Уважаемый читатель!

В этом номере представлены тезисы и клинические случаи V Московской международной гематологической школы имени С. П. Боткина (V Moscow International Hematological School of Young Scientists named after S. P. Botkin), ежегодной научной конференции, посвященной передовым фундаментальным и клиническим исследованиям в области онкогематологии и гематологии. Школа организована при участии четырех образовательных учреждений: кафедры гематологии и трансфузиологии имени академиков И. А. Кассирского и А. И. Воробьева Российской медицинской академии непрерывного профессионального образования, Московского многопрофильного научно-клинического центра им. С. П. Боткина ДЗМ (Москва), НИИ детской онкологии, гематологии и трансплантологии им. Р. М. Горбачевой Первого Санкт-Петербургского государственного медицинского университета имени академика И. П. Павлова (Санкт-Петербург) и АНО «Московская школа гематологии» (Москва).

Как и в прошлом году, бóльшая часть участников (53 %) получила возможность представить данные в виде устных докладов. К оценке работ было приглашено 17 российских и зарубежных экспертов. В соответствии с правилами, официальным языком конференции является английский. Суммарно к публикации были приняты 56 оригинальных работ, из которых 30 были отобраны для устных выступлений. Соответственно тематике поданных работ, они были распределены на 7 категорий:

- AGRESSIVE LYMPHOMA AND HODGKIN LYMPHOMA
- INNOVATIVE TREATMENT APPROACHES IN LYMPHOPROLIFERATIVE NEOPLASMS
- TRANSPLANTATION: FOCUS ON SUPPORTIVE CARE
- CHRONIC MYELOPROLIFERATIVE DISORDERS AND MDS
- ACUTE LEUKEMIA
- INDOLENT LYMPHOMAS AND MYELOMA
- BENIGN HEMATOLOGY AND TRANSFUSIOLOGY

Кроме того, в сборнике представлены наиболее интересные клинические случаи, поданные на конференцию.

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VI Московская международная школа молодых ученых по гематологии им. С. П. Боткина состоится в феврале — марте 2026 года. К участию принимаются тезисы оригинальных исследований и описания клинических случаев. Подробная информация о правилах подачи работ будет опубликована на сайте Московской школы гематологии (https://mshg.ru), на страницах журнала «Клиническая онкогематология. Фундаментальные исследования и клиническая практика». Ждем новых победителей на школе в 2026 году!

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

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AGRESSIVE LYMPHOMA AND HODGKIN LYMPHOMA

Prospective multicenter study on the effectiveness and safety of PET-adapted treatment for patients with newly diagnosed classical hodgkin lymphoma using ABVD and EACODD-14 chemotherapy regimens (HL-Russia-1)

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Objectives. The multicenter, prospective, investigator-initiated clinical study HL-Russia-1 (NCT04638790) was launched in November 2020. The primary objective is to assess the effectiveness and safety of first-line treatment for newly diagnosed classical Hodgkin Lymphoma (cHL) patients, utilizing a PET-adapted strategy with EACODD-14, ABVD and AVD chemotherapy regimens. Initial results were published in 2022. The projected enrolment is 400 patients by 2026. Here, we present an interim analysis of this four-year, ongoing prospective study.

Methods. From November 2020 to September 2024, 15 Russian hospitals joined the HL-Russia-1 study, contributing data on 216 patients to the coordinating center (Table 1, Figure 1). Of these, 184 patients with cHL began treatment according to study protocol, categorized by the German Hodgkin Study Group risk group classification:

- *Early stages, favorable prognosis:* 2–4 ABVD cycles followed by involved-site radiotherapy (ISRT);
- *Early stages, unfavorable prognosis:* 2 cycles of EACODD-14 followed by 2 cycles of AVD or 2–4 cycles of EACODD-14 based on PET-2 and PET-4, plus ISRT;
- *Advanced stages:* 6 cycles of EACODD-14 and RT for residual masses ≥ 2.5 cm.

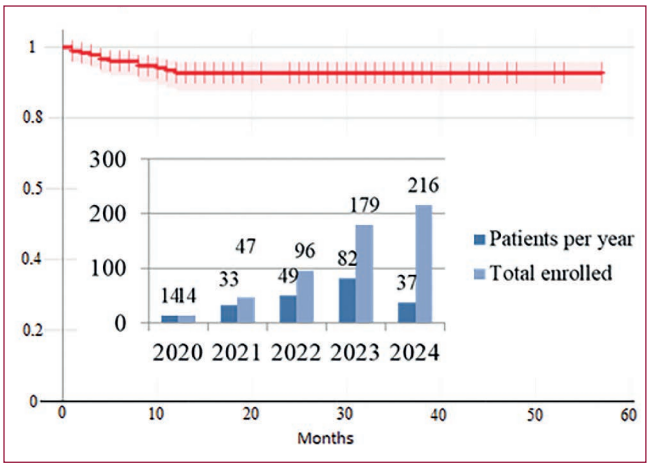

Figure 1. Progression-free survival and dynamics of patient enrollment in the HL-Russia-1 study

Table 1. Patients' characteristics

Parameter	Value
Submitted to coordinating center, n	216
Included in study population analysis, n	204
Median age, years (range)	30 (18–64)
Gender, n (%)	
Female	122 (60)
Male	82 (40)
Histological variant, n (%)	
Nodular sclerosis, unspecified	92 (45)
Nodular sclerosis type 1	58 (28)
Nodular sclerosis type 2	28 (14)
Mixed cellularity	16 (8)
Lymphocyte-depleted	0
Lymphocyte-rich	4 (2)
Unspecified	6 (3)
Prognostic group by GHSG criteria, n (%)	
Early stages, favorable prognosis	24 (11.8)
Early stages, unfavorable prognosis	59 (28.9)
Advanced stages	121 (59.3)

Survival analysis was conducted for patients who started at least one cycle of chemotherapy. Clinical data were collected following Good Clinical Practice standards and entered into the OpenClinica Community Edition, an open-source clinical data management system hosted on the Pirogov Center's IT infrastructure, with support from the Pirogov Center Digital Development Laboratory. Descriptive statistics were calculated, and Kaplan-Meier survival analysis was conducted to estimate the two-year progression-free survival.

Results. Among the 184 patients who started treatment per protocol, the treatment effectiveness at PET-2 was evaluated in 150 patients: 110 (73.3 %) achieved a Complete Metabolic Response (CMR), 36 (24 %) a partial MR, 2 (1.3 %) — stable disease, while 2 patients (1.3 %) had primary refractory cHL. Radiation therapy was administered for 44 patients (22 %). At the time of this analysis, assessment of the complete treatment program's effect was available for 75 patients: 69 maintained a complete or partial metabolic response, and 6 experienced progression or recurrence of cHL (Table 2). With a median follow-up of 17 months (range 1–57), all patients are alive; 69 are in confirmed remission. A primary refractory course was noted in 2 patients, and early relapse was detected in 4 patients (treatment failures — 8 % among those evaluated) from the group with unfavorable prognosis and advanced stages. The estimated two-year progression-free survival rate for the entire cohort is 92.7 % (Figure 1). No statistically significant differences in progression-free survival were observed between the prognostic groups at this time.

Conclusions. Since the inception of the HL-Russia-1 study, 15 clinics across Russia have participated. Interim results demonstrate the high effectiveness of the EACODD-14 regimen in advanced stages of cHL and successful PET-adapted therapy implementation across both federal and regional centers. This multicenter approach facilitates the recruitment of a large number of cHL patients in a relatively short period, enabling the evaluation of current standard treatment regimens in routine clinical practice and establishing a platform for trials involving new drugs and treatment approaches for Hodgkin Lymphoma.

Table 2. Response assessment for those who completed full treatment program in HL-Russia-1 study

GHSG Prognostic Group	Remission, under ongoing observation	Relapse or disease progression	Pending data	Total
Early stages, favorable prognosis	4	0	20	24
Early stages, unfavorable prognosis	20	2	37	59
Advanced stages	45	4	72	121
Total	69	6	129	204

Long-term outcomes of allogeneic hematopoietic stem cell transplantation with fludarabine-bendamustine conditioning and posttransplantation cyclophosphamide in r/r Hodgkin lymphoma

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Introduction. Despite significant advancements in treatment for classic Hodgkin lymphoma, the prognosis for patients with relapsed or refractory disease (r/r HL) remains dismal. Allogeneic hematopoietic stem cell transplantation (allo-HSCT) continues to be the only curative treatment option available for this group. While the efficacy of allo-HSCT is well-established, the optimal conditioning regimen and graft-versus-host disease (GVHD) prophylaxis for r/r HL remain undefined.

Study Objective. This study aimed to assess the outcomes of allo-HSCT using a fludarabine-bendamustine (FluBe) conditioning regimen and GVHD prophylaxis with post-transplant cyclophosphamide (PTCy) in patients with r/r HL.

Methods. A retrospective analysis was conducted on 69 patients with r/r HL who underwent allo-HSCT between 2014 and 2021 at the Raisa Gorbacheva Research Institute. The median age was 27 years (range 19–49). All patients received a reduced-intensity conditioning regimen (fludarabine 30 mg/m^2 and bendamustine 130 mg/m^2 per day for 3 days) combined with PTCy-based GVHD prophylaxis.

Results. Engraftment was documented in 64 patients (93 %). The three-year overall survival (OS) was 84 % (95% CI 74–99), while the event-free survival (EFS) was 65 % (95% CI 54–79). The cumulative incidence of relapse (CIR) and non-relapse mortality (NRM) at three years were 21 % (95% CI 12–33) and 12 % (95% CI 6–23), respectively.

Allo-HSCT from haploidentical donors was associated with higher NRM, as well as reduced OS (HR 4.04, 95% CI 1.16–14.00, p = 0.035) and EFS (OR 4.21, 95% CI 1.79–9.90, p = 0.001). Conversely, allo-HSCT with unrelated donors demonstrated a lower relapse incidence (OR 0.21, 95% CI 0.05–0.83, p = 0.02) and improved EFS (OR 0.30, 95% CI 0.12–0.74, p = 0.009).

PBSC as a graft source were associated with advantages over bone marrow, including reduced relapse rates (OR 0.15, 95% CI 0.03–0.65, p = 0.002), higher EFS (OR 0.31, 95% CI 0.12–0.80, p = 0.01), and survival free from severe GVHD and relapse (OR 0.45, 95% CI 0.21–0.98, p = 0.02). Allo-HSCT performed during complete response showed a trend toward improved OS (OR 0.22, 95% CI 0.05–1.05, p = 0.06) compared to patients with active r/r HL at the time of transplantation. However, this factor did not significantly impact other transplantation outcomes. The cumulative incidence of grades II–IV acute GVHD (aGVHD) was 37 % (95% CI 26–50), while grades III–IV aGVHD occurred in 20 % (95% CI 22–33). Chronic GVHD (cGVHD) had a cumulative incidence of 30 % (95% CI 20–44), with moderate or severe cGVHD developing in 17 % (95% CI 8–31). Acute GVHD was associated with a lower post-transplant relapse rate (OR 0.5, 95% CI 0.50–1.7, p = 0.01). However, grade III–IV aGVHD significantly increased transplant-related mortality (OR 2.4, 95% CI 0.57–10.1, p = 0.04) and the likelihood of developing chronic GVHD (OR 6.30, 95% CI 2.49–15.9, p = 0.002). The three-year survival without severe GVHD and relapse after allo-HSCT was 53 % (95% CI 39–65).

Conclusions. Allo-HSCT using the FluBe-PTCy regimen demonstrates favorable outcomes for r/r HL. Treatment outcomes were significantly impacted by donor type, graft source and pre-transplant disease status.

Predictive factors of autologous stem cell transplantation outcomes after anti-PD-1 treatment in patients with relapsed/refractory classical Hodgkin lymphoma

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Objectives. Anti-PD-1 are highly effective treatment option for relapsed/refractory (r/r) classical Hodgkin Lymphoma (cHL). However, long-term progression-free survival (PFS) rate remains unsatisfactory. Consolidation with autologous stem cell transplantation (ASCT) after anti-PD-1 is relatively safe and feasible option even among previously chemorefractory patients. Nevertheless, there is not enough data regarding predictors of ASCT efficacy after anti-PD-1.

Aims. To identify predictive factors of ASCT outcomes after anti-PD-1 in patients with r/r cHL.

Methods. We retrospectively analyzed patients received anti-PD-1 based treatment as second-line or later therapy and subsequently underwent ASCT between 2018 and 2024. Patients who received salvage therapy between anti-PD-1 and ASCT were not eligible.

Response was assessed using the Lugano criteria 2014 and LYRIC. PFS and overall survival (OS) were estimated using the Kaplan-Meier method. Factors including number of lines of systemic therapy before anti-PD-1, interval from anti-PD-1 to ASCT (< 60 days or > 60 days) and refractory status to the last line prior to anti-PD-1 therapy were analyzed in the context of PFS impact. Safety was assessed using Common Terminology Criteria for Adverse Events (CTCAE) (v5.0).

Results. 97 patients were included in the final analysis. The median age at ASCT was 35 years (range, 19–56). The median number of prior systemic therapies before pretransplant anti-PD-1 was 2 (range, 1–7). 64 % of patients were refractory to one, 35 % to two, and 13.4 % to three consecutive lines of therapy immediately before pretransplant anti-PD-1. 30 % of patients received brentuximab vedotin (BV) prior to anti-PD-1 and 56.7 % of these patients were BV refractory. Anti-PD-1 was administered as monotherapy (38.2 %, n = 37) or in different combinations with chemotherapy (61.8 %, n = 60).

The median number of anti-PD-1 cycles in a pretransplant line was 6 (range, 2–52) with median time from the last anti-PD-1 dose to ASCT of 84 days (range, 23–365). Pre-ASCT PET status: complete response (85.6 %), partial response (8.2 %), progressive disease (2 %) and indeterminate response (4.2 %). Major conditioning regimens for ASCT were BEAM (31 %) and BeEAC (67 %). 9,2 % of patients received post- ASCT BV maintenance and 8,2 % of patients anti-PD-1 maintenance.

At a median follow-up of 24 months, 2-year OS and PFS were 89 % and 80 %, respectively (Figure 1). Causes of death included transplant- related toxicity (5 patients), secondary AML (1 patient), progressive chronic heart failure (1 patient) and progressive cHL (2 patients). No significant PFS differences were observed based on the number of prior therapies, the time interval to ASCT and refractory status before anti-PD-1.

Anti-PD-1 therapy did not negatively impact on stem cell mobilization, harvesting and engraftment (Table 1). 4 patients experienced fatal cardiotoxicity and 1 patient — fatal cardiotoxicity in combination with fatal pulmonary toxicity. These cases likely had an immune-related genesis associated with anti-PD-1. Early transplant-related mortality was 5.2 %.

Conclusions. Our results contribute to the growing evidence supporting the safety and efficacy of ASCT consolidation following anti-PD-1 in r/r cHL. Attention should be paid to an early detection of possible life-threatening immune related adverse events. Among all analyzed factors there were no significant that predicts ASCT outcomes.

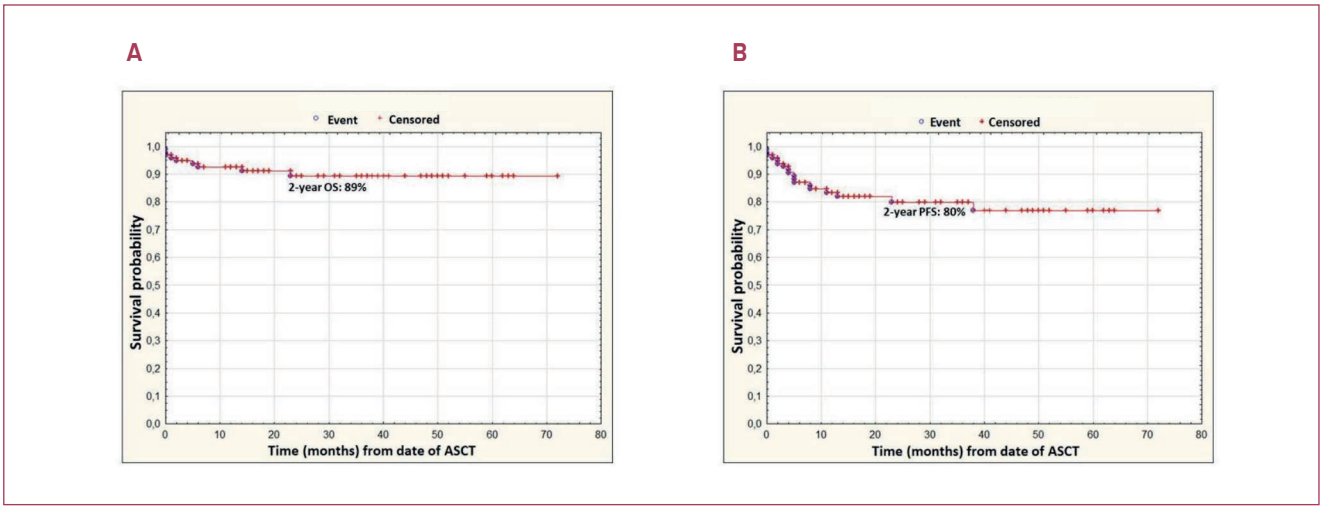

Figure 1. Survival outcomes. (A) Overall survival in all transplanted patients (n = 97). (B) Progression-free survival in all transplanted patients (n = 97)

Table 1. List of analysed parameters

Term parameter	3.2 (1.6–14.5)
Median number of CD34+ cells reinfused, n (range)	10 (8–26)
Median time to ANC > 0.5 × 10^9/L, d (range)	13 (7–43)
Grade 2 anemia, n (%)	38 (39.2)
Grade 3 anemia, n (%)	48 (49.5)
Documented infections, n (%)	36 (37.1)
Clostridial colitis, n (%)	11 (11.3)
Neutropenic fever, n (%)	84 (86.5)
Grade 3–4 mucositis, n (%)	6 (6.1)
Grade 3–4 enteropathy, n (%)	8 (8.2)
Engraftment syndrome, n (%)	11 (11.3)
Grade 4–5 cardiac toxicity, n (%)	7 (7.2)
Grade 5 lung toxicity, n (%)	1 (1)
Median days on parenteral antibiotics, n (range)	7 (0–23)
Median days on G-CSF, n (range)	9 (0–26)
PEG-G-CSF administration, n (%)	1 (1.03)
Median number of platelet transfusions, n (range)	3 (1–31)
Median number of RBCs transfusions, n (range)	1 (0–15)
Median duration of hospitalization, d (range)	23 (14–72)
Transplant-related mortality at 100 days, n (%)	5 (5.2)

Autologous hematopoietic stem cell transplantation and nivolumab as maintenance therapy in relapsed and refractory classical Hodgkin lymphoma

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Introduction. Chemotherapy have improved the prognosis of patients with classical Hodgkin's lymphoma (cHL), but 20–30 % of patients has disease relapse. The choice ot therapy for relapsed or refractory (r/r) cHL is autologous hematopoietic stem cell transplantation (autoHSCT), preceded by salvage chemotherapy. There are currently no randomized studies comparing the efficacy of different salvage chemotherapy. According to Santoro et al, the 5-year progression-free survival with BeGEV followed by autoHSCT is 59 %. The Nivo-BeGEV seems optimal because it has satisfactory toxicity and high efficacy.

Objectives. To evaluate the efficacy of autoHSCT ± maintenance with nivolumab in r/r cHL.

Methods. This prospective clinical study was conducted at the National Medical Research Centre for Hematology, Moscow, Russian Federation from 2018 to 2024. The study included 122 patients: 70 men, 52 women. All patients were examined before therapy according to clinical guidelines. Patient characteristics are presented in Table 1. After confirmation of r/r cHL, were administered 2 courses of Nivo-BeGEV. When remission was achieved, we did BeEAM conditioning and autoHSCT. Patients were given maintenance therapy with nivolumab for a year after completion of therapy if checkpoint inhibitors were available.

Results. The study included 122 patients with r/r cHL. The Nivo-BeGEV was implemented in 31/122 (25.4 %) patients in the National Medical Research Centre for Hematology and 91/122 (74.6 %) patients in other hospitals.

112/122 (91.8 %) patients after Nivo-BeGEV remission was achieved: after 2 cycles 83/122 (68 %). Mobilization of HSC was ineffective in 9/102 (7.4 %), refusal of autoHSCT in 20 cases (16.4 %).

25 patients who didn't undergo auto-HSCT received maintenance therapy with nivolumab.

AutoHSCT was performed in 91/122 (74.6 %) patients. In 2 cases, autoHSCT couldn't be performed due to the effect Nivo-BeGEV. After autoHSCT, maintenance with nivolumab was performed 42/91 (46.1 %), 49/91 (53.9 %) patients didn't receive it.

With an observation period from 3 to 73 (median 24) months, the 3-year relapse-free survival in the group of patients who underwent autoHSCT with nivolumab maintenance was 100 %, without maintenance 89.9 % (p = 0.03). In the groups without autoHSCT, with

Table 1. Characteristics of patients in r/r cLH (n = 122)

Parameters	Value
Males, n (%)	70 (57.4)
Females, n (%)	52 (42.6)
Median (range) age, years	33 (19–65)
B-symptoms at the time of starting Nivo-BeGEV, n (%)	35 (28.7)
Bone marrow involvement at the time of starting Nivo-BeGEV, n (%)	12 (9.8)
Bone involvement at the time of starting Nivo-BeGEV, n (%)	57 (46.6)
Extranodal lesions at the time of starting Nivo-BeGEV, n (%)	57 (46.6)
«Bulky» before Nivo-BeGEV, n (%)	49 (40.1)
Radiation therapy before Nivo-BEGEV, n (%)	40 (32.7)
Median (range) of therapies at time of Nivo-BeGEV	2 (1–7)

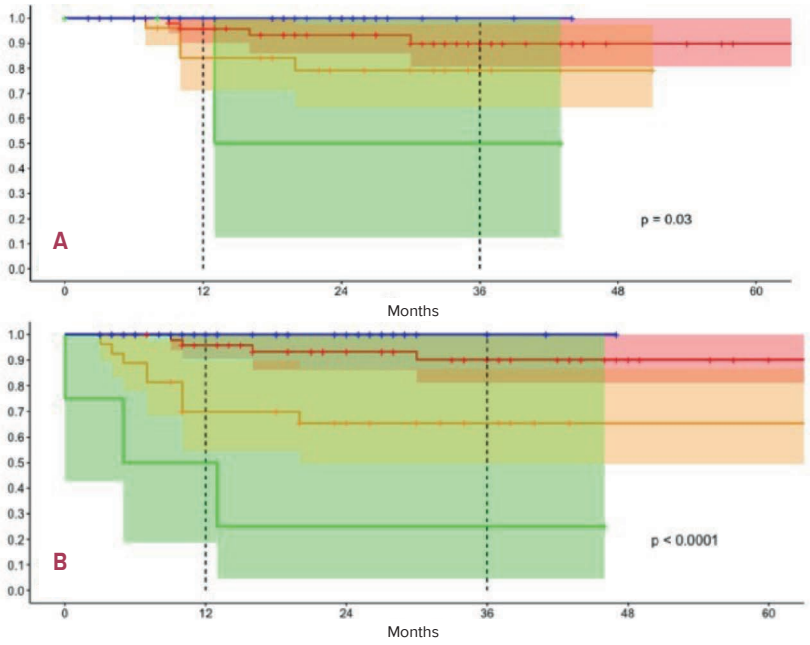

Figure 1. (A) Relapse-free survival. (B) Event-free survival: red line — autoHSCT without maintenance therapy with nivolumab, green line — without autoHSCT without maintenance therapy, orange line — without autoHSCT with maintenance therapy with nivolumab, blue line — autoHSCT with maintenance therapy with nivolumab

or without maintenance 79.2 % and 50 % (p = 0.03) (Figure 1, A). The 3-year event-free survival in the group without autoHSCT without or with maintenance was 25 % and 65.5 % (p < 0.0001). In the groups of patients who underwent autoHSCT with or without maintenance 100 % and 90.1 % (p < 0.0001) (Figure 1, B).

Conclusions. Study shows that autoHSCT demonstrates the best results in terms of relapse-free survival, event-free survival compared to patients who failed autoHSCT. Considering that 7.4 % of patients failed mobilization HSC, it is necessary to consider the feasibility of collection of HSC before the second-line or after the first anti-relapse therapy. According to research relapse will occur in up to 50 % of patients, despite autoHSCT. To improve the results, it is possible to use maintenance therapy after autoHSCT. It has been shown that maintenance with nivolumab increases the chances of relapse-free survival. Thus, support with checkpoint inhibitors is preferable for all patients, especially for those who are not candidates for autoHSCT.

Comparison of toxicity and efficacy of conditioning regimens (BeEAC, LEAM, CLV) before autologous stem cell transplantation for the treatment of primary refractory and relapsed Hodgkin's lymphoma

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Background. High-dose chemotherapy (HDCT) followed by autologous transplantation of hematopoietic stem cells (ASCT) is the gold standard of treatment for patients with primary-refractory and relapsed forms of Hodgkin's lymphoma (R/R HL). The aims of conditioning regimen are to eradicate the

Table 1. Non-hematologic toxicity of different regimens

Characteristic	CLV (n = 78)	LEAM (n = 129)	BeEAC (n = 72)
Oral mucositis (WHO criteria), Grade III and IV, n (%)	2 (2,6)	10 (7,8)	7 (9,7)
Enteropathy, Grade III and IV, n (%)	2 (2,6)	18 (13,9)	10 (13,9)
Cardiotoxic effects, n (%)	1 (1,3)	3 (2,3)	5 (6,9)
Pulmonary toxicity, n (%)	1 (1,3)	0 (0)	3 (4,1)
Hepatic toxicity (CTCAE 5.0, 2017), Grade III and IV, n (%)	1 (1,3)	4 (3,1)	2 (2,8)
Infection, n (%)	53 (68)	98 (76)	52 (72,7)

tumor and increase the depth of remission. There are several most commonly used conditioning regimens for HDCT followed ASCT. Retrospective comparisons of different conditioning regimens before auto-HSCT remain relevant for assessing efficacy and toxicity and optimizing approaches to auto-HSCT in the absence of randomized studies.

Objectives. Comparison conditioning regimens (CLV, LEAM, BeEAC) before auto-HSCT for patients with primary refractory and relapsed HL in single center.

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.

Results. *Hematologic toxicity of different regimens (CLV, LEAM, BeEAC).* All patients had engraftment. 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 — 9 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. 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, nephrotoxicity, or infectious complications in different regimens. Transplant-related mortality (until D + 30) was: CLV — 1,3 %, LEAM — 3,1 %, BeEAC — 2,8 % (p > 0,05) (Table 1).

Efficiency of condition regimens. The highest rate of complete response after HDCT and auto-HSCT was in BeEAC (p < 0.001). Progression-free survival was comparable in all groups. Comparison of overall survival (OS) and progression free survival (PFS) of different regimens is shown in Figures 1,2.

Conclusion. HDCT followed ASCT is the best therapeutic approach for a R/R HL. BeEAC, LEAM and CLV conditioning regimens being considered as viable alternatives. Our results suggest a comparable efficacy of BeEAC, LEAM and CLV conditioning in terms of survival and disease control. However, we also observed higher rates of gastrointestinal and cardiac toxicities in patients transplanted after LEAM and BeEAC. Differences in the

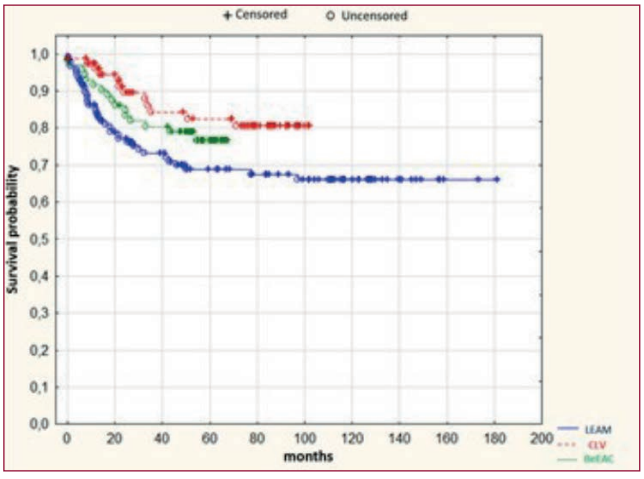

Figure 1. Overall survival (p = 0,04)

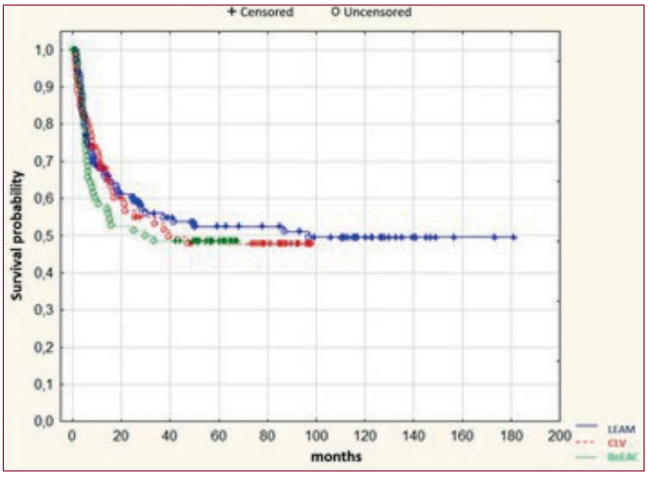

Figure 2. Progression-free survival (p = 0,66)

non-hematological toxicity profile of these regimens may serve as a criterion for personalized choice of conditioning regimen in patients with different comorbidities. 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.

Treatment outcomes in young patients with previously untreated mantle cell lymphoma: results from single institute experience

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Background. Mantle cell lymphoma (MCL) is accounts for up to 5–10 % of all B-cell lymphomas worldwide, characterized by the presence of t(11;14)(q13;q32), which juxtaposes the CCDN1 gene with the immunoglobin heavy chain locus, leading to overexpression of cyclin D1.

The disease occurs predominantly among middle-aged and elderly men (median age 65–75 years, M:W/4:1). MCL is characterized by an extremely heterogeneous course, from indolent non-nodal forms to aggressive variants with rapid rates of tumor progression, short response to chemotherapy and frequent relapses. The diversity of clinical manifestations of MCL requires a different approach to treatment.

Objectives. We aimed to evaluate the clinical characteristics and the efficacy of different immunochemotherapy regimens among young patients with previously untreated MCL.

Methods. 38 patients (pts) under 60 years with MCL had been treated from 2010 to 2024 in "National Medical Research Center of oncology named after N.N. Blokhin" were included in the study. Men were 27 (71 %), III–IV stages were detected in 34 (89 %) pts, B-symptoms — 20 (53 %), LDH < ULN — 15 (40 %) pts. Bone marrow involvement detected in 23 (60 %), splenomegaly in 17 (45 %) pts. According to the international prognostic index (MIPI), 10 pts were included in the high-risk group, 13 — intermediate, 15 — low-risk. The blastoid variant of MCL occurring in 13 %, higher Ki-67 proliferation index (Ki-67 ≥ 30 %) in 26 % pts.

Results. Since the analysis covers a long period of time over 15 years, the treatment programs were differed. 26 pts received intensive regimens (R-Hyper-CVAD/R-MA — 4 pts, R-CHOP/R-HDAra-C — 11 pts, R-CHOP/R-DHA(P,Ox) — 11 pts, 7 of 11 used BTK inhibitor (ibrutinib) in combination with R-CHOP). As a consolidation of the achieved response, 14 pts underwent autologous stem-cell transplant and 8 pts with CR are scheduled to undergo auto-HSCT. 12 pts received several nonintensive regimens (R-BAC, R-CHOP, VR-CAP). Most patients (90 %) have been receiving rituximab maintenance for 2–3 years. The objective effect (OE) (CR+nCR) of the treatment was achieved in 92 % of patients. The 3-year progression-free survival (PFS) rate was 69 % (median 39 months), overall survival — 95 % (median 84 months).

Intensive treatment, independent of regimens types, are highly effective (3-year PFS 82 %, median 132 months) compared to non-intensive regimens (3-year PFS 31 %, median 23 months) for pts with MCL (p = 0,001).

Conclusion. Intensive immunochemotherapy regimens are highly effective for young patients with MCL. The search for effective and non- toxic combinations, adding ibrutinib during induction and as maintenance, is still going on, it will allow to determine the optimal treatment for MCL patients in the future.

Keywords: mantle cell lymphoma, treatment.

First-line therapy for primary central nervous system lymphoma in Saint Petersburg: retrospective multicenter study

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Introduction. Primary central nervous system lymphoma (PCNSL) is a rare type of non-Hodgkin lymphoma, characterized by an aggressive clinical course. Currently in Russia there is neither sufficient information about the profile of patients with PCNSL nor standardized approaches to treatment.

Objectives. The aim of this study was to assess clinical and epidemiological characteristics of patients (pts) with PCNSL, the therapeutic landscape, as well as treatment outcomes and factors influencing them.

Methods. The study included 110 adult pts with histologically confirmed diagnosis of PCNSL from 9 centers in St. Petersburg who received treatment between 2010 and 2024. Main characteristics of pts and disease are summarized in Table 1.

Results. Median time from the onset of symptoms to the first visualization was 0,6 mo (0,0–25,4), to diagnosis — 2,7 mo (0,5–146), to the start of treatment — 3,6 mo (0,6–34,4). Median time from diagnosis to initiation of therapy was 0,7 mo (0,03–25,6). A delay in therapy from diagnosis of more than 0,7 mo was of worse overall survival (OS) (p = 0,041). In 3 % of pts (n = 3), the diagnosis was verified after beginning therapy. Stereotactic biopsy was performed in 48 % pts (n = 53), while surgical resection of the tumor was done in 52 % (n = 57). As first-line therapy, 94 % of pts (n = 104) received immuno- and/or chemotherapeutic regimens (ICT), 5 % of pts (n = 5) received radiation therapy (RT) with (n = 1) or without (n = 4) subsequent use of chemotherapy, and 1 pt (1 %) was treated by only glucocorticosteroids. Among all pts with CD20-positive PCNSL, 83 % (n = 90) received rituximab in first line. In the structure of ICT, regimens based on high-dose methotrexate (HD-MTX) accounted for 90 % (n = 94). The most frequently used ICT was protocol R-HD-MTX-AraC, which was applied to 40 % pts (n = 42). More detailed information about treatment is presented in Table 2. Among pts receiving ICT, the rate of overall response (OR) and complete response (CR) was 60 % (n = 62) and 27 % (n = 28), respectively. The disease status of 12 % pts (n = 12) remained unknown due to death before restaging. In the initial RT group, OR and CR was confirmed in 80 % pts (n = 4). At the data cut-off, median follow-up from the time of diagnosis was 17,8 mo (0,4–151,1). In the total group, 2-year OS was 43,7 % (median 19,4 mo), and 2-year progression-free survival (PFS) was 30,8 % (median 8,4 mo) (Figure 1). Among pts with OR, only 38 % pts (n = 25) received subsequent consolidation: 24 % (n = 16) - autologous hematopoietic stem cell transplantation, 11 % (n = 7) — RT, 3 % (n = 2) — combination of these methods. The 2-year OS in pts with OR who received consolidation was 82 % versus 45,6 % (median 19,4 mo) without consolidation (p = 0,005), and the 2-year PFS was 68,3 % versus 28 % (median 9,2 mo), respectively (p = 0,001) (Figure 2).

Table 1. Baseline characteristics

Characteristic	n = 110 (100 %)
Sex, n (%)	
male	45 (41)
female	65 (59)
Age at diagnosis, median (range)	57 (21–77)
ECOG score, n (%)	
ECOG 1	31 (28)
ECOG 2	40 (36)
ECOG 3	30 (27)
ECOG 4	9 (8)
HIV-infection, n (%)	
HIV-negative	103 (94)
HIV-positive	7 (6)
Histologic subtype, n (%)	
Diffuse large B-cell lymphoma	106 (96)
GCB subtype	15 (13)
non-GCB subtype	44 (40)
unknown	47 (43)
High-grade B-cell lymphoma, NOS, n (%)	2 (2)
Burkitt lymphoma	1 (1)
Peripheral T-cell lymphoma	1 (1)
Localization of the lesions, n (%)	
Brain	91 (83)
Leptomeningeal	1 (1)
Combined	18 (16)
Brain + leptomeningeal	15 (13)
Brain + intraocular	2 (2)
Brain + spinal cord	1 (1)
Nature of the lesions, n (%)	
Deep structure lesion	78 (71)
Multifocal lesions	59 (54)
Deep structure and multifocal lesions	50 (45)

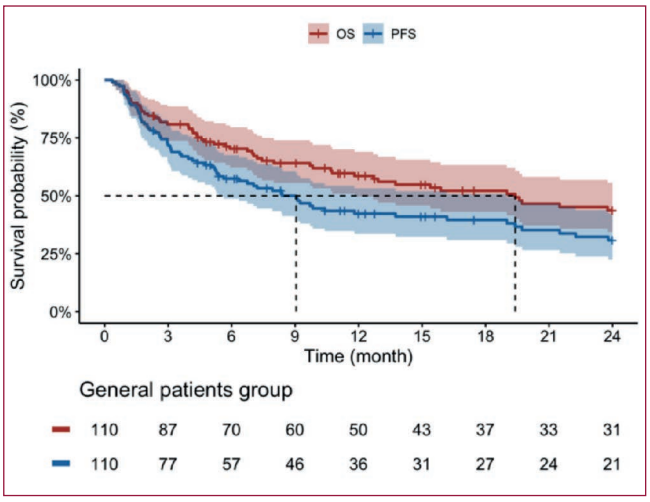

Figure 1. Overall and progression-free survival in general group

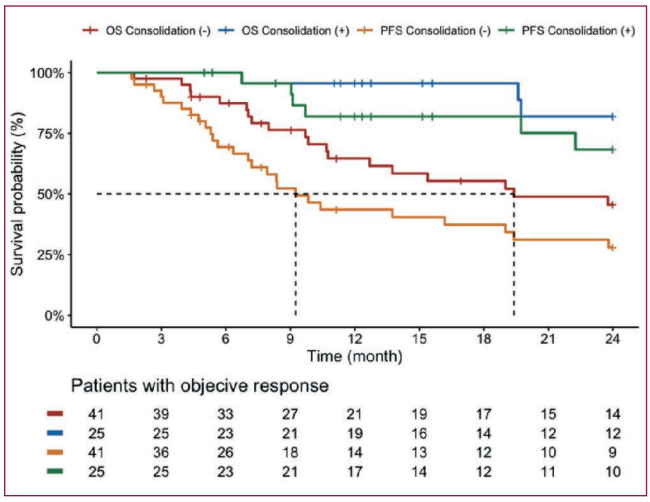

Figure 2. Impact of consolidation on overall and progression-free survival in patients with objective response

Table 2. Characteristics of first line therapy

Characteristic	n (%)
Immuno- and/or chemotherapy	**104 (94)**
One agent	8 (8)
Two agents	23 (22)
Three agents	54 (52)
≥4 agents	19 (18)
Radiotherapy	**5 (5)**
Radiotherapy alone	4 (4)
Radiotherapy + Lomustine	1 (1)
Glucocorticoids	**1 (1)**
High-dose methotrexate regimens	**94 (90)**
R-MTX-AraC	42 (40)
R-MTX	13 (13)
R-MTX-Temozolomide	9 (9)
R-MTX-Vin-Procarbazine/Dacarbazine	7 (7)
MTX-AraC	6 (6)
R-MTX-AraC-Thiotepa	5 (5)
MTX	5 (5)
R-MTX-Vin-Thiotepa	2 (2)
R-MTX-Vin	1 (1)
R-MTX-Vin-Dacarbazine-Lenalidomide	1 (1)
R-MTX-Procarbazine-Lomustine	1 (1)
R-MTX-Carmustine	1 (1)
R-MTX-Procarbazine	1 (1)
Other regimens (R-DeVIC ± Temozolomide, R ± Temozolomide, R ± Nivolumab, AraC-Vin, Vin-Lomustine)	**10 (10)**
Rituximab in CD20-positive lymphoma	**90 (83)**
Consolidation response	**25 (38)**
AutoHSCT	16 (24)
Radiotherapy	7 (11)
AutoHSCT + Radiotherapy	2 (3)

Conclusions. The analysis identified a number of problems faced by pts with PCNSL: excessive surgical interventions, delays in making the correct diagnosis and initiating treatment, use of suboptimal treatment regimens, and failure to consolidate response. In pts who underwent consolidation, survival rates were comparable with global data.

Comparative effectiveness of the NHL-BFM-90 and R-CHOP programs in HIV-infected patients with Burkitt's lymphoma

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Background. People living with HIV (PLWH) have an increased risk of developing malignant neoplasms compared to the general population. The life expectancy of a patient with HIV infection on antiretroviral therapy (ART) is currently 60 to 75 years, but depends largely on the CD4-positive cell count at HIV diagnosis and

patient compliance. Currently, the risk of developing NHL during HIV infection remains 11–200 times higher than in immunocompromised patients, despite the use of personalised, highly specific ART. By the age of 75, the cumulative incidence of NHL in HIV-infected patients is 4.4 %, compared with 0.01 % in HIV-uninfected patients. Indicators of HIV infection — low CD4+ count and high viral load (VL) — are negative factors for chemotherapy in HIV-associated lymphoma. Burkitt's lymphoma (BL) is one of the most common lymphoproliferative HIV-associated diseases with a worse prognosis than diffuse large B-cell lymphoma.

Objectives. Our aim was to compare the toxicity and effectiveness of NHL-BFM-90 and R-CHOEP chemotherapy protocols in HIV-infected patients with BL for the period from 2012 to 2022 at the hematology department of the Moscow Clinical Scientific Center.

Methods. The results of treatment of 32 HIV-infected patients with BL were analyzed who received therapy at the hematology department of the Moscow Clinical Scientific Center from 2012 to 2022.There were two cohorts: group 1 (18 patients) who were treated with the R-CHOEP protocol and group 2 (14 patients) treated with the NHLBFM-90 protocol. Median age were 33 years and 28 years respectively.

Results. The 3-year overall survival (OS) was 46 % in the R-CHOEP arm and 72 % in the NHL-BFM-90 arm. Due to toxicity, the development of bacterial and fungal complications with damage to lung tissue and the gastrointestinal tract in the first group, the intercourse intervals were extended to a maximum of 42 days and up to 56 days in the second group. The number of patients with a complete treatment programme (6 courses of RCHOEP) was 8, with 10 patients for the NHL BFM-90. The prescription of a subsequent line of therapy in group 1 was due to primary resistance in 100 % of cases. In the second group, 2 patients had resistance and 2 patients had progression of HIV infection. The number of serious complications did not correlate with the choice of treatment option, but was directly related to the duration of HIV infection, the level of CD4+ lymphocytes and the viral load.

Summary/Conclusion. Treatment of BL in HIV PLWH with high-dose chemotherapy NHL-BFM-90 protocol has an OS advantage compared to the less toxic chemotherapy according to the R-CHOEP program.

Pathomorphologic aspects of the tumor microenvironment in predicting the course of nodular sclerosis classical Hodgkin lymphoma

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Introduction. Nodular sclerosis classical Hodgkin lymphoma (NSCHL) is a common subtype of Hodgkin lymphoma, characterised by a distinctive nodular pattern and the presence of fibrotic bands. Notwithstanding the favourable survival rates associated with the current therapeutic modalities, approximately 30 % of cases experience relapse or resistance. The tumour microenvironment (TME) in NSCHL is of critical prognostic importance, with cellular components such as macrophages, granulocytes, B-cells and T-cells having the potential to impact patient outcomes.

Methods. The study examined formalin-fixed paraffin-embedded histological samples of lymph nodes from 70 patients diagnosed with NSCHL and treated between 2006 and 2020. The standard first-line chemotherapy regimens employed were ABVD (n = 10) and BEACOPP-14 (n = 60) (Table 1).

Immunohistochemical staining identified TME cells that exhibited markers. The following markers were identified: CD163, CD68, CD15, CD20, CD4, and CD8. The analysis employed the statistical software package SPSS for the purposes of testing, including the construction of Kaplan-Meier survival curves and the application of Cox regression.

