10 A Review and an Update of European LeukemiaNet Recommendations for the Management of Chronic Myeloid Leukemia

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10.1 Introduction

The first version of the European LeukemiaNet (ELN) recommendations for the treatment of chronic myeloid leukemia (CML) was published in 2006 [1], the second and the third ones were published in 2009 and in 2013, respectively [2, 3]. Over this period, the ELN recommendations have provided an internationally shared basis for the treatment and monitoring of CML, contributing to the improvement of the management of CML. Over this period, patients with CML have enjoyed a survival that is nearly identical to the survival of the general population [4, 5], with an acceptable quality of life, due to the high efficacy and the low toxicity of the targeted treatment. Other ELN recommendations and reviews concerning the management of BCR-ABL kinase point mutations, the side-effects, and the toxicity of tyrosine kinase inhibitors (TKI) were published in 2011 and in 2016, respectively [6, 7]. Now the recommendations have been updated and published [8]. In this chapter we analyze and discuss the evolution of the ELN recommendations over a 15-year period, and we compare the last version with other recent recommendations and guidelines that have been proposed by the European Society of Medical Oncology (ESMO) [9], the Italian Group for Hematologic Diseases of Adults (GIMEMA) [10], the British Society of Haematology (BSH) [11], and the National Comprehensive Cancer Center Network (NCCN) [12].

10.2 The Phases of CML

More than 95% of patients are diagnosed in the chronic phase (CP), 2–3% are diagnosed in the accelerated phase (AP), and 2–3% are diagnosed in the blastic phase (BP) [1–3, 8, 9]. The patients who are diagnosed in AP or in BP require TKI as the patients who are diagnosed in CP, but, in many cases, they require also allogeneic stem cell transplantation (SCT) [8]. In the chemotherapy era, almost all patients were progressing to BP, either directly (blast crisis) or

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through a transient AP. In the TKI era, the rate of progression is much lower (<10%) than in the chemotherapy era [8], but the recognition of the disease phase is still important. It is noticeable that in spite of progress in molecular biology, the boundaries between the three phases are mostly based on the same clinical and hematologic criteria that were selected many years ago [13, 14].

The 2013 version of the ELN recommendations [3] proposed the following definitions: for AP 15–29% blast cells, or blasts plus promyelocytes in blood or marrow >30%, with blasts <30%, or a platelet count <100 × 10^9/L unrelated to treatment, or another clonal chromosome abnormality (ACA) in Ph + cells (ACA/Ph+); for BP, a blast cell percentage ≥ 30% in blood or marrow or blast cell involvement of non-hematopoietic tissues or organs, excluding spleen and liver.

In the latest 2020 ELN version [8], the boundaries between CP and AP are no longer specified. Therefore, one could still rely on the definition of AP given in the 2013 ELN recommendations [3] or rely on another definition, which includes provisional criteria of response to TKI, as proposed in the 2017 WHO classification [15]. This uncertainty reflects doubts on whether the term "AP" should be maintained and used in clinical studies, as it has been for so many years, or if the term "AP" should be removed. As a matter of fact, in the TKI era it is difficult, and it is not very useful to assess the status of the disease based on clinical and hematological findings because the status of the disease can be assessed earlier, based on molecular response. A patient who "fails" (being resistant or intolerant) four TKIs has already entered into a phase of the disease that puts him at a high-risk of dying of leukemia [10], without taking into consideration blood cell counts and differential, particularly without waiting for a progressive increase of blast cells or the development of splenomegaly. In addition, the emergence of high-risk additional chromosome abnormalities in Ph + cells (ACA/Ph+) during TKI treatment is another confirmed signal of progression [16–22], and the finding of other somatic mutations may be also important [23]. For these reasons, the ELN 2020 recommendations use the term "end-phase CML," which comprises "early progression with emerging high-risk ACA and late progression with failing hematopoiesis and blast cell proliferation." BP is a late feature of progression, defined by the ELN only by the blast cells count (≥30%) in blood or marrow. In contrast, in the 2017 WHO classification [15], the definition of BP is still based on a proportion of blast cells ≥20% or on a blast cell involvement of other non-hematopoietic tissues or organs. Importantly, not all patients dying of CML reach the BP-defining blast levels.

