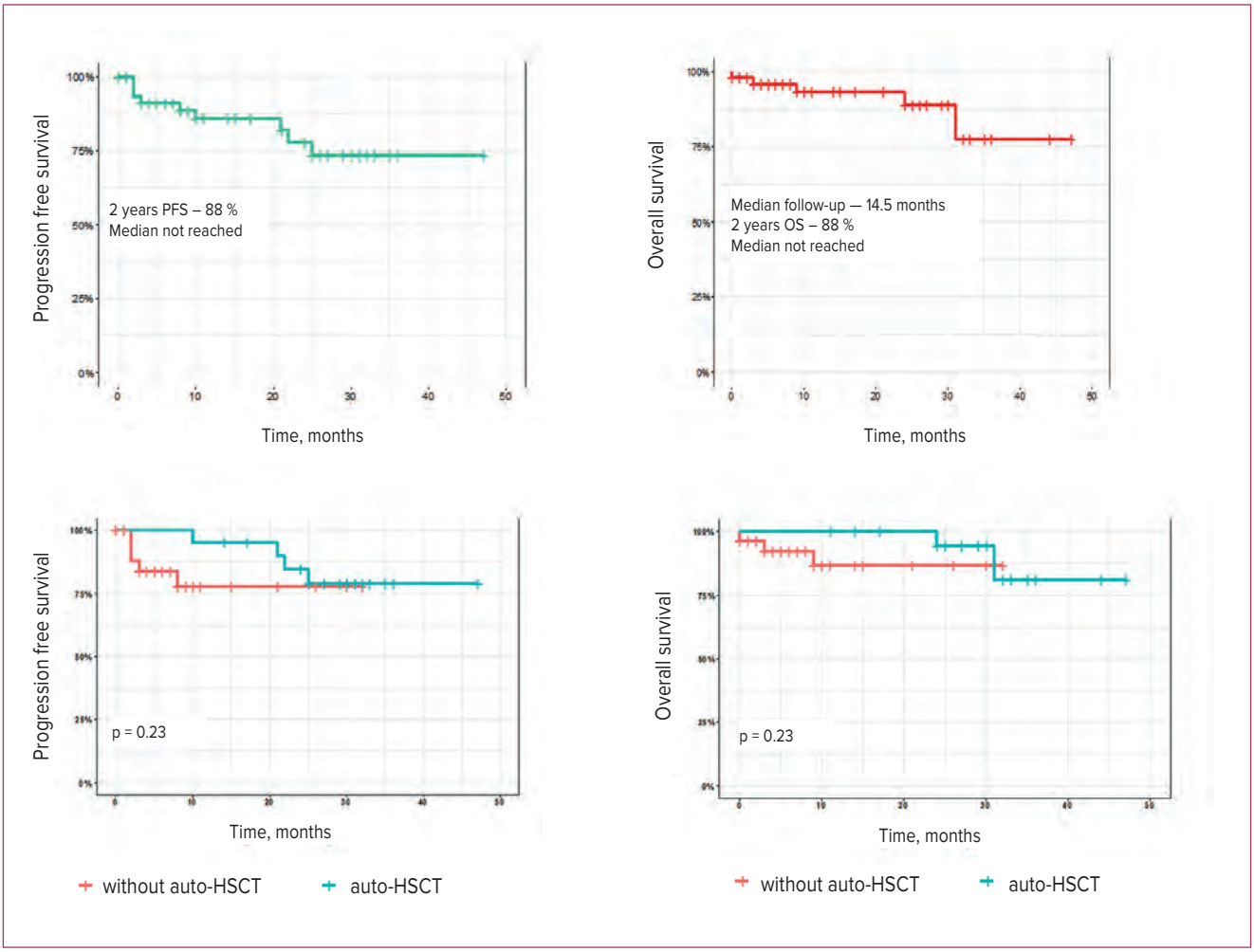

Figure 1. Progression free survival and overall survival

MRD-adapted strategy. The response was estimated according to International Myeloma Working Group criteria (IMWG, 2016). Risk stratification was carried out according to mSMART 3.0 criteria. The Kaplan Meier method was used to estimate survival and differences between curves were assessed using the logrank test.

Results. Among 50 patients in Russian Cancer Research Center named after N.N. Blokhin with newly diagnosed multiple myeloma who received VRD regimen, 80 % received 4 induction cycles (median — 5). The overall response rate was 90 % (complete response — 34 %, a very good partial response — 45 %, partial response — 11 %). Four patients experienced progression; 3 patients died. Seven patients achieved MRD-negative status (NGF ~ 10^{-5*}) after induction cycles (16 %). Patients with high cytogenetic risk (n = 9) had worse results (complete response — 2, a very good partial response — 4), and only one patient achieved MRD-negative status. By November, 2023 forty-four patients completed induction phase, 21 received stem cell transplant, five have been given consolidation therapy and thirteen — supportive therapy. The median age of patients was 55 years (34–65), twenty-seven were males (54 %). Disease stages were following: R-ISS: I — 27 (54 %), II — 9 (18 %), III — 14 (28 %). Nine patients (18 %) had high cytogenetic risk (del17p, t(4;14), t(14;16), amp 1q21). PET/CT scans were performed on admission to the hospital, before and after stem cell transplant. On the disease onset (according to PET/CT scans) 80 % of patients had unfavorable prognosis (more than three extramedullary lesions, SUVmax > 4,2). During induction therapy 70 % of patients had vertebroplasty. With a median follow-up of 14.5 months, twelve-month progression free survival (PFS) was 86 % (Figure 1), twelve-month overall survival (OS) was 93 %. More importantly OS and PFS were tend to be higher in patients who had administered stem cell transplant.

Conclusions. Triple-component VRD regimen being administered as induction therapy among newly diagnosed multiple myeloma patients associates with thorough antitumor effect, patients with high cytogenetic risk included. On the other hand, frequency of achieving MRD-negative status remains low, which is not contradictory to previous scientific research data. Currently the end point is personalization of chosen therapy according to MRD status after stem cell transplant.

Comparison of outcomes between patients with early-stage cHL who received consolidation with versus no radiotherapy

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Abstract. Key Words: Hodgkin lymphoma, Hodgkin disease, early stage, radiotherapy, radiation.

Introduction. The incorporation of radiotherapy into the initial treatment protocols for classical Hodgkin lymphoma (cHL) may vary across different medical institutions. Some institutions follow a PET-adapted approach, while others reserve radiotherapy for patients with bulky disease. Additionall, there's a strategy that involves administering fewer cycles of chemotherapy and subsequently using radiotherapy, regardless of PET scan results. Our study focuses on the outcomes of patients with classic Hodgkin lymphoma treated at two tertiary care centers in the Middle East. The retrospective analysis of collected data aims to uncover any differences between patients who underwent radiotherapy and those who did not.

Patients and methods. Our retrospective analysis involved reviewing the medical records of patients diagnosed with early-stage cHL who underwent treatment between 2011 and 2022. Two independent reviewers meticulously gathered and cross-checked the data for accuracy. Our analysis assessed the rates of complete remission and relapse. To determine the endpoints of overall survival and progression-free survival, we employed the Kaplan-Meier method for statistical analysis.

Results. Total of 231 patients (130 female 101 males) with median age of 28 years fulfilled the inclusion criteria (Table 1). Mean Follow-up time is 59 months. Most patients had nodular sclerosis subtype (84.7 %) and 88.3 % had stage II with 71.4 % having B symptoms. Significant number of patients had bulky disease (27.2 %). All patients except 4 received ABVD with average number of cycles given was 5 cycles. In total, 182 patients received radiotherapy and 49 did not. At end of chemotherapy and radiation complete metabolic remission was documented in 93.1 % of the patients.

Four of 171 (2.3 %) of patients with negative interim PET had disease relapse at EOT-PET. All of these patients had radiotherapy. Thirteen patients of the group with positive interim PET were not consolidated with radiotherapy with 4/13 (30.8 %) relapses occurred in comparison with 8/38 (21.1 %) in the group who had positive interim and were irradiated.

Relapse rates among patients who had negative EOT-PET and got radiotherapy versus no radiotherapy were 4.3 % (7/164) and 2.2 % (1/46) respectively. Of the 21 patients who had a positive EOT-PET, 18 patients received consolidation with radiotherapy and three did not and proceeded to another line of chemotherapy. 5/18 (27.8 %) patients who were irradiated because of positive EOT-PET had disease relapse.

Table 1. Patients characteristics, early-stage disease cHL chemo alone vs chemo and RT (n = 231)

	Chemotherapy (n = 49)	Chemotherapy with radiotherapy (n = 182)	Total	p-value
Age, Median (IQR)	26 (15)	29 (16)	28(16)	0.106[a]
Gender, n (%)				0.267
Female	31 (63.27)	99 (54.40)	130 (56.28)	
Male	18 (36.73)	83 (45.60)	101 (43.72)	
Initial Stage, n (%)				0.891
1	6 (12.24)	21 (11.54)	27 (11.69)	
2	43 (87.76)	161 (88.46)	204 (88.31)	
HL Subtype, n (%)				0.009*†
Nodular Sclerosis	35 (71.43)	158 (88.27)	193 (84.65)	
Lymphocyte-depleted	1 (2.04)	0 (0.00)	1 (0.44)	
Lymphocyte-rich	6 (12.24)	8 (4.47)	14 (6.14)	
Mixed Cellularity	7 (14.29)	13 (7.26)	20 (8.77)	
ECOG, n (%)				0.048*†
0	28 (57.14)	7 (31.82)	35 (49.30)	
1	18 (36.73)	15 (68.18)	33 (46.48)	
2	3 (6.12)	0 (0.00)	3 (4.23)	
Comorbidities, n (%)				0.000*†
No	30 (62.50)	150 (83.33)	180 (78.95)	
One	18 (37.50)	21 (11.67)	39 (17.11)	
More than one	0 (0.00)	9 (5.00)	9 (3.95)	
IPS Score, n (%)				0.000*†
0	15 (31.91)	2 (1.10)	17 (7.46)	
1	15 (31.91)	14 (7.73)	29 (12.72)	
2	6 (12.77)	3 (1.66)	9 (3.95)	
3	4 (8.51)	161 (88.95)	165 (72.37)	
4	6 (12.77)	1 (0.55)	7 (3.07)	
5	1 (2.13)	0 (0.00)	1 (0.44)	
Hemoglobin < 10 gm/dL, n (%)	5 (10.20)	23 (12.99)	28 (12.39)	0.600
Lymphocyte, n (%)	15 (30.61)	3 (13.04)	18 (25.00)	0.148†
Bulky Disease, n (%)	9 (18.37)	54 (29.67)	63 (27.27)	0.115

* $p \leq 0.05$ is significant.

a Wilcoxon rank-sum test P value.

† Fisher's exact test P value.

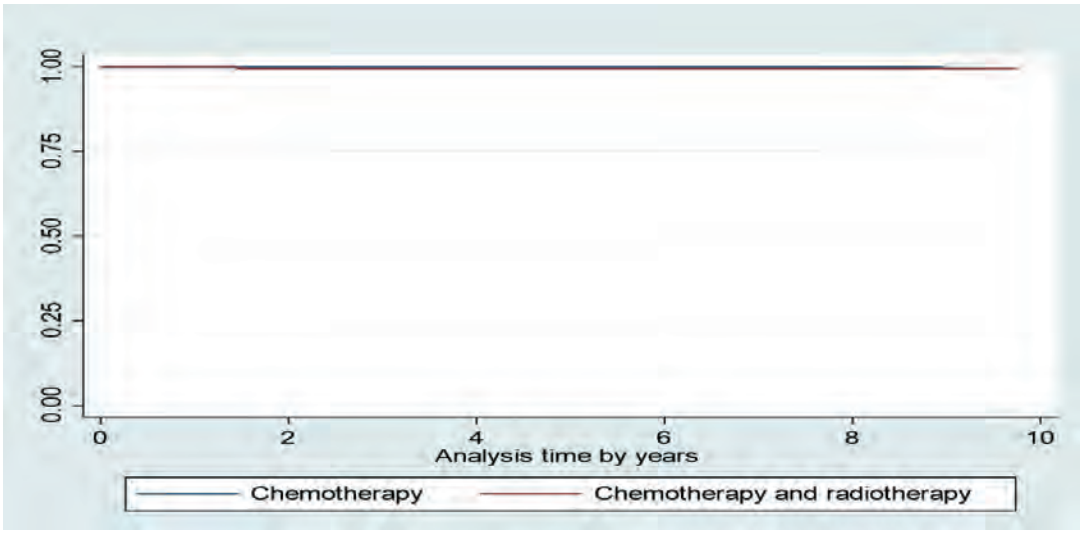

Figure 1. Kaplan-Meier survival estimates of chemotherapy compared to chemotherapy with radiotherapy

At data cut-off (11/2022) there was no significant difference in PFS rate (p = 0.75) between patients who underwent radiation (6.6 %; 12/182) in comparison with the group of patients who were not irradiated (8.2 %; 4/49). Overall survival was similar (Figure 1).

Conclusions. While our real-world data doesn't favor routine consolidation with radiotherapy for early-stage cHL patients with negative EOT-PET, our findings highlight radiotherapy's effectiveness in curing a substantial percentage of individuals with positive EOT-PET.

Conflict of Interest Statement. All other authors state that they have no conflicts of interest.

Logistic regression model as an additional mathematical method for predicting the course of disease in patients with diffuse large B-cell lymphoma (DLBCL)

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Introduction. Diffuse large B-cell lymphoma (DLBCL) is the most common form of lymphoma. The addition of rituximab, an anti-CD20 monoclonal antibody, to the CHOP regimen (which contains cyclophosphamide, doxorubicin, vincristine, and prednisolone) resulted in significant improvements in treatment outcomes. Most people, depending on their prognostic factors, are completely curable with treatment strategy containing rituximab and CHOP regimen (R-CHOP). However, up to 40 % of patients have disease that is refractory to this treatment or suffer a relapse after an initial response [1].

Diagnosis of large B-cell lymphomas is based on a detailed examination of the tumor tissue. In addition to morphological characteristics, accurate classification of lymphoma requires specific tests, including immunohistochemistry, flow cytometry, fluorescence in situ hybridization (FISH) and molecular testing [2]. Patients with newly diagnosed DLBCL have great heterogeneity in progression-free survival (PFS). The International Prognostic Index (IPI) was developed in 1993 for better patients' stratification by risk and therapeutic strategies selection. IPT defines 4 clear prognostic groups of patients

with DLBCL. Particularly important is the identification of high- and low-risk groups, which differ significantly in clinical outcome and relapse-free survival. However, there remains a demand to develop prognostic assessment systems for better risk stratification of patients and selection of those who are most in need of new treatments [3]. The use of machine learning methods in predicting the course and outcome of the disease is a highly promising area. The use of predictive models in clinical practice as a decision support system (DSS) will help a multidisciplinary team of specialists choose the optimal treatment tactics.

Objectives. To construct a prognostic model for assessing potential outcomes of first-line therapy for DLBCL.

Research objectives. 1. To construct a predictive model to assess potential outcomes of first-line therapy based on retrospective data. 2. To assess the possibility of using clinical, immunohistochemical and cytogenetic data as prognostic factors.

Materials and methods. Primary medical records from the Krasnoyarsk Regional Clinical Oncology Dispensary named after A.I. Kryzhanovsky and Nuclear Medicine Center of the FSRCC FMBA of Russia was used in the study in the period from 2018 to 2022. Following the results of selection, 83 patients diagnosed with DLBCL were included in the study. All patients received drug therapy according to the R-CHOP regimen. The age of the participants ranged from 22 to 85 years (median — 60 years). There were 39 men (47 %) and 44 women (53 %) in the study.

To assess the possible response to the first-line therapy, we studied data characterizing the unique immunophenotype and clinical features of DLBCL: immunohistochemical and cytogenetic studies, information on the presence/absence of symptoms of tumor intoxication, time period from diagnosis to treatment initiation, stage of the disease, lesions, as well as visual assessment of the results of first-line therapy using the Deauville scale.

Mathematical analysis was carried out using the SPSS application package. The logistic regression method was used to predict the probability of presence/absence of a complete response to first-line therapy for DLBCL depending on the main predictors. In order to do this, a dependent variable was introduced that takes one of two values: 1 — meaning an absence of a complete metabolic response, or 0 — meaning a complete metabolic response. Also, a set of independent variables (predictors) were used. Basing on the values of independent variables, the probability of accepting one or another value of the dependent variable was calculated.

Results and discussion. It was found that a complete metabolic response (1–3 points on the Deauville scale) after the first-line therapy according to the R-CHOP regimen was observed in 50 (60.2 %) patients out of 83 in the analysis of the treatment effectiveness. Our result of complete metabolic response is a bit lower, in comparison with the study led by Thomas M. Habermann, where the author describes the result of a complete response rate of 77 % [4]. This difference can be justified by the small sample used in our study, which requires replenishment of the number of observations.

Among the 17 patients included in the test group, a complete response was observed in 13 people, while 4 of them were refractory to the treatment. Let us note that the model we made classified 11 people into the favorable prognosis group, and the remaining study participants were assigned to the incomplete response group. Thus, the model correctly predicted the possible response to first-line therapy in 84.62 % of cases, which characterizes its high quality (accuracy — 88.2 %, sensitivity — 100 %, specificity — 84.6 % AUC — 0.923).

Predictors associated with an increased risk of first-line treatment failure for DLBCL were identified. One of them is advanced disease stage ≥ III ($p = 0.007$), which correlates with the same IPI score criterion. Coexpression of c-MYC and BCL2 ($p = 0.014$) also aggravates the course of disease. Yoon SO et al. studied the effect of various proteins expression on life expectancy in people with DLBCL, where coexpression of the MYC and BCL-2 genes was associated with lower survival, comparing to a case of absence of their expression. Also, presence of the BCL-6 gene had no effect on patients' life expectancy [5].

The influence of molecular subtypes of DLBCL on the prognosis was also established: the best response to the first-line therapy according to the R-CHOP regimen was seen in patients with DLBCL of GCB subtype in comparison with ABC subtype ($p < 0.001$), which is due to the suppression of apoptosis genes in the ABC subtype of DLBCL, as well as suppression BCL6, which acts as a transcriptional repressor for B-cell differentiation [6]. Let us emphasize that mediastinal lymph nodes lesion, which also tips the scales towards first-line therapy failure ($p < 0.001$), was also a predictor in our model.

14.4 % (n = 12) of patients in our study had more than 1 extranodal lesion ($p = 0.001$). This predictor also worsens prognosis, which also correlates with IPI, which has a similar factor.

On the other side, symptoms of tumor intoxication symptoms and patient's age did not affect the prognosis ($p = 0.898$ and $p = 0.177$, respectively). It is worth paying attention to the fact that most of the participants belonged to the older age group, and the median age was 61 years. This fact confronts us with the need to replenish the sample with younger participants.

Considering the time before the start of therapy, we determined a positive effect on the prognosis in cases where the time before treatment initiation was in the range from 2 to 10 weeks, but this dependence turned

out to be statistically insignificant. Western literature describes a slightly different favorable interval for starting therapy — 5–8 weeks [7]. However, the difference in results highlights the need to discuss the limitations of our study. It is noteworthy that this is the only factor that depends on the doctor.

The importance of pre-assessing patients' potential treatment response to determine potential treatment outcome has been emphasized by many studies [8, 9]. The aim of this work was to create an accurate and practical model based on logistic regression using clinical, immunohistochemical and cytogenetic data as variables. At the same time, predictive efficiency, practical utility and availability of data necessary for the method to work are balanced.

The model currently includes four variables that can be obtained in routine clinical practice: stage ≥ III, coexpression of c-MYC and BCL2, molecular subtype of lymphoma, and presence/absence of mediastinal lymph node lesion. It is promising to expand the predictors used, which will increase the accuracy of the prognosis.

This method may be useful as a clinical decision support tool. It will allow doctor to assess the risk of first-line R-CHOP therapy failure in patients diagnosed with DLBCL and prioritize alternative treatment regimens.

Conclusions. Machine learning in the field of predicting the course and outcome of the disease is a highly promising area. The use of predictive models in clinical practice as DSS does not devalue doctor's work, but significantly improves a personalized approach in medicine, helping multidisciplinary team specialists to choose optimal treatment tactics.

Key words: DLBCL, logistic regression, prognostic factors, immunohistochemical study.

References

1. Tilly H, Morschhauser F, Shen LH, et al. Polatuzumab Vedotin in Previously Untreated Diffuse Large B-Cell Lymphoma. The New England Journal of Medicine. 2022;386(4):351–363. doi: 10.1056/NEJMoa2115304.

2. Shen LH, Salles G. Diffuse Large B-Cell Lymphoma. The New England Journal of Medicine. 2021;384(9):842–858. doi: 10.1056/NEJMra2027612.

3. Ruppert SA, Dixon GJ, Salles G, et al. International prognostic indices in diffuse large B-cell lymphoma: a comparison of IPI, R-IPI, and NCCN-IPI. Blood. 2020;35(23):2041–2048. doi: 10.1182/blood.2019002729.

4. Vitolo U, Trněný M, Belada D, et al. Obinutuzumab or Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone in Previously Untreated Diffuse Large B-Cell Lymphoma. J Clin Oncol. 2017;35(31):3529–3537. doi: 10.1200/JCO.2017.73.3402.

5. Yoon SO, Jeon YK, Paik, et al. MYC translocation and an increased copy number predict poor prognosis in adult diffuse large B-cell lymphoma (DLBCL), especially in germinal centre-like B cell (GCB) type. Histopathology. 2008;53(2):205–17. doi: 10.1111/j.1365-2559.2008.03076.x.

6. Blenk S, Engelmann J, Weniger M, et al. Germinal center B cell-like (GCB) and activated B cell-like (ABC) type of diffuse large B cell lymphoma (DLBCL): analysis of molecular predictors, signatures, cell cycle state and patient survival. Cancer Inform 2007;12:3:399–420.

7. Phipps C, Lee YS, Ying H, et al. The impact of time from diagnosis to treatment in diffuse large B-cell lymphoma. Leukemia and lymphoma. 2018;59(10):2336–2341. doi: 10.1080/10428194.2017.1422863.

8. Sehn LH, Berry B, Chhanabhai, et al. The revised International Prognostic Index (R-IPI) is a better predictor of outcome than the standard IPI for patients with diffuse large B-cell lymphoma treated with R-CHOP. Blood. 2007;109(5):1857–61. doi: 10.1182/blood-2006-08-038257.

9. Ruppert AS, Dixon JG, Salles G, et al. International prognostic indices in diffuse large B-cell lymphoma: a comparison of IPI, R-IPI, and NCCN-IPI. Blood. 2020;135(23):2041–2048. doi: 10.1182/blood.2019002729.

СЕССИЯ 3 МИЕЛОПРОЛИФЕРАТИВНЫЕ ЗАБОЛЕВАНИЯ

Long-term results of targeted therapy for myelofibrosis at the Moscow City Hematology Center of Botkin City Clinical Hospital, predictors of treatment efficacy

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Introduction. Primary and secondary myelofibrosis (MF) remains prognostically unfavorable despite the existence of various methods for its treating. Therapy with targeted drug ruxolitinib has significantly improved the overall survival (OS) of MF patients. The assessment of long- term treatment outcomes in real clinical practice and detection of factors indicating worse prognosis are highly relevant.

Objectives. To evaluate the efficacy of long-term treatment with ruxolitinib in patients with MF resistant to standard therapy and to determine factors predicting the effectiveness of targeted treatment.

Methods. The prospective study included 206 patients with MF (primary MF — 154 (75 %), postpolycythemic — 39 (19 %), postthrombocythemic — 13 (6 %)) in chronic phase who received ruxolitinib as a 2nd or subsequent line of therapy: 95 (46 %) men and 111 (54 %) women aged 18–84 years (median (Me) = 62) years. Clinical and hematologic examination, morphologic and genetic evaluations, including next-generation sequencing (on biomaterial from 106 patients preserved in biobank) were performed before the ruxolitinib therapy. Median duration of the disease before ruxolitinib prescription was 75 (1–432) months. Survival rates were estimated by the Kaplan-Meier method starting at the moment of ruxolitinib therapy initiation. The results of therapy, OS and progression-free survival (PFS) rates were investigated in relation to a variety of factors.

Results. Median of ruxolitinib therapy was 24 (1–116) months. Clinical and hematological response by 1 month of treatment was: complete and partial — 14 % (n = 29), clinical improvement — 20 % (n = 41), stabilization of disease — 57 % (n = 117); by 3 months — 21 % (n = 43), 34 % (n = 70), 36 % (n = 74) respectively, by 12 months — 34 % (n = 70), 21 % (n = 43), 34 % (n = 70); 9 (18 %) patients had no response. Signs of tumor intoxication were gone in a month after the beginning of treatment in 25 (20 %) patients, in 3 months — in 52 (42 %), in 12 months — in 77 (62 %) of 125 patients who had them. Normalization of spleen size was observed in 38 (20 %), 58 (30 %), 86 (45 %) of 192 patients with splenomegaly respectively. It became possible to avoid the transfusion dependence in 19 (27 %), 28 (40 %), 38 (54 %) of 71 patients requiring transfusions earlier. The OS rate: from the start of ruxolitinib therapy was 87 % at 12 months, 75 % at 2 years, 68 % at 3 years, 53 % at 5 years; PFS — 68 %, 56 %, 46 %, 32 %, respectively. Significant differences in PFS were obtained in patients younger or older than 60 years ($p < 0,01$), with different DIPSS risk scores ($p < 0,05$), previously treated with hydroxyurea and interferon or not ($p < 0,05$), with a white blood cell count before starting ruxolitinib therapy ≥ or < 15×10^9/L ($p < 0,05$), platelet count ≥ or < 100×10^9/L ($p < 0,05$), Hb level ≥ or < 100 g/L ($p < 0,05$), fibrosis grade 1, 2 or 3 ($p < 0,05$). Such differences were also observed depending on the presence or absence of mutations in different driver genes ($p < 0,05$), in the presence or absence of JAK2 variant allele frequency positive dynamics during ruxolitinib therapy ($p < 0,05$), additional high- risk mutations ($p < 0,05$), different types of additional mutations detected by NGS method (pathogenic, of uncertain significance, benign) ($p < 0,05$) and presence or absence of pathogenic SETBP1 mutation ($p = 0,003$). At the same time significantly different 5-year survival rates without blast crisis were observed between groups with JAK2 and MPL ($p = 0.001$), JAK2 and TNS

(p = 0.002) mutations, and 5-year survival rates without fibrosis progression were observed between groups with pathogenic and benign (p = 0.031); indeterminate and benign (p = 0.001) additional mutations. Age (p < 0.01), different DIPSS risk score (p < 0.05), MF variant (p < 0.05), interferon therapy (p < 0.05), leukocyte count (p < 0, 05), platelets count (p < 0.05), Hb level (p < 0.05), grade of fibrosis (p < 0.05), driver mutation variant (p < 0.05), CALR variant allele frequency at the time of ruxolitinib administration (≥ 50 %, < 50 %) (p = 0.01), presence or absence of positive dynamics of JAK2 variant allele frequency during ruxolitinib therapy (p < 0.05), presence of additional high-risk mutations (p < 0.05), especially SETBP1 (p = 0.003), ASXL1 (P = 0.002) mutations, type of additional mutations (p < 0.05), number of additional pathogenic mutations (p < 0.05) had a significant impact on OS.

Conclusions. The study showed high efficacy of ruxolitinib in cases of MF resistant to standard therapy, identified clinical, laboratory and genetic markers significantly associated with the effectiveness of ruxolitinib therapy and survival rates.

Results of targeted therapy for advanced forms of systemic mastocytosis

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Introduction. Mastocytosis is a heterogeneous group of diseases characterized by excessive proliferation and accumulation of clonal (neoplastic) mast cells in one or more organs. Pathogenesis is associated with the occurrence of somatic mutations in genes involved in the regulation of mast cell activation. The most common mutation is found in KIT gene (point mutation of exon 17, D816V). It leads to phosphorylation of tyrosine kinase and transformation of factor-dependent cell growth into factor-independent. In addition, it blocks apoptosis and rapid proliferation of mast cells, which leads to their accumulation and further activation. Aggressive systemic mastocytosis, systemic mastocytosis associated with hematologic neoplasm and mast cell leukemia are the most aggressive variants of systemic mastocytosis, requiring cytoreductive therapy. Midostaurin, a multikinase mutation-independent KIT inhibitor is currently, the only targeted therapy for systemic mastocytosis approved in Russia. Its efficacy was shown in clinical trials; however, it is well known that results of the therapy in clinical practice often differ from clinical trials due to the differences of patients' characteristics (comorbid status, stable disease parameters etc.). Considering mastocytosis is to be a rare diagnosis, the amount of published data for the clinical use of midostaurin in Russia is limited.

Objectives. To evaluate the effectiveness and safety of midostaurin in patients with advanced variants of systemic mastocytosis in clinical practice.

Methods. The analysis included 13 patients (7 (54 %) male and 6 (46 %) female) who received midostaurin as therapy for systemic mastocytosis (aggressive systemic mastocytosis — 9 (69 %), systemic mastocytosis associated with a hematologic neoplasm — 4 (31 %)). The KIT D816V mutation was detected in 10 patients (77 %), and two patients were KIT D816V negative, but showed JAK2 mutation. The median age at the diagnosis was 73 (61–87) years, the median age for start of midostaurin therapy was 74 (61–88). Patients were assigned to the following groups according to the predictive scale for common forms of mastocytosis based on clinical data (IPSM): SM1 — 1 patient (8 %), SM2 — 3 patients (23 %), SM3 — 8 patients (61 %), SM4 — 1 patient (8 %).

Results. Ten patients (77 %) achieved clinical improvement, and others (23 %) had stabilization of the disease. The most common nonhematologic adverse events were nausea (38 %), vomiting (15 %), and diarrhea (46 %); they were not exceeding 2nd grade. The adverse events were successfully controlled by symptomatic therapy. Hematological toxicity of 1–2 grades was also observed: anemia in 6 patients (46 %), thrombocytopenia in 5 patients (38 %). The overall 2-year survival rate was 75 %. The median overall survival in the group was not reached.

Conclusions. Results of the conducted study confirm the effectiveness and safety of midostaurin therapy for systemic mastocytosis in real clinical practice.

Key words: systemic mastocytosis, targeted therapy, midostaurin, KIT mutation, real clinical practice.

The challenges in diagnosis and monitoring chronic myeloid leukemia (CML) patients in the Republic of Bashkortostan

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Introduction. To determine treatment success in chronic myeloid leukemia (CML) it is necessary to monitor hematological, cytogenetic and molecular-genetic indicators. Minimal residual disease (MRD) is an excellent prognostic tool during the course of the disease. The achievement of major molecular response (MMR) and complete cytogenetic response (CCyR) is a favorable predictor for progression-free survival.

Objectives. The purpose of this study is to assess the implementation of cytogenetic and molecular-genetic testing in patients with CML while making diagnosis and during the first year of treatment.

Methods. The study included 127 patients with CML (68 men and 59 women; the median age was 57 years (range 18–85). The frequency of monitoring was determined by the Russian clinical guidelines on the diagnosis and treatment of CML from 2022.

Results. CML J.E. Sokal and ELTS scores at diagnosis were available in 46 % (n = 58), all patients were in chronic phase. Cytogenetic data at diagnosis was obtained in 67,7 % (n = 86) of patients, a typical BCR-ABL transcript type was detected in 86.6 % (n = 110). The number of cytogenetic and molecular-genetic tests performed during the first year of treatment is presented in Figure 1, 2. The

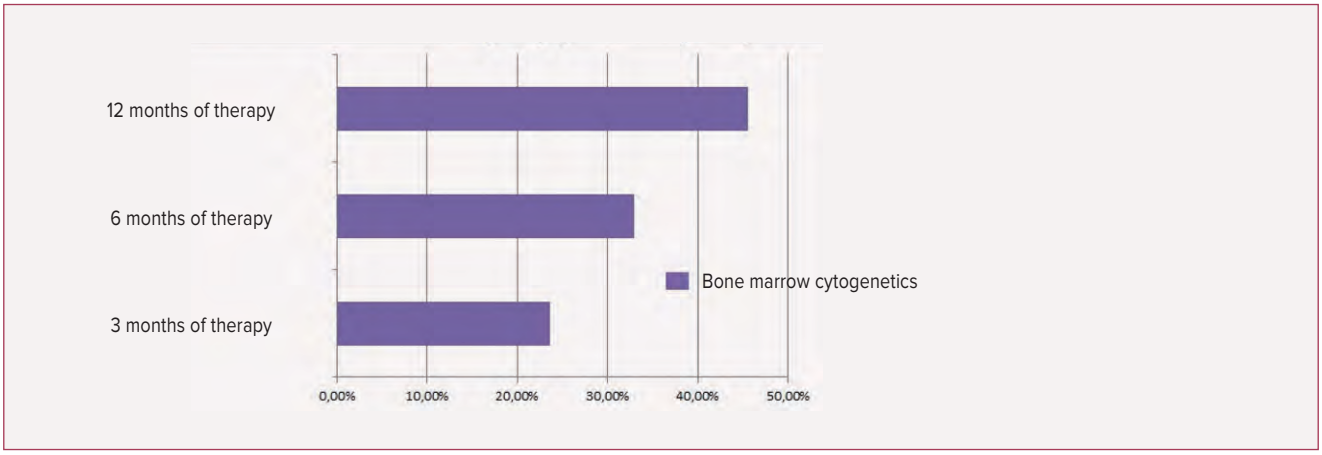

Figure 1. The number of completed cytogenetic tests during the first year

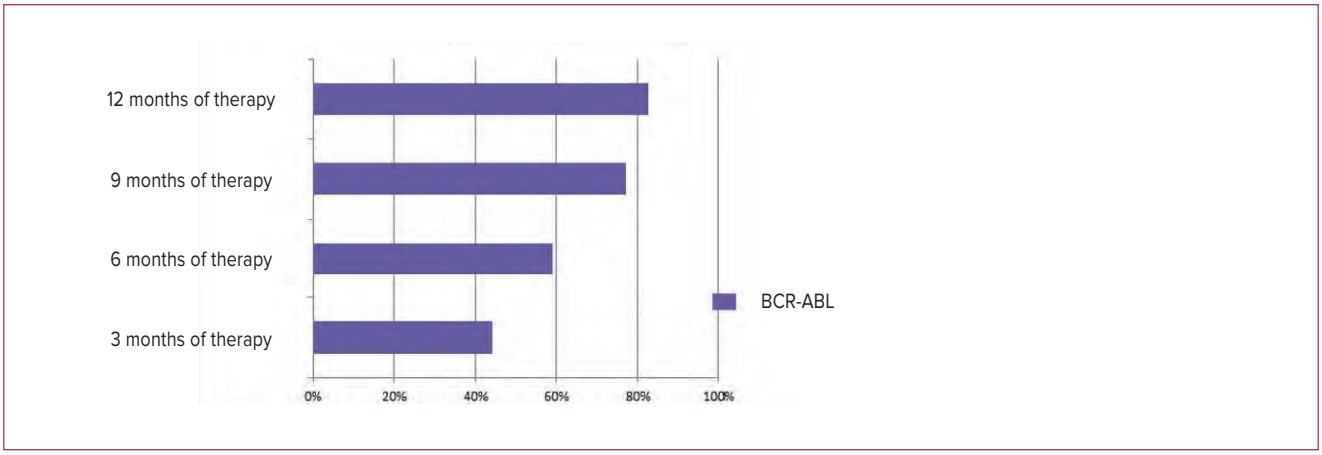

Figure 2. The number of completed molecular genetic tests during the first year

least amount of cytogenetic and molecular-genetic tests was performed within the first 6 months of treatment and its number increased by the end of the first year. MMR was achieved in 82 % of patients, but CCyR was detected only in 32 % of patients.

Conclusions. While making a diagnosis CML specific risk scores are used in less patients, cytogenetic and molecular-genetic tests are conducted in most patients. The assessment of molecular and cytogenetic response is conducted within the required timeframe in a low number of patients and increases by the end of the first year of treatment. Noteworthy isa lowpercentage of cytogenetic tests performedwithin the first year of treatment. The maintenance of CMLregister and increase of diagnostic testing availability in the Republic enables timely monitoring of therapy and its management if needed.

Ophthalmological manifestations in patients with primary, postthrombocythaemic and postpolycythaemic myelofibrosis

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Introduction. Chronic myeloproliferative neoplasms (CMPN) are a group of clonal hematological neoplasms characterized by the proliferation of myeloid cells in the bone marrow. Ophthalmological manifestations of CMPN are quite diverse. According to the literature, direct damage to the organ of vision, orbit and adnexa of the eye occurs due to infiltration of neoplastic tissue cells. There are also secondary changes in the organ of vision in CMPN associated with hematological abnormalities, such as thrombocytosis, erythrocytosis and leukocytosis. Disturbances in the microvascular circulatory system lead to both reversible neuro-ophthalmological symptoms (transient and migraine-like ischemic attacks) in the form of blurred vision, transient monocular blindness, hemianopsia, scintillating scotoma, and to more serious, vision-threatening manifestations of hyperviscosity and hypocoagulation of the blood - retinal vascular microaneurysms, ischemic cotton wool lesions, retinal hemorrhages, hemorrhages in vitreous body, dilation, tortuosity of the retinal veins, occlusion of the veins, retinal arteries and optic nerve, papilledema, neovascularization. In foreign literature, the incidence of ophthalmological manifestations in patients with ET and IP is from 7.5 to 25 %, however, there are no data on the prevalence of ophthalmological manifestations in patients with CMPN (CML and Ph-negative CMPN) in the Russian Federation.

Objectives. To evaluate the incidence and nature of ophthalmological manifestations in patients with primary, postthrombocythaemic and postpolycythaemic myelofibrosis during long-term therapy with ruxolitinib.

Methods. At the Moscow City Ophthalmology Center, the Moscow City Hematology Center of the Botkin Hospital and at the Department of Ophthalmology of the Russian Medical Academy of Postgraduate Education (RMAPO), 37 patients were examined — 18 men (48.6 %) and 19 women (51.4 %). The average age is 58.6 years. In this group there are 29 patients with primary myelofibrosis, 1 with post-thrombocythemic and 7 with post-polycythemic.

Results. According to the results of an objective examination, ophthalmological changes characteristic of CMPN according to the literature were identified in 47 % of cases (n = 16). Dry eye syndrome was detected in 9 patients (26 %), corkscrew-shaped, tortuous vessels of the conjunctiva — in 14 patients (41 %) (Figure 1), dilatation and tortuosity of the retinal arteries and veins — in 16 patients (47 %), hemorrhages of various sizes on the fundus (drop-shaped, streak-shaped, Roth spots) — in 10 patients (29 %) (Figure 2). These changes occurred both against the background of stabilization of the disease (in 8 patients (50 %)) and against the background of a partial response to therapy (in 5 patients (32 %)). In addition, concomitant pathology was identified that was not specific to CMPN - choroidal nevus — in 2 patients (4 %), PVCR with retinal rupture — in 3 patients (6 %), dry form of AMD (including ERM) in 6 patients (13 %), newly diagnosed glaucoma in 1 patient (2 %), angioid streaks in 1 patient (2 %), pupillary membrane in 1 patient (2 %).

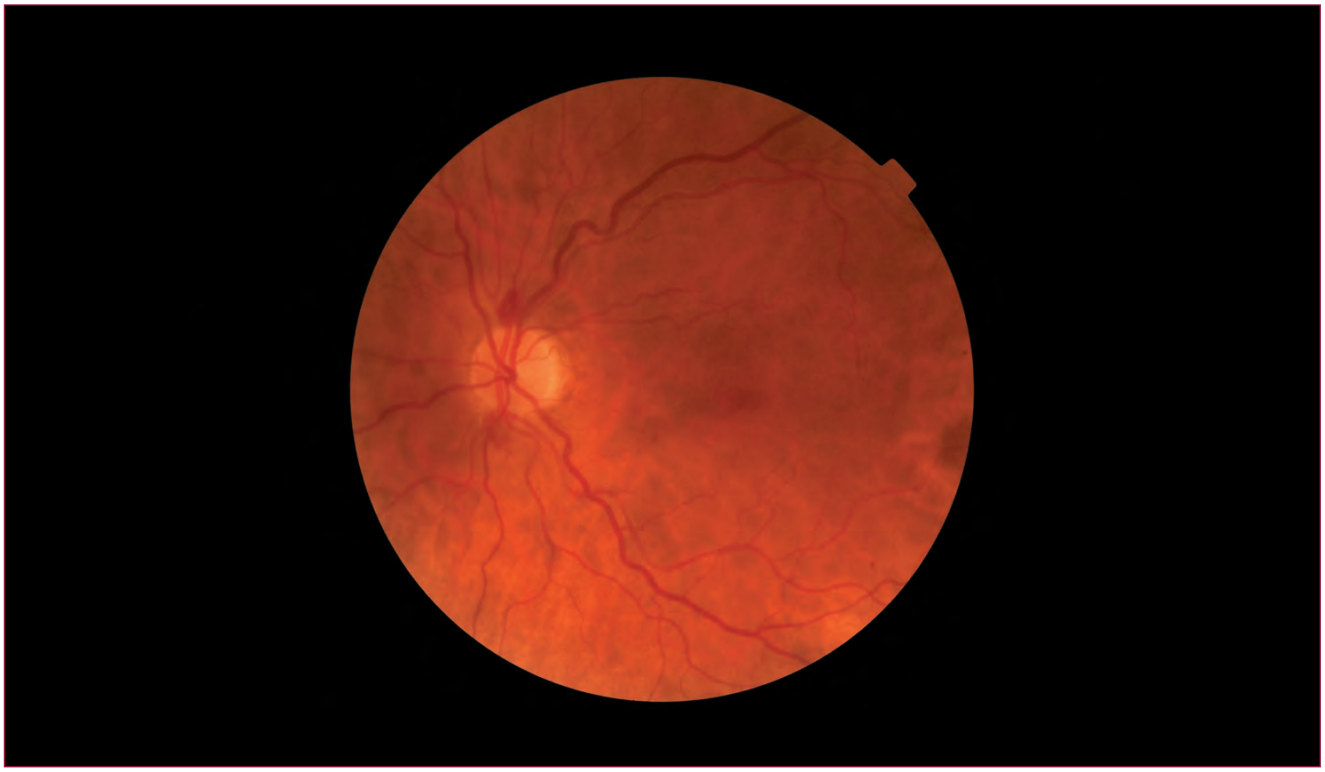

Figure 1. Various-sized hemorrhages in the fundus (drop-shaped, streak-shaped, Roth spots).