Results. Elevated levels of CD163-positive tumor-associated macrophages in the microenvironment (≥ 7.9 %) have been linked to a range of unfavourable outcomes, including diminished treatment response (p = 0.001), heightened relapse risk (OR > 10), and a reduction in both the five-year overall survival (OS) and event-free survival (EFS) rates. A positive correlation was observed between high CD68 levels (≥ 12.1 %) and lower rates of complete response (p = 0.01), indicating a potential negative prognostic impact. The presence of elevated CD15-positive granulocytes (≥ 8.5 %) found to be associated with B symptoms, advanced stages, and reduced OS and EFS (p = 0,001). A reduced relative proportion of CD20-positive B-cells in the tumor microenvironment is a characteristic feature of patients who experience

Table 1. Clinical and morphologic characteristics of patients

Characteristics	N (%)
Sex	
male	34 (48,6)
female	36 (51,4)
Morphologic type (BNLI)	
NS I	48 (69,5)
NS II	22 (30,5)
Stage (Ann Arbor)	
I	2 (2,9)
II	31 (44,3)
III	19 (27,1)
IV	18 (25,7)
B symptoms	
yes	38 (54,3)
no	32 (45,7)
Prevalence	
localised	24 (34,3)
generalised	46 (65,7)
Chemotherapy	
ABVD	10 (14,3)
BEACOPP-14 (EACOPP-14) и BEACOPP-escalated	60 (85,7)
Response	
Complete remission	39 (55,7)
Diminished treatment response	31 (44,3)

relapse and chemotherapy refractoriness. This is associated with a low event-free survival (EFS) rate. The risk of developing an adverse event in patients with subthreshold marker expression (< 17.2 %) was found to be 4.2 times higher than in patients with higher CD20+ levels (p = 0.003). Neither marker of T-cells (CD4+ and CD8+) significantly impacted the disease course, indicating a limited prognostic value. The results of the multivariate Cox regression analysis demonstrated that the factor most significantly associated with an increased risk of an adverse event in EFS is the presence of suprathreshold levels of CD163+ expressing macrophages (≥ 7.9 %) in biopsy specimens of lymph nodes that are involved in the pathological process.

Conclusions. Elevated CD163+ and CD68+ macrophages, high CD15+ granulocytes, and low CD20+ B-cells correlate with adverse NSCHL outcomes. The quantification of these markers may facilitate the refinement of prognostic models and the personalisation of treatment strategies. Multifactorial Cox regression analysis identified high levels of CD163-positive tumor-associated macrophages in the microenvironment (≥ 7.9 %) as a standalone negative predictor for NSCHL progression in the selected cohort of NSCHL patients.

Analysis of chemical elements in the bone marrow in patients with hemoblastoses by synchrotron radiation based X-ray fluorescence (SR- XRF)

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Introduction. Identifying available markers for early diagnostics, predicting therapy response and monitoring hemoblastoses is an important task for the medical community. Over the last decade, methods for assessing the mineral homeostasis of the body by the levels of chemical elements in hair, nail plates and blood serum have been actively developed. Despite the prospects of this area of research, it should be noted that the elemental composition of blood serum and hair does not provide objective information on the content of chemical elements in the primary organ for hematopoiesis — the bone marrow (BM), which is especially important for patients with hemoblastoses. The aim of the study is to analyze the distribution of trace elements in the BM using the XRF-SI method in patients with hemoblastoses before and after polychemotherapy.

Objectives. The study included 33 patients aged 22 to 67 years, observed at Novosibirsk City Hematology Center. Among them were 20 patients with lymphomas (8 patients with Hodgkin's lymphoma (HL), 12 with non-Hodgkin's lymphomas (NHL) and 13 patients with acute leukemia (AL).

Methods. The BM was collected by sternal puncture before the start of treatment and after the 1st and 2nd courses of chemotherapy. After collection, the material was transported to Budker Institute of Nuclear Physics, after which the procedure of sample preparation and measurement was carried out at the VEPP-3 accelerator complex using the SR-XRF method (Figure 1).

Results. Analysis of changes in the microelement composition in patients with HL revealed that at the onset of the disease, the concentrations of bromine (Br) in the BM were higher compared to those measured after polychemotherapy ($p = 0.02$). In patients with AL, the concentration of strontium (Sr) ($p = 0.01$) and rubidium (Rb) ($p = 0.02$) were higher before treatment compared to the results of the study conducted after completion of the first course of polychemotherapy. A significant increase in the concentration of molybdenum (Mo) in the BM was determined in patients with HL after polychemotherapy compared to patients with AL ($p = 0.04$). With increasing age of patients, a decrease in the concentration of copper (Cu) ($r = -0.54$, $p = 0.04$) and arsenic (As) ($r = -0.56$, $p = 0.03$) was noted, and the amount of thorium (Th) in the bone marrow increased ($r = 0.52$, $p = 0.04$) at the onset of the disease. At the same time, a trend towards a more uniform decrease in the content of Zn, Br, Rb, Ca at three control points was detected in comparison with similar results revealed for Cu, the content of which decreased by 3.5 times. After the administered chemotherapy, only the iron concentrations were higher in patients with AL. The Cu/Zn ratio differs for lymphomas and AL, which may indicate metabolic differences between these tumors.

Conclusions. Further work in this study will be aimed at identifying early predictors of a refractory-recurrent course of hemoblastoses using the highly specific SR-XRF method in order to develop individual programs for prevention, supportive treatment and rehabilitation.

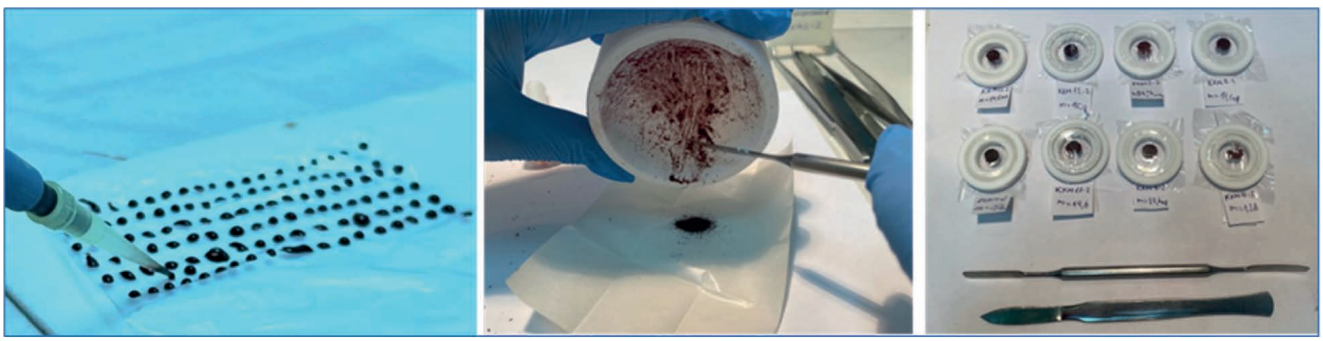

Figure 1. Sample preparation prior to testing

Using mathematical modelling to develop a personalised approach to prevent bone loss in patients with Hodgkin's lymphoma

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Introduction. Preventing the delayed side effects of chemotherapy in the active, able-bodied population is an urgent task in modern healthcare. Hodgkin's lymphoma (HL) affects young people and modern treatment methods can achieve 5-year survival rates of up to 90 %. Chemotherapy affects almost all body systems, including the endocrine system, which can lead to the development of osteoporosis. The favorable prognosis of patients with HL makes the development of prognostic models to assess bone mineral density (BMP) and timely preventive measures important.

Objectives. To develop a prediction model for BMP decline in patients with HL who have received pathogenetic therapy.

Materials and methods. The study included 90 people over 18 years of age, 60 of whom were patients with HL and 30 were controls. Age, sex and anthropometric data were comparable between the groups. All patients received chemotherapy in accordance with the standards of medical care. None received radiotherapy. Body mass index and body surface area were calculated according to the Mosteller formula. Thyroid and pituitary hormones, sex hormones, cortisol, immunoreactive insulin and insulin-like growth factor were assessed. Different combinations of factors were specified and variables were selected by mathematical modelling. The model was trained and tested. The training sample was 80 % and the test sample was 20 %. Data were processed using descriptive statistics, logistic regression, variance, discriminant and ROC analysis, Spearman and Matthews rank correlation coefficients, Mann-Whitney, Pearson's χ^2 and Fisher's criteria were calculated and the Shapirko-Wilk test was performed.

Results. The identification of the mutual influence of the levels of somatotrophin (STH), luteinising hormone (LH), insulin-like growth factor (IGF) and body surface area on BMP allowed us to develop a prognostic model for the presence of osteoporosis, which has the following form PPO= 1/(1 + e^(–x)), where PPO is the probability of predicting the outcome, the presence of the disease, x = + 3.292 × (STH level) + 2.986 × (IGF level) + 0.033 × (LH level) – 1.881 × (body surface area, m^2), e is the Euler number equal to 2.71808. The critical point of the PPO value was found to be equal to 0.49. This means that when the cut-off is above 0.49, osteoporosis prophylaxis is warranted. On the test sample the model performs with an accuracy of 64.7 % [47.1; 82.4] %, sensitivity of 62.5 % [28.6; 88.9] %, specificity of 66.7 % [40.0; 90.9] %, ROC-AUC = 70.8 % [47.2; 90.0] %. On the training sample with accuracy 76.7 % [65.1; 88.4] %, sensitivity 77.8 % [60.9; 93.8] %, specificity 76.0 % [61.9; 90.0] %, ROC-AUC = 86.2 % [75.4; 95.4] %. The obtained regression model is of good quality, has practical significance and can be used as an independent diagnostic algorithm determining the possibility of timely decision making about the start of preventive measures of osteoporosis in young patients with HL after treatment in the absence of densitometry results.

Conclusion. We recommend the use of our model to determine the likelihood of osteoporosis and the need for preventive measures in young patients with LH after chemotherapy in the absence of densitometry.

INNOVATIVE TREATMENT APPROACHES IN LYMPHOPROLIFERATIVE NEOPLASMS

Molecularly-adapted therapy for untreated diffuse large B-cell lymphoma

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Introduction. Diffuse large B-cell lymphoma (DLBCL) is a potentially curable but biologically heterogeneous lymphatic malignancy. The standard therapeutic option, R-CHOP, demonstrates unsatisfactory results both in the short and long term. To improve efficacy without additional toxicity, it is worth considering the possibility of applying biologically-oriented therapy.

Objectives. To evaluate the clinical efficacy and toxicity of genotype-directed R-CHOP-X program in patients with untreated DLBCL in the context of real-world clinical practice.

Materials and methods. A single-center prospective interventional clinical trial included 30 patients with untreated DLBCL between September 2023 and September 2024. The median age was 60 (38–78) years. Twenty-three patients (77 %) were classified as high-risk for progression according to the International Prognostic Index. The genotype distribution in the cohort was as follows: MCD — 7 %, N1 — 20 %, BN2 — 7 %, EZB — 16 %, ST2 — 7 %, and NOS — 43 %.

Results. Thirty patients received personalized genotype-directed therapy. Twenty-one patients (70 %) completed treatment: the overall response rate was 100 % (complete metabolic response — 100 %). Nine patients (30 %) are currently undergoing therapy: the overall response rate is 100 %. At 12 months, overall survival (OS) and progression-free survival (PFS) were equal and amounted to 100 % [95% CI 100, 100]. Hematotoxicity was assessed based on the number of cycles (n = 144): grade III-IV neutropenia was observed in 7 % of cycles, grade III-IV anemia and thrombocytopenia in 1.4 % and 3.5 % of cycles, respectively. Non-hematological toxicity was generally no more than grade I-II.

Conclusion. The results of this clinical trial are promising and provide preliminary evidence for the benefit of personalized genotype- directed cancer therapy in untreated DLBCL. This therapeutic strategy demonstrates high clinical efficacy, particularly in the main target group — high-risk DLBCL, with low toxicity. Further randomized studies are needed to confirm the efficacy and introduce this new approach into routine clinical practice.

Results of anti-BCMA bispecific antibody therapy of triple-class-exposed relapsed/refractory multiple myeloma

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Introduction. Multiple myeloma treatment commonly includes the administration of proteasome inhibitors, immunomodulatory drugs, anti-CD38 monoclonal antibodies. Nevertheless, prognosis of patients who relapses after receiving standard treatment is generally poor, and therapy options are limited and either toxic or suboptimal. B-cell maturation antigen (BCMA) is considered as a promising target for myeloma therapy. BCD-248 (Biocad) is a modified IgG1 antibody that targets both CD3 and BCMA, thus induces T-cell response against BCMA-expressing myeloma cells, leading to their lysis and death.

Table 1. Characteristics of the patients at baseline

Characteristics	Patients
Age	
Median (range), yr	61.7 (47.0–74.0)
Sex, n (%)	
Male	6 (37.5)
Female	10 (62.5)
Median time since diagnosis (range), yr	6.6 (2.8–13.9)
≥ 1 Extramedullary plasmocytoma, n/total n (%)	1/16 (6.25)
ECOG performance-status score, n (%)	
0	0/16 (0)
1	5/16 (31.25)
2	11/16 (68.75)
International Staging System class, n/total n (%)	
N/A	7/16 (43.75)
I	3/16 (18.75)
II	5/16 (31.25)
III	1/16 (6.25)
High-risk cytogenetic profile, n/total n (%)	
Chromosome 1 abnormalities (Gain or Amp 1q)	5/16 (31.25)
Median no. of lines of previous therapy (range)	6.5 (3.13)
Previous stem-cell transplantation, n (%)	5/16 (31.25)
Previous radiotherapy, n (%)	1/16 (6.25)
Previous triple-class therapy exposure, n (%)	16/16 (100 %)

Objectives. To evaluate the effectiveness and safety of BCD-248 in patients with triple-refractive multiple myeloma, who received treatment at Moscow Multidisciplinary Scientific and Clinical Center named after S.P. Botkin.

Methods. We enrolled 16 patients in phase I clinical trial of BCD-248 who had relapsed or refractory myeloma after at least three therapy lines, including triple-class exposure to an immunomodulatory drug, a proteasome inhibitor, and an anti-CD38 antibody, and had progressive and measurable disease at screening. Detailed description of patient's characteristics is listed below (Table 1). Patients received BCD-248 subcutaneously every 21 days at different dosing, according to the protocol. The response to the treatment was assessed during Cycle 4.

Results. The median observation time was 8.8 months. The overall response rate, including partial response or better, was 50 % (8/16 patients) (Figure 1, A). One patient (6.25 %) had minimal response to therapy, and one patient (6.25 %) died before planned assessment. No complete responses were observed. Out of responders, the vast majority received the established optimal dose of the drug as 3 mg/kg (7/9 patients had partial response or better). Of whom was treated with inferior dosage (< 3 mg/kg), 1 out of 7 had partial response (Figure 1, B). The median duration of progression-free and overall survival was 7.2 months and 12 months, respectively (Figure 1, C).

Common adverse events included cytokine release syndrome (in 62.5 % of the patients; no grade 3–4), neutropenia (in 68.8 %; grade 3 or 4, 56.3 %), anemia (in 56.3 %; grade 3 or 4, 43.8 %), and thrombocytopenia (in 12.5 %; grade 3 or 4, 12.5 %). Infections were frequent (in 75 %; grade 3 or 4, 56.3 %). Neurotoxic events occurred in one patient (cerebral edema, grade 4). A total of 9 patients (56.3 %) died, 6 out of 9 attributed to progressive disease. Three patients died from severe lung infection.

Conclusions. BCD-248 therapy resulted in a good response in patients with triple-class–exposed relapsed or refractory multiple myeloma. Better response was achieved in cohort receiving established optimal dose of the drug. Cytopenias and infections were common; toxic effects that were consistent with T-cell redirection were mostly grade 1 or 2.

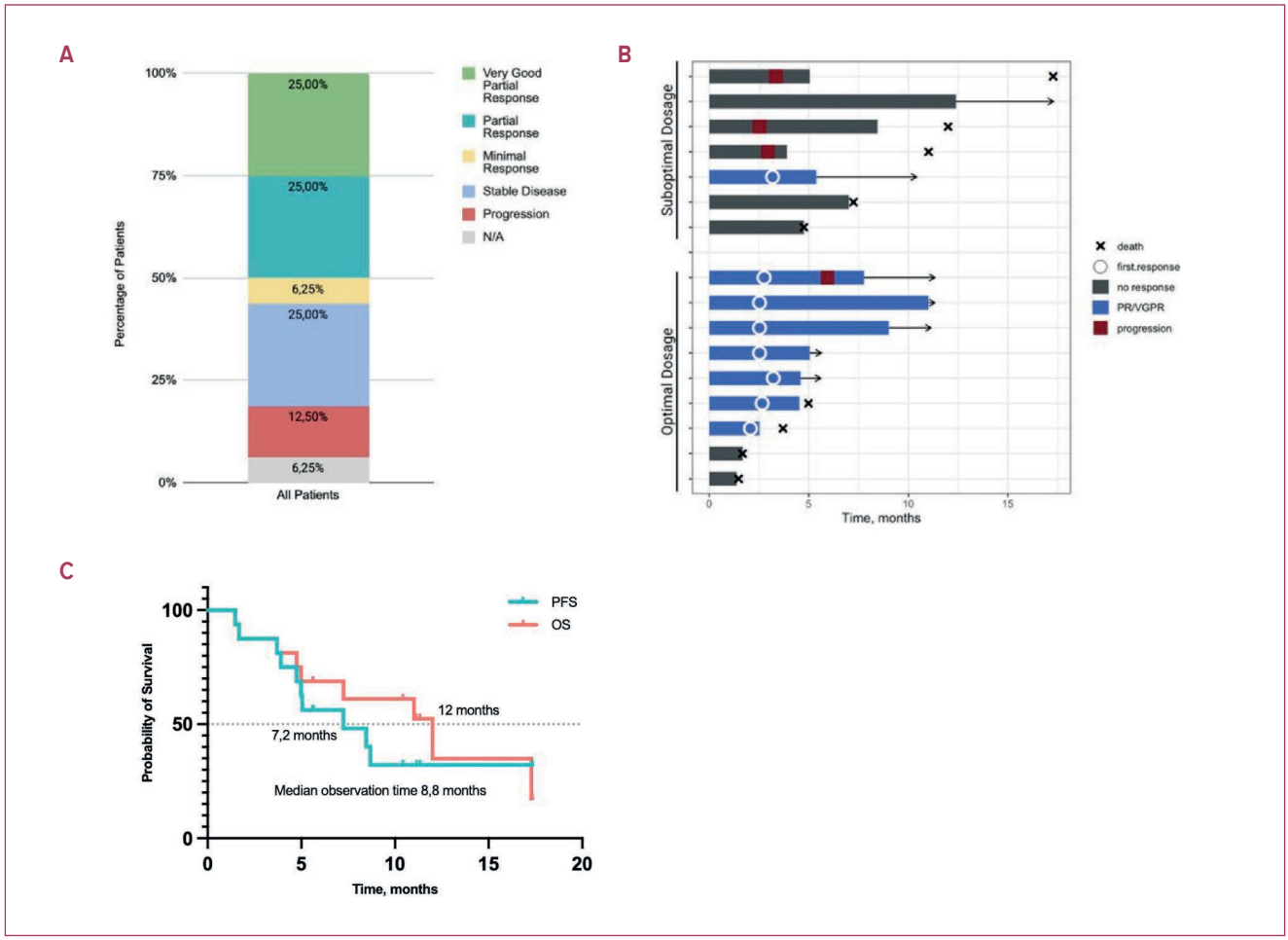

Figure 1. (A) Rate of overall response. (B) Treatment response in 16 patients. N/A — not assessed (patient died before planned assessment of response). (C) Kaplan–Meier analysis of progression-free and overall survival

Results of phase II clinical trial of efficacy and safety of prolgolimab monotherapy or in combination with bendamustine in second-line for classic Hodgkin lymphoma (NCT05757466)

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Background. Prolgolimab (Prolgo), an anti-PD-1 inhibitor, has been proven effective and safe in treating melanoma. Considering the biological characteristics of classic Hodgkin's lymphoma (cHL), it's anticipated that Prolgo's efficacy could extend to cHL as well. Long-term remission has been observed following PD-1 therapy, including its use as a second-line treatment. Therefore, incorporating Prolgo into a PET-adapted second-line therapy might not only prolong remission but also potentially cure cHL patients who respond to immunotherapy, possibly eliminating the need for autologous stem cell transplantation (auto-HSCT).

Methods. This prospective, multicenter, single-arm, phase 2 clinical trial includes adult patients (pts) with histologically confirmed relapsed or refractory (r/r) cHL after first line therapy PD-1 inhibitors (NCT05757466). According to study protocol pts receive 6 cycles of Prolgo

(1 mg/kg every 2 weeks) with subsequent assessment of response, those with complete response (CR) continue Prolgo for up to 24 cycles. If the CR is not achieved pts are switched to combination therapy (Prolgo 1 mg/kg D1,15; Bendamustine 90 mg/m^2 D1,2, 28-day cycle, for up to 3 cycles). Response assessments are performed every 3 months by PET-CT or CT, using LYRIC and Lugano criteria. The severity of adverse events (AE) was determined according to the CTCAE Version 5.0. The primary endpoint was overall response rate (ORR): CR and partial response (PR). Secondary endpoints included overall survival (OS), progression-free survival (PFS), duration of response (DOR), and AE. We conducted intention-to-treat (ITT) analysis for safety and per-protocol (PPA) analysis for efficacy, due to significant protocol deviation in 2 pts and early withdrawal of consent in 1 pts in one study center.

Results. A total of 23 pts with r/r cHL were enrolled at 3 sites from April 2023 to October 2024. The PPA included 20 pts who adhered strictly to the study protocol. Eighteen pts (90 %) completed all 6 cycles of Prolgo, among which 7 pts (39 %) achieved CR, 7 (39 %) — PR, 2 (12 %) — IR, one pts each demonstrated stable disease and disease progression. Among patients who achieved an CR after 6 cycles, no loss of response was recorded at the time of the last follow-up evaluation. Five pts (28 %) had already completed 24 cycles of therapy. The median of DOR for the entire group accounted for 6 months. Nine patients (53 %) were switched to the Prolgo-bendamustine arm. All patients who completed combination therapy achieved an objective response (CR n = 7, PR n = 1). Auto-HSCT was performed in 28 % (n = 5) pts. With a median follow-up of 10 months (1–18), all pts were alive, and 1-year PFS was 87 % (95% CI 71–100 %). In the safety ITT analysis (n = 23), the rate of grade (gr) 1–2 AE was 48 % (n = 11), and gr 3 AE — 17 % (n = 4: rash, diabetes mellitus onset, pneumonia, and renal colic).

Conclusion. This study is one of the first assessing Prolgo efficacy and safety as second-line therapy for cHL, aiming to avoid auto-HSCT in early CR patients. Preliminary data show an expectable toxicity profile and promising efficacy — patients achieve remissions while omitting chemotherapy and auto-HSCT.

Efficacy and safety of combination therapy with brentuximab vedotin and bendamustine in refractory and relapsed peripheral T-cell lymphomas: a retrospective analysis

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Introduction. According to current data, the incidence of peripheral T-cell lymphoma (PTCL) is 10–15 % of all non-Hodgkin lymphomas, predominantly in individuals over 60 years old. Nodular PTCL (nPTCL) is characterized by lymph node involvement, however, tumor lesions can occur in any location, determining the clinical picture of the disease. Therapy for newly diagnosed nPTCL involves courses including doxorubicin, cyclophosphamide, vincristine, and prednisolone (CHOP). Approximately 70 % of patients experience disease relapse within the first 2–3 years after completion of first-line therapy. The choice of the most effective therapy for patients with R/R nPTCL remains relevant, due to cumulative comorbidity and, consequently, the inability to conduct intensive treatment regimens, and the lack of standardized therapeutic management of relapses. Brentuximab vedotin monotherapy or in combination with DHAP, ESHAP, GDP, ICE chemotherapy regimens is recommended as second-line and subsequent therapy. Bendamustine and brentuximab vedotin (BvB) are proposed as an alternative, demonstrating high efficacy when agent used as monotherapy [1, 2]. Currently, the BvB combination is not included in Russian clinical guidelines, however, considering the results of studies on the use of these drugs in monotherapy and combination, it seems appropriate to consider this treatment option for Russian patients with R/R forms of PTCL.

Objectives. To evaluate the efficacy and safety profile of the BvB combination in the treatment of R/R nodular PTCL, the frequency of overall (ORR), complete (CR) and partial (PR) response, overall (OS) and progression-free (PFS) survival.

Materials and methods. A retrospective study was conducted by reviewing medical records of patients with R/R forms of nPTCL who were treated at state-funded institutions of the Moscow Department of Health from June 2008 to August 2024, who received a combined BvB treatment program. The course involved six (or until disease progression or unacceptable

toxicity) administrations of Brentuximab vedotin at a dose of 1.8 mg/kg on day 1, Bendamustine 90 mg/m^2 on days 2 and 3, the next course was started on day 22 from the beginning of the previous one. The Kaplan-Meier survival analysis method was used in the event analysis.

Discussion. Despite the small number of patients (n = 39), a significant advantage of using the combination is already being determined. In addition to an acceptable profile of hematologic (grade 3 and 4 complications were identified in 52 % of patients) and non-hematologic (grade 3 and 4 complications — in 39 % of patients) toxicity, encouraging PFS — 4.4 months, OS — 12.0 months were noted. It is worth noting the group of patients who received BvB in the 2nd line, for whom PFS was 6.5 months, ORR achieved 56.5 % (Figure 1).

Conclusion. The use of BvB in the 2nd line of therapy demonstrated a favorable toxicity profile and encouraging PFS and OS. In the context of high BPB, there is an opportunity to prepare candidates for consolidation Auto-HSCT or Allo-HSCT. A study is planned with an expanded sample size, a comparative analysis with a group of patients who received regimens in the 2nd, 3rd and subsequent lines of therapy, including other chemotherapeutic agents.

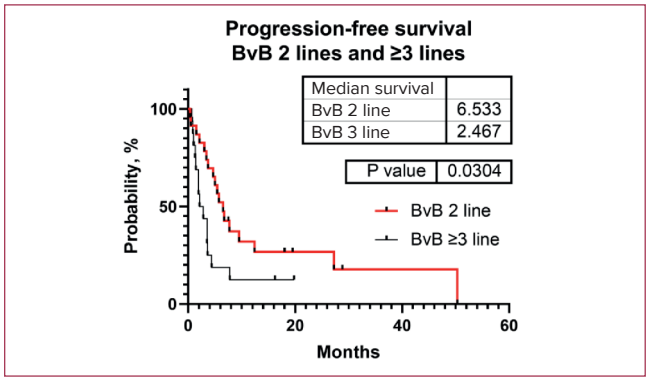

Figure 1. Progression-free survival BvB 2 lines and ≥ 3 lines

References

1. Horwitz SM, et al. Objective responses in relapsed T-cell lymphomas with single-agent brentuximab vedotin. Blood. 2014; 123(20): 3095–3100.

2. Damaj G, et al. Results from a prospective, open-label, phase II trial of bendamustine in refractory or relapsed T-cell lymphomas: the BENTLY trial. J Clin Oncol. 2013; 31(1): 104–10.

Successful use of mosunetuzumab in real clinical practice

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Introduction. Mosunetuzumab is a novel CD3×CD20 bispecific antibody that has shown encouraging results in the treatment of relapsed B-cell non-Hodgkin's lymphoma (B-NHL), particularly follicular lymphoma (FL) (Lihua, JCO 2024, Bosch F, Clin Lymphoma Myeloma Leuk. 2024, Matasar, Clinical Lymphoma, Myeloma and Leukemia, 2024).

Objectives. To evaluate the efficacy and safety of mosunetuzumab therapy in real clinical practice.

Materials and methods. Patients with relapsed B-NHL treated at the S. P. Botkin hospital from 2021 to 2024 who received mosunetuzumab as monotherapy were included in the study. The study included 9 patients with FL, 3 patients with diffuse B-cell lymphoma (DBCL) and 1 patient with mantle cell lymphoma (MCL). Response was assessed according to the Lugano 2014 criteria after the third treatment, and adverse events were evaluated using the CTCAE toxicity scale v. 5.0.

Results. Since 2021, 14 patients with B-NHL have received mosunetuzumab therapy. 13 of them were available for response assessment (Table 1). Adverse events (AEs) related to drug administration were reported in 2/13 (15 %) patients. In both cases, a mild cytokine release syndrome was observed, which did not require the use of interleukin-6 receptor monoclonal antibodies or their analogs. No neurotoxicity syndrome was observed. Throughout treatment, haematological and non-haematological toxicities did not exceed grade 2 and did not require dose reductions or discontinuation. The overall response (OR) was 69 %: complete remission (CR) in 4/13 (30 %); partial response (PR) in 1/13 (7 %); disease stabilisation (DS) in 5/13 (38 %). All patients who achieved CR had follicular lymphoma. Three patients in CR underwent autologous haematopoietic stem cell transplantation (autologous HSCT) for consolidation. With more than 24 months of follow-up after autologous HSCT, none of these patients have relapsed. One patient in CR remains on dynamic follow-up, which is currently over 36 months. 2-year overall survival (OS) and progression-free survival (PFS) were 69 % and 53 %, respectively. Median OS and PFS were not achieved (Figures 1–4).

Conclusions. In real-world clinical practice, mosunetuzumab has demonstrated high efficacy and a minimal toxicity profile in the treatment of B-cell lymphoma. The drug is effective as both salvage and bridge therapy prior to high-dose chemotherapy with haematopoietic stem cell support.

Table 1. Patients' characteristic

Characteristics of patients	N (%)
Median age at the time of initiation of therapy, median (range)	57 years (37–67)
Gender (male)	8 (61)
ECOG, N (%)	
0–1	10 (76)
2 and more	3 (24)
Subtype of B-NHL included in the study, N (%)	
Diffuse large B-cell lymphoma	3 (24)
FL (1–2 cytological type/3 cytological type)	9 (69) (4/5)
Mantle cell lymphoma	1 (7)
Ann Arbor, N (%)	
I–II	1 (7)
III–IV	12 (93)
B-symptoms, N (%)	2 (15)
Number of previous therapy lines, median (range)	6 (2–9)
Previous lines of therapy, N (%)	
Venetoclax-containing regimens	6 (46)
Polatuzumab vedotin-containing regimens	2 (15)
Autologous hematopoietic stem cell transplantation in the anamnesis	1 (7)
Disease status, N (%)	
Refractoriness to any line of therapy	9 (69)
Refractoriness to the last line of therapy	7 (53)
Primary refractoriness	4 (30)
Duration of Mosunetuzumab therapy, median (range)	42 days (21–174)
Median number of mosunetuzumab cycles (range)	3 (2–9)

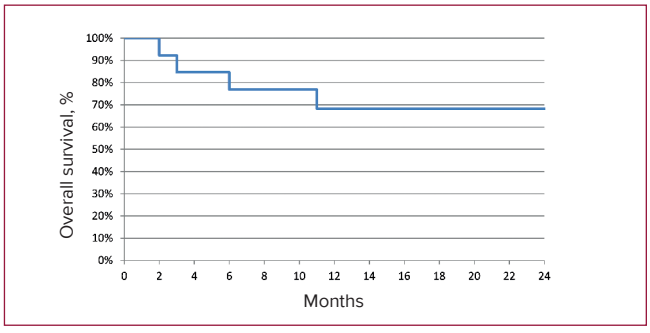

Figure 1. Overall survival (n = 13)

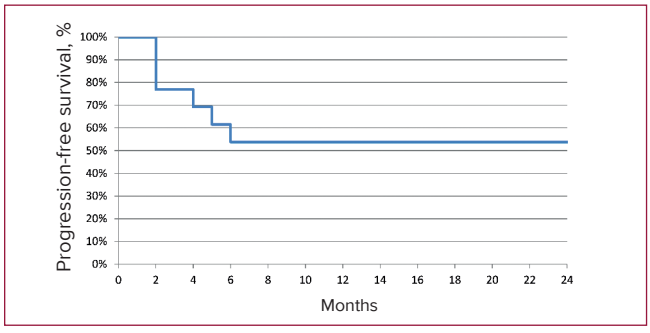

Figure 2. Progression-free survival (n = 13)

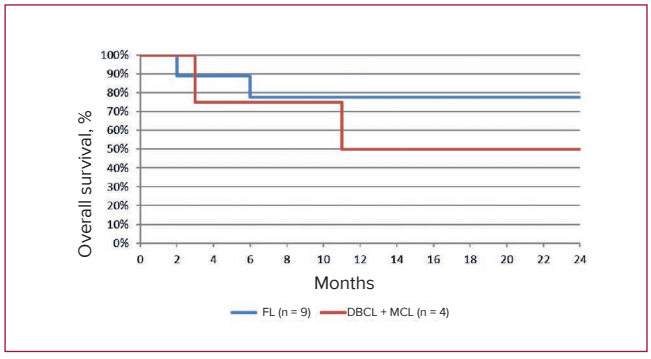

Figure 3. Overall survival depending on the diagnosis

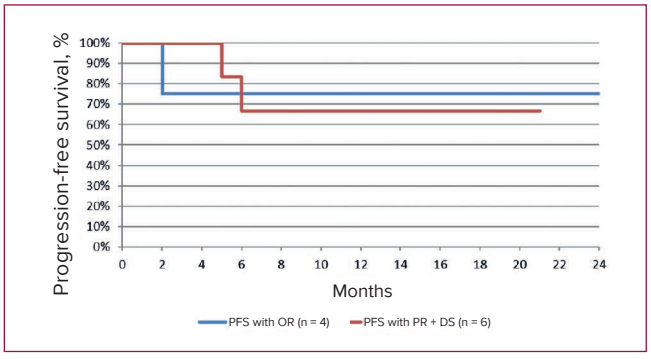

Figure 4. Progression-free survival depending on the response to therapy

TRANSPLANTATION: FOCUS ON SUPPORTIVE CARE

Early discontinuation of empiric antibiotic therapy in allogeneic hematopoietic stem cell transplant recipients

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Introduction. The safety of early discontinuation of empirical antibiotic therapy (EABT) for febrile neutropenia (FN) until neutrophil counts recover to greater than 0.5 × 10^9/L in hematologic patients has been confirmed and recommended in the absence of evidence of documented infection. The minimum time for continuation of EABT is 72 hours and persistent apyrexia for more than 48 hours. The safety of early discontinuation of EABT in recipients of allogeneic hematopoietic stem cell transplantation (allo-HSCT) is insufficiently studied; published data are limited to a few studies in a mixed patient population.

Material and methods. The single-center retrospective study included 42 adult allo-HSCT recipients between January 2022 and December of 2023 who underwent early discontinuation of EABT until neutrophil counts recovered above 0.5 × 10^9/L without documented infection. The aim of the study was to evaluate the safety of the early discontinuation approach in allo-HSCT recipients: recurrence of FN, bloodstream infection, sepsis/septic shock, transfer to ICU, and death within 30 days from the date of early EABT discontinuation. The median follow-up was 334 days (62–967). EABT was performed considering unsterile sites colonization according to the standard operating procedure of the RM Gorbacheva Research Institute, Pavlov University.

Results. The median time of febrile neutropenia (FN) onset after allo-HSCT was 3 days (–6...+15). The median neutrophil count at the time of FN onset was 0.27 × 10^9/L (0–2.88). Carbapenem-containing regimens were used as first-line EABT in 32 patients (76.2 %), while 10 patients (23.8 %) received regimens containing inhibitor-protected cephalosporins. At FN debut, 29 (69 %) patients were colonized with extended spectrum beta-lactamase-producing strains. The median duration of EABT was 8 days (3–22). The median neutrophil count at EABT withdrawal was 0.06 × 10^9/L (0–0.48). Staphylococcus epidermidis blood culture from a CVC was registered in 8 patients (19 %) but did not meet the bloodstream infection criteria and did not affect EABT withdrawal. FN recurrence occurred in 16 patients (38 %). The median time of FN relapses after first-line EABT withdrawal was 4 days (0–15). The median neutrophil count at FN relapses was 0 × 10^9/L (0–2.12). Carbapenem-containing EABT was resumed in 14 cases (87.5 %) and inhibitor-protected cephalosporin therapy in 2 cases (12.5 %). Three patients (7.15 %) were diagnosed with gram-negative bloodstream infections due to Enterobacter hormaechei, Pseudomonas aeruginosa and Escherichia coli. One episode of sepsis/septic shock was recorded within 30 days after EABT withdrawal; no deaths were registered. One patient was transferred to the intensive care unit due to a cardiac rhythm disturbance. 100-day overall survival was 92.8 % (95 % CI 79.3–97.6). One patient died after relapse of the underlying disease, one patient died due to graft failure, and one patient died due to grade 4 gastrointestinal acute GVHD.

Conclusions. The results of a retrospective study in a limited number of patients demonstrate the safety of early discontinuation of empirical antibiotic therapy in allo-HSCT recipients, but a prospective randomized trial is required.

Incidence of infectious complications in patients with acute GVHD after post-transplant cyclophosphamide-based prophylaxis

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Background. Acute graft-versus-host disease (GVHD) remains a significant complication following allogeneic hematopoietic stem cell transplantation (allo-HSCT), with infectious complications contributing to decreasing survival outcomes. Post-transplant cyclophosphamide has emerged as an effective strategy for GVHD prevention, but its impact on infectious complications (IC) remains incompletely understood.

Methods. Single center retrospective study included 148 adult patients with acute GVHD after the first allo-HSCT with post-transplant cyclophosphamide GVHD prophylaxis from 2014 to 2024. The analysis of infectious complications was carried out from the onset of GVHD up to the 100-day mark. The median time of acute GVHD onset was 33 days (14–109). The median follow-up time was 564 days (22–3067).

The analysis was performed in accordance with the statistical recommendations of EBMT.

Results. 100-day cumulative incidence (CI) of 1st episode of bacterial infection (BI) was 33.7 % [95 % CI 26.3–41.4]. The most common localizations were pneumonia and blood stream infection (BSI) with 23 (46 %) and 9 (18 %) cases, respectively. The main pathogens were gram-negative (GN) bacteria — 28 cases (56 %), especially — Klebsiella pneumoniae (17 cases, 61 %). Among those patients CI of 2nd episode of BI was 36 % [95 % CI 23.1–49.1], with the same localization pattern — pneumonia and BSI with 7 episodes each (36.8 %). The second episode of BI was predominantly caused by Klebsiella pneumonia as well (10 cases, 52.6 %). Median onset time of 1st BI episode – 35.5 days (0–98). Median onset time of 2nd episode — 52 days (1–99). 100-day CI of GN BSI was 13.5 % [95 % CI 8.6–19.6 %)]. Median time of onset was 31.5 days (0–91).

100-day CI of CMV-infection was 59.6 % [95 % CI 51.2–67.1]. The most frequent localizations were blood/bone marrow — 69 cases (79.3 %) and GI tract involvement — 13 cases (14.9 %). Median time of CMV-infection onset — 20 days (0–85). 100-day CI of HHV-6 infection was 35.1 % [95 % CI 27.6–42.8], with predominantly GI tract involvement — 35 cases (67.3 %). Median time of HHV-6 infection onset was 8 days (0–93).

100-day CI of invasive fungal disease (IFD) was 19.6 % [95 % CI 13.7–26.4], with lungs involvement in 24 cases (82.7 %) and mostly caused by Aspergillus spp. (23 cases, 79.3 %). Median time of IFD onset — 35 days (0–95).

In multivariable analysis aGVHD with GI tract involving ($p = 0.0005$) and colonization with carbapenem resistant gram-negative bacteria before GVHD onset ($p = 0.0098$) correlated with higher CI of GN BSI. GI tract involvement correlated with higher CI of HHV-6 infection ($p = 0.015$). And HSCT performing as a “salvage” therapy was significant risk factor for development of invasive fungal disease ($p = 0.0007$).

Conclusions. Incidence of IC varied from 19.6 % to 59.6 % and depended on the etiology of infection. The key risk factors were GVHD severity, GI involving, colonization with MDR GN bacteria and HSCT performed as “salvage” therapy.

Clinical significance of HHV-6 DNA detection in saliva of patients before and after allo-HSCT

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Introduction. The significance of the detection of human herpesvirus 6 (HHV-6) in saliva is currently unclear. Studying the relationship between the detection of this virus and the occurrence of post-transplant complications will allow the correct interpretation of laboratory results in routine clinical practice.

Objectives. To investigate the association between the detection of HHV-6 DNA in saliva obtained from patients after allogeneic hematopoietic stem cell transplantation (allo-HSCT) and the development of oral mucositis.

Methods. The study group consisted of 100 patients (52 women and 48 men), aged 28 to 48 years. All patients underwent allogeneic hematopoietic stem cell transplantation in National Medical Research Centre for Hematology from October 2022 to January 2024. In all patients saliva was studied on the pre-transplant period, on day 0 and further once a week until +28 days. We used the traditional technique of accumulating saliva in the oral cavity and spitting it into a disposable sterile tube in a volume of at least 1 ml of saliva. Determination of the presence of HHV-6 was performed by PCR. Also all patients were examined for oral mucositis symptoms according to CTCAE, WHO.

Results. There were no patients with symptoms of mucositis in the pre-transplant period and on day 0. Maximum number of mucositis was detected at +14 days (50 %) (Figure 1). In 18 % of patients before allo-HSCT HHV-6 DNA was detected in saliva, while signs of oral mucositis were absent in all patients at the time of the study. On day +7 after transplantation, only 15 % of patients with mucositis had HHV-6 detected in saliva. At the same time in patients without mucositis HHV-6 in saliva was detected in 22 %. And at +14 days the situation remained the same. Thus, no correlation between detection of HHV-6 DNA in saliva and presence/absence of oral mucositis in the first 2 weeks after allo-HSCT was revealed. Also, no association was found between the detection of HHV-6 DNA in saliva and the presence/absence of oral mucositis during the recovery period (+21 and +28 days) after allo-HSCT (Figure 2).

Conclusions. Salivary glands are a natural "depot" for HHV-6, which should be kept in mind when prescribing antiviral therapy based on saliva PCR data, since the virus in this case is not necessarily associated with the development of active infection. The isolation of HHV-6 only in a saliva sample from a person cannot be a reliable sign of HHV-6 associated mucositis or confirmation of HHV-6 infection of any localization. Approaches to the diagnosis and therapy of oral viral mucositis require clarification.

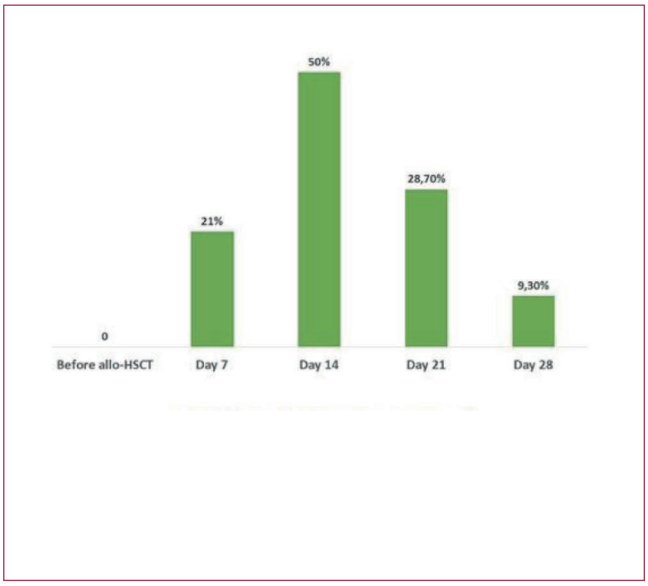

Figure 1. Prevalence of oral mucositis after allo-HSCT

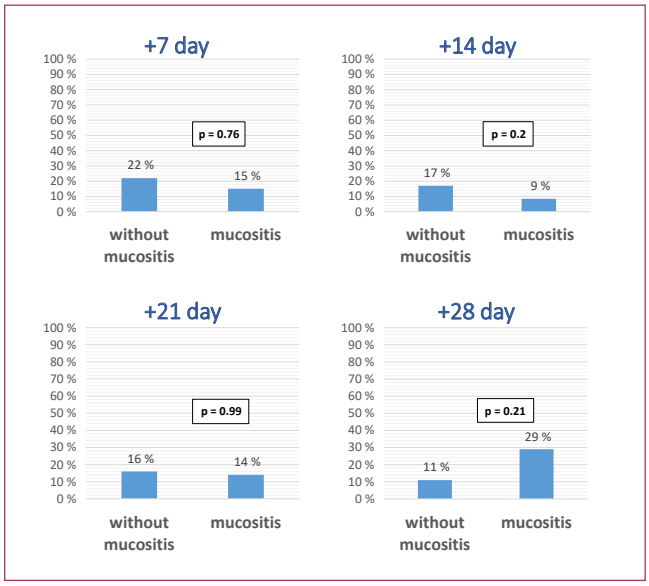

Figure 2. Detection of HHV-6 DNA in saliva of patients after allo-HSCT

Features of acute steroid-refractory graft-versus-host disease therapy with ruxolitinib in children

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Background. Allogeneic hematopoietic stem cell transplantation (alloHSCT) is a well-established treatment for many hematologic malignant and non- malignant diseases in children. One of the main life-threatening complications of this approach is an acute steroid-refractory graft-versus-host disease (srGVHD). Recent data shows that disruption of JAK-STAT pathway with JAK1/2 — inhibitor Ruxolitinib (Ruxo) reduces effector T-cell activity which allows to get a response and decrease early transplant associated mortality in patients with srGVHD. According to the results of Phase III study, Ruxo was approved for treatment srGVHD in adults, although there are still small data on the treatment efficacy and toxicity in children.