10.3 Prognostic Factors

10.3.1 Baseline

Historically, CML was an almost always fatal disease, but it was well recognized that survival could range between few and many years, already in the chemotherapy era. The Sokal score [13], which was proposed as early as 36 years ago, based on the survival of patients treated with conventional chemotherapy, was found to predict response and survival also for patients treated with interferon-alpha and for patients treated with TKIs, particularly with imatinib. By the Sokal score, about 40% of patients are classified low-risk, about 40% are classified intermediate risk, and about 20% are classified high-risk. Other prognostic scores have been developed based on patients treated by interferon-alpha (EURO or Hasford score) [24], and in patients treated with imatinib (EUTOS score) [25]. Both EURO and EUTOS scores predict response and survival also in patients treated with imatinib. However, in the TKI era the causes of death are changed: about 50% of the CML patients who die, die in remission and not of leukemia. Therefore, another prognostic score, the Eutos Long-Term Survival Score (ELTS) [26] has been proposed. It has the merit of distinguishing the patients according to the risk of dying of leukemia: by the ELTS score about 60% of patients fall in the low-risk group, with a probability of dying of leukemia of 1–2%, about 30% in the intermediate-risk group, with a probability of dying of leukemia of 5–10%, and only about 10% in the high-risk group, with a probability of dying of leukemia of 10–20%. The last ELN recommendations [8] and the GIMEMA [10] and the BSH [11] recommendations recommend to use, prospectively, the ELTS score. The ELTS score is calculated using age, spleen size,

platelet count, and blast cell percentage in blood as it was the Sokal score. It is noticeable, and a bit unexpected, that after two decades of molecular studies, the prognosis at baseline is still based on clinical and hematologic findings and that splenomegaly is still assessed by manual palpation of the spleen, expressed as the maximum distance below the costal margin.

The calculation of the Sokal and of the ELTS scores is reported in Table 10.1. Both scores provide valuable information of long-term survival, and both are currently used to plan treatment because it is believed that low-risk patients may have a maximum benefit using imatinib in the first line. This belief is supported by solid evidence. It is also believed that high- and also intermediate-risk patients may benefit more of the earlier, first line, use of the "more potent" second-generation TKIs, but this expectation is not supported by solid evidence [8–11]. As a matter of fact, the strategies of treatment of high-risk patients have never been specifically designed and tested, such as the choice of the TKI, the doses, the role of allogeneic SCT, and the degree of the molecular response, optimal, warning or failure at the conventional cornerstones (3, 6, 12 months, and later).

Sokal and ELTS are not the unique prognostic factors that have been identified and proposed. Several reports have highlighted the importance of ACA/Ph + (including trisomy 8, +Ph, isochromosome 17 [i(17q10], trisomy 19, −7/−7q, 11q23 or 3q26.2 aberrations, and complex abnormalities [16–22, 27]), so that ACA/Ph + have been now recognized as baseline high-risk factors irrespective of Sokal and ELTS [8, 10]. Other factors were proposed [28–41], including the low expression of the organic cation transporter (OCT1) that prevents the influx into the cells of imatinib, the high expression and some polymorphisms of the MDR1 (ABCB1) proteins that increase the efflux of TKI from the cells, a high level of the cancerous inhibitor of PP2A (CIP2A), some polymorphisms or the deletion of BIM more frequently found in Asian countries, the KIR2DS1 genotype associated with resistance to imatinib, a high serum level of tryptase, the fiber content in bone marrow biopsies, and also the immunophenotype showing the simultaneous detection of lymphoid markers in blast cells. Although some of these factors could theoretically be useful to guide the choice beteween imatinib and second-generation TKIs, none of these factors have come into clinical use, and none were recommended so far.

The transcript type of the major BCR-ABL gene may influence to some extent the sensitivity to TKIs, the e13a2 (b2a2) type being less sensitive to TKIs than the e14a2 (b3a2) type and, accordingly, the probability of achieving a deep molecular response and a treatment-free remission [42]. Until now, the BCR-ABL transcript type has not been included as a prognostic parameter in the ELN 2020 recommendations.

Different gene expression profiles (GEP) associated with progression from CP to advanced phases, and with some degree of resistance to imatinib, were reported already years ago [43]. More recently the introduction of new, next-generation, molecular biotechnologies has called attention to the value of additional somatic genomic abnormalities [44], similar to those that have been detected in acute leukemia, in the myelodysplastic syndromes, and also in healthy, elderly people [45]. These studies could pave the way to new targeted therapies.