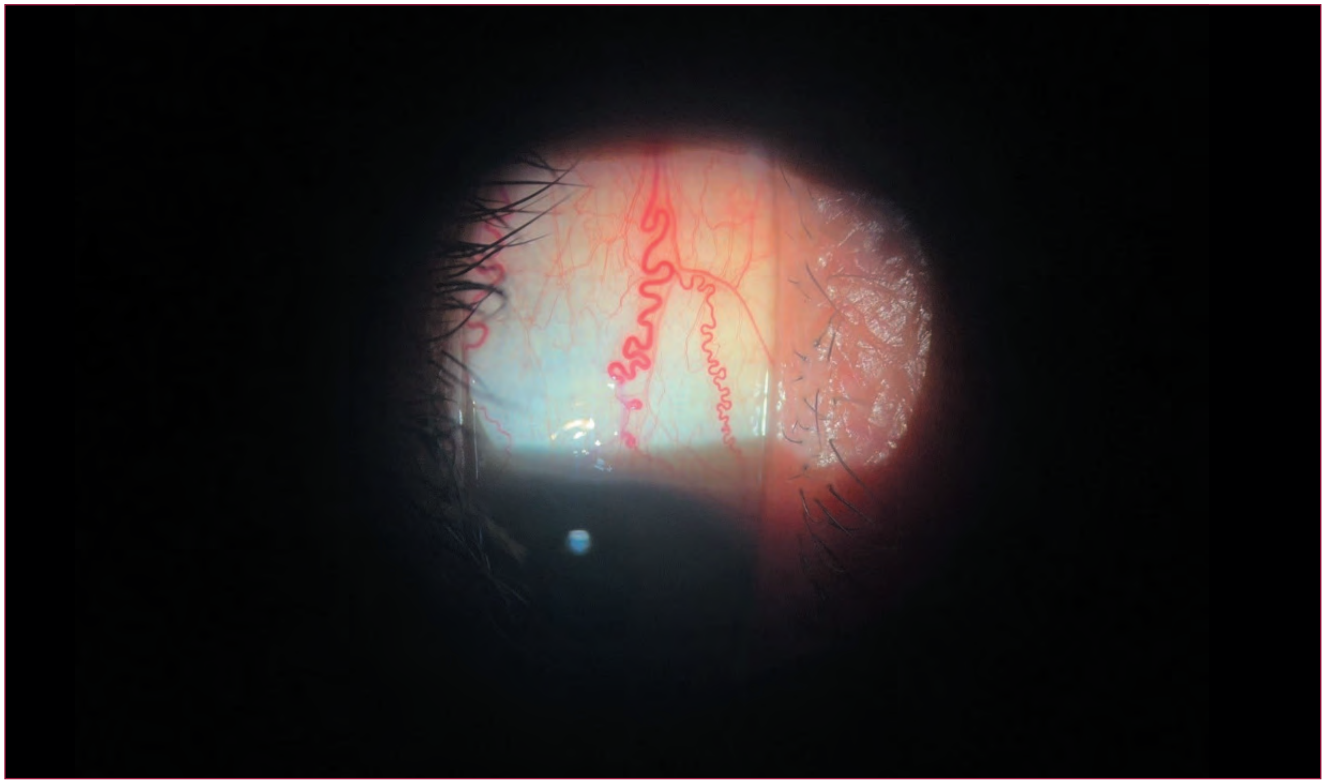

Figure 2. Twisted vessels of the conjunctiva

Conclusions. In patients with MF receiving ruxolitinib, a variety of disease-related ophthalmological changes are detected in 47 % of cases. A combined ophthalmological and hematological examination is important for monitoring patients diagnosed with CMPN, determining treatment tactics and preventing irreversible consequences for both the visual organ and the entire body.

Endothelial dysfunction in patients with chronic myeloid leukemia treated with second generation tyrosine kinase inhibitors

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Abstract. Cardiovascular system complications that develop during chemotherapy are of growing concern. We examined 152 patients with chronic myeloid leukemia treated with tyrosine kinase inhibitors. The study proved the significant diagnostic role of homocysteine, endothelin-1, vascular growth factor, lipid spectrum parameters, as well as non-invasive diagnostic methods such as volumetric sphygmometry and three-dimensional echocardiography with determination of global longitudinal myocardial deformation in early recognition of adverse events from the cardiovascular system in patients with chronic myeloid leukemia.

Introduction. CML belongs to the group of myeloproliferative neoplasms characterized by the uncontrolled growth of myeloid cells at different stages of maturation without loss of ability to differentiate, hyperplasia of myeloid tissue, myeloid metaplasia of hematopoietic organs associated with a chromosomal anomaly — translocation t(9;22)(q34;q11), as a result of which a chimeric oncogene is formed BCR-ABL 1, responsible for the synthesis of tyrosine kinase p210 [1].

The use of small molecules of tyrosine kinase inhibitors (TKI) in the treatment of chronic myeloid leukemia (CML) has significantly changed the outlook on the survival prognosis of this group of patients [2, 3]. Randomized multicenter clinical trials (IRIS, DASISION, ENESTnd) have demonstrated good treatment results however due to need of daily treatment with tyrosine kinase inhibitors it is natural for patients to develop adverse events, in particular metabolic and cardiovascular complications: lipid and carbohydrate metabolism disorder, thrombotic and atherosclerotic vascular disease [4, 5]. It is important that during the course of treatment with TKI, we can see early and long-term side effects both. The effect of TKI on both pathological BCR-ABL tyrosine kinase and other kinases involved in the regulation of normal vascular and myocardial endothelium activity causes the occurrence of cardiovascular system complications [6-8]. At the same time, according to the recommendations of the LeukemiaNet 2016 society, the diagnosis of adverse events from some organs and systems, including from the vascular endothelium, is still complicated [9].

Objectives. Determination of the features of the development of endothelial dysfunction and contractility of the left ventricle (LV) in patients with CML taking tyrosine kinase inhibitors of the I and II generations for a long time.

Methods. 152 CML patients aged 30 to 55 years treated with I and II generations tyrosine kinase inhibitors for 6 months or more were examined on the basis of the Department of Hospital Therapy with courses of polyclinic therapy and transfusiology of the Samara State Medical University and the National Medical Research Center for Hematology (Moscow). Group 1 (n = 31) included patients treated with imatinib at a dose of 400 mg/day, group 2 (n = 32) — dasatinib at a dose of 100 mg/day, group 3 (n = 32) — nilotinib 800 mg / day. The comparison group consisted of 30 patients treated with imatinib (average dose 600 mg / day), the control group consisted of 27 patients with newly diagnosed CML. All patients had been done the necessary clinical, laboratory and instrumental research methods to verify and monitor the course of the disease. The biochemical blood test included total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL) and very-low-density lipoprotein cholesterol (VLDL), triglyceride (TG), atherogenic index (AI). Endothelial function was evaluated using biochemical indicators (C-reactive protein, fibrinogen, homocysteine, endothelin-1, vascular endothelial growth factor (VEGF)). The condition of the vascular wall was evaluated by measuring the ancle-brachial index (ABI), the cardio-ankle vascular index (CAVI) and the intima-media complex thickness (IMCT) during color flow mapping of the brachiocephalic vessels (CFM BCV). The contractility of the LV myocardium was evaluated based on the results of echocardiography (determination of the ejection fraction (EF) by constructing a 3D model and global longitudinal strain (GLS) of the LV).

Results. In groups of patients with CML treated with II generation TKI (dasatinib 100 mg, nilotinib 800 mg), the most significant изchanges in the lipid spectrum are noted. Thus, after treatment with nilotinib 800 mg, the TC level was 6.33 ± 0.26 mmol/l, LDL — 4.28 ± 0.23 mmol/l, VLDL — 0.87 ± 0.21 mmol/l, TG — 1.86 ± 0.04 mmol/l, which is significantly ($p < 0.001$) higher than in other research groups. The HDL level was characterized by a significant ($p < 0.001$) decrease to 1.17 ± 0.08 mmol/l in comparison with other patient groups. After treatment with dasatinib, there is a less significant increase in the concentration of TC and TG, however, significantly ($p < 0.05$) different in comparison with the control group. In group 2, a slight increase in AI of 4.11 % ($p < 0.01$) was detected only in comparison with the control group; In group 3, the AI value was 3.95 ± 0.23, which was significantly higher ($p < 0.001$) than in other research groups.

The indices of ABI and CAVI in the control group, in patients of the 1st group and the comparison group did not differ significantly. It is noted that the ABI index was significantly reduced in patients in group 3 (0.93 ± 0.06 c.u.), and significantly ($p < 0.001$) differed from the values in other research groups. The ABI index in patients treated with dasatinib 100 mg is 1.27 ± 0.04 c.u., which is significantly ($p < 0.05$) lower than in the control groups comparison group and in the group of patients treated with imatinib 400 mg. The values of the CAVI index in patients of the 2nd and 3rd groups had opposite trends: the highest value of the cardio-ankle vascular index increase (8.53 ± 0.17 c.u.) was observed in group of patients treated with nilotinib 800 mg than in the other groups. When performing CFM BCV in patients with CML treated with II generation TKI, statistically significant changes of the IMCT were revealed: in groups of patients treated with nilotinib 800 mg and dasatinib 100 mg the values of IMCT (1.34 ± 0.02 mm and 0.87±0.08 mm, respectively) were significantly ($p < 0.01$) higher than in other groups.

Patients with CML shows features confirming the presence of endothelial dysfunction: a significant increase ($p < 0.01$) in the levels of homocysteine, endothelin-1 and VEGF (15.07 ± 0.22 mmol/l, 0.89 ± 0.04 fmol/ml and 168.49 ± 13.07 pg/ml, respectively) in group 3 in comparison with groups 1 and 2 (9.68 ± 0.76 mmol/l and 10.41 ± 0.73 mmol/L, 0.21 ± 0.03 fmol/ml and 0.41 ± 0.02 fmol/ml, 55.31 ± 7.54 pg/ml and 109.81 ± 13.01 pg/ml, respectively), as well as with the comparison group (10.21 ± 0.34 mmol/L, 0.33 ± 0.06 fmol/ml, 77.07 ± 6.78 pg/ml) and the control group (10.18 ± 0.42 mmol/L, 0.09 ± 0.04 fmol/ml, 37.01 ± 5.84 pg/ml).

Additionally, we revealed changes confirming the development of subclinical myocardial dysfunction in patients with CML treated with II generation TKI: in groups of patients treated with nilotinib 800 mg and dasatinib 100 mg the GLS values (–13.55 ± 0.15 and –15.43 ± 0.27, respectively) were significantly ($p < 0.001$) lower than in other groups. At the same time, LVEF in patients of all groups has a high correlation with the results of the measurement of global longitudinal strain ($r = 0.81$, $p < 0.05$).

Correlation analysis showed a significant pronounced dependence of all markers of endothelial dysfunction (CRP, fibrinogen, homocysteine, ET-1, VEGF), lipid metabolism parameters (total cholesterol, LDL, VLDL, HDL, TG, AI) and indicators of LV myocardial contractility.

Conclusions. The treatment with II generation TKI in patients with CML leads to a more pronounced and significant change in the function of the endothelium, which is manifested by an increase of the biochemical markers level, an increase in the intima-media complex thickness and vessel wall's remodeling, and these changes are especially pronounced when patients treated with nilotinib at a dose of 800 mg per day.

A non-invasive method for evaluating the contractility of the LV myocardium based on echocardiography results (determination of the ejection fraction (EF) by constructing a 3D model and global longitudinal strain (GLS) of the LV) seems promising from the point of view of identifying the initial manifestations of systolic dysfunction in patients with preserved LVEF, which determines further prospects for the research work.

The above parameters can serve as additional differential diagnostic criteria in evaluating the early development of cardiovascular complications in patients with CML, which in the future will reduce the non-hematological toxicity-related lethal outcomes. This will ensure an improvement in the prognosis of the disease and timely prevention of cardiovascular events, but also significantly improve the quality of life of this category of patients.

Key words: chronic myeloid leukemia, cardiovascular complications, endothelium, myocardial contractility.

References

1. Ministry of Health of the Russian Federation. Clinical guidelines "Chronic myeloid leukemia" Available by: https://oncology-association.ru/wp-content/uploads/2020/09/hronicheskij_mielolejkoz.pdf

2. Ovsyannikova EG, Kaplanov KD, Klitochenko TYu et al. Mutational status of imatinib-resistant patients with chronic myeloid leukemia. 2012;4:16–24.

3. Baccarani M, Castagnetti F, Gugliotta G et al. Treatment recommendations for chronic myeloid leukemia. Mediterr J Hematol Infect Dis. 2014;6:e2014005.

4. Giles FJ, Mauro MJ, Hong F et al. Rates of peripheral arterial occlusive disease in patients with chronic myeloid leukemia in the chronic phase treated with imatinib, nilotinib, or non-tyrosine kinase therapy: a retrospective cohort analysis. Leukemia. 2013;27(6):1310–1315. DOI: 10.1038/leu.2013.69.

5. Chai-Adisaksopha C, Lam W, Hillis C. Major arterial events in patients with chronic myeloid leukemia treated with tyrosine kinase inhibitors: a meta-analysis. Leuk Lymphoma. 2016;57(6):1300–1310. DOI: 10.3109/10428194.2015.1091929

6. Zeifman AA, Chelysheva EY, Turkina AG et al. The role of selectivity of tyrosine kinase inhibitors in the development of side effects in the treatment of chronic myeloid leukemia. Clinical oncohematology. 2014;7(1):16–27.

7. Anhel N, Delgado DH, Lipton JH. Cardiovascular toxicities of BCR-ABL tyrosine kinase inhibitors in chronic myeloid leukemia: preventive strategies and cardiovascular surveillance. Vasc. Health Risk. Manage. 2017;13:293–303.

8. Steegmann JL., Baccarani M, Breccia M et al. European LeukemiaNet recommendations for the management and avoidance of adverse events of treatment in chronic myeloid leukaemia. Leukemia. 2016; 30(8):1648–1671.

9. Bulayeva NI, Golukhova EZ. Endothelial dysfunction and oxidative stress: role in the development of cardiovascular pathology. Creative cardiology. 2013;1:14–22.

Clinical features and treatment strategies in patients with CMML

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Introduction. Chronic myelomonocytic leukemia (CMML) is a chronic myeloproliferative disease characterized by dysplasia of peripheral blood and bone marrow cells, sustained peripheral blood monocytosis and an inherent risk for transformation to acute myeloid leukemia (AML). The only curative option for CMML is allogeneic hematopoietic stem cell transplantation (allo-HSCT).

Objectives. Aims of this study was to analyze clinical features of CMML patients, assess outcomes of therapy and factors influencing overall survival (OS).

Materials and methods. A total of 84 patients with a verified diagnosis of CMML, observed at the RM Gorbacheva Research Institute from 2011 to 2023, were included retrospectively. Two-year OS was assessed with the Kaplan-Meyer method and log-rank test. A Cox regression model was used in order to perform an univariate analysis to determine factors influencing OS

Results. Median age at diagnosis was 56 years (range 17–88). According to the 2016 WHO criteria 24 (29 %) patients were classified as CMML-0, 16 (20 %) — CMML-1, 44 (51 %) — CMML-2 group. Median follow up time for alive patients was 24 months. During the observation period, 28 (33 %) patients developed a transformation into acute myeloid leukemia (AML), with the median time of 6,5 months from the primary diagnosis. Two-year OS was 51 % (CI 95 %, 40.5-64.1), with a median of 24 months. In univariate Cox regression models a statistical tendency towards lower OS was noted with the increased number of bone marrow blasts at disease onset (HR = 1.03, p = 0.079), absolute monocyte count in peripheral blood (HR = 1.03, p = 0.075), documented transformation into AML (HR = 1.9, p = 0.08), and shorter time to allo-HSCT (HR = 0.82, p = 0.08). As a first-line therapy, the most effective strategies were the use of hypomethylating agents with a complete remission rate (CR) — 27 % and acute non-lymphoblastic leukemias protocols (CR rate — 42 %). Allo-HSCT was performed in 21 (25 %) patients, of whom 13 (62 %) previously went through the AML transformation. The one-year OS for patients after allo-HSCT in the status of CR was 100 % (n = 5), while those without achieved CR (n = 16) was 28 % (95 % CI 11.1–71.8, p = 0.018). Main mortality causes after allo-HSCT were: relapse (n = 6, 55 %), primary non-engraftment (n = 1, 9 %) and infectious complications (n = 4, 36 %).

Conclusions. The choice of treatment strategies for patients diagnosed with CMML remains unclear.

Allo-HSCT stands as an only curative treatment option for CMML patients, however, further investigation into predictors of progression and the determination of the optimal timing for transplantation is needed.

Next generation sequencing (NGS) for patients with primary myelofibrosis

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Introduction. Determination of driver mutations in *JAK2, CALR* and *MPL* genes is the gold standard in the molecular diagnosis of patients with primary myelofibrosis, one of the Ph-negative myeloproliferative neoplasms. However, the genomic landscape of such patients is very wide and standard methods cannot provide a complete

picture of the course and prognosis of PMF patients, and sometimes even confirm the clonality of the disease. The next generation sequencing (NGS) method allows to simultaneously analyze an extensive panel of genes, as well as assess the level of allele burden of identified variant with mutations. This fact makes NGS an important tool in identifying pathogenic mutations and predicting the course of the disease in patients with PMF.

Objectives. To evaluate the possibilities of using NGS in the diagnosis and determination of prognostic features of the disease course in PMF patients.

Materials and methods. The study included 33 patients (11 men and 22 women) aged from 27 to 85 years (Me = 56 years). The diagnosis of PMF was previously established in all patients. All patients were analyzed for the presence of mutations in driver genes — in 19/33 (58 %) cases mutation in the *JAK2* gene (V617F) was detected, 6/33 (18 %) *CALR*, 3/33 (9 %) *MPL*, 5/33 (15 %) did not have mutations in any of the driver genes ("triple negative status"). For all patients, sequencing was performed using a 121-gene myeloid panel with an average read depth of 200× or 1000× on a MiSeq instrument (Illumina). The threshold as 3 % allele frequency (VAF) threshold was used. The clinical significance of mutations was determined using the COSMIC, ClinVar and Franklin databases. For survival analysis, the Kaplan–Meier method was used, with statistical significance assessed using the Cox-Mantel test.

Results. During the NGS analysis, genetic abnormalities were identified in all studied patients, on average 5 mutations per patient (1–18 per patient). In 90 % of the samples studied (30/33), 1 to 5 pathogenic mutations were detected (Me = 2). For 2 out of 5 patients with triple negative status, somatic mutations were found, which made it possible to confirm the clonality of the disease using NGS and establish a diagnosis. Pathogenic mutations in non-driver genes were found in 16/33 patients. These genes perform various functions — epigenetic regulation (*ASXL1* (10/16), *TET2* (6/16), *IDH1,2* (2/30), *EZH2* (1/16), *SETBP1* (1/16), *DNMT3A* (2/16)), RNA splicing (*SRSF2* (2/16), *U2AF1* (2/16)), signal transduction (*CBL* (2/16), *RAS* (2/16), *APC* (2/16)), chromatin remodeling (*ATRX* (2/16) and transcription factor (*RUNX1* (1/16) and *GATA* (1/16)). It was shown that the presence of any additional pathogenic mutation is significantly (p = 0.03) associated with a decrease in event-free survival. Moreover, the number pathogenic mutations also affects the prognosis: patients with ≥ 3 mutations have a significantly reduced event-free survival (p = 0.02) compared with patients with fewer (Figure 1). For patients with a known allele burden of *JAK2* mutations at the onset of the disease (16/19) it was shown that the V617F allele burden ≥ 18 % (Me in the group) (8/16) correlates with mutations in the epigenetic regulation genes *TET2* and *ASXL1* (5/8).For the group of patients 11/33 who ever took Ruxolitinib, a trend to a decrease in event-free survival for those who had 2 or more pathogenic mutations (p = 0.08) was shown (Figure 2).

Conclusions. NGS data make valuable information to confirm the clonal nature of the disease, prognostication, and and decision-making process in management of PMF patients.

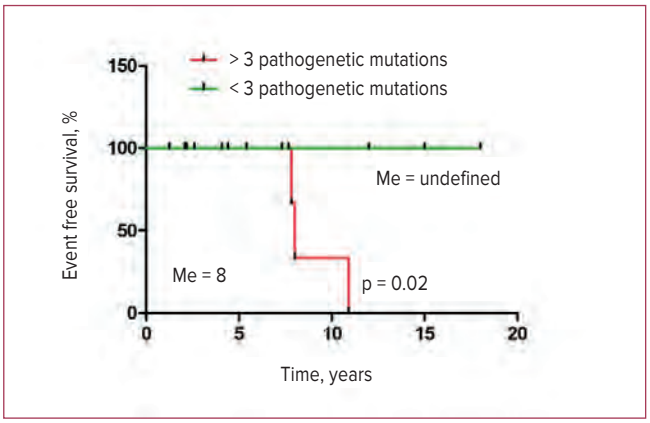

Figure 1. Influence of the number of pathogenic mutations on event-free survival of patients with PMF

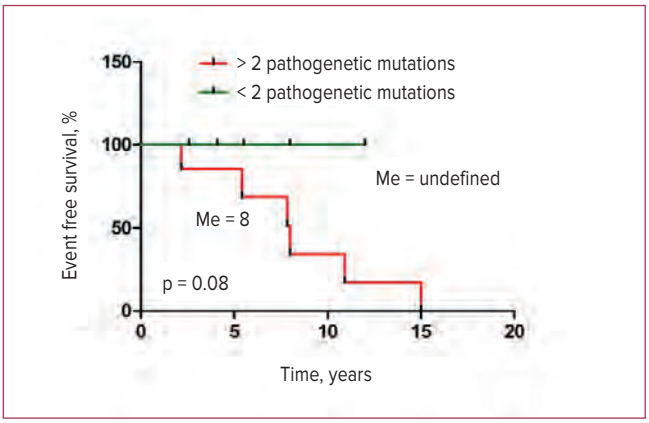

Figure 2. Influence of the number of pathogenic mutations on event-free survival of patients with PMF treated with ruxolitinib

Prevalence of somatic mutations in chronic myeloid leukemia patients

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Introduction. A search for molecular factors associated with prognosis and treatment failure in chronic myeloid leukemia (CML) patients is ongoing worldwide. Somatic mutations in the genes involved in cell proliferation are usually detected in advanced phases of CML and are rarely found at diagnosis of chronic phase (CP). The therapy choice in CML-CP patients with therapy failure after ≥ 2 lines of tyrosine kinase inhibitors (TKIs) remains challenging, and the analysis of the additional molecular markers in this population could be relevant.

Objectives. To compare prevalence of somatic mutations in some genes related to proliferation and differentiation of myeloid cells between CML patients with resistance/progression and optimal response.

Methods. Among >200 patients receiving TKI, groups were selected depending on the response to TKI therapy: group 1 (n = 29) — patients in CP with treatment failure by ≥ 2 TKIs according to ELN 2020 criteria (n = 21) and in the blast phase (BP) (n = 8); and group 2 — patients, achieved deep molecular response including patients in remission without treatment (n = 12). DNA was isolated from blood collected at the time of response. Next-generation sequencing (NGS) panel included some genes associated with prolipheration and differentiation of myeloid cells(*ASXL1, DNMT3, FLT3, IDH1, IDH2, NPM1, RUNX1, SF3B1, SRSF2, TET2, TP53, U2AF2, KIT, WT1, CEBPA, ZRSR2, JAK2, GATA2, ABL1*). Sample preparation was performed using Prep&SeqTM U-target modules (PARSEQLAB, Russia), and NGS was performed using the Illumina platform.

Results. The median level of *BCR::ABL1*^{IS} in group 1 was 54 % (range, 4–150 %). Of 29 patients, 19 (66 %) had ≥ 1 mutation. Overall, 31 mutations in 7 genes were detected, ranging from 1 to 4 per patient. The frequency of mutations among all genes was as follows: *ABL1* — 42 %, *ASXL1* — 26 %, *RUNX1* — *10 %, DNMT3A, CEBPA, WT1* — 6.3 % each, *NPM1* — 3 % (Figure 1). The median variant allele frequency (VAF) was 29 % (range, 5–50 %). The most frequently mutated genes were *ABL1* — in 10 (35 %) patients, and *ASXL1* — in 8 (28 %) patients. Of 10 patients with an

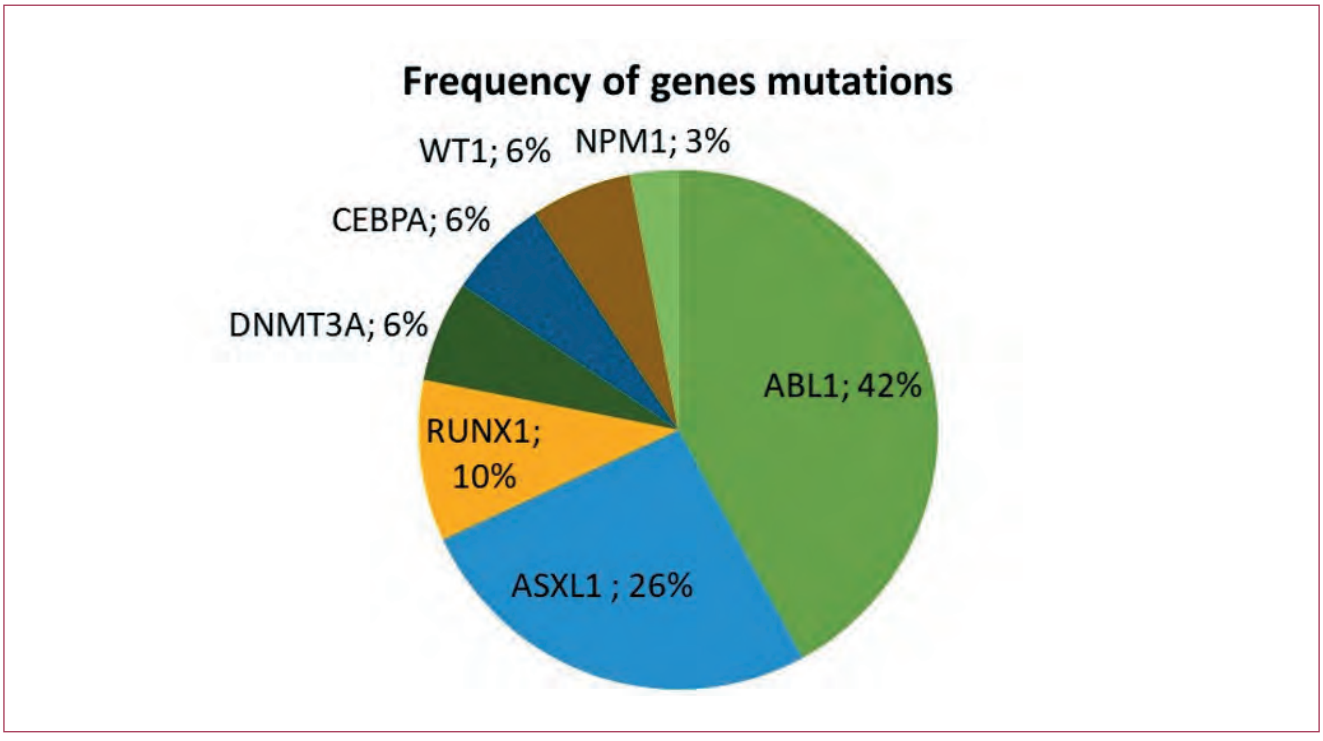

Figure 1. Frequency of mutations among all genes in the group of patients with resistant CML-CP or Bp

ABL1 kinase domain mutation, 6 (60 %) also had another somatic mutation. The combination of *ABL1* and *ASXL1* mutations occurred in 3/29 patients (10 %). Among 8 patients with BP, 6 had ≥ 1 mutations: in *ABL1* genes — 3 patients, *RUNX1* — 2 patients, *CEBPA*, *ASXL1, NPM1* genes — 1 patient each.

Group 2 included 12 patients with *BCR::ABL1*^{IS} level ≤ 0.1 %. In 1/12 patients (8 %) a *DMNT3A* mutation with VAF 5 % was detected.

Conclusions. Mutations in *BCR::ABL1* and *ASXL1* genes were the most frequent in resistant CML patients, including their combination in 10 % of patients. In the group of patients with CML-CP and resistance or BP, the frequency of somatic mutations was 66 %, while in the group of patients with molecular response - 8 %. Larger prospective trials and analysis of the mutant clones' dynamic are needed to evaluate their possible input to CML resistance and progression.

Mutational profile of resistant forms of chronic myeloid leukemia

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Introduction. Chronic myeloid leukemia (CML) is a clonal hematopoietic disease associated with a characteristic chromosomal translocation t(9;22)(q34;q11). This translocation results in the formation of a chimeric BCR::ABL gene encoding a constitutively active tyrosine kinase. The presence of mutations in the BCR::ABL kinase domain leads to the development of resistance to tyrosine kinase inhibitor (TKI) therapy. However, although the presence of mutations in the BCR::ABL kinase domain is a key factor in the development of resistance to TKIs, there are other genetic abnormalities that can also influence disease progression, prognosis and the development of resistance to therapy.

Objectives. Using the NGS method, determine the mutational profile of resistant forms CML and evaluate the impact of the found mutations on the development of resistance to TKIs.

Methods. The study included 50 patients. Group 1 — 32 patients with BCR::ABL-independent resistance (18 men and 14 women) aged 14 to 74 years (Me = 44). Group 2 (control) — 11 patients who responded to treatment (5 men and 6 women aged 33 to 75 years (Me = 58). Group 3 — 7 patients with BCR::ABL-dependent resistance (3 men and 4 women) aged 9 to 67 years (Me=34). Karyotyping showed the presence of additional chromosomal aberrations (ACAs): in group 1 in 23 % of patients, group 2 in 18 % of patients and in group 3 in 28 % of patients. All patients underwent NGS analysis of a myeloid panel consisting of 118 genes with a read depth of 200x-1000x on a MiSeq device (Illumina). The clinical significance of the identified mutations was assessed using the COSMIC, VarSome and Franklin databases. Survival was analyzed using the Kaplan-Meier method, with statistical significance assessed using the Cox-Mantel test.

Results. In the control group, pathogenic mutations were not detected. Mutations of unknown clinical significance were found in 81 % of patients. The most common mutations were found in the TET2, KMT2D and NF1 genes. In the BCR::ABL-independent resistance group, pathogenic mutations were found in 25 % of patients. Pathogenic mutations were found in the gene involved in Ras/MAPK pathway activation PTPN11, the epigenetic regulators EZH2 and ASXL1, the proto-oncogene RHOA, the transcription factor RUNX1, and the gene involved in DNA methylation DNMT3A. Mutations of unknown clinical significance were detected in all patients. The most common mutations of unknown clinical significance were found in the genes NF1, TET2, KMT2D, NOTCH2, BCR, ETV6, and ATM. In the BCR::ABL-dependent resistance group, pathogenic mutations were detected in 28 % of patients. Pathogenic mutations were found in the transcription factor RUNX1 and the epigenetic regulator gene ASXL1. Mutations of unknown clinical significance were detected in all patients. The most common mutations were found in the TET2, KMT2D, NOTCH2, ATM, ATRX, and IKZF1 genes. The presence of pathogenic mutations significantly ($p = 0.01$) reduced overall survival in the BCR::ABL-independent resistance group. The median overall survival in patients with pathogenic mutations was 43 months, while the median overall survival in patients without pathogenic mutations was 123 months. In the BCR::ABL-dependent resistance group, the presence of pathogenic mutations tended to decrease overall survival ($p = 0.07$). Mutations in the ASXL1 and RUNX1 genes are associated with an unfavorable disease outcome, which may be due to activation of the alternative signaling pathways PI3K, MAPK and JAK/STAT. The presence of ACAs reflects genomic instability, and the combination with pathogenic mutations significantly ($p = 0.04$) reduces event-free survival in the BCR::ABL-independent resistance group (Figure 1).

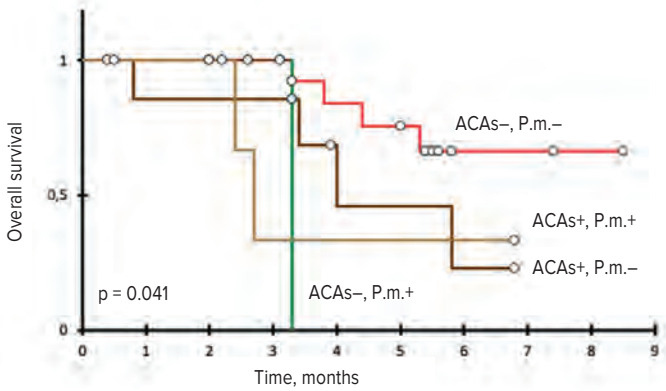

Figure 1. Overall survival

Conclusions. The molecular mechanisms underlying the development of resistance to TKIs are not only associated with the presence of mutations in the BCR::ABL kinase domain. The use of NGS allows us to identify possible pathways for the development of BCR::ABL-independent resistance and to assess disease progression. However, there remain patients in whom pathogenic mutations or additional chromosomal aberrations have not been identified, indicating the need for further research.

СЕССИЯ 4
ТРАНСПЛАНТАЦИЯ

Allogeneic hematopoietic stem cell transplantation for therapy-related myelodysplastic syndrome: a 10-year matched retrospective cohort study

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Introduction. Therapy-related myelodysplastic syndrome (t-MDS) has poor prognosis and requires allogeneic hematopoietic stem cell transplantation (HCT).

Objectives. In this study, we evaluated the effect of HCT on the outcome of patients with t-MDS and compared the key outcomes of HCT in patients with t-MDS in comparison with de novo MDS (d-MDS).

Methods. Our single-center study included 51 t-MDS patients, 16 of whom received HCT, observed at the R.M. Gorbacheva Research Institute from 2010 to 2023, with 11 patients being observed prospectively. To compare the overall survival (OS) of t-MDS patients with or without HCT, we utilized Kaplan-Meier analysis, time-dependent analysis, and a 10-month landmark analysis. The HCT t-MDS group was analyzed separately in comparison with a historical cohort of patients with d-MDS who underwent HCT. Sixteen t-MDS patients were matched to d-MDS patients. The matching factors included age at the time of HCT, IPSS-R, adverse cytogenetic risk, and donor type. We hypothesized that t-MDS and d-MDS patients may have similar 5-year OS when treated with HCT. The analysis was performed using RStudio (v2022.07.2).

Results. Table 1 summarizes characteristics of t-MDS patients. With a median follow-up of 11 months (1-116), the 2-year OS for whole group was 24 % (95 % CI 13–24 %). Factors affecting the OS of patients with t-MDS were analysed. Primary malignancy type, its status at t-MDS onset, and therapy type did not affect OS ($p = 0.23$, $p = 0.77$, $p = 0.45$, respectively). HCT was performed in 31 % (n = 16) of patients, with the median time from t-MDS diagnosis to HCT being 10 months (5–17). According to log-rang test for whole cohort (n = 51), HCT significantly improved 2-year OS (44 % (95 % CI 24–79 %) versus 10 % (95 % CI 3–31 % in non-recipients), $p < 0.001$), while in a 10-month landmark analysis (n = 28) there was just a tendency to 2-year OS improvement (58 % (95 % CI 34–100 %) versus 29 % (95 % CI 14–61 %), $p = 0.08$). Using a multivariable model in which HCT was considered as time-dependent covariate, HCT was not associated with lower risk of death compared with patients not receiv-

Table 1. The characteristics of patients with t-MDS

	n = 51
Hematological malignancy as primary malignancies, n (%)	35 (69)
Classical Hodgkin's lymphoma	12 (24)
Non-Hodgkin's lymphoma	11 (21)
Chronic lymphocytic leukemia	5 (10)
Acute myeloid leukemia	1 (2)
Acute promyelocytic leukemia	4 (8)
Acute lymphoid leukemia	1 (2)
Chronic myeloid leukemia	1 (2)
Solid malignancy as primary malignancies, n (%)	16 (31)
Breast cancer	7 (14)
Other types	9 (17)
Type of therapy, n (%)	
Chemotherapy only	24 (47)
Radiation therapy only	4 (8)
Chemoradiation therapy	23 (45)
Complete remission of primary cancer at the time of MDS diagnosis, n (%)	38 (75)
Median time from primary cancer to MDS, median in years (range)	5 (0,4–19)
Complex karyotype, n (%)	24 (47)

ing HCT (HR, 1.37; 95 % CI 0.6–2.9, p = 0.4). The OS of HCT t-MDS group did not vary by cytogenetic risk (p = 0.44), IPSS-R risk (p = 0.49) or timing of HCT within the first year of diagnosis (p = 0.6) (Figure 1).

Regarding the comparison of HCT outcomes in t-MDS and d-MDS, in total, 16 t-MDS and 48 d-MDS were matched in a 1:3 ratio. Patients shared similar baseline characteristics between groups (Table 2). With median follow-up for two groups of 32 months (4–134 months), there was no difference in 5-year OS between t-MDS and d-MDS groups (27 % (95 % CI 9–76 %) versus 46 % (95 % CI 32–66 %), p = 0.52). The incidences of engraftment for neutrophil were 86 % and 88 %, for platelets were 79 % and 81 % for t-MDS and d-MDS, respectively (p > 0.05 for both). Also, the median time to neutrophil engraftment and platelet recovery was similar between the two groups: 19 and 21 days for neutrophil, 15 and 16 days for platelets for t-MDS and d-MDS, respectively (p > 0.05 for both). The incidence of acute GVHD was 31 % (n = 5) and 38 % (n = 18) in t-MDS and d-MDS groups, respectively (p = 0.87). The incidence of chronic GVHD was 31 % (n = 5) for the former and 35 % (n = 17) for the letter (p = 0.64).

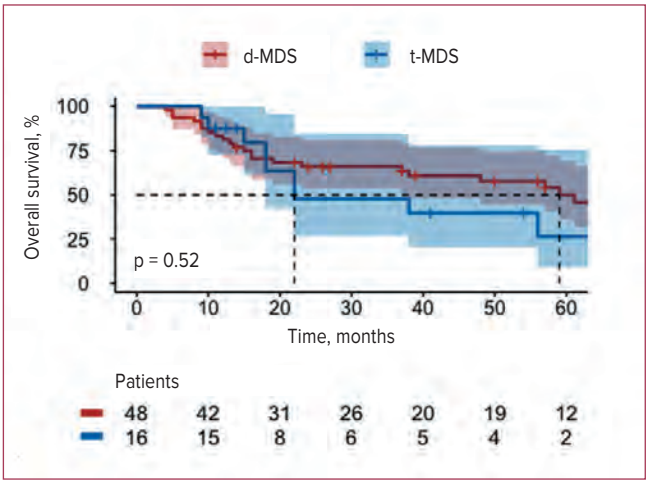

Figure 1. Overall survival

Conclusions. Although HCT appears to improve survival when assessing the group without considering the time to transplantation, the difference becomes less evident when conducting landmark and time-dependent analyses. Among MDS patients treated with HCT we observed no difference in 5-year OS and the other key outcomes between t-MDS and d-MDS when appropriately matched by propensity score. Thus, patients with t-MDS, despite being known to have an unfavorable prognosis compared to patients with d-MDS, nevertheless have comparable survival when performing HCT.

Table 2. The characteristics of HCT patients after the propensity-score matching

	t-MDS (n = 16)	d-MDS (n = 48)
Age at the time of HCT, median (range)	43 (31-59)	45 (18–76)
IPSS-R, n (%)		
Very Low and Low	2 (13)	3 (6)
Intermediate	1 (6)	9 (19)
High and Very High	13 (81)	36 (75)
Adverse cytogenetic risk (abnormal 7, complex karyotype), n (%)	11 (69)	29 (60)
HLA-matched (10/10) donor, n (%)	75 (12)	73 (35)

Biochemical markers of inflammation in the early diagnosis of infectious complications in patients with lymphoproliferative disorders after autologous hematopoietic stem cell transplantation

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Introduction. Febrile neutropenia (FN) is a common complication in patients with hematological malignancies after high-dose chemotherapy following autologous hematopoietic stem cell transplantation (autoHSCT). In fact, FN may be the only sign of infection in this cohort of patients and the use of biochemical markers of inflammation (biomarkers) can be crucial for early diagnosis and management of further infectious complications (IC). Long-term neutropenia, immune deficiency and other factors together can rapidly worsen the patient's condition, increasing the risk of developing sepsis and septic shock. Thus, it is necessary to have auxiliary op-

tions for assistance in promptly monitoring the patient's condition dynamics.

Objectives. To evaluate the diagnostic and prognostic significance of biochemical markers of inflammation, presepsin, procalcitonin and C-reactive protein, in patients with lymphoproliferative disorders after autoHSCT.

Methods. 139 patients (pts) over 18 years old were included in the study: 61 with Hodgkin lymphoma, 35 — non-Hodgkin's lymphoma, 42 — multiple myeloma and 1 with Waldenstrom macroglobulinemia; 75 — women, 64 — men. The median age was 41 years (18–66). The conditioning regimens were as follows: CBV, BEAM, BeEAC or melphalan 200 mg/m^2. Depending on the presence of infectious complications (IC) pts were divided into two groups: a group consisting of pts with IC (n = 99), and a group — without IC, or control group (n = 40). Biochemical markers of inflammation, presepsin (PSP), procalcitonin (PCT) and C-reactive protein (CRP) were assessed on the day of admission (DA), D+1 after stem cells infusion, D+3, D+7 and on the day of discharge from the hospital (DD). In the group with IC biomarkers were also assessed at the time of fever onset, 6 hours after and on the 2, 3 and 4 days after its beginning. These points could coincide with planned days of biomarkers samples assessing. The median day of fever development was 5 days (1–10) (Figure 1).

Results. CRP levels in the group with IC began to rise on D+3. Significant differences between study days were noted when comparing D+3 and D+1, D+7 and D+3, the day of discharge and D+7. In the control group the biomarker began to increase later - on D+7 the value was 34.35 mg/l. Differences were observed when comparing between D+7 and D+3 (p = 0.00000045) and DD and D+7 (p = 0.032). When comparing CRP levels between study groups there were statistically significant differences on the DA, D+1, D+3 and D+7. A comparative analysis of PCT between study days in the group of IC demonstrated a statistically significant increase of the biomarker on D+1 compared to the DA (p = 0.03) and D+7 compared to D+3 (p = 0.0005). Also there was a significant difference between the DA and D+1 (p = 0.0103) in the control group, but no differences between other study days. PCT demonstrated significant differences between the two groups at the same study points as CRP did. PSP level increase was observed starting from D+1 in the group with IC. Comparing PSP levels by study day, significant differences were observed between D+1 and the DA, D+3 and D+1, and D+7 and D+3. There was no statistical significance between the days of the study in the control group. When comparing PSP by study days between the two groups, differences were observed on days +3 and +7 and also on the DD. The study also determined the importance of biomarkers in assessing the effectiveness of antibacterial therapy and relationship between the dynamics of inflammatory biomarkers and bacteremia in pts with lymphoproliferative disorders after auto-HSCT. Antibacterial therapy efficacy was assessed in the group of pts with IC. A significant decrease in the marker level with successful antibacterial therapy indicates the ability of this marker to predict the success of antibacterial therapy and the possibility of its correction. Only PSP showed the ability to predict the effectiveness of antibacterial therapy. Significant differences were obtained in the level of PSP on the third and fourth days after the onset of fever. Bloodstream infection (BSI) was microbiologically confirmed in 21 pts (21.2 %). None of the biomarkers showed a relationship between their dynamics and BSI on standard days of the study and also at the time of fever onset and following points (Table 1).