Methods. The single-center retrospective study was involved 77 patients younger than 18 years with hematological diseases after alloHSCT with acute srGVHD. Median age was 7 y.o. (0.7–18), with 22 (28.6 %) females and 55 (71.4 %) males. Within 56 (72.7 %) malignant diseases 35 (45.5 %) were ALL, 13 (16.9 %) were AML, 5 (6.49 %) with other hemoblastosis and 3 (3.90 %) with solid tumors. Among non-malignant 8 (10.4 %) had aplastic anemia, 6 (7.79 %) had MPS type 1. First HSCT was performed in 63 (81.8 %) patients, second in 10 (13 %), third in 4 (5.2 %).

Haploidentical related donor (Haplo) was used in 59 (76.6 %) patients, MRD in 2 (2.6 %), MUD/MMUD in 16 (20.8 %). As a graft source BM was used in 63 (82.9 %) patients, PBSC in 13 (17.1 %). For conditioning MAC was used in 40 (51.9 %) cases, RIC in 37 (48.1 %). Post-transplant cyclophosphamide was used at days +3, +4 for aGVHD prophylaxis in 64 (84.2 %) patients, antithymocyte globulin in 17 (22.4 %). Toxicity was based on NCI CTCAE 5.0. Ruxolitinib was administrated with a median starting dose of 0.2 (0.01–0.6) mg/kg. Time from ruxolitinib initiation to the event were used for assession of 3-year overall survival(OS), failure-free survival(FFS), nonrelapse mortality(NRM) and relapse incidence(RI). Events for FFS were relapse, death, or escalation of immunosuppression.

Results. Median follow-up time after Ruxo initiation was 782 days (8–2838). Baseline grade II srGVHD had 38 (49.4 %) patients, 26 (33.8 %) had grade III, 13 (16.9 %) had grade IV. Gastrointestinal (GI) tract was involved in 36 (46,8 %) patients, liver in 22 (28,6 %), skin in 73 (94,8 %). Partial response(PR) was documented in 9 (12 %) patients. Median time to PR was 7 days (1–112). Complete response rate (CRR) at 1 year after HSCT was 75 % (95% CI 63–84 %), median time to CR was 16 days (1–255). Severe srGVHD (grade 3 and 4) ($p < 0.001$) (Figure1), 2nd or 3rd HSCT ($p = 0.005$), Haplo ($p = 0.036$) and RIC ($p = 0.035$) were predictive for worse CRR. At the time of 3 year after HSCT Ruxo was stopped in 62 % (95% CI 49–72 %). 2nd or 3rd HSCT ($p = 0.033$) and Haplo ($p = 0.008$) increased time of Ruxo administration. OS was 70 % (95% CI 57–80 %), GI involvement ($p = 0.045$), absence of any response to Ruxo ($p < 0.001$) and HSCT from female donor to male recipient ($p = 0.022$) decrease OS. FFS, NRM and

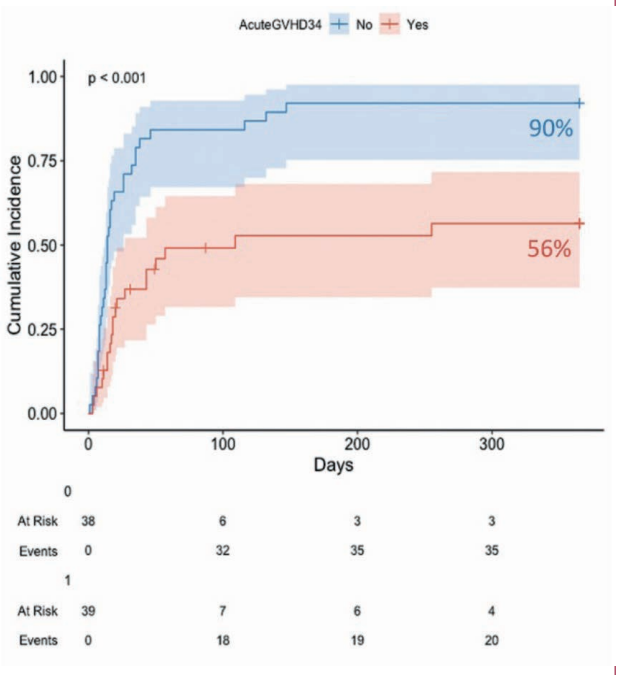

Figure 1. Complete response rate according to GVHD

RI were 55 % (95% CI 53–65 %), 20 % (95% CI 11–31 %), 34 % (95% CI 21–47 %) respectively. During Ruxo administration were documented more grade 2–4 anemia, thrombocytopenia, leukopenia, lymphopenia and neutropenia (p < 0.001). There was no case of secondary graft failure. Grade 2–4 liver (p = 0,114) and kidney (p = 0,07) toxicities were uncommon.

Conclusions. Ruxolitinib is an effective therapy of acute srGVHD in children with manageable side effects.

Early complications of autologous HSCT in elderly patients with multiple myeloma

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Introduction. Autologous hematopoietic stem cell transplantation (auto-HSCT) is the most efficacious method of achieving remission consolidation in patients with multiple myeloma (MM). As the number of transplants in older patients continues to rise, it is imperative to examine post-transplant complications in MM patients across different age groups.

Methods. The data from 126 MM patients who underwent auto-HSCT at the Kirov Research Institute of Hematology and Transfusiology between 2020 and 2023 were subjected to analysis. The patients were divided into two groups: the first group included patients younger than 60 years of age (n = 76), and the second group consisted of patients aged 60 to 69 years of age (n = 50). The principal demographic characteristics and disease status of the study participants are presented in Table 1.

Melphalan-based conditioning regimens were used in 100 % of patients. In the first group, myeloablative conditioning regimens predominated (70.7 %). In the second group, reduced-intensity conditioning regimens were more often used (52 %).

The frequency of infectious (febrile neutropenia, sepsis, sinusitis, pneumonia, soft tissue infection, catheter-associated infection, Clostridium-associated colitis) and non-infectious (mucositis, enteropathy, toxic dermatitis, pancreatitis, nephropathy, hepatitis, cardiotoxicity) early post-transplant complications was compared across age groups.

The statistical significance of the findings was determined by means of a Chi-square test, with a significance level of $p < 0.05$.

Results. Patients aged 60 years and older compared to younger patients exhibited a higher incidence of febrile neutropenia (72.0 % vs. 48.7 %) (p = 0.010) and cardiotoxicity (10.0 % vs. 0 %) (p = 0.005). A trend toward higher rates of sepsis, sinusitis, mucositis and toxic hepatitis was observed in younger patients compared to older patients. Early post-transplant mortality in the group of patients under 60 years was 1.3 %; in patients over 60 years it was not recorded.

Conclusions. It was demonstrated that patients aged 60 years and older exhibiteda higher incidence of febrile neutropenia and cardiotoxicity. However, the frequency of life-threating complications did not increase in comparison to patients younger than 60 years.

Furthermore, younger patients exhibited a more severe course of mucositis, higher frequency of toxic hepatitis, which is likely attributable to the higher-intensity conditioning regimens they received.

Table 1. Patients' characteristics

Characteristics	< 60 years fo age	60–69 years fo age
Total	76	50
Men, n (%)	39 (51.3 %)	20 (40.0 %)
Women, n (%)	37 (48.7 %)	30 (60.0 %)
Age median	52 ± 6.6	62 ± 2.5
Pretreatment (more than two lines of therapy prior to autologous HSCT), n (%)	15 (19.7 %)	3 (6.0 %)
Primary resistant disease (PRD), n (%)	16 (21.1 %)	10 (20.0 %)
Very good particial response (VGPR), n (%)	63 (82.9 %)	48 (96.0 %)
Complete response (CR), n (%)	13 (17.1 %)	2 (4.0 %)

CHRONIC MYELOPROLIFERATIVE DISORDERS AND MDS

The outcomes of patients with blast crisis chronic myeloid leukemia with and without allogeneic hemopoietic stem cell transplantation

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Introduction. Even in the era of tyrosine kinase inhibitors (TKIs) the outcomes of patients with blast crisis (BC) chronic myeloid leukemia (CML) continues to be poor. Median overall survival (OS) according to the literature does not exceed 12 months. At the same time the issue of the role and timing of transplantation remains relevant.

Objectives. This study was meant to compare outcomes in BC CML cohorts based on whether these patients received allogeneic hemopoietic stem cell transplantation (alloHSCT).

Patients and methods. From 2001 to 2024, 170 patients with BC CML were included in this study. The diagnosis of BC CML was verified according to the World Health Organization 2022 criteria. Among all patients alloHSCT was realized in 79 patients (46 %) and was not performed in 91 patients (54 %). The groups with and without alloHSCT were comparable in crucial biological charachteristics (additional chromosomal abnormalities (ACAs) (p = 0.4); complex karyotype / 3q26 (p = 0.3); BCR::ABL1 mutations (p = 0.5); extramedullary disease (EM) (p = 0.4).

Median time from BC to alloHSCT was 10 months (0.5–72). AlloHSCT was performed from matched-related donor (n = 18, 22 %), haploidentical donors (n = 11, 14 %), matched unrelated donors (n = 30, 39 %), mismatched unrelated donors (n = 20, 25 %). The main reasons for not performing alloHSCT were lack of response to therapy (62 %), disease progression (26 %) and donor unavailability (12 %). Overall survival (OS) was defined as the time from the start of treatment to death or last visit.

Results. With a median follow-up of 63.3 months (57.1–69.5) 5-year OS in the total patient cohort was 26.5 % (95% CI 19.5–33.8).

The median OS of patients with alloHSCT by landmark analysis performed 6 months from the date of BC was 60 months (16.3–NA), compared to 21.4 months (7.7–NA) in the group without alloHSCT (p = 0.044) (Figure 1). Performing alloHSCT within the first 10 months of BC verification by landmark analysis does not demonstrate an impact on improvement in OS (p = 0.3).

ACAs (HR 3.1, 95% CI 1.7–5.8, p < 0.001), including complex karyotype/3q.26 (HR 2.8, 95% CI 1.5–5.1, p = 0.001) had a negative impact on OS regardless of alloHSCT performance according to single-factor

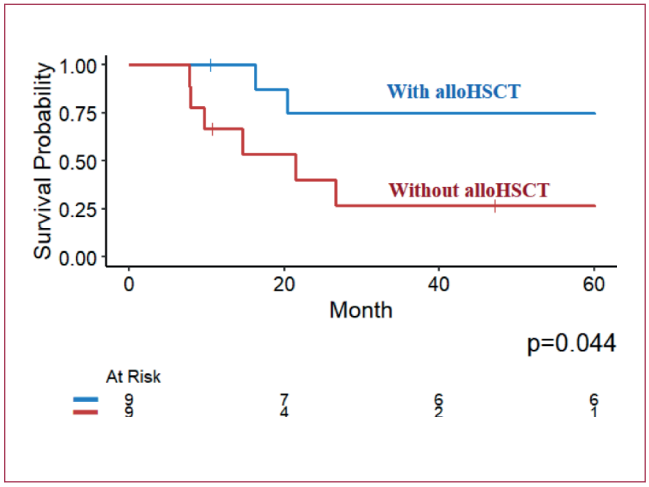

Figure 1. Overall survival of patients with BC CML depending on alloHSCT performed (landmark analysis at 6 months)

analysis. Age, time of BC development (BC be novo vs BC after CP/AP), immunologic variant of BC, mutations in BCR::ABL1 gene, EM and variant of BC therapy had no effect on OS.

According to multivariate analysis the crucial predictor improving the OS was alloHSCT (HR 0.3, 95% CI 0.2–0.4, p < 0.001). While any ACAs statistically significantly worsened the prognosis (HR 1.9, 95% CI 1.3–2.8, p = 0.002).

Conclusions. In spite of the widespread use of 2nd and 3rd generation TKIs the prognosis of patients with BC CML is still dismal. AlloHSCT demonstrates its advantage in patients with BC in the era of new-generation TKIs. At the same time performing alloHSCT in the first 6 months demonstrates the best results. In order to improve the results in this cohort these patients should be directed to transplant center as soon as the second chronic phase is achieved.

The use of NGS and cytogenetic analysis in assessing the prognosis and treatment efficacy of patients with Ph-negative myeloproliferative diseases

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Background. The genetics of Ph-negative myeloproliferative diseases include not only driver mutations, but also mutations in a wide range of genes, as well as chromosomal abnormalities.

Objectives. To assess the role of NGS profiling and cytogenetic analysis in evaluating the prognosis of the disease and the effectiveness of treatment for patients with Ph-negative myeloproliferative neoplasms.

Patients and methods. The study included 140 patients (55 men and 85 women) with a diagnosis of polycythemia vera (39/140), essential thrombocythemia (27/140), or primary myelofibrosis (74/140). Cohort median age was 54 years (IQR 19–85).

Main outcomes measures. A panel of 118 genes with an average reading depth of 1000x on MiSeq was used. The clinical significance of mutations was determined using a limit of 3 % variant allele frequency and COSMIC/Franklin databases. Chromosome analysis was performed using fresh bone marrow aspirates and G-banding with trypsin stain. For statistical analysis, the Kaplan-Meier method was used, with statistical significance assessed using the Cox-Mantel and chi-square tests.

Results. 51 % of patients (71/140) had 1 to 5 pathogenic mutations (Me = 1). The presence of any pathogenic mutation was associated with a decrease in EFS and OS (P = 0.0421 and P = 0.0052). The number of pathogenic mutations also affected the prognosis: in patients with ≥ 2 mutations, EFS and OS were significantly reduced (P < 0.001 and P = 0.003) compared to patients with fewer mutations. The cohort of patients (42/140) ever treated with Ruxolitinib showed decreased OS and EFS for those with ≥ 2 pathogenic mutations (P = 0.0314 and P = 0.0316). At the same time, for a group with ≥ 2 pathogenic mutations OV, but not EFS was increased in patients who had ever taken Ruxolitinib, but not in patients taking any other available therapy (P = 0,0168). The ASXL1 allele burden ≥ 30 % reduced EFS, but not OS (P = 0.0322). For 10 out of 23 patients with triple-negative status, pathogenic mutations were found in SRSF2 (4/10), ASXL1 (3/10), IDH1 (2/10), TET2 (2/10), RUNX1 (1/10, NF1 (1/10), HRAS (1/10), SH2B3 (1/10). The detection of pathogenic mutations in these patients allowed to confirm the clonality of the disease. The NGS study also revealed a favorable group of patients with triple-negative status (13/23) without pathogenic mutations. Cytogenetic analysis was performed for 76/140 patients. 13/76 patients presented with cytogenetic abnormalities: 3/13 had del(13) and 1/13 each had +8;+21; +8,del(9);del(11); del(7); +9,+t(1;9)+t(1;3); 1-2dup(1); der(22)t(1;22); -7; and inv(3)(q21q26),+6,+8,+9,-17,+3 with variations. The presence of a chromosomal aberration was associated with EFS and OS decrease (P = 0.0213 and P = 0.0266), but it did not affect the treatment effectiveness of Ruxolitinib (P = 0.51 and P = 0.58 for OS and EFS). The presence of cytogenetic abnormalities was significantly more common in patients with ≥1 pathogenic mutation (P = 0.0154).

Conclusions. Combined cytogenetic studies and mutation analysis make it possible to predict the course of the disease and evaluate the effectiveness of therapy.

Rare cases of JAK2 and CALR mutations in patients with chronic myeloid leukemia

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Introduction. While it is generally believed that the presence of a Ph chromosome and a driver mutation in Ph-negative MPNs are mutually exclusive, there is growing evidence in the literature that these two events can occur together.

Objectives. Using targeted high-throughput sequencing (NGS) to study the molecular genetic landscape of patients with both CML and Ph-MPNs, and to evaluate the characteristics of the disease course when these two pathologically significant events occur together.

Materials and methods. The study included DNA samples from peripheral blood cells of 336 patients (152 women and 184 men). The patients were aged 19–90 years (Me = 57). Mutations in the *JAK2*, *CALR* and *MPL* genes were analyzed for all patients. For patients with driver mutations, NGS analysis was performed on 118 myeloid genes using the MiSeq platform (Illumina), with an average depth of 1,000 reads.

The clinical significance of these mutations was assessed using the Franklin and Varsome databases.

Results. Ph-MPN driver mutations were found in 1.8 % of patients (6/336). The V617F mutation in the *JAK2* gene was detected in 1.2 % (4/336) of patients. Insertion of 5 nucleotides in the 9th exon of the *CALR* gene was present in 0.3 % (1/336) of the patients, and deletion of 52 nucleotides in the *CALR* gene was also found in 0.3 % of patients (1/336). No mutations were detected in the *MPL* gene.

During the NGS study, pathogenic mutations were detected in 16.7 % (1/6). Specifically, tryptophan was replaced by a stop codon in 1051 positions of the BCOR gene (8.61 %). *BCOR* mutations occur in about 16 % of the blast phase and contribute to the transformation of CML.

Mutations of unknown significance were found in 100 % of patients (6/6) in the genes *CUX1* (33.3 %), *KDR* (16.7 %), *FAT1* (16.7 %), *BRCA1* (16.7 %), *PTCH1* (16.7 %), *APC* (16.7 %), *KLF2* (16.7 %), *BCORL1* (16.7 %), *KMT2C* (16.7 %), *SH2B3* (16.7 %). Two patients had the same mutation — replacement of threonine with methionine in the 1384 position of the *CUX1* gene. This variant is not described in the literature in CML, however, mutations in the *CUX1* gene occur in patients with Ph-negative MPNs. In a patient with an allele burden of the T1384M mutation of 48.8 %, CML is a secondary disease, with the main one being true polycythemia with transformation into myelofibrosis.

The use of first-generation tyrosine kinase inhibitors (TKIs) did not achieve an optimal response in all patients. With therapy with subsequent generations of TKIs, a major molecular response was achieved in 83.3 % (5/6), however, with a decrease in the relative expression of the *BCR::ABL* gene in 50 % (2/4), the allelic load of the V617F mutation of the *JAK2* gene increased, which presumably indicates the existence of two different clones or subclones.

Conclusions. The molecular mechanisms that lead to the emergence of additional clones in patients with CML remain unclear. NGS sequencing, which allows studying the genetic landscape of patients with myeloproliferative diseases, contributes not only to the identification of additional molecular events, but also to understanding the molecular mechanisms of clonal evolution and the emergence of additional clones.

Efficacy of lenalidomide in myelodysplastic syndrome

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Introduction. Lenalidomide is highly effective in myelodysplastic syndrome (MDS) with deletion 5q (del(5q). Red blood cell transfusion independence achieving in 65–70 % of patients. Cytogenetic remission (CR) reaching in 35–40 % of patients. Red blood cell transfusion dependence (RBC-TD), thrombocytopenia < 100 × 10^9/L, TP53 mutation are predictors of therapy failure. The optimal duration of treatment has not yet been determined.

Methods. A total of 41 pts, including 6 (15 %) men and 35 (85 %) women, median (Me) age 62 years (range, 59 to 65), were enrolled and received lenalidomide. The distribution by MDS variants according to the WHO 2017 classification was as follows: MDS with isolated del(5q) — 26 (63 %), MDS with multilineage dysplasia (MDS-MLD) — 8 (19 %), MDS with excess blasts1 (MDS-EB1) — 7 (17 %). Lenalidomide was administered at a daily dose of 10 mg for 21 days, orally, of every 28-day cycle in 33 (80 %) of pts, in 8 (20 %) of pts in alternative regimens due to cytotoxicity and adverse events. The response to treatment was assessed after 2, 4, 6, 12, and 24 cycles.

Results. Standard metaphase analysis was performed in 39 pts, isolated del(5q) was detected in 22 (56 %) of pts, accompanied by 1 other aberration — 9 (23 %), by 2 aberrations in 1 (3 %) pts. The karyotype was normal in 6 (15 %) pts, there were no mitoses in 1 (3 %) pts. In these pts, del(5q) was detected by FISH. Distribution of pts by risk groups (IPSS-R) was: very low risk — 1 (2 %), low risk — 10 (24 %), intermediate — 27 (67 %) and high — 3 (7 %) of pts. RBC-TD was observed in 38 (93 %) of pts. The hemoglobin was 24–92 (Me 60) g/L, leukocytes — 1.3–9.4 (Me 3.58) × 10^9/L, ANC — 0.3–4.5 (Me 1.6) ×10^9/L, platelets — 86–1170 (Me 308) × 10^9/L. Bone marrow fibrosis was observed in 14 (34 %) of pts. TP53 mutation was examined in 7 (17 %) of pts and detected in 2 (29 %) of pts. JAK2 mutation was examined in 13 (32 %) pts, among them 10 (24 %) pts had initial thrombocytosis > 450 × 10^9/L, and detected in one (8 %) of pts with platelets count 309 × 10^9/L.

Hematologic response (HR) was achieved in 30 (73 %) of pts, including complete clinical and hematological remission (CHR) in 27 (90 %) of pts, among them 6 pts with MDS-EB1, after 2–4 (Me 2) cycles. CR was achieved in 13 (46 %) of 28 pts after 2–6 (Me 4) cycles. Loss of CR was confirmed in 4 (11 %) pts.

Four (9 %) pts progressed to MDS-EB2, the Me time was 1.4 years (range, 0.4 to 3.9). Allogeneic hematopoietic stem cell transplantation was performed in 2 (6 %) of pts. Both patients are currently alive. Four (9 %) pts died from unknown causes.

Conclusion. Lenalidomide treatment promotes HR and CHR in 73 % and 90 % pts respectively. Lenalidomide is effective in both MDS with del(5q) and MDS-EB1 with del(5q), and does not increase the risk of AML.

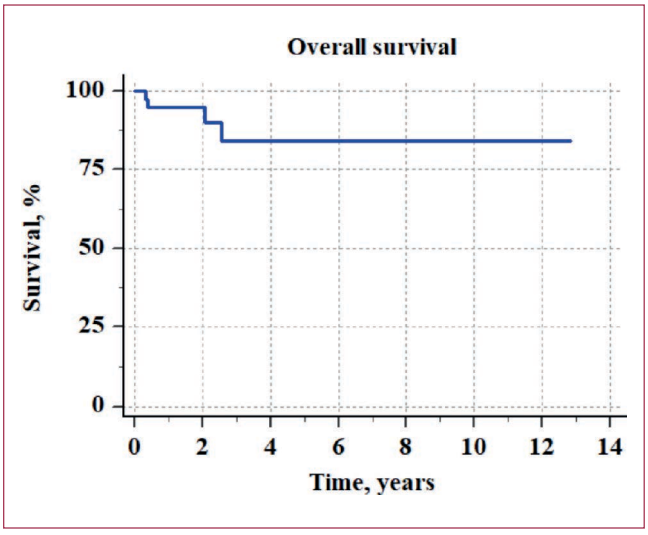

Figure 1. Five-year overall survival was 85 %

Modern aspects of the treatment of acute myeloid leukemia with myelodysplasia-related change

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Introduction. Acute myeloid leukemia (AML) is a malignant disease of the blood system, the substrate of which is myeloid cells of various degrees of differentiation. The clinical course and prognosis of acute myeloid leukemia with myelodysplasia-related change (AML-MRC) remains debatable. At the moment, the therapy of this group of patients remains a difficult task.

Objectives. to evaluate the results of treatment of patients with AML-MRC depending on the genetic profile when using standard approaches to the therapy of acute myeloid leukemia.

Methods. A retrospective analysis of the medical histories of 137 patients with acute myeloid leukemia aged 18 to 81 years was carried out at the Hematology Department no. 3 of the Minsk Scientific-Practical Center of Surgery, Transplantation and Hematology. Patients were treated in accordance with the current clinical Protocol №43 dated 01.06.2017 "Diagnosis and treatment of patients older than 18 years with newly diagnosed AML". Statistical calculations were carried out in the statistical package of the STATISTICA 10 program.

Results. According to the ELN 2022 classification, patients are divided into 3 groups depending on the detected genetic changes: favorable risk — 14 patients, intermediate risk — 105 patients, adverse risk — 18 patients. Among 137 patients diagnosed with AML, there were 43 cases of AML with recurrent genetic abnormalities: 20 patients with t (15;17), 6 patients with t(8;21)/RUNX1::RUNX1T1, 5 patients with in-frame bZIP mutated CEBPA, 9 patients with mutated NPM1, 1 patients with t(9;22)/BCR::ABL1, 30 patients with AML-MRC and 66 patients with AML not otherwise specified (AML-NOS). Patients with t(15;17) were excluded from further analysis due to the use of the targeted therapy of the tretinoin in this group. The AML-MRC was observed in 21,9 % of all AML cases. Among the patients there were 17 men and 13 women; the average age of patients was 56,4 years (25–81 years). 9 out of 30 patients (30,0 %) had a prior history of myelodysplastic syndrome or myeloproliferative disease. In the analyzed subgroup of patients with AML with myelodysplasia related changes, the percentage of those who achieved complete remission after the first course of induction was 30,0 %; after the second line of therapy – 14,3 %. Chemoresistance was revealed in 36,7 % of cases. The median overall survival (OS) in the group of patients with AML-MRC was 17 monts, for the group with mutated NPM1 — 19 monts, for the group AML with t(8;21) — 21 monts, and for the group of patients with AML-NOS, AML with mutated CEBPA the median overall survival was not achieved during the follow-up period (Figure 1). The median OS of patients with AML-MRC has been the standard "7+3" chemotherapy was 336 days (n = 15), with hypomethylating agent therapy — 214 days (n = 6), with hypomethylating agent in combination with venetoclax — 525 days (n = 5), median OS of patients with FLAG-Ida was not achieved during the follow-up period.

Conclusions. Despite the successes achieved in the treatment of acute leukemia, the therapy of acute myeloid leukemia with changes associated with myelodysplasia remains unresolved. It is necessary to develop and implement new treatment regimens for AML-MRC.

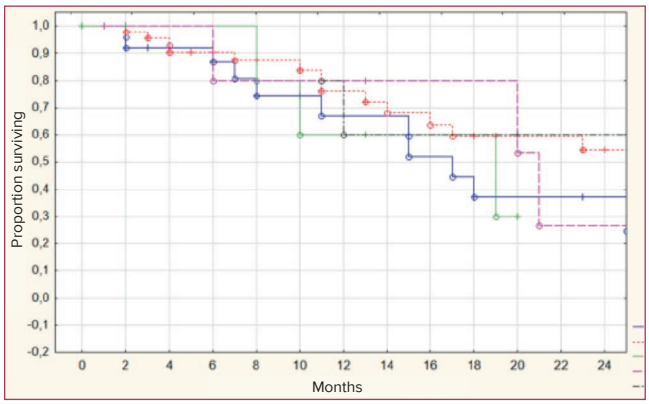

Figure 1. Overall survival of patients with acute myeloid leukemia

Chromosomal copy patterns in complex karyotypes of patients with myelodysplastic syndromes: data of standard cytogenetics, multicolor FISH, and MCB analysis

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Introduction. Myelodysplastic syndromes (MDS) are genetically heterogeneous diseases often accompanied by cytogenetic abnormalities. In some patients, MDS is associated with complex karyotypes (CK) that indicate a poor prognosis and a high probability of transformation into AML. The formation of a CK in MDS is often a result of chromothripsis. The presence of chromotripsis can contribute to the complexity of the disease and lead to the emergence of subclonal populations that are more resistant to therapy. The identification of specific chromosomal abnormalities and a detailed description of the karyotype play a crucial role in understanding MDS pathogenesis. However, the accurate identification of derivative and marker chromosomes in CK requires the use of molecular cytogenetics methods. In this study, we pay special attention to the non-random chromosomal copy patterns in CK of patients with MDS.

Patients. A total of 30 patients (16 women and 14 men, aged 2 to 86 years) with MDS associated with CK were included in the study.

Methods. Standard karyotyping of bone marrow cells was performed for all patients using GTG-banding techniques (analyzing a minimum of 20 metaphases). Multicolor FISH with chromosome-specific DNA probes (MetaSystems, Germany) was conducted for 22 patients. Multicolor banding (MCB) with segment-specific DNA probes (MetaSystems, Germany) was performed for 29 patients. In addition, we performed iFISH using DNA probes for «key» genes (analyzing a minimum of 200 nuclei). Figure 1 shows an example of reconstruction of the segment composition of a marker chromosome using GTG-banding and molecular cytogenetic methods.

Results. The contribution of numerical chromosomal abnormalities in the structure of CK — true monosomies (most commonly –7, 7/30) and true trisomies (most commonly +8, 6/30; and +21, 7/30) — is relatively low. Structural chromosomal rearrangements, such as unbalanced translocations (52,5 % of all aberrations, 25/30) and deletions (23 %, 19/30), are more prevalent.

Non-random losses of chromosomal material are typical of 5q (16/30; 5q15->5q32, 12/16), 7q (12/30; 7q22->7qter, 9/12) and 9q (5/30; 9q21->9qter, 4/5). Tendency for expansion in the karyotype is typical of 8q (11/30; 8q22->8qter, 10/11), 21q (10/30; 21q22->21qter, 10/10), 3q (5/30; 3q22->3qter, 4/5), 1q (3/30; 1q21.1->1q42.3, 3/3) and 9p (3/30; 9p21->9p11, 2/3).

For 8 patients with specific chromosomal gains, we performed iFISH and found minor clones that had not been previously identified. For 3/4 patients with 3–4 copies of 8q, we observed cells with 8–36 signals from MYC gene (8q24.21), and for 1/2 patient with 4-8 copies of 9p – multiple amplification signals from JAK2 gene (9p24.1). Figure 2 shows the results of iFISH.

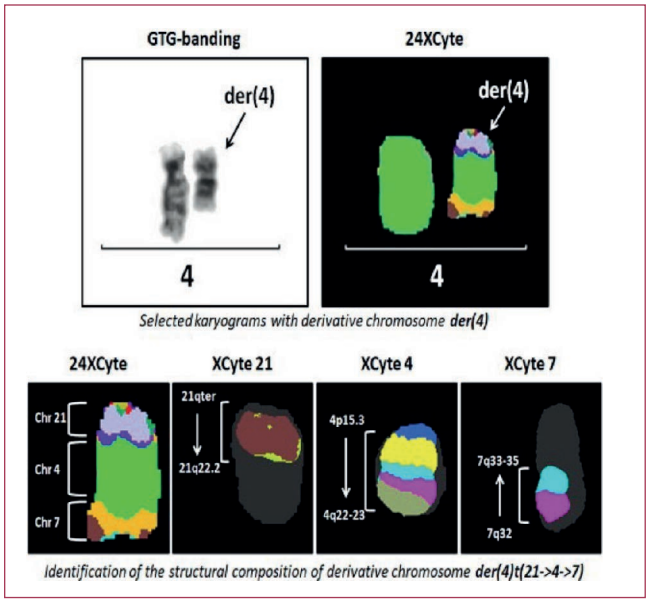

Figure 1. Example of using 24-multicolor FISH (mFISH) and multicolor FISH-banding (MCB) for reconstructing the genetic composition of a complex marker chromosome

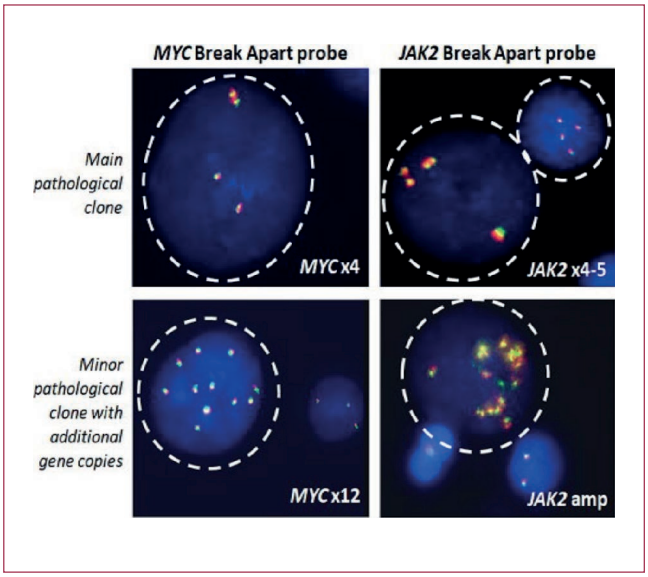

Figure 2. The results of iFISH demonstrate hidden genetic heterogeneity of pathological cells — the presence of minor subclones with increased copy number of proto-oncogenes

Conclusions. In MDS, the formation of a CK is accompanied by partial genomic aneuploidization, characterized by non-random and specific gains and losses of chromosomal material at the arm- and large segment levels. In cases with an increased copy number of specific chromosomal segments with "key" genes, additional iFISH should be performed to detect minor clones that may not be identified by metaphase analysis. In summary, describing the patterns of chromosomal copy number is an important task not only for diagnosis but also for fundamental research in MDS biology.

ACUTE LEUKEMIA

Reduction of a tumor clone in patients with Ph-negative acute lymphoblastic leukemia treated by blinatumomab: the length of therapy can be optimized

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Introduction. The usage of bispecific monoclonal antibody anti-CD19/anti-CD3 — blinatumomab — is effective method of treatment not only in patients with refractory/relapsed acute lymphoblastic leukemia (R/R B-ALL), but also in patients with persistence of minimal residual disease (MRD). The standard duration of cycle is 28 days, but also there are publications of effective administration during 14 days.

Objectives. To show the time of achievement of remission in patients treated by blinatumomab (R/R B-ALL, patients with persistence of MRD before the start of cycle).

Methods. We have analyzed the data of 15 patients with Ph-negative B-ALL, who were treated by blinatumomab in 2023-2024. Male to female ratio was 1:1,5. Median of age was 38 years (18–63). The indications for the therapy were: the persistence of MRD detected by flow cytometry at control points during chemotherapy under protocols "ALL-2016" and "ALL-2016m" (n = 8); patients with primary refractoriness (n = 3); patients with relapse (n = 3); patient with MRD-relapse (n = 1). There were two variants of cycle durations: using full dose 28 mcg/day in days 1–28; or adaptive dose 8,75 mcg/day in days 1–4 and after that administration of full dose 28 mcg/day in days 5–32. Bone marrow aspiration (BMA) was made on these points: before the start of cycle, on the 4th day of adaptive dose, on the 4th and the 14th days of full dose, at the end of cycle.

Results. 10 patients had BMA on the 4th day of adaptive dose, 4 of them had reached MRD-negativity at this point, 1 patient with relapse had reached complete remission — CR. 3 patients had BMA on the 4th day of the full dose, all of them had reached MRD-negativity. 8 patients had BMA on the 14th days of full dose, 5 of them had reached MRD-negativity (1 of them had MRD-negativity at 4th day of adaptive dose), 2 patients with relapse had reached CR at this point. 12 of the 15 patients had MRD-negativity at the end of cycle. The treatment of other 3 patients is not completed, but 2 of them had reached MRD-negativity on the 4th day of adaptive dose, 1 of them — on the 14th days of full dose. The dynamics of achievement of remission is shown in the Figures 1 and 2.

Conclusions. In treatment by blinatumomab, MRD-negativity at the end of the adaptive doses was achieved in 4 patients out of 10 (40 %). MRD-negativity at the 14th days of full dose was detected in all patients who had already achieved molecular remission at the end of the cycle. Due to these results, it could be perspective to reduce the length of cycle.

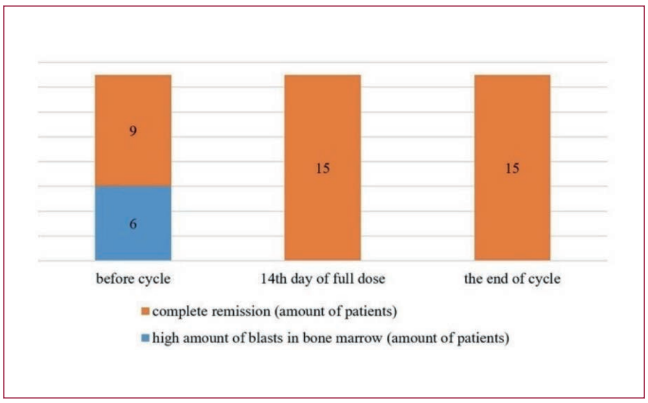

Figure 1. The speed of achievement of CR in patients treated by blinatumomab

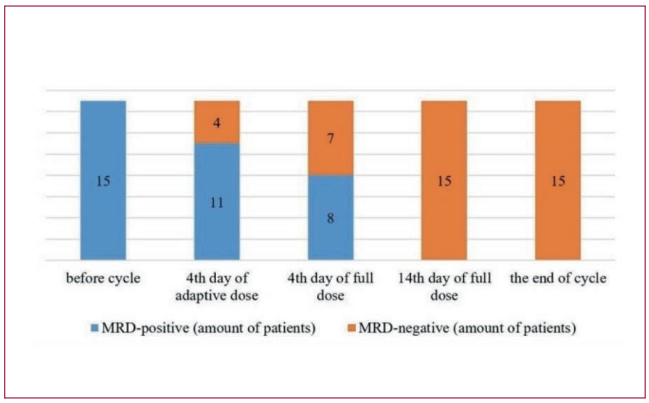

Figure 2. The speed of achievement of MRD-negativity in patients treated by blinatumomab

Allogeneic hematopoietic stem cell transplantation for intermediate-risk FLT3 mutated acute myeloid leukemia

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Introduction. The role of allogeneic hematopoietic stem cell transplantation (Allo-HSCT) in patients with genetically defined intermediate-risk acute myeloid leukemia (AML) in first complete remission (CR1) is controversial. Although the risk of relapse is the lowest with Allo-HSCT, this advantage can be offset by the higher risk of transplant-related mortality. In addition, a proportion of intermediate-risk patients may be treated with Allo-HSCT beyond CR1 after second-line therapy. In the presence of a mutation in the FLT3 gene (FLT3+), this problem is even more relevant due to the possibility of incorporating FLT3 inhibitors (FLT3i) in primary treatment, in relapse as well as post-transplant maintenance therapy.

Objectives. To evaluate the survival impact of Allo-HSCT performed in CR1 for patients with FLT3+ intermediate-risk AML in the pre-FLT3i era and with their use. To compare the survival of patients who underwent Allo-HSCT in CR1 and beyond it.

Materials and methods. This study included patients older than 18 years with FLT3+ intermediate-risk AML, according to ELN 2022 classification, observed at the RM Gorbacheva Research Institute from 2009 to 2024. Landmark analysis was used to compare survival rates in patients who did or did not receive Allo-HSCT in CR1. The time point for the analysis was the median time from diagnosis to Allo-HSCT in CR1 (6 months). Overall, relapse-free survival (OS, RFS) were analyzed using the Kaplan-Meier method and log-rank test.

Results. 225 patients were enrolled in the study. 115 of them received therapy with FLT3i, 110 — without FLT3i. The main characteristics of the groups are presented in Table 1.

The median follow-up time was 12 (1–130) months. 59 patients treated without iFLT3 were alive and in CR1 over 6 months, and were included in the landmark analysis. Two-year OS was 81 % (95 % CI 60–92) in the Allo-HSCT group and 54 % (95 % CI 33–71) in the remaining group, $p = 0.03$. RFS was 77 % (95 % CI 56–89) and 18 % (95 % CI 8–35), respectively, $p < 0.01$. In the group of patients receiving FLT3i, 54 patients were included in the analysis. Two-year OS was 85 % (95 % CI 60–95) in the Allo-HSCT group and 43 % (95 % CI 21–64) in the group without it, $p = 0.04$. RFS 75 % (95 % CI 49–89) and 14 % (95 % CI 4–29), respectively, $p < 0.01$. Two-year OS of patients who underwent Allo-HSCT before the introduction of FLT3i was 83 % (95% CI 63–92) when transplanted in CR1 and 41 % (95% CI 21–60) beyond it, $p < 0.01$. In the group using FLT3i, the rates were 85 % (95 % CI 60–95) and 45 % (95 % CI 21–67), respectively, $p = 0.02$.

Conclusion. Allogeneic transplantation in CR1 is the preferred option for consolidation of remission in patients with FLT3+AML of intermediate risk group, including those using FLTi target therapy.

Table 1. Characteristics of patients

	No FLT3i (n = 110)	FLT3i (n = 115)
Median age (range)	51 [18;81]	46 [18;76]
Sex, M/F	45/65	52/63
Mutational status, n (%)		
FLT3-ITD	92 (83.6)	97 (84.3)
FLT3-TKD	18 (16.4)	18 (15.7)
NPM1 mutation	37 (33.6)	30 (26.1)
De novo AML, n (%)	98 (89.1)	107 (93.0)
Extramedullary disease, n (%)	14 (12.7)	19 (16.5)
HSCT overall, n (%)	51 (46.4)	42 (36.5)
HSCT in CR1, n (%)	29 (26.4)	25 (21.7)
Donor type, n (%)		
MRD	10 (19.6)	8 (19.0)
MUD	18 (35.3)	15 (35.7)
MMUD	11 (21.6)	10 (23.8)
Haplo	12 (23.5)	9 (21.4)
Type of conditioning, n (%)		
MAC	6 (11.5)	9 (20.9)
RIC	46 (88.5)	33 (79.1)

Genetic landscape, ELN 2022 risk stratification and treatment features in AML patients in Russian Federation

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Introduction. Despite advances in the biological understanding and treatment of acute myeloid leukemia (AML) globally, there is a significant lack of comprehensive data regarding the genetic landscape and treatment outcomes in adult AML patients within the Russian Federation.

Available evidence indicates that survival rates in this population remain critically low, estimated between

Table 1. Group characteristics

Characteristic	n = 308
Age, years, median (range)	51.5 (18–83)
Gender, n (%)	
Male	146 (47.4)
Female	162 (52.6)
ELN 2022 risk, n (%)	
Favorable	74 (24)
Intermediate	151 (49)
Unfavorable	83 (27)
Previous MDS, n (%)	
Yes	48 (15.6)
No	260 (84.4)
Previous oncological disease, n (%)	
Yes	19 (6.2)
No	289 (93.8)
Induction therapy, n (%)	
7+3 (+/– FLT3-inhibitor)	172 (55.8)
Ven + HMA/LDAC	20 (6.5)
AzaldaAraC	7 (2.3)
LDAC	6 (2)
None	9 (2.9)
Unknown	94 (30.5)

10 % and 20 %. The 2022 European Leukemia Network (ELN) risk stratification system is widely adopted for predicting outcomes and guiding therapy worldwide. However, its prognostic relevance in the Russian context has yet to be thoroughly investigated.

Objectives. To assess the genetic landscape, treatment features and prognostic value of ELN 2022 risk stratification in a large cohort of AML patients in Russia.

Patients and methods. This analysis included 308 AML patients enrolled in the observational prospective study "Cooperative Program for the Diagnosis and Treatment of Acute Myeloid Leukemia in the Russian Federation" from October 2021 to April 2023 across 38 centers. The primary inclusion criterion was the indication for curative treatment based on the patient's age and somatic status. In addition to routine diagnostics, patients underwent karyotyping, immunophenotyping, molecular genetic analyses of bone marrow, and HLA typing of both patients and potential donors. Group characteristics are detailed in Table 1, while cytogenetic and molecular genetic features are summarized in Figure 1. For treatment response and survival analysis 22 patients were excluded due to failure to meet inclusion criteria, and 37 patients dropped out of observation.