10.3.2 During TKI Treatment

The response to TKIs, including the time to response and the depth of the response, are more

Table 10.1 The two main risk scoring systems, at diagnosis

Sokal	Exp 0.0116 × (age − 43.4) + 0.0345 × (spleen − 7.51) + 0.188 × ((platelets/700)^2 − 0.563) + 0.0887 × (blasts − 2.10)
	Low-risk < 0.80. intermediate 0.81–1.20 high > 1.21
	http://www.leukemia-net.org/content/leukemias/cml/cml_score index_eng.Html.
ELTS	0.0025 × (age/10)^3 + (0.0615 × spleen) + (0.1052 × blasts) + ((0.4104 × (platelets/1000)$^{-0.5}$).
	Low-risk ≤ 1.5680, intermediate risk 1.5680–2.2185, high-risk > 2.2185
	http://www.leukemianet.org/content/leukemias/cml/eutos_score/index_eng.html.

Age in years, spleen in cm below the costal margin; platelets × 1000; blasts in % (peripheral blood)

important than all baseline factors. Cytogenetics is still valuable, but the assessment of the BCR-ABL level by the international standard (IS) is more sensitive and more accurate than the cytogenetic response. The definition of molecular response during treatment, as proposed by the most recent recommendations and guidelines [8, 10–12], is discussed thoroughly in the next section. Still, the definition of the response and its interpretation for guiding the treatment are based on a single value, sometimes on two consecutive tests in case of borderline values. However, the value of the qPCR may be better assessed not by an absolute value, but by the time that is necessary to reach that value [46] and more generally by the dynamics of the decrease of the BCR-ABL transcript level [47]. There is some reluctancy to adopt these dynamic criteria in practice, which is regrettable, because they may help taking several important decisions, concerning both the early and the late switch from one TKI to another, particularly to improve the rate of treatment-free remission.

10.4 Response Definition: The Evolution of Treatment Recommendations

Imatinib (IMA) was approved in the first-line treatment of CML in 2003, and for a short period it was the only TKI that was available [1]. Soon after, due to the development and the approval of second-generation (2G) TKIs, nilotinib (NIL) and dasatinib (DAS), in second line (in the patients resistant to or intolerant of imatinib) [2], as well as in the first-line setting [3], the criteria for the assessment of response definition have been progressively modified, leading to a more flexible definition of the responses, either optimal or failure or suboptimal (warning), at several critical cornerstones. In the case of optimal response, the recommendation is to continue the same TKI at the same dose. In the case of failure, the recommendation is to switch to another TKI. When the response is suboptimal (warning), the recommendation is to consider another TKI, depending on several variables, including the patient's age, health conditions, comorbidities, tolerability, and also on the goal of the treatment, either survival and quality of life or the achievement of a condition of treatment-free remission (TFR).

The evolving scenario of response definition and treatment recommendations can be better appreciated comparing the ELN recommendations that were published from 2006 (first version) [1] to 2020 (fourth and last version) [8] (Table 10.1). In 2006 and in 2009 the early (3, 6, and 12 months) response was based on hematologic and cytogenetic data [1, 2]. In 2013 the response was based on cytogenetic or on molecular data [3]. In 2020 only the molecular data were considered because molecular tests are more sensitive than cytogenetics [8]. Moreover, they are performed on blood cells, so avoiding a marrow aspirate. However,cytogenetics is still recommended in case of molecular failure because the detection of ACA/Ph highlights the danger of progression.

In the last version of the ELN recommendations [8], at 3 months the response is optimal if BCR-ABL is $\leq 10\%$, it is warning if BCR-ABL is >10% in one test, and it is failure, if BCR-ABL is >10%, and the value is confirmed within 1–3 months; at 6 months it is optimal if BCR-ABL is $\leq 1\%$, it is warning if BCR-ABL is >1–10%, and it is failure if BCR-ABL is >10%; at 12 months the response is optimal if BCR-ABL is $\leq 0.1\%$ (MMR or MR 3.0), it is warning if BCR-ABL is >0.1–1%, and it is failure if BCR-ABL is >1%. The detection of mutations during treatment is always a marker of failure. After 12 months, and later on, if the BCR-ABL transcript level is $\leq 0.1\%$ (optimal response) ELN 2020 recommends to continue the same TKI, while in the case of BCR-ABL > 0.1–1% (warning) there is a choice, either to change or to continue. If the BCR-ABL transcript level is >1% (failure), ELN recommends changing the TKI. These definitions are the same as in the last but one version of 2013.

