

В редакцию журнала «Клиническая онкогематология. Фундаментальные исследования и клиническая практика» поступил обзор от профессора III Медицинской клиники медицинского факультета Гейдельбергского университета (г. Мангейм, Германия), председателя Европейской сети по изучению лейкозов «European LeukemiaNet» Рудигера Хельманна. По просьбе автора статья публикуется на английском языке.

### Современные возможности терапии первой линии хронического миелолейкоза в хронической фазе

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#### РЕФЕРАТ

Лечение ингибиторами тирозинкиназ (ИТК) принципиально изменило прогноз при хроническом миелолейкозе (ХМЛ). Рекомендации ELN-2013 предусматривают применение в качестве терапии первой линии ХМЛ иматиниба, дазатиниба или nilotinиба в равной степени, что определяет новый уровень ответа.

При использовании nilotinиба и дазатиниба ответ на лечение наблюдается в более короткий срок в сравнении с иматинибом в дозе 400 мг. Быстрый эффект также наблюдался при увеличении дозы иматиниба до 800 мг. Побочные эффекты ИТК 2-го поколения представляют серьезную проблему. Применение иматиниба не приводило к развитию тяжелых и длительных осложнений. Влияние быстрого противоопухолевого ответа на выживаемость послужило основанием для разработки новых критериев оптимального ответа и неудачи лечения. Уровень транскрипта BCR-ABL > 10% в соответствии с международной шкалой (IS) или обнаружение более 35% Ph-положительных метафаз к 6 мес. терапии оцениваются как неудача и показание к смене лечения. Определение этих критериев продолжает обсуждаться. Оптимизация терапии ИТК с целью достичь глубоких и длительных молекулярных ответов открывает возможности прекращения терапии и выздоровления.

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## Current best options for first line treatment of chronic phase chronic myeloid leukemia

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#### ABSTRACT

Treatment with tyrosine kinase inhibitors (TKI) has remarkably improved prognosis of chronic myeloid leukemia (CML). The 2013 ELN management recommendations recommend imatinib, dasatinib and nilotinib equally for first line treatment of CML and define new response levels.

Nilotinib and dasatinib induce responses faster than imatinib 400 mg. Faster responses are also observed with dose optimized imatinib 800 mg. Off-target effects of 2nd generation TKI are of concern. No serious long term side effects have been reported with imatinib. The impact of early response on survival has led to new definitions of optimal response and failure. More than 10% residual BCR-ABL transcripts according to the international scale (IS) or more than 35% Ph positive metaphases at 6 months are defined as failure and an indication for a change of treatment. The limitations of this definition are discussed. Optimization of TKI treatment to achieve deep and durable molecular responses provides a perspective for treatment discontinuation and cure of CML.