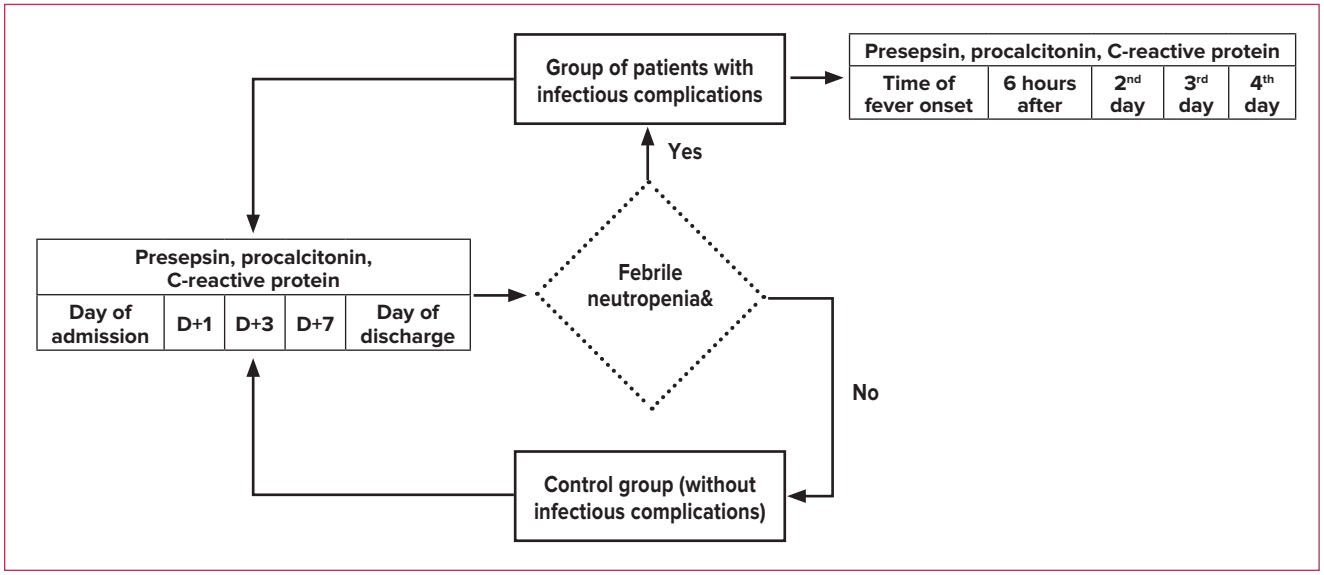

Figure 1. Study design

Table 1. Effectiveness of antibacterial therapy: presepsin dynamics (pg/ml)

PSP	Effective	Ineffective	U	Z	p-value	Z	p-value	N eff.	N ineff.
Time of fever onset	3582.5	1170.5	792.5	1.223	0.22	1.2235	0.22	69	27
6 hours after	2993.0	1193.0	715.0	–0.8	0.43	–0.797	0.43	66	24
2nd day	3332.0	1324.0	847.0	–0.52	0.6	–0.52	0.6	69	26
3rd day	3000.0	1465.0	515.0	**–2.8**	**0.005**	**–2.8**	**0.005**	69	24
4th day	3145.5	1607.5	660.5	**–2.29**	**0.02**	**–2.29**	**0.02**	69	27

Conclusions. The data showed that biomarkers of inflammation can be useful in the diagnosis of IC in patients with lymphoproliferative disorders after autoHSCT. Although none of them have superior diagnostic value for FN. PSP seems to have prognostic significance in antibacterial therapy therapy effectiveness assessment. There is no relationship between the biomarkers dynamics and bacteremia.

Comparison BeEAC vs LEAM vs CLV conditioning regimen before autologus stem cell transplantation in patients with relapsed and refractory Hodgkin lymphoma

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Introduction. High-dose chemotherapy (HDCT) followed by autologus stem cell transplantation (ASCT) is the gold standard of treatment for patients with refractory and relapsed Hodgkin lymphoma (R/R HL). Conditioning regimen plays a main role in auto-HSCT. Retrospective comparisons of different conditioning regimens before ASCT remain relevant for assessing efficacy and toxicity, and can optimize approaches to ASCT in the absence of randomized studies.

Objectives. Comparison of toxicity and efficacy conditioning regimens (BeEAC, LEAM, CLV) before autologus stem cell transplantation in patients with relapsed and refractory Hodgkin lymphoma.

Methods. In retrospective study were included 279 patients with HL, median age 30 years; 121 men and 158 women. All patients received HDCT and ASCT in National Medical and Surgical Center named after N.I. Pirogov (2006–2018). Conditioning regimens: CLV (cyclophosphamide, lomustine, etoposide) — 78 patients, LEAM (lomustine, etoposide, cytarabine, melphalan) — 129 patients, BeEAC (bendamustine, cytarabine, etoposide, cyclophosphamide) — 72 patients. Baseline characteristics of the patients enrolled in the study Table 1.

Results. Hematologic toxicity of different regimens (CLV, LEAM, BeEAC). All patients developed grade IV neutropenia, anemia with/without transfusion necessity, severe thrombocytopenia with transfusion requirements in most cases. Duration of neutropenia was the same — 8 days. Duration of thrombocytopenia in CLV regimen — 9 days, LEAM and BeEAC — 11 days ($p = 0,03$). Anemia Grade II (median) was identified in CLV, Grade III (median) in LEAM and BeEAC regimens ($p > 0,05$). Non-hematologic toxicity presented in Table 2. The development of severe mucositis of the oral cavity and other localizations dominated in LEAM. Cardiotoxicity was more prevalent in BeEAC. There were no significant differences in liver toxicity, pulmonary toxicity, renal toxicity, or infectious complications in different regimens. Efficacy of condition regimens. The highest rate of complete response after HDCT and auto-HSCT was in BeEAC ($p < 0.001$). The lowest overall survival was observed in the LEAM group (Figure 1). Progression-free survival was comparable in all groups (Figure 2). Transplant-related mortality (until D + 30) was: CLV — 1,3 %, LEAM — 3,1 %, BeEAC — 2,8 %. ($p > 0,05$).

Conclusions. HDCT followed ASCT is the best therapeutic approach for a R/R HL. BeEAC, LEAM and CLV conditioning regimens being considered as viable alternatives. Differences in the non-hematological toxicity profile of these regimens may serve as a criterion for personalized choice of conditioning regimen in patients with different comorbidities. Our results suggest more higher efficacy

Table 1. Characteristics of the patients enrolled in the study

Characteristics	BeEAC (n = 72)	CLV (n = 78)	LEAM (n = 129)
Sex			
Female	35 (48,6 %)	48 (61,5 %)	75 (58,1 %)
Male	37 (51,4 %)	30 (38,5 %)	54 (41,9 %)
Treatment before ASCT			
Chemotherapy	32 (44,4 %)	22 (28,2 %)	65 (50,4 %)
Chemotherapy and radiotherapy	40 (55,6 %)	56 (71,8 %)	64 (49,6 %)
Number of pervious chemotherapy lines			
1 line	1 (1,4 %)	1 (1,3 %)	2 (1,6 %)
2 lines	28 (38,9 %)	27 (34,6 %)	43 (33,3 %)
3 lines	17 (23,6 %)	29 (37,2 %)	45 (34,9 %)
4 lines	26 (36,1 %)	21 (26,9 %)	39 (30,2 %)
Status before ASCT			
Complete response	18 (14 %)	31 (39,8 %)	18 (14 %)
Partial response	71 (55 %)	37 (47,4 %)	71 (55 %)
Stabilization	23 (17,8 %)	9 (11,5 %)	23 (17,8 %)
Progression	17 (13,2 %)	1 (1,3 %)	17 (13,2 %)

Table 2. Non hematologic toxicity

Characteristics	BeEAC (n = 72)	CLV (n = 78)	LEAM (n = 129)
Oral mucositis			
(WHO classification)			
Grade I	18 (25 %)	14 (17,9 %)	17 (13,2 %)
Grade II	15 (20,8 %)	11 (14,1 %)	45 (34,9 %)
Grade III	6 (8,4 %)	2 (2,6 %)	6 (4,6 %)
Grade IV	1 (1,4 %)	0 (0 %)	4 (3,1 %)
Enteropathy (CTCAE 5.0 2017)			
Grade I	14 (19,5 %)	8 (10,3 %)	16 (12,4 %)
Grade II	5 (6,9 %)	3 (3,8 %)	44 (34,1 %)
Grade III	10 (13,9 %)	2 (2,6 %)	13 (10,1 %)
Grade IV	0 (0 %)	0 (0 %)	5 (3,9 %)
Cardiac toxicity	5 (6,9 %)	1 (1,3 %)	3 (2,3 %)
Pulmonary toxicity	2 (2,3 %)	1 (1,3 %)	0 (0 %)
Renal toxicity			
I	3 (4,2 %)	16 (20,5 %)	29 (22,5 %)
II	3 (4,2 %)	9 (11,5 %)	11 (8,5 %)
III	2 (2,8 %)	1 (1,3 %)	0 (0 %)
Hepatic toxicity (CTCAE 5.0 2017)			
Grade I	12 (16,7 %)	6 (7,7 %)	8 (6,2 %)
Grade II	8 (11,1 %)	5 (6,4 %)	10 (7,8 %)
Grade III	2 (2,8 %)	1 (1,3 %)	4 (3,1 %)
Grade IV	0 (0 %)	0 (0 %)	0 (0 %)
Infection	52 (72,2 %)	53 (67,9 %)	98 (75,9 %)

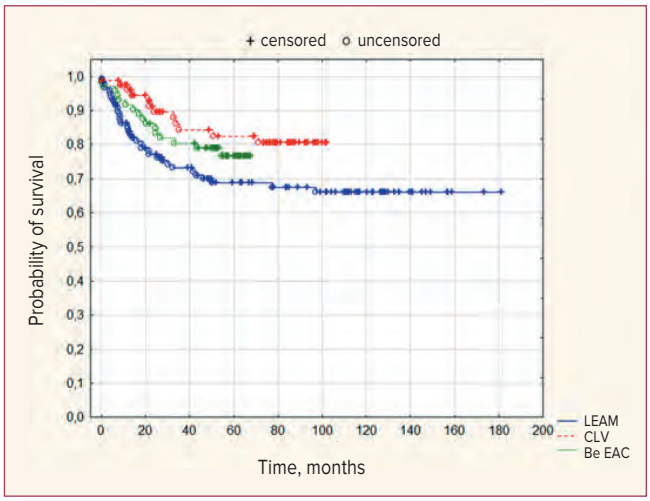

Figure 1. Overall survival (p = 0,04)

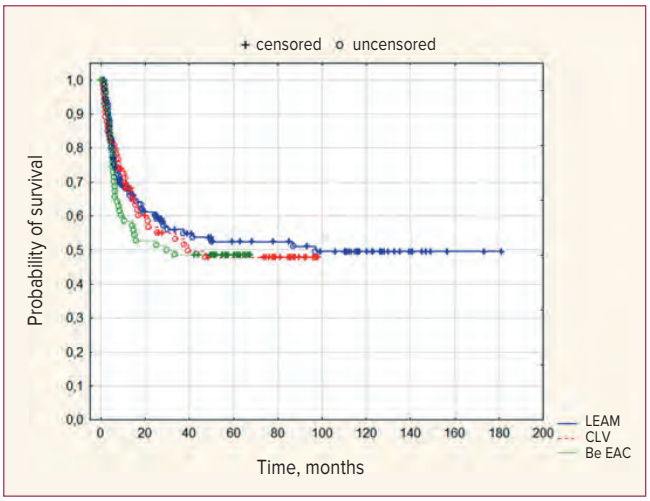

Figure 2. Progression free survival

of BeEAC conditioning in disease response. The worst OS in patients received LEAM can be explained by the fact that the regimen was used in our hospital earlier than others, when such drugs as Brentuximab vedotin and checkpoint inhibitors were not available to the patients with relapse after HDCT and ASCT.

Key words: HDCT, auto-HSCT, BeEAC, Hodgkin's Lymphoma, conditioning regimen, toxicity, transplantation. Conflict of interest: nothing to declare.

Fever in patients after haploidentical allogeneic stem cell transplantation

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Introduction. Haploidentical stem cell transplantation (haplo-HSCT) is associated with cytokine release syndrome (CRS). CRS with most cases of mild severity (grade 0 to 2) occurred in 59–89 % cases. Fever is the main symptom that presents early after haplo-HSCT. It is not pathognomonic sign of CRS or infectious diseases. Currently, there are no recommendations for the differential diagnosis of this condition after haplo-HSCT, in most cases patients are prescribed empirical antibiotic therapy (ABT).

Materials and methods. A local protocol "Fever in patients after allo-HSCT with HLA incompatibility and ATG-containing regimens" was introduced in RM Gorbacheva Research Institute since may 2020 as part of the standard operating procedure (SOP) for the stewardship of febrile neutropenia (FN) (Table 1). Protocol is used for differential diagnosis between fever of infectious origin and CRS for rationalization ABT in the first days after haplo-HSCT (D0–D+ 4). Colonization with multidrug-resistant gram-negative bacteria (MRGNB) and a previous infectious history (more than 30 days before hospitalization) were not indications for start of empirical ABT in patients who developed fever in D0–D+4. In patients who developed fever after the administration of post-transplant cyclophosphamide as part of the prevention of graft-versus-host disease on D+3, D+4, ABT was started according SOP of FN. 91 patients were enrolled in study group from May 2020 to December 2022 years, in the control group from January 2018 to May 2020 — 73 patients. The characteristics of the patients are presented in Table 2.

Results. Patient who had ABT at the moment of haplo-HSCT were excluded from the analysis: 27 patients in the study group, control group — 12 patients. Analysis of endpoints were performed in 64 patients of the study group, and 61 patients in the control group. Fever developed at D0-D+4 in 42 % (n = 27) cases of the study group, in the control group — 30 % (n = 18), p = 0.140. Colonization of carbapenem-resistant bacteria at the time of fever development was detected in 11 %

Table 1. Local protocol "Fever in patients after allo-HSCT with HLA incompatibility and ATG-containing regimens"

Clinical and laboratory signs of CRS Haemodynamic stability (tachycardia < 110 beats/min, normotension) Procalcitonin < 1 μg/l* **Without** localized infection	Without ABT Monitoring if fever persists (t > 38° C) daily: procalcitonin, lactate
Without clinical and laboratory signs of cytokine release syndrome Unstable hemodynamics (tachycardia > 110 beats/min, hypotension) Procalcitonin > 1 μg/l* Localized infection	ABT according SOP of FN (ANC < 500/mkl) ABT of localized therapy

ABT — antibiotic therapy; CRS — cytokine release syndrome; FN — febrile neutropenia; SOP — standard operating procedure.
* Level of procalcitonin — antibiotic therapy strongly encouraged

Table 2. The characteristics of the patients

Characteristics	Study group (n = 91)	Control group (n = 73)	P
	05.2020–12.2022	01.2018–04.2020	
Median age	34 (18–64)	32 (18–66)	NS
Male, n (%)	56 (61,5)	44 (60)	> 0,05
Diagnosis, n (%)			
AML	44 (48,3)	38 (53,5)	> 0,05
ALL	34 (37,4)	20 (27,3)	> 0,05
MPN	5 (5,5)	4 (5,4)	> 0,05
AA	3 (3,3)	3 (4,1)	> 0,05
Other	5 (5,5)	8 (10)	> 0,05
Relapse, n (%)	23 (25)	21 (28)	> 0,05
Conditioning regimen MAC, n (%)	50 (54,9)	44 (60,2)	> 0,05

(n = 3) and 16 % (n = 3), p = 0.592. Empirical ABT was prescribed in 7.4 % (n = 2) on D+2 in study group (lactate - 5.6 mmol/l (n = 1) and procalcitonin > 2 μg/l (n = 1)) and in 100 % (n = 18) cases on D0-D+4 in the control group, p < 0.001. Median lactate level at the time of development fever on D0 — 1.1 (0.6–1.8) mmol/l, D+1 — 1.1 (0.8–5.6) mmol/l, D+ 3 — 0.9 (0.8–1.2) mmol/l. Median procalcitonin level on D0 — 0.546 (0.144–0.840) μg/l, D+1 — 0.156 (0.141–0.4) μg/l, D+2 — 0.760 (0.15–2.6) μg/l, D+3 — 0.141 (0.141–0.143).

FN requiring empirical ABT in the study group occurred in 88 % (n = 22). The median day of development of FN after haplo-HSCT was 10 (5–14) days. Bloodstream infection (BSI) developed in 33 % (n = 9) in the study group and 44 % (n = 8) in the control group, p = 0.452. The median day of development of BSI after haplo-HSCT is 14 (5–18) vs 15 (3–30) days, respectively.

Overall survival during 30 days after haplo-HSCT in patients who developed fever in D0-D+4 in study and control groups was 100 % vs 78.9 %, p = 0.013 (Figure 1).

Conclusions. Implementation of a protocol for the differential diagnosis of fever in D0-D+4 to limit the use antibacterial therapy (p < 0.001). The rate of bloodstream infection was the same in the study group and the control group (p = 0.452). Overall survival during 30 days was better in the study group — 100 % (p = 0,013).

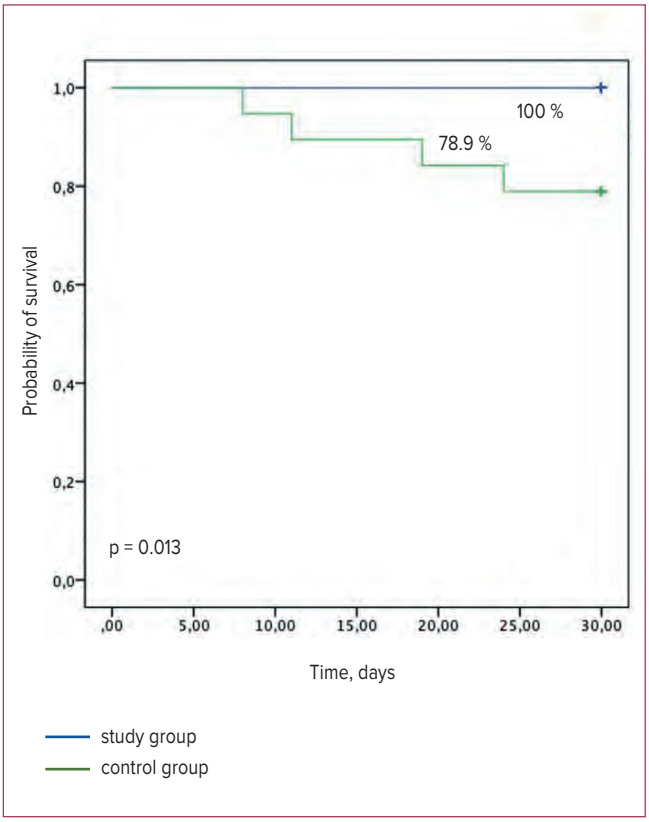

Figure 1. Overall survival during 30 days after haplo-SCT

Efficacy and safety of bendamustine-containing conditioning regimen prior to haploidentical allogeneic hematopoietic stem cell transplantation

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Introduction. As haploidentical hematopoietic stem cell transplantation (haplo-HSCT) technology has lately became more accessible, it became a feasible option for many patients with life-threatening conditions lacking completely matched related/unrelated donor. However, there is still a problem of primary graft failure (PGF) as it is associated with transplant-related mortality due to prolonged agranulocytosis and infections. Fludarabine (Flu) combined with busulfan (Bu) is a widely used conditioning regimen for allo-HSCT. There is, however, data on possible advantages of alternative regimen consisting of Flu and bendamustine (Be) in patients with chronic lymphocytic leukemia as it provides effective T-cell depletion and high engraftment rate even in haplo-HSCT recipients. Therefore, addition of Be to standard FluBu conditioning regimen may be an effective option in patients with highest PGF risks.

Objectives. This study aimes to evaluate the efficacy of Be combination with Flu and Bu containing conditioning regimen prior to haplo-HSCT for patients (pts) with malignant conditions transplanted in complete remission (CR).

Materials and methods. The study (NCT04942730) is prospective and currently includes 42 pts (Table 1). All pts received FluBuBe (Flu 30 mg/m^2 D-7, -6, -5, -4, -3, -2; Be 130 mg/m^2 D-7, -6; Bu dose depended on patient's age and performance status); the graft versus host disease (GVHD) prophylaxis regimen consisted of cyclophosphamide, tacrolimus and mycophenolate mofetil.

Results and discussion. The 1-year overall survival and event-free survival were 66 % (95 % CI 49.4–88.1) and 63.2 % (95 % CI 46.6–85.8), respectively. Probability of engraftment was 95 % (95 % CI 79–99), with 1 case of PGF reported. The median time to neutrophil and platelet engraftment were 21 (14–31) and 22.5 (11–85) days respectively. One-year cumulative relapse rate and relapse-free mortality were 10 % (95 % CI 2.4–26) and 26 % (95 % CI 11–45) respectively. Grade I–II acute GVHD was seen in 30 % (95 % CI 16–46) and Grade III–IV acute GVHD in 10 % (95 % CI 3.1–25) of cases.

Early post-transplant complications included: cytokine release syndrome with a cumulative incidence of 33 % (95 % CI 20–48), including 1 case of lymphohistiocytic syndrome; 1 case of veno-occlusive liver disease. Most common complications were bacterial infection seen in 79 % (95 % CI 61–90) of patients with sepsis developing in 30 % (95 % CI 16–46) of cases; invasive mycosis — 20 % (95 % CI 8.4–35) and viral reactivation —

Table 1. Patients' characteristics

Characteristic	n (%)	N
Sex		43
Male	19 (44.2)	
Female	23 (55.8)	
Median age (range)	41 (18–68)	43
Diagnosis		43
Acute myeloid leukemia	21 (48.8)	
Acute lymphoblastic leukemia	14 (32.5)	
Mixed phenotype acute leukemia	1 (2.33)	
Chronic myeloid leukemia	2 (4.65)	
Hodgkin lymphoma	1 (2.33)	
Myelodysplastic syndrome	2 (4.65)	
Non-Hodgkin lymphomas	1 (2.33)	
Status at transplant		39
CR 1	16 (40)	
CR 2–4	23 (60)	
Minimal residual disease		36
MRD+	24 (66.7)	
MRD–	12 (33.3)	

81 % (95 % CI 56–93) including cytomegalovirus infection 51.7 %, herpes virus type 6 41.4 %, Epstein-Barr virus 6.9 %.

Conclusions. The primary endpoint of the study was reached: the rate of engraftment and the rate of hematological recovery after haplo-HSCT were assessed. The addition of Be to FluBu in conditioning regimen was associated with low PGF incidence, although this combination was also characterized by toxicity resulting in high rate of infectious complications. We plan to further evaluate secondary endpoints within the ongoing study. Depending on results obtained a randomized trial may also be initiated.

Colonization by multidrug-resistant gram-negative bacteria in acute and chronic graft-versus-host disease

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Introduction. GVHD increases the risk and severity of infectious complications (IC) [1]. Colonization by MDR gram-negative (GN) bacteria correlates with a higher incidence of IC [2]. Currently, there are no widely accepted guidelines for empirical antibiotic therapy in patients with GVHD.

Objectives. To evaluate colonization of MDR GN bacteria in patients with acute and chronic GVHD, focusing on epidemiology, impact on IC incidence and outcomes.

Materials and methods. We performed analysis of IC from the onset of GVHD to the follow-up date [3]. Single center retrospective study included 131 and 128 adult patients with acute and chronic GVHD with median follow-up time 513 days (22–2688) and 1160 days (176–2854) after allo-HSCT respectively (Table 1). The analysis was carried according to the EBMT statistical recommendations.

Results. *Acute GVHD.* Incidence of colonization by ESBL-producing GN bacteria was 75.5 % (n = 99), CR-producing GN bacteria was 32 % (n = 42). Colonization was predominantly represented by Klebsiella pneumoniae (n = 52, 53 %), Escherichia coli (n = 15, 15 %).

The CI of GN bacterial infections was 28.2 % (95 % CI 20.8–36.1) and predominantly was caused by Klebsiella pneumoniae (n = 27, 71 %).

Presence of ESBL colonization significantly increases CI of GN bacterial infections: 33.3 % (95 % CI 24.3–42.6) vs 12.5 % (95 % CI 3.9–26.2), p = 0.0192, as well as CR colonization: 42.9 % (95 % CI 27.8–57.1) vs 21.3 % (95 % CI 13.5–30.3), p < 0.01.

The CI of GN bloodstream infections (BSI) is 12.9 % (95 % CI 7.9–19.3). We found no significant impact of the colonization variant nor ESBL (p = 0.18), or CR (0.16) on CI of BSI. Etiology presented by Klebsiella pneumoniae (n = 14, 82 %), Pseudomonas aeruginosa (n = 2, 12 %), Acinetobacter sp. (n = 1, 6 %).

Among patients diagnosed with BSI (n = 17) culture match between pathogen and colonization was 10 of 17 cases (59 %), matching mechanism of resistance: 8 out of 17 (47 %), death due to sepsis occurred in 16 of 17 cases (94 %).

Only presence of CR colonization significantly increases one-year non-relapse mortality (NRM): 38.4 % (95 % CI 23.9–52.8) vs 20.3 % (95 % CI 12.7–29.3), p = 0.0286.

Chronic GVHD. Incidence of colonization by ESBL-producing GN bacteria was 65.6 % (n = 84), CR-producing GN bacteria was 26.5 % (n = 34). Colonization was represented mostly by Klebsiella pneumoniae (n = 34, 63 %) and Escherichia coli (n = 14, 17 %).

The CI of GN BI was 16.9 % (95 % CI 10.9–24.1) and predominantly was caused by Klebsiella pneumoniae (n = 9, 39 %), Pseudomonas sp. (n = 5, 22 %) and Escherichia coli (n = 5, 22 %).

Presence of ESBL colonization significantly increases CI of GN BI: 22.2 % (95 % CI 13.9–31.8) vs 6.8 % (95 % CI 1.8–16.7), p = 0.0373. But there was no significant impact of CR colonization on CI of GN BI, p = 0.19.

The CI of GN BSI is 4.7 % (95 % CI 1.9–9.5). Presence of CR colonization significantly increases CI of BSI: 14.8 % (95 % CI 5.4–28.7) vs 1.0 % (95 % CI 0.1–5.2), p < 0.01.

Among patients diagnosed with BSI (n = 7) culture match between pathogen and colonization was 5 of 7 cases (71.5 %); matching mechanism of resistance: 6 out of 7 (86 %); death due to sepsis occurred in 5 of 7 cases (71.5 %).

There was no significant impact of colonization on outcomes in the cGVHD group.

Conclusions. In aGVHD group: presence of any MDR GN colonization significantly correlates with the higher CI of

Table 1. Patients' characteristics

	Acute GVHD group (n = 131)	Chronic GVHD group (n = 128)
Age, median (range), years	37 (18–67)	37 (18–67)
Sex, n (%)		
Male	64 (48.9)	67 (52.3)
Female	67 (51.1)	61 (47.7)
Standard	85 (64.9)	102 (79.7)
Salvage	46 (35.1)	26 (20.3)
Donor, n (%)		
Haplo	24 (18.3)	8 (6.2)
MRD	17 (13.0)	32 (25.0)
MUD	53 (40.5)	59 (45.9)
MMUD	37 (28.2)	29 (22.9)
Stem cell source, n (%)		
PBSC	100 (76.3)	70 (54.7)
BM	31 (23.7)	58 (45.3)
Conditioning regimen, n (%)		
RIC	114 (87.0)	104 (81.2)
MAC	17 (13.0)	24 (18.8)
GVHD grading, acute/chronic GVHD, n (%)		
2/I	63 (48.0)	25 (19.5)
3/II	55 (42.0)	55 (43.0)
4/III	13 (10.0)	48 (37.5)
Follow-up, median (range), days	513 (22–2688)	1160 (176–2854)

GN bacterial infections; presence of any MDR GN colonization did not affect the CI of GN bloodstream infections; CR colonization significantly increases 1-year NRM.

In cGVHD group: presence of ESBL GN colonization significantly correlates with the higher CI of GN bacterial infections; presence of CR colonization significantly correlates with the higher CI of GN bloodstream infections; MDR GN colonization did not significantly affect 3-year OS and NRM.

References

1. Miller HK, Braun TM, Stillwell T et al. Infectious Risk after Allogeneic Hematopoietic Cell Transplantation Complicated by Acute Graft-versus-Host Disease. Biol Blood Marrow Transplant. 2017;23(3):522–528. doi:10.1016/j.bbmt.2016.12.630.

2. Cattaneo C et al. Bloodstream infections in haematological cancer patients colonized by multidrug-resistant bacteria. Ann Hematol. 2018;97(9):1717–1726. doi: 10.1007/s00277-018-3341-6

3. Инфекционные осложнения в онкогематологии. Диагностика и лечение. Гематология и трансфузиология. 2023;68(2):12.

СЕССИЯ 5
БИОЛОГИЯ

Transcriptomic sequencing data as a tool for verifying biomarkers of the effectiveness of oncolytic therapy in combination with assessing the reproduction of oncolytic viruses in B-cell lymphoproliferative diseases

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Introduction. Despite the introduction of targeted therapy and significant advances in the treatment of tumors of the lymphatic system, the problems of drug resistance and ineffectiveness of therapy remain extremely relevant. One option for a personalized approach in resistant cases is the use of oncolytic viruses in combination and/or in combination with targeted therapy.

Objectives. Conducting and evaluating the results of full-transcriptome sequencing of samples of primary short-term cultures of lymphoid nature to identify genes and signaling pathways that affect the efficiency of viral replication.

Methods. Transcriptome sequencing to assess differentially expressed genes was performed on the Illumina HiSeq platform, using applications for analyzing gene list enrichment — the DAVI database with the KEGG database included in it. Replicative capacity was assessed in 54 primary short-term cultures of B-cell lymphoproliferative disorders. The strains of oncolytic viruses included in the study are LEV14, (live enterovirus vaccine 14 — a strain related to Coxsackie B5), Echovirus 12 (ECHO12), (PV1S) — vaccine strain of poliovirus type 1, (Sabin), Coxsackie A7 (CVA7), Coxsackie B6 (CVB6) and vesicular stomatitis virus, Indiana strain (VSV-I).

Results. In our study, when assessing the replication ability, primary short-term lymphoid cultures most efficiently replicated strains LEV14, ECHO12 and PV1S, which is presented in the heat map (Figure 1). A number of signaling pathways are involved in the replication of oncolytic viruses. About 2 thousand signaling pathways have been analyzed. The analysis of differentially expressed genes of cultured lymphoid tumor cells that are and are not capable of efficient replication of oncolytic strains, followed by enrichment analysis, revealed key signaling pathways that take part in the process of viral oncolysis. This is the endocytosis, RIG -receptor, MAPK signaling pathway. One of the fundamental sig-

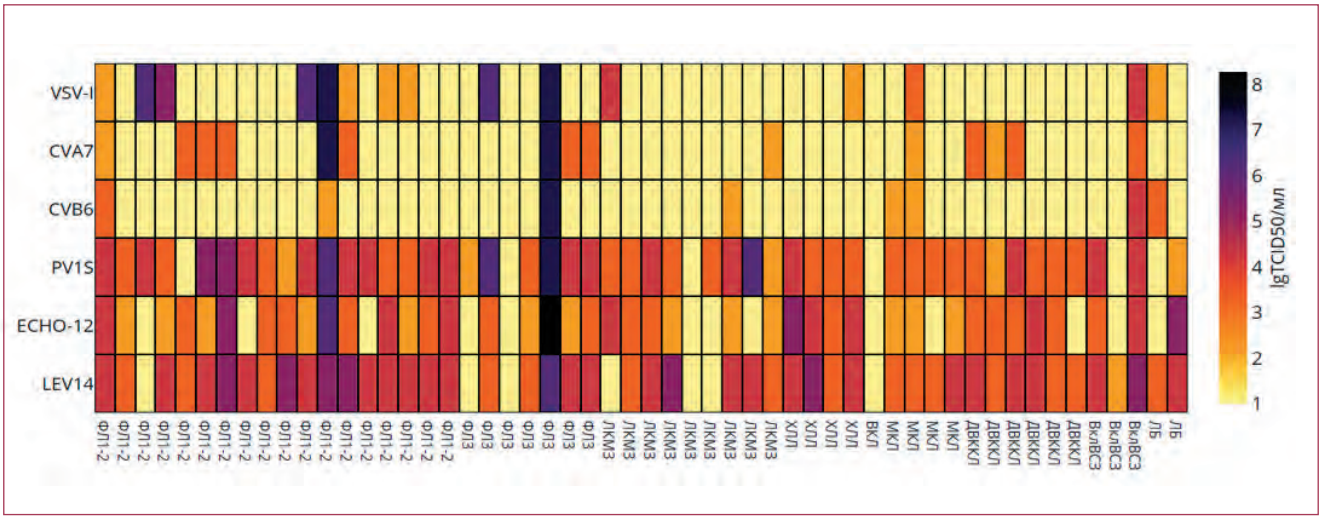

Figure 1. Heatmap. The color scale reflects the efficiency of viral replication in short-term culture samples. Scale from 1 (yellow) to 8 (purple) lgTCID 50/ml

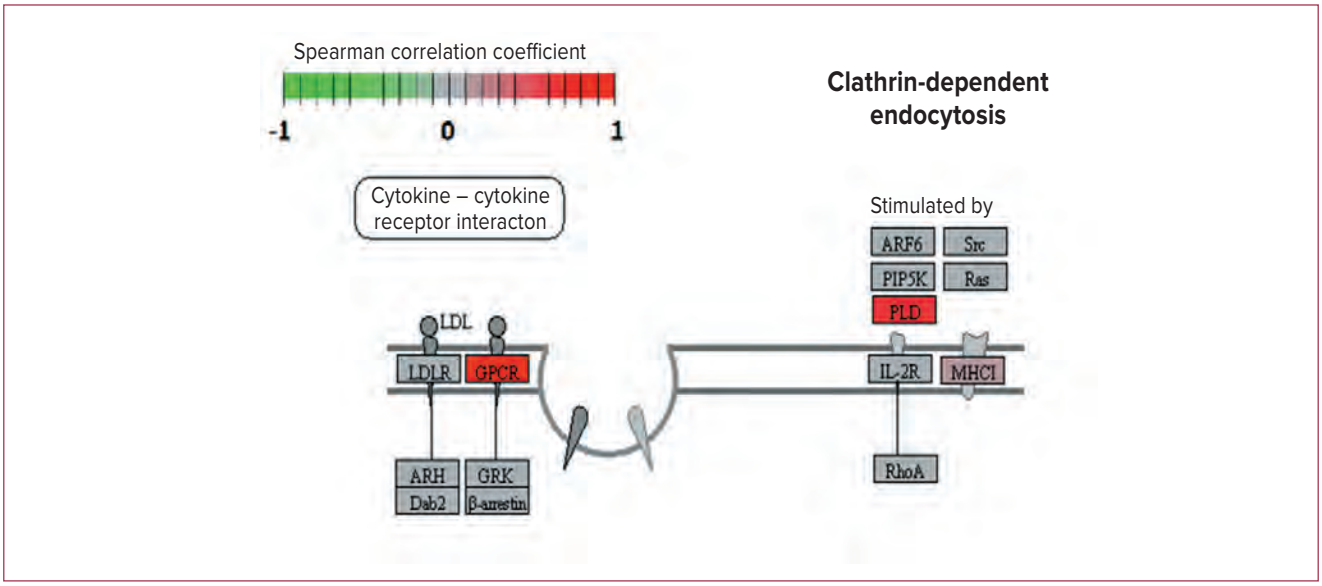

Figure 2. Endocytosis signaling pathway (p = 0.005)

naling pathways is the endocytosis pathway (Figure 2), it regulates the number of receptors functioning on the surface of cells. Receptors differ in their ability to undergo regulated endocytosis and can selectively enter into various clathrin-dependent and clathrin-independent interactions, so a decrease in the number of receptors present on the cell surface causes a weakening of the cell's sensitivity to an extracellular ligand. Expression of genes involved in the endocytosis signaling pathway PLG2 and GPCR are a key link in this signaling pathway. It is worth noting the important role of phospholipase D2 (PLD2); its high level of expression is associated with the ability of enteroviruses to replicate effectively in tumor cells (p = 0.012). Knockout of this gene in model cell lines resulted in the inability of enteroviruses to replicate effectively in these cells. In addition, among the important molecular genetic determinants, a G protein-coupled receptor (GPCR) was identified, which functions to activate intracellular signal transduction pathways (p = 0.005).

Conclusions. Assessment of differentially expressed genes and involved signaling pathways is one of the effective tools for studying the mechanisms of viral oncolysis in tumor cells of lymphoid origin and identifying the most optimal approaches to influence the tumor substrate. The results obtained indicate that the replication of the virus, which is highly sensitive to tumor cells of various histological origins, involves several signaling pathways that, to varying degrees, influence replication and its significance in the life of the cell. The set of interactions between signaling pathways and the genes involved in them plays a key role in the effects of the virus on the cell.

Key words: lymphoma, signaling pathway, cell culture.

Determination of mutation profile of acute promyelocytic leukemia using high-throughput sequencing (NGS)

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Introduction. Acute promyelocytic leukemia (APL) is a subtype of acute myeloid leukemia characterized by proliferation in the bone marrow of leukemic cells that morphologically resemble atypical promyelocytes and carry the t(15;17) translocation or its minor variants. It has been established that t(15;17) is found in CD34+ myeloid progenitor cells and thus represents an early event in leukemogenesis. At the same time, with the development of APL, additional gene mutations arise, which can cause clonal heterogeneity and differences in the clinical course of the disease.

Objectives. The aim of the study was to characterize the mutation profile of tumor cells in adult patients with APL using high-throughput sequencing (NGS).

Methods. Bone marrow samples from 4 patients with a verified diagnosis of APL, observed at the Sverdlovsk Regional Oncohematology Center were studied. The median age of patients was 44.3 years. All patients underwent standard karyotyping and determination of t(15;17) using the polymerase chain reaction (PCR) for chimeric PML-RARA transcripts. In two cases, in the absence of a significant result of standard karyotyping, fluorescent in situ hybridization (FISH) with a marker probe was additionally performed. The mutational status of 141 genes was determined on a MiSeqDX sequencer using the QIAseq Targeted DNA Human Myeloid Neoplasms Panel.

Results. The karyotype of leukemic cells in one case was normal, in another case unspecified due to the absence of mitoses, and in the rest two samples t(15;17) was detected by FISH. In all cases transcripts of the chimeric gene *PML-RARA* were determined by PCR with the median level of relative expression of 7.0 %. Leukemia-associated gene mutations were identified by NGS in only three cases. The median number of identified mutations was 3.0 (range from 1 to 6). Most frequently mutations were detected in the FLT3 and NRAS genes (n = 2), with one case each in *CALR*, *RUNX1*, and *WT1*. All patients were treated with regimens containing all-trans retinoic acid. One patient died from COVID-19 infection during induction of remission, 2 patients developed relapses, and in 1 case a stable long-term remission was observed. Relapses were detected both in the presence of leukemia-associated mutations in genes associated (c.35G>T in the *NRAS* gene) and in a patient in whom NGS did not reveal additional clinically significant mutations.

Conclusions. Thus, according to NGS typing, the mutational profile of APL is heterogeneous. Patients with various gene mutations may be candidates for differentiated treatment methods, including clinical trials of targeted drugs aimed at specific molecular targets.

The role of aberrant cytokine secretion in tyrosine kinase treatment failure in patients with chronic myeloid leukemia

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Introduction. Cytokines are mediators of vast amount of intercellular interactions which regulate proliferation and programmed cell death in cancer cells. Results from previous studies showed that aberrant cytokine secretion may contribute to blockade of cancer cells apoptosis and evading the targeting by current therapies. In this regard, evaluation of the cytokine profile of patients with chronic myeloid leukemia (CML) and their correlation with expression of proteins regulating proliferation, apoptosis and intracellular transport of drugs is a cutting-edge research, which enables to improve understanding the mechanisms of tumor progression, as well as the development of therapy resistance in patients with CML.

Objectives. The study aim was to investigate serum cytokine levels in patients with CML, and the possible use of these data in the prediction of therapy effectiveness.

Methods. 74 patients with chronic phase CML were enrolled in this study. Mean age was 54 ± 14 years (95 % CI 50–57). Quantification of serum concentration of cytokines (TNF-α, IL-1β, IL-2, IL-4, IL-6, IL-10, IL-17, IL-18, IFN-α, VEGF-A) using enzyme-linked immunosorbent assay and expression level of p53, c-Myc, p-glycoprotein was performed. First line tyrosine kinase therapy (TKI1) with imatinib was administered to 48 (64,9 %) patients, TKI2 therapy to 26 (35,1 %) patients. 50 (67,6 %) of patients managed to achieve major molecular response (MMR) with median follow-up time 4 years (1–9). Statistical analysis was carried out using the StatTech program v. 3.0.6. Mann-Whitney U test used for comparing differences between two independent groups. Correlation analysis between two quantitative indicators was carried out using Spearman's rank correlation coefficient. To investigate factors influencing the effectiveness of TKI therapy in CML patients logistic regression and ROC analysis were performed. A p value < 0,05 was considered significant.