In Table 10.2, the last ELN recommendations [8] are compared with the last ESMO (2017) [9] and NCCN (2.2021) guidelines [12], and with the recommendations that were recently proposed by GIMEMA (2019) [10] and by the BSH (2020) [11]. At 3 months, the response is defined as optimal by all recommendations and guidelines if the

Table 10.2 ELN definitions

Optimal response (= continue with the same TKI)					
Year	**3 months**	**6 months**	**12 months**	**18 months**	**Later**
2006	CHR	PCyR	CCyR	BCR-ABL ≤ 0.1%	NS
2009	CHR and Ph + ≤ 65%	Ph + ≤ 35%	CCyR	BCR-ABL ≤ 0.1%	Stable MMR
2013	PCyR or BCR-ABL ≤ 10%	CCyR or BCR-ABL ≤ 1%	BCR-ABL ≤ 0.1%	NS	MMR or better
2020[a]	BCR-ABL ≤ 10%	BCR-ABL ≤ 1%	BCR-ABL ≤ 0.1%	NS	BCR-ABL ≤ 0.1%
Suboptimal response or warning (= consider a switch to another TKI)					
Year	**3 months**	**6 months**	**12 months**	**18 months**	**Later**
2006	CHR	Ph+ > 35%	Ph + 1–35%	BCR-ABL > 0.1%	ACA/Ph+, response loss, mutations
2009	Ph+ > 95%	Ph + 35–95%	Ph + 1–35%	BCR-ABL >0.1–1%	MMR loss, mutations
2013	Ph + 36–95% or BCR-ABL > 10%	Ph + 1–35% or BCR-ABL > 1–10%	Ph + ≥ 1% or BCR-ABL > 0.1–1%	NS	ACA/Ph+
2020	BCR-ABL > 10%	BCR-ABL > 1–10%	BCR-ABL > 0.1–1%	NS	BCR-ABL > 0.1–1%
Failure (= switch to another TKI)					
Year	**3 months**	**6 months**	**12 months**	**18 months**	**Later**
2006	No HR	< CHR or Ph+ > 95%	Ph+ > 35%	Ph + ≥ 1%	Response loss
2009	< CHR	Ph+ > 95%	Ph+ > 35%	Ph + ≥ 1%	Response loss, mutations, ACA/Ph+
2013	< CHR or Ph+ > 95%	Ph+ > 35% or BCR-ABL > 10%	Ph + ≥ 1% or BCR-ABL > 1%	NS	Response loss, ACA/Ph+, mutations
2020	BCR-ABL > 10%, confirmed	BCR-ABL > 10%	BCR-ABL > 1%	NS	BCR-ABL > 1%, HR ACA/Ph+, resistance mutations

NS not specified, *HR* high-risk, *ELN* European LeukemiaNet. CHR = complete hematologic response (WBC count <10,000/μl, differential without immature granulocytes and with less than 5% basophils, platelet count <450,000/μl, nonpalpable spleen) ACA/Ph+ additional chromosomal abnormalities in Ph+ cells
Cytogenetic response (CyR): Ph+ >95% (no CyR), Ph + 66–95% (minimal CyR), Ph + 36–65% (minor CyR),Ph + 1–35% (Partial CyR), Ph + 0 (Complete CyR). Molecular response (MR): BCR-ABL >10% (no MR), BCR-ABL >1–10% (MR 1.0), BCR-ABL > 0.1–1% (MR 2.0), BCR-ABL ≤ 0.1% (MMR or MR 3.0), BCR-ABL ≤ 0.01% (MR 4.0)
[a]For patients aiming at TFR, the optimal response (at any time) is BCR-ABL1 ≤ 0.01% (MR4)