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#### INTRODUCTION

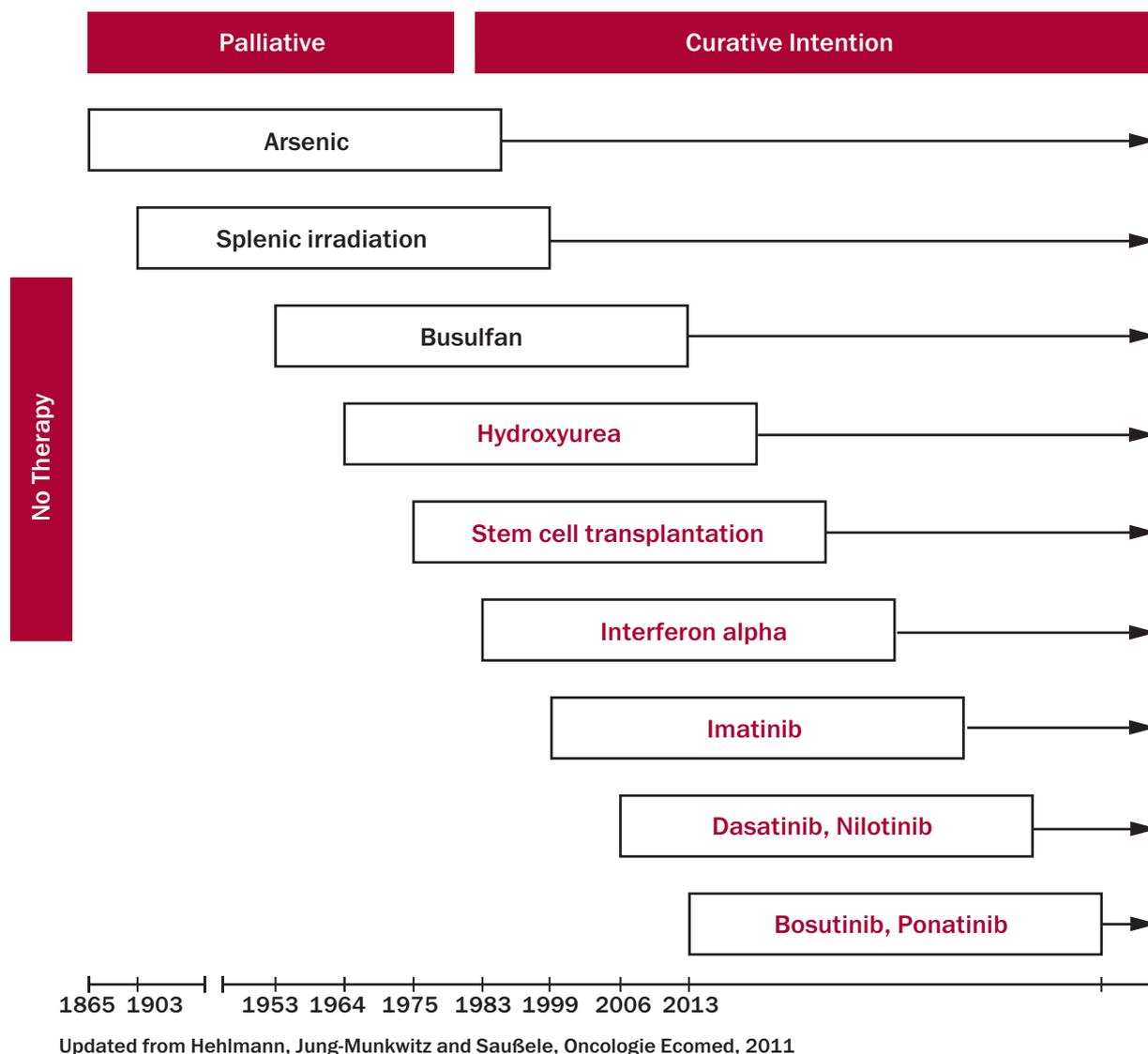
The 2013 ELN management recommendations [1] equally recommend imatinib, dasatinib and nilotinib as first line treatment of chronic myeloid leukemia (CML) in chronic phase (CP). There are differences between these three options regarding response, progression and safety. No definite differences regarding survival have been reported up to now. Differences in costs are minor at present [2], but may gain weight when generic imatinib becomes generally available in 2015.

Tyrosine kinase inhibitors are the preliminary end stage of a treatment evolution in CML that started 150 years ago (Fig. 1). Prolongation of life was first reported for hydroxyurea [3, 4] and for interferon- $\alpha$  [5, 6]. Cures became possible with the advent of allogeneic stem cell transplantation

[7–9]. These treatment modalities represented first line treatment options of choice before imatinib was approved for CML in 2001. The progress with survival of CML over the last 30 years is illustrated by the experience of the German CML Study Group (Fig. 2).