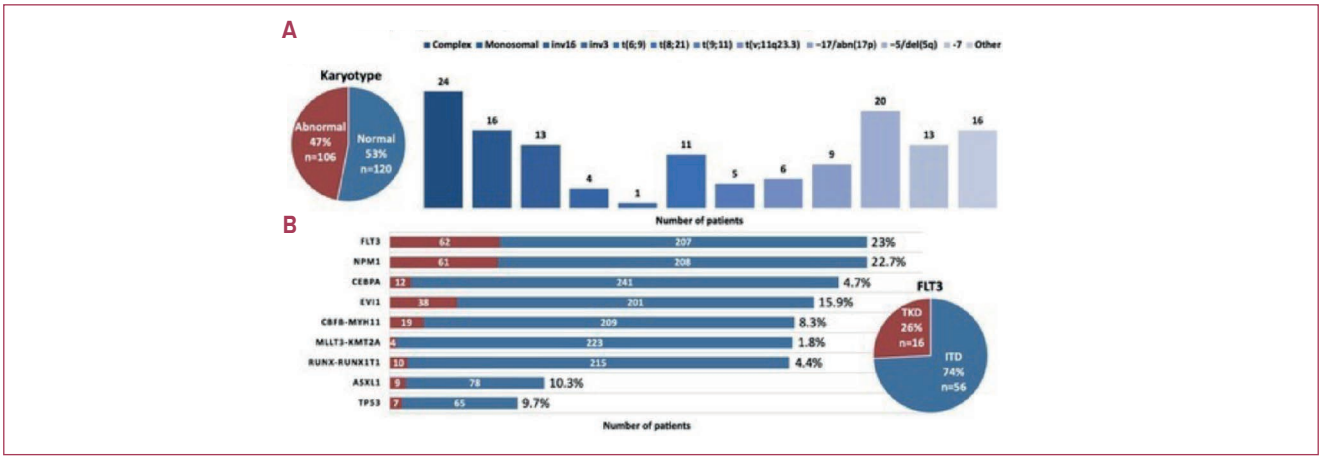

Figure 1. Cytogenetic (A) and molecular genetic (B) landscape

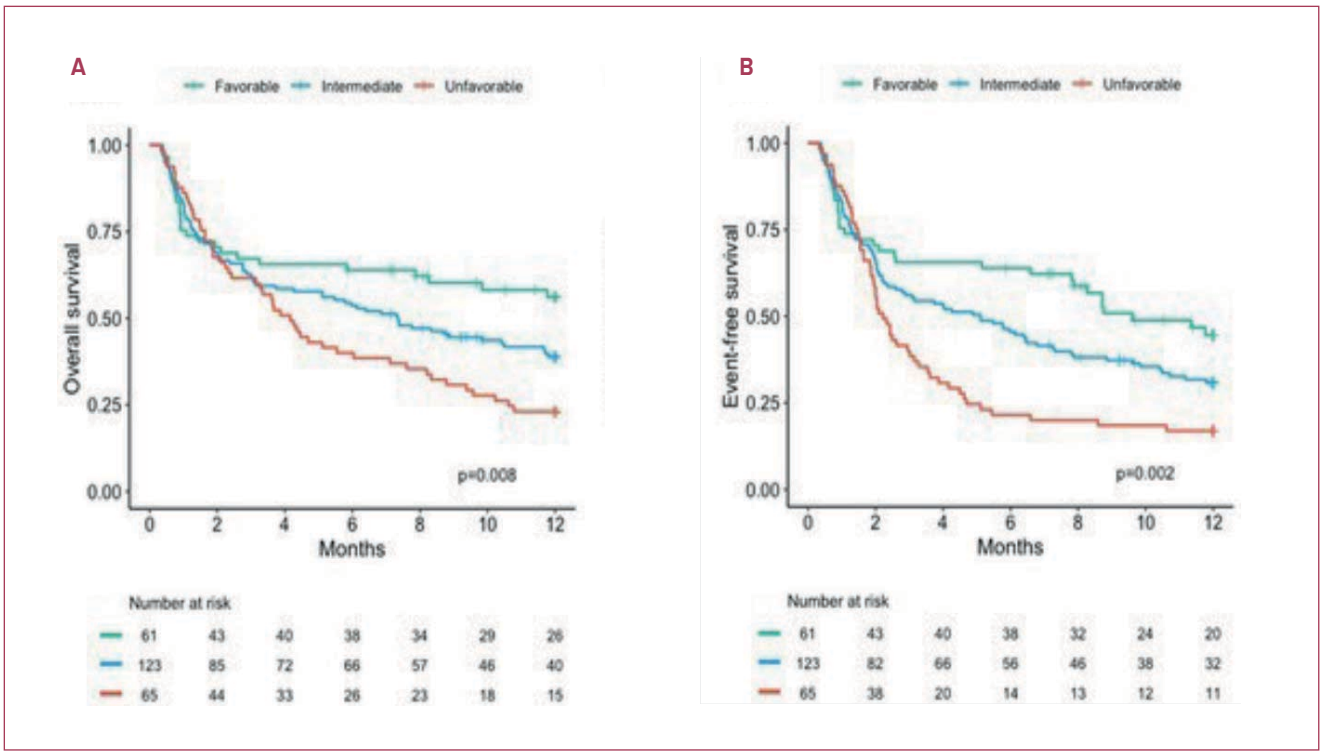

Figure 2. Impact of ELN 2022 risk on OS (A) and EFS (B)

Results. The median follow-up time for surviving patients was 17 (range: 6–32) months. Regarding responses to induction therapy, the rates of complete remission, primary refractoriness, and early mortality were 67.2 %, 0 %, 32.8 % in the favorable, 56.9 %, 8.1 %, 35 % in the intermediate, and 35.4 %, 24.6 %, 40 % in the unfavorable ELN risk groups, respectively ($p < 0.001$). One-year overall survival (OS) was 56.1 % (95 % CI 44.6–70.5), 38.9 % (95 % CI 31–48.7), 23.1 % (95 % CI 14.8–36) ($p = 0.008$), while event-free survival (EFS) was 44.6 % (95 % CI 33.2–59.9), 30.8 % (95 % CI 23.5–40.3), 16.9 % (95 % CI 9.9–29) ($p = 0.002$) in the favorable, intermediate and unfavorable ELN risk groups, respectively (Figure 2). Among patients who underwent allogeneic hematopoietic stem cell transplantation (alloHSCT) (n = 54), the median time from diagnosis to transplantation was 8.2 (range: 2.5–14) months. AlloHSCT from matched related, matched unrelated, mismatched unrelated, and haploidentical donors was performed in 13 % (n = 7), 26 % (n = 14), 38.8 % (n = 21) and 22.2 % (n = 12) of patients, respectively. AlloHSCT was conducted in the first remission in 79.6 % (n = 43) of patients, in the second remission in 9.3 % (n = 5), in the status of active disease in 11.1 % (n = 6). One-year OS after alloHSCT was 64.9 % (95 % CI 52.7–80).

Conclusions. The genetic landscape of Russian AML patients is comparable to global data. Cytogenetic and molecular genetic analyses at the onset of AML are crucial for risk stratification. The ELN risk stratification demonstrates its prognostic value in predicting induction response rates, overall survival (OS), and event-free survival (EFS). A high rate of induction-related mortality was observed, particularly in the unfavorable ELN risk group, highlighting the need for further advancements in AML treatment protocols during induction therapy.

Selection of optimal bridge therapy to allo-HSCT in patient with R/R AML

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Objectives. To compare intensive chemotherapy (IC) versus non-intensive regimens as bridge therapy to allogeneic stem cell transplantation (allo-HSCT) in patients with relapse/refractory (R/R) acute myeloid leukemia (AML).

Methods. The retrospective study included 131 patients (67 women, 64 men), median age — 41 years, 70 (53,4 %) with relapsed and 61 (46,6 %) with refractory AML. According to ELN classification, 55 (42 %) patients have adverse risk. Extramedullary disease (ED) was observed in 24 patients (18,3 %). 80 patients (61,1 %) received IC (FLAG+/–Ida), 51 patients (38,9 %) received VEN-combined regimens (in FLT3-positive patients (n = 18) gilteritinib was added). Allo-HSCT was planned 116 patients (88,5 %).

Results. Overall response rates were comparable (69 % for IC and 72,9 % for VEN combination, p = 0,647). The median time to response was shorter in the IC group than in the VEN group (0,85 months vs 0,98 months, respectively, p = 0,001). In the analysis of the subgroups, the IC was associated with a significantly higher incidence of overall response than the VEN group in CBF-positive AML (83,3 % vs 0 %, p = 0,022). In patients with ED the incidence of overall response was 80 % in the VEN group and 25 % in the IC (p = 0,047), in those with adverse risk, 78,3 % vs 48 %, respectively (p=0,040); and in those with secondary AML, 85,7 % vs 16,7 %, respectively (p = 0,029). In FLT3-positive AML the rate of overall response was similar (63,3 % for IC vs 70,8 % for VEN group, p = 0,446). Mortality at 30 days and SAEs were similar in the two groups (11,2 % for IC and 6,1 % for VEN group, p = 0,534; 33,8 % vs 19,6 %, respectively, p = 0,111). In the VEN group, more patients proceeded to allo-HSCT (95,2 % vs 78,4 %, p = 0,017). The OS and RFS after allo-HSCT were comparable (13,9 months for IC vs 24,07 months for VEN combination, respectively, p = 0,584; was not reached for IC vs 27,87 months for VEN combination, respectively, p = 0,625).

Conclusions. The VEN combination provides a comparable efficacy, tolerability and survival after allo-HSCT to salvage AML. The IC is more effective in CBF-positive AML, the VEN combination in patients with adverse risk, secondary AML, ED. In FLT3-positive patients IC and VEN-combination were comparable.

The genomic heterogeneity of acute myeloid l eukemias from favorable risk group

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Background. CBF-AML and *NPM1*+AML define large distinct genetic subset and are considered a favorable risk markers in the absence of *FLT3*-ITD mutation. Despite this, 30–50 % of them experience relapse, and the factors that drive relapse are still not fully understood.

Objectives. To investigate factors that predict inferior outcome in a uniformly treated and well-characterized population of patients with favorable risk AML.

Methods. The study included 40 AML patients with mutated *NPM1* and normal karyotype and 25 patients with t(8;21) and 21 patients with inv(16). Samples were analyzed by morphology, karyotyping, PCR and high-throughput sequencing using a custom panel consisting of 118 genes.

Results. Most patients with t(8;21) (74 %) had additional chromosomal aberrations (mainly -X/-Y) and only 33 % of patients with inv(16) had additional chromosomal aberrations (p = 0.01). In 96 % of CBF-AML patients at least 1 mutation was detected. The highest frequency of occurrence in both groups had mutations in *NRAS*+*KRAS*, *KIT*. Patients with t(8;21) had significantly more mutations than with inv(16) (p = 0.03). Prognostically unfavorable mutations in chromatin modifiers (*ASXL1*(20 %), *EZH2*(7 %)), or cohesin genes (*RAD21*(13 %), *SMC3*(7 %)) were detected only in t(8;21) AML. There was a trend toward worse relapse-free survival in patients with t(8;21) compared with those with inv(16) (p = 0.072). Mutations in genes involved in the activation of signaling pathways were found to negatively affect the relapse-free survival of patients with CBF-AML (p = 0.04).

In the group of *NPM1*+AML, 100 % patients had at least one mutation with an average of 5 mutations per patient (1–9). Patients with *FLT3*-ITD mutations had a 5-year overall survival (OS) of 34 %, compared to patients without *FLT3*-ITD, 55 %(p = 0.001). We identified a small group of patients who lived more than 5 years after the diagnosis of AML, where there was a trend toward a decreased presence of myelodysplasia-related gene mutations (p = 0.211). In the group of 29 patients without *FLT3*-ITD 14 patients (48.3 %) had relapse after consolidation chemotherapy. We compared mutations at diagnosis and relapse in 10 patients — only 2 patients relapsed with exactly the same mutations. Mutations in *FLT3* and *IDH1*/2 were both acquired and lost at relapse. Mutations in *NRAS* were more frequently lost at relapse. Various cytogenetic abnormalities were acquired at relapse (4/10,40 %). The mean number of mutations at diagnosis in relapse group was 5.5, compared to 3.9 in patients without relapse (p = 0.041). Patients with *NPM1/DNMT3A/IDH1/2*mut combination showed a trend toward lower OS (p = 0.09) (Figure 1).

Summary/Conclusion. AML patients from the favorable prognostic group have a highly heterogeneous molecular genetic profile. AML with t(8;21) and inv(16) have significant differences in morphological, cytogenetic, and molecular-genetic characteristics, which makes it reasonable to analyze them separately. Mutations in *KIT* gene as well as other mutations of genes involved in activation of signaling pathways negatively affect the relapse-free survival of CBF-AML patients. High allelic ratio of mutations in *NPM1* gene, presence of more than 2 additional mutations, mutations associated with myelodysplasia, *FLT3*-ITD and *FLT3*-ITD/DNMT3A mutations significantly reduce the OS of *NPM1*+AML patients. The peculiarities of molecular genetic characteristics of individual AML variants can be used for individualization of target therapy.

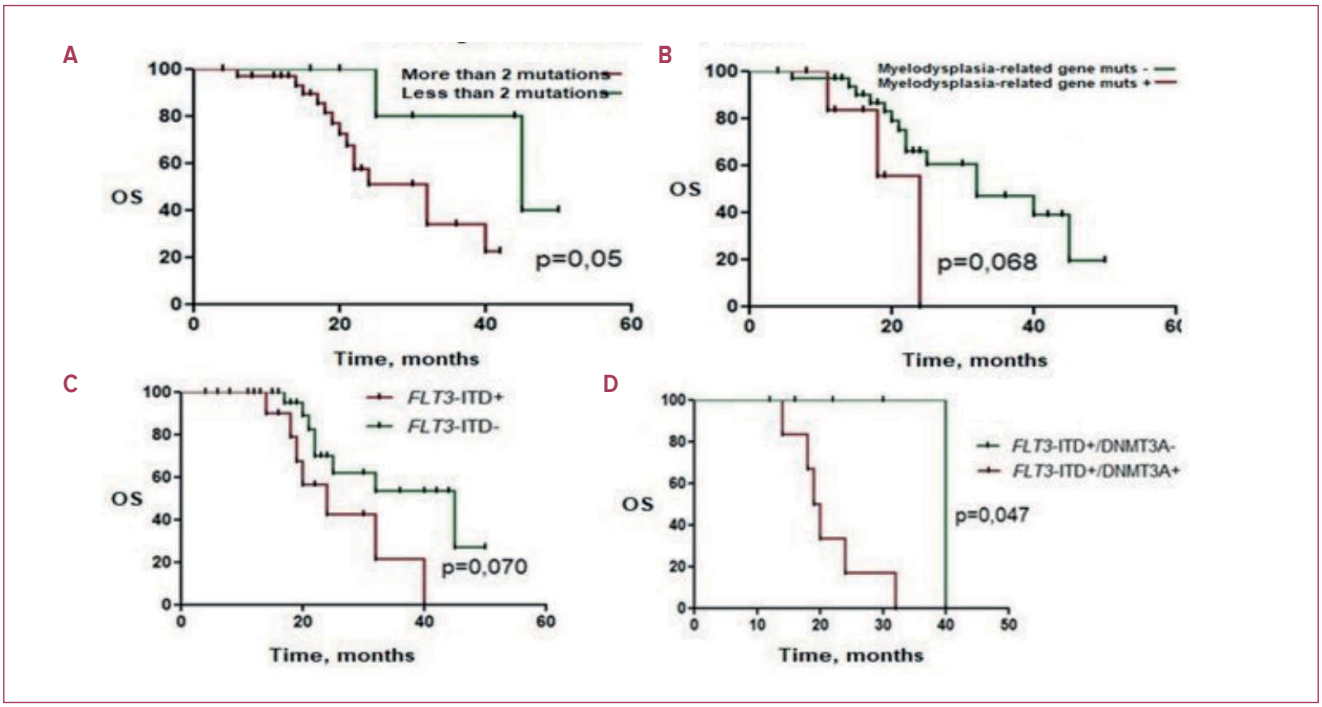

Figure 1. Overall survival of patients with NPM1+AML

Significance of mutations in *ASXL1* and *DNMT3A* genes in patients with acute T-cell lymphoblastic leukemia/lymphoma

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Introduction. Genetic mutations accumulate in blood stem cells with age. Some of them have an advantage over normal cells, leading to the development of clonal hematopoiesis (CH). The genes most commonly associated with CH include *DNMT3A*, *TET2* and *ASXL1*. These mutations and their impact on the development of hemoblastosis have been studied and described in patients with acute myeloid leukemia (AML), whereas in T-cell acute lymphoblastic leukemia/lymphoma (T-ALL/LL), they have hardly been explored.

Objectives. To determine the significance of *DNMT3A*, *ASXL1* and *TET2* mutations in patients receiving therapy of the RALL-2016 study.

Materials and methods. 59 patients diagnosed with T-ALL/LL were included in the study: 44 (75 %) were males and 15 (25 %) — females. The distribution: 17 (29 %) ETP,11 (18,5 %) near-ETP, 8 (13,5 %) TI/II, 22 (38 %) TIII, 1 (1 %) TIV. In patients with mutations, the research was also realized in material from remission and relapse.

Results. 7 (12 %) of patients had mutations associated with CH: in *ASXL1* — 3 (5 %) patients and in 4 (7 %) — *DNMT3A*. The median age in the group of patients with mutations was 39 (23–49), in the group without mutations — 30 years (18–55). Median hemogram scores in the group with mutations were close to normal levels in contrast to the group without mutations, but the differences were not statistically significant. In the group without mutations: leukocyte 18.56 × 10^9/μl, hemoglobin 110 g/l, platelets — 85 × 10^9/μl, in the group with mutations 12.54 × 10^9, 133 g/l and 174 × 10^9/μl, respectively. Mediastinal involvement in the group with mutation was 5 (71 %), without mutations — 34 (65 %), central nervous system involvement — 2 (28 %) and 15 (29 %), respectively. Median LDH in the group with mutations was 299 U/L and 777 U/L in the group without. Complex karyotype rearrangements in the group without mutations 12 of 51 (37 %) and in 4 of 7 (57 %) in the group with mutations.

In the group of patients with *DNM3A* and *ASXL1* mutations, refractoriness was confirmed in 2 (29 %), and 1 patient failed to achieve remission after multiple lines of chemotherapy, 5 patients who achieved remission (100 %) developed relapse. In the group of patients without mutations: refractoriness was confirmed in 4 (8 %) and relapse in 13 (28 %) (p = 0.09 and p = 0.01, respectively). It is worth noting that out of 7 patients with mutations, 2 (29 %) developed relapse with change to AML. We identified similar mutations in patients in relapse, but they had additional mutations in these genes. No mutations were detected in remission in these patients.

The 2-year OS was 14 % in the group with mutation and 81 % in the group without (p < 0.001), the RFS was 77 % in the group without, while in the group with mutation all patients developed relapse within 2 years (p < 0.001) (Figure 1).

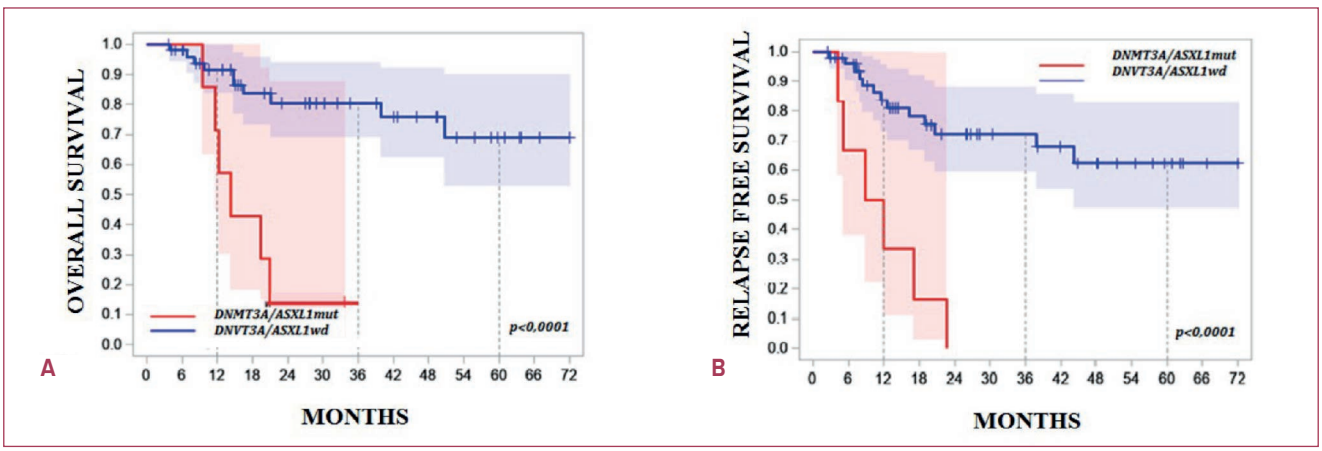

Figure 1. Overall and relapse-free survival according to DNMT3A and ASXL1 mutation status

Conclusion. Mutations in genes associated with CH are an independent risk factor for unfavorable prognosis and can be a predictor of disease relapse. Identical mutations persist in relapses. Patients with these mutations should be highlighted as a high-risk for relapse and consider performing allo-HSCT in the first remission of the disease and/or using additional non-chemotherapeutic treatments.

Treatment outcomes of patients with secondary acute myeloid leukemia: a retrospective analysis

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Introduction. Secondary acute myeloid leukemia (AML) presents a significant clinical challenge due to its association with a sharp decline in overall survival (OS). The aggressive course of the disease and the limited applicability of intensive therapeutic regimens render the prognosis for such patients unfavorable.

Objectives. To analyze the efficacy of therapy in patients with secondary AML and identify factors affecting prognosis.

Methods. The study included a cohort of patients (n = 40) (Table 1) observed at the S.P. Botkin Moscow Multidisciplinary Clinical Center. The median age at AML diagnosis was 65 years (range 30–77 years). The median follow-up period was 9.3 months. The cohort comprised 62.5 % males and 37.5 % females. Patients had AML evolve from myelofibrosis (42.5 %), myelodysplastic syndrome (MDS) (30 %), chronic myelomonocytic leukemia (CMML) (17.5 %), polycythemia vera (PV) (5 %), and essential thrombocythemia (ET) (5 %).

Statistical analysis was performed using GraphPad Prism software, version 8.0.0 for Windows (GraphPad Software, USA, www.graphpad.com). Survival curves were constructed using the Kaplan–Meier method, and differences between groups were assessed using the log-rank test. A p-value of less than 0.05 was considered statistically significant. Descriptive methods were used to characterize the sample.

Results. The median time from the initial diagnosis to evolve into AML was 3 years. The median OS from the initial hematologic diagnosis was 59 months (Figure 1, A) and did not differ significantly between diagnoses: 70.1 months for myeloproliferative neoplasms (MPNs), 45.5 months for MDS, and 50.3 months for CMML ($p = 0.3969$). From the time of transformation into AML, the median OS was 12.9 months (Figure 1, B).

In patients with secondary AML, venetoclax-based therapy was associated with improved OS with a median of 18.8 months compared to 4 months for those who did not receive venetoclax ($p = 0.0013$) (Figure 1, C). A response to therapy for secondary AML was achieved in 50 % of patients, with a median remission duration of 8.3 months, creating an opportunity for allogeneic hematopoietic stem cell transplantation. The longest remission durations were observed in patients with prior MDS (15.9 months), compared to shorter duration in CMML (5.85 months) and myelofibrosis (5.2 months). Achieving remission significantly increased OS: 23 months versus 9.2 months for those who did not achieve remission ($p < 0.0001$) (Figure 1, D).

Patients who had not received prior treatment for the initial diagnosis demonstrated improved OS following AML transformation — 31.1 months compared to 10.5 months for those who received treatment ($p = 0.0137$) (Figure 1, E).

Conclusion. The addition of venetoclax to treatment regimens and the achievement of remission were key factors associated with improved overall survival in patients with secondary AML. Patients who did not receive treatment for the primary disease demonstrated better survival after transformation into AML; however, this did not impact OS from the time of the initial hematologic diagnosis. These results highlight the need for further research to optimize treatment approaches for secondary AML, taking into account the characteristics of the primary disease and its therapy.

Table 1. Baseline demographic, clinical, and molecular characteristics of patients with secondary AML

Characteristics		Values
Age at AML Diagnosis, years, median (range)		65 (30–77)
Male, n (%)		25 (62,5)
Female, n (%)		15 (37,5)
Primary Diagnosis		**n (%)**
Myelofibrosis		17 (42,5)
MDS		12 (30)
CMML		7 (17,5)
PV		2 (5)
ET		2 (5)
Mutations in Primary Disease		**n (%)**
JAK2 V617F		11 (27,5)
MPL		3 (7,5)
ASXL1		2 (5)
Deletion 7q		2 (5)
CALR		2 (5)
Complex karyotype with clonal evolution		2 (5)
Other (trisomy 8, inversion 3, translocation t(8;11)(q13;p14))		3 (7,5)
No data		20 (50)
Mutations in AML		**n (%)**
Monosomy 7 or deletion 7q		7 (17,5)
Trisomy 8		3 (7,5)
TP53		3 (7,5)
FLT		2 (5)
Complex karyotype with clonal evolution		2 (5)
Deletion 20q		2 (5)
Other (EVI, ASXL1, IDH1, translocations: t(12;17), t(5;15), t(1;13) (q10;q10))		6 (15)
No data		27 (67,5)
Received Treatment, n (%)	**Primary Disease**	**AML**
	28 (70)	38 (95)
Number of years from primary diagnosis to AML transformation, median (range)		**All patients**
		3 (0–25)
		Was the Primary Disease Treated?
	Yes	**No**
	5 (0–25)	1,5 (0–11)
		Was there a Response to Therapy for Primary Disease?
	Yes	**No**
	10 (1–25)	2 (0–9)
Death		28 (70)

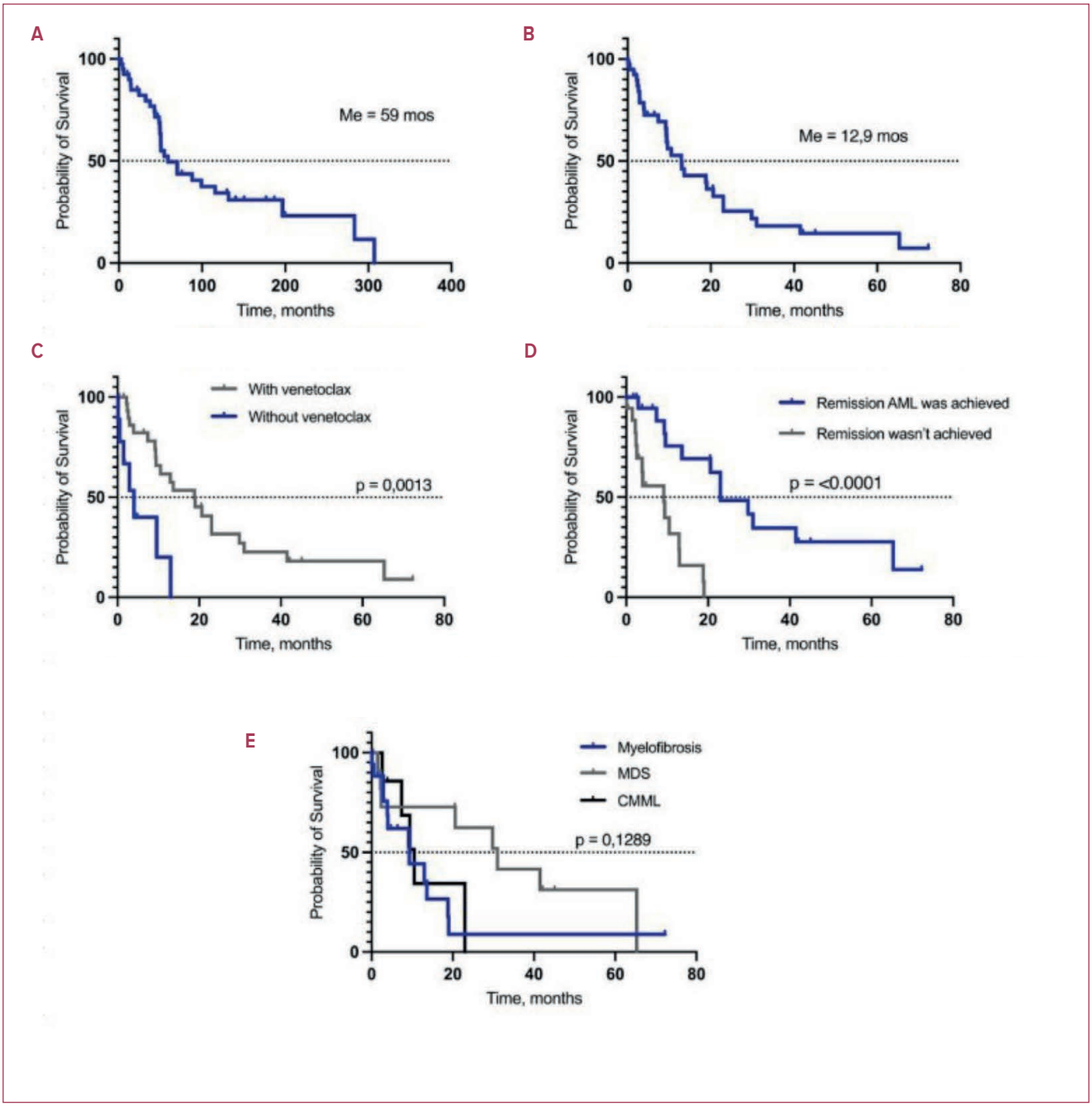

Figure 1. (A) Overall survival. (B) Overall survival from AML. (C) Overall survival from AML according to Venetoclax-based regimen. (D) Overall survival from AML according to remission of AML. (E) Overall survival from AML according to primary diagnosis

Impact side effects of specific therapy in combination with venetoclax on outcome in patients with acute myeloid leukemia

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Introduction. One of the targeted drugs used to treat acute myeloid leukemia (AML) is venetoclax, a selective inhibitor of the antiapoptotic protein BCL-2. In a study by Mohamed Jiffry M.Z. et al, venetoclax in the treatment of patients with resistant AML provides a survival benefit comparable to that seen in patients with primary AML. In a multicenter, randomized, double blind, placebo-controlled study, DiNardo et al found that the most common serious complications of the combination of azacitidine with venetoclax are thrombocytopenia grade 3–4, neutropenia and infections.

Objectives. To study the incidence of adverse reactions of specific therapy with a combination of venetoclax in patients with AML and to affect the impact side effects on outcome in patients with acute myeloid leukemia.

Materials and methods. The prospective cohort study included 22 adult patients with AML who received specific therapy in combination with venetoclax from November 2022 to October 2024 on the basis of the hematology department №3 of the Minsk Scientific Practical Center of Surgery, Transplantology and Hematology. Microsoft Excel 2016 and R Studio 2024.09.0 were used for statistical data analysis. The overall survival of the study group was estimated using the Kaplan-Meier method. Analysis results were considered statistically significant at $p < 0.05$.

Results. The age of the patients ranged from 24 to 80 years (median — 61.5 years), among them there were 14 women (63.6 %) and 8 men (36.4 %).

All patients, depending on clinical and laboratory status, were prescribed venetoclax in combination with hypomethylating agents, low doses of cytarabine or ruxolitinib, 3 patients (13.6 %) received specific therapy in combination with venetoclax as the first line at the diagnosis of AML, 19 patients (86.4 %) in relapsed and refractory forms of AML.

Remission was achieved in 9 patients with AML (41 %), of which transplantation was performed in 4 patients (18.1 %), relapses during combination therapy with venetoclax were reported in 3 patients (13.6 %).

Due to serious side effects (stage 3–4 thrombocytopenia, neutropenia and infection), courses with the addition of venetoclax were interrupted in 16 patients (72.7 %), among them — in 14 patients in 87.5 % of cases due to infectious complications.

At the time of analysis the death was reported in 9 AML patients (41 %). The results of overall 2-year survival in the groups of patients with the presence and absence of complications during specific therapy in combination with venetoclax were presented in Figure 1.

Overall survival in the cohort of patients with complications was 43.8 %, the median overall survival was 20.8 months. Overall survival in the cohort of patients without complications was 100 %, the median overall survival was not achieved. There are differences in survival between the complication cohort and the non-complication cohort ($p = 0.038$).

Conclusion. Thus, the presence of serious side effects during specific therapy with a combination of venetoclax statistically significant affects the survival of patients with AML.

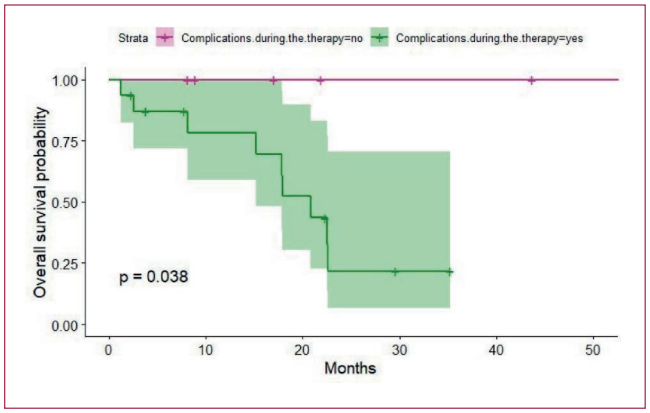

Figure 1. Overall survival on venetoclax-supplemented therapy depending on the presence of complications

Venetoclax plus hypomethylating agents in relapsed/refractory acute myeloid leukemia: a real-life experience

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Introduction. Acute myeloid leukemia (AML) is a heterogeneous malignancy with a great variation in disease outcomes. Despite great advances in chemotherapy, there is still up to 35–45 % of patients being refractory to treatments or relapsed [1]. Venetoclax-based regimens have shown promise in treating R/R AML [2]. In the present study, we aim to provide we evidence on the efficacy of this combination in R/R AML by reporting our data.

Patients and methods. All included patients were diagnosed with R/R AML and received at least one line of intensive therapy. Patients who previously received either single-agent VEN or VEN-combination were not included in the study. Refractoriness was defined as being unable to achieve a remission after at least one cycle of intensive induction chemotherapy. Azacitidine in combination with venetoclax was administered in accordance with the ELN 2022 recommendations.

Results. A total of 45 patients were included in the study (Table 1). The median age was 55 years (range: 24–73). A total of 20 (44,5 %) patients received AzaVen treatment for primary refractory disease, 10 (22,2 %) for early relapse and 15 (33,3 %) for late relapse. The median number of prior therapies was 1 (range 1–3), and 64,4 % patients received 1 lines of therapy. Three patients have allo-HSCT before and 11 after AzaVen.

The median follow-up duration was 19 months. The median number of treatment cycles was 4 (range 1–36). The overall response rate to the therapy was 66.7 %. Eight patients achieved CR, 5 — CRh, 5 — CRi, and 12 — MLFS. Nine patients were refractory to this therapy, and the response could not be assessed in 6 patients. After 1 cycle of therapy, 63.3 % of patients achieved remission; after 2 cycles — 26.7 %; and the remaining patients (10 %) — by the end of the 3rd cycle. The median duration of remission was 28 months (Figure 1, A). The type of relapse and the number of prior lines of therapy (Figure 1, B) had no impact on the duration of response.

The median overall survival for the whole cohort was 31 months (Figure 1, C). Patients who underwent Allo-HSCT had the highest median overall survival compared to those who did not undergo the procedure, undefined vs. 28 months, respectively. Additionally, patients with late relapse had a longer median overall survival compared to those with early relapse or primary refractory AML, 69 months versus 20.5 months and 15 months, respectively (Figure 1, D). Therefore, the first induction cycle of therapy and Allo-HSCT significantly impact overall survival. The deeper and earlier the first response to therapy, the greater the chances of prolonged overall survival. The number of prior lines of therapy did not affect overall survival in our study.

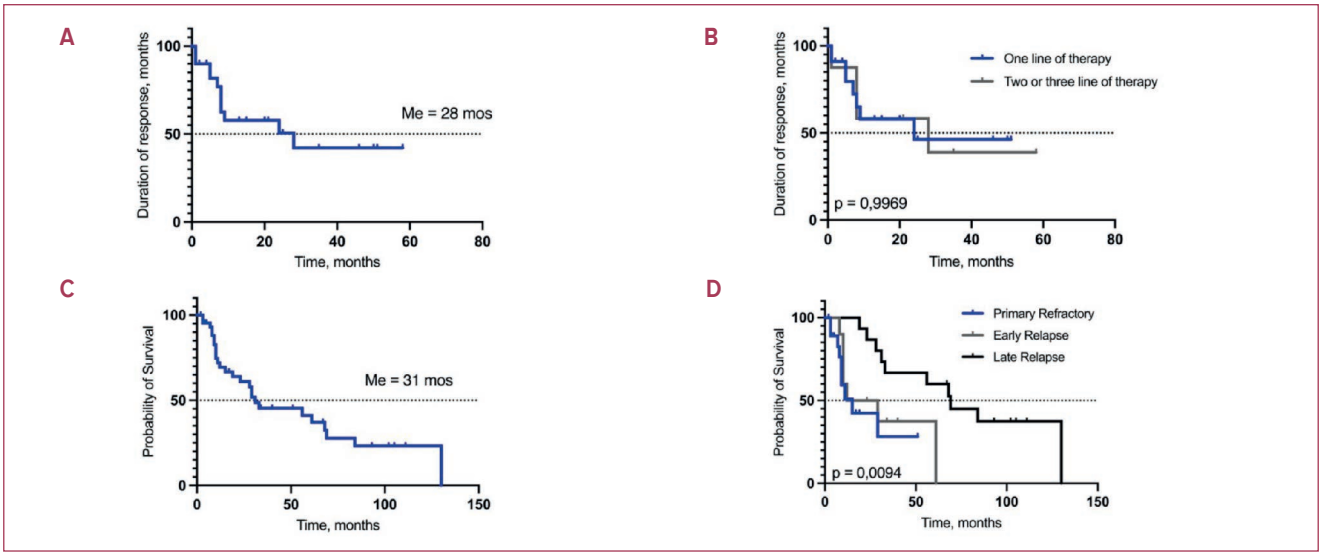

Figure 1. (A) Duration of response. (B) Duration of response according to lines of therapy. (C) Overall survival. (D) Overall survival according to the type of relapse

Table 1. Baseline population's characteristics

Baseline population's characteristics	All patients (n = 45)
Age, years, n (%)	
Median (range)	55 (24–73)
< 50	16 (35,6)
50–60	15 (33,3)
> 60	14 (31,1)
Sex, n (%)	
Female	23 (51,1)
Male	22 (48,9)
ECOG PS, n (%)	
0–1	28 (62,2)
2–4	17 (37,8)
FLT3 status, n (%)	
Mutated	7 (15,6)
Wild type	35 (77,8)
Not available	3 (6,7)
Type of AML, n (%)	
De novo	41 (91,1)
Secondary	4 (8,9)
Type of relapse, n (%)	
Primary refractory	20 (44,5)
Early relapse	10 (22,2)
Late relapse	15 (33,3)
Number of prior AzaVen lines of therapy, n (%)	1 (1–3)
1	29 (64,4)
2	9 (20)
3	7 (15,6)
Allo-HSCT, n (%)	14 (31,1)
Allo-HSCT before AzaVen	3 (6,7)
Allo-HSCT after AzaVen	11 (24,4)

Conclusion. The AzaVen is an effective treatment option for patients with R/R AML, regardless of the type of relapse or the number of prior lines of therapy. It demonstrates a rapid response and a high remission rate, and it can also serve as a bridge to Allo-HSCT.

Real-data outcomes of newly diagnosed AML treated with venetoclax and azacitidine

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Introduction. The incidence of acute myeloid leukemia (AML) increases with age, with nearly half of diagnoses occurring in patients over 70 years old. Accurate prognostication remains challenging for patients treated with venetoclax-based regimens.

Objectives. To evaluate the efficacy of the therapy administered to elderly patients and the factors influencing the outcomes of low-intensity targeted therapy.

Materials and methods. This retrospective study included a cohort of patients (n = 37) treated at the S.P. Botkin City Clinical Hospital. All patients had newly diagnosed acute myeloid leukemia and had not received any prior therapy. The median age was 65 years (range 41–88 years), with 51 % of patients being over 70 years old (Table 1). The median follow-up period was 8 months.

Table 1. Baseline population's characteristics

Baseline population's characteristics	All patients (n = 37)
Age, years, n (%)	
Median (range)	65 (41–88)
< 60	4 (11)
60–70	14 (38)
> 70	19 (51)
Sex, n (%)	
Female	20 (54)
Male	17 (46)
ECOG PS, n (%)	
1	4 (10)
2	21 (58)
3	7 (19)
4	5(13)
ELN 2022, n (%)	
Favorable	5 (13)
Intermediate	7 (19)
Adverse	25 (68)
Type of AML, n (%)	
De novo	26 (70)
Secondary	11 (30)
The degree of neutropenia at the time of diagnosis, n (%)	
Hyperleukocytosis	5 (13)
0	11(30)
1	2 (5)
2	2 (5)
3	10 (28)
4	7(19)
Allo-HSCT, n (%)	
Yes	4 (11)
No	33 (89)
NGS, n (%)	
RUNX1	8 (22)
NPM1 без FLT3	6 (16)
NPM1 с FLT3	2 (5)
FLTS-ITD	3 (8)
FLT3-TKD	2 (5)
FLT3	4 (11)
KMT2A	1 (13)
KMT2A rearrangement	3 (8)

Table 1. Continution

GATA2 MECOM(EVI1)	1 (3)
MUT CEBPA	2 (5)
MECOM(EVI1) rearrangement	1 (3)
DNMT3A	6 (16)
mutTP53	6 (16)
IDH1	4 (11)
IDH2	7 (19)
ASXL1	4 (11)
BCOR	2 (5)
EZH2	2 (5)
SH2B3	2 (5)
SF3B1	3 (8)
SRSF2	19 (51)
STAG2	5 (14)
U2AF1	2 (5)
GATA2	6 (16)
KIT	4 (11)
TET2, TET2-ASL1	7 (19)
KRAS	3 (8)
NRAS	2 (5)
UNIVARIATE ANALYSIS	
ECOG	1.02 (0.12–8.71, p = 0.989)
	2.24 (0.25–20.08, p = 0.472)
	7.45 (0.76–72.61, p = 0.084)
AML	2.00 (0.24–16.67, p = 0.522)
	1.32 (0.35–4.97, p = 0.682)
Infect	2.15 (0.69–6.67, p = 0.185)
NPM1FLT3neg	2.61 (0.67–10.17, p = 0.165)
NPMFLT3pos	1.18 (0.15–9.10, p = 0.874)
FLT3ITD	0.72 (0.09–5.58, p = 0.752)
FLT3TKD	0.00 (0.00–Inf, p = 0.998)
FLT3	0.54 (0.07–4.15, p = 0.552)
t (9;11)	19.74 (1.96–198.44, p = 0.011)
KMT2	1.36 (0.18–10.60, p = 0.767)
GATA2	3.76 (0.47–30.17, p = 0.212)
CEBRA	5.96 (1.26–28.18, p = 0.024)
MECOM	3.76 (0.47–30.17, p = 0.212)
DNMT3a	0.92 (0.20–4.15, p = 0.914)
TP53	3.65 (1.11–11.99, p = 0.033)
IDH1	0.00 (0.00–Inf, p = 0.998)
IDH2	0.53 (0.11–2.42, p = 0.410)
ASXL1	0.55 (0.07–4.22, p = 0.563)
BCOR	0.00 (0.00–Inf, p = 0.999)
EZH2	1.12 (0.14–8.61, p = 0.916)
RUNX1	0.81 (0.22–2.96, p = 0.753)
SH2B3	0.00 (0.00–Inf, p = 0.998)
SF3B1	0.67 (0.09–5.22, p = 0.706)

Table 1. Continution

SRSF2	0.40 (0.13–1.23, p = 0.110)
STAG2	0.77 (0.10–6.08, p = 0.803)
KIT	1.63 (0.36–7.38, p = 0.527)
TET2	1.37 (0.37–5.05, p = 0.633)
complex karyotype	10.21 (2.38–43.70, p = 0.002)
5q	3.53 (0.96–12.97, p = 0.057)
7q	1.37 (0.30–6.21, p = 0.685)
monosomal karyotype	0.00 (0.00–Inf, p = 0.998)
17p	8.13 (1.63–40.53, p = 0.011)
KRAS	1.39 (0.18–11.00, p = 0.754)
NRAS	1.67 (0.21–13.21, p = 0.628)

Results. The median duration of therapy was 8 months. At the time of the final analysis, 16 patients were still on treatment. Therapy was discontinued for 19 patients (5 due to disease progression, 14 due to death).