Table 10.3 ELN, NCCN, BSH, GIMEMA, and ESMO latest definitions

Optimal response (= continue with the same TKI)				
	3 months	**6 months**	**12 months**	**Later**
ESMO 2017	Ph + ≤ 35% or BCR-ABL < 10%	Ph + 0% or BCR-ABL < 1%	BCR-ABL < 0.1%	BCR-ABL < 0.01%[a]
GIMEMA 2019	BCR-ABL ≤ 10%	BCR-ABL ≤ 1%	BCR-ABL ≤ 0.1%	BCR-ABL ≤ 0.01%
BSH 2020	BCR-ABL ≤ 10%	BCR-ABL ≤ 1%	BCR-ABL ≤ 0.1%	BCR-ABL ≤ 0.1%
ELN 2020[b]	BCR-ABL ≤ 10%	BCR-ABL ≤ 1%	BCR-ABL ≤ 0.1%	BCR-ABL ≤ 0.1%
NCCN 2.2021	BCR-ABL ≤ 10%	BCR-ABL ≤ 10%	BCR-ABL ≤ 0.1%[a] BCR-ABL > 0.1–1%[c]	NS
Suboptimal response or warning (= consider a switch to another TKI)				
	3 months	**6 months**	**12 months**	**Later**
ESMO 2017	Ph + 36–95% or BCR-ABL > 10%	Ph + 1–65% or BCR-ABL ≥ 1–10%	Ph + 0% or BCR-ABL ≥ 0.1–1%	BCR-ABL ≥ 0.1–1%
GIMEMA 2019	NS	BCR-ABL > 1–10%	BCR-ABL > 0.1–1%	BCR-ABL > 0.01–0.1%
BSH 2020	BCR-ABL > 10%	BCR-ABL > 1–10%	BCR-ABL > 0.1–1%	BCR-ABL 0.1–1%
ELN 2020	BCR-ABL > 10%	BCR-ABL > 1–10%	BCR-ABL > 0.1–1%	BCR-ABL > 0.1%
NCCN 2.2021	BCR-ABL > 10%	NS	BCR-ABL > 1–10%	NS
Failure (= switch to another TKI)				
	3 months	**6 months**	**12 months**	**Later**
ESMO 2017	<CHR or Ph+ > 95%	Ph+ > 35% or BCR-ABL > 10%	Ph + ≥ 1% or BCR-ABL > 1%	Relapse, loss of MMR
GIMEMA 2019	<CHR or BCR-ABL > 10%, confirmed	BCR-ABL > 10%	BCR-ABL > 1%	BCR-ABL > 0.1%, mutations
BSH 2020	NS	BCR-ABL > 10%	BCR-ABL > 1%	BCR-ABL > 1%
ELN 2020	BCR-ABL > 10%, confirmed	BCR-ABL > 10%	BCR-ABL > 1%	BCR-ABL > 1%, HR ACA/Ph+, resistance mutations
NCCN 2.2021	NS	BCR-ABL > 10%	BCR-ABL > 10%	NS

NS not specified, *HR* high-risk, *ELN* European LeukemiaNet, *ESMO* European Society of Medical Oncology, *NCCN* National Comprehensive Cancer Network, *GIMEMA* Gruppo Italiano Malattie Ematologiche dell' Adulto (Italian Group for Adult Hematologic Diseases), *BSH* British Society of Haematology, *CHR* complete hematologic response (WBC count <10,000/μl, differential without immature granulocytes and with less than 5% basophils, platelet count <450,000/μl, nonpalpable spleen) ACA/Ph+ additional chromosomal abnormalities in Ph+ cells

Cytogenetic response (CyR): Ph+ >95% (no CyR), Ph + 66–95% (minimal CyR), Ph + 36–65% (Minor CyR), Ph + 1–35% (Partial CyR), Ph + 0 (Complete CyR). Molecular response (MR): BCR-ABL >10% (no MR), BCR-ABL >1–10% (MR 1.0), BCR-ABL >0.1–1% (MR 2.0), BCR-ABL >0.01–0.1% (MMR or MR 3.0), BCR-ABL ≤ 0.01% (MR 4.0)

[a]If treatment goal is TFR

[b]For patients aiming at TFR, the optimal response (at any time) is BCR-ABL1 ≤ 0.01% (MR4)

[c]if treatment goal is long-term survival

BCR-ABL transcript level is ≤10%, while it is defined as a failure if BCR-ABL is >10% (confirmed in two consecutive tests) by ESMO, GIMEMA, and ELN 2020. No definition of failure at 3 months is given by the BSH and by NCCN 2.2021. At 6 months, if BCR-ABL is ≤1% the response is optimal by ESMO, GIMEMA, BSH, and ELN 2020, but not by the NCCN (BCR-ABL 1–10%), and the response is failure by all recommendations and guidelines if BCR-ABL is >10%. At 12 months, if BCR-ABL transcript level is ≤0.1% (MMR), the response is optimal in all recommendations, while it is a failure if BCR-ABL is >1%, with the exception of NCCN 2.2021 (> 10%). After the first year of treatment, the response is optimal if BCR-ABL is ≤0.1% by ESMO, BSH, and NCCN 2.2021, but only if BCR-ABL is ≤0.01% by GIMEMA while the response is failure if BCR-ABL is >1% by ELN 2020, but if it is >0.1% by GIMEMA. The definition of later responses was not specified by ESMO, BSH, and NCCN 2.2021.