Imatinib profoundly changed the natural course of CML. Much of our knowledge stems from the International Randomized study on Interferon and STI 571 (former name of imatinib) abbreviated IRIS [10, 11]. Meanwhile a second randomized study that compares two doses and three combinations of imatinib has matured, the German CML Study IV [12]. Table 1 lists the main features and results of these two randomized studies. At 10 years, 83–84% of imatinib treated patients are still alive, and the rate of complete cytogenetic remission (CCR) at 2 years is about 80%. Patients in

## 150 Years of CML Therapy



**Fig. 1.** 150 years of CML therapy

CCR have been shown to have a life expectancy similar to that of the general population [13].

A remarkable feature of imatinib is its long term safety. No serious toxicity has surfaced since its first clinical use in 1998. A limitation of imatinib is that about a third of imatinib treated patients develop resistance or serious intolerance to imatinib [14]. Mutations of the kinase domain of BCR-ABL are a frequently observed, well documented cause of resistance [15]. Dasatinib and nilotinib (approved in 2006 and 2007) can overcome most resistance mutations and appear to be better tolerated in many patients. The problem of these drugs is the appearance of life threatening toxicities in some patients. This article will summarize the current best options for first line treatment of CP CML.

#### Rationale of CML-therapy

According to current understanding of CML-pathogenesis BCR-ABL is thought to stimulate signaling and proliferation and to promote genetic instability and DNA damage (Fig. 3). Early and rapid reduction of BCR-ABL would reduce genetic instability and progress to advanced phase. 2nd generation TKI as well as dose optimized imatinib act more rapidly and reduce BCR-ABL tumor load faster

than imatinib 400 mg. Further treatment optimization, for instance by early switching of suboptimal treatment might further decrease rates of progression and death and increase rate of cure.

#### 2nd generation TKI

All studies with 2nd generation TKI first line show that responses are achieved faster than with imatinib 400 mg [16–21]. This applies to cytogenetic and molecular remissions at all levels (CCR, major molecular remission (MMR), MR<sup>4</sup>, and MR<sup>4.5</sup>). Observation time of all studies is not long enough to decide whether not only the remission rates, but also the remission levels are higher with 2nd generation TKI than with imatinib 400 mg. There are fewer mutations [22] and less early progressions with 2nd generation TKI, particularly with nilotinib. This might indicate a survival advantage in the future. But at present, no convincing survival advantage has been shown.

#### High dose imatinib

Several studies have shown that imatinib 800 mg also induces remissions faster [23–26]. A randomized study