The median overall survival at the time of the final analysis had not been reached (Figure 1, A). The median EFS was 12 months (Figure 1, B). Among the 13 patients who died, the causes of death included AML progression (n = 3) and infectious complications (sepsis, lung infections) (n = 10). In our study, the ELN 2022 risk classification did not impact overall survival (OS) or event-free survival (EFS) in patients receiving Azacitidine and Venetoclax therapy (Figure 1, C–D). In univariate analysis, the following factors were found to significantly impact overall survival: t(9;11), CEBPA, TP53, complex karyotype and abn (17p) (Table 1). The median duration of response was 38 months. Remission was achieved in 25 patients (67.5 %). Complete remission was observed in 7 patients (28 %), complete remission with incomplete recovery in 5 patients (20 %), complete response with partial recovery was observed in 3 patients (12 %), morphological leukemia-free state in 7 patients (28 %). Among those who achieved remission, 21 patients (84 %) had remission after the first cycle of therapy, 2 patients after the second cycle, and 2 patients after the third cycle. In the adverse-risk group, remission was achieved in 79 % of patients; in the intermediate-risk group, 71 %; and in the favorable-risk group, 60 %.

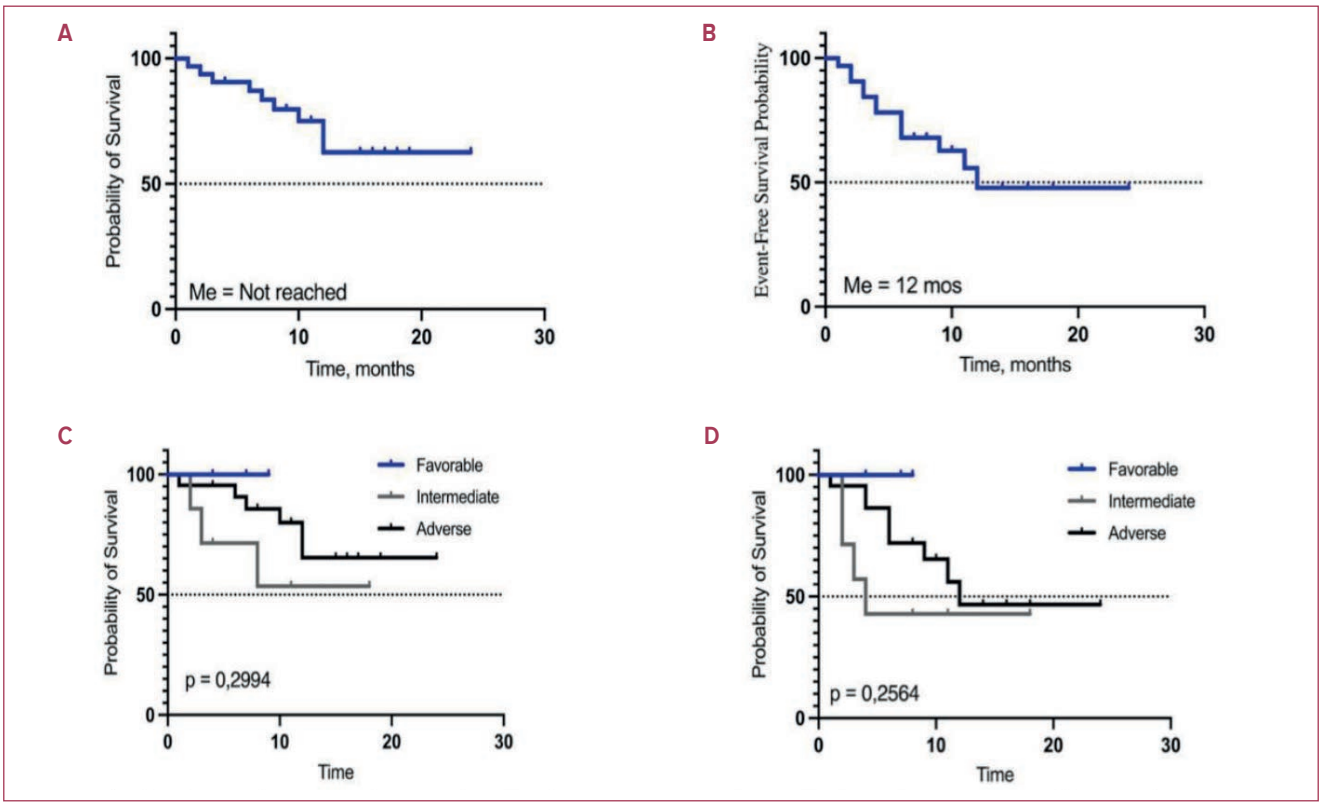

Figure 1. (A) Overall survival. (B) Event-free survival. (C) Overall survival according to the risk ELN 2022. (D) Event-free survival according to the risk ELN 2022

NGS results were obtained for all 37 patients. The most common mutations were SRSF2 (51 %), RUNX1 (22 %), IDH2 (19 %), TET2 (19 %), DNMT3A (16 %), TP53 (16 %), and FLT3-ITD (8 %).

During the first cycle of therapy, the following complications were observed: grade 4 neutropenia — 7 patients (19 %), grade 3 anemia — 24 (65 %), grade 4 thrombocytopenia — 17 (46 %), and infections — 19 (51 %). 30-day and 60-day mortality rates were 8 % and 12 %, respectively.

The median hospitalization during the first cycle was 16 days (range: 0–43). Two patients were treated on an outpatient basis. The median delay to the start of the second cycle was 16.5 days (range: 0–55).

Conclusions. The combination of AzaVen demonstrates good tolerability, clinically significant benefits in overall survival, remission rates. In our study, the ELN 2022 risk classification did not affect OS or EFS.

Clinical features and prognostic significance of PML-RARa isoforms in patients with acute promyelocytic leukemia

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Introduction. Acute promyelocytic leukemia (APL) accounts for 5-15 % of all cases of acute myeloid leukemia. Its pathogenesis is based on reciprocal translocation t(15;17)(q24;q21), leading to the fusion of the promyelocytic leukemia (PML) gene and alpha-retinoic acid (RARa) gene. The product of this interaction, a chimeric PML-RARα protein, blocks the differentiation of myeloid cells at the promyelocyte stage, leading to the development of APL. The PML gene can experience breaks in different breakpoint cluster regions (bcr), leading to the formation of various types of transcripts, the most common are bcr1, bcr2, and bcr3.

Despite numerous studies investigating the relationship between isoform type and clinical characteristics at the onset of disease, the course and outcome of the disease, no consensus on the prognostic significance of the transcript isoform. Some studies have shown an association between the bcr3 and unfavorable prognostic factors, such as initial hyperleukocytosis, CD34 expression by tumor cells, a high incidence of intracranial hemorrhage. However, other studies have found no correlation between bcr isoforms and the presence of these unfavorable factors.

Objectives. To investigate the association between the type of PML-RARα transcript and clinical and laboratory features in patients with APL before treatment.

Materials and methods. The study from 2022 to 2024 included 31 patients with APL (9 men, 22 women), aged 18 to 90 years (median 48) observed at the Kommunarka City Clinical Hospital. The diagnosis was made according to the clinical guidelines. The chimeric transcript PML-RARα was determined using real-time PCR. Initially, the average platelet count was 32×10^9/L (5–204×10^9/L), leukocyte — 15×10^9/L (0.3–104×10^9/L), fibrinogen level — 1.7 g/L (0.54–5.39 g/L). 8 (26 %) patients were classified as high-risk (Le ≥ 10×10^9 /L), while 21 (68 %) were classified as low-risk (Le < 10×10^9 /L). Isoform bcr1 was detected in 16 (53 %) patients, bcr2 in 1 (3 %), bcr3 in 14 (44 %). The differentiation syndrome was diagnosed in 12 (39 %) patients. CD34 expression was detected in 7 (23 %) patients.

Results. Depending on the bcr isoforms, patients were divided into two groups: 17 had bcr1 or bcr2, 14 had bcr3 (Table 1). There were no significant differences in age, gender, platelet count, fibrinogen level between these groups. The average initial value of leukocytes was significantly higher in the bcr3 group compared to the bcr1/bcr2 group (29×10^9/l vs. 4×10^9/l). Development of differentiation syndrome (64 % vs. 19 % (p = 0,03)), CD34+ expression (43 % vs 7 % (p = 0,03)) were more common in the bcr3 group. At the start of treatment intracranial hemorrhagic complications were noted in 8 (26 %) patients from the general group. In the bcr1/bcr2 group, these complications occurred in 12 % of patients, in the bcr 3 group — in 42 % (p = 0.064). In 2 patients from the bcr3 group cerebral hemorrhage led to death.

Table 1. Clinical and laboratory characteristics of patients included in the study

Characteristics	Bcr1/ bcr2 (n = 17)	Bcr3 (n = 14)	p
Age, years	48,0 (19,1–69,4)	48,75 (22,2–80,4)	0,6163
Sex, n (%)			
male	5 (30)	4 (29)	
female	12 (70)	10 (71)	
Average platelet count (max–min), × 10^9/l	37 (5–204)	26 (10–63)	0,5
Average leukocyte count (max–min), × 10^9/l	4,1 (0,3–104)	29 (0,57–30,4)	0,015
Average fibrinogen level (max–min), g/l	1,73 (0,81–4,34)	1,73 (0,54–5,39)	> 0,9
Risk group, n (%)			0,01
low	16 (96 %)	7 (50 %)	
high	1 (1 %)	7 (50 %)	
Intracranial hemorrhage, n (%)	2 (12 %)	6 (42 %)	0,064
The differentiation syndrome, n (%)	3 (19 %)	9 (64 %)	0,03
CD 34 expression, n (%)	1 (7 %)	6 (43 %)	0,01

Conclusions. The revealed relationship between the PML-RARα isoform bcr3 and high initial leukocytosis, incidence of differentiation syndrome, CD34 expression on tumor cells, suggests that this isoform may be a potential predictor of unfavorable prognosis in patients with APL.

INDOLENT LYMPHOMAS AND MYELOMA

Outcomes of allogeneic hematopoietic stem cell transplantation in high-risk chronic lymphocytic leukemia patients

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Introduction. The role of allogeneic hematopoietic stem cell transplantation (alloHSCT) in chronic lymphocytic leukemia (CLL) has decreased in recent years due to the emergence of new effective targeted agents for the treatment of this disease. However, for a certain group of heavily pretreated or high-risk CLL patients with no other therapeutic options, alloHSCT remains important. Limiting factors for alloHSCT are the risks of possible serious immune complications such as graft-versus-host disease (GvHD) and infections, especially in older patients. Due to the fact that in most high-risk CLL patients it is possible to achieve a complete response (CR) as a result of Bruton's tyrosine kinase inhibitors (BTK), BCL-2 inhibitor and especially in their combined application, including in the first line of therapy, the choice of the time point for alloHSCT becomes relevant.

Objectives. Analysis of the results of alloHSCT in patients with high-risk CLL.

Methods. The patients were treated and observed at the pre- and post-transplantation period in two centers: RM Gorbacheva Research Institute, Saint Petersburg and S. P. Botkins's City Clinical Hospital, Moscow. AlloHSCT was completed in all patients at the RM Gorbacheva Research Institute in the period from 2006 to 2023. Baseline and demographic characteristics and previous therapy are summarized in Table 1. The specific features of alloHSCT are summarized in Table 2. Statistical analyses were conducted using R version 4.3.2.

Results. The median follow-up after alloHSCT was 44 (3–160) months. Three-year overall survival (OS) and progression-free survival (PFS) were 73 % (CI 56.7–84.2) and 61 % (CI 44.1–74.1), respectively (Figure 1). Non-relapse mortality was 20 % (CI 9.2–33.9). The cumulative incidence of acute graft-versus host disease (GvHD) was 47 % (CI 8–14.6) and chronic GvHD was 31 % (CI 17.2–46.7). There was difference in 3-year OS between patients in CR/partial response (PR) and stable disease (SD)/progression disease (PD) before alloHSCT: 85 % (CI 51.2–96.0)/ 88 % (CI 58.6–96.7) and 33 % (CI 8.9–77.4)/50 % (CI 18.4–75.3), respectively (Figure 1). Ibrutinib was administered to 15 patients after alloHSCT

Table 1. Baseline demographic characteristics and previous therapy

Number of patients, n	44
Gender, Male /female, n (%)	31/13(71/29)
Median age, years (range)	50 (31–69)
Median number of previous therapy lines, (range)	4 (1–8)
TP53 aberrations, n (%)	15 (34)
Complex karyotype, n (%)	9 (20)
BTK inhibitors therapy before alloHSCT, n (%)	26 (59)

Table 2. The specific features of alloHSCT

Donor, n (%)	
MRD	12(27,5)
MUD	20(45)
MMUD	12(27,5)
The status at the moment of alloHSCT, n (%)	
CR	20 (45)
PR	14 (32)
SD	3 (7)
PD	7 (16)
Number of patients with known MRD status, n (%)	33(75)
MRD before alloHSCT, n (%)	
Positive	24 (73)
Negative	9 (27)
Conditioning regimens, n (%)	
Myeloablative conditioning	1 (2)
Reduced-intensity conditioning	43 (98)
Fludarabine-bendamustine	26 (59)
Fludarabine-busulfan	2 (5)
Rituximab-fludarabine-bendamustine	10 (23)
Other fludarabine-containing regimens	5 (11)
Other regimens	1 (2)
Posttransplant cyclophosphamide prophylaxis, n (%)	33 (75)

MRD — minimal residual disease; CR — complete response; PR — partial response; SD — stable disease, PD — disease progression; BTK — Bruton's tyrosine kinase.

with a median time of 3.8 months and 4 of them developed relapse. Remission of the disease remained in 22 (71 %) patients. Conversion of PR to CR was observed in 11/14 patients, PD to CR in 3/7 patients. Non-engraftment with remission of the disease was noted in 5/30 patients, non-engraftment with no remission in 1/30 patient.

Conclusions. AlloHSCT is an effective treatment option for patients with high-risk CLL. The difference between CR/PR and SD/PD before alloHSCT impacts OS results. We have not received data indicating that post-transplant administration of BTK inhibitors prevents the development of relapses.

Keywords: chronic lymphocytic leukemia, allogeneic hematopoietic stem cell transplantation.

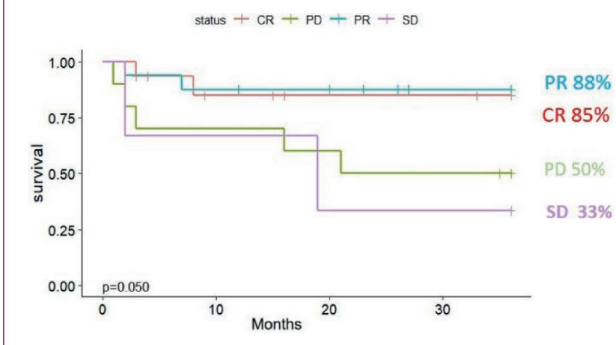

Figure 1. Three-year overall survival depending on disease status

Effect of ibrutinib on risk of cardiovascular and hemorrhagic complications in patients with chronic lymphocytic leukemia

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Introduction. Ibrutinib has changed the management of patients with chronic lymphocytic leukemia (CLL). Despite efficacy in the treatment of CLL, cardiovascular complications, particularly atrial fibrillation (AF), remain one of the reasons for discontinuation of ibrutinib. Currently, the European Society of Cardiology guidelines for cardio-oncology 2022 do not fully address the management of patients with ibrutinib.

Objectives. To evaluate the effect of ibrutinib therapy on the risk of cardiovascular complications and safety of anticoagulant therapy in patients with CLL.

Methods. The retrospective cohort study included 641 patients (60 % men, 40 % women, median age — 67 [60; 75] years) with CLL who were followed at the Botkin Moscow City Clinical Hospital and received ibrutinib therapy (median duration of ibrutinib therapy — 30 months). The median follow-up time was 36 months. The primary endpoint was the occurrence of AF. In addition, we recorded bleeding (according to the BARC classification), thrombotic complications (ischemic stroke, myocardial infarction, venous thromboembolism (VTE)) and death (with cause).

Results. The most common cardiovascular complications on the ibrutinib therapy were AF, which occurred in 17 % of patients, and AH, which developed or worsened in 14 % of patients. During 5 years of follow-up, 39 % of patients died. The main causes of death were CLL progression (34 %) and infectious complications (32 %). The incidence of death from cardiovascular diseases (CVD) was 10 %.

Among all patients with AF on ibrutinib therapy, 15 % of patients had new-onset AF. The incidence of new-onset AF during the first 30 months of follow-up (Me time of ibrutinib therapy) was 9 events per 100 patient-years. The incidence of AF during for the next 30 months was 4 events per 100 patient-years.

We compared risk factors for AF in patients with (n = 93) and without AF (n = 228) before ibrutinib therapy. The majority of patients with AF were older and more comorbidities before ibrutinib therapy (Table 1).

The following outcomes were evaluated in these patients: thrombotic and hemorrhagic complications. Compared to patients without AF, patients with new-onset AF had a higher incidence of both thrombotic complications (1 % vs 17 %, p < 0.0001), most commonly VTE, and bleeding (32 % vs 56 %, p < 0.0001).

Table 1. Clinical characteristics of patients with new-onset atrial fibrillation and without atrial fibrillation during ibrutinib therapy

Parameter	Patients with AF during follow-up (n = 93)	Patients without AF during follow-up (n = 228)	p
Age over 60 years old, n (%)	80 (86)	155 (68)	0.0008
Female, n (%)	38 (41)	98 (43)	0.8379
Arterial hypertension, n (%)	73 (79)	155 (68)	0.0924
Coronary artery disease, n (%)	26 (30)	37 (16)	0.0199
Chronic heart failure, n (%)	10 (11)	9 (4)	0.0213
Chronic kidney disease, n (%)	55 (59)	104 (46)	0.0208
Diabetes mellitus, n (%)	23 (25)	34 (15)	0.0432
Stroke, n (%)	6 (7)	4 (2)	0.0304
Obesity, n (%)	25 (27)	45 (20)	0.8176
Cancer of the second localisation, n (%)	29 (31)	52 (23)	0.1366
Chemotherapy before ibrutinib, n (%)	78 (84)	181 (79)	0.3276

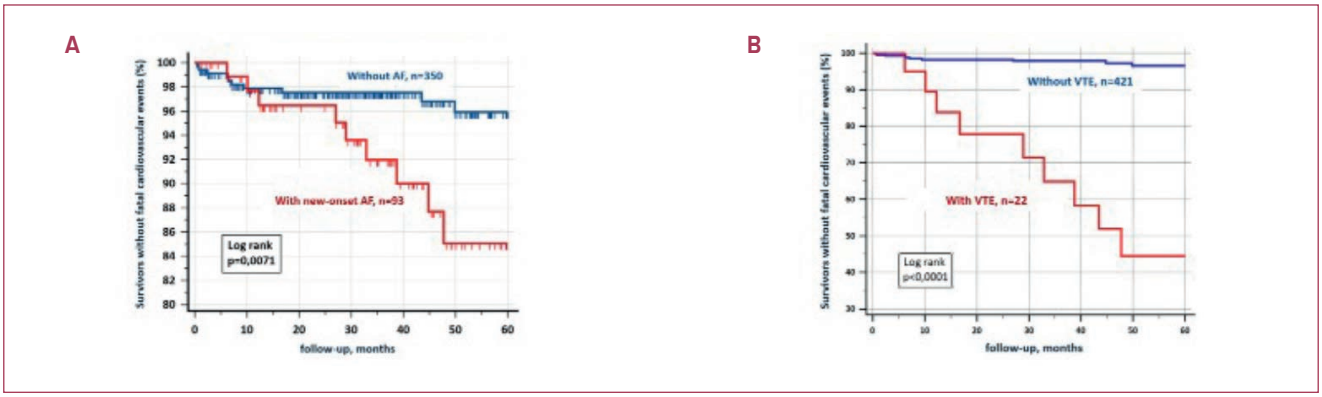

Figure 1. Effect of ibrutinib on cardiovascular mortality in patients with CLL

11 % (n = 48) of patients had thrombotic complications. The independent risk factors for thrombotic complications were cancer of other localization and new-onset AF on ibrutinib therapy. Bleeding was observed in 32 % (n = 72) of patients. Risk factors for clinically significant and major hemorrhagic complications (BARC 2–5) were chronic kidney disease, thrombocytopenia and new-onset AF.

When excluding CLL progression and infectious complications as causes of death, AF and VTE occurring during ibrutinib treatment increased the incidence of death from CVD (Figure 1). In the structure of cardiovascular mortality in patients with AF, VTE occurred more frequently.

Conclusion. The most common cardiovascular complications of ibrutinib therapy are AF and the development of AH. New-onset AF on ibrutinib therapy is associated with an increased incidence of both thrombotic complications, most commonly VTE, and hemorrhagic complications. In patients with CLL, new-onset AF during ibrutinib therapy was associated with an increased incidence of death from CVD, most commonly VTE.

Updated results of combination treatment with ibrutinib and venetoclax in patients with chronic lymphocytic leukemia and complex karyotype: 4-year follow-up

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Objectives. Studies by Kittai (2021) and Al-Sawaf (2020) showed an adverse impact of complex karyotype (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.

Methods. This study included patients with CLL and a CK of high cytogenetic complexity, ≥ 5 chromosomal abnormalities, or a complex karyotype in combination with a 17p deletion (del17p). The first retrospective cohort included patients who received ibrutinib monotherapy (Imono) until progression or toxicity starting from May 2015. The second prospective cohort included patients receiving the combination of ibrutinib and venetoclax (IVen) after 3 months of ibrutinib monotherapy from July 2019. Combination therapy was continued until intolerable toxicity, progression or achievement of complete remission (CR) with MRD(–) status in the bone marrow assessed by flow cytometry in three consecutive measurements 3 months apart. If MRD(–) status was not achieved by 24 months, venetoclax was discontinued and ibrutinib continued indefinitely.

Results. There were 56 patients in the first cohort and 50 patients in the second cohort (Table 1). The patient characteristics in both groups were comparable. At data cut off 15 patients were still receiving combination therapy. Nine patients did not complete planned treatment for reasons other than MRD(–) CR or progression. Among them 5 patients have died (4 — COVID-19, 1 — complicated abdominal infection), 4 experienced unmanageable toxicity (3 — persistent neutropenia grade 4 with recurrent infections, 1 — reactivation of hepatitis B). Most of these patients have achieved response by the time of treatment cessation (1 — CR MRD(–), 4 — CR MRD(+), 3 — non evaluable, 1 — progression). In total 15 patients achieved MRD(–) CR, among whom 5 stopped treatment earlier. One patient had progression with Richter transformation during combination therapy. Among the rest 9 patients 1 had MRD(–) PR and 9 had MRD(+) CRs. These 9 patients continued ibrutinib monotherapy. The rate of MRD-negativity was gradually increasing during treatment period from 26 % at 3 months to 62 % at 12 months of combined treatment among evaluable patients. Three patients underwent allogeneic transplantation. None of MRD(–) patients demonstrated recurrence of MRD during the first year of observation. In an Imono cohort 33 patients had progression, 11 died before progression, 3 stopped treatment for toxicity. 28 patients were switched to venetoclax after progression. With a median follow-up of 32,5 months IVen regimen showed a better progression-free survival (PFS) compared to Imono (p = 0.001, HR 2.77, 95 % CI 1.62–4.75) (Figure 1). There was no difference in overall survival (OS) (p = 0.25, HR 1.46, 95 % CI 0.77–2.79) (Figure 1).

Table 1. Patients' characteristics

Characteristics	Ibrutinib	Ibrutinib + Venetoclax	p
Patients, total	56	50	?
Median age (range)	65 (34–84)	63 (37–80)	
Male/female	34/22	27/23	0.06
Binet stage			0.48
A	—	—	
B	30 (54 %)	34 (68 %)	
C	26 (46 %)	16 (32 %)	
ECOG			
0–1	40 (71 %)	43 (86 %)	
2–4	16 (29 %)	7 (14 %)	
High-CK (5 or more aberrations)	46 (84 %)		
CK (3 or more aberrations) + deletion 17p	10 (16 %)		
Deletion 17p	39 (67 %)		
Unmutated IGVH	49/49 (100 %)		
Median previous therapy lines (range)	2 (0?7)		
Richter transformation	5 (9 %)		

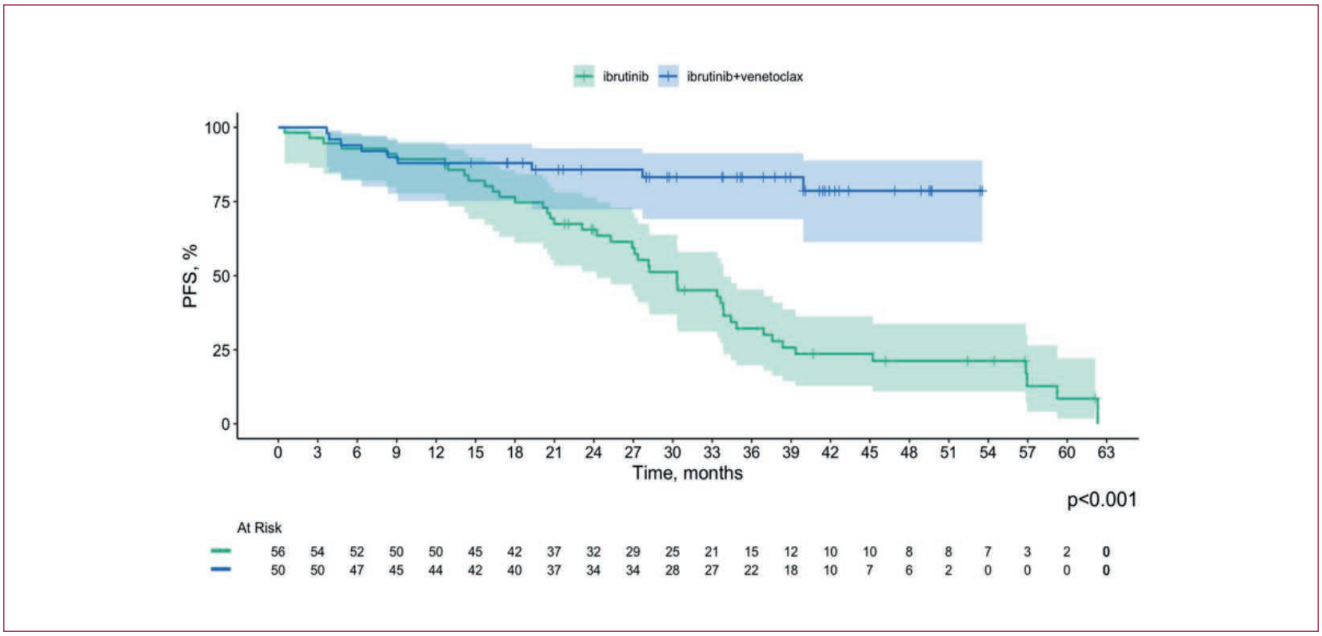

Figure 1. Progression free survival in patients receiving ibrutinib and venetocax in combination or ibrutinib as a monotherapy

Conclusion. After 4 years of follow-up, IVen regimen shows significant benefit in PFS compared to Imono in patients with CK, supporting its use in such high-risk group of patients. Despite the unfavorable prognosis, most patients achieve MRD-negative response, complete therapy and have no early relapses.

Moscow experience of acalabrutinib treatment in patients with CLL in first line and R/R: matching-adjusted indirect comparison (MAIC) versus ibrutinib

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Introduction. The first BTK inhibitors, ibrutinib, demonstrated a significant improvement in overall survival among previously untreated CLL patients in the RESONATE-2 study, compared to chlorambucil (Barr, 2018). The second-generation BTK inhibitor, acalabrutinib, became available in Russia in 2020. The comparative ELEVATE-RR study confirmed the similar efficacy of ibrutinib and acalabrutinib (Woyach, 2024). The aim of our study is to characterize patients receiving acalabrutinib therapy in Moscow and to compare the findings with outcomes from first-generation BTK inhibitor therapy across various risk groups.

Methods. This retrospective study included 848 patients from two cohorts: the primary cohort receiving acalabrutinib monotherapy (n = 106) since 2020 and the comparison cohort receiving ibrutinib therapy (n = 742) since 2015 at the Botkin Hospital in Moscow. A separate comparative analysis was conducted on treatment outcomes in patients receiving first-line therapy and those with relapses. Due to differences in

inclusion criteria and the timing of drug administration, the population characteristics of the two cohorts differ. Patient relapsed data from the ibrutinib cohort were re-weighted to match the acalabrutinib cohort using method of moments approach, adjusting for well-established prognostic factors reported in both studies (age, Binet stage, del(17p), number of prior lines of therapy). Chi-square test was used to compare proportional outcomes; Mann-Whitney — non-parametric continuous data; time to treatment failure (TTTF) and overall survival (OS) were compared using Kaplan-Meier analysis and log-rank test.

Results. In the first cohort, the median age of patients was 71 years (range 41–87), with an equal number of men and women. According to the analysis, the main reasons for treatment discontinuation were death due to infection (18 %), disease progression (12 %), and combined progression with death (35 %). The median follow-up duration was 15 months. Therapy was discontinued due to bleeding and arrhythmia in 6 % of cases each. Overall, 19 patients (18 %) achieved complete remission on acalabrutinib, while 33 (31 %) achieved partial remission, and progression was observed in only 11 patients (10 %). Del17p mutation was identified in 40 out of 93 patients (43 %), and an unmutated IGHV variant was present in 59 out of 69 patients. Seventy-five patients (72.1 %) were at Binet stage B, while 29 patients (27.9 %) were at stage C (Table 1).

Table 1. Characteristics of patients receiving acalabrutinib

Characteristic	N (%)
Total patients	106
Median age (range)	71 (41–87)
Men/women	53/53
Binet stage at the start of therapy:	
A	—
B	75 (72.1 %)
C	29 (27.9 %)
CIRS, median (range)	5 (0–15)
Deletion 13q	9/55 (16.4 %)
11q deletion	16/54 (29.6 %)
Trisomy 12	3/54 (5.5 %)
Deletion 17p	40/93 (43.0 %)
Unmutated IGVH variant	59/69 (85.5 %)
Median of previous lines of therapy (range)	1 (0–7)
1 line/relapse	19/87
Reason for cancellation	
Death — COVID-19	6 (35 %) — 3 (18 %)
Progression	2 (12 %)
Progression + death	6 (35 %)
Arrhythmia	1 (6 %)
Bleeding	1 (6 %)
Other	1 (6 %)
Complete remission	19 (18 %)
Partial remission	33 (31 %)
Progression	11 (10 %)
Not rated	24 (23 %)
Stabilization	19 (18 %)

Table 2. Comparison of characteristics for acalabrutinib and ibrutinib as first-line therapy

Characteristic	Acalabrutinib	Ibrutinib	P
Total patients	19	52	—
Median age (range)	67 (55–84)	73 (40–92)	0.0549
Men/women	8/11	26/26	0.5555
Binet stage at the start of therapy			
A	—	—	—
B	16 (84,2 %)	30 (62,5 %)	0.0842
C	3 (15,8 %)	18 (37,5 %)	0.0842
Deletion 13q	3/12 (25.0 %)	2/18 (11.1 %)	0.3173
Deletion 11q	2/12 (16.7 %)	1/21 (4.8 %)	0.2525
Trisomy 12	0/13 (0.0 %)	4/17 (23.5 %)	0.0603
Deletion 17p	9/18 (50.0 %)	26/47 (55.3 %)	0.7003
Unmutated IGVH variant	14/15 (93.3 %)	27/31 (87.1 %)	0.5241

No significant differences were identified in baseline characteristics between patients receiving acalabrutinib and ibrutinib as first-line therapy. These data are presented in Table 2.

TTTF and OS were comparable (Figure 1, A, B).

After adjustment, the median age in the acalabrutinib and ibrutinib cohorts was 70 years, number of prior lines of therapy was 2, all other prognostic factors were similarly well matched in both cohorts. Following the matching-adjusted indirect comparison (MAIC) analysis, TTTF and OS in relapsed patients in both cohorts showed no significant differences (Figure 1, C, D).

Discussion. The efficacy of acalabrutinib was comparable to ibrutinib in patients with previously untreated and relapsed/refractory CLL. The primary reasons for discontinuing acalabrutinib therapy were disease progression and death due to infections, while arrhythmias and bleeding did not significantly impact discontinuation. An overall response was achieved in 49 % of patients, of whom 31 % reached partial remission.

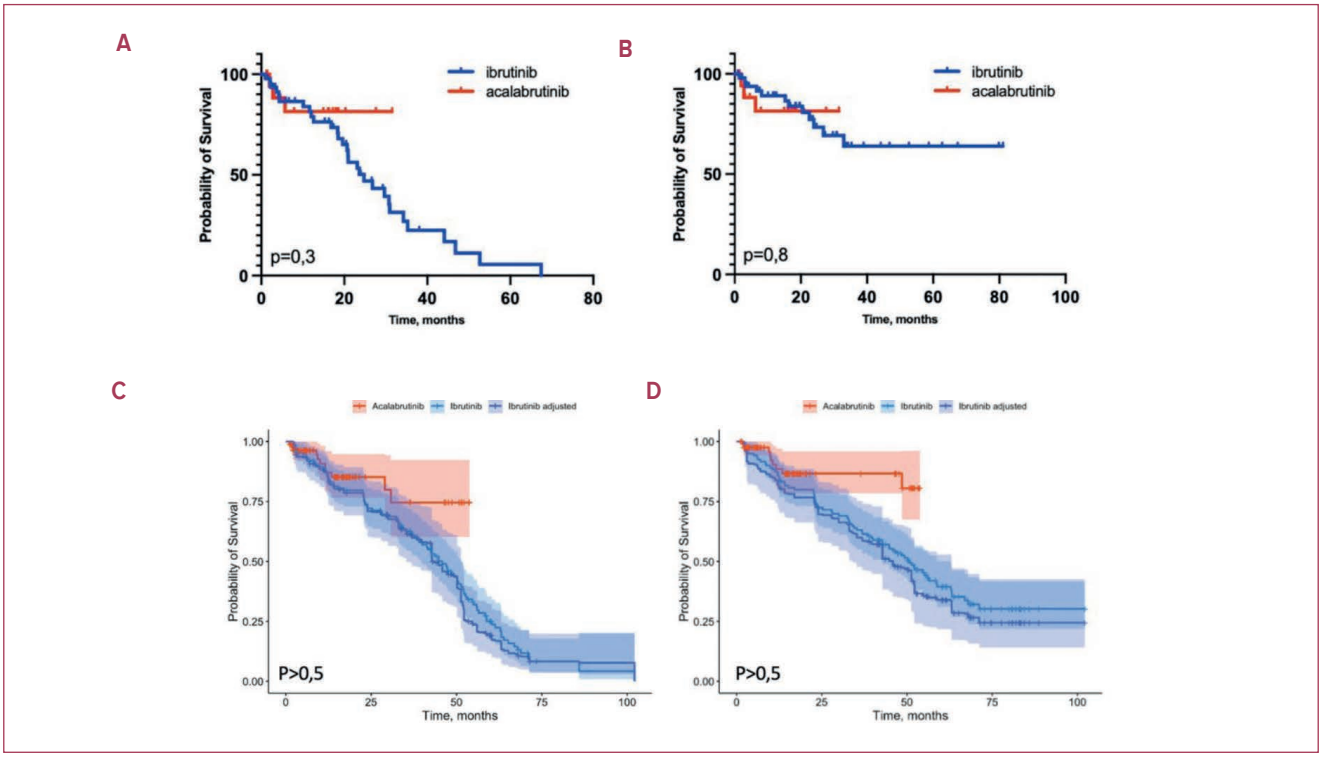

Figure 1. (A) Time to treatment failure for acalabrutinib and ibrutinib as first-line therapy. (B) Overall survival for acalabrutinib and ibrutinib as first-line therapy. (C) Matching-adjusted indirect comparison time to treatment failure for acalabrutinib and ibrutinib in relapsed patients. (D) Matching-adjusted indirect comparison Overall survival for acalabrutinib and ibrutinib in relapsed patients.

Clinicopathologic characteristics of the disease in patients with marginal zone lymphomas: a single center experience in Krasnodar region

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Introduction. Marginal zone lymphoma (MZL) is the second most common type of indolent non-Hodgkin's lymphoma (iNHL) and shows significant clinical heterogeneity. The occurrence of MZL is often a consequence of chronic antigenic stimulation by Helicobacter pylori antigen, hepatitis C virus, and MZL may regress with treatment of the infection. The geographical distribution of iNZHL may vary. Despite appropriate choice of first-line therapy, approximately 15 % of patients with iNHL develop resistance. The majority of patients relapse, with each relapse occurring more rapidly than the previous one.

Objectives. To analyse the peculiarities of clinical course and disease progression in patients with marginal zone lymphoma in Krasnodar.

Materials and methods. A retrospective cohort study of patients with marginal zone lymphoma observed in Krasnodar Clinical Oncological Dispensary №1 from 2019 to 2024 was conducted. Comparison of frequencies was performed using the χ^2 method. Kaplan-Meier survival curves were compared using the log-rank test with SPSS 23.0.

Results. Sixty patients (25 males) were included in this retrospective study. The median age at diagnosis was 61 (36–76) years. The incidence of nodal, extranodal and splenic marginal zone lymphoma was 20 (34 %), 35 (58 %) and 5 (8 %), respectively, and in 53 cases (88 %) they were diagnosed at an advanced stage. Helicobacter pylori (HP) was investigated in all 6 patients with gastric MALT lymphoma and HP was detected in 4 out of 6. The prevalence of HP in the total group was only 13 % (8 patients). The detailed characteristics of the patients prior to first-line treatment are summarised in Table 1. The following regimens were used as first-line therapy for MZL: R-CHOP/CHOP, R-CVP/CVP, BR and rituximab monotherapy in 19 (32 %), 11 (18 %), 9 (15 %) and 1 (2 %) patients, respectively. Splenectomy

Table 1. Characteristics of patients` before the start of the first line therapy

Characteristics	Nodal MZL	Extra-nodal MZL	Splenic MZL
N of pts in each groups`	20 (34 %)	35 (58 %)	5 (8 %)
Sex			
Male	5 (25 %)	19 (54 %)	1 (20 %)
Female	15 (75 %)	16 (46 %)	4 (80 %)
Age (Me, range, years)	60 (36–75)	59 (37–76)	56 (47–68)
Stage of disease by Ann Arbour classification III/IV	17 (85 %)	34 (97 %)	2 (40 %)
Bone marrow involvement (by PET/CT or by biopsy)	10/16 (63 %)	10/29 (34 %)	1/4 (25 %)
What are the extranodal zones (only for extranodal MZL)			
Lungs		7 (20 %)	
Stomach		5 (14 %)	
Orbital cavity		2 (6 %)	
Salivary gland		2 (6 %)	
Breast		2 (6 %)	
Liver		2 (6 %)	
Larynx		**2** (6 %)	
Throat		**2** (6 %)	
Other localizations		**11 (30 %)**	
"Bulky" disease	0	1 (3 %)	1 (20 %)
HCV positive pts	1 (5 %)	6 (17 %)	1 (20 %)
Ki 67 %			
> 10 %	2/15 (13 %)	6/22 (27 %)	1/3 (33 %)
≤ 10 %	13/15 (87 %)	16/22 (73 %)	2/3 (67 %)
CD5+	18/20 (78 %)	26/31 (84 %)	4/4 (100 %)

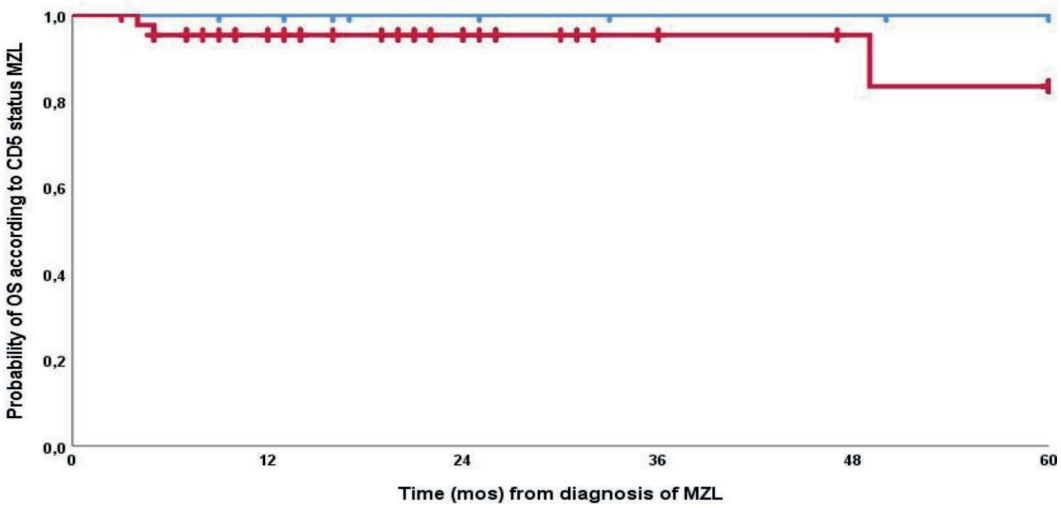

Figure 1. Overall survival on first-line therapy of MZL, according to the type of MZL

was performed in 10 patients (15 %), other surgical procedures in 4 patients (partial gastrectomy in 1, lung resection in 1, orbitotomy in 1, pancreatic head resection in 1). Radiotherapy was given to 3 patients (5 %). HP eradication therapy was used as the initial treatment in 3 patients (5 %). The median duration of first remission was 9 (1–188) months. According to PET/CT/MSCT results, a complete response was achieved in 25/60 (42 %) and a partial response in 18/60 (30 %). Recurrence and progression after first-line failure were reported in 15/60 (25 %) patients. Of these, 4/15 (27 %) in the nodal MZL group, 8/15 (53 %) in the extranodal group and only 3 (20 %) in the splenic group, p = 0.086. There were 3 transformations to Hodgkin lymphoma and NHL. With a median follow-up from diagnosis to last visit of 21 (1–188) months, there were 5 (8 %) deaths. The median OS was not achieved and the probability of 5-year OS was 81 % (Figure 1). The median event-free survival was 53 months.

Conclusions. The distribution of MZL subtypes is consistent with published data. The use of available therapeutic regimens shows high efficacy in the first-line treatment of MHL. Many patients in the Krasnodar region are diagnosed at late stages. Relapses are common in the nodal MZL group.

Analysis of the molecular profiling of the patients with multiple myeloma by next-generation sequencing

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Introduction. The results of sequencing a panel of genes by means of the NGS make it possible not only to determine the prognosis, but also, thanks to the accumulation and systematization of data, the detection of new mutations, contribute to a deeper understanding of the pathogenesis of multiple myeloma (MM) and the development of new targeted drugs.

Objectives. The aim of the study was to consider the prognostic significance of gene mutations in patients with MM using NGS data analysis.

Methods. A study was conducted in 33 patients with a median MM age of 58 (38–81). The median follow-up was 29.8 months with a maximum follow-

Table 1. Characteristics of patients

Characteristics	Total (n = 33)
Sex, n (%)	
Female	17 (51.5)
Male	16 (48.5)
Median age at the time of observation, years old	58 (38–81)
Stage, n (%)	
I	10 (30.3)
II	13 (39.4)
III	10 (30.3)
Stage according to Durie Salmon, n (%)	
I	1 (3.1)
II	9 (28.1)
III	23 (68.8)
High-risk cytogenetic abnormalities according to Fish, n (%)	
del 17p	2 (6.0)
t(14;16)	1 (2.0)
CKS1B/1q21	2 (6.0)
CDKN2C/1p32	2 (6.0)
Stage according to SMART3.0, n (%)	
I stage	2 (6.0)
II stage	7 (20.0)

up period of 13 years. All patients underwent mutation screening using an NGS panel of probes for 118 genes on the NextSeq Illumina platform by pair-terminal reading. The data analysis is performed in the statistical programming language R v4.2.2. To determine the prognostic significance of all mutations found in each patient, the tumor mutation load (TML) was calculated, which was defined as the number of mutations per 1 megabase (Mb) of the coding sequence. The median TML was 5.0 mutations/Mb.