In conclusion, all recommendations agree on the definition of failure at 6 months. The major difference is in the level of the transcript at 12 months: a value >1% is a failure, by all the European recommendations, but not by GIMEMA that defines a failure even at lower BCR-ABL transcript level (≤ 0.1%, or MMR), and not by the American guidelines that define failure only if that value is much higher at >10%. These are important differences that cannot easily be explained because although it is almost universally recognized that achieving a major molecular response (MMR) is required for a "normal" survival, there is no consensus on the cut-off value of transcript level, and there is no agreement on the time that may take to achieve the MMR.

Among the European recommendations, an important difference is in the level of the transcript after 1 year of treatment. For ELN 2020, ESMO, and the BHS, the response is optimal if BCR-ABL is ≤0.1% (MMR), while for GIMEMA the response is optimal only if BCR-ABL is ≤0.01% (MR 4.0). As already noticed, for ELN 2020 and the BSH the response at 12 months is a failure if BCR-ABL is >1%, while for GIMEMA it is already a failure if BCR-ABL is >0.1% (less than MMR). The reason of these differences is that the ELN 2020 and the BSH recommendations privilege survival, although they highlight that achievement of TFR may be a valid aim of treatment for selected patients, using a shared decision-making policy, while the GIMEMA recommendations privilege always the achievement of a deeper molecular response for treatment-free remission. In any case, the existence of differences at several cornerstones warns that in case of borderline values of the BCR-ABL transcript, a second test should be performed before deciding to continue or to change a TKI.

10.5 Treatment

10.5.1 First-Line

Four TKIs are currently approved as the first-line treatment of newly diagnosed CP CML: imatinib, nilotinib (Tasigna, Novartis Pharma), dasatinib (Sprycel, Bristol-Myers Squibb), and bosutinib (Bosulif, Pfizer). The respective approved doses are 400 mg once daily (OD), 300 mg twice daily (BID), 100 mg OD, and 400 mg OD. The last version of ELN recommendations [8], as well as ESMO, BSH, and NCCN 2021 [9, 11, 12], do not give priority to a TKI over another one as first-line treatment. Dasatinib, nilotinib, and bosutinib have been tested against imatinib in company-sponsored randomized trials [48–56]. The results of these trials have provided the basis for approval of these TKIs in the first-line setting. Dasatinib, nilotinib, and bosutinib have never been evaluated formally in comparative clinical trials. Furthermore, comparisons among different trials, either company sponsored or academic, are quite challenging because the patient selection and the endpoints are different and are differently evaluated. The choice of the first-line treatment, anyway, is mainly based on the final endpoint of the treatment and on patient's comorbidities. Imatinib remains the reference drug because most physicians have a long experience with it and because clinically relevant or life-threatening complications have not been reported so far.Therefore, imatinib remains, probably, the safest drug. During the last 20 years imatinib has been studied

not only in company-sponsored trials but also in important academic trials [57, 58]. Moreover, imatinib is currently less expensive than dasatinib, nilotinib, and bosutinib. Recently, the brand product Gleevec has been substituted in most countries by generic products, which are further less expensive. By comparison with imatinib 400 mg OD, dasatinib and nilotinib induce faster and deeper responses but the 5-year progression-free survival and the OS were reported to give marginal improvement with respect to imatinib [51, 53]. The same considerations apply to bosutinib vs. imatinib but with a much shorter observation period of 2 years [56]. There is a consensus favoring imatinib in elderly patients, in case of comorbidities, and in case of CML low-risk (the 5-year LRS of low-risk patients is higher than 95%) and favoring nilotinib, dasatinib, or bosutinib in case of high-risk. Moreover, the choice between nilotinib, dasatinib and bosutinib is influenced by comorbidities (cardiovascular risk, lung disease) and cost, which differs from country to country. However, the most important guide to the choice is the goal of treatment. If the goal of treatment is OS, imatinib may be sufficient. If the goal of treatment is a condition of treatment-free remission (TFR), it is likely that more patients will achieve that condition if they are treated first line with a second-generation TKI, but this expectation must still be proven.