### Survival with CML over time The German CML-Study Group experience

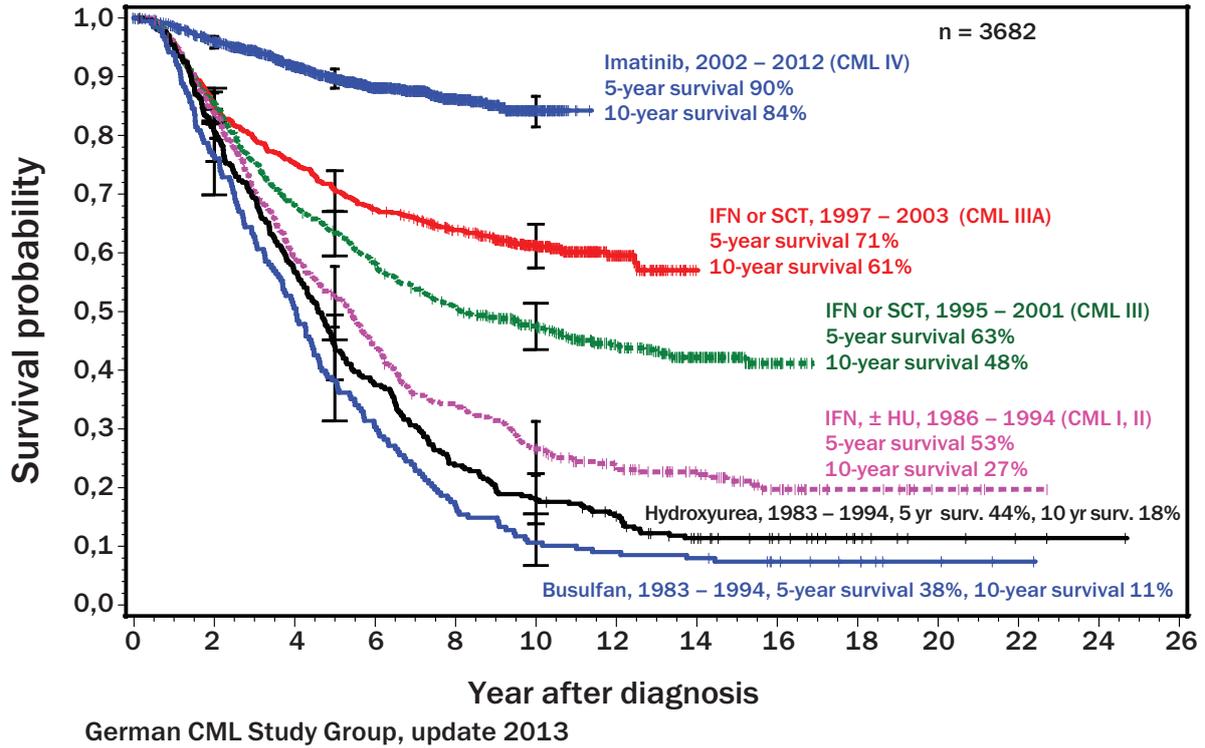


Fig. 2. Survival with CML over time. The German CML Study Group experience

Table 1. Imatinib after 10 years — Results from randomized trials

Study	CML Study IV	IRIS
Recruitment	7/2002–3/2012	6/2000–1/2001
Sample size, <i>n</i>	1551	1106
Patients	No age limit, newly diagnosed	18–70 years, newly diagnosed
No of therapy groups	5	2
Median observation time, years	6.5 (max 11.5)	NA (8 in 2009, max 11.5 in 2012)
10 year OS, %	84	83.3
Number of deaths, <i>n</i>	185	194
CCR at 12 months, %	63	69
CCR at 24 months, %	82	76
Most frequent AEs	GI, edema, myalgia/arthritis, rash, fatigue, cytopenias, elevated transaminases + liver disease, elevated creatinine + kidney disease	Edema, GI, musculoskeletal pain, rash, fatigue, cytopenias, hypophosphatemia, elevated transaminases and bilirubin