Results. Among the patients, the ones belonging to stage III according to the B. Durie, S. Salmon system prevailed — 68.8 %, 20.0 % of patients were assigned to the high cytogenetic risk group according to the mSMART3.0 classification. The characteristics of the patients are presented in Table 1.

Courses of CVD — 52.0 %, VD — 24.2 %, VMP — 9.1 %, Dara-containing programs — 9.1 %, PAD — 5.6 % were conducted as the 1st line therapy regimen. Most patients after the 1st line therapy achieved a partial response — 42.4 % (the frequency of objective response was 84.9 %), relapse after treatment was observed in 18.2 % of patients, progression — in 15.1 %.

NGS revealed 357 mutated genes, 1.96 % of genes (n = 7) potentially oncogenic, 1.68 % of genes (n = 6) oncogenic, most of the identified mutations were probably benign 66.1 % (n = 236). The mutational landscape of the studied population is shown in Figure 1.

In the analysis of survival, the 3-year survival rate in patients with the ATM mutation was 72.9 % (95% CI 47.0–100.0), in the group with the unmutated ATM variant — 100.0 %, p = 0.013.

The threshold value of TML was calculated using ROC analysis for overall survival rate, according to which the TML value of 4.98 mutations/Mb was statistically significant. Thus, all patients were divided into 2 groups: with low TML — 57.6 % (19/33) and with high TML — 42.4 % (14/33). Three-year overall survival rate in the group with high TML was 76.2 % (95% CI:55.6–100.0), in patients with low TML — 100 %, p = 0.045. High tumor mutation load is significantly an unfavorable prognostic parameter, which was confirmed in the Cox regression analysis, the relative risk for 3-year PFSwas 5.74 (95% CI 1.19–27.70), p = 0.029.

Conclusions. It has been established that a high tumor mutation load is a significant negative prognostic factor in patients with MM. A mutation in the ATM gene had an adverse effect on the survival of patients with MM.

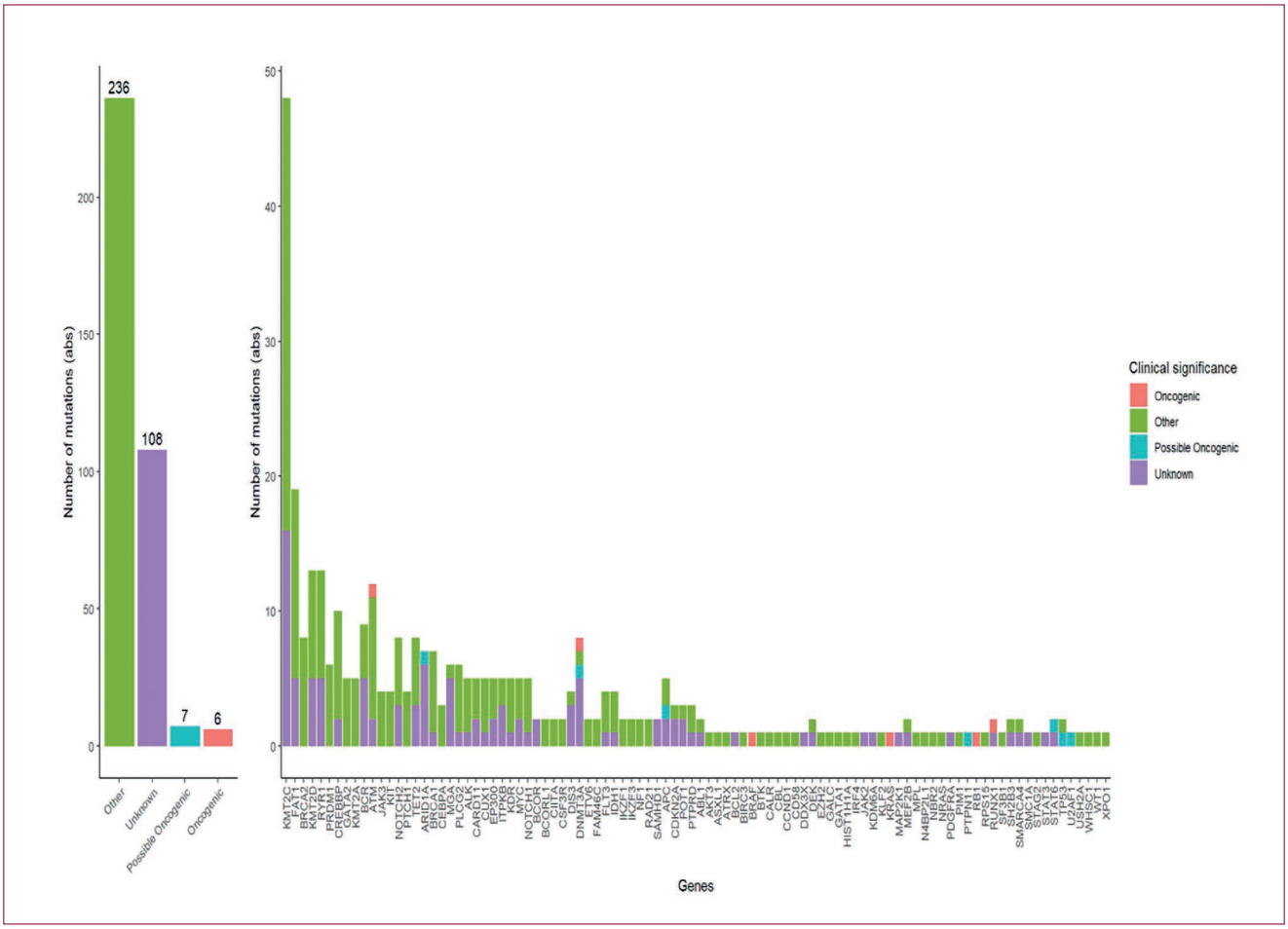

Figure 1. The mutational landscape of the studied population (n = 33)

The significance of endothelial dysfunction in patients with AL amyloidosis

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Introduction. The criteria for organ involvement and their prognostic significance in patients with AL amyloidosis (AL-A) are well-defined. However, the role of vascular damage in AL-A is poorly understood and its pathogenetic significance has not been determined. Endothelial (ED) dysfunction is important in vascular pathologies. The presence of ED in patients with AL-A has been demonstrated *in vitro* studies.

However, data on the concentration of biochemical markers of endothelial damage in these patients is extremely limited. Currently, there are no studies demonstrating the dynamics of changes in the content of these markers against the background of treatment.

Objectives. To study biochemical markers of endothelial dysfunction in patients with AL-A at diagnosis and after anti-tumor therapy.

Materials and methods. The study group included 30 patients with AL-A. The median age was 59 years (34–73 years). Asymmetric dimethylarginine (ADMA), big endothelin (bigET), and E-selectin levels were determined in serum using an enzyme-linked immunosorbent assay (ELISA). The study was performed before and after the completion of induction therapy (bortezomib, cyclophosphamide, dexamethasone). The comparison group consisted of 10 patients with multiple myeloma

(MM) with secretion of free light immunoglobulin chains. The control group comprised 10 healthy volunteers without chronic diseases with a median age of 56 years (45–60 years).

Results. In patients with AL-A, the median serum E-selectin level was significantly higher than in patients with MM and healthy volunteers (60 ng/mL vs 33.5 ng/mL vs 31 ng/mL respectively, p < 0.001). ADMA levels were also higher in patients with AL-A compared to the comparison group and the control group (0.63 μmol/L vs 0.51 μmol/L vs 0.39 μmol/L respectively, p = 0.03). No differences in bigET levels were found. An increase in at least one ED marker at diagnosis was observed in 27 (90 %) patients with AL-A.

After treatment, 16 (54 %) patients achieved a hematologic response (PR — 8 patients, VGPR — 5 patients, CR — 3 patients). An organ response was observed in 9 (30 %) patients (PR in 6 patients and VGPR in 3 patients).

After the therapy, patients who achieved a hematologic response showed a decrease in E-selectin and ADMA levels. The median E-selectin level decreased from 83 ng/mL to 58 ng/mL (p = 0.001). A decrease in ADMA levels was observed only in patients with hematologic and organ response to therapy (before treatment 0.67 μmol/L, after treatment 0.51 μmol/L, p = 0.008). Importantly, in 5 (55 %) of 9 patients with organ response, ADMA levels decreased to normal values. In the absence of hematologic response, no decrease in either E-selectin or ADMA levels was observed.

Conclusion. Ninety percent of patients with AL-A have laboratory signs of ED at disease debut. The decrease in ED marker levels upon achieving hematologic response confirms the pathogenetic significance of free light immunoglobulin chains in endothelial cell damage. It is possible that improvement in endothelial function after effective therapy and improved organ perfusion are among the pathogenetic links in organ response in systemic AL-A.

The results of morphological diagnosis of AL-amyloidosis

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Introduction. To diagnose amyloidosis, it is necessary to confirm the presence of amyloid in the tissue. To determine the type of amyloid, immunohistochemical and immunofluorescence methods of research, electron microscopy, as well as proteomic analysis are used.

Objectives. To analyze the results of histological studies, determine the frequency of amyloid detection in different sites, and evaluate the results of amyloid typing.

Materials and methods. A retrospective analysis of histological studies of 260 patients with AL-amyloidosis, observed at the R. M. Gorbacheva Scientific Research Institute of Pediatric Oncology, Hematology and Transplantation from January 2004 to August 2024, was performed. To confirm the presence of amyloid in tissues, a total of 560 biopsies were performed: 178 biopsies of targeted organs: kidneys (n = 144), heart (n = 9), liver (n = 5), lungs (n = 7), tongue (n = 4), lymph node (n = 7) and 382 biopsies of accessible loci: skin (n = 38), subcutaneous fat aspirate (n = 55), skin with subcutaneous adipose tissue (n = 31), bone marrow trepanobiopsy (n = 152), gastrointestinal tract (n = 41), buccal mucosa (n = 38). Congo red staining with birefringence in polarized light was used to detect amyloid. Amyloid typing was carried out using immunohistochemistry and immunofluorescence methods.

Results. Amyloid was detected in 100 % of heart, liver and tongue biopsies, in 95 % of kidney biopsies; however, other types of non-amyloid lesions were found in 5 % of cases with plasma cell dyscrasias (MIDD, etc.). In lymph nodes, amyloid was found in 88 % of cases. Amyloid was identified in the following accessible biopsy sites: in 84 % of skin biopsies, in 94.5 % of subcutaneous fat aspirates, in 77 % of skin biopsies with subcutaneous adipose tissue, in 51.3 % of bone marrow trepanobiopsies, in 70.6 % of gastrointestinal tract biopsies and in 92 % of buccal mucosa biopsies. Biopsy of 2 accessible sites revealed amyloid in 98 % of cases, biopsy of 3 sites — in 100 %. To determine the best combinations of available histological sites for diagnosing amyloidosis, various loci were analyzed in pairs.

Due to various reasons (small amount of amyloid, unavailability of reagents, etc.), the protein was not typed in all biopsies.

Amyloid typing in targeted organs was performed in kidney biopsies — 100 %, in heart — 78 %, in liver — 40 %, in tongue — 25 %, in lymph nodes — 28.6 %.

Amyloid typing at accessible sites was extremely rare: only in 3 skin biopsies and in 6 skin with subcutaneous adipose tissue biopsies.

Conclusions. The likelihood of detecting amyloid and its subsequent typing is higher in the case of a targeted organ biopsy. An alternative would be to perform biopsies of 2 accessible loci with almost 100 % detection of amyloid. However, it is necessary to improve sampling techniques, as well as methods for typing amyloid in the case of biopsy of accessible sites.

Immunophenotypic characteristics of malignant plasma cells in patients with AL-amyloidosis and multiple myeloma

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Introduction. Plasma cell neoplasms are characterized by a progressive course and require differential diagnosis at early stages in order to start treatment early. Thus, up to 40 % of patients with AL-amyloidosis are diagnosed more than 1 year after the first clinical symptoms appear and, when 25 % of these patients already have irreversible damage to the heart or kidneys, and such patients die within the first 12 months. The use of plasma cell immunophenotyping is important to clarify the clonality of an aberrant clone. AL-amyloidosis and multiple myeloma show similar clinical phenotypes.

Objectives. To compare the immunophenotypic characteristics of malignant plasma cells in the bone marrow of patients with AL-amyloidosis and multiple myeloma using flow cytometry.

Methods. The retrospective study included 40 patients, 19 patients (47.5 %) with AL-amyloidosis and 21 patients (52.5 %) with multiple myeloma, who underwent a complex of treatment at the Minsk Scientific and Practical Center for Surgery, Transplantation and Hematology in Minsk, Republic of Belarus. All patients underwent morphological and immunophenotypic examination of bone marrow cells. The diagnostic panel used included the determination of CD56, CD81, CD27, CD28, CD117 expression.

Results. The percentage of clonal plasma cells during immunophenotyping of bone marrow cells among the patients with AL-amyloidosis ranged from 1.12 to 12.5 (median 3 %), among the patients with multiple myeloma ranged from 2.4 to 52.4 (median 10.4 %). CD27 expression was found in 9 (42.8 %) patients with multiple myeloma, and in 16 (84.2 %) with AL-amyloidosis. Statistical processing of data on the immunophenotypic characteristics of plasma cells in patients with amyloidosis and multiple myeloma is presented in Table 1. Restriction of the light chains of λ among the patients from AL-amyloidosis group was 78.9 %, from multiple myeloma group — 23.8 %. The differential diagnosis of multiple myeloma and AL-amyloidosis is shown in Figure 1.

Table 1. Statistical processing of data on the immunophenotypic characteristics of plasma cells in patients with amyloidosis and multiple myeloma

CD expression	Multiple myeloma	AL-Amyloidosis
CD56+	14	13
CD56–	7	6
Chi-squared criterion value = 0.014; significance level = 0.906		
CD81+	7	4
CD81–	14	13
The value of Fisher's exact criterion = 0.72; significance level > 0.05		
CD27+	9	16
CD27–	12	3
The value of the exact Fisher criterion = 0.00982; the significance level is < 0.05		
CD28+	6	11
CD28–	14	8
Chi-squared criterion value = 3.083; significance level = 0.08		
CD117+	16	15
CD117–	5	4
The value of the exact Fisher criterion = 1; significance level > 0.005		

Conclusions. 1. The number of bone marrow plasma cells was significantly lower among the patients with AL-amyloidosis (median 3 %) compared with the patients from multiple myeloma group (median 10.4 %).

2. Restriction of light chains λ (78.9 % of patients) prevailed over the restriction of light chains κ. in bone marrow cells among the patients with AL-amyloidosis.

3. Detection and preservation of CD27 expression as a criterion for early diagnostics of AL-amyloidosis is statistically significant in patients with AL-amyloidosis ($p < 0.05$).

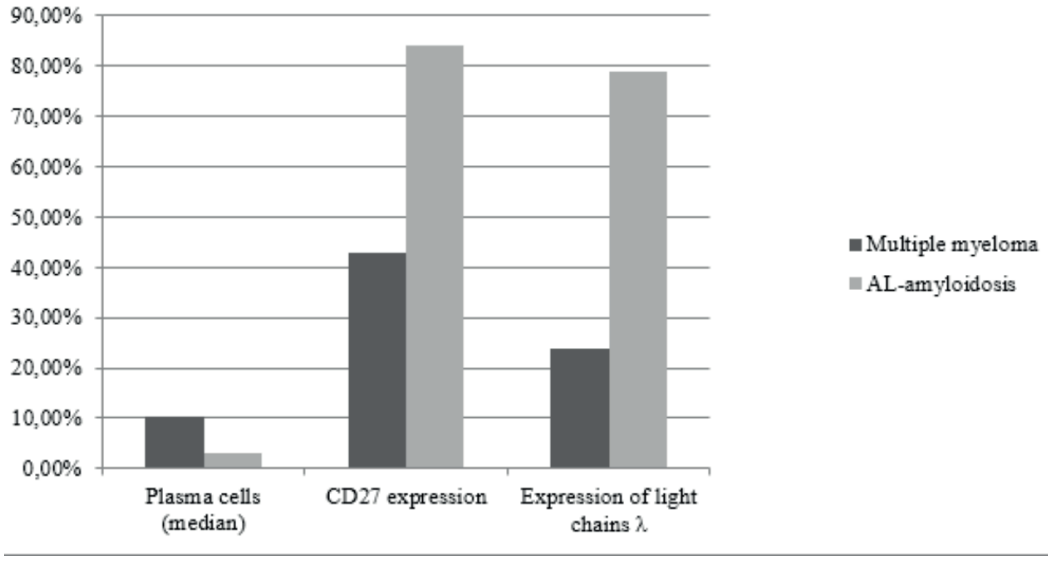

Figure 1. Differential diagnosis of multiple myeloma and AL-amyloidosis

Problems of therapy of recurrent and widespread localized AL amyloidosis

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Introduction. Treatment of localized AL amyloidosis (amyloidoma) involves surgical excision of amyloid masses. However, recurrences develop in 17–27 % of patients. There is no experience with systemic clonreducing therapy in patients with localized AL-A. We present the results of systemic antitumor therapy in three patients with recurrent and widespread localized AL-A.

Methods. Amyloid typing in biopsy specimens of affected organs was performed by immunohistochemical method. Chromogenic in situ hybridization (CISH) with probes to immunoglobulin light chains was used to verify the cell substrate. To exclude systemic AL-A, all patients underwent cytologic, histologic, and immunophenotypic examination of bone marrow. As clonreducing therapy, combinations of drugs including bortezomib, cyclophosphamide, dexamethasone, daratumumab, and lenalidomide were sequentially administered.

Results. In the first case (a 35-year-old woman), a recurrence of local AL-A with involvement of tonsils, larynx, trachea and bronchi was diagnosed 6 months after surgical treatment. Due to the development of acute airway obstruction, a tracheostomy tube was placed.No monoclonal secretion was detected, and systemic AL-A was excluded. Six courses of Dara-VCD therapy were performed, followed by Dara-Rd therapy for another year. The second case (a 70-year-old woman) was diagnosed with local AL-A with soft tissue involvement of the orbits, as a result of which the eye could not close.Bumpy skin neoplasms were visualized in the external parts of the orbits, ptosis of the upper eyelid of the right eye, slight exophthalmos were observed.In addition to both eyes, parotid and submandibular salivary glands were involved in the pathologic process, which were of stony density, measuring 6 × 4 × 5 cm and 5 × 3 × 6 cm. Previously, amyloid masses were repeatedly excised and radiation therapy was performed, after which a relapse developed again within a year.Due to the massiveness of the lesion and corneal perforation, the left eye was removed. Monoclonal secretion (SLC λ 545 mg/L) was detected in this patient, and systemic AL-A was excluded.VCd therapy was prescribed, followed by transfer to Dara-Rd due to insufficient reduction of monoclonal secretion.On the background of the second line of therapy, a reduction of SLC λ to 36.5 mg/L (by 94 %) was achieved.In the third case (a 50-year-old woman) there was a widespread process with AL-amyloid deposition in the form of tumor formations under the tongue, affecting tonsils, salivary and lacrimal glands. Monoclonal secretion was absent, and systemic AL-A was excluded. VCd therapy was prescribed, followed by Dara-Rd as second-line therapy.

At a median follow-up of 1 year, stabilization of the process was observed in all patients and some reduction in the size of the affected palatine tonsils and submandibular salivary glands was noted.

Conclusions. In all observations, single enmeshed plasma cells were inside amyloid masses and were absent in the bone marrow; target organ involvement was excluded. Monotypic plasma cells in amyloid masses could be detected only by CISH. Due to the absence of monoclonal secretion (in two cases) and the long time required for amyloid reduction, it was not possible to evaluate the efficacy of therapy. In this regard, targeting drugs of three classes were used. Stabilization was observed in all patients within a year.

Monoclonal gammopathy of renal significance and paraproteinemic kidney lesions in the practice of a nephrologist and hematologist

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Introduction. The concept of monoclonal gammopathy of renal significance (MGRS) was first introduced in 2012 and expanded in 2019. MGRS is a pathological condition caused by the proliferation of a clone of B lymphocytes or plasma cells that does not meet the criteria for initiation of treatment for oncohematological indications, but produces nephrotoxic monoclonal immunoglobulin leading to specific renal damage with a steady progression of renal dysfunction and a worsening prognosis of the disease. Paraproteinemic kidney disease (PKD) is caused by the presence of a lymphoproliferative disease in which the tumour clone secretes nephrotoxic monoclonal immunoglobulins. It is therefore advisable to involve both a haematologist and a nephrologist in the diagnosis of MGRS and PKD. Their diagnosis requires morphological examination of kidney tissue samples.

Objectives. To evaluate clinical and laboratory data and morphological variants of renal damage in MGRS and PKL.

Materials and methods. The data of 11 patients with morphologically verified MGRS and PKL treated in the Nephrology Department of the Krasnoyarsk Regional Clinical Hospital in 2020–2024 were retrospectively studied. To analyse demographic indicators, clinical, laboratory and morphological data, the study group was divided into two subgroups. The first subgroup included 6 patients with MGRS, the second subgroup — 5 patients with lymphoproliferative diseases.

Results. The study included 4 women (36.4 %) and 7 men (63.6 %), aged 28 to 80 years (65 (54; 67)). Among patients with PKD were 3 men (60 %) and 2 women (40 %), aged 42 to 80 years (65 (65;69)). MGRS was diagnosed in 6 patients, of whom There were 4 men (66.7 %) and 2 women (33.3 %). The age of the patients ranged from 28 to 67 years (61 (54;66)). All patients with MGRS and PKD had proteinuria, which amounted to 6.496 ± 6.604 g/day, while the total protein varied from 47.3 to 70.3 g/l. The glomerular filtration rate of the patients at the time of diagnosis of MGRS and PKD was 35.5 ± 41.5 ml/min/1.73 m^2. Fatal outcome occurred in 5 patients, representing 45.5 % (Table 1). It should be noted that there were no significant differences between the MGRS and PKD groups. There were no statistically significant differences in mortality rates (p = 0.855132).

Table 1. Clinical and morphological characteristics of patients

Patient serial number	Age (years)	Lymphoproliferative disease	Morphological variant of kidney damage	Proteinuria (g/day)	Total protein (g/l)	Glomerular filtration rate (ml/min/1.73m²)	Lethal outcome (months)
1	65	Marginal zone lymphoma	Proximal light chain tubulopathy	0.108	47.3	65	0,25
2	59	0	Proximal light chain tubulopathy	0.392	63	13	8
3	67	0	AL-amyloidosis	0.1	70.3	77	
4	28	0	Monoclonal deposit disease	3.56	63.8	25	
5	66	0	AL-amyloidosis	2.67	53.6	10	4
6	54	0	Monoclonal deposit disease	13.1	49.6	67	
7	42	Multiple myeloma	Proximal light chain tubulopathy	0.996	57.6	36	
8	65	Mantle cell lymphoma	Proximal light chain tubulopathy	0.782	56.3	6	
9	63	0	AL-amyloidosis	6.44	57	12	2
10	80	Multiple myeloma	AL-amyloidosis	9.01	58.3	46	2
11	69	Chronic lymphocytic leukemia	Monoclonal deposit disease	3	54.4	9	

Conclusion. The results obtained and the high mortality demonstrate the importance of early diagnosis of MGRS and PKL. It is worth noting that the lack of criteria for the diagnosis of lymphoproliferative disorders does not reduce the clinical significance of MGRS. The occurrence of proteinuria in patients with lymphoproliferative disease may indicate the development of paraproteinemic renal disease. The variety of forms of PKD requires the involvement of a morphologist for its diagnosis. At the same time, the presence of nephrotic proteinuria in a patient with a slight decrease in total protein may indicate the development of MGRS. Therefore, if a patient has monoclonal gammopathy of renal significance and paraproteinemic kidney disease, it is advisable to form a multidisciplinary team that includes a haematologist, nephrologist and pathologist.

Genetic polymorphisms and risk of cardiovascular dysfunction in patients with lymphoproliferative diseases

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Introduction. Cardiovascular dysfunction often accompanies treatment of malignant lymphomas. The concept of modern medicine assumes the earliest possible verification of adverse cardiovascular events, including the study of genetic polymorphisms.

Objectives. To identify the relationship of genetic polymorphisms with the risk of cardiovascular dysfunction in patients with lymphomas.

Materials and methods. In a prospective study we analyzed the relationship of genetic polymorphisms with the risk of cardiovascular dysfunction in 34 patients with follicular lymphoma, treated with R-CHOP. Patients were divided into 2 groups: the group with cardiovascular toxicity (n = 12, median age 42.4 years) and the group without cardiovascular toxicity (n = 22, median age 39.8).

Cardiovascular dysfunction was verified based on patient complaints, decrease in left ventricular ejection fraction >1 0 % of baseline or in absolute terms less than 53 % and/or a decrease in longitudinal systolic deformation of the left ventricle > 12 % of baseline, and/or an increase in NT-proBNP > 125 pg/ml. Assessment was carried out before treatment, after 3 and 6 cycles.

Results. All patients at the time of inclusion did not have a history of cardiovascular diseases, had a negative result of stress echocardiography, and were comparable in gender, age, body mass index, smoking history, physical examination data. Of the 347 selected candidate genes, significant ($p < 0.05$) associations were identified for 8 SNVs in the genes ABCB1, ABCC5, PRKAG2, RYR2, SLC22A7 and SCN5A. A comparative analysis of alleles showed that the carriage of allele 2 for all 8 SNVs increases the likelihood of developing cardiovascular dysfunction. Statistically significant associations were found for 3 SNVs, the carriage of the allele G of the rs2032582 variant of the ABCB1 gene (OR = 4.83; 95% CI 1.52–15.37; p = 0.004), the allele C of the rs10925391 variant of the RYR2 gene (OR = 3.29; 95% CI 1.05–10.30; p = 0.029) and the allele G of the rs4149178 variant The SLC22A7 gene (OR = 3.83; 95% CI 1.05–13.92; p = 0.032) increases the risk of cardiovascular dysfunction by 3.29–4.83 times. The analysis of genotypes identified 4 SNVs that increase the likelihood of developing cardiovascular toxicity: the T (TT+CT) allele of the rs1879257 variant of the ABCC5 (OR = 4.96; 95% CI 1.06– 23.16; p = 0.036), the G (GG+AG) allele of the rs4149178 of the SLC22A7 (OR = 6.3; 95% CI 1.3–30.53; p = 0.02), the T (TT+CT) allele of the rs13224758 of the PRKAG2 (OR = 5.56; 95% CI 1.02–30.33; p = 0.045) and allele C (CC+AC) of the rs10925391 of the RYR2 gene (OR = 6.01; 95% CI 1.24–30.09; p = 0.022). Two SNVs were associated with a reduced risk of cardiovascular dysfunction, the T (TT+TG) allele of the rs2032582 of the ABCB1 (OR = 0.18; 95% CI 0.04–0.87; p = 0.031) and the T (TT+TC) allele of the rs6797133 of the SCN5A (OR = 0.2; 95% CI 0.04–0.94, p = 0.036). Combination of GAC alleles rs2032582, rs3729856 and rs6797133 variants was associated with an increased probability of cardiovascular dysfunction (OR = 10.29; 95% CI 1.75–60.45, p = 0.009).

Conclusion. Further study of the prognostic significance of genetic polymorphisms in relation to the risk of developing cardiovascular dysfunction will optimize patient management, timely initiate cardioprotective strategies and avoid early and delayed adverse cardiotoxic events.

Sensitivity of tumor clone B-lymphocytes to vincristine as a prognostic factor of the effectiveness of therapy of lymphoproliferative diseases

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Introduction. One of the reasons for the poor effectiveness of treatment in patients with lymphoproliferative diseases is the resistance of tumor cells to chemotherapeutic agents (Chen J, Blood 2021, Urso A, Cancers (Basel), 2024).

Objectives. To analyse the relationship between the sensitivity of tumor clone B lymphocytes to vincristine and markers of multidrug resistance and response to therapy.

Materials and methods. B-cells isolated from peripheral blood and bone marrow of 43 patients with small B-cell lymphoma treated at the Novosibirsk Regional Clinical Hospital No. 2 were analysed. The sensitivity of the tumor cells to cytostatic drugs was assessed using the water-soluble tetrazolium salt (WST-1) assay. The expression level of the MDR1 gene mRNA was determined by real-time PCR (Figure 1), and the expression level of P-glycoprotein (P-gp) on the tumor cell membrane was determined by immunocytochemistry of bone marrow smears (Dallavalle S, Drug Resist. Updat. 2020, Kolesnikova M, J Pers Med. 2019, Mesci S, Int. J. Sci. Lett. 2019). The expression of MDR1 and P-gp was assessed before treatment and during chemotherapy. Response to treatment was evaluated after 4 cycles of induction chemotherapy. The non-parametric Spearman correlation coefficient (r) was used to determine the relationship between the indicators in the groups. Results were considered statistically significant at $p < 0.05$.

Results. The study showed a weak but statistically significant direct correlation between MDR1 expression and sensitivity to vincristine ($r = 0.25$, $p < 0.05$). No statistically significant correlation was found between P-gp expression and sensitivity to vincristine. Most tumor cells showed low levels of MDR1 mRNA expression (75 % of patients). Moderate expression was found in 20 % of patients and high expression in 5 % of patients. Patients whose tumor cells showed moderate and high levels of MDR1 expression had refractory/recurrent disease. In patients who had received prior chemotherapy for lymphoma or other tumors more than one year before the current episode, MDR1 and P-gp expression increased over time. On average, there was a direct correlation between the response in patients who received vincristine as part of their chemotherapy and the sensitivity of tumor B cells to vincristine ($r = 0.61$, $p < 0.05$). A correlation was found between tumor cell resistance to vincristine and ZAP-70 expression ($r = 0.61$, $p < 0.05$). All 9 patients who initially had high sensitivity to vincristine based on the WST1 test and received it as part of a chemotherapy regimen responded to therapy and went into remission; patients who were found to have in vitro resistance to vincristine (40 % of patients) proved to be refractory to chemotherapy regimens including vincristine.

Conclusion. The sensitivity of tumor clone B lymphocytes to vincristine may be considered a prognostic factor for the efficacy of therapy in lymphoproliferative diseases.

Experience with pomalidomide therapy in patients with relapsed/refractory multiple myeloma

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Background. Pomalidomide (POM) is an immunomodulatory and antineoplastic agent used in the treatment of multiple myeloma (MM). In vivo studies have demonstrated limited cross-resistance between lenalidomide and POM. POM has shown good efficacy in patients with relapsed and refractory (R/R) MM, including those refractory to both lenalidomide and bortezomib.

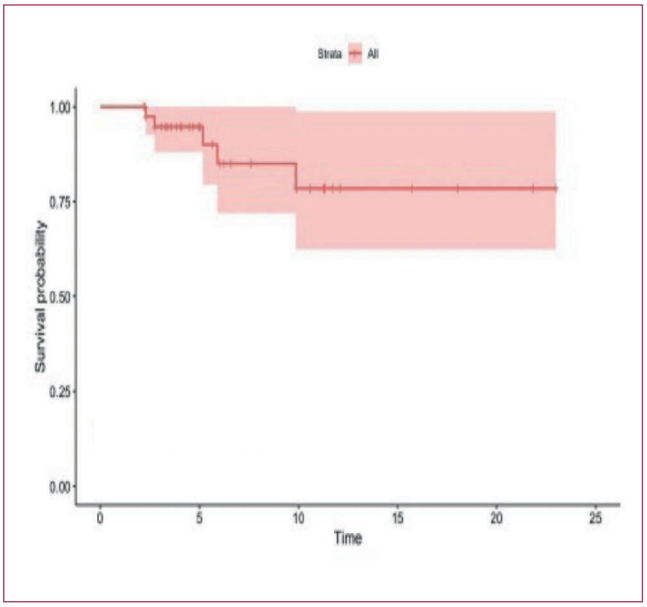

Figure 1. Overall survival

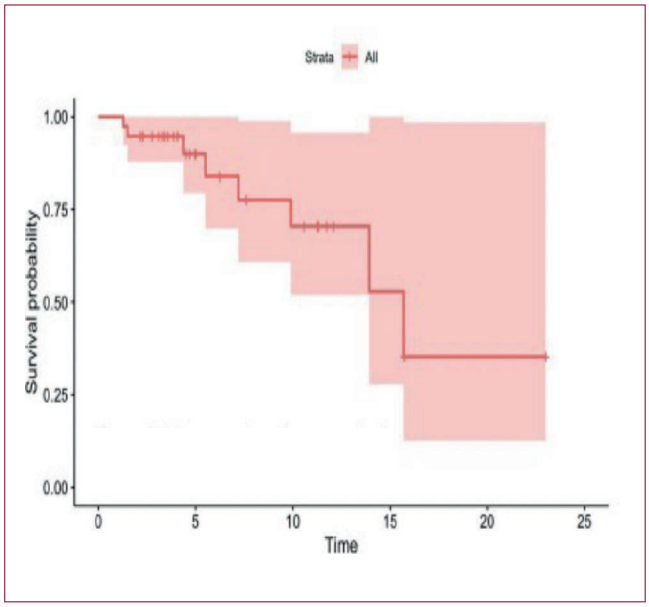

Figure 2. Progression-free survival

Methods. This study included 42 patients, all receiving pomalidomide-based chemotherapy (CT). The mean age was 53 years (range 35–72 years). The median follow-up period was 7.0 months (range 2.1–23 months). According to the Durie-Salmon (DS) staging system, 6 (14 %) patients were Stage I, 23 (55 %) were Stage II, and 13 (31 %) were Stage III.

Results. Response assessment was performed every 2 cycles of CT according to International Myeloma Working Group (IMWG) criteria. After the first 2 cycles of CT, response could be assessed in 26 patients; the objective response rate was 77 %. Of these, 4 patients (15 %) achieved a very good partial response, 9 (35 %) achieved a partial response, and 7 (27 %) achieved a minimal response. Six patients (23 %) were refractory to pomalidomide. The 12-month overall survival rate was 78 % (Figure 1) and the 12-month progression-free survival rate was 70 % (Figure 2). Pomalidomide therapy was well-tolerated; no treatment-limiting adverse events were observed.

Conclusion. Pomalidomide is effective and safe for use in combination with alkylating agents (cyclophosphamide, bendamustine), anthracyclines (pegylated liposomal doxorubicin), proteasome inhibitors (bortezomib, carfilzomib), monoclonal antibodies (daratumumab), and other agents in adult patients with R/R MM.

Real-world impact of minimal residual disease assessment in patients treated with venetoclax containing regimens with relapsed/refractory CLL

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Introduction. Minimal residual disease (MRD) status is a predictive marker for progression-free survival (PFS) in chronic lymphocytic leukemia (CLL) treated with venetoclax and anti-CD20 antibodies (Al-Sawaf, 2024; Kater, 2020). However, the relationship between MRD elimination and outcomes in venetoclax-treated, ibrutinib-refractory patients remains unclear. This study aimed to assess MRD dynamics and its predictive value in relapsed CLL patients treated with venetoclax-based regimens after ibrutinib compared to after chemoimmunotherapy (CIT).

Methods. This retrospective observational study analyzed two cohorts: patients with progression on ibrutinib and those with relapse/refractoriness after CIT. All patients had at least one MRD assessment in bone marrow via 6-color flow cytometry. Treatment included venetoclax monotherapy or in combination with an anti-CD20 antibody. MRD was assessed every 3–6 months until progression or death, with any missing values filled by the previous recorded value.

Event-free survival (EFS) was defined as time from therapy start to progression, and overall survival (OS) as time from therapy start to death. Kaplan-Meier estimates were used for time-to-event data, and comparisons of EFS and OS were made using log-rank. The Fisher exact test was used to compare proportional results.

Results. The study included 136 patients with relapsed CLL: 88 receiving venetoclax following ibrutinib and 48 after CIT (Table 1).

Table 1. Patients' characteristics

Characteristics	After ibrutinib	After CIT
Total patients	88	48
Median age (range)	65 (35–85)	65 (48–78)
Men/women	54/34	33/15
Binet stage at the start of therapy		
A	2 (2,3 %)	1 (2,1 %)
B	58 (65,9 %)	28 (58,3 %)
C	28 (31,8 %)	19 (39,6 %)
Deletion 13q	29/48 (60,4 %)	15/31 (48,4 %)
Deletion 11q	21/48 (43,8 %)	14/29 (48,3 %)
Trisomy 12	6/48 (12,5 %)	5/28 (17,9 %)
Deletion 17q	44/85 (51,8 %)	8/43 (18,6 %)
Unmutated IGVH variant	56/59(94,9 %)	30/39 (76,9 %)
Median of previously lines of therapy (range)	3 (1–9)	1 (0–6)
ECOG		
0	28 (31,8 %)	17 (35,4 %)
1	39 (44,3 %)	29 (60,4 %)
2	17 (19,3 %)	1 (2,1 %)
3	2 (2,3 %)	1 (2,1 %)
4	2 (2,3 %)	0
Therapy regimen		
MONOVen	32 (36,4 %)	4 (8,3 %)
GVen	44 (50 %)	40 (83,3 %)
RVen	12 (13,6 %)	4 (8,3 %)

In the CIT cohort, patients achieving undetectable (< 0.01 %) MRD gradually increased, peaking at 18 months. Progression occurred only in high MRD (> 1 %) cases, and Richter transformation occurred in one case with undetectable MRD (Figure 1, A).

Patients with ibrutinib refractoriness demonstrated asynchronous enlargement of progression group from either undetectable MRD group or low (0,01–1 %) and high groups (Figure 1, B). Meanwhile, landmark EFS and OS analyses revealed that patients with high, low and undetectable MRD represent 3 distinct predictive groups. The most perceptible predictive value was showed during MRD assessment at 3rd month of treatment (Figure 1, C–D). A group of patients with high MRD were primarily refractory, low — progressed within 2 years after treatment stop, undetectable — have not reached median EFS. The same but less prominent trends were observed for 6th and 12th months of observation for EFS and OS.

Patients were stratified by established prognostic factors (age ≥ 65, del(17p), and IGHV status), with no significant differences in MRD dynamics across these subgroups (Figure 1, E–J).

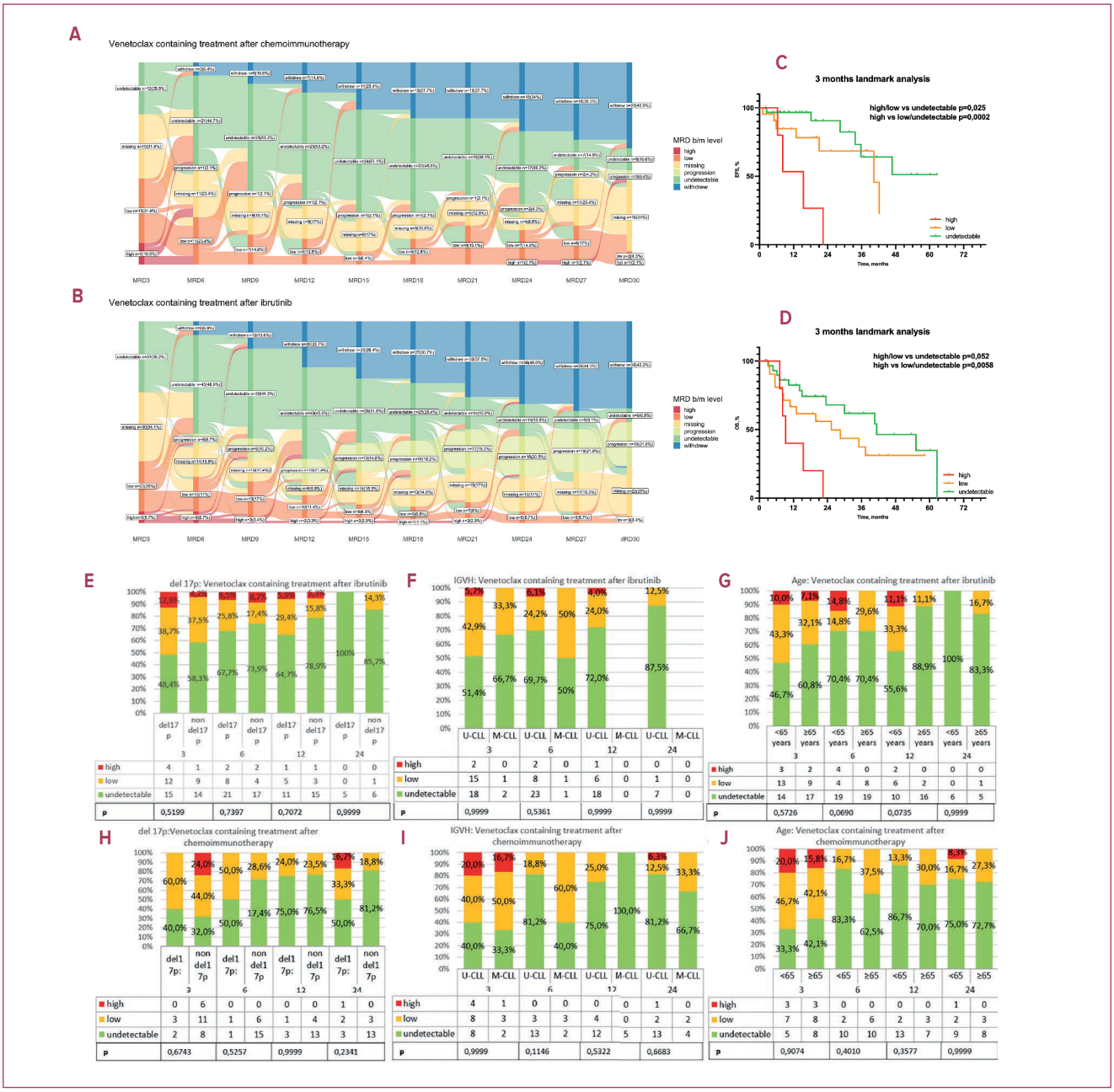

Figure 1. (A) MRD swimmer's plot: venetoclax containing treatment after chemoimmunotherapy. (B) MRD swimmer's plot: venetoclax containing treatment after ibrutinib. (C) Event-free survival depending on the level of MRD. (D) Overall survival depending on the level of MRD. (E, F, G) MRD dymamics in patients receiving venetoclax after ibrutinib depending on del(17p) (E), IGHV status (F), and age (G). (H, I, J) MRD dymamics in patients receiving venetoclax after chemoimmunotherapy depending on del(17p) (H), IGHV status (I), and age (J)

Conclusion. In ibrutinib-pretreated patients, MRD status at three months stratified distinct risk groups, indicating primary refractory, early relapse, and late relapse subgroups. Unlike CIT-treated patients, progression occurred even in those with undetectable MRD in the ibrutinib-refractory cohort, suggesting a limited negative predictive value of MRD for these patients. Prognostic factors such as age, IGHV mutation status, and 17p deletion did not significantly impact MRD dynamics in both cohort.

This study suggests that MRD in bone marrow may be a less reliable biomarker for patients with ibrutinib refractoriness, highlighting a potential need for alternative MRD assessment sites, such as lymph nodes or by cell-free DNA analysis, to improve prognostic accuracy.

BENIGN HEMATOLOGY AND TRANSFUSIOLOGY

Development of oxygen-carrying medications suitable for use as blood substitutes in emergency situations

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Emergency situations when immediate blood transfusion is required are quite common in medicine, but blood of the right group, Rh factor and in the right quantity is not always available. In this case, blood substitutes based on the function of oxygen transfer on the basis of perfluororganic compound (PFOC) can be useful. Such blood substitutes are universal, since they have neither blood group nor Rh factor. They are produced on the basis of synthetic components, so they are hypoallergenic for most patients and absolutely sterile.

However, the widely known blood substitute 'Perftoran', which passed clinical trials and registered as a pharmaceutical medication, had a very serious disadvantage. It was unstable during prolonged storage as a liquid, so it was necessary to store it only in frozen form at a temperature not higher than -18°C. Before use, it had to be defrosted slowly, because in case of rapid defrosting it lost its effects - the size of emulsion micelles increased, as a result of which the emulsion was destroyed.