Results. Identifying treatment failure predictors with respect to achieving MMR with TKI demonstrated multidirectional effect of proinflammatory and anti-inflammatory cytokines on cancer cell elimination (Figure 1). Thus, patients who did not achieve MMR, showed significantly higher concentration of proinflammatory cytokines, which may lead to DNA damage, mutation accumu-

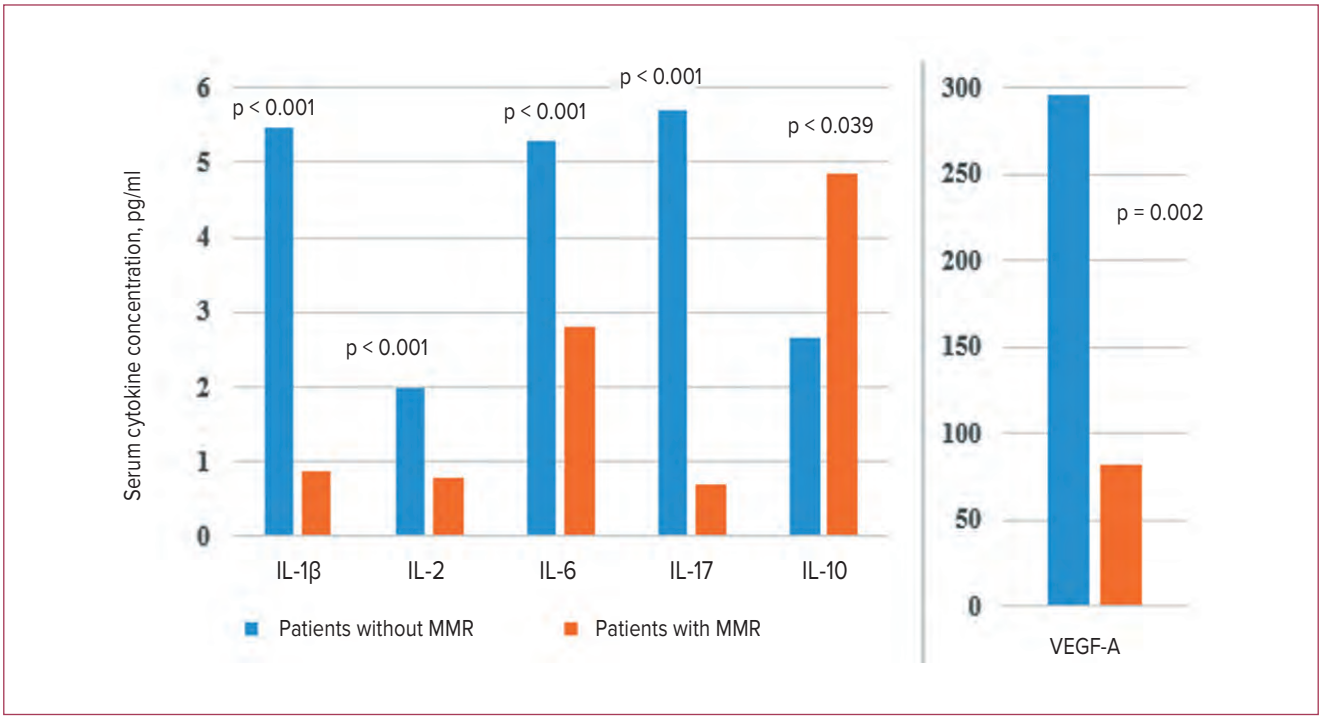

Figure 1. Serum cytokine serum concentrations in CML patients with MMR and without MMR

lation and selection of TKI-resistance cancer cells, and vascular endothelial growth factor VEGF-A, which may lead to the dissemination of malignant cells and development of sites of extramedullary hematopoiesis. Bone marrow samples of patients with CML without MMR revealed a significantly lower expression level of c-Myc (2 (1–5) % vs 9 (6–11) %, $p < 0.001$) and p53 (2 (2–3) % vs 7 (5–8) %, $p = 0.011$) and, on the contrary, significantly higher expression of multidrug resistance protein p-glycoprotein (21 (14–31) %) compared to patients with MMR (12 (7–18) %, $p < 0.001$). The hallmark of patients without MMR was significantly higher concentration of the anti-inflammatory cytokine IL-10, which exhibits anti-oncogenic properties. The concentration of the proinflammatory cytokine IL-1β, which was one of the most significant predictors of treatment failure with TKIs (OR = 0.518, 95 % CI 0.369–0.727, $p < 0.001$), inversely correlated with the expression of c-Myc ($r = -0.933$, $p < 0.001$) and p53 ($r = -0.652$, $p < 0.001$) in bone marrow and directly correlated with of p-glycoprotein expression ($r = 0.425$, $p = 0.019$), which may indicate the synergism of these biomarkers in the mechanisms of tumor progression of CML. Results of ROC-analysis confirmed the high level of sensitivity (86, %) and specificity (80,6 %) of this method which showed very good quality of model (AUC = 0,831, 95 % CI 0,788–0,952, $p < 0,001$).

Conclusions. Overproduction of proinflammatory cytokines in CML patients is associated with the risk of not achieving MMR with TKI therapy. Inactivation of the transcription factors c-Myc and p53, as well as overexpression of p-glycoprotein, which correlate with high serum concentrations of IL-1β, may suppress the tumour cells sensitivity to TKIs due to blockade of apoptosis, cell cycle arrest and disruption of intracellular drug transport.

Differences in the proteome of multipotent mesenchymal stromal cells of patients with acute myeloid leukemia from that of healthy donors

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Introduction. In acute myeloid leukemia (AML), the functions of bone marrow stromal microenvironment are altered. Multipotent mesenchymal stromal cells (MSCs) are one of the pivotal elements of bone marrow stroma. MSC alterations occurring in AML are actively researched. Analysis of proteins that make up MSCs (MSCs' proteome) may identify new research areas for correcting MSCs function and thus restoring hematopoiesis in AML patients.

Objectives. The aim of the study was to reveal the differences between the MSC proteomes of AML patients and healthy donors.

Methods. The study was conducted on MSCs from bone marrow of 3 female AML patients and 3 healthy donors (1 female and 2 male). Bone marrow samples (3–5 ml) were obtained during a diagnostic puncture in patients, or exfusion in donors. All donors and patients gave the informed consent prior to sampling. To obtain mononuclear cells, bone marrow was mixed with an equal volume of αMEM medium containing 0.2 % methylcellulose (1500 cP). After 40 minutes and sedimentation of erythrocytes and granulocytes, suspended mononuclear cells were collected and culture medium was added. MSCs were cultured in αMEM medium with 10 % fetal calf serum, 2 mM glutamine, 100 U/ml penicillin and 50 mg/ml streptomycin at 37ºC and 5 % CO2. To study their proteome, MSCs at the 2nd passage were seeded into T25 or T175 flasks at 4000 cells per cm^2 of flask bottom area. When the cells reached confluence, the flasks were washed 5 times with phosphate buffer without Ca2+ and Mg2+ and cells were cultured for 24 hours in RPMI-1640 medium without serum, phenol red and antibiotics. The cells were removed with a scraper, centrifuged, and the dry pellet was frozen at -70°C. Protein analysis was performed with Orbitrap Q Exactive HF-X mass spectrometer equipped with a nano-electrospray (nano-ESI) source and a nanoflow high-pressure chromatograph (UPLC Ultimate 3000) with a C-18 reverse-phase column (100um x 300mm). The results were analyzed in Scaffold 5 (version 5.1.0) for validation and meta-analysis. STRING online service (string-db.org) and GO database (Gene Ontology) were used to characterize the identified proteins.

Results. 4062 proteins were identified in total. Of those, 813 were exclusive for AML patient MSCs and 328 were exclusive for donor MSCs. The content of proteins considered to be MSC markers — CD73 (endo-5'-nucleotidase, NT5E), CD105 (endoglin, ENG) and CD90 (THY1) was reduced in the proteome of AML patients' cells. However, according to flow cytometry data, the surface expression of CD73 and CD90 on MSCs from patients was increased, and CD105 was decreased. It is possible that fundamental differences in these research methods lead to these discrepancies in results. In MSCs of patients, the amount of proteins involved in transmembrane receptor protein tyrosine kinase signaling pathways was increased (including such receptors themselves — PDGFRA, ROR1, ephrin receptors EPHB2 and EPHA5; ligands of such receptors — FGF2, CSF1, GDF15 and others; transcription factor STAT3), which indicates the activated state of these cells (Figure 1). Those receptors are involved in the regulation of proliferation, angiogenesis, cell migration. Upregulated expression of their ligands may be important for MSCs' autocrine stimulation as well as paracrine support of malignant cells. On the other hand, the content of 43 proteins connected to Wnt signal pathway (including its key regulators PORCN and RECK) is decreased in patient MSCs' proteome compared to donor cells (Figure 2). Wnt signaling results in cytoskeleton rearrangements and gene expression, and regulates cell adhesion, migration, communication and differentiation. In particular, it is important for osteogenic differentiation of MSCs. At the same time, proteasomal proteins were downregulated in patients' MSCs (20 out of 40 PSM proteins identified were downregulated). Most of those are implicated in Wnt signaling as well. Proteasomes cleave proteins and as such are responsible for protein catabolism of the cells. They are also essential for immunological status of the cell as they provide peptides for presenting antigens in main histocompatibility complexes (MHCs, also called human leukocyte antigens or HLAs). In both MSC proteome and secretome HLA-ABC content was increased in AML. It appears that in AML, while MSCs cleave less proteins and have less antigens for presenting, they express more major histocompatibility complex molecules that do the presenting. β2-microglobulin and MIF were decreased in the MSC proteome but increased in the secretome. Complement

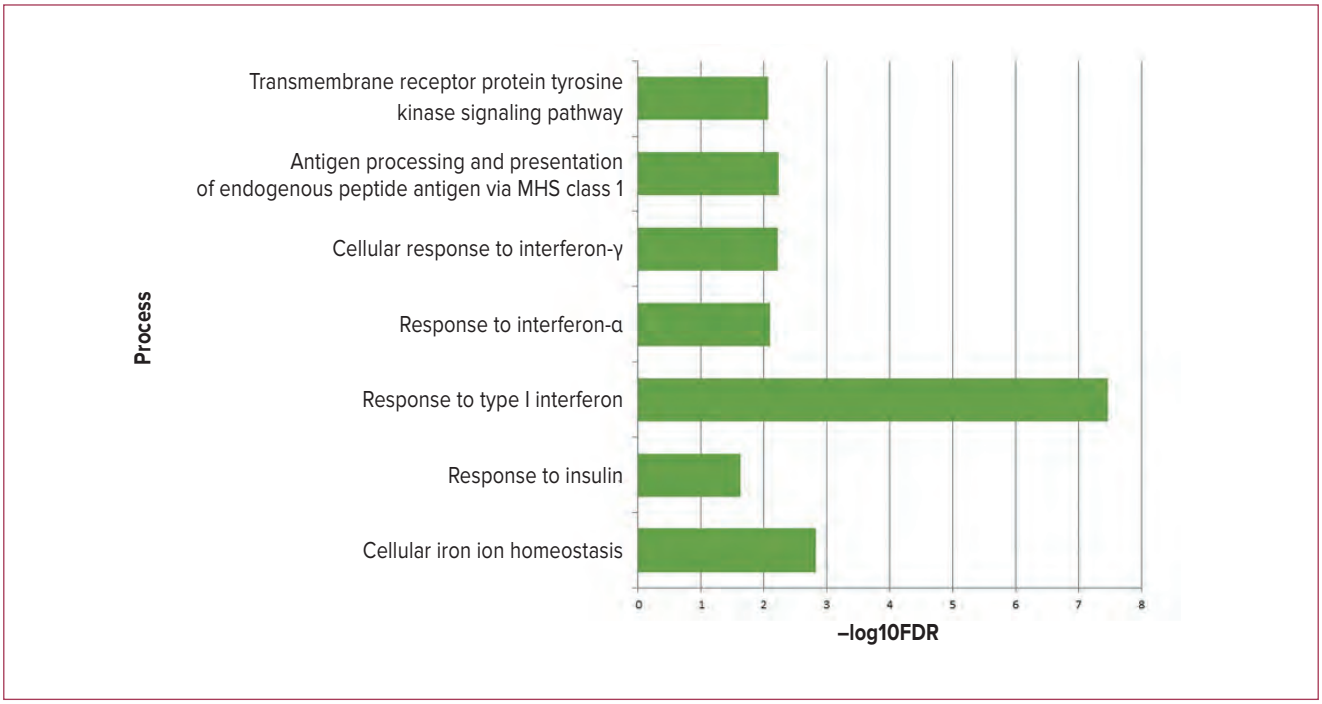

Figure 1. Some of the processes annotated in GO database the components of which were upregulated in AML patients' MSCs compared to donors'.

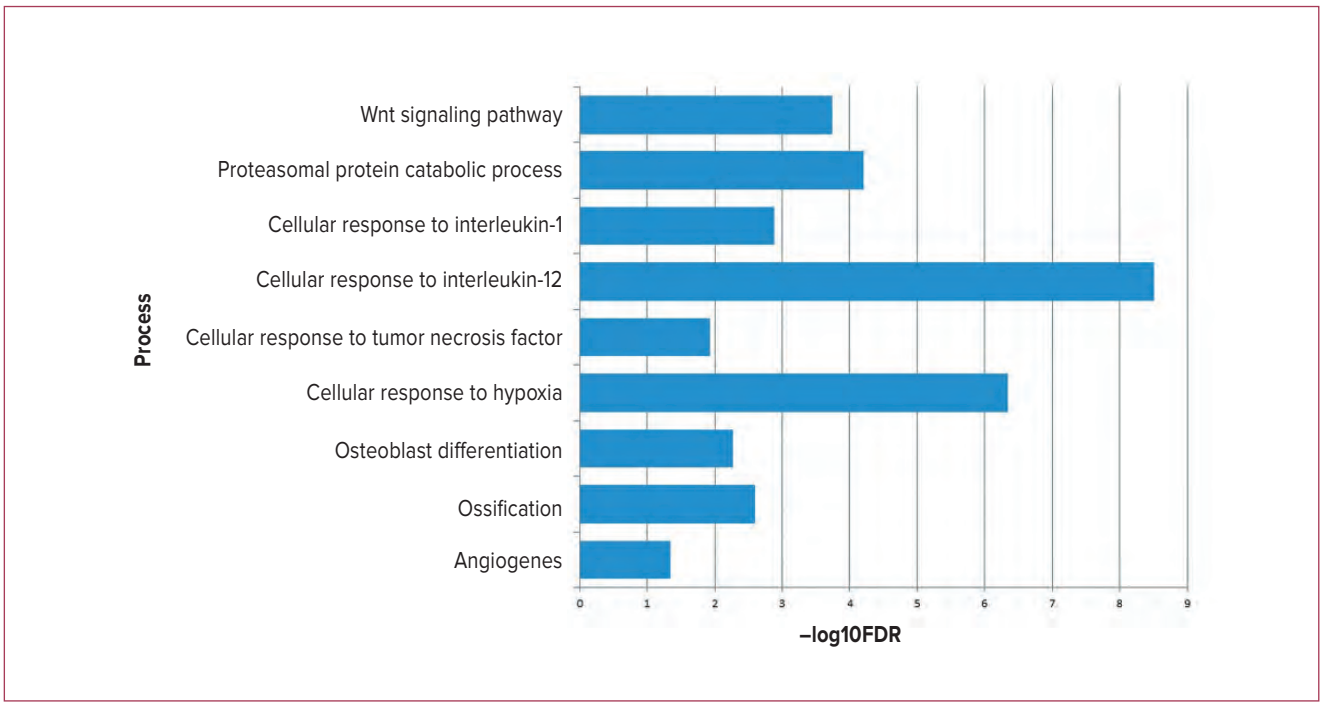

Figure 2. Some of the processes annotated in GO database the components of which were downregulated in AML patients' MSCs compared to donors'

components C1s and C3 were upregulated in MSC proteome; in secretome, C1s was upregulated as well while C3 was downregulated. In addition, in AML MSCs' proteome contained less proteins participating in responses to IL1, IL12 and TNF, important pro-inflammatory cytokines, but more proteins participating in interferon α and γ responses. This indicates that the immunological function of MSCs is altered in AML. In the secretome of patients' MSCs, the levels of proteins secreted in response to hypoxia, including CXCL12, PGC1A, POSTN, PTK2B, were significantly increased, while in the proteome the levels of POSTN and other proteins associated with the response to hypoxia were reduced (PGC1A, POSTN, PTK2B levels were not altered in proteome).

In MSCs of patients, proteins related to osteogenesis and osteogenic differentiation (various collagens — COL1A1, COL1A2, COL11A1, COL5A2, COL6A1, MMP2 metalloprotease, OSTF1 — osteoclast stimulating factor 1, necessary for bone remodeling, and others) were reduced, while proteins related to adipogenic differentiation and insulin response (VPS13C, ICAM1, TCIRG1, IDE, INPPL1, RAB8B, GSK3B, MTOR, SRC, FABP3, PTPRA, GRB2, GSTP1, MYO5A, RELA, SHC1, PDK2, C2CD5, DENND4C) were increased. These observations are supported by the decrease in components of Wnt signaling pathway, as it is essential for MSCs' osteogenic differentiation. Patients' MSCs had an increased content of proteins related to iron metabolism (SKP1, MT2A, NEDD8, IREB2, ABCB6, SRI, FTH1, NUBP1, APP, ACO1, CUL1, NEO1, SLC30A7, SLC31A1, FTL, TF, CAND1), including both heavy and light chains of ferritin, a protein responsible for transport and storage of iron ions. Iron overload is known to occur to MSCs in several hematological diseases, such as β-thalassemia and myelodysplastic syndrome. Iron-damaged MSCs cannot effectively support hematopoiesis. Another example may be the aging of the organism, when the iron accumulation increases while the proportion of MSCs obtained from bone marrow decreases. The expression of proteins associated with angiogenesis was reduced in patients' MSCs (MMP2, ITGAV, C19orf10, MCAM, CDH13, THY1, ANPEP, NCL, RTN4, CAV1, ANXA2, FN1, EPHA2, PTGS2, CTGF, RBM15, ENG, CLIC4, POFUT1, PDCD10, ITGB1, CDC42, C1GALT1, TGFBI, DAG1, ACTG1, PLCD3), which may be a consequence of excess iron, which is able to reduce MSCs' angiogenic potential.

Conclusions. The proteome of MSCs from patients with AML differs from the proteome of MSCs from healthy donors. The changes affect the main functions of MSCs — differentiation, regulation of the immune response and response to cytokines. The iron metabolism and the regulation of angiogenesis are also altered. In some aspects, changes in the proteome do not coincide with the changes in the secretome and surface phenotype of MSCs in AML. All the changes happening to MSCs are important for understanding the processes occurring in the bone marrow in AML. The study was supported by a grant from the Russian Science Foundation project № 22-15-00018, https://rscf.ru/project/22-15-00018/

Key words: acute myeloid leukemia, multipotent mesenchymal stromal cells, proteome.

Spatial transcriptomics analysis of anaplastic large cell lymphoma using Visium technology

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Introduction. Pediatric ALK+ anaplastic large cell lymphoma (ALC+ ALCL) is an aggressive and heterogeneous T-cell tumor that has a relatively favorable prognosis with chemotherapy and targeted agents. However, there are groups of patients who may remain refractory or have disease recurrence. Thus, there is a need to isolate and study the different biological patterns of this lymphoma to further improve therapeutic approaches. In addition, the role of tumor heterogeneity and immune microenvironment is largely unknown for this type of lymphoma. Modern research methods, such as next-generation sequencing and spatial transcriptomics, provide new opportunities to better understand the biology of ALCL.

Objectives. Investigate of the transcriptional profile, tumor microenvironment and cellular composition of ALK+ ALCL in children using the Visium 10x technology (USA).

Methods. Visium spatial transcriptomics data were obtained for 4 pediatric cases of ALK+ ALCL diagnosed in the pathology department of the Dmitry Rogachev National Research Center. Biopsy material from a lymph node was used as tumor material. Sequencing was performed on the NextSeq500/550 platform (Illumina, USA). The obtained data were analyzed for 2 samples using Seurat, Cell2locatian and STdeconvolve software in R and Python programming languages.

Results. For each sample, spatial transcriptomics data were analyzed, resulting in the identification of different clusters depending on the expression profile. The clustering results correlated well with morphology. Thus, clusters that correlated with the tumor and microenvironment were identified, including zones of active neoangiogenesis with increased expression of genes responsible for vascular endothelial proliferation (e.g., CD34 and VWF) in one sample and residual lymphoid structures in another sample (Figure 1). In both samples, the immune microenvironment was located at the tumor borders. Identification of spatially variable genes showed, for one sample, increased expression of the prognostically relevant FN1 gene in areas of active inflammation, and for the second sample, the presence of a stress response and zonal overexpression of heat shock proteins and ubiquitin C. Both samples were subjected to cell type deconvolution by reference and reference-free methods, which revealed a predominance among the immune microenvironment of T cells expressing the TIM3+ receptor, a marker of dysfunctional T cells subsets (Figure 2, A). A large number of Treg and macrophages (predominantly M2-compartmentalized) were also observed (Figure 2, A). The B-cell lineage was marginally represented and mainly localized in residual lymphoid structures. However, in both samples, immune cells did not infiltrate the tumor, in which we also found significant heterogeneity at the level of individual cell subpopulations (Figure 2, B).

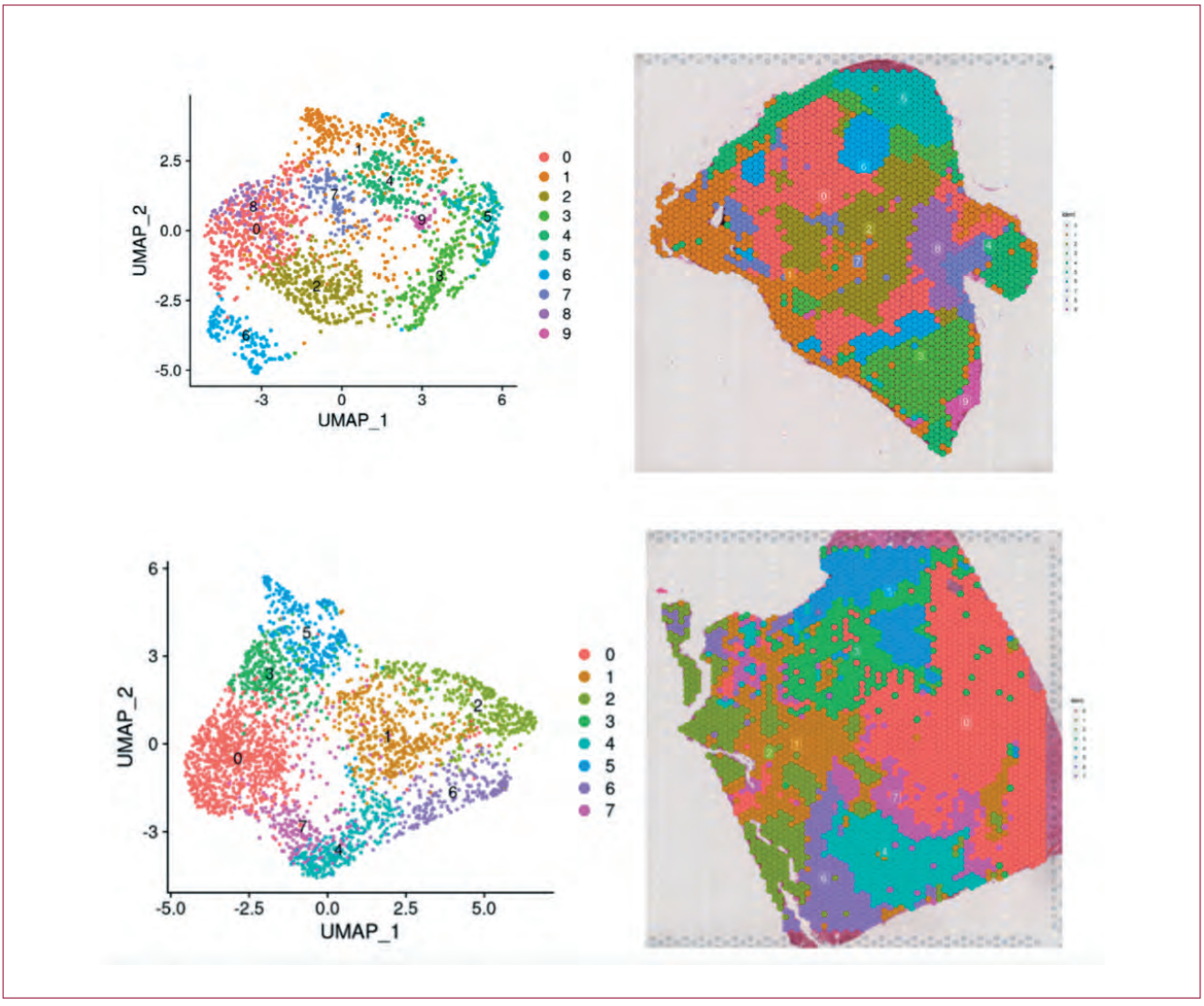

Figure 1. UMAP-plot and spatial-plot for the analyzed samples

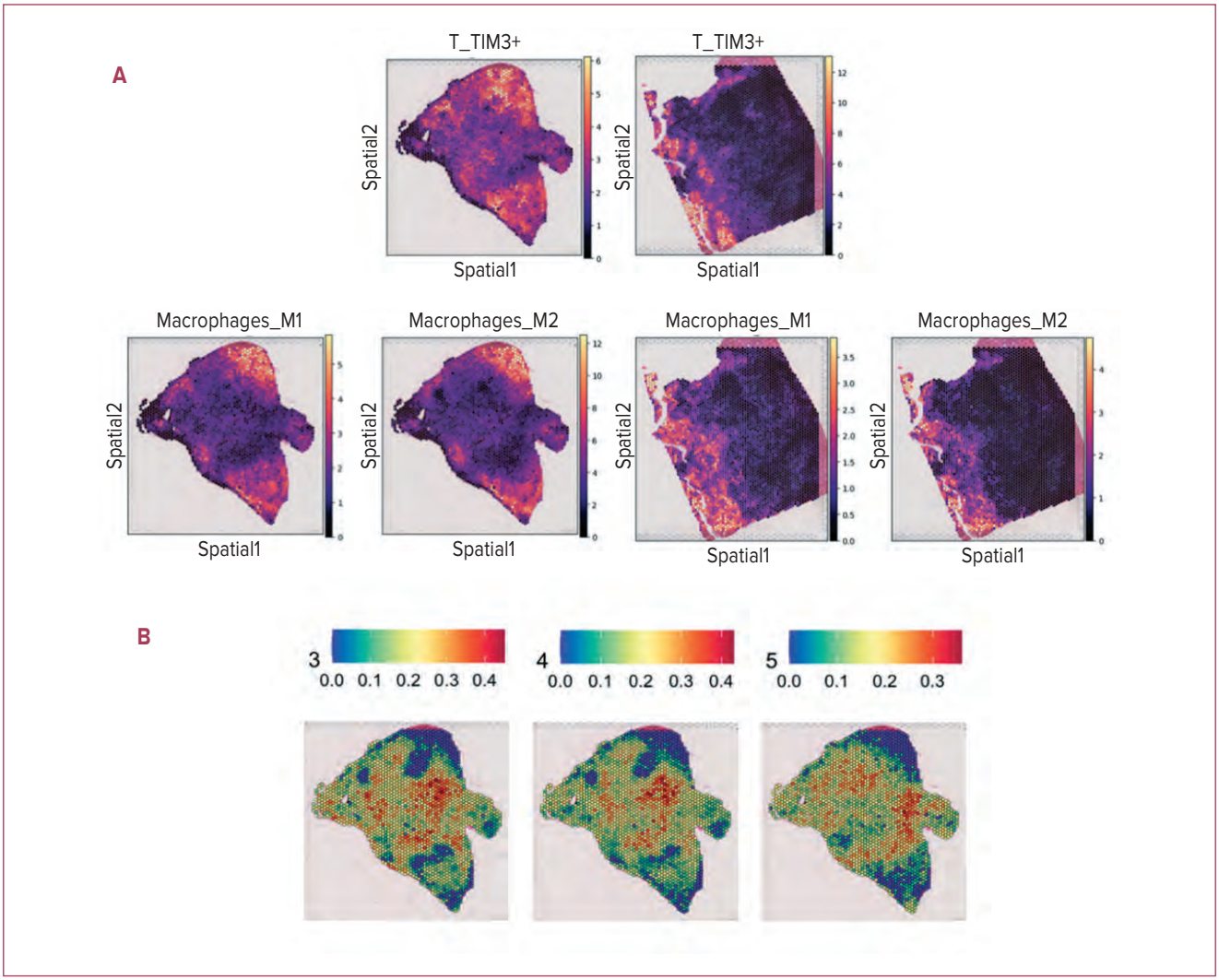

Figure 2. (A) Spatial distribution of TIM3+ T cells and M1/M2 macrophages. (B) Visualization of tumor heterogeneity. The 3 different cellular subtypes that compose the tumor are shown

Conclusions. Our results demonstrate that pediatric ALK+ ALCL is a highly heterogeneous tumor. Investigation of the immune microenvironment showed that the immune response is highly suppressed and does not effectively control lymphoma growth. We also found high expression of TIM3 molecule in T cells, which can be used as a potential target for immunotherapy.

Prognostic significance of MYC gene aberrations in lymphogenesis of mantle cell lymphoma

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Introduction. Mantle cell lymphoma (MCL) is a non-Hodgkin B-cell lymphoma characterized by particularly aggressiveness and short overall survival with frequent recurrence and low sensitivity to standard-dose intensity chemotherapy. In the vast majority of cases, patients are diagnosed with the t(11;14)(ql3;q32) translocation, which leads to increased expression of the nuclear protein cyclin D1 and disruption of cell cycle regulation. Currently, new data on the lymphomagenesis of MCL have begun to appear, devoted to the study of the role of the MYC gene. Despite the fact that translocations involving MYC are the main diagnostic criterion for Burkitt lymphoma, their key role in the oncogenetic transformation of MCL has also been noted. A distinctive feature of a tumor with combined disorders of the CCND1 and MYC genes is a high uncontrolled proliferative activity of cells due to a block of apoptosis and impaired repair of damaged DNA, which serves as a predictor of the occurrence of additional genetic aberrations. Today, it is relevant to study the impact of MYC gene aberrations on overall and disease-free survival and to study a highly aggressive subgroup of MCL, "double-hit" MCL, characterized by a combination of translocation t(11;14)(q13;q32) and MYC gene aberrations.

Objectives. To determine the incidence and prognostic impact on overall survival (OS) and disease-free survival (DFS) of MYC gene aberrations in 117 patients with MCL and to identify a group of patients with "double-hit" MCL.

Methods. The results of standard cytogenetic and FISH studies of 117 patients with a histologically confirmed diagnosis of MCL are presented. Karyotyping was performed on G-banding-stained metaphase plates obtained from bone marrow or peripheral blood cells. Translocation t(11;14)(q13;q22), aberrations involving the TP53 and MYC genes, were detected by FISH study using locus-specific DNA probes.

Results. MYC gene abnormalities were detected by FISH analysis in 29/117 patients (24,8 %) with MCL. The study revealed the genetic heterogeneity of MYC gene aberrations: rearrangement involving MYC was found in 2/29 (7,0 %) patients, MYC amplification (from 1 to 14 additional copies) — in 23/29 (79,3 %), an additional copy of MYC with deletion of the telomeric region of MYC — in 3/29 (10,3 %), amplification of MYC with deletion of the centromeric region of MYC — in 1/29 (3,4 %). In patients with MYC changes, the karyotype was analyzed in 65,5 % (19/29) of cases. Chromosomal aberrations were detected in 9/19 patients (47,4 %): in 8/9 (88,9 %) complex changes in the karyotype, in 1/9 (11,1 %) — isolated translocation t(11;14)(q13;q32). A FISH study with a DNA probe to detect aberrations of chromosome 17 found such disorders as deletion of the TP53 gene and monosomy of chromosome 17 in 11/29 (37,9 %) patients. Statistical analysis demonstrated a significant effect of MYC gene changes on the reduction in median OS in patients with MCL compared with patients without MYC changes (43 months vs 108 months, $p = 0.013$). The most unfavorable effect on the duration of OS of patients with MCL was found for the combination of MYC gene amplification with deletion of the centromeric region of MYC, which was 15 months ($p = 0.028$). Multivariable regression analysis revealed an independent unfavorable effect of MYC aberrations on OS of patients with MCL ($b \pm SD = -0.21 \pm 0.08$, $p = 0.05$), and the greatest tendency towards a negative effect when assessing DFS ($b \pm SD = -0.20 \pm 0.11$, $p = 0.30$). "Double-hit" MCL, characterized by MYC gene abnormalities and t(11;14)(q13;q32) translocation, was found in 22/117 (18,8 %) patients. The karyotype in this subgroup was analyzed in 16/22 (72,7 %) patients. An aberrant karyotype was detected in 9/16 (56,3 %) patients, predominantly (8/9 (88,9 %)) complex numerical and structural changes in the karyotype were detected (from 4 to 23–25 aberrations). FISH study revealed from 1 to 14 additional copies of MYC in 20/22 (90,9 %) patients, MYC amplification with deletion of the telomeric region of MYC in 1/22 (4,5 %), in 1/22 (4,5 %) — MYC amplification with deletion of the centromeric region of MYC. In 45,5 % (10/22) of cases, patients were diagnosed with TP53 gene disorders: 7/10 (70,0 %) — TP53 deletion, 3/10 (30,0 %) — monosomy of chromosome 17.

Conclusions. MYC gene aberrations are a prognostically significant factor that determines the unfavorable clinical course of mantle cell lymphoma and are highly associated with genomic instability and the detection of complex karyotype changes during karyotyping. The combination of standard cytogenetic testing and FISH analysis significantly increases the detection rate of the tumor clone, and thus helps to more accurately diagnose patients with mantle cell lymphoma and identify a group of high-risk patients with "double-hit" mantle cell lymphoma. Thus, the significant unfavorable effect of MYC gene disorders on the prognosis of the disease allows us to recommend the inclusion of screening for the presence of changes in the MYC gene using the FISH method for all patients with mantle cell lymphoma.

Molecular-genetic profile and different prognostic impact of recurrent gene mutations in chronic lymphocytic leukemia

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Introduction. Chronic lymphocytic leukemia (CLL), is a hematologic malignancy characterized by the uncontrolled proliferation of mature B lymphocytes and heterogeneous clinical course. Advances in clinical management include improvements in our understanding of the prognostic value of different genetic lesions, particularly those associated with chemoresistance and progression to highly aggressive forms of CLL, and the advent of new therapies targeting crucial biological pathways. At the present time the treatment decision still relies on conventional parameters (such as clinical stage and lymphocyte doubling time). Research of the genetic landscape of CLL patients will help in creating new algorithms of patients treatment using a personalized approach and targeted therapies.

Objectives. To analyze the genomic heterogeneity of CLL using NGS (next-generation sequencing) and evaluate the impact of the most common aberrations on prognosis.

Methods. We studied 67 patients with CLL: 43 (62.7 %) men and 24 (37.3 %) women, median age was 62 years (27–82). Standard protocols were used to analyze the mutational status of immunoglobulin heavy chain (IGHV) genes, assessment of chromosomal aberrations using fluorescence in situ hybridization (FISH) (assays for 11q, 13q, 17p and trisomy 12), mitogen-stimulated karyotype where complex karyotype was defined as the presence of ≥ 3 aberrations. For all patients, NGS was performed using a panel of 118 genes on a Miseq sequencer (Illumina). Time-to-first-treatment (TTFT) was defined as the time from verification of diagnosis to initiation of first therapy. Overall survival (OS) was defined as the time from diagnosis verification to the date of last patient contact.

Results. According to the results of FISH study, 3 groups of patients were identified: with favorable prognosis (isolated del13q14) — 14/62 (22.6 %), intermediate (trisomy 12, no aberrations) — 22/62 (35.5 %) and unfavorable (del17p13 and del11q22) — 26/62 (41.9 %). Cytogenetic study showed a complex karyotype in 4/49 (8.2 %) patients. Using a threshold of 98 % homology with the germinal gene revealed 12/57 (21.1 %) patients with mutated VH genes, 45/57 (78.9 %) patients with non-mutated ones. The parallel sequencing method of 118 genes revealed mutations in 59/67 (88.1 %) patients. A total of 151 mutations were detected: 124 missense mutations, 8 nonsense mutations, 15 with frameshift, 3 mutations in splicing regions, and 1 deletion without frameshift. The most frequent (≥ 1 %) mutations were detected in the following genes: NOTCH1 (22.4 %), SF3B1 (17.9 %), XPO1 (16.4 %), TP53 (14.9 %), MGA (9.0 %), ATM (7.5 %), IKZF3 (7.5 %), 4.5 % of cases in FBXW7, RPS15, BRAF genes and 3.0 % of cases in BIRC3, NOTCH2, KRAS genes. Two or more mutations were found in 40/60 (66.7 %) patients. Mutations in NOTCH1 receptor are associated with non-mutated IGHV status ($p = 0.002$), as well as with the presence of mutations in TP53 gene ($p = 0.002$). To date, a large amount of data has been accumulated indicating the involvement of XPO1 gene in oncogenesis and the possibility of using it as a therapeutic target in CLL. In our study, all pathogenic mutations in XPO1 gene were found in codon E571, 3 mutations with unknown clinical significance were also detected (D624G in 2 patients and c.591-3dupT). Association of mutations in tumor suppressor TP53 with del17p ($p = 0.001$) and mutations in XPO1 gene ($p = 0.002$) was shown. In 3/10 patients with TP53 mutations, the allele burden of the mutation was below 10 %. We analyzed the correlation between mutation status and prognosis of the disease course. Shorter TTFT duration was observed in patients with non-mutated IGHV status ($p = 0.043$), mutations in NOTCH1 ($p = 0.026$) and SF3B1 ($p = 0.081$) genes. In the OS study, the most unfavorable outcome was associated with mutations in SF3B1 gene ($p = 0.024$) and non-mutated IGHV status ($p = 0.038$) (Figure 1).

Conclusions. Patients with CLL have a highly heterogeneous molecular genetic profile. Mutations in NOTCH1, SF3B1, TP53, XPO1 and MGA genes are the most frequent molecular events in CLL patients. The mutational status of IGHV, NOTCH1 and SF3B1 genes has a significant impact on the prognosis of the course of CLL. The use of the latest molecular genetic technologies, such as high-throughput sequencing, makes it possible to obtain a detailed characterization of the mutational profile for each patient, which is critical for CLL patients due to the high frequency of mutations and the emergence of effective targeted therapies.

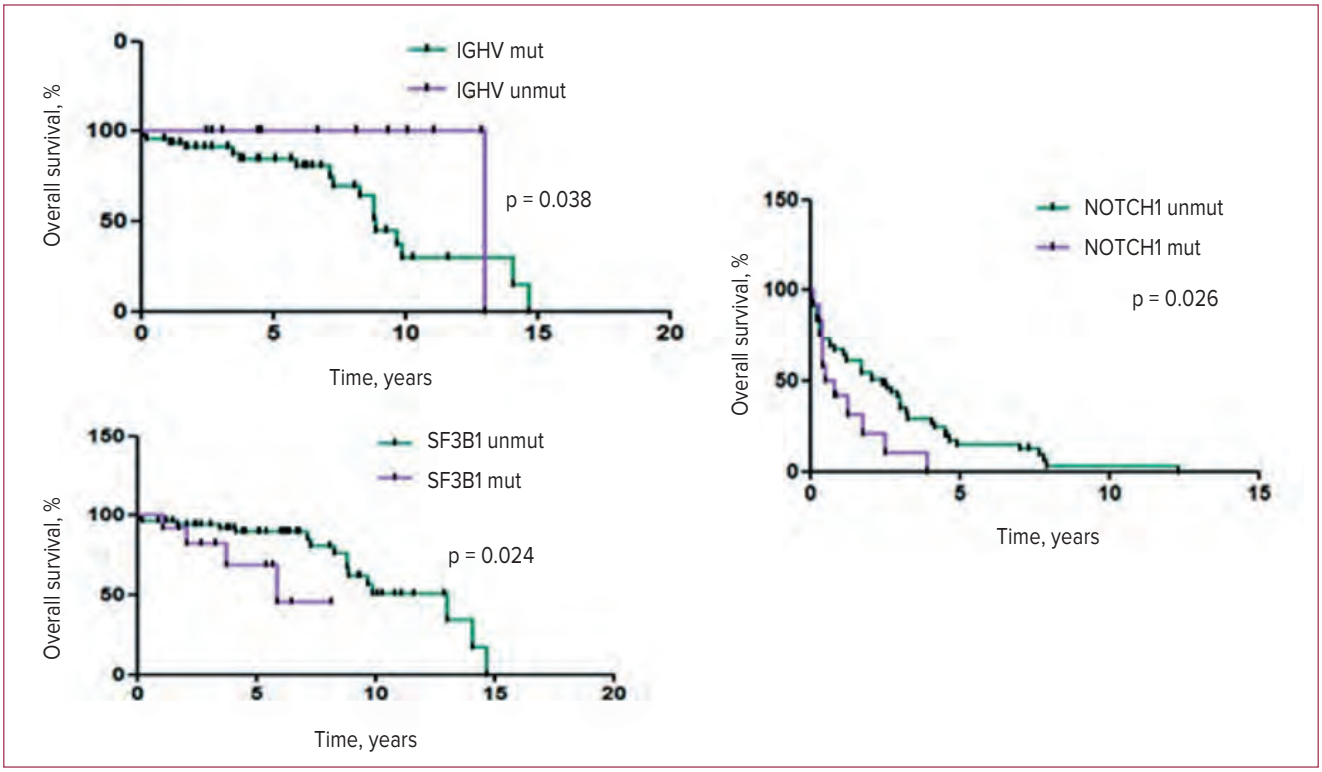

Figure 1. Prognostic impact of the molecular-genetic abnormalities in CLL patients

BTK and *PLCG2* gene mutations in Russian CLL patients with resistance to covalent BTKI

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Introduction. Bruton's tyrosine kinase inhibitors (BTKi) have shown high efficacy in the treatment of chronic lymphocytic leukemia (CLL) but some patients develop resistance leading to disease progression and treatment failure. (Byrd J.C., 2015) Disease progression in CLL patients receiving BTKi is often associated with mutations in Bruton's tyrosine kinase (BTK) and phospholipase Cg2 (PLCG2) genes acquired during treatment (Woyach J.A., 2017; Liu T.M., 2015). Genetic lesions affecting the regulatory domains of BTK and/or PLCg2 lead to increased enzyme activity and disruption of intercellular signaling. Multiple mutations in the BTK and PLCG2 genes can provide permanent activation of BCR signaling pathway despite BTK inhibition, thus affecting the viability of tumor cells by means of BTK regulation bypass. (Lampson B.L., 2018) While mutations in the BTK gene are described in sufficient detail, data on the occurrence of PLCG2 gene mutations in Russian patients with progressive CLL are very limited. Timely detection of BTK and PLCG2 gene mutations before a relapse in CLL patients should make it possible to change the treatment tactics accordingly.

Objectives. The prevalence and allele load of BTK and PLCG2 gene mutations in Russian CLL patients with resistance to covalent BTKi: measurement by next generation sequencing (NGS).

Methods. The study included DNA samples from 60 CLL patients relapsed on BTKi therapy: 36 men and 24 women (median age 66 years). Ibrutinib and acalabrutinib received 57 and 3 patients accordingly. The median duration of BTKi therapy until CLL progression was 34.5 months (9–73 months). Mutations in BTK (exons 11, 15, and 16) and PLCG2 (exons 19, 20, and 24) genes and their variant allelic frequencies (VAF) were assessed by NGS on MiSeq apparatus (Illumina, USA).

Results. BTK/PLCG2 gene mutations were identified in 38 patients (63 %). The most common BTK c.1442G>C mutation was found in 31 patients (52 %), and c.1442G>T mutation was found in 3 patients (5 %). At the same time in 9 cases (15 %) two to four mutations were detected simultaneously in codon C481 of the BTK gene. Other regions of the BTK gene were subject to mutations much less frequently. In 1 patient, a single mutation p.L528W:c.1583T>G (VAF 3.1 %) was identified in 16 exon of the BTK gene. In one patient, 2 mutations were simultaneously detected in different exons of BTK gene - p.C481S:c.1442G>C (VAF 33 %) and p.T316A:c.946A>G (VAF 0.55 %). Mutations in PLCG2 gene were found in only two patients - in both cases with a low allelic load and with mutations in 15 exon of BTK gene at the same time. In 1 patient, two lesions were detected: p.L845F:c.2535A>C (VAF 3.4 %) in PLCG2, as well as a mutation p.C481S:c.1442G>C (VAF 25 %) in BTK. In the second patient, four mutations were detected: p.L845F:c.2535A>C in PLCG2 (VAF 1.6 %) and three mutations in BTK - p.C481S:c.1442G>C (VAF 30 %), c.1442G>T (VAF 8 %) and c.1442G>A (VAF 2 %). Only one patient had p.C481S:c.1442G>C mutation in BTK with VAF>1 % during the first year of treatment; in 26 (68 %) patients mutations were detected after 24 months of therapy.