### Role of BCR-ABL in CML

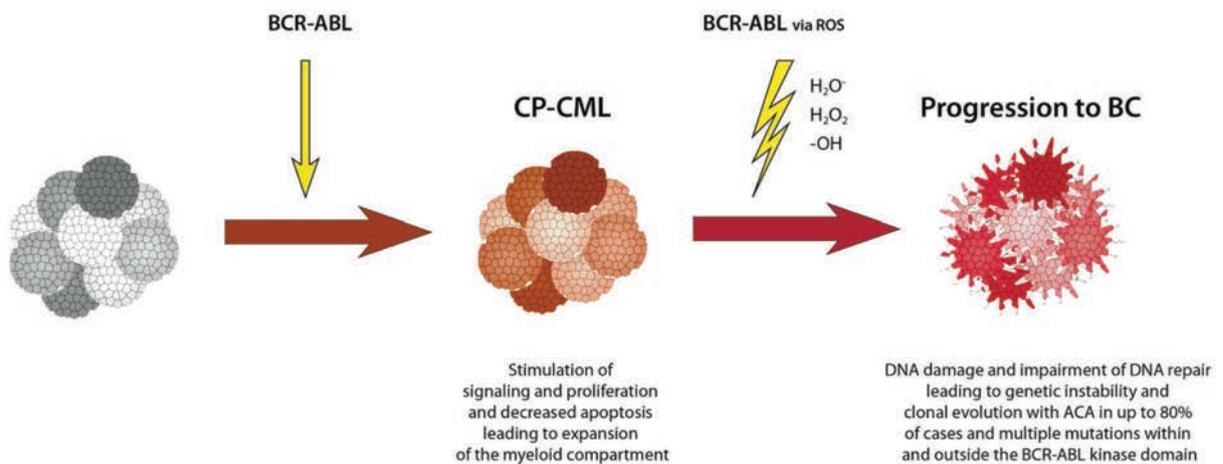
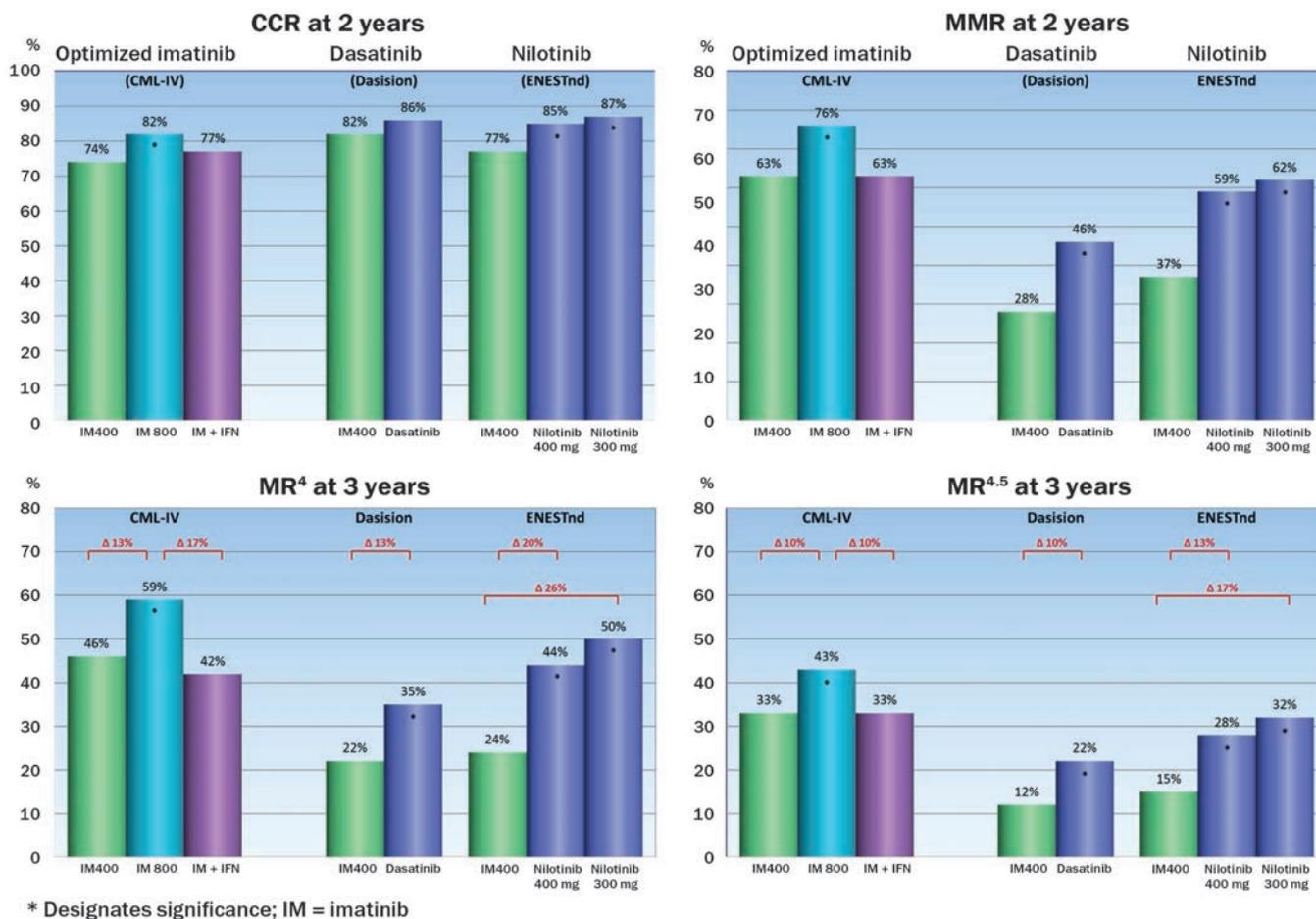