The group of authors of the Russian Federation patent No. 2469714 from the Federal State Unitary Enterprise 'State Scientific Centre "NIOPIK" came the closest to creating a stable medication with gas transfer function based on perfluororganic compounds. In order to increase the stability of the medication, they replaced polymeric non-ionic emulsifiers (Poloxamer P407, proxanol 268) or amphoteric emulsifiers - phospholipids, used in most similar developments, with newly synthesised, original low molecular weight anionic emulsifiers. Characteristics of newly developed emulsions in comparison with known samples are given in Table 1.

Using such emulsifiers, it was possible to obtain medications with oxygen transfer function based on perfluororganic compounds, which withstood storage in liquid form in a refrigerator at temperatures ranging from +4 to +8 °C for three years (Figure 1) and one year of storage at room temperature. The control was carried out before the change of the emulsion micelle size. During the whole storage period, this parameter of perfluororganic compounds changed insignificantly, while the appearance of the medication remained practically unchanged — it was a transparent liquid with weak violet or bluish opalescence, without traces of stratification and noticeable turbidity.

Table 1. Characteristics of perfluororganic compounds emulsions

N°	Name of the perfluororganic compounds emulsion	Perfluorocarbons content, wt. %	Surfactant content, %	Average emulsion particle size, nm	Viscosity, centipoise
1	Perftoran (Russian Federation)	20	4	250	4.0
2	Fluosol-DA (USA)	20	N/A	N/A	N/A
3	Oxyfluor (USA)	20	N/A	220–250	4.0
4	Oxygent (USA)	20	N/A	160/180	4.1
5	Faberlic (Russian Federation)	20	6	220	25.0
6	Oxycyte (USA)	50	4	200–300	N/A
7	Perftorox -20 (Russian Federation)	20	1	190	1.2
8	Perftorox -40 (Russian Federation)	40	2	200	2.1
9	Perftorox -50 (Russian Federation)	50	2,5	210	3.8
10	Perftorox -60 (Russian Federation)	60	3	220	6.2

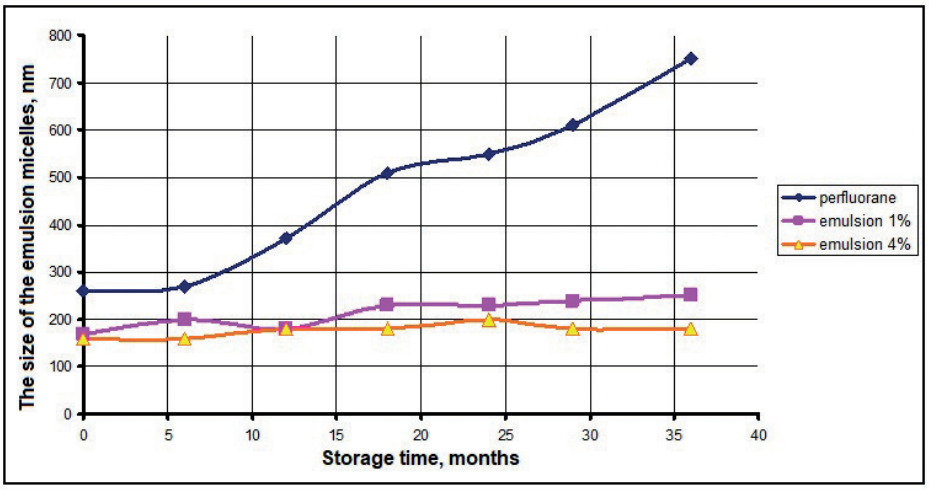

Figure 1. Dependence of particle sizes in 20% perfluororganic compounds emulsions on the time of storage in the refrigerator

The emulsification technology was also changed, instead of high-pressure emulsifier the ultrasonic emulsification unit was used, which allowed to sharply simplify the emulsification technology, reduce the emulsification process time and simplify the scaling, which leads to a significant increase in the productivity of such a unit in relation to high-pressure emulsifiers. Emulsification control is carried out by laser scattering method, according to the spectrum of emulsion micelle size distribution. This allows, if necessary, to adjust the emulsification process within certain limits and always obtain emulsion with the specified size distribution of emulsion micelles.

A whole series of medications with different oxygen capacity and different methods of application can be developed, for example, a concentrate can be obtained, which will be diluted with physiological solution to the required concentration at the place of application.

Diverse clinical manifestations and complexities of acquired hemophilia a: insights from four case studies

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Acquired hemophilia A is a rare and life-threatening autoimmune disease that is accompanied by the formation of antibodies to factor VIII of the blood coagulation system. This pathogenetic mechanism leads to severe, often spontaneous bleeding and its complications. The disease is of particular clinical importance in patients with comorbidities requiring a special approach to therapy. We would like to present four different clinical cases of patients with this disease. These clinical cases reflect the complexity of the management of patients with acquired hemophilia as well as comorbidities. This experience will be useful to clinicians for a successful diagnosis and a comprehensive approach to the treatment of the disease.

1. Acquired hemophilia in a postpartum woman complicated by massive hemorrhage. A 32-year-old woman presented with massive haemorrhage in the right tibia, occurring 4 months after delivery. Coagulogram showed prolonged APTT (104 sec) and critically low factor VIII (3.2 %), with confirmed inhibitor (5 Bethesda units). Rituximab therapy stabilised the patient and led to recovery of clotting factors. This case highlights the autoimmune hemorrhagic syndrome in the postpartum period and the efficacy of Rituximab.

2. Acquired hemophilia in patient with peptic ulcer disease and recurrent bleeding. A 73-year-old female patient was admitted with severe ulcer bleeding (Forrest 2B) from the antral stomach. Examination confirmed acquired hemophilia A with a reduced factor VIII level of 8.3 %. The patient underwent three endoscopic hemostasis procedures combined with anti-inhibitor

therapy, which eventually stabilised his condition. This case highlights the importance of a comprehensive approach combining anti-inhibitor therapy with effective control of hemostasis in the ulcer, which is crucial for the management of patients with overlapping conditions such as peptic ulcer disease and acquired hemophilia.

3. A patient with multiple metachronous neoplasia and autoimmune inhibitory hemophilia. A 73-year-old patient with chronic myeloid leukaemia and concomitant chronic myelomonocytic leukaemia presented with signs of bleeding. Examination revealed a low-responsive factor VIII inhibitor (2.5 Bethesda units). Treatment with Rituximab and anti-inhibitor drugs improved hemostatic parameters. This case highlights the complexity of treating acquired hemophilia in patients with multiple oncohematological diseases requiring support with anti-inhibitors.

4. Acquired hemophilia A in patient with spinal osteomyelitis and recurrent hemorrhages. A 79-year-old patient was admitted in July 2024 with massive hematomas and subconjunctival hemorrhage due to acquired hemophilia A. Initial therapy with Rituximab and Feiba partially stabilised the condition. Later, the patient developed osteomyelitis of the lumbar spine, confirmed by MRI and CT. Cytosis (6400 cells/μl) and Staphylococcus aureus were detected in the cerebrospinal fluid. Despite rituximab therapy, APTT remained high (> 60 sec), indicating persistent inhibitory activity. The patient was successfully treated with antibiotics and maintenance anti-inhibitor therapy, reducing the risk of bleeding and eliminating the infection.

Conclusion. The four presented cases demonstrate the diversity of clinical manifestations of acquired haemophilia A and highlight the need for a multidisciplinary and individualised approach in the treatment of such a rare pathology. In each case, combined therapy with Rituximab and anti-inhibitor drugs was used, which allowed to control the hemorrhagic syndrome.

CLINICAL CASES

CAR-T cell refractory multiple myeloma in young patient — a clinical case report

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Introduction. A 40-year-old male patient presented with complaints of general weakness and mild chest/costal pain syndrome from January 2017. CBC showed mild anemia with HGB — 106 g/l. Biochemical parameter tests showed very high total protein levels: 140 g/l, albumin — 40 g/l, LDH — 330 u/l, creatinine — 115 mcmol/l, B2-microglobulin — 2.58 mcg/ml. CT showed multiple cranial and spinal lytic lesions, up to 20 × 10 mm. Multiple myeloma was suspended and additional tests were performed: IFE — IgGλ 68,57 g/l, BJP — not detected, BM examination — 43.2 % plasma cells, del (17p13) — in 20.0 % plasma cells, and monosomy 13 were detected by FISH. Patient was diagnosed with multiple myeloma, IgGλ, R-ISS II.

Treatment. Patient was treated as follows (RosNIIHT, Saint Petersburg): 1st line: ×6 VD 31.03.2017, ×2 VDPACE 02.09.2017 — PR; 2nd line: ×4 RVD 09.11.2017 with tandem auto-HSCT 13.02, 04.06.2018; PD 09.2021; 3rd line: ×16 PVD (DREAMM — 8, NCT04484623) 12.10.2021 — PR, PD — 09.2022; 4th line: ×4 DaraIxaDex 10.12.2022, PD 04.2023; 5th line: ×2 DPACE 27.04.2023, PD 07.2023; 6th line: ×2 KBD 04.08.2023; 09.2023 — SD.

Because of the patient's young age, disease prognosis, and absence of further treatment modalities, the patient was recommended for CAR-T cell therapy. A special combination was used for achieving response in 7th line: IsaPomCarfDacVenAtraDex 10.2023 (ККВ№2, Vladivostok) — PR 11.2023.

After confirmation of the PR patient was referred for CAR-T cell consolidation (BOE Chengdu Hospital): 14.12.2023: 4sCAR BCMA/CD138, 2,8 × 10^8/kg + 4sCAR19, 2,6 × 10^8/kg + 02.01.2024: 4sCAR-317, 2 × 10^8/kg + 4sCAR-CS1, 2 × 10^8/kg.

All CAR-T cell populations were rapidly decreased by the end of Jan 2024 and patient continued with both CP and BP from 02.2024. There were 81 % plasma cells in BM. BM FISH was showed amp(1q21) CKS1B; del(1p32) CDKN2C in 72 % and del(17p13) TP53 — 72,5 % plasma cells correnspondingly.

For the next attempt, in 8th line, a CarfDexVenNivoAza combination was used — SD 04.2024, followed by anti-CD10 CAR-T cell.

Despite all treatment approaches, rapid CP with multiple soft tissue and bone marrow lesions, CNS symptomatic, pancytopenia, hypocoagulation, and BP (M-protein — 74 g/l) occurred by 05.2024. Death was reported at 13.06.2024.

Conclusions. Multiple myeloma is still an incurable disease and is usually more aggressive in younger individuals. Early treatment intensification is associated with a longer remission period and a better quality of life. CAR-T cell therapy consolidation should be used in earlier lines of treatment, if possible. Post CAR-T relapses have the worst prognosis and a very short survival period.

Partial response to venetoclax and bendamustine therapy in a case of de novo T-prolymphocytic leukemia

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Background. T-prolymphocytic leukemia (T-PLL) is a rare and aggressive hematologic malignancy. A portion of patients can be cured with alemtuzumab induction followed by allogeneic hematopoietic stem cell transplant. However, nowadays alemtuzumab is accessible only through a distribution program from the manufacturer, therefore its use in Russian Federation is virtually inaccessible. Thus, there is no established standard treatment to T-PLL, and different centers try to implicate other forms of therapy.

Methods. We report a case of a 65-year-old woman with de novo T-PLL who was treated with bendamustine and venetoclax with following

allogeneic hematopoietic stem cell transplant consolidation from her daughter.

Results. Treatment with bendamustine and venetoclax resulted in a partial response including marked reduction of the peripheral lymphocyte count, improvement in anemia and thrombocytopenia, splenomegaly and pleural effusion resolution, and a numerical reduction in the percentage of prolymphocytes in the bone marrow. The combination was well tolerated with the exception of moderate neutropenic infection.

Conclusion. This case shows promising results of venetoclax and bendamustine combination as a viable non-alemtuzumab-based treatment option for de novo T-PLL.

Introduction. T-cell prolymphocytic leukemia (T-PLL) is an aggressive mature T cell neoplasm that typically involves peripheral blood, bone marrow, lymph nodes, liver, spleen, and skin. It is a very rare disease that comprises 2 % of cases of mature lymphocytic leukemias in adults aged > 30 years [1].

It is characterized by the proliferation of small to medium-sized prolymphocytes with a mature post-thymic T-cell phenotype [2], showing expression of CD2, CD5, CD3, and CD7. In 60 % of cases, the cells are CD4-positive and CD8-negative. In 25 %, they coexpress CD4 and CD8, a feature which is almost exclusive to T-PLL. CD52 is usually expressed at high density [3].

The most frequent chromosome abnormality in T-PLL involves inversion of chromosome 14 with breakpoints in the long arm at q11 and q32 with involvement of the TRA locus and TCL1A and TCL1B. Abnormalities of chromosome 8 are common. Molecular and FISH studies also show deletions at 11q23 (the locus for ATM). Abnormalities of chromosomes 6 (present in 33 % of cases) and 17 (in 26 %) have also been identified in T-PLL [4].

The disease course is aggressive, with a median survival of 1–2 years. Although no standard curative option exists, the use of the monoclonal anti-CD52 antibody, alemtuzumab, has improved the outcome and survival in T-PLL [5], allowing for high-dose therapy options aimed at eradicating the disease, with a minority experiencing long-term disease-free survival following allogeneic stem cell transplantation [6, 7]. However, the access to Alemtuzumab in Russian Federation is extremely limited due to a lack of its commercial supply and distribution program from the manufacturer, making such therapy option unavailable for the majority of T-PLL patients.

We report a case of newly diagnosed T-PLL that achieved partial response with bendamustine and venetoclax with following allogeneic hematopoietic stem cell transplant consolidation from her daughter.

Case presentation. A 65-year-old woman with no significant medical comorbidities presented to our hematology unit with progressive lethargy and dyspnea on exertion for the past 2 months. She had no significant family history.

At presentation, she had a score of 4 on the Eastern Cooperative Oncology Group performance-status scale (ECOG). On physical examination, she had macular rash on her face and trunk (Figure 1, A), facial and periorbital swelling (Figure 1, B), palpable spleen of 15 cm, mild lymphadenopathy up to 1.5 cm, dullness to percussion and decreased breath sounds over both lungs.

Her complete blood count revealed normochromic normocytic anemia of 7.0 g/dL with leukocytosis of 869×10^9/L (predominantly lymphocytosis) and platelet count of 62×10^9/L. The other laboratory parameters on presentation are shown in Table 1.

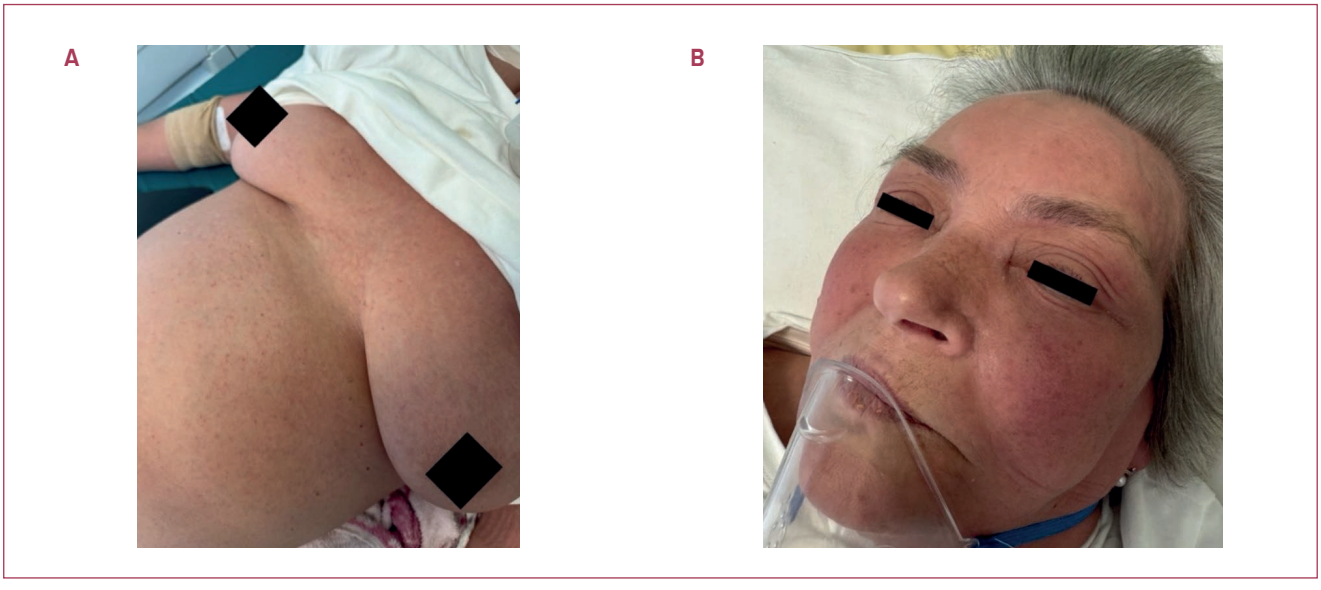

Figure 1. Skin findings at the presentation. (A) Macular rash on the trunk; (B) facial and periorbital swelling

Table 1. Laboratory parameters at the baseline

Laboratory parameters	Values (unit and normal range)
Hemoglobin	7.0 (13.5–16 g/dL)
Total white cell count	869.6 (4–9 × 10^9/L)
Absolute lymphocyte count	759 (1.2–3.2 × 10^9/L)
Platelet	62 (150–400 × 10^9/L)
Total protein	57.6 (66–83 g/L)
Albumin	35.4 (35–55 g/L)
Creatinine	153 (40–100 micromol/L)
Bilirubin	13.9 (5–21 micromol/L)
Lactate dehydrogenase (LDH)	2200 (90–180 U/L)
Serum uric acid	692 (68–117 micromol/L)
Serum calcium	2.1 (2.2–2.65 mmol/L)
Serum phosphate	0.9 (0.81–1.45 mmol/L)
Aspartate aminotransferase	51.95 (0–35 U/L)
Alanine aminotransferase	14.8 (0–35 U/L)
C-reactive protein (CRP)	3.1 (0–6 mg/L)
HIV 1 and 2 serology	Non-reactive

Ultrasound of the pleural spaces and the abdomen revealed bilateral pleural effusion up to 1.6 L and splenomegaly (189 × 87 mm).

A peripheral blood film (Figure 2) showed a marked hypercellularity of abnormal lymphoid cells which were pleomorphic, moderate to large in size, and contained multiple coarse chromocenters in convoluted nuclei with irregular nuclear outline and scanty cytoplasm. Bone marrow examination was not initially performed because of substantial peripheral leukocytosis.

Peripheral blood flow cytometry analysis showed 99 % abnormal population of cells expressing CD2, CD3, CD4, TCRab, CD5. The cell population was negative for CD8, CD16, CD56, CD19.

Fluorecent in situ hybridization (FISH) of the abnormal lymphocytic population revealed monoallelic deletion of TP53 (17p13), cMYC (8q24) amplification, and 22q11 deletion in > 90 % of cells, TCRAD (14q11) translocation with unidentified partner in 62 %, 11q23 deletion in 57 %, trisomy of 16th chromosome and monosomy of 9th chromosome in 20 % and 16 %, respectively.

In view of the peripheral blood and flow cytometry findings, as well as clinical presentation she was diagnosed as having active T-PLL. Diagnostic criteria of T-PLL are listed below in Table 2.

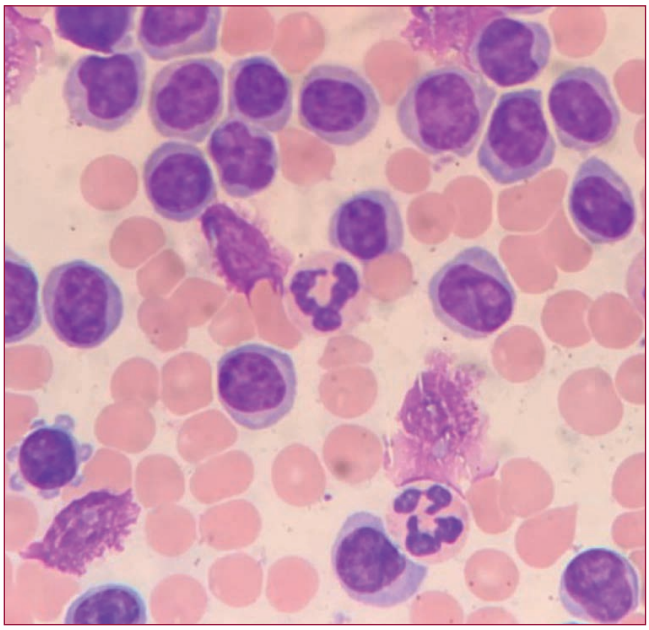

Figure 2. Peripheral blood film at the presentation shows showed marked hypercellularity of abnormal lymphoid cells which were pleomorphic, moderate to large in size, and contained multiple coarse chromocenters in convoluted nuclei with irregular nuclear outline and scanty cytoplasm.

Table 2. Consensus criteria for diagnosis, staging, and treatment response assessment of T-cell prolymphocytic leukemia (Staber P, Herling M, Bellido M, et al, Blood 2019;134:1132–1143)

The diagnosis of T-PLL is established if all 3 major criteria are met or if the first 2 major criteria and 1 minor criterion are met.	
Major Criteria	**Minor Criteria**
> 5 × 10 %L cells of T-PLL phenotype in peripheral blood or bone marrow	Abnormalities involving chromosome 11 (11q22.3; ATM)
T-cell clonality (by PCR for TRBITRG, or by flow cytometry)	Abnormalities in chromosome 8: idic(8)(p11), t(8;8), trisomy 8q
Abnormalities of 14q32 or Xq28 OR expression of TCL1A/B, or MTCP1*	Abnormalities in chromosomes 5, 12, 13, 22, or complex karyotype
	Involvement of T-PLL–specific site (eg, splenomegaly, effusion
*Cases without TCL1A, TCL1B, or MTCP1 rearrangement or their respective overexpression are collected as TCL1-family negative T-PLL.	

Due to the lack of clinical guidelines and access to Alemtuzumab-based therapy across Russian Federation, we decided to initiate bendamustine and venetoclax combination therapy based on growing body of literature supporting such regimen as a viable alternative treatment option [8].

She received 2 cycles of 4 days of bendamustine at dose of 100 mg, and started venetoclax since Day 3 of the first cycle with ramp-up from 100 mg to 800 mg during the first 2 weeks of therapy with aggressive infusion support. Therapeutic two-sided thoracocentesis was made to relieve dyspnea. Adverse events included laboratory tumor lysis syndrome with no clinical manifestations, neutropenia (grade 4), anemia (grade 3) and thrombocytopenia (grade 3), according to CTCAE 5.0. Non-hematologic complications included neutropenic fever attributed to pneumonia, which was successfully treated with antibiotic therapy.

Treatment resulted in complete resolution of fatigue and lethargy, skin lesions, pleural effusions, splenomegaly, improvement in erythrocyte and platelet count, and normalization of lymphocyte count. Bone marrow aspiration at Day 56 revealed 10.5 % of prolymphocytes. Criteria for partial response (PR) were met according to T-PLL ISG criteria (Table 3).

CR, all of the criteria have to be met; CRi, all CR criteria of group A are met but at least 1 in B is not achieved; PR, at least 2 parameters of group A and 1 of group B need to improve if previously abnormal; PD, at least 1 of the criteria of group A or group B has to be met; SD, all the criteria have to be met, constitutional symptoms alone do not define PD; SLD, sum of long-axis diameters of up to 3 target lesions. *Pleural or peritoneal effusion, skin infiltration, or CNS involvement. Staber P, Herling M, Bellido M, et al., Blood 2019;134:1132–1143.

After the second therapy cycle the patient and her relatives, including two siblings and the daughter,

Table 3. Consensus criteria for diagnosis, staging, and treatment response assessment of T-cell prolymphocytic leukemia

Group and Parameter	CR (all met)	PR (≥ 2 in A and ≥ 1 in B)	SD (all met)	PD (≥ 1 in A or B met)
Group A Lymph nodes	Long-axis diameters to < 1.0 cm	Decrease ≥ 30 % in SLD	Change of – < 30 % to + ≤ 20 %	Increase > 20 % in SLD
Spleen size	Spleen size < 13 cm	Decrease ≥ 50 % in vertical length beyond normal from baseline	Change of –49 % to +49 % beyond normal from baseline	Increase ≥ 50 % in vertical length beyond normal from baseline
Constitutional symptoms	None	Any	Any	Any
Circulating lymphocyte count	<4 × 10^9/L	≤ 30 × 10^9/L and decrease ≥ 50 % from baseline	>30 × 10^9/L or change of –49 % to +49 %	Increase ≥ 50 % from baseline
Bone marrow	T-PLL cells < 5 % of mononuclear cells	Any	Any	Any
Any other specific site involvement*	None	Any	Any	Any
Group B Platelet count	≥ 100 × 10^9/L	≥ 100 × 10^9/L or increase ≥ 50 % from baseline	Change of –49 % to +49 %	Decrease ≥ 50 % over baseline
Hemoglobin	≥ 11.0 g/dL (untransfused)	≥ 11 g/dL or increase ≥ 50 % from baseline	11.0 g/dL or < 50 % from baseline, or change < 2 g/dL	Decrease of ≥ 2 g/dL from baseline
Neutrophils	≥ 1.5 × 10^9/L	≥ 1.5 × 10^9/L or increase ≥ 50 % from baseline	Change of –49 % to +49 %	Decrease of ≥ 50 % from baseline

Table 4. Results of high-resolution HLA-typing of the patient and her relatives, which show complete HLA compatibility with patient's daughter

HLA locus	Patient	Patient's Daughter	Patient's Sister	Patient's Brother
A	02:01 25:01	02:01 25:01	02:01 25:01	02:01 03:01
B	13:02 18:01	13:02 18:01	13:02 18:01	13:02 35:01
C	06:02 12:03	06:02 12:03	06:02 12:03	06:02 04:03
DQB1	02:02 06:02	02:02 06:02	02:02 06:02	02:02 05:02
DRB1	07:01 15:01	07:01 15:01	07:01 15:01	07:01 01:01

underwent a high-resolution HLA-typing. Based on the results, the patient and her daughter emerged as fully HLA-matched (10/10 HLA loci; Table 4). Results were additionally reassessed, and no changes were made to the final conclusion. Out of siblings, one (sister) was fully matched, and the other (brother) was haploidentical.

Subsequently, the patient underwent consolidative therapy with a 10/10 matched peripheral blood stem cell transplant from her daughter with Flu/Be reduced-intensity conditioning (bendamustine 300 mg on days –6 to –5, fludarabine 50 mg on days –6 to –2). She received graft-versus-host (GVHD) prophylaxis with cyclophosphamide (1500 mg on day +3 and +4), abatacept (500 mg on day –1, +5, +14), tacrolimus, and vedolizumab (300 mg on day –1 and +14). On day +13, donor bone marrow engrafted successfully. No acute GVHD was registered.

Discussion. Very few trials have been conducted and published on T-PLL. Initial attempts with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or CHOP-like regimens have been particularly discouraging [9]. Up until now, there is currently no drug that carries FDA or EMA approval status for T-PLL [10]. The best first-line treatment to achieve a CR is IV alemtuzumab (anti-CD52) with an ORR higher than 90 % and PFS between 8 and 11 months [5, 11, 12]. Patients achieving a complete remission should be considered for consolidation therapy with an allogeneic stem cell transplant (aSCT), which provides 4-year overall survival in 30 % of patients [6, 7, 13, 14].

The point of interest in this case lies in a complete matching of HLA loci between the patient and her child. There are two explanations of this finding, first being an identical HLA-genotype of the father, which can be possible in close-relative marriages [15]. The second explanation is uniparental disomy, when a person receives two copies of a chromosome or its part from one parent and no copy from the other [16]. Uniparental disomy has been found to occur in about 1 in 2.000–3.500 births [16], thus the probability of inheriting the pair of 6th chromosomes from one parent is roughly 1 in 45.000–80.000 births. Although we did not investigate HLA-genotype of the patient's husband, either of these versions is unique and extraordinary, and, hopefully, such coincidence may translate in fewer treatment-related, better prognosis, and potential option for second aSCT from another fully-matched related donor in case of the relapse.

Despite the high OR with alemtuzumab therapy, the majority of patients ineligible for stem cell transplantation will relapse, with a median duration of remission for responders of less than 2 years [4]. After 1st relapse, the prognosis of T-PLL is dismal. There are preliminary in vitro and in vivo data to suggest that novel agents such as BCL2-inhibitors, HDAC inhibitors, and JAK3 inhibitors may have a therapeutic effect in relapsed/refractory T-PLL [17–21].

The literature regarding non-alemtuzumab-based first-line therapy is limited. However, in situation, when anti-CD52 antibody is inaccessible or contraindicated, there is an immense dilemma on which regimen to choose. Several studies show bendamustine and pentostatin front-line therapy as a feasible, yet not impressive alternative to alemtuzumab-based approach [22, 23].

The presented case shows a good response to venetoclax and bendamustine therapy of newly diagnosed T-PLL with acceptable toxicity. However, there are insufficient data to conclude, weather this regimen provides a durable remission and is a viable alternative to alemtuzumab. As it stands yet, non-alemtuzumab-based treatment of patients with de novo T-PLL remains a significant unmet need.

References

1. Matutes E, et al. Clinical and laboratory features of 78 cases of T-prolymphocytic leukemia. Blood. 1991; 78: 3269–74.

2. Matutes E, Garcia Talavera J, O'Brien M, Catovsky D. The morphological spectrum of T-prolymphocytic leukaemia. Br J Haematol. 1986; 64: 111–24.

3. Dearden CE. T-cell prolymphocytic leukemia. Med Oncol. 2006; 23: 17–22.

4. Staber PB, et al. Consensus criteria for diagnosis, staging, and treatment response assessment of T-cell prolymphocytic leukemia. Blood. 2019; 134: 1132–1143.

5. Dearden CE, et al. High remission rate in T-cell prolymphocytic leukemia with CAMPATH-1H. Blood. 2001; 98: 1721–1726.

6. Wiktor-Jedrzejczak W, et al. EBMT prospective observational study on allogeneic hematopoietic stem cell transplantation in T-prolymphocytic leukemia (T-PLL). Bone Marrow Transplant. 2019; 54: 1391–1398.
7. Krishnan B, et al. Stem cell transplantation after alemtuzumab in T-cell prolymphocytic leukaemia results in longer survival than after alemtuzumab alone: a multicentre retrospective study. Br J Haematol. 2010; 149: 907–910.
8. Hampel PJ, et al. Venetoclax treatment of patients with relapsed T-cell prolymphocytic leukemia. Blood Cancer J. 2021; 11: 47.
9. Catovsky D, et al. Prolymphocytic leukaemia of B and T cell type. Lancet. 1973; 2: 232–4.
10. Vardell VA, et al. T-cell prolymphocytic leukemia: Epidemiology and survival trends in the era of novel treatments. Am J Hematol. 2024; 99: 494–496.
11. Dearden CE, et al. Alemtuzumab therapy in T-cell prolymphocytic leukemia: comparing efficacy in a series treated intravenously and a study piloting the subcutaneous route. Blood. 2011; 118: 5799–5802.
12. Pawson R, et al. Treatment of T-cell prolymphocytic leukemia with human CD52 antibody. J Clin Oncol. 1997; 15: 2667–72.
13. Murthy HS, et al. Outcomes of Allogeneic Hematopoietic Cell Transplantation in T Cell Prolymphocytic Leukemia: A Contemporary Analysis from the Center for International Blood and Marrow Transplant Research. Transplant Cell Ther. 2022; 28: 187.e1-187.e10.
14. Guillaume T, et al. Allogeneic hematopoietic stem cell transplantation for T-prolymphocytic leukemia: a report from the French society for stem cell transplantation (SFGM-TC). Eur J Haematol. 2015; 94: 265–9.
15. Fida M, Webnda FN, Bangate RE. A family of matched parent-child hla haplotypes: a case study from bahrain. Reprod Biomed Online. 2019; 39: e73.
16. Nakka P, et al. Characterization of Prevalence and Health Consequences of Uniparental Disomy in Four Million Individuals from the General Population. The American Journal of Human Genetics. 2019; 105: 921–932.
17. Schrader A, Braun T, Herling M. The dawn of a new era in treating T-PLL. Oncotarget. 2019; 10: 626–628.
18. Boidol B, et al. First-in-human response of BCL-2 inhibitor venetoclax in T-cell prolymphocytic leukemia. Blood. 2017; 130: 2499–2503.
19. Stengel A, et al. Genetic characterization of T-PLL reveals two major biologic subgroups and JAK3 mutations as prognostic marker. Genes Chromosomes Cancer. 2016; 55: 82–94.
20. López C, et al. Genes encoding members of the JAK-STAT pathway or epigenetic regulators are recurrently mutated in T-cell prolymphocytic leukaemia. Br J Haematol. 2016; 173: 265–73.
21. Andersson EI, et al. Discovery of novel drug sensitivities in T-PLL by high-throughput ex vivo drug testing and mutation profiling. Leukemia. 2018; 32: 774–787.
22. Herbaux C, et al. Bendamustine is effective in T-Cell prolymphocytic leukaemia. Br J Haematol. 2015; 168: 916–919.
23. Morelli F, Sanna A. TCL-361: Bendamustine as Front-Line Therapy in T-Cell Prolymphocytic Leukemia: A Monocentric Experience. Clin Lymphoma Myeloma Leuk. 2021; 21: S414–S415.

Autologous hematopoietic stem cell transplantation in a patient with plasmablastic lymphoma and HIV infection

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Introduction. For the treatment of lymphoproliferative diseases (LPD) in HIV-infected patients, various chemotherapy approaches, hematopoietic stem cell transplantation (HSCT), in combination with antiretroviral therapy (ART) are used.

Clinical case. Patient M., 42 years old, in June 2023 noticed the appearance of a neoplasm on the lower jaw during a dental examination. A biopsy was performed, according to histological and immunohistochemical studies — the morphological corresponds to plasmablastic lymphoma (tumor cells express CD45, MUM1, CD138, CD38 and do not express CD30, CD3, CD20, PAX5, Ki67 — 98 %). The mutation in the TP53 gene also was detected. PET/CT showed a hypermetabolic neoplasm of soft tissues of the face and oral cavity on the right with dimensions (70 × 40 × 70 mm), metabolically active lymphadenopathy of the cervical lymph nodes, diffuse increased metabolism of the bone marrow. Trepanobiopsy showed that the bone marrow is also affected by the substrate of plasmablastic lymphoma. Given the association of this type of lymphoma with immunodeficiency states, the patient was tested for HIV infection, the result was positive.

Immune status at the time of diagnosis: CD4 — 53 (5 %), CD8 — 801 (70 %), CD4/CD8 — 0.7, HIV RNA — 298.778 cop/ml. ART was started at the same time (raltegravir, lamivudine, abacavir). Chemotherapeutic treatment included a pre-phase according to the CD scheme, 4 courses of DA-EPOCH + bortezomib. After 4 courses according to PET/CT, a complete metabolic response was achieved. Given his young age, preserved somatic status, and aggressive lymphoma variant, he was considered a candidate for Auto-HSCT for the purpose of consolidating remission. However, the patient did not see a hematologist for six months. In June 2024 PET/CT revealed a pathological accumulation in the left palatine tonsil. A biopsy was performed, the morphological picture and immunophenotype correspond to plasmablastic lymphoma. 2 courses of DHAP were performed. After 1 course of DHAP, apheresis of peripheral HSCs was performed. The number of HSCs is 7.97×10^6/kg, which is sufficient for auto-HSCT. According to the control PET/CT - a complete metabolic response. A decision was made to perform consolidating auto-HSCT. Immune status before transplantation: CD4 — 317 (27 %), CB8 — 504 (44 %), CD4/CD8 — 0.63. HIV RNA — less than 20 copies/ml. Pre-transplant conditioning was performed in the BeEAM mode, then auto-HSCT was performed, while taking ART, due to which the doses of etoposide were reduced by 50 %. In the early post-transplantation period, a single episode of febrile neutropenia was noted, stopped by second-line antibacterial therapy. Restoration of the leukocyte level on the +12th day after Auto-HSCT. Immune status 1 month after auto-HSCT: CD4 — 195 (24 %), CD8 — 500 (43 %), CD4/CD8 — 0.63, HIV RNA — less than 30 cop/ml.

Results and conclusions. In the second half of 2024, in the hematology department of the Loginov Moscow Medical Scientific Center of the Healthcare, 5 HIV-infected patients underwent: VDCT, mobilization and collection of stem cells (cytapheresis), 1 patient underwent Auto-HSCT. This clinical case and world experience show that the mobilization and infusion of HSCs, post-transplant complications, and recovery period in HIV-infected and HIV-uninfected patients with auto-HSCT are similar.

A clinical case of management of a patient with metachronous acute myeloid leukemia

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Modern achievements in the field of diagnostics and treatment of acute myeloid leukemia (AML) have made it possible to provide a personalized approach to the patient [1, 4]. Gene mutations, which play leading role in the pathogenesis of clonal evolution, are of great importance when managing patients during therapy prescription and deciding on the use of targeted medicine [2, 3].

Clinical case. Patient K., 53 years old, was diagnosed with acute promyelocytic leukemia (APL) in 2021. The diagnosis was based on clinical data, the results of a complete blood count, cytological and cytochemical examination of the bone marrow, and immunophenotyping. Cytogenetic study, fluorescence in situ hybridization (FISH), real-time polymerase chain reaction (PCR) for specific chromosomal aberrations, and detection of mutations in 141 genes using high-throughput sequencing on a MiSeqDX automated analyzer were also performed.

The cytogenetics failed to clarify the karyotype variant. FISH analysis of 100 nuclei revealed the chimeric PML/RARA gene signal in 90.0 % of cells. High-throughput sequencing revealed the c. 35G>T mutation in the NRAS gene. Remission was achieved using the standard therapy protocol. In 2023, at the 25th month of observation, the patient was diagnosed with acute myeloid leukemia with maturation (M2). Cytogenetics revealed the aberrant karyotype 46, XY, t(6;11) (q27;q23) / 46, XY. FISH analysis revealed the chimeric KMT2A/AFDN gene signal, corresponding to the t(6;11) translocation, contained in 80 % of cells. However, PML/RARA were not detected.

Due to the unfavorable prognosis and the absence of related and unrelated HLA-compatible donors, the patient underwent courses of therapy including the targeted medicine venetoclax, chemotherapy, ATRA and interferon. Remission was not achieved with maintenance therapy. In the 9th month of follow-up, a fatal outcome was recorded due to the refractory course of AML M2, which developed against the background of remission of APL. The patient had a total of 35 months of follow-up.

Conclusion. The described clinical observation determines the importance of molecular genetic studies for the management of patients with AML. The identification of significant aberrations allows choosing the optimal therapy tactics taking into account all factors, including the use of targeted drugs.

References

1. Cowell IG, Austin CA. Mechanism of generation of therapy related leukemia in response to anti-topoisomerase II agents. Int J Environ Res Public Health. 2012; 9(6): 2075–91.

2. Meyer C, Larghero P, Almeida Lopes B, et al. The KMT2A recombinome of acute leukemias in 2023. Leukemia. 2023; 37(5): 988–1005.

3. Виноградов А.В., Ласточкина Д.В., Анисимова И.В. и др. Клиническое течение острого миелоидного лейкоза у больной с мутациями SRSF2 и IDH2, идентифицированными с помощью высокопроизводительного секвенирования. Клиническая онкогематология. Фундаментальные исследования и клиническая практика. 2023; 16(S1): 148–9.

4. Виноградов А.В., Резайкин А.В., Сазонов С.В. и др. Мутационный статус острого миелобластного лейкоза с созреванием (М2) у взрослых больных. Медицинский вестник Северного Кавказа. 2021; 16(1): 18–21.

Clinical case of Ph-positive B-ALL with rare extensive skeletal involvement: first experience utilizing ponatinib and blinatumomab protocol in Kazakhstan

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Introduction. Philadelphia chromosome-positive B-cell Acute Lymphoblastic Leukemia (Ph+ B-ALL) is a rare but aggressive hematologic malignancy, with the clonal proliferation of immature B-lymphoblasts. While B-ALL typically presents with lymphadenopathy and mediastinal masses, cases involving extensive skeletal lesions are exceedingly rare. Here, we present a unique case involving a 36-year-old Asian male from Kazakhstan with Ph+ B-ALL, who presented with lower back pain and osteolytic lesions in the lumbar spine. This case marks the first reported use of a Ponatinib and Blinatumomab protocol for Ph+ ALL in Kazakhstan, highlighting the potential of personalized medicine in resource-limited settings.

Presentation. The patient initially presented with progressive back pain and night sweats. MRI revealed multiple osteolytic lesions in the lumbar spine, and a biopsy confirmed the diagnosis of B-ALL with the BCR-ABL1 fusion gene. Despite the presence of this gene, the clinical presentation, featuring extensive skeletal involvement, posed significant diagnostic challenges (Figure 1). The differential diagnosis included chronic myeloid leukemia (CML) in the lymphoid blast phase due to the low blast count and peripheral neutrophils, complicated by the patient's prior glucocorticoid use after vertebroplasty. However, further analysis confirmed the diagnosis of B-ALL.

Treatment was initiated with Ponatinib, a tyrosine kinase inhibitor (TKI), due to the patient's Ph+ status, along with Blinatumomab, a bispecific T-cell engager (BiTE) immunotherapy. The patient achieved bone marrow minimal residual disease (MRD)-negative status after the first induction course, but molecular MRD-positive disease persisted following two consolidation courses. Despite experiencing mild cytokine release syndrome during treatment, the patient tolerated the therapy well. However, a complete molecular response was not achieved, and the patient was recommended for allogeneic hematopoietic stem cell transplantation (allo-HSCT), which is challenging in Kazakhstan due to limited resources.

This case underscores the importance of a multidisciplinary diagnostic approach, integrating clinical, radiological, histopathological, and molecular analyses. The use of Ponatinib was driven by the patient's Ph+ status and limited access to allo-HSCT in Kazakhstan.

Combining Ponatinib with Blinatumomab reflects a targeted approach, offering potential benefits when traditional treatment options are inaccessible.

Conclusions. This case highlights the role of personalized medicine in managing rare hematologic malignancies, particularly in resource-limited settings. The first use of the Ponatinib and Blinatumomab protocol in Kazakhstan provides hope for expanding the treatment options available for Ph+ B-ALL. Despite the failure to achieve full molecular remission, this case offers insights into the effectiveness and challenges of targeted therapies for B-ALL.

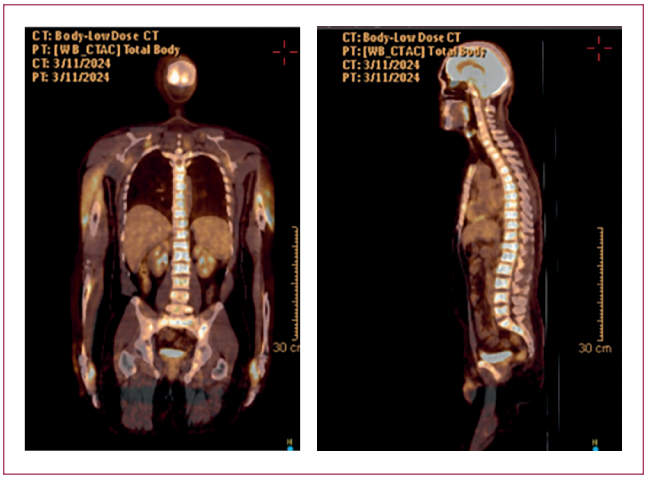

Figure 1. PET-CT scan before treatment (multiple lesions in bones)

Use of venetoclax in the therapy of multiple myeloma with translocation t(11;14)

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Introduction. A number of experimental studies have demonstrated that venetoclax plays a significant role in activating apoptosis in MM cell lines harbouring the 11;14 translocation [1]. Experience with venetoclax in both low and high cytogenetic risk multiple myeloma (mSMART), including those with translocation 11;14, has shown a statistically significant difference in the achievement of complete response, very good partial response and partial response in patients treated with venetoclax. Overall response rates ranged from 65 % [2] to 85 % in the Bellini study [3, 4].