Conclusions. Mutations in BTK/PLCG2 genes were detected in 63 % of CLL patients with disease progression during BTKi therapy, in 37 % cases the cause of resistance has not yet been established. Moreover, the majority of mutations in our sample were identified in codon C481 of the BTK gene in CLL patients who relapsed after 2 years of BTKi therapy. According to the literature, mutations in PLCG2 gene occur in patients with resistance to BTKi much less frequently than in BTK gene: in 3–10 % of cases as a single event and in 10–20 % simultaneously with BTK mutations, while in most cases BTK gene mutation VAF is significantly higher than that for PLCG2 gene. It is possible that in some cases of BTKi resistance, lesions in PLCG2 gene are secondary events in relation to BTK gene mutations and/or the result of clonal evolution of the tumor. However, our sample size is not sufficient to draw firm conclusions. Since clinical manifestations of resistance to BTKi appear after average 2 years, we suggest regular monitoring of BTK and/or PLCG2 gene mutations using AS-PCR and NGS every 3 months, starting from the second year of CLL treatment with these drugs. Early identification of disease progression predictor can provide valuable information for clinicians to consider alternative treatment options before clinical manifestation of BTKi resistance. According to our and literature data, ~30 % of patients with resistance to BTKi don't have mutations in BTK and PLCG2 genes. Therefore, alternative pathways for the development of BTKi resistance should also exist (Kadri S., 2017) and further studies on other potential BTKi resistance markers are required.

The impact of genetic abnormalities and autologous stem cell transplantation on survival in patients with newly diagnosed multiple myeloma

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Background. Studies carried out over the past decade, have greatly improved our understanding of the multiple myeloma molecular basis and mechanisms of the disease progression. Metaphase cytogenetics and fluorescence in situ hybridization (FISH) help us to identify the most frequent genetic abnormalities. Stratification of patients into various risk groups based on the chromosomal markers is employed by many centers to select and the optimize therapeutic strategy. However, the role of complex and combined genetic abnormalities, and autologous stem cell transplantation (ASCT) is still remains not completely clear.

Objectives. To determine the impact of genetic abnormalities and ASCT on overall and progression-free survival in patients with newly diagnosed multiple myeloma (NDMM).

Methods. The study included 159 patients (median age 63 years, range 28 - 83; male/female ratio — 1:1.37) with NDMM. FISH analyses were performed to detect primary IgH translocations, 13q (13q14/13q34) deletion, 1p32/1q21 amplification/deletion, TP53/17p deletion. We additionally looked for the t(4;14), t(6;14), t(11;14), t(14;16) and t(14;20) in patients with IgH translocation.

Table 1. Characteristics of aberrant and complex karyotypes

Aberrant karyotype (Two aberrations)	n	Complex karyotype	n
del13q and 1p32/1q21 amp/del	6	Hypodyploidy and del13q and 1q23/1p21 amp/del	1
t(4;14) and del13q	3	t(11;14) and del13q and 1q23/1p21 amp/del	1
t(11;14) and del13q	3	Hyperdiploidy and t(11;14) and del13q and TP53/del17p	1
translocation IgH and 1q32/1p21 amp/del	2	t(11;14) and **1q23/1p21 amp/del** and **TP53/del17p**	1
Hypodyploidy and del13q	1	del13q and **1q23/1p21 amp/del** and **TP53/del17p**	1
t(11;14) and 1p32/1q21 amp/del	1	Translocation IgH and Hypodyploidy and del13q and 1q23/1p21 amp/del	1
t(11;14) and t(4;14)	1	Hyperdiploidy and t(11;14) and 1q23/1p21 amp/del	1
t(11;14) and 1p32/1q21 amp/del	1	**t(4;14)** and **TP53/del17p** and del13q14	1
translocation IgH (unknown) and t(11;14)	1		

All patients received primary anti-myeloma therapy with bortezomib (PAD, CVD, VD, VMP).

Results. The frequency of genetic abnormalities in NDMM patients was 49 % (78/159). IgH translocation was detected in 26.4 % (42/159) patients: t(11;14) — in 16.3 % (26/159), t(4;14) — in 5.0 % (8/159); TP53/del17p — in 5.6 % (9/159); 1p32/1q21 amp/del — in 12 % (19/159); hypodiploidy — in 3.1 % (5/159); hyperdiploidy — in 1.25 % (2/159); del5q — in 0,6 % (1/159); other — not found. Aberrant karyotype was discovered in 11.9 % (19/159) patients, complex abnormalities (≥ 3 any aberrations) — in 5.0 % (8/159) patients, which included Double Hit (2 high-risk anomalies) found in 1.9 % (3/159) patients (Table 1).

The presence of an aberrant karyotype and complex karyotype were unfavorable prognostic markers compared to the standard risk group (SR) mSMART 3.0 (normal karyotype, t(11;14), hypodiploidy, hyperdiploidy, and other single anomalies) (Figure 1).

Based on our results, we performed a modification of the high-risk group (HR) mSMART 3.0 (delTP53/del17p, t(4;14), t(4;16), t(14;20), +1q, R-ISS III) including in this group patients with a 'complex karyotype' and Double Hit myeloma.

Stratification of patients into groups of molecular genetic risk according to the modification of mSMART 3.0 was carried out for 87 patients. The median OS in SR group (n = 53) was not reached, in mSMART 3.0mod HR group (n = 34) it was 50 months; the 5-year OS was 61 % and 38 %, respectively (p = 0.0073) (Figure 2).

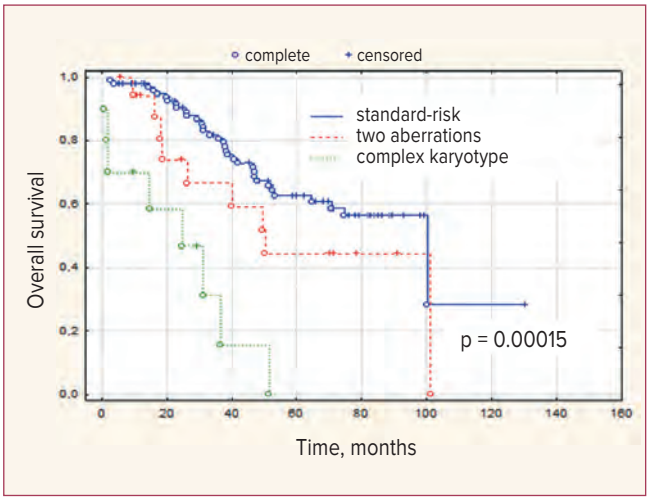

Figure 1. The impact of aberrant and complex karyotypes on overall survival of patients

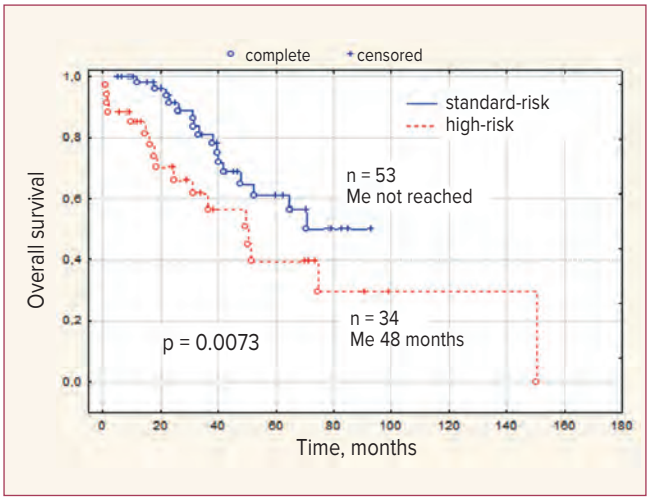

Figure 2. Overall survival of patients according to mSMART 3.0mod risk-stratification

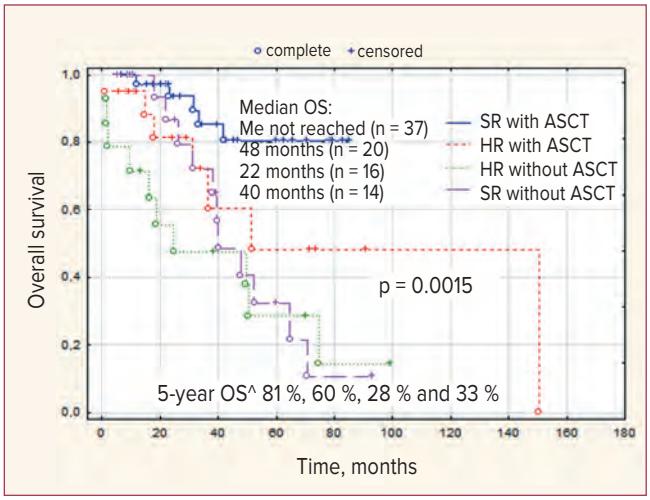

Figure 3. The impact of autologous stem cell transplantation on overall survival in various risk-stratification groups

The best results of OS and PFS were achieved in both groups of patients who had undergone autologous SCT. The median OS in SR group with ASCT (n = 37) was not reached, in HR group with autoSCT it was 48 months (n = 20); in SR group without ASCT — 40 months (n = 16); in HR group without ASCT — 22 months (n = 14); 5 year OS was 81 %, 60 %, 33 % and 28 %, respectively (p = 0.0015). The median PFS was not reached, it was 46, 22 and 19 months, respectively (p = 0.017) (Figure 3).

Conclusions. Aberrant karyotype, complex karyotype and double hit myeloma are unfavorable prognostic markers compared to standard risk abnormalities and the absence of abnormalities. The medians of OS and PFS were significantly higher in patients in SR group than in HR group according to mSMART 3.0mod. ASCT can improve treatment outcomes, especially in patients with HR.

References

1. Dispenzieri A, Rajkumar SV, Gertz MA et al. Treatment of newly diagnosed multiple myeloma based on Mayo Stratification of Myeloma and Risk-adapted Therapy (mSMART): consensus statement. Mayo Clin Proc. 2007;82:323–341.

2. Kumar SK, Mikhael JR, Buadi FK et al. Management of newly diagnosed symptomatic multiple myeloma: updated Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) consensus guidelines. Mayo Clin Proc. 2009;84:1095–1110.

3. Mikhael JR, Dingli D, Roy V et al. Management of newly diagnosed symptomatic multiple myeloma: updated Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) consensus guidelines 2013. Mayo Clin Proc. 2013;88:360–376.

СЕССИЯ 6 ТРАНСФУЗИОЛОГИЯ, ГЕМАТОЛОГИЯ

Determination of the number of donations as a risk factor for iron deficiency among blood donors

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Introduction. Each donation of whole blood leads to a loss of about 230 mg of iron, depending on the volume of blood supply. Multiple whole blood donations can lead to a high incidence of iron deficiency in human donors, especially in women. The progressive stage of iron deficiency, starting with the loss of iron depot followed by the development of iron deficiency erythropoiesis, eventually leads to iron deficiency anemia. In turn, anemia is a contraindication to donation and, therefore, leads to the medical withdrawal of the donor from donation.

Objectives. To assess the effect of the number of donations on the reduction of iron store in blood donors.

Materials and methods. The study included 179 whole blood donors, of which 89 were male and 90 were female. The median age for men was 34 years, for women — 37 years. Donors were divided into groups depending on the number of donations during the year. The control group consisted of new donors. The donor examination included serum ferritin levels, the threshold value of which was 30 ng/ml.

Results. In the group of male donors, a statistically significant difference was found between the groups depending on the number of donations ($p < 0,0001$). The median serum ferritin among men was 87,9 (49,5–115,9) ng/ml in the control group, 89,1 (50,7–139,4) ng/ml in the group of donors with 1 donation, 29,2 (16,8–110,3) ng/ml in the group with 2 donations, 36,2 (14,6–56,6) ng/ml — with 3 donations, 17,8 (12,5–29,1) ng/ml — with 4 donations. Female donors also showed differences among the study groups ($p < 0,05$). The value of ferritin among women was 33,4 (19,0–59,9) ng/ml for the control group, 17,25 (11,4–34,7) ng/ml for the group with 1 donation per year, 17,0 (13,3–28,5) for the group with 2 donations, 17,7 (13,2–23,6) ng/ml with 3 donations, 26,8 (12,0–47,8) ng/ml — with 4 donations. When conducting pairwise comparisons with the control group, it was revealed that 3 blood donations during the year ($p < 0,001$) have the greatest impact on the development of iron deficiency in men, whereas in women, the presence of 1 donation per year leads to the risk of iron deficiency. ($p < 0,01$).

Conclusions. The results obtained indicate a high risk of iron deficiency in both female and male blood donors. The hemoglobin level examined in donors before donation does not allow to verify iron deficiency in the body. In this regard, the study of iron metabolism in regular donors allows us to assess iron store and the need for iron for erythropoiesis.

Peculiarities of using viral neutralizing antibodies to COVID-19 in adult patients with lymphoproliferative diseases

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Introduction. Patients with oncohematologic diseases are at high risk of developing severe infectious complications. Information on the formation of cellular immune response is limited. In most cases, this group of patients is unable to form a full-fledged humoral immune response, due to the development

of secondary immunodeficiency states, severe course of the underlying disease, age, use of drugs that suppress the immune response. According to the largest works available, the severe course of COVID-19, which required hospitalization of patients to the intensive care unit, is approaching 20 %. The highest mortality is observed in the groups of patients with acute myeloid leukemia (40 %) and myelodysplastic syndrome (42.3 %). In view of the above, one of the available immunization methods for immunocompromised patients is the use of monoclonal virus-neutralizing antibodies (MAT) to COVID-19. Tixagevimab/cilgavimab is a combination of MAT that binds to the COVID-19 spike protein.

Objectives. To evaluate the safety and efficacy of tixagevimab/cilgavimab as pre-exposure prophylaxis for COVID-19 in adult patients with lymphoproliferative diseases.

Materials and methods. Fifty-four patients with oncohematologic diseases were included in the study (Table 1). The median age was 57 years (21–76), and the study group was predominantly female 55 % (n = 31). The median follow-up after administration of the drug was 21 (15–28.6) months. At the time of MAT administration, 69 % (n = 37) of patients were receiving induction and antiretroviral treatment. Twenty-eight percent (n = 15) of patients had been vaccinated prior to MAT administration. Sputnik V vaccine was used in 26 % (n = 14) of patients and Sputnik Lite vaccine in 2 % (n = 1) of patients, respectively. During the follow-up period, 17 % (n = 9) of patients received revaccination with Sputnik Lite vaccine. Prior to the introduction of tixagevimab/cilgavimab, 74 % (n = 40) of patients had COVID-19 infection, 5 % (n = 3) of whom had coronavirus infection twice (Table 1).

Results. During the follow-up period in the group of oncohematologic patients, 21 (39 %) had a coronavirus infection after MAT administration. Most infectious episodes (86 %, n = 18) were reported more than 6 months after pre-exposure prophylaxis. Some of them (38 %, n = 8) coincided with an upsurge in incidence between September-October 2023.

It should be noted that the majority of patients (n = 19, 90 %) after pre-exposure prophylaxis had mild or asymptomatic acute respiratory infections, while 10 % (n = 2) had moderate symptoms. One patient experienced COVID-19 infection three times within 6 months of MAT administration. None of the three episodes of infection required hospitalization, the infection was accompanied by mild acute respiratory symptoms. Patients' age (p = 0.78), ECOG status (p = 0.67), previous vaccination (p = 0.45), vaccine type (p = 0.63), chemotherapy (p ≥ 0.5) according to logistic regression did

Table 1. Characteristics of patients

Characteristics	**N = 54**
Age	57 (21–76)
Sex	
Males	24 (45 %)
Females	30 (55 %)
Diagnosis structure	
Hodgkin's lymphoma	10 (18 %)
Multiple myeloma	7 (13 %)
Follicular lymphoma	9 (18 %)
CLL	9 (15 %)
Other diagnoses	19 (34 %)
ECOG at the moment of vaccination	
0–1	51 (94 %)
2	3 (6 %)
Vaccination before administration of MAB	
Sputnik V	15 (28 %)
Sputnik light	14 (26 %)
Revaccination	1 (2 %)
Sputnik light	9 (17 %)
Therapy at the moment of vaccination	
Chemotherapy +/- monoclonal antibodies	9 (16 %)
Monoclonal antibodies	14 (25 %)
Targeted therapy	15 (27 %)
A history of Auto-HSCT	14(25 %)
A history of Allo-HSCT	1 (2 %)
No treatment	16 (32 %)

not affect the probability of coronavirus infection after MAT administration. Administration of monoclonal antibodies did not affect the risk of COVID-19 infection ($p \geq 0.8$). Prior vaccination did not affect the development of COVID-19 infection after MAT administration. The frequency of coronavirus infection episodes in vaccinated patients was 29 % versus 32 % in unvaccinated patients ($p = 0.52$). No fatalities were reported during the follow-up period.

Adverse events were rare and of mild severity according to NCI CTCAE v5.0 classification. Episodes of arterial hypertension in four patients, development of febrile fever in four patients, nausea in three patients should be emphasized.

Conclusions. In the conditions of seasonal outbreaks of infection, formation of new strains of COVID-19, the problem of prevention of COVID-19 infection remains urgent. According to our data, in the majority of cases in oncohematologic patients who received pre-exposure prophylaxis with MAT, COVID-19 disease proceeds in mild to moderately severe forms. When assessing the toxicity profile, single non-hematologic adverse events of grade 1–2 were recorded.

КЛИНИЧЕСКИЕ СЛУЧАИ

Редкий случай поражения центральной нервной системы при множественной миеломе

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Введение. Локализация множественной миеломы (ММ) в центральной нервной системе составляет около 1 % от всех случаев ММ. Из-за редкости и агрессивности заболевания стандарты терапии отсутствуют.

Описание клинического наблюдения. Пациенту в возрасте 62 лет в марте 2022 г. установлен диагноз: множественная миелома IgG lambda, IIIA DSS, ISS-I; плазмоцитома правой подвздошной кости размерами до 4,2 см и левой лопатки — до 5,6 × 4,1 см. Проведено 4 цикла терапии CVD и высокодозная химиотерапия (MEL200) с аутологичной трансплантацией гемопоэтических стволовых клеток. Рекомендованная поддерживающая терапия леналидомидом не проводилась.

По результатам контрольной ПЭТ-КТ от 18.04.2023 г.: выявлены околопозвоночные тканевые образования: паравертебрально слева на 8–9 межреберном уровне размером 2,0 × 1,5 см (Deauville — 2 балла); справа ретрокрурально размером 5,1 × 2,6 × 7,9 см (Deauville — 4 балла). На месте прежнего образования в левой лопатке наблюдаются склеротические изменения размером 3,5 × 2,5 см (Deauville — 2 балла). Образования располагаются экстрамедуллярно, не сопровождаются костно-деструктивными изменениями.

МРТ от 02.05.2023 г.: превертебрально/латероаортально визуализируется образование. Нижний полюс образования на уровне отхождения почечных артерий, верхний — на уровне Th9–Th10 позвонков.

С 10.05.2023 по 27.05.2023 г. проведен курс паллиативной дистанционной фотонной терапии на паравертебральное и паракруральное образования слева — СОД 30 Гр, на лопаточную область — СОД 30,3 Гр.

13.06.2023 г. обратился за консультативной помощью в РосНИИГТ ФМБА России.

В анализе крови от 14.06.2023: Hb — 154 г/л, лейкоциты — 4,6 × 10^9/л (п/я — 2 %, с/я — 64 %, лимфоциты — 24 %, моноциты — 10 %), тромбоциты — 285 × 10^9/л; креатинин — 46 мкмоль/л, общий кальций — 2,3 ммоль/л.

Миелограмма от 14.06.2023 г.: МКЦ — 69 × 10^9/л, плазматический ряд — 0,0 %.

Низкодозная КТ всего тела от 16.06.2023 г.: множественные остеодеструкции. Мягкотканные образования не выявлены.

20.06.2023 г. пациент госпитализирован в городскую больницу с подозрением на острое нарушение мозгового кровообращения. При госпитализации констатировано наличие сопора, судорожного синдрома, паралича Тодда. МРТ головы не выявило зон ишемии. В ликворе обнаружена гиперпротеинемия до 1,48 г/л, цитоз до 90 в мкл, патологические клетки не описаны. Заподозрено развитие менингита на фоне вторичного иммунодефицита. Назначена эмпирическая терапия цефтриаксоном, валацикловиром.

23.06.2023 г. ухудшение состояния до комы. Выполнена повторная люмбальная пункция, ликвор направлен в РосНИИГТ. Выявлены цитоз 120 в мкл, плазматические клетки — 92 % с фенотипом CD138+CD38+cytLambda+CD45–CD19–CD56+CD117–CD81dim+CD27–CD28+.

Установлен диагноз: множественная миелома IgG lambda, IIIA DSS, ISS-I; экстрамедуллярный рецидив с поражением центральной нервной системы. Инициирована терапия помалидомидом (через назогастральный зонд) и дексаметазоном, эндолюмбальное введение триплета 3 раза в неделю.

Ликвор от 26.06.2023 г.: цитоз снизился до 35 в мкл, плазматические клетки — 73 %.

В связи с развитием двусторонней пневмонии к антибактериальной терапии добавлены меронем и амикацин, внутривенные иммуноглобулины. Повторно выполнены микробиологические исследования для поиска очага инфекции.

Ликвор от 29.06.2023 г.: цитоз 2 в мкл, плазматические клетки — 12 %.

29.06.2023 г. получен результат посева бронхоальвеолярного лаважа от 26.06.2023 г.: *Klebsi-*

ella pneumoniae 10^9 (с продукцией карбопенемаз): инициирована терапия цефтазидим + [авибактам] с азтреонамом. Однако 30.06.2023 г. развилась полиорганная недостаточность, приведшая к смерти больного.

Выводы. Поражение ЦНС при ММ является крайне редким событием, требующим своевременной диагностики и начала терапии. Применение помалидомида и дексаметазона, проникающих через гематоэнцефалический барьер, в комбинации с эндолюмбальным введением триплетов служит оптимальной программой при вовлечении ЦНС. Добавление моноклональных антител является опцией, т. к. при внутривенном введении их концентрация в ликворе незначительна.

Клинический случай пациента с рецидивирующей/рефрактерной множественной миеломой

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Введение. В настоящее время терапия множественной миеломы может приводить к выживаемости 55 % пациентов в течение 5 лет. Однако, несмотря на использование триплетных и квадриплетных схем индукции, трансплантацию аутологичных стволовых клеток и поддерживающую терапию, миелома остается неизлечимой. При возникновении рецидива заболевания лечение представляется сложным и трудоемким процессом из-за биологической гетерогенности опухоли. За последние два десятилетия основное внимание клинических исследований при множественной миеломе было уделено преодолению лекарственной устойчивости. Особый интерес представляет применение новых способов лечения заболевания, в том числе и использование NK-клеток.

Цель. Представить клинический случай пациента с рецидивирующей/рефрактерной множественной миеломой.

Материалы и методы. Изучены материалы истории болезни, амбулаторной карты и проведенных методов исследования.

Результаты и обсуждение. Пациент А., 61 год. Больным себя считает с лета 2016 г., когда во время езды на машине почувствовал резкую боль в позвоночнике. Амбулаторно не обследовался, лечился самостоятельно, без значимого эффекта. В декабре 2016 г. пациент поступил в дежурное хирургическое отделение с острой болью в животе, при обследовании были выявлены изменения в общем анализе крови: эритроциты — 3,56 × 10^{12}/л, гемоглобин — 112 г/л, тромбоциты — 145 × 10^9/л, лейкоциты — 7,46 × 10^9/л, СОЭ 29 мм/ч. По данным биохимического анализа крови уровень общего белка составил 96,5 г/л. Пациент консультирован гематологом, назначено дообследование. По результатам рентгенографии черепа (декабрь 2016 г.) выявлены очаги деструкции в костях свода черепа. По результатам рентгенографии грудопоясничного отдела позвоночника (декабрь 2016 г.): множественные очаги деструкции тел и отростков позвонков, патологические переломы тел Th12–L3, L5. В связи с этим была проведена стернальная пункция, по данным миелограммы от 19.12.2016 г.: основная клеточная масса представлена плазматическими клетками, количество которых составило 60 %, среди плазмоцитов встречаются многоядерные формы. При электрофорезе белков сыворотки крови (декабрь 2016 г.) обнаружен парапротеин IgG kappa 34,6 г/л. По результатам электрофореза белков мочи с иммунофиксацией выявлена секреция белка Бенс-Джонса каппа 1,921 г/л. По результатам цитогенетического исследования кариотип нормальный. Уровень β2-микроглобулина составил 2,8 мг/л.

Поставлен диагноз: множественная миелома, диффузно-очаговая форма, IIIA стадия (по B. Durie, S. Salmon), I стадия по ISS, с наличием секреции парапротеина IgG kappa, множественных очагов деструкции тел и отростков позвонков, патологических переломов тел Th12–L3, L5, очагов деструкции в костях свода черепа.

В начале 2017 г. проведено 4 курса противоопухолевого лечения по схеме PAD. При последующем обследовании в общем анализе крови выявлено: лейкоциты — 6,7 × 10^9/л, тромбоциты — 102 × 10^9/л, эритроциты — 3,21 × 10^{12}/л, Hb — 90 г/л, СОЭ 62 мм/час. По данным биохимического анализа крови уровень общего белка составил 96 г/л. По результатам миелограммы от июня 2018 г.: 38,8 % составляют плаз-

матические клетки разных степеней зрелости, отмечается анизоцитоз элементов и ядер, встречаются многоядерные формы. По данным электрофореза белковых фракций сыворотки крови с иммунофиксацией секреция парапротеина составила 29,7 г/л. Диагностирована первичная резистентность.

С мая 2017 г. пациент получил 12 курсов по схеме Rd. По результатам миелограммы от июня 2018 г.: 5,8 % плазмоцитов. По данным электрофореза белковых фракций сыворотки крови с иммунофиксацией секреция парапротеина составила 4,8 г/л. Достигнут очень хороший частичный ответ.

Ухудшение состояния было отмечено в марте 2019 г., когда у пациента вновь появились жалобы на боли в пояснице. Проведена стернальная пункция, в миелограмме выявлено 23,4 % плазмоцитов. По данным электрофореза белковых фракций сыворотки крови с иммунофиксацией секреция IgG kappa составила 19,5 г/л. Диагностирован первый ранний рецидив заболевания.

Пациент получил 3 курса по схеме VRD, после чего в миелограмме от 21.11.2019 г. определялось 32 % плазмоцитов. Проведено FISH-исследование (апрель 2020 г.), заключение: в 5 % клеток выявлена амплификация локуса гена MYEOV/14q32. Транслокации t(11;14)(q13.3;q32.3), (4;14)(p16;q32), делеция/амплификация генов CKS1B/1q21 и CDKN2C/1p32, делеция генов DLEU/13q14.2, LAMP/13q34, TP53/17p13, моносомия хромосомы 17 не обнаружены.

С апреля 2020 г. пациент получил 5 курсов RCD. По результатам электрофореза белковых фракций сыворотки крови секреция парапротеина составила 30,8 г/л. Принято решение о проведении монотерапии даратумумабом. По данным электрофореза белковых фракций сыворотки крови, проведенного после 8 введений даратумумаба, уровень парапротеина составил 4,7 г/л, достигнут очень хороший частичный ответ. Пациент получил 16 курсов монотерапии даратумумабом, однако в контрольной миелограмме от 21.01.2021 г. было выявлено 45,2 % плазмоцитов. По результатам электрофореза белковых фракций сыворотки крови с иммунофиксацией секреция IgG kappa составила 35,4 г/л. Диагностирована рефрактерная форма заболевания.

С февраля 2021 г. пациент получал лечение по протоколу Krd, суммарно было проведено 9 курсов, после которых в контрольной миелограмме выявлено 1,2 % плазматических клеток. По данным электрофореза белковых фракций сыворотки крови с иммунофиксацией секреция парапротеина составила 5,5 г/л. Достигнут очень хороший частичный ответ.

С декабря 2021 г. наблюдался перерыв в лечении в течение 3 месяцев в связи с отсутствием препарата. С февраля 2022 г. была выявлена прогрессия заболевания: в миелограмме выявлено 29,6 % плазматических клеток. По данным электрофореза белковых фракций сыворотки крови с иммунофиксацией секреция IgG kappa составила 18,6 г/л. С апреля 2022 г. пациент прошел 2 курса по схеме DaraRD. По данным миелограммы от июня 2022 г.: 0,8 % плазматических клеток. М-компонент в γ-фракции составляет 1,6 г/л, достигнут очень хороший частичный ответ. По данным электрофореза белковых фракций сыворотки крови после 8 курсов DaraRD также сохранялся очень хороший частичный ответ.

После проведения 12 курсов по схеме DaraRD по результатам электрофореза белковых фракций сыворотки крови вновь наблюдалось увеличение уровня парапротеина до 4,2 г/л. В связи с иммунохимическим рецидивом заболевания пациент был включен в клиническое исследование «Разработка метода адоптивной иммунотерапии на основе натуральных киллеров пуповинной крови». Пациенту проводилась еженедельная внутривенная трансфузия донорского концентрата гемопоэтических стволовых клеток пуповинной крови, аллореактивных по KIR-рецепторам по типу рецептор–лиганд. Перед введением NK-клеток пациент получил лимфодеплетирующую химиотерапию на основе циклофосфамида. Введение NK-клеток сопровождалось подкожными инъекциями IL-2. По данным электрофореза белковых фракций сыворотки крови после четырехкратного введения NK-клеток пуповинной крови отмечается снижение секреции парапротеина до 4 г/л.

Выводы. 1. Несмотря на достижения в терапии множественной миеломы, заболевание остается неизлечимым для большинства пациентов.

2. Перспективна терапия направленного действия, воздействующая как на опухолевые клетки, так и на клетки окружения в костном мозге.

3. Необходимо использование трех- и четырехкомпонентных схем с таргетными препаратами для эффективной борьбы с опухолью с максимально ранних этапов терапии пациентов.

4. Добавление моноклональных антител увеличивает эффективность терапии, что позволяет использовать данные режимы для долгосрочной непрерывной терапии и профилактики рецидивов.

5. Новый способ терапии рецидивирующей/рефрактерной множественной миеломы на основе NK-клеток пуповинной крови, примененный впервые в России, представляется перспективным методом, требующим дальнейшего изучения и активного внедрения в клиническую практику.

Multiple myeloma treatment in patient with antitumor therapy induced cardiotoxicity: a daratumumab solution

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Background. Daratumumab is a CD38-directed cytolytic antibody IgG1k indicated for the treatment of adult patients with multiple myeloma, newly diagnosed and refractory or relapsed as well. Daratumumab is highly effective and shows low frequency of adverse events, while the cardiotoxicity rate is less than 0.01 %.

Objectives. To analyse a clinical case of newly diagnosed multiple myeloma showing Daratumumab curing options in female patient with previously administered antitumor therapy induced cardiotoxicity.

Clinical case. A 45-year-old Caucasian female has been treated in the local specialized hospital with IgG-kappa multiple myeloma with bone destruction, ISS — III. The left ventricular ejection fraction was 65 % in the disease onset. Since July, 2021 one course of PAD regimen has been administered (including bortezomib, doxorubicin, dexamethasone). Later patient presented to Russian Cancer Research Center named after N.N. Blokhin with tachycardia, ECOG PS 1–2, anemia (HGB 97 g/l). On this admission to hospital echocardiography has been held. The results were following: total dilatation of the heart chambers with hypokinesis of the left ventricle, severe systolic dysfunction, cardiac ejection fraction 31 %. The level of NT-proBNP was 29793 pg/ml. After severe cardiotoxicity had been stated specialized treatment has been instantly adjusted, resulting in the ejection fraction increasing (41 %) and NT-proBNP decreasing (285 pg/ml). Due to known cardiotoxicity rate of PAD regimen next line therapy was chosen as Daratumumab in monotherapy (16 mg/kg) along with constant instrumental and laboratory control of cardiac status. From November, 2021 to March, 2022 twelve injections (standard dosage) were administered. According to functional monitoring ejection fraction increasing has been stated along with NT-proBNP level decreasing, resulted in resolving the cardiotoxicity. By June, 2022 after sixteen injections the induction phase ending resulted in Very Good Partial Response (VGPR), complete metabolic response (according to PET/CT scans), while MRD-status remained positive (0,1 %). Resolved cardiotoxicity allowed us to successfully administer stem cells transplant on May, 2022 using gemcytabine chemomobilization and following high dose Melfalan (200 mg/m^2) therapy. The VGPR has been remaining after +100 days from transplantation (the cardiac ejection rate — 65 %, NT-proBNP — 7,3 pg/l, ECOG PS 0–1).

Conclusions. Compromised cardiovascular status along with first line therapy induced cardiac toxicity commonly limit therapeutic options. Administering Daratumumab in such tough clinical cases allows continuing standard chemotherapy regimen treatment despite patient's age and previous cardiac history resulting in tangible antitumor efficiency.

Клинический случай успешного лечения пожилого пациента с тяжелой коморбидной патологией и впервые выявленным острым миелобластным лейкозом

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Введение. Острый миелоидный лейкоз у пожилого человека, дебютирующий с тяжелых инфекционных осложнений, нередко ставит неразрешимую терапевтическую задачу. Проведение стандартной химиотерапии затруднено, а в отсутствие ремиссии разрешение инфекционных осложнений невозможно. Комбинированная терапия венетоклаксом и азацитидином представляет более безопасную альтернативу режиму «7+3» с последующей консолидацией, и это находит свое отражение в большом числе клинических исследований на эту тему.

Цель. Представить случай лечения пожилого пациента с первичным острым миелобластным лейкозом, дебютировавшим с субтотальной пневмонии, комбинацией венетоклакса и азацитидина, что позволило получить быструю ремиссию и купировать инфекционые осложнения.

Описание клинического случая. Пациент 69 лет в апреле 2021 г. отметил появление одышки, усиливающейся при минимальной физической нагрузке, выраженную слабость. При обращении к гематологу в гемограмме тяжелая анемия — Hb 48 г/л, лейкопения — 2,89 × 10^9/л. При дообследовании в отделении химиотерапии гемобластозов КОД в миелограмме субтотальная бластная пролиферация (бласты 64 %). Бласты преимущественно средних размеров с высоким ядерно-цитоплазматическим соотношением, округлой или неправильной формой ядер с 1–3 нуклеолами. Цитоплазма базофильная. В единичных клетках отмечаются азурофильная зернистость и палочки Ауэра. При цитохимическом исследовании МПО положительна в 10 %, PAS отрицательная, ФЛ положительная в 4 % клеток.

По результатам иммунофенотипирования в костном мозге выявлена бластная популяция 53,54 % с абберантным иммунофенотипом, соответствующим острому миелоидному лейкозу.

При стандартном цитогенетическом исследовании нормальный кариотип 46XY в 20 метафазах.

В гемограмме: Hb — 58 г/л, лейкоциты — 0,96 × 10^9/л, тромбоциты — 17 × 10^9/л, абсолютное число нейтрофилов — 0,31 × 10^9/л, СОЭ 70 мм/ч

Из сопутствующих заболеваний у пациента имелись хроническая обструктивная болезнь легких эмфизематозного типа, среднетяжелое течение, высокий риск обострений, класс D, обострение. Хроническое легочное сердце, субкомпенсация; ишемическая болезнь сердца, стабильная стенокардия 2 ф.кл. Пароксизмальная форма фибрилляции предсердий, риск по CHADS VASc5b, HASBLED 4b. Хроническая сердечная недостаточность IIA, 3 ф.кл. с нормальной фракцией выброса. Гипертоническая болезнь III стадии, целевой уровень артериального давления на фоне медикаментозной коррекции, риск 4. Алиментарно-конституциональное ожирение I степени (индекс массы тела 36,4 кг/м^2).

Учитывая тяжелую анемию, тромбоцитопению, проводилась заместительная гемокомпонентная терапия. 16.05.2021 г. повышение температуры до 39° С; к лечению добавлена двухкомпонентная антибактериальная, противогрибковая терапия. 17.05.2021 г. нарастание дыхательной и сердечно-сосудистой недостаточности. 17.05.2021 г. в 5:10 переведен в ОРИТ. По данным КТ органов грудной клетки (ОГК) от 17.05.2021 г.: в различных отделах обоих легких определяются инфильтраты 5–15 мм, сливающиеся в конгломераты. Наибольший объем поражения в S2 справа и S9–10 слева. Единичные лимфоузлы средостения до 14 мм. Констатирована двусторонняя полисегментарная очагово-сливная пневмония, лимфаденопатия. Проводилась терапия меропенемом 1 г 2 раза в сутки, левофлоксацин 500 мг 2 раза в сутки, к лечению добавлен позаконазол 5 мл 3 раза в день. 17.05.2021 г. в 19:15 отрицательная динамика, нарастание дыхательной, сердечно-сосудистой недостаточности, пациент переведен на ИВЛ, проводилась инотропная поддержка норадреналином. 19.05.2021 г. пароксизм фибрилляции предсердий. По данным ЭхоКГ, проводившейся на фоне фибрилляции предсердий, фракция выброса 61 %, мелкоочаговый фиброз межжелудочковой перегородки, признаки незначительной неравномерной гипертрофии миокарда левого желудочка. Умеренное расширение левого предсердия, относительная митральная недостаточность II степени. Признаки легочной гипертензии. Умеренное расширение правого предсердия, относительная трикуспидальная недостаточность II степени. Признаки наличия незначительного количества свободной жидкости в полости перикарда. В реанимационном отделении скорректирована терапия, восстановлен ритм, гемодинамика нестабильная.

При контрольной рентгенографии от 20.05.2021 г. отрицательная динамика, двусторонняя пневмония, справа тотальное поражение. Бронхопульмональная лимфаденопатия.

С 25.05.2021 г. проведена эскалация антибактериальной терапии (добавлен линезолид).

КТ ОГК от 31.05.2021 г.: динамика отрицательная. двусторонняя полисегментарная очагово-сливная пневмония. Лимфаденопатия. Двусторонний плеврит. Миокардит? Асцит. Изменения могут быть проявлением основного заболевания.

При повторной ЭхоКГ и консультации кардиолога от 31.05.2021 г. констатирован острый неревматический миокардит. Хроническая сердечная недостаточность IIБ, 3 ф.кл.

Учитывая длительность панцитопении, обусловленной основным заболеванием, и невозможность разрешения инфекционных осложнений без редукции опухоли, принято решение о начале терапии. Принимая во внимание коморбидность пациента, тяжесть его состояния, начало терапии острого лейкоза в стандартных режимах было сопряжено с высоким риском развития фатального состояния.

С 03.06.2021 г. начат 1-й курс неинтенсивной терапии в режиме азацитидин 75 мг/м^2 (150 мг) п/к в дни 1–7, венетоклакс 100 мг per os в дни 1–28, на фоне продолжения сопроводительной эмпирической терапии, гемотрансфузии и поддержания витальных функций.

04.06.2021 г. по данным контрольной рентгенографии ОГК двусторонняя пневмония с положительной динамикой.

07.06.2021 г. в 11:50 выполнена экстубация трахеи, продолжена подача увлажненного кислорода через лицевую маску.

Рентгенография ОГК от 07.06.2021 г.: двусторонняя пневмония со слабоположительной динамикой.

11.06.2021 г. у пациента клинически отрицательная динамика: сохраняется гипертермия, нестабильная гемодинамика поддерживается введением норадреналина, по данным рентгенографии ОГК увеличение объема инфильтрации. Совместно с клиническим фармакологом принято решение, учитывая ранее высокую предлеченность, сменить антибактериальную терапию: ципрофлоксацин 100 мг 2 раза в сутки в/в, меропенем 1 г 3 раза в сутки в/в, ванкомицин 1 г 2 раза в сутки.

15.06.2021 г. рентгенологически двусторонняя пневмония. Бронхопульмональная лимфаденопатия. В сравнении с исследованием от 11.06.2021 г. положительная динамика.

Во время нахождения пациента в ОРИТ сохранялась трансфузионная зависимость.

На фоне интенсивной терапии отмечалось улучшение показателей гемограммы, стабилизация гемодинамики.

18.06.2021 г. пациент переведен в отделение химиотерапии гемобластозов.

Рентгенография ОГК от 21.06.2021 г.: правосторонняя сегментарная пневмония. Диффузный пневмосклероз. Малый двусторонний плеврит. Расширение средостения.

На фоне лечения сохранялась лихорадка до 38 °С, с 22.06.2021 г. к лечению добавлен анидулофунгин 200 мг в 1-й день, далее по 100 мг в/в кап.

По данным рентгенографии ОГК от 25.06.2021 г.: правосторонняя сегментарная пневмония, положительная динамика от 21.06.2021 г. Диффузный пневмосклероз. Малый двусторонний плеврит. Расширение средостения.

На 22-й день терапии в режиме венетоклакс + азацитидин на фоне сопроводительной, антибактериальной, противогрибковой терапии лихорадка купирована, состояние пациента удовлетворительное, ликвидирована трансфузионная зависимость, необходимость в кислородной поддержке. В гемограмме от 29.06.2021 г.: Hb — 87 г/л, лейкоциты — 4,74 × 10^9/л, тромбоциты — 409 × 10^9/л, абсолютное число нейтрофилов — 2,5 × 10^9/л.

На 27-й день терапии в режиме венетоклакс + азацитидин выполнена стернальная пункция.

В миелограмме: миелокариоциты — 85 × 10^9/л, бласты — 0, промиелоциты — 2,4 %.

По результатам иммунофенотипирования в костном мозге клеток с аберрантным фенотипом не выявлено. Констатирована 1-я костномозговая ремиссия, с неопределяемой минимальной остаточной болезнью.

Далее проведено 6 курсов терапии в режиме венетоклакс + азацитидин. Проявлений гематологической, негематологической токсичности не отмечалось. При контрольном обследовании в марте 2022 г. сохранялась ремиссия, от дальнейшего лечения пациент отказался. За период динамического наблюдения по ноябрь 2023 г. в гемограмме показатели в пределах референсных значений, инфекционных осложнений не было. При контрольном обследовании в ноябре 2023 г. в гемограмме: лейкоциты — 9,53 × 10^9/л, нейтрофилы — 5,11 × 10^9/л, эритроциты — 5,73 × 10^{12}/л, Hb — 178 г/л, тромбоциты — 244 × 10^9/л. В миелограмме бласты 1,4 % при нормальной клеточности. По результатам иммунофенотипирования в костном мозге клеток с аберрантным фенотипом не выявлено.