Fig. 3. Role of BCR-ABL in CML-CP and blast crisis

## Summary of responses to dose optimized imatinib, dasatinib and nilotinib in comparison to standard imatinib



**Fig. 4.** CCR and MMR at 2 years, MR<sup>4</sup> and MR<sup>4.5</sup> at 3 years of imatinib, dasatinib and nilotinib. Data from randomized trials (CML study IV, Dasision, ENESTnd)

comparing imatinib 800 mg with imatinib 400 mg [27] could ascertain a faster remission rate with imatinib 800 mg up to 9 months, but not later on. Another randomized study, the German CML-Study IV [12], that also compared imatinib 800 mg with imatinib 400 mg, adapted the dose of imatinib 800 mg according to tolerability to avoid higher toxicity and to secure patients' compliance and found significantly faster cytogenetic and molecular responses with imatinib 800 mg than with imatinib 400 mg similar to what is being observed with 2nd generation TKI.

A summary of responses (CCR and MMR at 24 months, MR<sup>4</sup> and MR<sup>4.5</sup> at 36 months) to imatinib, dasatinib and nilotinib is shown in Fig. 4.

### Safety

Whereas frequent, but mostly mild adverse events may impact quality of life, no serious late toxicities have surfaced with imatinib since its first clinical application in 1998. In contrast, serious toxicities with fatalities have been reported with 2nd generation TKI: pulmonary arterial hypertension (PAH) in some patients treated with dasatinib reversible after dasatinib discontinuation [28] and peripheral arterial occlusive disease (PAOD) in 1–2.5 % of nilotinib treated patients [29, 30]. The vascular risk of nilotinib treatment can be recognized early by the ankle-brachial index (ABI) [30].

These off-target effects require careful selection and observation of patients to be treated with 2nd generation TKI. Long term observation will provide information on the exact frequency of these events.

### Prognostic predictors

Three risk scores are available for prognostic prediction at diagnosis: The Sokal score developed from chemotherapy (mostly busulfan) treated patients [31], the Euro score developed from interferon  $\alpha$  treated patients [32] and the most recent EUTOS score developed from imatinib treated patients [33]. All three scores can be used. Recently, clonal chromosomal abnormalities at diagnosis have been identified as an indicator of poor prognosis [34]. Patients with unbalanced abnormalities such as +8, +Ph, +19, and iso(17) at diagnosis should receive more intensive treatment early.

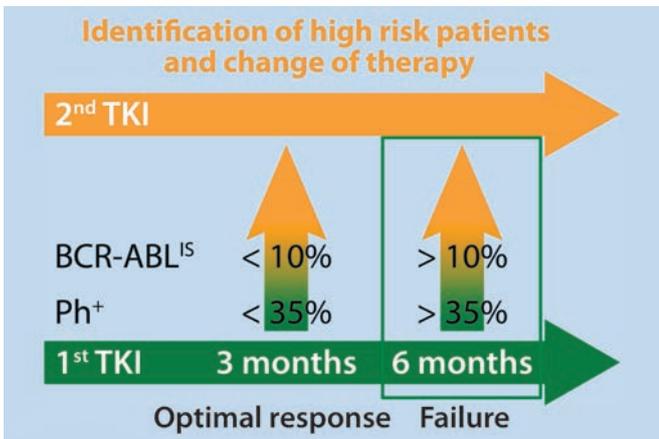
The currently most potent predictor of prognosis is response to therapy. BCR-ABL response levels more or less than 10 % according to the international scale (IS) at 3 and 6 months have been identified as early prognostic indicators [35, 36]. Deeper responses (MMR at 12 months, MR<sup>4.5</sup> at 48 months) are predictors of survival similar or superior (MR<sup>4.5</sup>) to CCR [12, 37] (Table 2). The deeper the molecular responses are, the less progressions are observed (Table 3). The response level at 6 months has been defined by the ELN