Case description. A 60-year-old male patient with a criterion-verified diagnosis of multiple myeloma, IgG kappa, IIIA st by DS, III by ISS, presented with an extraosseous component in the area of the sternum and right iliac bone. The diagnosis was made in December 2022 on the basis of trepanobiopsy and immunophenotyping of bone marrow cells, which showed 93 % plasma cells with CD45dim CD138+CD38+CD19–CD117–CD56–CD27+CD20+cyK+cyIgM+ phenotype. The M-grade was 50.5 %, Bence-Jones protein was not determined. Computed tomography of bone structures showed a widespread lytic process with the presence of a soft tissue component in the posterior segment of the left 9th rib, its pathological fracture; sternum handle; the largest transverse dimensions of the soft tissue component (up to 5.5 × 8.0 cm) in the right iliac bone and sacroiliac joint. The complex of symptoms of CRAB syndrome (anaemia, hypercalcaemia, bone foci) was present. The creatinine level was normal. First-line therapy for VCD was started in February 2023. Tolerability was relatively satisfactory, but no effect was observed after 4 courses of therapy. Serum M-gradient was 49.8 %, plasmacytoma size did not decrease significantly.

Since June 2023, 2 cycles of Rd regimen have been performed, also without effect. Disease progression was noted with growth of foci of plasmacytomas, appearance of Bence-Jones protein. The M gradient in the serum was 44.8 %. Since November 2023, therapy with daratumumab + pomalidomide + dexamethasone has been started. 6 courses have been administered. The tolerability of the therapy was satisfactory, but there was no significant effect. Disease stabilisation was confirmed. M-gradient was 46.1 %, Bens-Jones protein 13.8 %. Bone marrow cytology of March 2024 showed 43 % of the plasma cells.

Molecular cytogenetic study of February 2024 showed translocation t(11;14)(q13;q32) with additional signals of fused CCND1/IGH genes, duplication of normal IGH gene, 5 signals at 11q22, triplication of 6q21 and 15q22, deletion of MAF gene (16q23) in 35–40 % of cells, deletion of TP53 gene and duplication of 1q21 in 15 % of cells. The patient was therefore at high cytogenetic risk.

Taking into account the t(11;14) translocation, the patient was started on daratumumab + pomalidomide + dexamethasone + venetoclax in May 2024. The tolerability of the regimen is relatively satisfactory. Haematological toxicity was observed in the form of grade 1 thrombocytopenia.

There was a significant improvement after 12 cycles of therapy. A partial response was seen. At the time of presentation, according to the follow-up study of October 2024 — M-gradient is 20 %, Bence Jones protein is not detected, plasma cells are 2 % in the myelogram. There is no evidence of plasmacytomas enlargement according to the CT scan. Thus, the addition of venetoclax to DaraPomDex triplet in a primary refractory patient with high cytogenetic risk resulted in a significant effect after 12 cycles of therapy. These courses are planned until progression or unacceptable toxicity.

Conclusion. In this case report, a patient with high cytogenetic risk myeloma with t(11;14) translocation achieved a partial response when venetoclax was added to the triplet. This response was achieved after 12 courses of treatment and has been maintained to date. Venetoclax is synergistic with proteasome inhibitors and immunomodulatory drugs and suppresses the growth of plasma cells with high bcl-2 expression, particularly with t(11:14) [4, 5]. Detection of this translocation prior to first-line therapy in patients with low, intermediate or high cytogenetic risk will allow the timely administration of combinations with the addition of venetoclax.

Key words: multiple myeloma, t(11;14), venetoclax.

References

1. Touzeau C, et al. The Bcl-2 specific BH3 mimetic ABT-199: a promising targeted therapy for t (11; 14) multiple myeloma. Leukemia. 2014; 28(1): 210–2.

2. Kaufman JL, et al. Phase I/II study evaluating the safety and efficacy of venetoclax in combination with dexamethasone as targeted therapy for patients with t (11; 14) relapsed/refractory multiple myeloma. Blood. 2019; 134: 926.

3. Kumar SK, et al. Venetoclax or placebo in combination with bortezomib and dexamethasone in patients with relapsed or refractory multiple myeloma (BELLINI): a randomised, double-blind, multicentre, phase 3 trial. The Lancet Oncology. 2020; 21(12): 1630–42.

4. Kumar S, et al. Efficacy of venetoclax as targeted therapy for relapsed/refractory t (11; 14) multiple myeloma. Blood. 2017; 130(22): 2401–09.

5. Семочкин С.В. Длительная непрерывная терапия как новая стратегия лечения рецидивирующей или рефрактерной множественной миеломы. Онкогематология. 2020; 15(2): 29–41.

A case of severe cutaneous drug reaction with eosinophilia and systemic symptoms (DRESS) associated with lenalidomide in a patient with relapsed follicular lymphoma

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Introduction. DRESS (drug reaction with eosinophilia and systemic symptoms) is a rare but potentially life-threatening adverse drug reaction. We describe a case of DRESS associated with the use of lenalidomide for the treatment of relapsed/refractory follicular lymphoma (R/R FL).

Case description. A 51-year-old woman presented with follicular lymphoma since 2016 and had no significant comorbidity. Allergic history is unremarkable. The patient had previously undergone 2 lines of therapy (RCHOP and GB with bendamustine dose reduction due to myelotoxic neutropenia) and then received anti-CD20 monoclonal antibodies as maintenance therapy. On maintenance obinutuzumab, disease progression was observed. At relapse, local stage CD20+ follicular lymphoma was diagnosed with involvement of the small intestinal mesentery and formation of 'bulky' foci. Biochemical analysis was normal, with C-reactive protein slightly above normal at 9.3 mg/L. The blood count showed leukopenia (2.56×10^9/L) and lymphopenia (0.74×10^9/L). The eosinophil count was 5.2 % (0.13×10^9/L). The patient had secondary immunodeficiency (IgG 3.88 g/L).

Lenalidomide monotherapy was prescribed at a dose of 10 mg daily in a 28-day cycle (the dose was reduced due to persistent leucopenia after bendamustine). Concomitant therapy included co-trimoxazole, acyclovir, allopurinol and acetylsalicylic acid. On day 7 of lenalidomide administration, the results of physical examination and laboratory monitoring showed no negative dynamics. However, on day 10, the patient's condition deteriorated dramatically, with the appearance of a generalised dark pink maculopapular rash covering approximately 80 % of the body surface, moderate swelling of the face and hands, and fever above 38°C. Peripheral lymphadenopathy was absent, as were diarrhoea and vomiting. Biochemical analysis showed evidence of cytolysis (ALT-350 U/L, AST-111 U/L), and the CRP level increased to 55.5 mg/L. Hepatitis A, B and C were excluded. In the general blood count, leukopenia persisted, but a relative eosinophilosis of 13.7 % (0.43×10^9/L) was noted. A clinical diagnosis of DRESS in association with lenalidomide was made. Lenalidomide was immediately discontinued. Prednisolone 1 mg/kg body weight, antihistamines and enterosorbents were prescribed. One week after the start of treatment, the eosinophil count increased to 24.4 % (0.51×10^9/L) against a background of persistent leukopenia, and grade 3 myelotoxic neutropenia was observed. Complete resolution of the complication did not occur until 1.5 months later, and prednisolone was discontinued after 2 months. Further follow-up of the patient over 3 years revealed no recurrence of DRESS or manifestation of rheumatological disease, nor reactivation of herpes infections. During follow-up, the patient underwent more than 3 lines of therapy for R/R FL and had no new skin reactions.

Discussion. DRESS syndrome is a rare but serious adverse drug reaction that can result in significant morbidity and mortality. It is characterized by a constellation of symptoms that include fever, rash, eosinophilia, and involvement of multiple organ systems. The case presented illustrates a typical progression of DRESS following the administration of lenalidomide. The patient developed a rapidly progressive rash and systemic symptoms shortly after starting lenalidomide. The maculopapular rash covering a significant portion of the body, along with fever and elevated liver enzymes, were critical indicators of DRESS. The absence of gastrointestinal symptoms and peripheral lymphadenopathy, along with initial laboratory findings, initially complicated the clinical picture. However, the development of eosinophilia, elevated liver enzymes, and the acute onset of systemic symptoms ultimately led to the diagnosis.

As can be seen from the description, the case almost fulfils the 4 major RegiSCAR ('Regional Study of Serious Cutaneous Adverse Reactions') criteria, including fever, characteristic rash, haematological changes and organ involvement, which would suggest a definite DRESS. The eosinophilia does not reach the level of a major (> 1500 μL), but the patient was initially started on treatment with a myelotoxic leucopenia and this may have influenced the outcome. The patient experienced no recurrence of DRESS or related autoimmune diseases during a follow-up period of three years, nor did she suffer from opportunistic infections despite being on immunosuppressive therapy. The investigations carried out and the absence of any other autoimmune disease in the catamnesis, together with the prolonged but

complete resolution of symptoms after withdrawal of lenalidomide and administration of prednisolone, confirm the diagnosis. The timing of this complication, 10 days, is quite possible, although it is typical for DRESS to develop after 2 to 8 weeks of drug administration. We did not perform a skin biopsy, but there is no characteristic DRESS pattern in the skin biopsy.

The mechanisms by which lenalidomide can cause (DRESS) are not fully understood, but several hypotheses have been proposed based on its pharmacological actions and the nature of hypersensitivity reactions 1–5. Lenalidomide can induce T-cell proliferation and activation. In some patients, this may result in an exaggerated immune response against the drug or its metabolites, causing tissue injury that manifests as DRESS. This mechanism is similar to other drug hypersensitivity reactions where T-cell involvement leads to delayed-type hypersensitivity responses. Lenalidomide may promote the differentiation and activation of eosinophils via cytokine modulation (e.g., increased IL-5 production). Eosinophils play a significant role in tissue inflammation and damage in various hypersensitivity reactions, including DRESS.

The formation of reactive metabolites during the metabolism of lenalidomide could modify self-proteins, leading to the development of neoantigens. This modification may promote an immune response against these altered proteins, resulting in eosinophil activation and systemic symptoms. Lenalidomide's immunomodulatory effects may lead to the release of multiple pro-inflammatory cytokines, creating a "cytokine storm". This can amplify the inflammatory response in tissues and contribute to the clinical picture of DRESS, including fever, rash, and organ involvement.

In conclusion, while lenalidomide remains a valuable treatment option for conditions like follicular lymphoma, awareness of the risk for DRESS and other severe adverse reactions is essential. Clinicians must be ready to recognize early signs of DRESS, initiate prompt treatment, and ensure ongoing follow-up to mitigate potential long-term sequelae.

References

1. Kobayashi M, et al. A case of DRESS syndrome associated with lenalidomide. British Journal of Haematology. 2012; 157(1): 145–7.

2. Sullivan PM, et al. DRESS syndrome: recognition and management. Canadian Family Physician. 2011; 57(12): 1370–6.

3. Fitzgerald K, et al. DRESS syndrome associated with lenalidomide: a case report. Journal of Oncology Pharmacy Practice. 2017; 23(1): 28–31.

4. Danjoux M, et al. Patients with multiple myeloma receiving lenalidomide: a review of adverse events. Therapeutic Advances in Hematology. 2020; 11: 2040620720964383.

5. Kumar R, et al. (). Drug reaction with eosinophilia and systemic symptoms (DRESS): A rare but serious side effect of lenalidomide. The American Journal of Medicine. 2019; 132(11): e613–e615.

Complexities of treating acute myeloblastic leukemia in a patient with diverse comorbid conditions

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Introduction. Acute myeloblastic leukaemia (AML) is a clonal disease of haematopoietic tissues associated with mutations in haematopoietic stem cells leading to a block in differentiation and uncontrolled proliferation of immature myeloid cells. In the presence of concomitant hepatic pathology, chemotherapy (CT) is often complicated by the development and/or exacerbation of hepatotoxicity, requiring a review of treatment tactics and the selection of the optimal regimen.

Objectives. To demonstrate the possibility and efficacy of chemotherapy of AML with achievement of remission on the background of chronic viral hepatitis C.

Materials and methods. We present the clinical case of a 53-year-old patient diagnosed with acute myeloblastic leukaemia with aberrant expression of CD56+, in whom the examination revealed chronic viral hepatitis C with minimal biochemical activity, stage III liver fibrosis and diabetes mellitus. The induction courses ("7+3" with mitoxantrone, venetoclax + azacitidine) and 2 consolidation courses were carried out according to the protocol. Taking into account the combined pathology, severe infectious complications, massive lysis syndrome and uncorrectable hyperglycaemia were observed in the post-treatment period. After the second course of therapy, remission of the disease was achieved. At present, maintenance therapy is being continued with MDC + venetoclax, and the remission has been maintained.

Case description. Since October 2023 the patient suffered from anaemic syndrome (Hb 50 g/L), intoxication, periodic nosebleed. According to the results of examinations in haemogram: leukocytes 4.6×10^9/l, blasts — 6 %, severe anaemia (Hb 57 g/L), thrombocytopenia (20×10^9/l). Myelogram showed 48.8 % blasts, normal haematopoiesis was suppressed. Bone marrow immunophenotyping (IFT) showed CD56+

AML, 14.1 % mature immunophenotype monocytes with aberrant expression of CD56+. Cytogenetic analysis showed no abnormalities. Acute myeloblastic leukaemia with aberrant expression of CD56+ was confirmed. Investigations revealed chronic viral hepatitis C in the replicative stage with minimal biochemical activity (AlT 28.8 U/L, AsT 33.9 U/L). Fibroelastometry showed cirrhosis: F3 (stage III hepatic fibrosis). According to abdominal ultrasound, the liver was 150 × 75 mm and the spleen 130 × 63 mm. The first induction course was carried out according to the "7+3" protocol with mitoxantrone, which was interrupted on day 6 due to massive lysis syndrome, poorly correctable hyperglycaemia. The diagnosis of insulin-dependent diabetes mellitus was made for the first time, and the patient was subsequently no longer able to wean himself off insulin. Severe anaemia, haemorrhagic syndromes, infectious complications (pneumonia, bilateral submandibular lymphadenitis with abscess requiring surgical drainage) occurred during and after treatment. Eventually, all these life-threatening conditions were resolved. The 2nd induction course was performed according to the protocol venetoclax + azacitidine. Disease remission was achieved. Follow-up was with low-dose cytartabine + venetoclax. This treatment was well tolerated and no signs of hepatoxicity were observed.

Discussion. This case presents a complex clinical scenario involving a patient diagnosed with acute myeloblastic leukemia (AML) characterized by aberrant CD56 expression, complicated by significant comorbidities, including chronic hepatitis C with cirrhosis and newly diagnosed insulin-dependent diabetes mellitus. The complexity of managing AML in the context of these comorbidities underscores the need for a multidisciplinary approach to ensure optimal patient care.

Disease manifestation was typical, and the presence of CD56+ blasts is noteworthy as this aberrant expression can correlate with a more aggressive disease course and may influence treatment strategies. Chronic hepatitis C was confirmed through laboratory analyses, revealing a replicative phase with minimal biochemical activity, despite significant hepatic impairment as demonstrated by fibroelastometry. The identification of stage III hepatic fibrosis (F3) is crucial to consider during treatment planning, as it may impact hepatic metabolism of chemotherapeutic agents and the patient's overall tolerance to therapy. The initial induction chemotherapy regimen utilizing the "7+3" protocol alongside mitoxantrone faced substantial challenges. The development of massive lysis syndrome, accompanied by poorly controlled hyperglycemia and respiratory complications, highlights the risks associated with intensive chemotherapy in patients with underlying liver disease. The onset of insulin-dependent diabetes mellitus in this context also complicates management, as it necessitates careful monitoring and adjustment of therapeutic strategies to avoid exacerbation of metabolic derangements. The successful resolution of these acute life-threatening conditions was critical in allowing for subsequent therapy.

The decision to proceed with a second induction course using venetoclax and azacitidine reflects the evolving treatment landscape in AML, particularly for patients with specific genetic and phenotypic characteristics. Venetoclax, a BCL-2 inhibitor, combined with azacitidine, offers a favorable profile in terms of tolerability and effectiveness, especially in older adults or those with impaired liver function. In this case, the patient achieved disease remission, a notable achievement considering the preceding complications.

The switch to maintenance therapy with low-dose cytarabine and venetoclax is significant as it demonstrates adaptability in treatment planning to ensure the continued monitoring of disease status while mitigating the risk of hepatotoxicity—an important consideration in this case given the pre-existing liver condition. This approach not only maintains the therapeutic benefit but also allows for a more favorable tolerability profile.

Conclusion. This case illustrates the complexities of managing acute myeloblastic leukemia in patients with significant comorbidities such as chronic hepatitis C with cirrhosis and diabetes mellitus. Close monitoring and adjustment of treatment protocols in response to complications are essential to improve outcomes. The successful use of targeted therapies like venetoclax coupled with supportive measures serves as a promising strategy in similarly complex cases, paving the way for future research and clinical practices aimed at addressing such multifaceted clinical situations.

A clinical case of refractory iron deficiency anemia due to gastric antral vascular ectasia (GAVE)

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Abstract. Clinical case of severe, treatment-refractory, iron deficiency anemia in a patient with GAVE with attempted therapy with endoscopic argon-plasma coagulation is presented.

Introduction. Iron deficiency anaemia is normally a well-treatable condition. Iron deficiency anemia refractory to iron therapy and transfusions is extremely rare and requires a special diagnostic and therapeutic approach. Gastric antral venous ectasia (GAVE) is an infrequent but serious cause of gastrointestinal bleeding, responsible for 4 % of all non-variceal haemorrhages [4]. This pathology was first described in 1953 by Ryde et all [11]. Diagnosis is based on endoscopy and in some cases on histology materials. GAVE is characterised by a rather pathognomonic endoscopic picture represented by red spots organised in radial bands from the pylorus along the antrum, the changes may spread diffusely through the walls of the antrum (diffuse type) [12]. GAVE may be asymptomatic or accompanied by the clinic of anemia or overt gastrointestinal bleeding. While there is no known direct cause of GAVE, the condition is most common in those who have suffered from certain chronic conditions such as autoimmune disease (60 %) [9], cirrhosis (poor liver function) (30 %) [3], and atrophic gastritis. The treatment of GAVE includes drug therapy, endoscopic techniques and surgical methods [10]. Drug therapy does not play a crucial role in the treatment of GAVE-related bleeding. Endoscopic treatment, particularly argon plasma coagulation (APC), should be considered as first-line therapy for bleeding patients with GAVE [5, 10]. In addition to APC, laser photocoagulation, sclerotherapy, cryotherapy, band ligation, and radiofrequency ablation have been proposed [8]. In the domestic literature, information on the diagnosis and treatment of GAVE is extremely scarce. Analysis of the situation shows that the process of making the correct diagnosis of GAVE is long, and the choice of optimal tactics remains a difficult task. Iron deficiency anemia that develops as a result of repeated bleeding from ectasia of the antral veins may be refractory to treatment, requiring multiple hospitalizations, long term intravenous iron administration and repeated blood transfusions [2].

Case presentation. A 53-year-old white female with a 5-year history of mild anenia, more of less successfully treated with ferrous sulfate, without investigating the cause of the anemia. In November 2018 the patient noted a marked fatigue, shortness of breath during physical activity, brittle nails and hair. The laboratory test revealed hypochromic microcytic anemia, with hemoglobin value of 3.4 g/dl (normal range: 12–16 g/dl), hematocrit 13 % (normal range: 37–48 %), red blood cell count of 2.0 M/ml (normal range: 4.5–6.3 M/ml), mean corpuscular volume of 65 fl (normal range: 80–96 fl), and mean corpuscular hemoglobin of 17 pg (normal range: 27–34 pg). Other laboratory results showed: white blood cells 8.6 K/µl (normal range: 4.0–11.0 K/µl), platelets 320 K/µl (normal range: 150–400 K/µl), total bilirubin 7.4 µmmol/l (normal range: 1–21,5 µmmol/l), serum iron 3.3 µmol/l (normal range: 8–28 µmmol/l), erythrocyte sedimentation rate 28 mm/h (normal range: 2–20 mm/h). She was admitted to the hospital and treated with oral iron supplements, folic acid supplements and blood transfusions. Then she was discharge from the hospital with hemoglobin value of 8.2 g/dl. On an outpatient basis the patient continued intake oral iron supplements twice a day. 27.12.2018 she came to a control visit with hemoglobin value of 3.6g/dl in clinical blood count (CBC). Other laboratory results showed: red blood cell count of 1.9 M/ml, mean corpuscular volume of 68 fl, and mean corpuscular hemoglobin of 18,9 pg, white blood cells 6.1 K/µl, platelets 230 K/µl, folicid acid 20 ng/ml (normal range: 3.1–20 ng/ml), cobalamin 520.6 pg/ml (normal range: 187–883 pg/ml), erythropoietin 756 mU/mL, serum iron level 6.1 µmol/L, ferritin (after many blood transfusions) 194.9 µg/L (normal range: 11–204 ng/ml). She was repeatedly admitted to therapeutic department of the hospital. Gastroscopy dated 17.01.2019 revealed focal vascular ectasia of the antral part of the stomach (Figure 1–4). Colonoscopy dated 08.02.2019: no organic pathology was revealed. She was treated again with blood transfusions and oral intake of iron supplements. After that, she was discharged without significant clinical improvement. The patient was referred to a hematologist. 20.03.2019 she was hospitalised to the hematology department of the Chelyabinsk Regional Clinical Hospital with ECOG 2 due to anemic syndrome. Skin and visible mucous membranes were pale. Pulse was 88 per 1 min. Blood Pressue was 110–70 mmHg. Considering the refractory anemia the patient was examined to exclude other possible causes of anemia. No signs of autoimune deseases or liver disieses was found. Clinical blood count dated 20.03.2019: WBC — 4.3 × 10^{12}/L, HGB — 63g/L, RBC — 2.87 × 10^{9}/L, MCV — 74 fl, RET — 2.9 %, PLT — 330 × 10^{9}/L, EOS 5 %, band forms 1 %, segmented neutrophils 54 %, LYMP 36 %, MON 4 %, ESR 20 mm/h.

Other tests: C-reactive protein 1.7 mg/L, LDH 137 U/L, serum iron 3.01 mmol/L, folicid acid 10.10 ng/ml, cobalamin 219 pg/ml, ferritin 133 ng/ml, direct Coombs test negative, feces for occult blood negative. Bone marrow puncture: blasts — 0 % myelocytes — 3,5 % eos — 2,5 % neut — 42 % eritrocytes — 26 % lymp — 26 % plasmocytes — 1 %, sideroblasts — 0, normoblastic type of erythropoiesis with moderate macrocytosis, accelerated maturation of neutrophils. Bone marrow flow cytometry: polymorphocellular bone marrow with no aberrant expressions, no signs of lymphoproliferative disease. Gastroscopy dated 27.03.2019: In the antral section the gastric mucosa was brightly hyperemic. At close examination diffuse dilatation of mucosa vessels was noted. Conclusion: gastric antral vascular ectasia (GAVE). Considering clinical and laboratory signs of iron deficiency anemia (ferritin elevation was considered as a consequence of transfusion therapy), the patient started intravenous administration of iron supplements, which resulted to reduction of general weakness, increase in hemoglobim level from 63 to 107 g/L (without transfusions) for 4 weeks. The cause of the anemia was detected as chronic blood loss from ectasia of gastric veins. As a method of treatment of GAVE-syndrome, endoscopic hemostasis — argon plasma coagulation (APC) — was performed. APC was done by 2 sessions: 02.04.2019 and 30.04.2019.

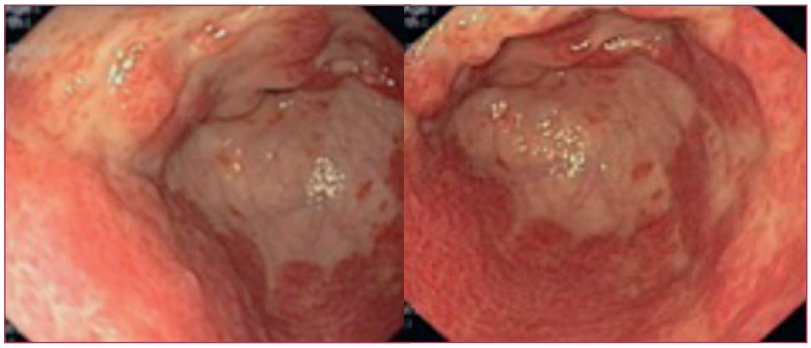

Figure 1. Before endoscopic treatment

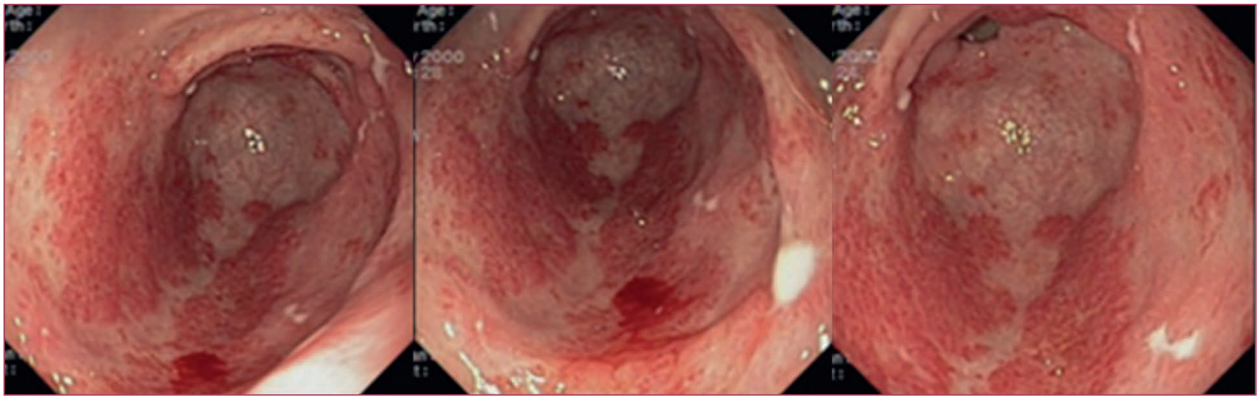

Figure 2. A month after the first APC session

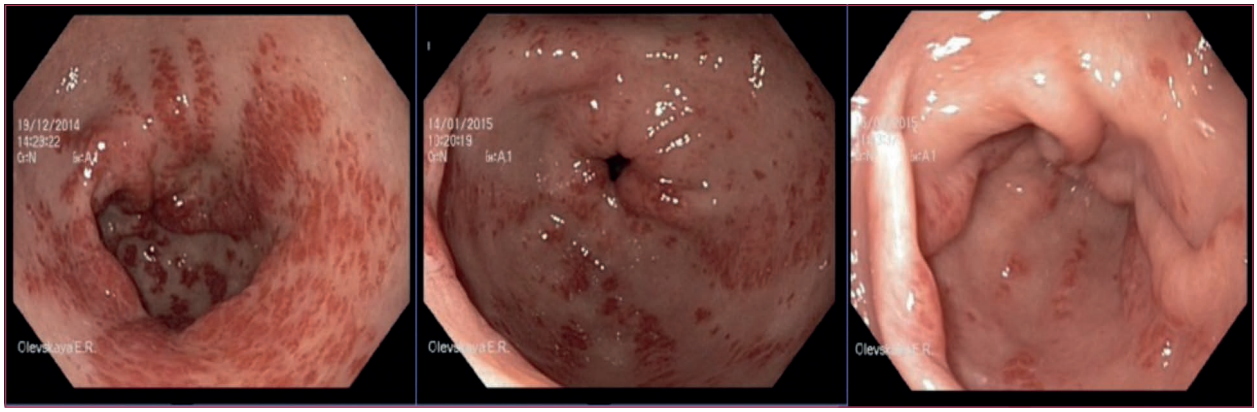

Figure 3. Result after 2 sessions of endoscopic treatment

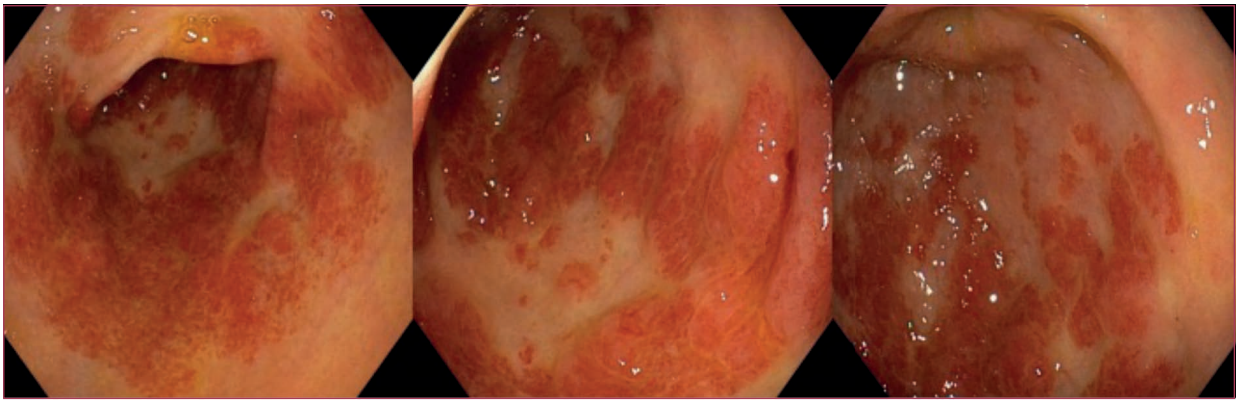

Figure 4. Gastroscopy from 04.09.2024 showed the signs of GAVE

Clinical blood count at discharge dated 09.05.2019: WBC — 6,4 × 10^9/L, PLT — 216 × 10^9g/L, MCHC — 314 g/L, MCH — 25,4 pg, MCV — 81 fl, HCT — 37,7 %, HGB — 118 g/L, RBC — 4,65 × 10^{12}/L. The patient was discharged from the hematological department with significant clinical and laboratory improvement, at the outpatient stage it was recommended to continue the oral intake of iron supplements. During 5 years the patient noted normalisation of her condition despite the persistence of mild anaemia. In summer of 2024 signs of anemia and sideropenic syndrome reappeared. Blood tests dated 05.09.2024: HGB — 107 g/L, PLT — 350 × 10^9/L, MCHC — 296 g/L, MCH — 23 pg, MCV — 77 fl, HCT — 36 %, RBC — 4,7 × 10^{12}/L, WBC — 9,1 × 10^9/L, Ferritin 8 ng/ml.

Another session of APC was applied as a treatment and led to clinical improvement.

Thus, the patient is currently clinically and laboratory stabilised and her overall health is satisfactory.

Conclusion. Thus, gastric antral venous ectasia (GAVE) may be a rare cause of refractory iron deficiency anemia. It is important to examine the gastrointestinal tract in patients with refractory iron deficiency anemia, including women of fertile age. Without elimination of the cause of bleeding (therapy of GAVE directly) treatment of such patients is unsuccessful. In the presented clinical case, the relevance of minimally invasive methods of surgical treatment of patients with GAVE draws attention due to its low traumatic nature and the possibility to avoid gastric resection even in case of recurrent bleeding from ectasised vessels. In addition, in comparison with drug therapy alone, surgical treatment tends to increase hemoglobin levels faster and maintain the achieved positive dynamics [1]. Considering the impossibility of complete elimination of antral vein ectasia, permanent prophylactic intake of iron supplements may be recommended for such patients.

Key words: gastric antral vascular ectasia, GAVE, refractory iron deficiency anemia, argon plasma coagulation.

References

1. Chalhoub JM, Umar J, Groudan K, et al. Endoscopic band ligation compared to thermal therapy for gastric antral vascular ectasia: A systematic review and meta-analysis. United European Gastroenterol J. 2021; 9(2): 150–8. doi: 10.1177/2050640620975243. Epub 2021 Feb 18. PMID: 33210983; PMCID: PMC8259375.

2. Che CC, Shiu SI, Ko CW, et al. Comparisons Between Endoscopic Band Ligation, Radiofrequency Ablation and Endoscopic Thermal Therapy for Gastric Antral Vascular Ectasia: A Meta-Analysis. Dig Dis Sci. 2023; 68(9): 3534–41. doi: 10.1007/s10620-023-08028-7. Epub 2023 Jul 25. PMID: 37490152; PMCID: PMC10444674.

3. Donna M. Berry Gastric Antral Vascular Ectasia (Watermelon Stomach). Gastroenterology. 1996; 18: 164–6.doi.org/10.1097/00001610-199509000-00002 Actions

4. Dulai GS, Jensen DM, Kovacs TO, et al. En-doscopic treatment outcomes in watermelon stomach patients with and without portal hypertension. Endoscopy. 2004; 36: 68–72. doi.org/10.1055/s-2004-814112

5. Fuccio L, Zagari RM et al. Endoscopic argon plasma coagulation for the treatment of gastric antral vascular ectasia-related bleeding in patients with liver cirrhosis. Digestion. 2009; 79: 143–150. doi.org/10.1159/000210087

6. Garcia MC, Zhou J, Henning D, et al. Unique epitopes in RNA helicase II/Gu protein recognised by serum from a watermelon stomach patient. Mol Immunol. 2000; 37: 351–359. doi.org/10.1016/s0161-5890(00)00062-6

7. Grady D, Rubin SM, Petitti DB, et al. Hormone therapy to prevent disease and prolong life in postmenopausal women. Ann Intern Med. 1992; 117: 1016–37. doi.org/10.7326/0003-4819-117-12-1016

8. McCarty TR, Hathorn KE, Chan WW, Jajoo K. Endoscopic band ligation in the treatment of gastric antral vascular ectasia: a systematic review and meta-analysis. Endosc Int Open. 2021; 9(7): E1145–E1157. doi: 10.1055/a-1401-9880. Epub 2021 Jun 21. PMID: 34222641; PMCID: PMC8216786.

9. Novitsky YW, Kercher KW, Czerniach DR, Litwin DE. Water-melon stomach: pathophysiology, diagnosis, and management. J Gastrointest Surg. 2003; 7: 652–66. doi.org/10.1016/s1091-255x(02)00435-3

10. Olevskaya ER, Tarasov AN. Application of various endoscopic techniques in the treatment of GAVE-syndrome, South-Ural State Medical University, Ministry of Healthcare of the Russian Federation, Chelyabinsk, Russia, 2016. doi: 10.17116/endoskop201622242-44

11. Selinger ChP, Ang YS. Gastric Antral Vascular Ectasia (GAVE): An Update on Clinical Presentation, Pathophysiology and Treat-ment. Digestion. 2008; 77(2): 131–137. doi.org/10.1159/000124339

12. Zepeda-Gómez S, Sultanian R, Teshima C, et al. Gastric antral vascular ectasia: a prospective study of treatment with endoscopic band ligation. Endoscopy. 2015; 47(6): 538–40.

Small cell variant of anaplastic t-cell lymphoma — description of a clinical case from the morphologist's point of view

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Introduction. Small cell anaplastic large cell lymphoma (ALCL) is a rare subtype of T-cell lymphoma with an unfavourable prognosis regardless of ALK gene expression. The two-year survival rate for patients with small cell ALCL is 50 %, compared to 73 % for the classical type.

Objective. To describe a clinical case of the small cell variant of anaplastic T-cell lymphoma with clinical and morphological analysis.

Clinical case. The patient is a 36-year-old female. The disease presented with a pronounced musculoskeletal pain syndrome in the lumbar spine, right lower extremity, inability to stand upright, paresthesias of the inner surface of the right lower extremity. The patient received symptomatic therapy for 2 months, due to lack of improvement on the background of treatment the patient was transferred to the State Budgetary Institution M.F. Vladimirsky MONIKI for further examination. The results results were obtained: intra-abdominal and retroperitoneal lymphadenopathy, zone of pathological infiltration in the retroperitoneal space of paravasal and perivertebral localisation, destruction of vertebrae Th12-L5, peritoneal carcinomatosis, ascites, anasarca, hepatosplenomegaly, inferior vena cava thrombosis, bilateral hydrothorax with compression atelectasis of basal lung sections, hydropericardium. Surgical treatment was performed by extirpation of supraclavicular lymph nodes. extirpation. Microscopic examination of the lymph node revealed a round-cell solid tumour with relative signs of polymorphism, prominent nuclei, scattered medium-sized cells with transparent cytoplasm and horseshoe-shaped nuclei. High mitotic and apoptotic activity was observed. The morphological picture was highly suspicious for lymphoma/lymphoproliferative disease (Figure 1). According to the 1st panel of the immunohistochemical (IHC) study, the absence of CD20, CD3, CD5 expression in the tumour infiltrate was detected with adequate internal and external controls (Figure 2). Diffuse positive reaction with CD45 was noted, while reactions with PanCK, CD138 were negative. High proliferative activity index with ki-67 up to 80 % was observed. This excluded tumours with epithelial and plasma cell histogenesis. 2nd panel of IHC — reaction with CD43, TDT, bcl-6, bcl-2, PAX5, S-100, CD79 — negative. Mature B-cell tumours, tumours with neurogenic differentiation and lymphoblastic leukaemia were excluded. For differential diagnosis between myeloid sarcoma and small cell variant of anaplastic lymphoma the 3rd stage of IHC was performed. Diffuse positive reaction of CD30, CD4 in tumour cells was noted (Figure 3), while there was no reaction of CD34, CD117. Considering the morphological structure, clinical data and IHC data, the changes correspond to highly aggressive anaplastic T-cell lymphoma, small cell variant.

According to the clinical guidelines for the treatment of T-cell lymphoma, the patient is indicated to undergo induction courses of PCT according to the BV-CHP protocol (brentuximab vedotin, cyclophosphamide, doxirubicin, prednisolone) with concomitant therapy.

Conclusions. We present a small-cell variant of anaplastic large-cell lymphoma for mandatory inclusion of this type of lymphoma in the morphological differential series, especially on a small volume of diagnostic material. This tumour can be confused with reactive processes, so a multidisciplinary approach is necessary. The prognosis of this variant of ALCL is extremely unfavourable due to its aggressive course and frequent bone marrow involvement in patients.

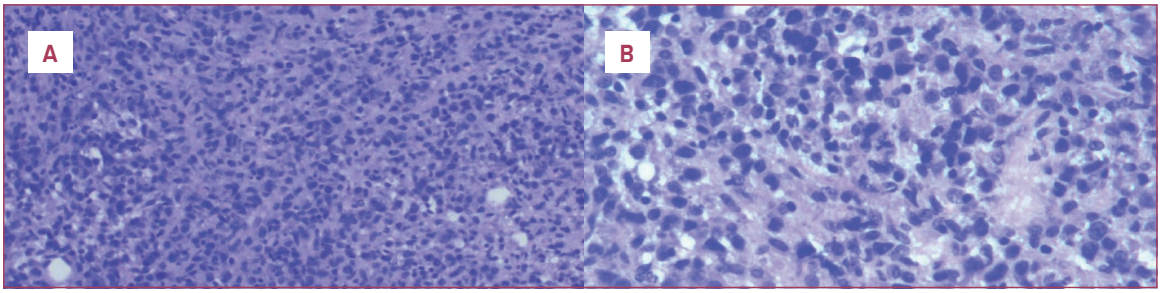

Figure 1. Anaplastic T-cell lymphoma — small cell variant, hematoxylin and eosin staining: (A) lymph node pattern is obliterated due to polymorphous cellular infiltrate ×20/0,40; (B) medium-sized cells with clear cytoplasm and horseshoe-shaped nuclei are seen ×40/0,65.

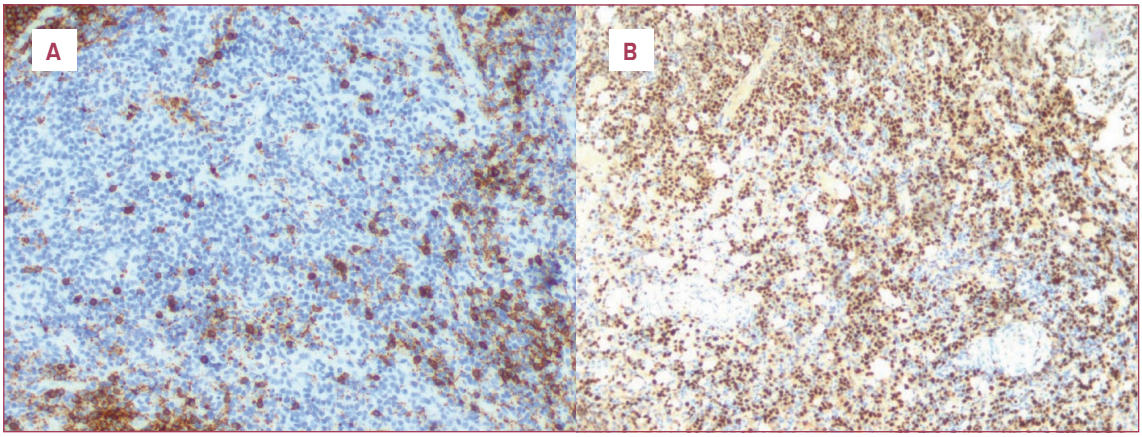

Figure 2. Anaplastic T-cell lymphoma — small cell variant: (A) Negative reaction with Cd20 in the tumour infiltrate. IHC, CD20, ×20/0.40; (B) high mitotic activity. IHC, ki-67, ×10/0,25

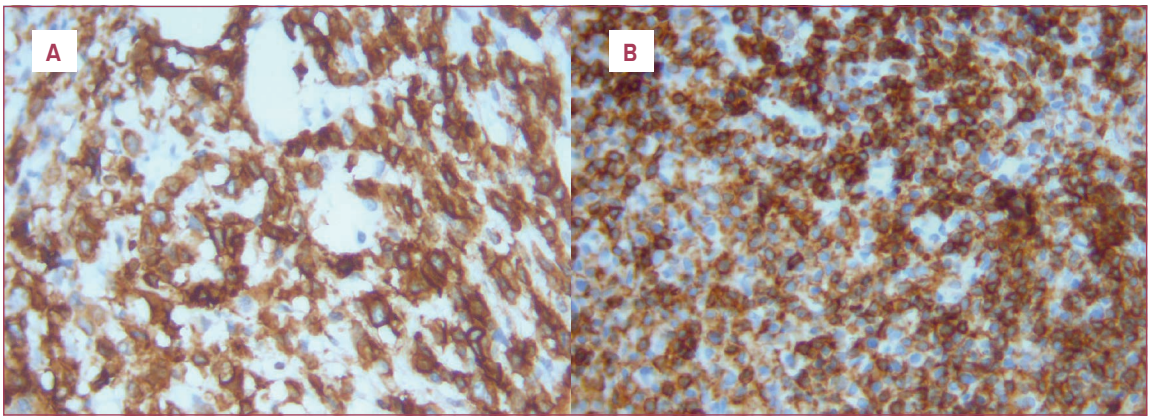

Figure 3. Anaplastic T-cell lymphoma — small cell variant. (A) Positive reaction with CD30 in tumour cells. IHC, Cd30 ×40/0.65; (B) positive reaction with CD4 in tumour cells. IHC, Cd4 ×40/0,65

Keywords: anaplastic large cell lymphoma, the small cell variant, morphology.

References

1. Dutta R, Ramteke P, Mathur SR, et al. Small Cell Variant Anaplastic Large Cell Lymphoma Presenting as Leukemia: A Case Report and Review of Literature. Indian Journal of Pathology and Microbiology. 2022; 65(3): 705. https://doi.org/10.4103/ijpm.ijpm_443_21.

2. Grigoropoulos RL, Wright P, Van t'Veer MB, et al. Pitfalls in the Diagnosis of Anaplastic Large Cell Lymphoma with a Small Cell Pattern. Case Reports in Hematology. 2013; 1–6. https://doi.org/10.1155/2013/840253.

3. Santonja C, Morillo-Giles D, Prieto-Pareja E, et al. Leukaemic Presentation of Small-Cell Alk-Positive Anaplastic Large Cell Lymphoma in a Young Woman—Report of a Case with 9-Year Survival. Medicina. 2023; 59(9): 1628. https://doi.org/10.3390/medicina59091628.

4. Summers TA, Moncur JT. The Small Cell Variant of Anaplastic Large Cell Lymphoma. Archives of Pathology & Laboratory Medicine. 2010; 134(11): 1706–10. https://doi.org/10.5858/2008-0624-RSR.1.

5. Zecchini Barrese T, Sagramoso C, Bacci F, Sabattini E. Small Cell Variant of Anaplastic Large Cell Lymphoma with Leukemic Presentation: A Diagnostic Challenge. Revista Brasileira de Hematologia e Hemoterapia. 2017; 39(3): 269–73. https://doi.org/10.1016/j.bjhh.2017.05.009.