Заключение. Таким образом, данный случай демонстрирует возможность проведения терапии острого лейкоза у пожилого пациента со значимой коморбидностью на фоне тяжелых инфекционных осложнений. Пациент провел в стационаре 56 койко-дней, из них 33 в ОРИТ. На фоне терапии венетоклаксом в комбинации с азацитидином удалось достичь ремиссии, восстановления показателей гемограммы и разрешения инфекционных осложнений.

Применение триоксида мышьяка в рецидиве острого промиелоцитарного лейкоза во время беременности

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Резюме. Описан клинический случай применения триоксида мышьяка в рецидиве острого промиелоцитарного лейкоза, дебютировавшего во время беременности во втором триместре, при сроке 16 недель.

Введение. Острый промиелоцитарный лейкоз (ОПЛ) составляет около 10 % случаев острого миелоидного лейкоза (ОМЛ) и характеризуется сбалансированной транслокацией между хромосомами 15 и 17, в резуль-

тате которой происходит слияние гена промиелоцитарного лейкоза и рецептора ретиноевой кислоты альфа (RARA), что обеспечивает чувствительность к лечению химиотерапией на основе антрациклинов и дифференцирующим агентам, таким как полностью трансретиноевая кислота (ATRA). При этом частота излечения составляет около 90 % [1]. Хотя современная комбинированная терапия ATRA и триоксидом мышьяка (ATO) эффективна для достижения полной ремиссии у большинства пациентов, применение этой схемы у беременных женщин остается спорным. ATO обладает значительным трансплацентарным переносом и высокой эмбриотоксичностью [2, 3]. В связи с этим его применение при беременности не рекомендуется. Исследования, сочетающие ATRA и химиотерапию антрациклинами, проведенные за последние два десятилетия, показали практически полное отсутствие первичной резистентности, 90–95% показатели полной ремиссии и 85–90% показатели долгосрочной выживаемости.

Одноцентровое исследование из Гонконга с использованием перорального препарата ATO также показало отличные долгосрочные результаты при рецидиве ОПЛ [2].

В Австралии капсулированный пероральный препарат ATO в настоящее время проходит испытания биодоступности в рамках ALLG (ACTRN12616001022459), а в США и Европе будет проведено международное многоцентровое исследование III фазы, в котором сравниваются ATRA плюс пероральный ATO и ATRA плюс ATO у пациентов с ОПЛ без высокого риска с целью определения роли пероральных производных мышьяка в первой линии терапии.

Кроме того, лечение ОПЛ представляет собой сложную задачу из-за присущего ему гиперфибринолитического состояния, синдрома дифференцировки, вызванного лечением, а также инфекционных осложнений [1]. Беременность, связанная с ОПЛ, встречается крайне редко и усложняет ее ведение [3–5]. ОПЛ и его лечение во время беременности могут привести к материнским осложнениям, таким как коагулопатия и аборты, а также к осложнениям для плода, таким как преждевременные роды и внутриутробная задержка роста [6].

Клинические сведения о тактике лечения ОПЛ при беременности в основном базируются на отчетах о случаях, реестрах, клинических испытаниях с небольшим размером выборки или исследованиях, проведенных по нерандомизированному дизайну. Поэтому особые аспекты ведения таких пациентов нуждаются в обсуждении. В настоящем исследовании представлен успешный клинический опыт применения триоксида мышьяка в сочетании с ATRA в позднем рецидиве (2 года 2 месяца) ОПЛ, дебютировавшего во время беременности в гестационном сроке 16 недель (II триместр).

Описание клинического случая. Пациентка З., 39 лет, поступила в гематологическое отделение в ГКБ № 7 с жалобами на общую слабость, периодические носовые и десневые кровотечения. Общую слабость отмечает в течение 10 дней, носовые и десневые кровотечения были 7 дней назад и прекратились самостоятельно. На диспансерном учете у гематолога ранее не состояла. Встала на учет к гинекологу по беременности в сроке 12 недель + 4 дня. Общее состояние при поступлении тяжелое за счет опухолево-интоксикационного и геморрагического синдромов. Температура тела 36,6 °С. В сознании, адекватна. Кожные покровы и видимые слизистые бледной окраски, отмечаются единичные экхимозы на местах инъекций.

В анамнезе жизни — сахарный диабет у матери, рак шейки матки у бабушки. Операции: кесарево сечение в 2012 и 2017 гг. В 2019 г. оперирована по поводу разрыва кисты. Гинекологический анамнез: беременность — 4.

1-я беременность — в 2005 г., роды, без осложнений.

2-я беременность — в 2012 г., кесарево сечение.

3-я беременность — в 2017 г., кесарево сечение.

4-беременность — 06.04.2020 г. (данная).

Обследования. Общий анализ крови от 30.01.2020 г: лейкоциты — 0,6 × 10^9/л, эритроциты — 1,97 × 10^{12}/л, Hb — 66 г/л, тромбоциты — 26 × 10^9/л, подсчет тромбоцитов — 39 × 10^9/л.

Миелограмма: бластные клетки — 53,2 %. Костный мозг гиперклеточный, на 53,2 % представлен бластными клетками крупных размеров, с высоким ядерно-цитоплазматическим соотношением, округлой формы ядрами, в цитоплазме отмечается обильная азурофильная зернистость и пучки палочек Ауэра. По данным иммунофенотипирования в образце костного мозга выявлена патологическая популяция клеток, составляющая 48 % по CD45. Клетки имеют промежуточную степень гранулярности. Суммарный фенотип патологической популяции CD117+CD13+CD33+HLA–DR–CD34–MPO+, характерный для миелоидной направленности дифференцировки. При цитогенетическом исследовании костного мозга хромосомных перестроек не выявлено. По данным FISH обнаружена перестройка гена *PML-RARA*, t (15.17). На основании указанных данных установлен диагноз: острый промиелоцитарный лейкоз, впервые выявленный, группа промежуточного риска, индукция ремиссии. Беременность в сроке 15 недель + 6 дней. Отягощенный акушерский анамнез. Рубец на матке (2).

Лечение. Проведен курс химиотерапии: индукция по схеме AIDA (ATRA в дозе 45мг/м^2 + даунорубицин в дозе 60 мг/м^2). Констатирована костномозговая ремиссия после завершения курса индукции. Контрольное исследование: в миелограмме бластов 1,6 %. Цитогенетическое исследование костного

мозга: хромосомной патологии не выявлено. УЗИ беременной: беременность в сроке 21 неделя. Угроза прерывания беременности. Был продолжен курс консолидации I по схеме AIDA с сопроводительной и гемотрансфузионной терапией. Пациентка была выписана после проведенного курса в связи с улучшением состояния, достигнута костномозговая ремиссия, срок беременности 23 недели + 5 дней. В сроке беременности 25 недель + 2 дня проведена лапароскопическая операция, экстренное кесарево сечение поперечным разрезом в нижнем сегменте по показанию «полное предлежание плаценты». Ребенок умер. Была проведена перевязка маточных артерий с обеих сторон по О'Лири, стерилизация маточных труб по Мадленеру. Далее продолжены курсы: консолидация II с 13.04.2020 г. по 15.05.2020 г., консолидация III с 30.05.2020 г. по 14.06.2020 г. по схеме AIDA. Сохранялась костномозговая ремиссия. В миелограмме от 05.05.2020 г.: бластные клетки — 1,20 %. FISH костного мозга на PML-RARA от 07.05.2020 г.: перестройки не выявлено. Пациентка была переведена на курс поддерживающей терапии с 07.08.2020 г. по 02.09.2022 г. (2 года 2 месяца). Терапия поддерживающего курса: ATRA 45мг/м^2 с 1-го по 15-й день, 6-меркаптопурин 50 мг/м^2/сут, метотрексат 15 мг/м^2 в сутки. Каждые 3 месяца проводилась пункция костного мозга. До 02.09.2022 г. сохранялась костномозговая ремиссия. В сентябре 2022 г. констатирован рецидив № 1. В общем анализе крови от 02.09.2022 г.: лейкоциты — 1,27 × 10^9/л, эритроциты — 3,65 × 10^{12}/л, Hb — 125,0 г/л, тромбоциты — 112 × 10^9/л. В миелограмме от 02.09.2022 г.: бластные клетки — 25,60 %. Со слов пациентки, в течение 4 мес. не принимала 6-меркаптопурин, на последнем курсе поддерживающий терапии (июнь 2022 г.) пропустила прием ATRA (Весаноид) (предварительно 5 дней) из-за тошноты. Госпитализирована в ГКБ № 7 в отделение гематологии для проведения курса АТО + ATRA. Перед началом курса в общем анализе крови: лейкоциты — 1,11 × 10^9/л, эритроциты — 3,67 × 10^{12}/л, Hb — 127,0 г/л, тромбоциты — 103 × 10^9/л. Миелограмма от 06.09.2022 г.: бластные клетки — 54,0 %. По данным иммунофенотипирования от 06.09.2022 г. в образце костного мозга выявлена патологическая популяция клеток, составляющая 36 % от общего числа ядросодержащих событий. Трансформированные клетки слабопозитивны по CD45, имели низкую степень гранулярности. Фенотип патологической популяции CD117+CD13+CD33+CD15+HLA+DR+CD34+MPO+ в сравнении с первичным иммунофенотипированием от 31.01.2020 г. (М3) без изменений. FISH-исследование: в 60 % клеток выявлена перестройка гена *PML/RARA* t(15:17).

Пациентка получила курс индукционной терапии согласно протоколу АТО + ATRA с достижением ремиссии на 30-й день терапии (бласты 2,4 %). После завершения индукционного курса проведены еще 4 курса консолидации ремиссии по схеме АТО + ATRA. Переносимость лечения удовлетворительная, из побочных эффектов отмечалась головная боль в первые 3–4 дня терапии, прошла самостоятельно. В данное время пациентка продолжает поддерживающую терапию, в контрольных анализах сохраняется костномозговая ремиссия.

Заключение. Несмотря на развитие позднего рецидива болезни, течение острого промиелоцитарного лейкоза на фоне беременности, отягощенный акушерский анамнез и сопутствующие заболевания, наличие перерывов в лечении в связи отсутствием препарата, пациентке удалось достигнуть второй полной ремиссии. Комбинация ATRA + АТО служит эффективной схемой терапии в рецидиве ОПЛ. Случаи рецидива ОПЛ, выявленные во время беременности, крайне редки, поэтому их описание представляется важным практическим материалом для врачей-гематологов.

Ключевые слова: ОПЛ, острый промиелоцитарный лейкоз, АТО, триоксид мышьяка, ATRA, беременность, поздний рецидив.

Литература

1. Sanz MA, Fenaux P, Tallman MS et al. Management of acute promyelocytic leukemia: Updated recommendations from an expert panel of the European LeukemiaNet. Blood. 2019;133:1630–1643.

2. Gill H, Yim R, Lee HKK et al. Long-term outcome of relapsed acute promyelocytic leukemia treated with oral arsenic trioxide-based reinduction and maintenance regimens: A 15-year prospective study. Cancer. 2018;124(11):2316–2326.

3. Saleh AJ, Alhejazi A, Ahmed SO et al. Leukemia during pregnancy: Long term follow up of 32 cases from a single institution. Hematol Oncol Stem Cell Ther. 2014;7:63–68. doi: 10.1016/j.hemonc.2014.03.001.

4. Jain N, Hubbard J, Vega F et al. Spontaneous remission of acute myeloid leukemia: Report of three cases and review of the literature. Clin Leuk. 2008;2:64–67.

5. Pentheroudakis G, Orecchia R, Hoekstra HJ, Pavlidis N. Cancer, fertility and pregnancy: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2010;21(Suppl 5):v266–v273. doi: 10.1093/annonc/mdq198. ESMO Guidelines Working Group.

6. Santolaria A, Perales A, Montesinos P, Sanz MA. Acute promyelocytic leukemia during pregnancy: A systematic review of the literature. Cancers (Basel). 2020;12(968) doi: 10.3390/cancers12040968.

Паранеопластический дерматомиозит в дебюте миелодиспластического синдрома: клинический случай из амбулаторной практики

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Введение. Экзантемы различного характера служат объективным непатогномоничным симптомом паранеопластического синдрома [1, 2, 4, 13, 14]. В структуре паранеопластического синдрома, по данным эпидемиологических исследований разных лет, проиллюстрированы клинические наблюдения пациентов с идиопатическими воспалительными миопатиями (ИВМ), как с состояниями, ассоциированными с развитием опухоли. Основными представителями группы ИВМ являются полимиозит и дерматомиозит [1, 14]. Однако при изучении вопроса взаимосвязи миелодиспластических процессов как онкогематологических состояний, ассоциированных с ИВМ, такие случаи объективизации нозологической формы крайне редки и, по данным исследований, составляют 6,3 % [1]. Как правило, в гематологической практике экзантемы проявляются в виде геморрагической сыпи и телеангиэктазий, реже в виде лейкемид. При этом задача первичной дифференциальной диагностики в таких случаях обычно стоит перед специалистом амбулаторного звена. Следует отметить, что информированность врачей о паранеопластическом синдроме имеет большое значение для ранней диагностики опухолей, поскольку развитие классической клинической картины ИВМ может предшествовать клинической манифестации онкологического заболевания, возникнуть одновременно с ним, и в ряде случаев диагностика опухоли предшествует проявлениям ИВМ.

Цель. Описание клинического случая.

Материалы и методы. В клинико-диагностическое отделение гематологии и химиотерапии с дневным стационаром РосНИИГТ обратился мужчина 75 лет с жалобами на высыпания симметричного характера по всему телу в течение трех месяцев, мышечную слабость, невыраженный кожный зуд, отечность орбит. У пациента неотягощенные эпидемиологический и аллергологический анамнезы.

Объективно: кожно-мышечный синдром характеризовался распространенной эритемой на лице, на лбу, на волосистой части головы, на груди и спине (зоны «декольте», «шали»), параорбитальным отеком. Выявлена проксимальная мышечная слабость, пациентом отмечены явления дисфонии и дисфагии. Видимые слизистые чистые, бледные проявления геморрагического синдрома отсутствовали (рис. 1).

Лабораторные исследования позволили исключить маркеры инфекций-оппортунистов и ревматологическую патологию. Креатинфосфокиназа — 46 Ед/д (норма 0–190 Ед/л), концентрация сывороточного иммуноглобулина Е — 211,9 МЕ/л (норма 0,0–100,0 МЕ/мл). Пациент был серонегативен по анти-Jo-1.

В гемограмме — трехростковая цитопения, гиперхромия, макроцитоз (эритроциты — 2,49 × 10^{12}/л, Hb — 73 г/л, MCV — 101,4 фл, MCH — 36,9 пг, MCHC — 364 г/л, лейкоциты — 2,0 × 10^{9}/л, ANC — 0,9 × 10^{9}/л, тромбоциты — 68 × 10^{9}/л, моноциты — 17,3 %, лимфоциты — 49,5 %) и ускоренная СОЭ 34 мм/ч. В биохимическом анализе крови: B12 — 424 пг/мл, ферритин — 712,5 мкг/л, фолиевая кислота — 8,8 нмоль/л, лактатдегидрогеназа — 271 Ед/л, железо сыворотки — 19,19 мкмоль/л.

Учитывая трехростковую цитопению, у пациента заподозрен миелодиспластический синдром. В костном мозге бласты 8 %, дисплазия гранулоцитарного, эритроидного и мегакариоцитарного ростков (> 10 %), повышено число моноцитов (11,6 %), среди которых встречаются моноциты с гиперсегментацией ядер и выраженной вакуолизацией цитоплазмы, и клеток лимфатического ряда (17,2 %). Иммунофенотипирование клеток костного мозга не выполнялось. По результатам стандартного цитогенетического исследования плификация локуса гена MECOM/3q26 с делецией центромерного участка выявлена в 28,0 % проанализированных интерфазных ядер.

Таким образом, у пациента был верифицирован миелодиспластический синдром IPSS 1,5 б., IPSS-R 2 б., с неспецифическими проявлениями в виде иммуновоспалительной миопатии по типу дерматомиозита.

Дифференциальная диагностика указанной экзантемы в амбулаторных условиях не позволяет выполнить некоторые специфические исследования, такие как электронейромиография. Принимая во внимание высокий риск инфекционных осложнений, биопсия кожи не выполнена.

Обсуждение. В структуре миелоидных неоплазий клинические манифестации ИВМ описаны редко [4, 6, 7, 9, 11, 12]. Встречающиеся описания сводятся к патогенетическим механизмам, связанным с инфильтрацией клетками патологического клона, моноцитами с выраженной вакуолизацией цитоплаз-

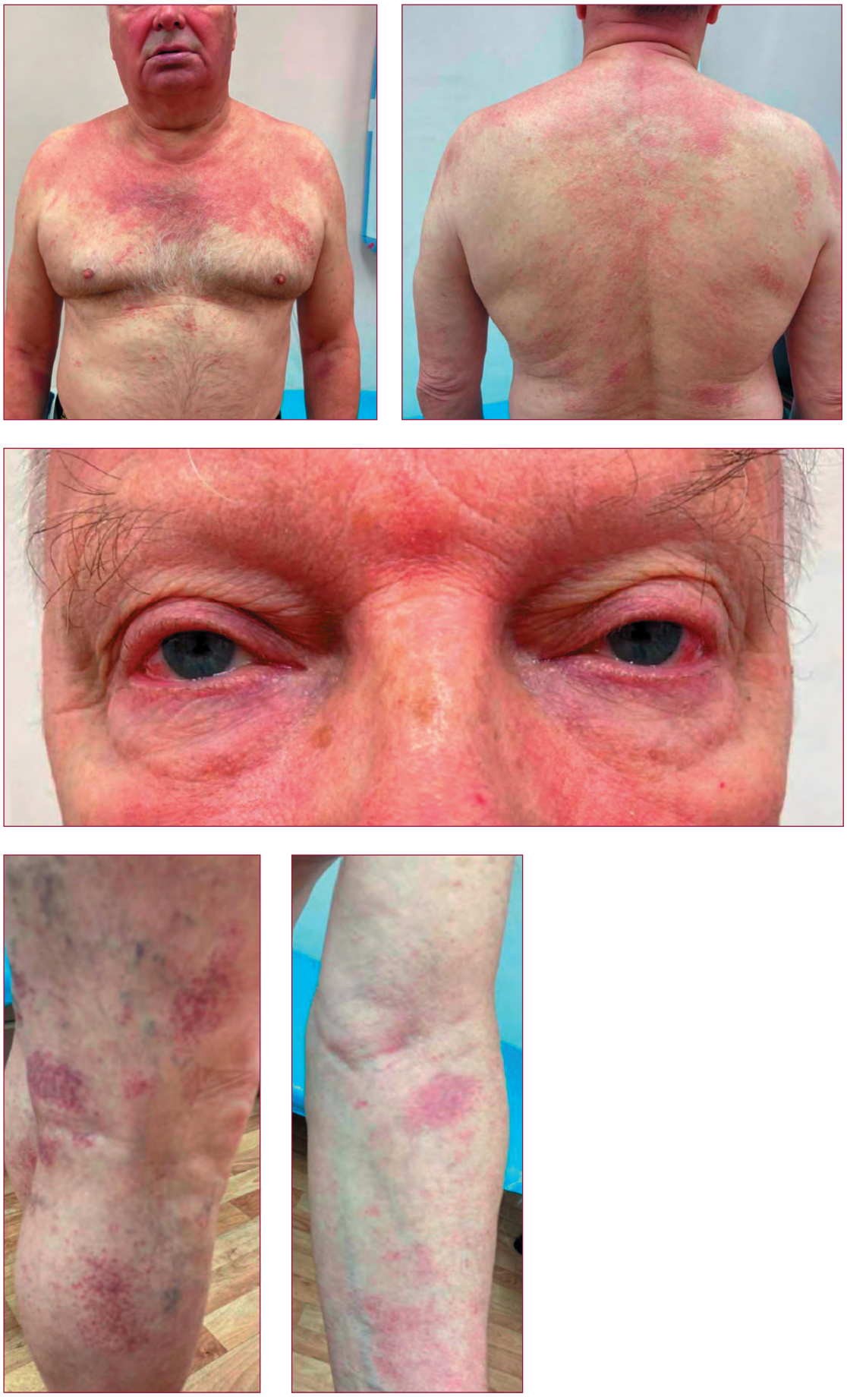

Рис. 1. (*А, В*) Эритема на лице, (*Б*) на спине, (*Г, Д*) на руках и ногах

мы, лимфоцитами и нейтрофилами участков кожи, подкожно-жировой клетчатки и мышц, активацией гистиоцитов и тканевых макрофагов [2]. Немногочисленные данные свидетельствуют о необходимости описания подобных клинических вариантов с целью систематизации и изучения.

Заключение. С указанными жалобами пациент осматривался врачами разных специальностей в течение двух месяцев до обращения к гематологу, что позволяет отнести данный клинический случай к числу предшествующих клинической манифестации онкологического заболевания. Исход диагностического поиска является подтверждением ассоциации опухолевого процесса и паранеопластического синдрома, а в представленном примере миелодиспластического синдрома с иммуновоспалительной миопатией — дерматомиозитом. Отдельно следует отметить, что описанный клинический пример призывает помнить об экзантеме как о маске болезни, о патологическом процессе в дебюте возможного онкологического заболевания.

Литература

1. Антелава О. А., Хелковская-Сергеева А. Н., Чичасова Н. В. и др. Миозит, ассоциированный со злокачественными опухолями. Научно-практическая ревматология. 2016;54(3):289–298.

2. Белоусова И. Э, Казаков Д. В., Самцов А. В. Лимфопролиферативные заболевания кожи. Клиника и диагностика. М.: ГЭОТАР-Медиа, 2022.

3. Ведяшкина М. С., Дубровская А. М., Лопатина О. В. и др. Клинический случай односторонней латероторакальной экзантемы. Педиатрическая фармакология. 2020;17(4):340–344.

4. Ambrosone L, Migliaresi S, Rambaldi A, Rambaldi M. Adult polyomyositis/dermatomyositis associated with acute myeloid leukemia. A case report. Clin Rheumatol . 1995;14(2):217–219.

5. Arnold JA, Ranson SA, Abdalla SH. Azathioprine-associated acute myeloid leukaemia with trilineage dysplasia and complex karyotype: a casereport and review of the literature. Clin Haematol. 1999;21(4):289–292.

6. Carrera C, Cibeira MT, Iranzo P et al. Dermatomyositis associated with acute myeloid leukaemia: a paraneoplastic association or a drug-induced phenomenon? Acta Derm Venereol. 2004;84(5):401–402.

7. Shrivastav A, Kumar V,Pal J. Dermatomyositis associated with acute myelocytic leukemia. Rheumatol Int. 2010;30(5):671–673.

8. Lima M, Coutinho J, Bernardo L et al. Philadelphia positive T-cell acute lymphoblastic leukemia with polymyositis, migratory polyarthritis and hypercalcemia following a chronic myeloid leukemia. Ann Hematol. 2002;81(3):174–177.

9. Evans FJ, Hilton JH. Polymyositis associated with acute monocytic leukemia: case report and review of the literature. Can Med Assoc J. 1964;12(91):1272–1275.

10. Hill CL, Zhang Y, Sigurgeirsson B et al. Frequency of specific cancer types in dermatomyositis and polymyositis: a population-base study. Lancet. 2001;357:96–100.

11. Sugawara T, Endo K, Kimura J et al. () Dermatomyositis associated with acute promyelocytic leukemia. Am J Hematol. 1992;40(3):242–243.

12. Shen J-K, Ding YM, Zhou WJ, Jin J. Polymyositis/dermatomyositis associated with acute myelocytic leukemia. Rheumatol Int. 2008;28:1265–1267.

13. Hill CL, Zhang Y, Sigurgeirsson B et al. Frequency of specific cancer types in dermatomyositis and polymyositis: a population-base study. Lancet. 2001;357:96–100.

14. Wakata N, Kurihara T, Saito E, Kinoshita M. Polymyositis and dermatomyositis associated with malignancy: a 30-year retrospective study. Int J Dermatol. 2002;41(11):729–734.

Гидроксимочевина в лечении кожной формы гистиоцитоза из клеток Лангерганса

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Введение. Гистиоцитоз из клеток Лангерганса (ГКЛ) относится к редким клональным заболеваниям гистиоцитов и дендритных клеток. Ведущей причиной развития ГКЛ считают мутацию в генах митоген-активируемых протеинкиназ (МАПК). Заболевание может протекать как с формированием одиночного очага, так и в виде диссеминированного процесса с вовлечением одной или нескольких систем органов. Описаны варианты с изолированным поражением кожи. Крупных исследований по лечению кожных форм ГКЛ у взрослых не проводилось. Терапия первой линии обычно включает малые дозы метотрексата. Кроме того, применяют этопозид, таргетные препараты, винбластин и гидроксимочевину.

Описание клинического случая. У пациента умеренный зуд волосистой части кожи головы появился в возрасте 16 лет. В 2022 г., в возрасте 23 лет, в связи с нарастанием лимфореи, болезненных ощущений и гиперкератоза кожи волосистой части головы выполнена биопсия кожи с гистологическим и иммуногистохимическим исследованием.

В дерме обнаружен диффузный инфильтрат преимущественно из клеток гистиоцитарно-макрофагального ряда с крупными гиперхромными ядрами бобовидной конфигурации и экспрессией CD1a и CD207. Диагностирован гистиоцитоз из клеток Лангерганса. При панельном секвенировании ДНК 69 генов мутаций, описанных при гистиоцитарных и миелоидных (включая МАПК) опухолях, не выявлено.

По результатам совмещенной позитронно-эмиссионной томографии всего тела и магнитно-резонансной томографии головного мозга других очагов не обнаружено. Констатировано изолированное кожное поражение.

С декабря 2022 г. начата терапия метотрексатом 25 мг один раз в неделю. Уже после первого приема отмечена значительная положительная динамика в виде уменьшения зуда, лимфореи, однако из-за развития тяжелых нежелательных явлений (диарея, тошнота и рвота в течение 3–4 дней после приема) лечение было прекращено, и кожные изменения вновь стали нарастать. С апреля 2023 г. проводится лечение гидроксикарбамидом по 1000 мг в сутки. Уже через месяц отмечено разрешение высыпаний, зуда, боли и лимфореи (рис. 1). Терапия продолжается в течение восьми месяцев. Пациент переносит лечение удовлетворительно.

Заключение. Лечение пациента с изолированным поражением кожи гистиоцитозом из клеток Лангерганса гидроксикарбамидом в дозе 1000 мг в сутки привело к стойкому ответу.

Ключевые слова: гистиоцитоз из клеток Лангреганса, гидроксимочевина, митоген-активируемые протеинкиназы.

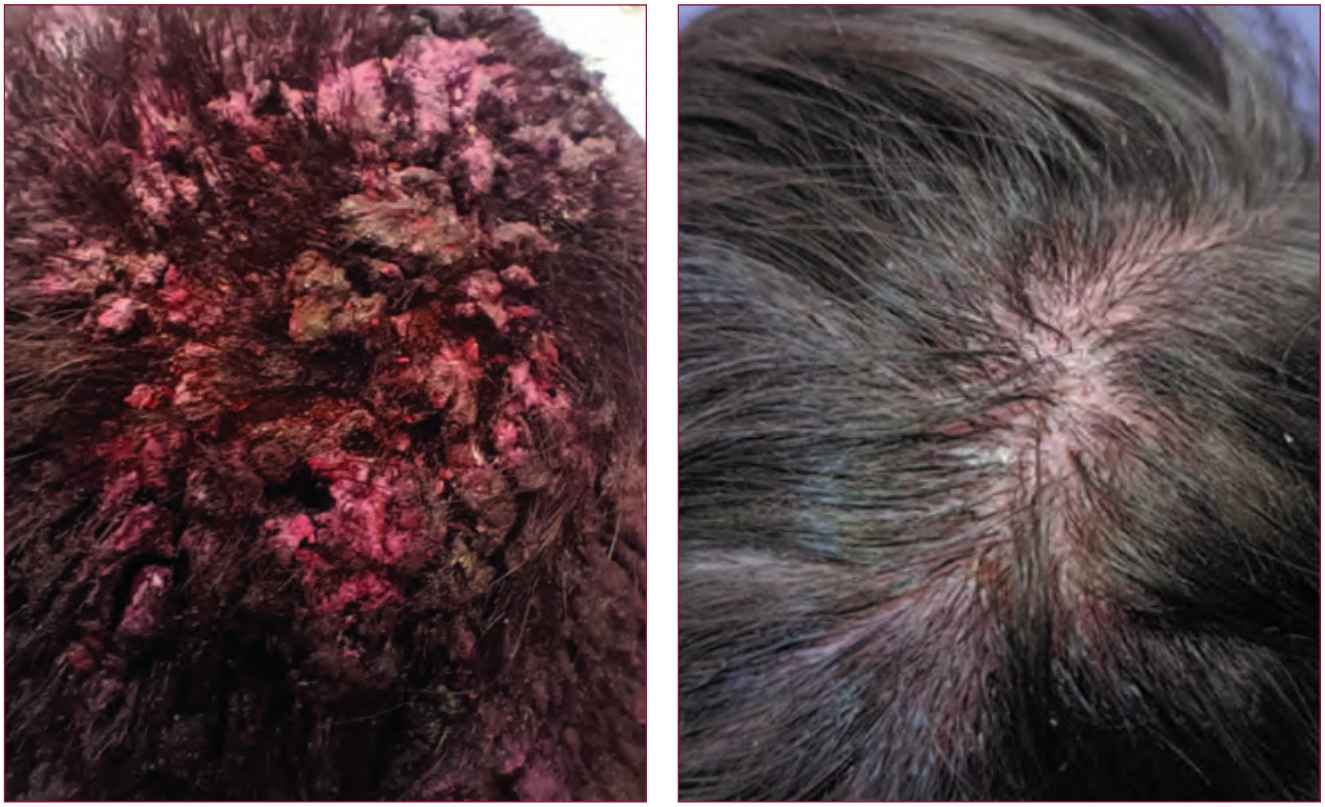

Рис. 1. Пациент, 23 лет: (*А*) кожа волосистой части головы до начала химиотерапии (корки обработаны фукорцином); (*Б*) через месяц после начала лечения гидроксимочевиной

Сложности дифференциальной диагностики между аутоиммунным и тройным негативным первичным миелофиброзом: описание клинического случая

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Введение. Фиброз костного мозга может возникать в результате самых разных состояний: от злокачественных новообразований до неопухолевых состояний, таких как инфекции, эндокринные нарушения и аутоиммунные заболевания [1]. Фиброз обычно наблюдается при гематологических злокачественных новообразованиях, включая миелопролиферативные новообразования (МПН), миелодиспластический синдром и, редко, лимфопролиферативные заболевания [2]. Наиболее распространенной причиной фиброза костного мозга служит первичный миелофиброз (ПМФ).

Аутоиммунный миелофиброз (АИМФ) — редкая этиология фиброза костного мозга и чаще всего сопровождается другими аутоиммунными заболеваниями, такими как системная красная волчанка, ревматоидный артрит, синдром Шегрена, язвенный колит и первичный билиарный цирроз, при этом в большинстве случаев поражаются женщины в возрасте до 40 лет. АИМФ часто связан с доброкачественными гематологическими состояниями, такими как аутоиммунная гемолитическая анемия, идиопатическая тромбоцитопеническая пурпура и синдром Эванса.

У пациентов с АИМФ наблюдаются цитопения и аутоантитела, а также характерный неклональный миелофиброз при исследовании костного мозга. АИМФ отличается от ПМФ отсутствием спленомегалии, эозинофилии или базофилии, а также отсутствием аномальной миелоидной, эритроидной или мегакариоцитарной морфологии.

Крайне важно дифференцировать АИМФ от ПМФ, поскольку клиническое течение, прогностические последствия и варианты лечения сильно различаются. Возможность дифференцировать два заболевания часто осложняется перекрытием патологических признаков и тем фактом, что аутоиммунные нарушения, такие как наличие аутоиммунных серологических реакций, могут быть выявлены в обоих заболеваниях. Цитокин-зависимые механизмы стимулируют фиброз костного мозга как при АИМФ, так и при ПМФ; однако преобладающий источник цитокинов, включая трансформирующий фактор роста β (TGF-β), γ-интерферон (IFN-γ), интерлейкин-8 (IL-8), IL-2, IL-17 и липокалин-2 (LCN2), вероятно, различается: цитокины, полученные из лимфоидных агрегатов, управляющих АИМФ, и цитокины, полученные из мегакариоцитов и тромбоцитов, опосредующие фиброз при ПМФ. В конечном счете клональность является определяющей особенностью ПМФ, а драйверные мутации (*JAK2*, *MPL* или *CALR*) обнаруживаются в 90 % случаев [3].

Описание клинического случая. Пациентка 1991 г. р. с ноября 2022 г. стала отмечать дискомфорт, боль слева в подреберной области, снижение массы тела до 12 кг за 4 мес. Со слов, постепенное увеличение размеров селезенки отмечает ориентировочно с 2018 г. Пациентка отрицала личный/семейный тромботический и геморрагический анамнезы.

Амбулаторно диагностирована гипохромная анемия легкой степени тяжести, гипербилирубинемия за счет неконьюгированной фракции. По данным КТ абдоминального сегмента с контрастированием картина гепатомегалии, выраженной спленомегалии с обширными гиподенсивными участками с инфильтрацией клетчатки вокруг селезенки и сдавленной левой почки, с осумкованным выпотом вокруг, внутрибрюшной лимфаденопатией. По данным УЗИ размеры селезенки 21,4 × 11,6 см (площадь 199 см^2).

В период с ноября 2022 г. по август 2023 г. была обследована у гематолога. В анализе крови: Hb — 87 г/л, лейкоциты — 5,34 тыс/мкл, тромбоциты — 170 тыс/мкл, цветной показатель — 0,80, эритроциты — 3,61 млн/мкл. В формуле: лимфоциты — 12 %, моноциты — 3 %, палочкоядерные — 3 %, сегментоядерные — 81 %, эозинофилы — 1 %. На основании снижения уровня гемоглобина до 87 г/л, ретикулоцитоза (6 %), повышения концентрации лактатдегидрогеназы до 459 Ед/л, положительной прямой пробы Кумбса, снижения гаптоглобина менее 8,0 мг/дл констатирована аутоиммунная гемолитическая анемия средней степени тяжести.

Внимание привлекли изменения в коагулограмме: АЧТВ — 112,2 с, МНО — 1,67, протромбиновое время — 18,4 с, ПТИ — 56 %. Обнаружен дефицит факторов свертывания крови VII, VIII, IX с наличием ингибиторов к факторам VIII, IX.

По результатам цитологического исследования костного мозга отмечалось расширение эритрона.

Проведено гистологическое исследование костного мозга — выявлена гиперплазия миелоидной ткани с гранулоцитарным сдвигом влево; пролиферация зрелых мегакариоцитов с атипичной морфологией (клетки с уродливыми гипо-, гиперлобулярными, дисморфными ядрами); с формированием преимущественно рыхлых скоплений среди клеток миелоидной ткани, с обнаружением на поверхности костных

балок; диффузный ретикулиновый фиброз (MF-1 — 80 %, MF-2 — 20 %).

Данных за лимфопролиферативное заболевание по результатам иммунофенотипирования не обнаружено. ПНГ-клон был исключен. Выявлен антинуклеарный фактор (АНФ) на HEp-2-клетках 1:1280 (мембранный тип свечения).

Проведен 2-й этап обследования на определение молекулярно-генетического профиля: мутации в генах *JAK2 V617F, CALR* (мутации 9-го экзона), *MPL* (мутации 515-го кодона), *ASXL1* (кодоны 574–1082) не обнаружены.

В феврале 2023 г. у пациентки произошел острый окклюзирующий флеботромбоз бедренно-подколенного сегмента левой нижней конечности. На момент осмотра без признаков флотации. Проходимость подвздошно-бедренного и берцового сегментов правой нижней конечности сохранена. В условиях отделения сосудистой хирургии проводилась антикоагулянтная терапия.

По результатам проведенных дообследований у пациентки верифицирован первичный миелофиброз (MF-1 — 80 %, MF-2 — 20 %). Группа промежуточного риска 2 по критериям IPSS (2 балла). Наличие дефицита факторов VI, VIII, IX и ингибиторов к VIII, IX и аутоиммунная гемолитическая анемия расценены как аутоиммунные осложнения основного заболевания.

С учетом наличия аутоиммунных осложнений и выраженного фиброза у пациентки проводилась дифференциальная диагностика между АИМФ на фоне системного заболевания (системная красная волчанка?) и миелофиброзом при МПН (первичный миелофиброз, вторичный миелофиброз).

Была определена следующая тактика:

1. С учетом подтвержденного миелофиброза с целью уменьшения размеров селезенки, В-симптомов, улучшения качества жизни решено начать специфическую терапию препаратом из группы ингибиторов JAK-киназ — руксолитиниб в дозе 40 мг/сут (по 20 мг 2 раза в день).

2. Несмотря на высокие риски геморрагических осложнений на фоне дефицита факторов системы гемостаза VIII, IX, необходимо продолжить антикоагулянтную терапию надропарином кальция в дозе 0,6 мл 2 раза в день в течение 2 недель с последующим возможным переводом на ривароксабан.

3. Обсуждался вопрос о начале иммуносупрессивной терапии в связи с наличием аутоиммунных осложнений. Однако, учитывая отсутствие выраженных проявлений геморрагического синдрома и наличие острого флеботромбоза, в связи с высоким риском тромботических осложнений решено временно воздержаться от начала терапии.

Начата специфическая терапия руксолитинибом 40 мг в сутки с февраля 2023 г.

В июле 2023 г. ангиохирургом отменена антикоагулянтная терапия ривароксабаном. При контрольном УЗДГ вен нижних конечностей в августе 2023 г. посттромбофлебитическая болезнь бедренно-подколенного сегмента левой нижней конечности. Реканализация до 10 %, неудовлетворительная. Не исключен ретромбоз, на момент осмотра без признаков флотации (табл. 1).

С учетом отягощенного тромботического анамнеза было решено провести обследование на предмет гематогенных тромбофилий. Выявлено соотношение волчаночного антикоагулянта LA1/LA2: 2,15, антитела к β2-гликопротеину IgM > 100 ед/мл (норма менее 5), антитела к β2-гликопротеину IgG 6,0 ед/мл. Исследования проведены на фоне тромбоза, высокая вероятность некорректных результатов (на момент обследования результаты УЗДГ были в работе). Пациентке рекомендован контроль не менее чем через 12 недель. Рекомендации не выполнены.

На момент обследования пациентка оказалась беременной в сроке 4 недели (пациентка не знала). Беременность закончилась выкидышем.

В настоящее время пациентка принимает руксолитиниб 15 мг 2 раза в день.

Относительно наличия у пациентки приобретенной гемофилии проведено обсуждение, и мы пришли к консенсусу, что у пациентки нет данных за истинный дефицит факторов системы гемостаза и ингибиторов к ним, на основании отсутствия геморрагического синдрома, наличия тромбозов, а также в связи с тем, что снижена активность сразу нескольких факторов свертывания, определяемых клоттинговыми тестами, т. е. результаты скрининга (и смешивания) тестов могут имитировать наличие ингибиторов анти-FVIII. Обычно к ним относятся состояния, связанные с длительным АЧТВ, не корректируемым тестом на смешивание, т. е., например, присутствием волчаночных антикоагулянтов (LA), как в нашей ситуации.

Диагностировать истинную приобретенную гемофилию возможно посредством хромогенного теста, однако в связи с отсутствием реактивов в Республике Казахстан, а также в лабораториях-партнерах Российской Федерации проведение данного исследования до сих пор невозможно.

Таблица 1. Клинико-лабораторные показатели в динамике

	Селезенка, см	Фактор VII, %	Фактор VIII/ ингибитор, %/ БЕ	Фактор IX/ ингибитор, %/ БЕ	Hb, г/л	PLT, тыс./мкл	WBC, тыс./мкл	АЧТВ, с
До терапии	+28	56,0	14,70/5,6	1/5,25	87	170	5,34	112,2
Апрель 2023 г.	+10	78,40	26,20/–	8/1,025	94	109	2,7	112,8
Август 2023 г. (ретромбоз)	+8	76,2	32.40/355,84	26/–	105	229	4,4	52,3

Заключение. Дифференцирование между ПМФ и неопухолевым АИМФ имеет первостепенное значение, поскольку прогноз и варианты лечения различны. Однако диагностика может быть осложнена из-за совпадения результатов в двух формах заболевания.

Ниже представлены ключевые отличительные особенности АИМФ и ПМФ [3] (табл. 2).

Дифференцированная диагностика ПМФ и АИМФ затрудняется в первую очередь двумя факторами: тонкими различиями в морфологии костного мозга и возможным наличием аутоантител при ПМФ. Лимфоцитарная инфильтрация подтверждает диагноз АИМФ, а мегакариоцитарная атипия подтверждает диагноз ПМФ.

Высокая распространенность аутоиммунных явлений, связанных с ПМФ, затрудняет дифференциальную диагностику. Хотя при АИФМ ожидается наличие сопутствующего аутоиммунного заболевания или серологических признаков аутоантител, что обычно документируется прямым результатом антиглобулинового теста, положительными антинуклеарными антителами (как в случае с нашей пациенткой), ревматоидным фактором, но ни одно из этих серологических исследований не является специфичным для АИМФ [4]. По данным шведского исследования, сравнивавшего 11 039 пациентов с МПН и группу контроля (n = 43 550), у больных с уже установленным аутоиммунным заболеванием риск развития МПН был повышен на 20 %. Аутоиммунными заболеваниями, связанными с этим повышенным риском, были идиопатическая тромбоцитопеническая пурпура, болезнь Крона, ревматическая полимиалгия, гигантоклеточный артериит, синдром Рейтера и апластическая анемия [5].

Однако связь между аутоиммунными заболеваниями и МПН остается неясной, и, вероятно, здесь задействованы различные факторы. Одна из гипотез заключается в том, что воспаление, связанное с аутоиммунным заболеванием, приводит к неопластической трансформации. С другой стороны, совпадение аутоиммунных заболеваний и МПН может быть связано с совпадением генетической и экологической восприимчивости. Кроме того, возможно, что лечение аутоиммунных заболеваний, включая противовоспалительные средства и иммунодепрессанты, изменяет клеточную среду костного мозга, что, в свою очередь, способствует развитию МПН.

Из-за невозможности в некоторых случаях четко дифференцировать ПМФ и АИМФ только на основании патологических особенностей и тестирования на антитела особенно важно оценить полную клиническую картину. Оба состояния часто сопровождаются цитопениями, однако у пациентов с ПМФ обычно наблюдается гораздо большее количество симптомов, включая конституциональные симптомы, и часто наблюдаются изнурительная усталость и диффузная боль в костях. Пациенты с АИМФ часто имеют минимальную симптоматику, которая может быть прямым следствием анемии, если она имеется. Спленомегалия также может быть отличительным фактором.