**Table 2.** BCR-ABL response levels have prognostic value

At 3 and 6 months	≤ 10% BCR-ABL <sup>IS</sup> predictive of PFS and OS with imatinib, dasatinib, nilotinib [35, 36, 42, 43]
At 12 months	MMR and CCR equally predictive of OS [12]
At 48 months	MR <sup>4.5</sup> more predictive of OS than CCR [37]

**Table 3.** Progressions according to depth of response

Response	Observation time,		Deaths, n	Progressions, n
	years	5-year survival, %		
CCR	4.7	94	47	13
MMR	4.5	95	42	9
MR <sup>4</sup>	3.8	97	17	1
MR <sup>4.5</sup>	3.0	97	6	0



**Fig. 5.** Identification of high risk patients and change of therapy by early molecular response

expert panel [1] as a criterion for switching treatment to another TKI (Fig. 5).

**ELN-management recommendations**

Taking the experience with 2nd generation TKI and the recognition of the relevance of early response into account, the ELN expert panel has revised the response definitions for first line treatment with imatinib, dasatinib and nilotinib [1] (Table 4). The category “suboptimal response” has been incorporated in a “warning” category. Optimal response is now less than 10 % BCR-ABL<sup>IS</sup> or less than 35 % Ph+ metaphases at 3 months, less than 1 % BCR-ABL<sup>IS</sup> or CCR at 6 months and less than 0.1 % BCR-ABL<sup>IS</sup> (MMR) at 12 months. Failure is defined as no complete hematologic remission or more than 95 % Ph-positivity at 3 months, more than 10 % BCR-ABL<sup>IS</sup> or more than 35 % Ph-positive metaphases at 6 months, and BCR-ABL<sup>IS</sup> more than 1 % and no CCR at 12 months. All three TKI are recommended equally for first line treatment of CP-CML. Further treatment recommendations are based on the response definitions in Table 5.

Early allogeneic stem cell transplantation is limited to the few suitable patients with very low transplantation risks according to the EBMT-score (score 0 and 1). Data of the

CML-Study IV show that survival of patients transplanted early in CP (ca. 90 % at 3 years) is similar to that of TKI treated patients [38].

**DISCUSSION**

Current evidence shows that cytogenetic and molecular responses occur earlier with dasatinib and nilotinib than with imatinib 400 mg in first line treatment of CP-CML [39, 40]. Optimized high dose imatinib at an initial dose of 800 mg adapted to tolerability also induces earlier cytogenetic and molecular responses similar to 2nd generation TKI [12]. There are fewer initial mutations [22] and progressions to accelerated and blast phase with 2nd generation TKI than with imatinib which may provide a small early advantage over imatinib. But also with imatinib the initial progression rate is very low with only few progressions to blast crisis after 4 years [41]. No convincing survival advantage has been shown for any TKI in spite of faster responses and fewer early progressions with 2nd generation TKI. There may be a small but definite safety advantage of imatinib over 2nd generation TKI. Taken everything together the equal recommendation by ELN of all 3 TKI for first line treatment of CP-CML seems justified.

The data from virtually all studies with imatinib, nilotinib and dasatinib show that early response indicates better progression-free and overall survival [35, 36, 42, 43]. There are no data from prospective studies to show that an early switch from one TKI to another improves survival. All early response data come from retrospective analyses of subgroups from studies that were not designed to analyze the impact of early response. The observed differences between TKI are much more significant for responses than for outcome. Switching may be useful in some patients but may harm others (switch many to benefit few). The late off-target side effects of 2nd generation TKI are worrisome in this context, although their exact mechanism and frequency are still unknown.