Клональность служит основным отличительным фактором между ПМФ и АИМФ. Мутации в трех генах-драйверах *JAK2*, *CALR* и *MPL* обнаруживаются в 90 % случаев ПМФ. Мутация-драйвер не выявляется менее чем в 10 % случаев ПМФ, а субклональные мутации не выявляются примерно в 20 %, что может со-

Таблица 2. Ключевые отличительные особенности аутоиммуного и первичного миелофиброза

Признаки	ПМФ	АИМФ
Гистологическая картина костного мозга		
Мегакариоциты	Пролиферация или атипия	Отсутствие кластеров/атипии
Миелоидная/эритроидная дисплазия	+/–	–
Базофилия или эозинофилия	+/–	–
Лимфоцитарная инфильтрация	+/–	+
Остеосклероз	+/–	–
Лабораторные критерии		
Анемия	+/–	+/–
Лейкоцитоз	Обычно +	+/–
Повышение концентрации лактатдегидрогеназы	Обычно +	+/–
Аутоантитела	+/–	+
Клинические особенности		
Конституциональные симптомы	Часто	Нечасто
Спленомегалия	Часто	Отсутствует/нечасто
Другие признаки		
Лейкоэритробластоз	+	+/–
Мутации генов *JAK2 V617F, CALR, MPL*	+ (90 % случаев)	–

здать проблему при дифференциации ПМФ и АИМФ, как в данном клиническом случае.

Гистологическая картина не оставляет сомнений в диагнозе ПМФ, но в то же время имеется высокий титр антинуклеарного фактора (АНФ) на HEp-2-клетках 1:1280 (мембранный тип свечения), который характерен для аутоиммунных цитопений, аутоиммунных заболеваний печени (первичный билиарный цирроз, склерозирующий холангит), линейной склеродермии, антифосфолипидного синдрома, смешанных заболеваний соединительной ткани. Вышеуказанные заболевания могут быть как первопричиной изменений в костном мозге и системе гемостаза, так и сопутствующей патологией.

Наличие самостоятельного аутоиммунного заболевания у пациентки остается под вопросом ввиду того, что она не прошла дообследование у ревматолога.

АИМФ и ПМФ являются разными состояниями, однако совпадение их костномозговых и клинических особенностей может представлять собой диагностическую проблему для врача. Чтобы различать эти два разных диагноза, важно учитывать клиническую картину в дополнение к лабораторным, патолого-анатомическим и молекулярным данным.

Литература

1. Kuter DJ, Bain B, Mufti G et al. Bone marrow fibrosis: pathophysiology and clinical significance of increased bone marrow stromal fibres. Br J Haematol. 2007;139(3):351–362.

2. Etienne A, Gruson B, Chatelain D et al. Myelofibrosis-associated lymphoproliferative disease: retrospective study of 16 cases and literature review [published online November 25, 2009]. Adv Hematol. 2009;2009:179847. doi:10.1155/2009/179847.

3. Marcellino B, El Jamal SM, Mascarenhas JO. Distinguishing autoimmune myelofibrosis from primary myelofibrosis. Clin Adv Hematol Oncol. 2018;16(9):619–626. PMID: 30256778

4. Piatek CI, Vergara-Lluri ME, Pullarkat V et al. Autoimmune myelofibrosis: clinical features, course, and outcome. Acta Haematol. 2017;138(3):129–137.

5. Kristinsson SY, Landgren O, Samuelsson J et al. Autoimmunity and the risk of myeloproliferative neoplasms. Haematologica. 2010;95(7):1216–1220.

Клинический случай успешного применения венетоклакса и обинутузумаба в лечении пациента с хроническим лимфоцитарным лейкозом с неблагоприятным прогнозом (наличием делеции 17p)

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Введение. Применение венетоклакса (селективного ингибитора антиапоптотического белка Bcl-2) как единственного терапевтического агента в качестве 1-й линии терапии в лечении хронического лимфолейкоза с неблагоприятным прогнозом (наличием делеции 17p) показало высокую эффективность препарата [4], и следующим этапом исследования терапевтических возможностей стала комбинированная терапия. Высокоэффективной оказалась комбинация венетоклакса в сочетании с обинутузумабом [3]. Представлен клинический случай хронического лимфолейкоза с неблагоприятным прогнозом (наличием делеции 17p) и рефрактерностью к стандартной иммунохимиотерапии RFC с положительным эффектом от комбинированной терапии венетоклаксом и обинутузумабом.

Описание клинического случая. Пациент — мужчина, 58 лет. Болезнь дебютировала в марте 2022 г. с увеличения периферических лимфоузлов, профузной потливости, похудания, нарастания общей слабости, в анализе крови — абсолютный лимфоцитоз. В мае 2022 г. терапевтом проведена МСКТ органов брюшной полости и грудной клетки: выявлены спленомегалия (171 × 146 × 109 мм), конгломераты абдоминальных лимфоузлов (до 28–51 мм в диаметре), увеличение лимфоузлов средостения (до 20–26 мм), периферических шейных, подчелюстных (до 24–34 мм), подмышечных (конгломераты до 64 мм) лимфоузлов. Направлен к онкологу. 30.05.2022 г. проведена эксцизионная биопсия левого подмышечного лимфоузла, гистологически: картина лимфопролиферативного поражения, проведено иммуногистохимическое (ИГХ) исследование тканей лимфоузла: хронический лимфолейкоз (ХЛЛ)/В-клеточная лимфома из малых лимфоцитов. ПЭТ-КТ от 27.06.2022 г.: картина увеличения внутригрудных, аксиллярных, шейных лимфоузлов, лимфоузлов забрюшинного пространства, таза с повышенной фиксацией радиофармпрепарата. Учитывая данные ИГХ, для дальнейшего лечения направлен к гематологу Челябинской областной клинической больницы (ЧОКБ). При объективном осмотре — массивная лимфаденопатия, конгломераты периферических лимфоузлов до 6 см. Гиперплазия миндалин II степени. Нижний полюс селезенки на 3 см выступает из-под реберной дуги. Профузная ночная потливость, похудание на 20 кг за полгода, мучительный кашель с приступами удушья

ввиду значительного увеличения внутригрудных лимфоузлов. Клинический анализ крови (24.08.2022 г.): лейкоциты — 171 × 10^9/л, базофилы — 1 %, юные — 2 %, палочкоядерные нейтрофилы — 3 %, сегментоядерные нейтрофилы — 11 %, лимфоциты — 79 %, моноциты — 4 %, эритроциты — 4,6 × 10^{12}/л, Hb — 123 г/л, тромбоциты — 199 × 10^9/л. Биохимический анализ крови: лактатдегидрогеназа — 371 ЕД/л, креатинин — 144,3 мкмоль/л, мочевина — 10,9 ммоль/л, мочевая кислота — 549 мкмоль/л, АСТ — 19 ЕД/л, АЛТ — 16 ЕД/л. Иммунофенотипирование (ИФТ) периферической крови: иммунофенотип опухолевых клеток (85,8 %): CD19+ CD5+ CD23+ sKappa+ CD43+ CD200+ CD20+ CD22+(dim), соответствует ХЛЛ. УЗИ органов брюшной полости: размеры селезенки 167 × 71 мм. В проекции гепатопанкреатодуоденальной зоны, а также в воротах селезенки, параковально, парааортально и по ходу подвздошных сосудов визуализируется множество гипоэхогенных лимфоузлов размерами до 60 × 42 мм, расположенных в виде конгломератов. Учитывая наличие массивной лимфаденопатии (шейные лимфоузлы до 12 × 6 см, подмышечные до 10 см, паховые до 8–10 см, живот увеличен за счет конгломератов лимфоузлов), В-симптомов, начата курсовая иммунохимиотерапия по программе RFC (доза флударабина снижена с учетом клиренса креатинина). В ходе первого курса — синдром лизиса опухоли с развитием острого почечного повреждения. На введение ритуксимаба — инфузионная реакция в виде потрясающего озноба. С августа по ноябрь 2022 г. пациент получил 4 курса RFC, эффекта от терапии не достигнуто — сохранялась массивная периферическая лимфаденопатия, В-симптомы, абсолютный лимфоцитоз в анализе крови (28.10.2022 г.): лейкоциты — 42,6 × 10^9/л, абсолютное число лимфоцитов — 39,6 × 10^9/л, тромбоциты — 187 × 10^9/л, Hb — 99 г/л, эритроциты — 3,53 × 10^{12}/л. В октябре 2022 г. получены результаты исследования FISH периферической крови на определение мутации TP53: делеция локуса гена TP53/17p13 выявлена в 88 % проанализированных интерфазных ядер. Учитывая наличие делеции 17p, отсутствие эффекта от программы RFC, принято решение о переводе пациента на вторую линию терапии венетоклаксом и обинутузумабом (программа V-GEN). С декабря 2022 г. начат прием венетоклакса с постепенной эксалацией дозы с 20 до 400 мг в сутки. Синдрома лизиса опухоли зарегистрировано не было. В январе 2023 г. начата курсовая терапия обинутузумабом. Обинутузумаб вводили в дозе 100 мг в день 1, 900 мг в день 2, 1000 мг в дни 8, 15, далее 1000 мг в сутки в день 1. Обинутузумаб вводился с премедикацией 20–12 мг дексаметазона, 20 мг димедрола, 1,0 г парацетамола, инфузионных реакций не было. На фоне терапии отмечена положительная динамика после первого же курса лечения: уменьшение размеров лимфоузлов, уменьшение лейкоцитоза, исчезновение В-симптомов. Нежелательные явления III–IV степени: нейтропения, тромбоцитопения, анемия — зарегистрированы не были, фебрильной нейтропении и синдрома лизиса опухоли на фоне лечения зарегистрировано не было. Всего было проведено 6 курсов по программе V-GEN, курсовая терапия закончена в июне 2023 г. При обследовании в июне 2023 г. констатирована клинико-гематологическая ремиссия заболевания: лимфаденопатии нет, В-симптомов нет, ECOG 0–1. Клинический анализ крови: лейкоциты — 4,3 × 10^9/л, эритроциты — 5,3 × 10^{12}/л, Hb — 146 г/л, тромбоциты — 183 × 10^9/л. УЗИ органов брюшной полости: признаков лимфаденопатии, спленомегалии нет. Далее пациент продолжил прием венетоклакса амбулаторно 400 мг в сутки в постоянном режиме. При контрольном обследовании через 10 мес. терапии (ноябрь 2023 г.): самочувствие удовлетворительное, В-симптомов нет. ECOG 0–1. Периферические лимфоузлы не увеличены, селезенка не пальпируется, печень по краю реберной дуги. Клинический анализ крови (28.11.2023 г.): лейкоциты — 6,8 × 10^9/л, абсолютное число лимфоцитов — 3,03 × 10^9/л, эритроциты — 5,3 × 10^{12}/л, Hb — 154 г/л, тромбоциты — 251 × 10^9/л. Миелограмма: лимфоциты — 45,5 %, костный мозг умеренно клеточный. Эритропоэз нормобластический. Лимфоцитоз. Гранулоцитарный росток представлен зрелыми формами. Мегакариоциты не обнаружены. Иммунофенотипирование костного мозга: полиморфноклеточный костный мозг. В-лимфоциты не обнаружены. МСКТ органов грудной клетки и брюшной полости: определяются единичные увеличенные брыжеечные лимфоузлы справа с тяжистыми контурами, наибольшим размером 10 × 14 мм; единичный увеличенный подмышечный лимфоузел слева размером 13 × 14 мм. Таким образом, сохраняется клинико-гематологическая ремиссия ХЛЛ. Пациент продолжает прием венетоклакса 400 мг в сутки в постоянном режиме. Планируется продолжить прием до февраля 2024 г. (12 мес.) с последующим решением вопроса о стоп-терапии.

Заключение. В представленном клиническом случае обращает на себя внимание достижение полной клинико-гематологической ремиссии на комбинированной терапии венетоклаксом и обинутузумабом у пациента с неблагоприятным прогнозом ХЛЛ (наличием делеции 17p) с рефрактерностью к стандартной иммунохимиотерапии RFC. На данной комбинации препаратов эффект был достигнут после первого курса, через 6 мес. лечения достигнута полная клинико-гематологическая ремиссия, которая сохраняется через 10 мес. от терапии.

Венетоклакс обладает p53-независимым механизмом действия, что объясняет его эффективность у пациентов, утративших чувствительность к флу-

дарабину. Однако наибольшие перспективы данный препарат имеет в составе комбинаций, в частности, с обинутузумабом, в том числе в 1-й линии терапии [1]. Привлекательным моментом является конечность терапии, т. е. возможность отмены таргетных препаратов после достижения МОБ-негативности у пациентов [2].

Ключевые слова: хронический лимфоцитарный лейкоз, del 17p, венетоклакс, обинутузумаб.

Литература

1. Бялик Т. Е. Венетоклакс в лечении хронического лимфолейкоза (обзор литературы). Онкогематология. 2018;13(2):32–38. Doi: 10.17650/1818-8346-2018-13-2-32-38.

2. Стругов В. В., Стадник Е. А., Зарицкий А. Ю. Эффективность венетоклакса в терапии хронического лимфолейкоза (обзор литературы). Онкогематология. 2017;12(4):18–26. Doi: 10.17650/1818-8346-2017-12-4-18-26.

3. Fisher K., Al-Sawaf O., Fink A.M. et al. Venetoclax and obinutuzumab in chronic lymphocytic leukemia. Blood. 2017;129(19):2702–2705. DOI: 10.1182/blood-2017-01-761973. PMID: 28325865.

4. Seymour JF. Venetoclax plus obinutuzumab therapy for front-line treatment of chronic lymphocytic leukaemia. Lancet Oncol. 2020;21(9):1128–1130. DOI:1016/S1470-2045 (20)30484-8.

Терапия раннего рецидива рефрактерной лимфомы из клеток зоны мантии после аллогенной трансплантации костного мозга

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Введение. Аллогенная трансплантация кроветворных стволовых клеток является единственным методом, позволяющим достигать долгосрочных ремиссий у пациентов с лимфомой из клеток мантийной зоны (ЛМК). Ранние рецидивы после интенсивной индукционной терапии и аутоТГСК фактически некурабельны [1]. Использование комбинаций новых препаратов позволяет достичь максимально возможной безрецидивной выживаемости с минимальной токсичностью. Приводим наблюдение по использованию комбинации аклабрутиниба с венетоклаксом в качестве 7-й линии терапии у пациента с ЛМК в раннем рецидиве после аллоТГСК.

Описание клинического случая. Пациент, мужчина 42 лет, обратился с жалобами на слабость, утомляемость, увеличение объема живота и боли во всех отделах живота. В физикальном статусе были увеличены все группы периферических лимфатических узлов от 1,5 до 2,5 см, селезенка занимала всю левую половину живота с нижним полюсом в малом тазу. При обследовании по данным эзофагогастродуоденоскопии обнаружились недостаточность кардии, геморрагический гастрит, рубцовая деформация и две язвы луковицы двенадцатиперстной кишки, бульбит и дуоденит. По данным УЗИ выявлена выраженная спленомегалия 40 × 15 × 30 см и увеличение подпеченочных лимфатических узлов до 18 мм; в анализах крови: анемия (Hb — 93 г/л), лейкоцитоз 38 тыс/мкл, бласты 73 % и тромбоцитопения до 32 тыс/мкл. По результатам стернальной пункции тотальный бластоз костного мозга.

Из примечательных анамнестических данных вирусный гепатит С (????), употребление внутривенных наркотических веществ (на момент обращения не употреблял около 8 лет).

На основании биопсии аксиллярного лимфоузла и костного мозга, иммунофенотипического исследования лимфоцитов и бластных клеток установлен диагноз: CD20+ В-клеточная лимфома из клеток зоны мантии, бластоидный вариант с поражением селезенки, печени, периферических и абдоминальных лимфоузлов, костного мозга, IVBb стадии, высокая группа риска по MIPI (7 баллов).

Пациенту в качестве первой линии терапии проведено 5 курсов R-CHOP-14, эффекта не получено, констатировано первично-резистентное течение. В ноябре 2016 г. выполнена спленэктомия. Далее переведен на режим R-DHAP. После 2 циклов получена полная ремиссия. С учетом высокого риска в марте 2017 г. пациенту выполнена аутоТГСК (режим кондиционирования BeEAM). Далее получал поддерживающую терапию препаратом ритуксимаб. По результатам контрольного исследования МОБ — полная ремиссия. В течение периода поддерживающей терапии в анализах показатели крови в норме.

Через год отметил появление новообразований на мошонке и половом члене. По данным МРТ мошонки — признаки опухоли кавернозных тел с распространением на головку полового члена. При биопсии с иммуногистохимическим исследованием констатирован рецидив лимфомы из клеток зоны мантии (МОБ–) с экстрамедуллярным поражением.

Пациенту проведено в качестве 3-й линии терапии 5 циклов R-BAC с интратекальной профилактикой нейролейкемии № 2. Получен только частичный ответ в виде уменьшения размеров лимфоузлов, сохранялся абсолютный моноцитоз, повышенный

уровень лактатдегидрогеназы, эпизодически появлялись бугристые образования на половых органах и объемные образования в кавернозных телах. С октября 2019 г. в качестве 4-й линии получал леналидомид в монорежиме, суммарно было проведено 13 курсов, с достижением частичного ответа.

Далее с ноября 2020 г. был переведен на терапию ибрутинибом в дозе 560 мг в сутки. Через 6 мес. снова получен частичный ответ в виде уменьшения лимфоузлов, сокращения количества образований на половых органах. Запланирована аллоТГСК, найден донор. С июля 2021 г. прогрессия: по данным ПЭТ-КТ появление новых увеличенных аксиллярных лимфоузлов, увеличение размеров и метаболической активности бронхопульмональных и паховых лимфоузлов, появление увеличенных тазовых и забрюшинных лимфоузлов — до 5 баллов по Deauville. С учетом прогрессии аллогенная трансплантация отложена. В качестве 6-й линии назначена R-GemOx № 2 + ибрутиниб 560 мг в сутки. В контрольной ПЭТ-КТ от 21.09.2021 г. уменьшение размеров и метаболической активности всех групп лимфоузлов до 3 баллов по Deauville.

17.11.2021 г. выполнена аллоТГСК от неродственного полностью совместимого донора (режим кондиционирования FluBe). На этом фоне уменьшение размеров очагов полового члена. Вследствие развития ранней острой реакции «трансплантат против хозяина» кожи III степени к лечению добавлены глюкокортикостероиды в дозе 1 мг/кг с достижением полного ответа. Рецидив развился в декабре 2021 г. — в виде роста образований полового члена.

Далее получал венетоклакс 200 мг в сутки и акалабрутиниб по 200 мг в сутки. 27.12.2021 г. констатирован полный химеризм, по данным иммунофенотипирования периферической крови без признаков опухолевой В-клеточной популяции, по данным ПЭТ-КТ от 04.2022 г.: полный метаболический ответ.

В мае 2022 г. перенес пневмонию, во время заболевания прием препаратов приостановлен, на этом фоне снова отметил появление образований на половом члене — терапия продолжена в прежнем объеме, но выполнена дополнительно лучевая терапия на экстрамедуллярные очаги.

С августа 2022 г. признаки прогрессии в виде нарастания лейкоцитоза, появление в верхней трети икроножной мышцы, в мягких тканях правого бедра и в мягких тканях шеи справа образований максимальным размером до 30 × 10 × 15 мм. Доза венетоклакса увеличена до 400 мг в сутки. В настоящее время, спустя год сохраняется частичный ответ, образования уменьшились в объеме более чем на половину, образований на половом члене не наблюдается. В анализах крови сохраняется умеренный лейкоцитоз до 14 × 10^9/л, лимфоцитоз до 47,5 % (7,1 тыс/мкл), моноцитоз до 12 % (1,8 тыс/мкл), остальные показатели крови в норме.

Заключение. В данном клиническом наблюдении мы демонстрируем значимую эффективность новых комбинаций таргетных препаратов в лечении лимфомы из клеток зоны мантии. Пациент с бластоидным вариантом и высоким риском MIPI получал терапию в соответствии с Российскими рекомендациями и ожидаемо оказался рефрактерен к терапии первой линии, с непродолжительным ответом на последующие варианты терапии. Комбинация таргетных препаратов с традиционными схемами терапии позволили провести сначала ауто-, а затем и аллогенную трансплантацию. В рецидиве после трансплантации пациент продолжил терапию ингибитором BTK и венетоклаксом, что позволило вновь добиться ремиссии. В настоящее время, спустя 8 лет от момента постановки диагноза, пациент находится в частичной ремиссии.

Литература

1. Воробьев В.И., Тумян Г.С., Фалалеева Н.А. и др. Лимфома из клеток мантии. Клинические рекомендации. Современная онкология. 2020;22(3):6–23.
2. Hoster E, Dreyling M et al. A new prognostic index (MIPI) for patients with advanced stage mantle cell lymphoma. Blood. 2008;111:558–565.
3. Determann O, Hoster E, Ott G et al. Ki-67 predicts outcome in advanced-stage mantle cell lymphoma patients treated with anti-CD20 immunochemotherapy: results from randomized trials of the European MCL Network and the German Low Grade Lymphoma Study Group.Blood. 2008;111:2385–2387.
4. URL: https://cyberleninka.ru/article/n/mantiynokletochnaya-limfoma-istoriya-sovremennye-printsipy-diagnostiki-lechenie-obzor-literatury.

Клинический случай успешного лечения грибовидного микоза низкими дозами гемцитабина у пожилого пациента

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Введение. Грибовидный микоз (ГМ) — самый частый вариант первичной эпидермотропной Т-клеточной лимфомы кожи — 65 %, что составляет всего 1 % всех неходжкинских лимфом и 50 % первичных лимфом кожи [1]. Более 75 % случаев ГМ наблюдается у пациентов старше 50 лет, средний возраст дебюта заболевания — 55–60 лет [2]. Диагноз ГМ устанавливается на основании комплексной оценки картины заболевания, гистологического и иммуногистохимического исследований (ИГХИ) биоптатов из очагов поражения кожи [1, 2]. Согласно рекомендациям Международного общества по лимфомам кожи и Европейской организации по изучению и лечению рака (ISLE-EORTC staging system), выделяют четыре стадии ГМ, которые, собственно, и определяют течение, прогноз заболевания и вариант лечения [2]. Ранние (IA, IB, IIA) стадии патологического процесса отличаются индолентностью в течение многих лет или десятилетий, хорошей пятилетней выживаемостью (до 80–90 %), в то время как поздние стадии (IIB–IVB), напротив, характеризуются быстрой пролиферацией кожных узлов с вовлечением лимфатических узлов, внутренних органов, крови, крупноклеточной трансформацией [2, 3]. Ожидаемая продолжительрность жизни у пациентов с развернутыми стадиями ГМ колеблется в пределах 3–5 лет. Лечение ГМ крайне вариабельно, зависит от стадии заболевания, повреждения системного иммунного ответа, трансформации в лимфосаркому и включает применение наружных методов лечения (топическую, фототерапию) на ранних стадиях и цитокины, цитостатики и моноклональные антитела на поздних стадиях заболевания [1, 4, 5, 6]. В связи с тем что более 50 % пациентов с ГМ попадают в поле зрение гематологов на поздних стадиях заболевания ввиду схожести ранних клинических проявлений ГМ с хроническими доброкачественными дерматозами, а также высокой частотой (до 40 %) ложноотрицательных результатов гистологического исследования, весьма актуальным является определение терапевтических опций для этой категории пациентов [3, 7]. Иммунотерапия интерфероном-α позволяет достичь эффекта у 40–60 % больных и лишь у 10 % полных ремиссий [2, 5, 8]. Среди противоопухолевых средств, доказавших свою эффективность при опухолевой стадии и внекожной генерализации ГМ, выделяется гемцитабин. В наиболее крупных мировых исследованиях P. L. Zinzani и M. Duvic при лечении гемцитабином (по схеме 1200 или 1000 мг/м^2 в 1, 8, 15-й дни 28-дневного цикла, всего 6 циклов) частота общих ответов у пациентов с резистентными формами ГМ составила 70 и 68 %, а полных ремиссий 11 и 8 % соответственно [9, 10]. Основным побочным эффектом, ограничивающим лечебные возможности препарата, является миелотоксичность. В исследованиях у 25 % больных развивалась панцитопения III степени, в основном лейкопения. В литературе есть единичные работы об использовании малых доз гемцитабина при солидных опухолях и рефрактерных формах ГМ, продемонстрировавших, однако, достаточную эффективность на уровне 79 % при лучшей переносимости за счет снижения частоты развития миелотоксической цитопениии [8]. Учитывая преимущественно пожилой контингент пациентов, а также необходимость длительной терапии, применение гемцитабина в малых дозах при ГМ представляет практический интерес.

Описание клинического случая. Пациент И., 68 лет. Дебют заболевания в 2019 г. в виде появления эритематозных пятен на коже груди и живота. Лечился у дерматолога в течение двух лет с диагнозом «псориаз» топическими глюкокортикостероидами с непродолжительным положительным эффектом. В 2021 г. ухудшение состояния в виде увеличения размеров и площади эритематозных пятен, появления бляшек и опухолевидных образований на коже туловища, сопровождавшихся зудом. Направлен на консультацию к гематологу. С целью гистологической верификации проведена биопсия кожного лоскута. Результаты ИГХИ: клетки, формирующие дермальный инфильтрат, в подавляющем большинстве имеют Т-клеточную дифференцировку и экспрессирует CD3, CD7, CD5, CD4. Ki-67 35 %. Клетки инфильтрата не экспрессируют CD10, CD23, CD34. Полученная иммуноморфологическая картина с учетом клинических данных свидетельствует в пользу ГМ. С целью уточнения распространенности процесса выполнено ультразвуковое исследование, рентгенография, компьютерная томография (КТ) — признаков лимфопролиферативного процесса не обнаружено. Установлен диагноз: ГМ, поздняя стадия IIB. Пациенту начата терапия интерфероном-α по схеме: 3 млн ЕД через день с эскалацией дозы до 5 млн ЕД. Дальнейшее наращивание дозы препарата не проводилось в связи с наличием побочных эффектов: гриппоподобного синдрома, трансфераземии. На фоне лечения отмечена положительная динамика в виде уменьшения размеров пятен и бляшек, уплощения опухолевых образований, однако полного регресса элементов не отмечалось. С мая 2023 г. прогрессирование заболевания в виде роста, генерализации кожных узлов с дальнейшим их изъязвлением. Локально: на коже груди, живота визуализируются бугристые узлы красновато-коричневого цвета с синюшным оттенком, шелушащиеся, размерами от 2 до 10 см, склонные к слиянию, с язвенными дефектами, размерами до 3 см с серозно-геморрагическим отделяемым (рис. 1). По данным ПЭТ-КТ: на коже и в мягких тканях туловища многочисленные гиперметаболические образования, размерами 92 × 21 мм с изъязвлением кожи, SUV = 9,40. Билатеральные аксиллярные, паховые лимфоузлы увеличены до 20 мм, SUVmax = 5,81.

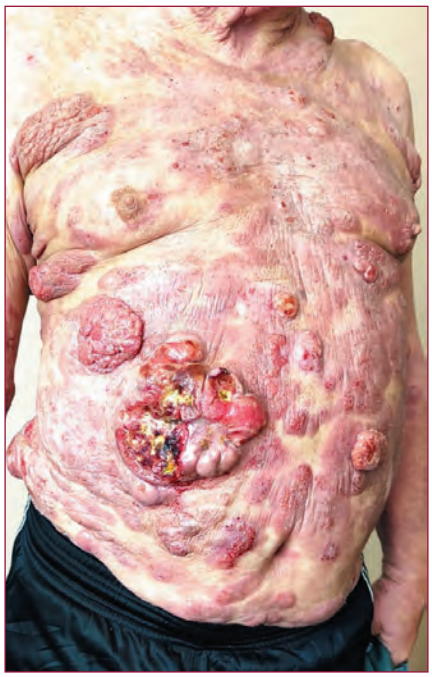

Рис. 1. Пациент И. Поражения кожи до начала терапии гемцитабином

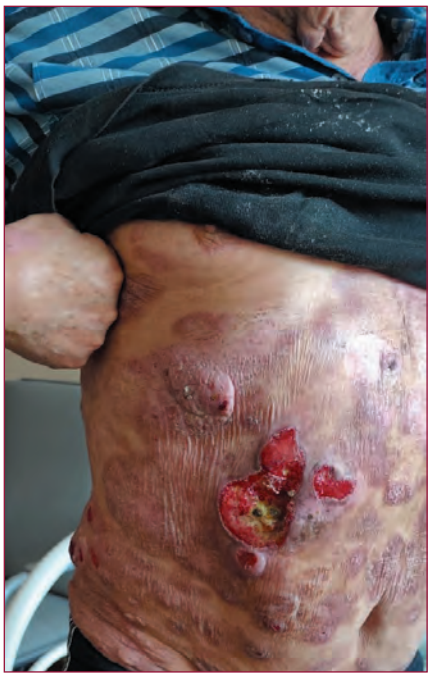

Рис. 2. Пациент И. Кожные проявления после 4 курсов терапии гемцитабином

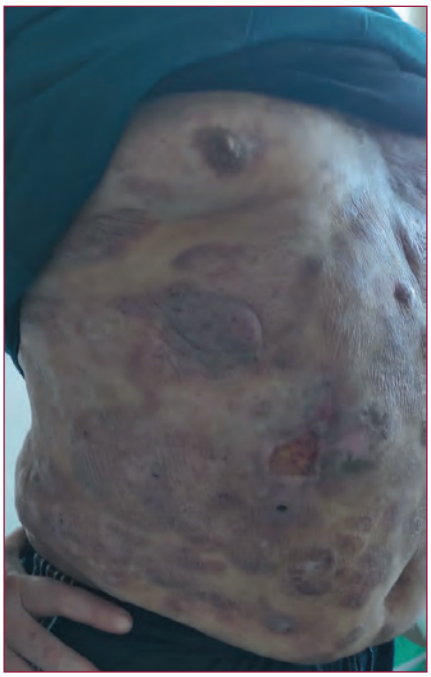

Рис. 3. Пациент И. Регресс опухолевых образований кожи после 10 курсов терапии гемцитабином

В общем анализе крови без отклонений. Выполнена повторная биопсия кожного образования: морфологическая картина характеризуется субстратом ГМ с признаками крупноклеточной трансформации. Диагноз: ГМ, поздняя стадия IIIA. Пациент консультирован в «НМИЦ гематологии», рекомендована монотерапия гемцитабином в дозе 250 мг/м^2 в/в капельно в виде длительной инфузии в течение 6 часов 1 раз в неделю. Уже через 1 мес. от начала терапии отмечался выраженный клинический эффект в виде уменьшения площади, побледнения, уплощения опухолевых образований (рис. 2). На момент написания публикации проведено 10 курсов терапии гемцитабином. По данным ПЭТ-КТ: уменьшение количества, размеров, уровня метаболической активности образований кожи, размерами 14 × 54 мм, SUVmax = 3,8; билатеральных аксиллярных, паховых лимфоузлов до 9 мм, SUV = 3,63. Локально: регресс опухолевых образований, изъязвлений кожи (рис. 3). Введение препарата пациентом переносилось удовлетворительно. Из побочных эффектов наблюдалась цитотоксическая цитопения — анемия I–II степени (Hb 98–102 г/л); нейтропении, тромбоцитопении зарегистрировано не было.

Заключение. Использование малых доз гемцитабина у пациента с поздней стадией ГМ, резистентной к стандартной терапии интерферонами-α, продемонстрировало клиническую эффективность. Данная схема является особенно актуальной у пожилых пациентов, учитывая длительность ее применения и низкую миелотоксичность.

Ключевые слова: грибовидный микоз, гемцитабин, низкие дозы, Т-клеточная лимфома кожи.

Литература

1. Потекаев Н. Н., Морозова В. С., Барях Е. А. и др. Современные методы терапии грибовидного микоза. Клиническая дерматология и венерология. 2022;21(4):538–546. https://doi.org/10.17116/klinderma202221041538

2. Клинические рекомендации. Грибовидный микоз (утв. Минздравом России); Общероссийская общественная организация «Российское общество дерматовенерологов и косметологов»; Российское профессиональное общество онкогематологов. 2020.

3. Виноградова Ю. Е., Цыба Н. Н., Гилязитдинова Е. А., Луценко И. Н. Опыт лечения грибовидного микоза и синдрома Сезари в зависимости от стадий заболевания. Результаты собственных исследований и обзор литературы. Клиническая онкогематология. 2009;2(4):326–333.

4. Филоненко Е. В., Иванова-Радкевич В. И. Фотодинамическая терапия в лечении больных грибовидным микозом. Biomedical Photonics. 2022;11(1):27–36. doi: 10.24931/2413–9432–2022–11-1-27-36

5. Илюшкина Е. А., Кравченко С. К., Звонков Е. Е., Лезвинская Е. М. Клинический случай успешного лечения опухолевой стадии грибовидного микоза рофероном А. Российский журнал кожных и венерических болезней. 2012;6:7–10.

6. Горенкова Л. Г., Белоусова И. Э., Кравченко С. К. и др. Современные возможности терапии первичных кожных Т-клеточных лимфом: первые результаты применения брентуксимаб ведотина в Российской Федерации. Современная онкология. 2021;23(3):447–452. Doi: 10.26442/18151434.2021.3.201204

7. Нефедьева Ю. В., Зиганшин О. Р., Старцева Е. Ю. Грибовидный микоз: случай из практики. Клиническая дерматология и венерология. 2018;17(4):46–50. https://doi.org/10.17116/klinderma20181704146

8. Горенкова Л. Г., Пенская Е. А., Кравченко С. К. и др. Лечение резистентных форм грибовидного микоза и синдрома Сезари. Клиническая онкогематология. 2017;10(3):366–371. Doi: 10.21320/2500-2139-2017-10-3-366-371

9. Zinzani PL, Baliva G, Magagnoli M et al. Gemcitabine treatment in pretreated cutaneous T-cell lymphoma: experience in 44 patients. J Clin Oncol. 2000;18(13):2603–2606. Doi: 10.1200/jco.2000.18.13.2603.

10. Marchi E, Alinari L, Tani M et al. Gemcitabine as frontline treatment for cutaneous T cell lymphoma: phase II study of 32 patients. Cancer. 2005;104(11):2437–2441. Doi: 10.1002/cncr.21449

Tecvayli™ (teclistamab-CQYV) Monotherapy first experience in patient with refractory multiple myeloma in Russia

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Background. On October 25, 2022, the Food and Drug Administration (FDA, USA) granted accelerated approval to Tecvayli™, the first bispecific B-cell maturation antigen (BCMA)-directed CD3 T-cell engager, for adult patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody and have demonstrated disease progression on the last therapy. The Russian governments hasn't approved Tecvayli™ yet.

Objectives. To present and analyze the first Teclistamab monotherapy experience in patient with triple-class-exposed refractory multiple myeloma in Russia.

Description. A 39-year-old Caucasian female has been treated in Russian Cancer Research Center named after N.N. Blokhin since December, 2022 with IgG-Kappa multiple myeloma, ISS — III, R-ISS — III, R2-ISS 3 points (high risk), mSMART — high risk (amp 1q21). The progression of disease was extremely aggressive with extramedullary spreading involving liver, CNS and both mammary glands. Within eight months of ineffective therapy including the proteasome inhibitor, two immunomodulatory agents, the anti-CD38 antibody, cytostatic agents and radiation therapy the refractory type of disease progression was stated. Hematopoietic stem cell transplant and CAR T-cell therapy were not considered due to inefficiency of the treatment that had been held earlier and due to massive tumor growth along with severe vital status (lower limb monoplegia, third cranial nerve disorder, pelvic floor dysfunction). The last silver lining was bispecific monoclonal antibody (Tecvayli™) monotherapy. Starting on August, 2023 Teclistamab therapy had been initiated after the health government approval was granted. According to step-up dosing schedule we have been escalating as following: day 1 — 0,06 mg/kg (4,5 mg), day 3 — 0,3 mg/kg (22,0 mg), day 5 — 1,5 mg/kg (108,0 mg), afterwards — 1,5 mg/kg (108,0 mg) once weekly. By November, 2023 eight injections (566,5 mg total) were administered along with Varicella-Zoster, Cytomegalovirus and Pneumocystis prophylaxis.

Results. Teclistamab resulted in patient's vital status clinical improvement (according to HRQoL scale) while the median duration of response was 1.5 month. PET/CT scans were administered after 2.5 months of specific treatment (Figure 1). According to the results partial metabolic response (DS 4, IMPeTUs) and MRD-negativity status had been achieved along with control points reducing. Adverse events were following: cytokine release syndrome (CRS) grade 1 (ACTCT) — while escalating up to 0,3 mg/kg; neurologic toxicity, including Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) grade III (without CRS) — while escalating up to 1,5 mg/kg; hypogammaglobulinemia (IgG 1,39 g/l); induced cytotoxity.

Conclusions. Nowadays the number of patients with triple-class-exposed relapsed or refractory multiple myeloma is increasing extremely. The complexity of applying CAR T-cell therapy in Russia along with scanty variety of treatment methods make that increasing cohort hopelessly palliative and get in the way of preventing refractoriness. We presented the first experience of Teclistamab monotherapy treatment in Russia demonstrating antitumor efficacy along with clinically significant improvement of patient's somatic status and giving hope to those who ran out of other options. Life-threatening or fatal reactions still can occur in patients receiving Tecvayli™, thus it is important to monitor vital signs in order to withhold Teclistamab therapy and adjust special treatment if it's necessary until adverse events resolves, although it shows favourable toxicity profile and results in tangible antitumor efficiency.

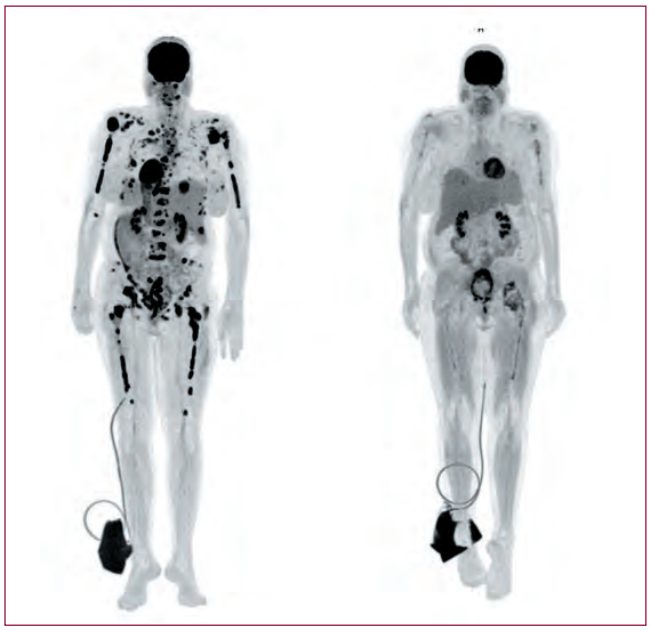

Figure 1. PET/CT scans (using FDG) before and after seven injections of Teclistamab administering

Дефицит XIII фактора свертывания (клинический случай)

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Введение. Дефицит XIII фактора (болезнь Лаки-Лоранда) относится к редким нарушениям свертывания крови с частотой встречаемости около 1–2 на 1 000 000 населения. Дефицит фактора XIII, по данным Всемирной федерации гемофилии и национальных регистров, составляет 6,5 % в группе редких коагулопатий. Дефицит фибринстабилизирующего фактора (ФСФ) наследуется по аутосомно-рецессивному типу. Гомозиготный врожденный дефицит фактора XIII может быть обусловлен дефектами либо F13A (дефект 2-го типа), либо F13B (дефект 1-го типа). В данном случае уровень фактора XIII в плазме определяется ниже 5 %, и заболевание проявляется выраженным геморрагическим синдромом. У гетерозиготных носителей преобладает латентное течение болезни.

Описание клинического случая. Пациент 52 лет. Дебют кровотечения отмечался в неонатальном периоде в виде кровоточивости из пуповинного остатка. С раннего детства отмечает появление спонтанных гематом мягких тканей, однократно был эпизод забрюшинной гематомы (1986 г.), почечного кровотечения, длительного кровотечения после прикуса языка. Стоматологические манипуляции, экстракции зубов (местная регионарная анестезия) также осложнялись кровотечениями. В 1992 г. — спонтанный разрыв селезенки, выполнена спленэктомия. В 2004 г. трижды выполнялась операция по поводу флегмонозного аппендицита с осложнением в виде перитонита. В 2016 г. — ОНМК по геморрагическому типу. КТ головного мозга от 09.11.2016 г.: подострая внутримозговая гематома в левом полушарии мозга небольших размеров. После ОНМК отмечает повышение артериального давления до 150/100 мм рт. ст. Контрольная МРТ головного мозга: данных за внутримозговую гематому не было выявлено.

В 1982 г., в возрасте 11 лет, обследован в Кировском НИИ ГиПК и установлен диагноз: гемофилия А, легкая форма (выписки не сохранились). При развитии гематом мягких тканей получал трансфузии свежезамороженной плазмы (СЗП), в 1990-х гг. проводилась трансфузия криопреципитата с хорошим гемостатическим эффектом.

Повторное обследование 03.02.2010 г. (Мордовская РСПК) — активность фактора VIII 7,5 %. С заместительной гемостатической целью получал концентраты фактора VIII (на домашнем лечении) и СЗП стационарно, причем лучший эффект отмечает от трансфузии СЗП по сравнению с концентратом фактора VIII. В настоящее время трансфузии компонентов и препаратов крови проводятся с премедикацией дексаметазоном (были аллергические реакции в виде крапивницы на СЗП и криопреципитат).

Коагулограмма от 02.02.2021 г. (Морозовская ДГКБ): АЧТВ — 24,1 с (28–43), фактор VIII — 388 %, ристомицин-кофакторная активность vWF — 123,6 % (60,8–239,8), антиген vWF — 185,2 % (66,1–176,3).

Наследственность по геморрагическим заболеваниям отягощена (у младшей сестры в возрасте 1 года развился инсульт, умерла в 8 лет). Имеются две дочери, геморрагического синдрома у них не отмечалось. Сопутствующие заболевания пациента — хронический вирусный гепатит С (принимает гепатопротекторы курсами), гипертоническая болезнь (принимает конкор 5 мг/сут).

Результаты обследований (НМИЦ гематологии от 07.121.2023г.). Коагулограмма: АЧТВ — 28,3 с (29–38), фибриноген — 2,14 г/л, протромбин по Квику — 90,4 % (70,0–130,0), фактор VIII — 197,7 % (50–150), ингибитор фактора VIII не обнаружен (0–0,6), фактор IX — 94,3 % (50-150), фактор Виллебранда — 218,2 % (61–180), ристомицин-кофакторная активность vWF — 108,1 % (60,8–239,8), фактор XIII — 2,3 % (75,2–154,8).

На основании полученных клинико-лабораторных данных у пациента верифицирован наследственный дефицит фактора XIII (2,3 %) (D68.2 Наследственный дефицит других факторов свертывания). Учитывая тяжелое клиническое течение заболевания с рецидивирующими спонтанными геморрагическими эпизодами, в том числе жизнеугрожающих локализаций (забрюшинная гематома, ОНМК по геморрагическому типу), с заместительной профилактической целью показаны трансфузии СЗП 3–5 мл/кг массы тела каждые 28 дней или криопреципитата 3 дозы с премедикацией. Дополнительно при кровотечении из слизистых — транексамовая кислота по 750 мг 2 раза в сутки.

Заключение. Таким образом, представлен клинический пример редкой наследственной коагулопатии с дефицитом фактора свертывания крови XIII, проявившейся неоднократными рецидивирующими кровотечениями с периода новорожденности, подтвержденной лишь при повторных коагулологиче-

ских исследованиях. Для постановки диагноза подобных заболеваний требуется тщательная оценка семейного анамнеза, симптомов болезни, наличие хорошо оснащенной лаборатории. В рассматриваемом нами случае отмечался характерный «пупочный геморрагический синдром», несоответствие тяжелого геморрагического синдрома и нормальных гемостазиологических лабораторных показателей, что заставило заподозрить редкий дефицит XIII фактора свертывания крови и направить пациента для дальнейшей диагностики в специализированный стационар.

Приобретенная гемофилия А: трудности диагностики и лечения

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Введение. Приобретенная гемофилия А — редкое аутоиммунное заболевание, характеризующееся возникновением спонтанной кровоточивости при отсутствии кровотечений в семейном или личном анамнезе. В основе патогенеза лежит выработка аутоантител к фактору VIII (FVIII) свертывания крови [1]. Заболевание может быть заподозрено при изолированном удлинении АЧТВ при скрининговом коагулологическом исследовании, значительном снижении активности FVIII свертывания крови и выявлении ингибитора к FVIII [2]. Достоверных сведений о заболеваемости в мире и России нет. По данным Европейского реестра приобретенной гемофилии (EACH2), в котором проанализирован 501 случай за период с 2003 по 2009 г., средний возраст дебюта составляет 74 года. Частота встречаемости среди мужчин и женщин практически одинакова, при исключении случаев, связанных с беременностью, и женщин старше 65 лет (поскольку женщины имеют более высокую продолжительность жизни). Среди ассоциированных состояний, возможно связанных с выработкой антител против FVIII свертывания крови, наиболее часто диагностируются: злокачественные новообразования (любого типа) — 11,8 %, аутоиммунные заболевания — 13,4 %, роды — 8,4 %, инфекции — 3,8 %, дерматологические заболевания — 1,4 %, медикаментозное лечение — 3,4 %, прочие причины — 11,6 %. В 50 % случаев причина, послужившая выработке ингибитора, остается неизвестной [1].

Цель. Проанализировать существующие подходы к диагностике и лечению приобретенной гемофилии А. Оценить их эффективность на примере клинического случая.

Методы. Проведен анализ данных литературных источников, описан клинический случай приобретенной гемофилии А.

Результаты. При изучении информации о данной патологии выяснилось, что в отечественной учебной и методической литературе данные о приобретенной гемофилии практически отсутствуют. Не упоминается заболевание и в актуальных стандартах и клинических рекомендациях, а в периодических изданиях описываются только отдельные клинические наблюдения. Все это является одной из причин недостаточной подготовленности практикующих врачей к оказанию помощи таким пациентам. Наиболее систематизированные сведения по заболеванию представлены в международных рекомендациях по диагностике и лечению приобретенной гемофилии А (последняя публикация в июле 2020 г.) [2]. Терапия проводится по двум направлениям: компенсация нарушенных функций гемостаза (заместительная терапия концентратами факторов свертывания крови, препаратами шунтирующего действия (антиингибиторный коагулянтный комплекс, эптаког-α активированный), в т. ч. таргетными препаратами (эмицизумаб)) и элиминация ингибитора (иммуносупрессивная терапия). В настоящее время для пациентов с активностью FVIII > 1 % и ингибитором < 20 BE/ml рекомендуется в первой линии терапии использовать глюкокортикостероиды 3–4 недели. При неэффективности проводимой терапии добавить ритуксимаб или циклофосфамид в качестве препаратов второй линии. Для пациентов с активностью FVIII < 1 % и ингибитором > 20 BE/ml рекомендовано использовать в первой линии глюкокортикостероды 3–4 недели совместно с ритуксимабом либо циклофосфамидом на выбор, во второй линии использовать также ритуксимаб либо циклофосфамид (в зависимости от того, какой препарат использовался ранее) (рис. 1). Важно знать, что у пациентов, не получавших иммуносупрессивную терапию, наблюдались спонтанные ремиссии, но этот исход непредсказуем. Также стоит отметить, что в реестре EACH2 единственным параметром, который отличал пациентов, ответивших на лечение, от тех, кто не от-

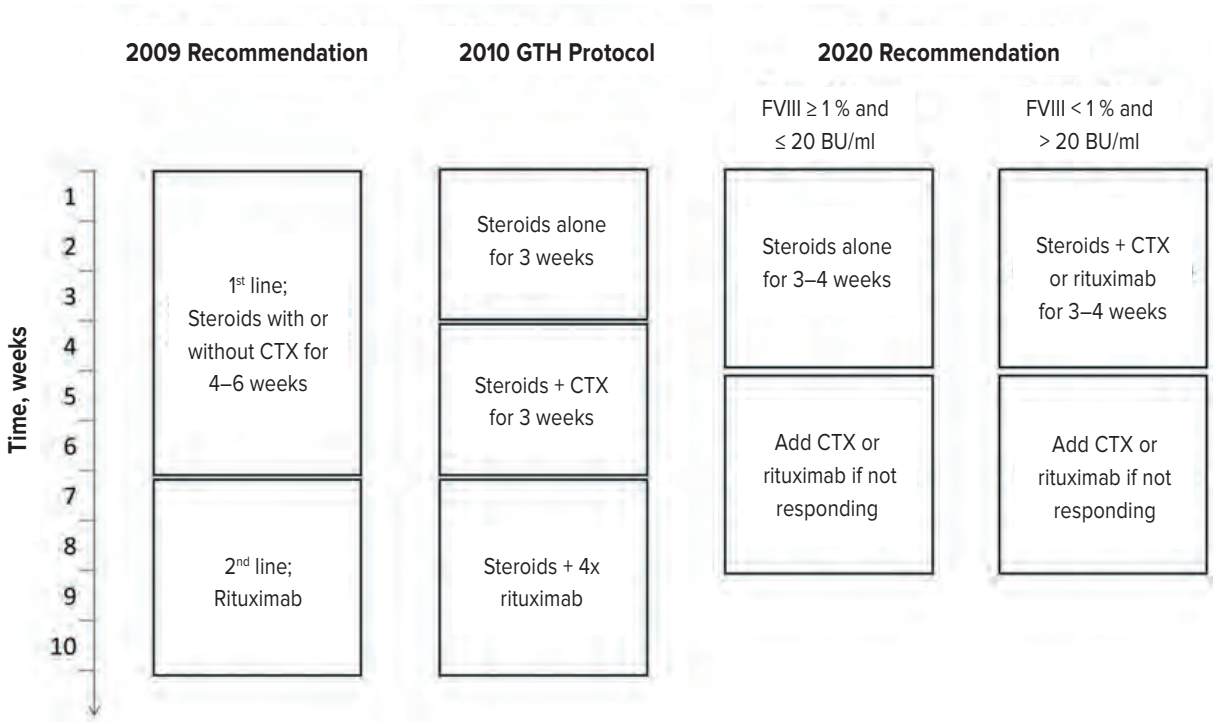

Рис. 1. Обзор международных рекомендаций по диагностике и лечению приобретенной гемофилии А

ветил, была задержка во времени начала лечения [2]. Для пациентов с врожденной гемофилией, так же как для пациентов с приобретенной формой, характерно изолированное удлинение АЧТВ, снижение активности FVIII, выявление ингибитора к FVIII (при проводимой ранее заместительной терапии плазменными факторами). Однако для врожденной гемофилии характерен отягощенный семейный анамнез, болеют преимущественно мужчины, важной особенностью является коррекция при выполнении теста смешивания, чего нет при приобретенной форме [3].

Описание клинического случая. Пациент Г., 43 лет, поступил в клинику факультетской терапии ВМедА имени С. М. Кирова 3 октября 2023 г. более чем через 3 месяца после возникновения первых проявлений патологической кровоточивости. Известно, что в середине мая перенес ОРВИ, лечился самостоятельно. Через 2 недели после возникновения респираторных симптомов отметил резкую боль и припухлость в области правого коленного сустава. Терапевтом диагностирован деформирующий артроз, назначена терапия нестероидными противовоспалительными препаратами (без эффекта). 20 июня вакцинирован по специальным показаниям одновременно от вируса гепатита А, дифтерии, столбняка, брюшного тифа и кори. Спустя несколько дней после вакцинации отметил появление болей в голеностопных суставах, ограничивающих движение, постоянное повышение температуры тела до 37,3–37,5 °С. Спустя еще несколько дней отметил резкую боль, ощущение распирания в мышцах правой голени по заднемедиальной поверхности. 29 июня был госпитализирован в хирургическое отделение (г. Волгоград) с подозрением на тромбофлебит глубоких вен правой голени. При обследовании в стационаре в скрининговой коагулограмме отмечается изолированное удлинение АЧТВ до 72 с. Дополнительно исследована активность фактора Виллебранда — 239,4 % (норма 50–160 %) и активность FVIII < 2 % (норма 50–150 %). 29 августа проведена телемедицинская консультация со специалистами ВМедА им. С. М. Кирова, заподозрена приобретенная гемофилия А, рекомендовано продолжить обследование и лечение в специализированном гематологическом стационаре. 3 октября, спустя почти 1 мес. после консультации, пациент переведен в клинику факультетской терапии ВМедА. При поступлении отмечаются признаки артроза мелких и крупных суставов, на правом предплечье и левой голени отцветающие массивные гематомы до 10 см в диаметре. Из опроса известно, что семейный и личный анамнез пациента по кровоточивости не отягощен. В коагулограмме: изолированное удлинение АЧТВ > 240 с, FVIII — 1,6 %, ингибитор FVIII — 230 БЕ/мл. На серии

КТ-снимков выявляется увеличение объема правой подвздошной мышцы с наличием инкапсулированного компонента в ее структуре — более вероятно, соответствует лизирующейся гематоме. Таким образом, подтвержден диагноз «приобретенная гемофилия А». В нашем случае пациент, согласно ранее упомянутым международным рекомендациям по диагностике и лечению приобретенной гемофилии А, попадет во вторую группу (FVIII < 1 %, ингибитор > 20 БЕ/мл). На следующий день с момента поступления пациенту инициирована пульс-терапия метилпреднизолоном по 1000 мг в 1, 2, 3-й дни с последующим переходом на пероральный прием преднизолона в дозе 1 мг/кг, а также ритуксимаб 375 мг/м^2 в 3, 10, 17, 24-й дни. Однако желаемого ответа на терапию не было получено: АЧТВ от 30 октября — 57,8 с, активность FVIII — 1,5 %. В связи с этим с 3 ноября пациент переведен на терапию второй линии: преднизолон в комбинации с циклофосфамидом 1000 мг 1 раз в неделю дважды и далее по 200 мг в сутки перорально до достижения насыщающей дозы — 5 г. За время наблюдения 6 и 7 ноября отмечались жалобы на появление новых гематом в области правого плеча, нижней части спины (рис. 2), увеличение в объеме и боль в коленном суставе, алая кровь в стуле. По жизненным показаниям были выполнены переливания свежезамороженной плазмы. При этом в коагулограммах от 6 и 7 ноября АЧТВ составляло 36,6 и 42,2 с соответственно. При дальнейшем наблюдении симптомов кровоточивости не было. В контрольной коагулограмме во ВМедА имени С. М. Кирова от 13 ноября АЧТВ — 35,8 с, FVIII — 9,0 %. В этот же день образец плазмы пациента отправлен в ФГБУ «НМИЦ ДГОИ им. Дмитрия Рогачева» МЗ РФ, где получены следующие результаты: АЧТВ — 83,3 с, FVIII — 0,2 %, ингибитор к FVIII — 19 БЕ/мл. В данной ситуации стоит учитывать, что транспортировка образцов осуществлялась в замороженном виде в другой город в течение нескольких суток, поэтому результаты исследований не коррелируют между собой. По данным от 30 ноября: активность FVIII — 32,4 %, активность ингибитора к FVIII не выявляется. Признаков кровоточивости не определяется. Пациент продолжает находиться под наблюдением медицинской службы.

Заключение. Низкая осведомленность специалистов различного профиля о данной патологии приводит к затруднению и увеличению времени установки диагноза, а следовательно, задержке инициации терапии.

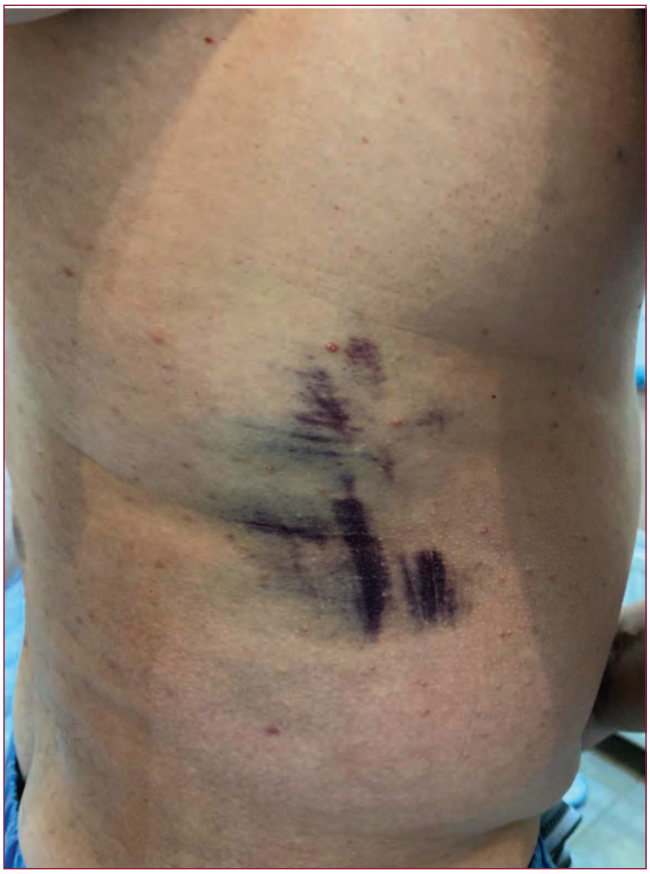

Рис. 2. Межмышечная гематома задне-боковой поверхности спины

Отсутствие препаратов для гемостатической терапии и их высокая стоимость также приводят к сложностям оказания медицинской помощи данной категории пациентов. Для пациентов с приобретенной гемофилией характерно спонтанное возникновение кровоточивости, не коррелирующее с лабораторными показателями.

Литература

1. Knoebl P, Marco P, Baudo F et al., on behalf of the EACH2 Registry Contributors. Demographic and clinical data in acquired hemophilia A: results from the European Acquired Haemophilia Registry (EACH2). J Thromb Haemost. 2012;10:622–631.

2. Tiede A, Collins P, Knoebl P et al. International recommendations on the diagnosis and treatment of acquired hemophilia A. Haematologica. 2020;105(7):1791–1801. doi: 10.3324/haematol.2019.230771. Epub 2020 May 7. PMID: 32381574; PMCID: PMC7327664.

3. Суренков А. А., Орел Е. Б., Зозуля Н.И., Двирнык В. Н. Особенности клинико-лабораторной диагностики редкой коагулопатии — приобретенной гемофилии. Гематология и трансфузиология. 2022;67(4):535–550.

Наследственный сфероцитоз, ассоциированный с течением парвовирусной инфекции: клинический случай из практики

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Введение. Наследственный сфероцитоз — наследственная гемолитическая анемия, развивающаяся вследствие дефекта мембраны эритроцитов, приводящего к характерному изменению формы эритроцитов (сфероциты), которая гетерогенна по степени тяжести клинических проявлений, дефектам мембранных белков и типу наследования. Течение заболевания варьирует по клиническим проявлениям от бессимптомного до тяжелого с массивным гемолизом — гемолитическим кризом. Обычно имеется отягощенный семейный анамнез и типичная клиническая и лабораторная картина, поэтому диагноз может быть поставлен часто достаточно легко, без дополнительных лабораторных исследований. Возраст постановки диагноза весьма варьирует. В большинстве случаев — детский и подростковый возраст, но может быть и во взрослом возрасте, даже на седьмом — девятом десятилетии жизни, т. к. наследственный сфероцитоз не всегда рассматривается как причина образования камней в желчном пузыре и спленомегалии. Бессимптомное течение наследственного сфероцитоза выявляется (особенно в детском возрасте) после апластического криза, вызванного парвовирус-B19-инфекцией, или после гриппа. Приводится клиническое наблюдение тяжелого течения наследственного сфероцитоза, впервые диагностированного у пациента молодого возраста.

Цели. Целью данной работы является освещение проблемы диагностики гемолитических анемий, в том числе наследственных. В большинстве случаев имеется недооценка тяжести течения наследственного сфероцитоза, особенно осложненного апластическим кризом. Из-за относительно редкой встречаемости данного заболевания в популяции по сравнению с другими видами анемий пациенты помногу лет ходят с неверным диагнозом.

Методы. В качестве методов данной работы использовался тщательный сравнительный анализ медицинской литературы, а также статей из журналов. В качестве клинического случая был использован собственный недавний опыт лечения пациента с тяжелым наследственным сфероцитозом, осложненным апластическим кризом.

Результаты. Впервые наследственный сфероцитоз был описан в 1871 г. бельгийскими врачами C. Vanlair и J. Masius как случай гемолитической анемии. У пациента наблюдались желтуха, выраженная спленомегалия, острые боли в верхней части живота, анемия с наличием мелких красных сферичных глобул, которые они назвали «микросфероциты». В основе патогенеза наследственного сфероцитоза лежит дефицит или дисфункция белков цитоскелета эритроцита, главным образом спектрина, который приводит к нарушению морфологии эритроцита. Эритроцит превращается в микросфероцит. В мазке периферической крови микросфероциты имеют вид мелких клеток без центрального просветления. Микросфероциты избирательно захватываются и разрушаются селезенкой, что играет ключевую роль в клинических проявлениях этого заболевания. Клиническая картина наследственного сфероцитоза очень разнообразна. Чаще всего заболевание проявляется в детском или подростковом возрасте под влиянием провоцирующих факторов, таких как перенесенная инфекция, переохлаждение, хирургическое вмешательство и т. д. Для наследственного сфероцитоза характерно волнообразное течение: периоды ремиссии, сменяющиеся периодами гемолитического криза. К классической «триаде» симптомов относятся: анемия, желтуха, спленомегалия различной степени выраженности. Частым осложнением является желчнокаменная болезнь, которая возникает за счет образования билирубиновых камней в желчном пузыре. Натолкнуть на мысль о наследственном сфероцитозе позволяют рутинные анализы крови (клинический, биохимический), в которых выявляются ретикулоцитоз, гипербилирубинемия за счет непрямой фракции билирубина, повышение уровня лактатдегидрогеназы. Чаще всего у пациентов с легкой или средней степенью тяжести наследственного сфероцитоза наблюдается компенсированный гемолиз с легко или умеренно выраженной анемией либо без нее, в то время как тяжело болеющие пациенты становятся трансфузионно-зависимыми. В классическом случае постановка диагноза не вызывает сложностей. Диагноз ставится на основании данных семейного анамнеза, клинических, лабораторных данных. К методам лабораторной диагностики относятся: 1) клинический анализ крови с морфологической оценкой эритроцитов, расчетом эритроцитарных параметров и подсчетом количества ретикулоцитов; 2) биохимический анализ крови с обязательным определением уровня билирубина в сыворотке крови с подсчетом их фракций, ЛДГ, печеночных ферментов (АЛТ, АСТ); 3) тест с использова-

нием флуоресцентного красителя эозин-5-малеимида; 4) эктацитометрия. Основные принципы лечения наследственного сфероцитоза: 1) при легкой форме заболевания специфического лечения не требуется, проводится динамическое наблюдение пациента; 2) при среднетяжелой форме заболевания проводится заместительная гемотрансфузионная терапия (трансфузии эритоцитарной взвеси); 3) при тяжелой форме заболевания показано проведение спленэктомии; 4) также проведение спленэктомии показано при легкой форме заболевания в сочетании с уже имеющейся на момент постановки диагноза желчнокаменной болезнью. К основным и самым грозным осложнениям наследственного сфероцитоза относят: желчнокаменную болезнь, обусловленную хроническим гемолизом и гипербилирубинемией; апластический криз, ассоциированный с парвовирусной инфекцией. При одновременном инфицировании парвовирусной инфекцией у пациента развивается тяжелый апластический криз. Парвовирус обладает высоким сродством к клеткам-предшественникам эритроцитов, которое обусловлено присутствием на их поверхности антигена, благодаря которому вирус способен проникать внутрь клетки. Люди, у которых этот антиген отсутствует, не чувствительны к парвовирусной инфекции, а инфицирование не приводит к развитию аплазии эритроидного ростка.

Описание клинического случая. Приводим собственное клиническое наблюдение. Пациент Р., 19 лет, поступил в клинику факультетской терапии Военно-медицинской академии в феврале 2023 г. из г. Омска. На момент осмотра пациент жалоб активно не предъявлял. Со слов больного, с детства отмечал периодическое появление желтушности кожных покровов, иктеричность склер, потемнение мочи. Впервые изменения в анализе крови были выявлены в июле 2022 г., когда на фоне течения ОРВИ был выполнен клинический анализ крови, в котором было отмечено появление анемии (эритроциты — 3,23 × 10^{12}/л, Hb — 107 г/л), эритроцитарные индексы в выписке представлены не были, поэтому судить о характере анемии не представляется возможным. В сентябре 2022 г. во время нахождения в инфекционном стационаре по поводу функционального расстройства желудка в анализе крови сохраняется анемия, также впервые выявлена гипербилирубинемия за счет непрямой фракции билирубина (общий билирубин — 65,52 мкмоль/л, прямой билирубин — 9,59 мкмоль/л). В ноябре 2022 г. по данным клинического и биохимического анализов крови без динамики по сравнению с предыдущими месяцами, но добавилось повышение уровня ЛДГ до 466 МЕ/л. Считает себя больным с января 2023 г., когда заболел ОРВИ. Во время болезни неоднократно отмечал потемнение мочи. По данному поводу был госпитализирован в инфекционное отделение. По результатам обследования при поступлении в анализах крови: нормохромная нормоцитарная анемия тяжелой степени тяжести (эритроциты — 1,75 × 10^{12}/л, Hb — 58 г/л, гематокрит — 17,3 %, MCV — 98,5 fl, MCH — 32,9 пг), значимая гипербилирубинемия за счет непрямой фракции билирубина (общий билирубин — 113,74 мкмоль/л, прямой билирубин — 16,14 мкмоль/л), почти трехкратное повышение ЛДГ (до 715 МЕ/л). По данным УЗИ органов брюшной полости визуализируются множественные конкременты в желчном пузыре, выраженная спленомегалия (селезенка 160 $см^2$). Выполнен скрининг на аутоиммунную гемолитическую анемию. Антиэритроцитарные антитела не выявлены, прямая проба Кумбса отрицательна. Установлен предварительный диагноз: гемолитическая анемия тяжелой степени, неуточненной этиологии. Гемолитический криз. Согласован перевод в специализированное гематологическое отделение ГКБ № 1 им. А. Н. Кабанова. При поступлении в отделение в анализах крови отмечалось снижение уровня гемоглобина до 32 г/л, выраженная ретикулоцитопения (1 промилле), нормальный уровень ЛДГ. Остальные показатели без динамики. Выполнена аспирационная биопсия костного мозга. В миелограмме обращало на себя внимание увеличение уровня бластных клеток до 3,2 %, гипоплазия эритроидного ряда (до 3,1 %). По данным кривой Прайс—Джонса: кривая смещена влево, средний диаметр эритроцитов 5 мкм, преобладают микроцитарные формы. По результатам гистологического исследования костного мозга: специфических изменений не было выявлено, все ростки кроветворения присутствуют.

Перед выпиской выполнена повторная миелограмма, по результатам которой эритроидный ряд расширился до 28,8 %, бластные клетки не визуализируются, отмечаются эритроциты с базофильной зернистостью и межъядерные мостики. За время нахождения в гематологическом стационаре были выполнены заместительные гемотрансфузии в объеме 1970 мл. Ввиду того, что выписка из стационара была представлена не полностью, то немного непонятным осталось обоснование проведения глюкокортикостероидной терапии преднизолоном в стартовой дозировке 120 мг/сут с постепенным снижением каждые 3 дня на 30 мг/сут до полной отмены. Тем не менее на фоне проведенного лечения было достигнуто увеличение уровня гемоглобина до 91 г/л, уменьшение проявлений анемического синдрома (уменьшение выраженности слабости, купирование одышки). В конце января согласован перевод в клинику факультетсткой терапии Военно-медицинской академии им. С. М. Кирова с диагнозом: гемолитическая анемия тяжелой степени, впервые возникшая, неуточненного генеза. При поступлении в клинику факультетской терапии в ходе тщательного расспроса пациента было обнаружено, что у отца пациента

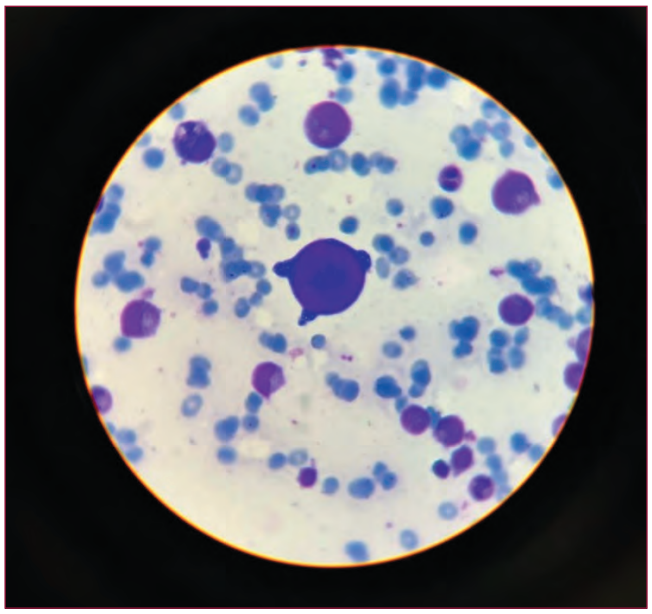

Рис. 1. Гигантский проэритробласт с отчетливыми нуклеолами

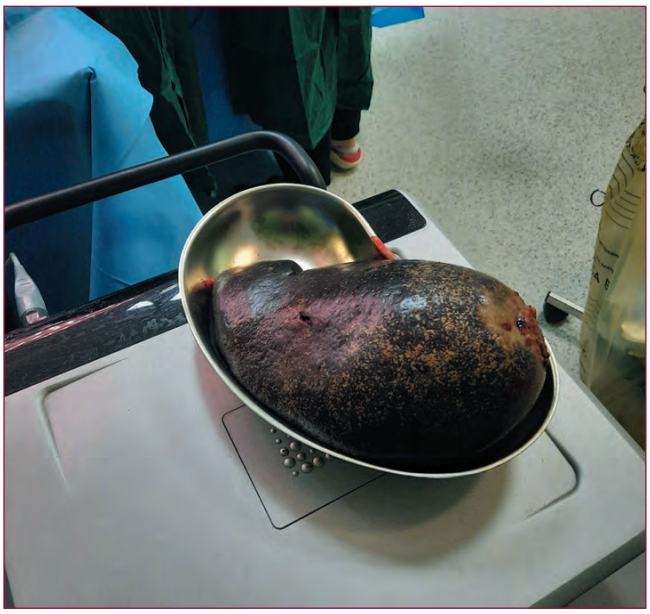

Рис. 2. Удаленная селезенка пациента

имелись на протяжении всей жизни точно такие же симптомы, как и у самого пациента (периодическое потемнение мочи, желтушность кожных покровов, иктеричность склер). По данным объективного осмотра обращает на себя внимание бледно-желтый цвет кожных покровов, дискомфорт при пальпации в левой эпигастральной области и в левом подреберье, признаки спленомегалии по результатам глубокой пальпации и перкуссии (перкуторно размеры 16 × 8 см). За время нахождения в стационаре в течение почти двух месяцев (февраль, март) значимо картина клинического анализа крови не менялась: сохранялась нормохромная нормоцитарная анемия легкой степени тяжести, отмечалось появление ретикулоцитоза (максимально до 70 промилле). В биохимическом анализе крови имелись скачки уровня общего билирубина от 30 до 130 мкмоль/л, уровень ЛДГ находился в пределах референсных значений. Заведующей лабораторией клиники факультетской терапии произведен пересмотр материалов аспирационной биопсии костного мозга, выполненной в г. Омске. По данным миелограммы имеется большое количество гигантских проэритробластов с отчетливыми нуклеолами (рис. 1), которые, по всей видимости, ошибочно были приняты за недифференцированные бласты врачами-морфологами в г. Омске. Именно гигантские проэритробласты натолкнули на мысль об инфицировании пациента парвовирусом. Позднее лабораторно было подтверждено наличие парвовирусной инфекции в организме (обнаружены антитела IgG, IgM к парвовирусу B19, ДНК парвовируса). В рамках дифференциальной диагностики с другими заболеваниями системы крови выполнены следующие исследования: прямой антиглобулиновый тест (отрицательный), иммунофенотипическая диагностика ПНГ (ПНГ-клон не выявлен), определение уровня витаминов B12, B9 (обнаружен дефицит фолиевой кислоты), электрофорез фракций гемоглобина (без патологии). Специфический тест на связывание эозин-5-малеимида показал сниженную интенсивность флюоресценции ЭМА, что позволяет думать о наличии дефекта либо дисфункции белкового компонента цитоскелета эритроцитов (наследственного сфероцитоза). По данным пересмотра гистологического исследования костного мозга, сделанного в г. Омске: морфологическая картина может свидетельствовать в пользу гемолитической анемии. По результатам гистологического исследования костного мозга, выполненного в клинике факультетской терапии: морфологическая картина не исключает поражение парвовирусной инфекцией. Цитогенетическое исследование костного мозга клональных повреждений не выявило. С учетом выполненного обследования был выставлен окончательный диагноз: наследственный сфероцитоз, тяжелое течение. Апластический криз, ассоциированный с парвовирусной инфекцией. С целью определения дальнейшей тактики лечения проведен консилиум совместно с хирургами, по результатам которого в соответствии с клиническими рекомендациями показано выполнение спленэктомии (рис. 2). Так как холецистолитиаз протекает бессимптомно, то от проведения холецистэктомии было принято на тот момент воздержаться.

Заключение. Подводя итог данной работы, можно сделать ряд выводов:

1. Наследственный сфероцитоз в большинстве случаев протекает в легкой и среднетяжелой формах.

2. При инфицировании парвовирусной инфекцией у пациента с наследственным сфероцитозом может развиваться тяжелый апластический криз.

Favorable response to PD-1 inhibitor for treatment of mediastinal follicular dendritic cell sarcoma: a case report

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Introduction. Follicular dendritic cell sarcoma (FDCS) is a rare and aggressive malignancy that affects intranodal and extranodal follicular dendritic cells (FDC). FDC are mesenchymal-derived cells located in the B follicles, where they capture, retain and present antigens to surrounding B cells. Due to the rarity of this disease, in the literature often are presented the series of case reports. To date there is no standard therapeutic protocol for FDCS, and different approaches have been applied including surgery, radiotherapy and chemotherapy. Complete surgical excision is the gold standard of localized disease, chemotherapy is mostly used for patients with metastatic FDCS. Programmed death-1 (PD-1)/programmed death factor ligand-1 (PD-L1) checkpoint inhibitors are the main strategies of immunotherapy and have made breakthrough progress in the treatment of various cancers. However, there are only a few studies on the use of PD-1/PD-L1 inhibitors in patients with FDCS.

Objectives. To study PD-L1 expression and BRAFV600E mutation in tumor tissue of a patient with FDCS and evaluate the possibility of using new drugs depending on the results obtained.

Description of the case. A 34-year-old man presented with complaints of severe shortness of breath at rest, swelling of the face and upper limbs, fever in November 2022 years. During the examination, 3 massive tumor formations of the anterior and posterior mediastinum with maximum measuring more than 8 cm each with ingrowth into the pericardium and development bilateral hydrothorax and hydropericardium. Histological analysis of the tumor revealed a neoplasm, consisting of solid fields of neoplastic cells of ovoid, round and irregularly shaped with round, moderately hyperchromic nuclei; cells vortices form focally, small ones are visible among the described cells lymphocytes. Mitotic activity is low. In IHC studies it has place diffuse expression by cells CD21, CD23, CD35, EMA, Podoplanin, Vimentin, CD99, weak CD117, lack of expression of panCK, EBER, CK20, CD34, TdT, CD20, CK19, PAX-8, CD5, PLAP, Chromogranin, S100, CD30. The PD-L status of the tumor was determined separately: the cellularity of the sample was more than 100 tumor cells, Combined Positive Score — 100, TPS — 95 %, IC — 5 %. Thus, the diagnosis was formulated — follicular sarcoma dendritic cells with high expression of PD-L1.

As first-line treatment was chosen immunotherapy combined with chemotherapy. Carrying out surgical or radiation therapy were not possible due to the extent of the tumor. The patient received first cycle of the AIM (doxorubicin plus ifosfamide), then treatment was continued according to the EPOCH regimen (etoposide, prednisolone, vincristine, cyclophosphamide, doxorubicin) + Nivolumab (at a dose of 3 mg/kg every 2 weeks). After 2 cycles of chemotherapy and 4 Nivolumab, the patient's condition significantly improved, partial remission was achieved (according to RECIST criteria) with a reduction in tumor size by more than 50 %. To achieve better local tumor control, radiotherapy is planned after completion additional 2 cycles of chemotherapy and then the patient will continue to receive Nivolumab monotherapy.

Conclusions. This case suggests that a combination of immunotherapy and chemotherapy as first-line treatment might be a new therapeutic option for metastatic FDCS. It seems appropriate to determine PD-L1 expression all patients with FDCS. A better understanding of the molecular profile and drivers of this tumor may lead to new therapeutic strategies.

A clinical case of newly diagnosed CLL with intestinal involvement in a young patient followed by therapy with the venetoclax-obinutuzumab combination

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Background. Chronic lymphocytic leukemia (CLL) is a B-cell tumor manifested by the accumulation of atypical mature B-lymphocytes in peripheral blood, spleen, lymph nodes, and bone marrow. Extranodal lesions in CLL may be manifested by involvement of the lungs, skin, kidneys, and central nervous system. Cases of intestinal involvement in CLL have been reported quite rarely (1). Isolated cases of intestinal involvement in CLL have been described in the literature: intestinal infiltration on screening colonoscopy in a 71-year-old patient with CLL (2) and a 57-year-old patient with asymptomatic CLL newly diagnosed by immunohistochemistry, whose clinical manifestation of the disease occurred 6 months after diagnosis in the form of diarrhea, B-symptoms, and lymphadenopathy, and histological examination revealed generalized leukemic intestinal infiltration (3).

Objectives. To describe a clinical case of a young patient with chronic lymphocytic leukemia with intestinal involvement.

Clinical observation. Female B., 23 y.o. Since August 2021, she has been suffering from frequent diarrhea. She was examined by a gastroenterologist and an infectious disease specialist, no data on gastrointestinal pathology and infectious diseases were revealed. According to the results of ultrasound examination of the peripheral lymph nodes in December 2021, generalized lymphadenopathy was revealed (submandibular lymph node (LN) on the right max 2.9 × 1.1 cm, on the left max 2.7 × 1, 3cm; in the axillary areas on both sides, LN on the right max 1.9 × 0.85 cm, on the left max 1.7 × 0.67 cm; In the inguinal area there were nodes on both sides: on the left max 1.7 × 0.52 cm, on the right max 1.8 × 0.67 cm). According to the ultrasound scan on 11.2021: spleen 11.0 × 5.3 cm, in the projection of the portal vein, parapancreatic LN max. size of 3.1 × 1.25 cm were found. According to EGD and irrigoscopy, no organic pathology was found. MSCT of the thoracic organs: enlargement of mediastinal LN up to 1.2 cm, axillary up to 1.5 cm, supraclavicular up to 1.1 cm, splenomegaly. Patient was consulted by a hematologist. In the CBC of February 2022: Hb 127 g/l, leukocytes 6.6 × 10^9/l, ALC 3.56 × 10^9/l, a small number of broad-plasma lymphocytes, platelets 212 × 10^9/l. According to the results of bone marrow flow cytometry, B-cells with the phenotype CD19k+CD5+CD23+CD20+CD79b+CD38 were detected. Myelogram: bone marrow of normal cellularity, lymphocytes 29.5%. In April 2022, according to the results of fibrocolonoscopy, multiple foci of lymphoid mucosal hyperplasia were revealed, predominantly of the right colon (taking into account clinical findings and suspicion of lymphoproliferative disease, lymphoma was not excluded) and mild ileitis. According to the histological examination of the axillary node in April 2022, the pattern of the histological structure was completely erased due to diffuse-pseudonodular proliferation of tumor cells with the characteristics of small lymphocytes and prolymphocytes. According to immunohistochemistry analysis, tumor cells express CD 20, CD 23, CD 5, BCL2 and did not express CyclinD1, CD3, TdT, CD10, BCL6, PD1, CD30. A network of follicular dendritic cells was absent due to the absence of cells expressing CD21. The Ki67 index is 10%. Histological and immunohistochemistry (IHC) examination of the intestinal mucosa: submucosal lymphoid follicles were detected in one of the fragments. In the IHC study, CD20, CD23, CD5 were expressed by B-lymphocytes that form follicles, and an admixture of T-lymphocytes surrounding lymphoid follicles expressing CD3 is determined. The proliferative activity of the lymphoid infiltrate according to Ki67 is low. CyclinD1 was expressed in scattered histiocytes. The immunomorphological picture, taking into account clinical data, corresponds to damage to the intestinal wall by chronic lymphocytic leukemia/B-cell lymphoma from small lymphocytes. In the immunohistochemical examination of the bone marrow, tumor cells expressed CD20, PAX5, CD5, CD23 and did not express: CyclinD1, CD3. The immunomorphological picture, taking into account clinical data, corresponds to bone marrow damage in chronic B-cell lymphocytic leukemia. PET/CT scan from April 2022: LN of the deep cervical group on both sides, axillary and inguinal areas, with minimal FDG metabolism - dimensions 1.1 cm, SUVmax 1.47. According to the results of standard karyotyping (20 metaphases were analyzed with the addition of PMA+Lectin), the karyotype was 46XX. PCR of heavy chain gene rearrangements (04.05.2022) — the status of VDJ genes of IgH heavy chain immunoglobulin genes of this clone was unmutated (100 % > 98 %). Mutation TP53 (04/28/2022) was not detected. A revision of histological blocks (LN, large intestine, bone marrow) was carried out in St. Petersburg, the diagnosis of CLL/Lymphoma from small lymphocytes has been confirmed.

Based on the clinical data, lymphoma of small lymphocytes/chronic lymphocytic leukemia was verified, with lesions of the cervical, supraclavicular, axillary, inguinal, intra-abdominal lymph nodes, spleen, large intestine, bone marrow. Intermediate risk group for MPI.

Considering the young age of the patient, the presence of risk factors (unmutated variant of IGHV), in order to reduce the risk of immunosuppression and to achieve a deep MRD-negative status of the disease, it was decided to conduct fixed-duration therapy with targeted agents: venetoclax in combination with obinutuzumab (4). September 2022, Venetoclax + obinutuzumab therapy has been started according to the protocol, with a gradual increase in the dose (ramp-up) of Venetoclax. From October 2022, the dose of venetoclax has been increased up to 400 mg/day. The tolerability of therapy is satisfactory, no adverse events have been recorded during the therapy.

During the control examination in January 2023 (the 4th month of combination therapy), according to flow cytometry data T-cells were isolated in peripheral blood, B-cells were absent. Ultrasound scan of abdominal organs: spleen 9.9 × 4.0 cm (N 12.0 × 5.5 cm), single hypoechoic lesions in the hepatic portal up to 0.8 × 0.4 cm. Ultrasound of LNs: single submandibular LNs on both sides with preserved differentiation of 1.1 × 0.3 cm, along the vascular bundle of the neck on both sides single LN of a similar structure 1.6 × 0.7 cm. Posterior cervical LN single hypoechoic without differentiation into layers on both sides 0.7 × 0, 25 cm, in the axillary areas on both sides of single LNs: on the right up to 1.5 × 0.5 cm, single without clear differentiation 0.9 × 0.3 cm; on the left with preserved differentiation of 1.7 × 0.7 cm, single without clear differentiation 0.8 × 0.4 cm., in the inguinal areas on both sides single LN with preserved differentiation of 1.2 × 0.4 cm. In March 2023, obinutuzumab therapy was completed (6 cycles). According to the results of colonoscopy, no organic pathology was detected. Histological examination of the intestinal mucosa: morphological picture of ileitis and colitis of moderate activity. According to the results of histological examination of the bone marrow, there were no signs of tumor damage to the bone marrow. The number of mature lymphocytes in the myelogram is 16.50 %. Partial MRD negative remission has been achieved.

In October 2023, the full course of venetoclax + obinituzumab therapy was completed. According to the results of the control study, the size of the spleen and liver were within the age norm. There were no data for lymphadenopathy of intra-abdominal and retroperitoneal lymphadenopathy. Moderate lymphadenopathy of the peripheral l/d remains: in the axillary area on both sides on the left side of the LN 1.1 × 0.4 cm, on the right 1.1 × 0.38 cm, with preserved and not preserved internal structure, in the inguinal area on the left LN 1.1 × 0.32 cm, on the right 1.0 × 0.33 cm with preserved and not preserved internal structure. In CBC — HB 121 g/l, leukocytes 4.28 × 10^{9}/l, platelets 129 × 10^{9}/l, ALC 2.75 × 10^{9}/l.

Conclusions. This clinical case demonstrates a rare case of CLL in a young patient with involvement of the intestinal mucosa in the pathological process. Modern therapy of a fixed duration for 12 months (a combination of a BCL-2 inhibitor of venetoclax and a monoclonal anti-CD20 antibody obinutuzamab) made it possible to achieve complete MRD negative remission of the disease without manifestations of toxicity.

References

1. Abella E, Gimenez T, Gimeno J, et al. Diarrheic syndrome as a clinical sign of intestinal infiltration in progressive B-cell chronic lymphocytic leukemia. Leuk Res. 2009;33:159–61.

2. Aje KT, Abegunde AT, Mirza K. Intestinal Infiltration of Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Found on Screening Colonoscopy. Vol 14.; 2022:e21037-e21037. doi:10.7759/cureus.21037

3. Goncalves R, Sousa R, Banhudo A, et al. Endoscopic findings in chronic lymphocytic leukemia. American journal of clinical oncology. 2000;23(6):599–601. doi:10.1097/00000421-200012000-00014

4. Romero D. Venetoclax-obinutuzumab combinations are effective in fit patients with CLL. Nature reviews Clinical oncology. 2023;20(8):503–503. doi:10.1038/s41571-023-00786-7