An important perspective for the future is treatment discontinuation. Several studies show that unmaintained discontinuation can be achieved in a substantial minority

**Table 4.** Response definitions for any TKI first line, all patients (CP, AP and BP)

Time	Optimal response	Warnings	Failure
Base-line		High risk Major route CCA/Ph+	–
3 months	BCR-ABL <sup>IS</sup> ≤ 10 %* Ph+ ≤ 35% (PCyR)	BCR-ABL <sup>IS</sup> > 10 %* Ph+ 36–95%	No CHR* Ph+ > 95%
6 months	BCR-ABL <sup>IS</sup> < 1 %* Ph+ 0% (CCyR)	BCR-ABL <sup>IS</sup> 1–10 %* Ph+ 1–35%	BCR-ABL <sup>IS</sup> > 10 %* Ph+ > 35%
12 months	BCR-ABL <sup>IS</sup> ≤ 0.1 %* (MMR)	BCR-ABL <sup>IS</sup> 0.1–1 %*	BCR-ABL <sup>IS</sup> > 1 %* Ph+ > 0%
Then, at any time	MMR or better	CCA/Ph– (–7, or 7q–)	Loss of CHR Loss of CCyR Loss of MMR, confirmed** Mutations CCA/Ph+

\* and/or \*\* in 2 consecutive tests, of which one ≥ 1 % IS: BCR-ABL on International Scale.

Table 5. Treatment recommendations

Line	Event	TKI, standard dosage <sup>1</sup>					Transplantation				
		Imatinib 400 mg/qd	Nilotinib 300 mg/bid	Dasatinib 100 mg/qd	Bosutinib 50 mg/qd	Ponatinib 45 mg/qd	Search for HLA type, + sibbs	unrelated donor	alloSCT consider	recommended	Chemotherapy
Chronic phase											
1 <sup>st</sup>	Baseline	x	x	x			X <sup>2</sup>				
2 <sup>nd</sup>	Intolerance to 1 <sup>st</sup> TKI	Any other TKI approved 1 <sup>st</sup> line									
	Failure 1 <sup>st</sup> line of	Imatinib	x <sup>8</sup>	x	x	x	x	x	x		
		Nilotinib		x	x	x	x	x	x		
		Dasatinib	x <sup>8</sup>		x	x	x	x	x		
3 <sup>rd</sup>	Intolerance to/failure of two TKI	Any remaining TKI									
Any	T315I mutation					x	x	x	x		
Accelerated or blast phase											
In newly diagnosed, TKI naive patients	Start with	X <sup>3</sup>		X <sup>4</sup>			x	x			
	No optimal response, BP									X <sup>7</sup>	X <sup>5</sup>
TKI pre-treated patients			Any of the other TKI				X <sup>6</sup>			X <sup>7</sup>	X <sup>5</sup>

<sup>1</sup> Choice of the TKI consider tolerability and safety, and patient characteristics (age, comorbidities).

<sup>2</sup> Only in case of baseline warnings (high risk, major route CCA/Ph+).

<sup>3</sup> 400 mg/bid.

<sup>4</sup> 70 mg/bid or 140 mg/qd.

<sup>5</sup> May be required before SCT to control disease and to make patients eligible to alloSCT.

<sup>6</sup> In case of T315I mutation.

<sup>7</sup> Only patients who are eligible for alloSCT, not in case of uncontrolled, resistant BP.

<sup>8</sup> 400 mg bid in failure setting.

qd: once daily; bid: twice daily.

of patients, if molecular responses to TKI are deep and durable enough [44, 45]. Treatment costs and problems with quality of life due to lifelong TKI treatment could be solved by the achievement of a cure. Progress with deeper molecular responses e.g. at the MR<sup>4.5</sup> or MR<sup>5</sup> response levels [37, 46] will increase the proportion of candidates for TKI discontinuation. A Europe-wide study (EURO-SKI) stops TKI under controlled conditions. This could be an important step towards cure of CML.

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