10.5.2 Second-Line and beyond

In the second-line treatment, imatinib, nilotinib, dasatinib and bosutinib can be used at different doses: up to 400 mg BID for imatinib and nilotinib, up to 140 mg OD for dasatinib, and up to 600 mg OD for bosutinib [3, 59–61]. Finally, ponatinib (Iclusig, Takeda/Incyte) is licensed at a dose of 45 mg OD [62, 63] as second line for patients failing previous TKIs (USA), while in most EU countries the second line use is licensed for patients failing nilotinib or dasatinib first line, or in patients harboring the T315I mutation.

In the second-line treatment, four main scenarios are recognizable. Scenario no. 1 is that of intolerance to first-line treatment (toxicity). In that case, switching to nilotinib, dasatinib, or bosutinib should be prioritized over ponatinib because it is a situation very similar to first line. Scenario no. 2 is that of failure of first-line treatment (resistance). In that case, the choice of the second-line TKI will be guided by BCR-ABL1 mutations (if a mutation is found), by age, comorbidities, the type of side effects of first-line therapy, physician experience, and TKI availability and cost. Regrettably, there are no trials comparing the five available TKIs in second line. Ponatinib will always be the drug of choice in the case of T315I mutation [62, 63]. Scenario no. 3 is that of "warning" at early milestones (3–6 months), particularly in the case of BCR-ABL1 transcript level > $10\%^{IS}$ at 3 months (absence of early molecular response, EMR). EMR predicts the rate and the depth of late molecular response as well as progression-free survival (PFS) and overall survival, and EMR is achieved more frequently with second-generation TKIs than with imatinib [51, 53]. Not achieving EMR with imatinib suggests considering an early switch to a second-generation TKI; the absence of EMR with a second-generation TKIs in first line is a more worrisome situation, in which strict monitoring is mandatory and switching to ponatinib should be considered. Scenario no. 4 is that of the patient who is an optimal responder but never reaches a deep molecular response, so that he or she becomes a candidate for a late switch to another TKI, looking for treatment discontinuation and TFR [64, 65]. A careful patient selection is required to balance the benefit of a possible future TFR versus the potential new toxicities after switching to another TKI. In summary, in the case of scenarios no. 1 and 2, the TKI must be changed; in the case of scenarios no. 3 and 4, the TKI should or may be changed, and prospective studies are needed to assess the benefit and cost of the change.

An important and mostly uncovered issue is that of dose. All five TKIs were approved in second line at a specific dose: imatinib 400 mg OD to 400 mg BID, nilotinib 400 mg BID, dasatinib 100–140 mg OD, bosutinib 500–600 mg OD, and ponatinib 45 mg OD. Regrettably, there are no robust data with different doses, but there is a general consensus that in many patients all these TKIs are overdosed. Today, nilotinib and

dasatinib in second line are mostly used at a dose of 300 mg TD and 100 mg OD, respectively. The dose of bosutinib is likely to be higher than required and unnecessarily toxic. Recent data suggest that in second line a lower starting dose of bosutinib with response-driven dose escalation up to 400 mg OD is effective and well tolerated, at least in elderly patients [66]. Ponatinib is used at 45 mg only in a minority of cases (those bearing a T315I mutation or showing a high level or resistance to previous TKIs); the starting dose of 30 mg OD is preferred in most instances [8]. Ponatinib is currently tested at 30 or 15 mg OD to better balance efficacy versus cardiovascular toxicity [67]. Moreover, once MMR is achieved, ponatinib dose can be reduced to 15 mg OD with careful monitoring of response.

The scenario of third-line treatment is very heterogeneous, including patients who can still be rescued to an optimal response and patients at high-risk of progression and death [68–72]. Third-line treatment has an important impact on survival and may provide an essential bridge to allogeneic stem cell transplantation (allo-SCT). For these reasons, the patients who fail two or more TKIs should be referred to a center specialized in the treatment of CML, and allogeneic stem cell transplantation should be considered [8].

There are no published studies comparing different TKIs in third line. Ponatinib may be the first, or the last choice, because it covers almost all known mutations. Asciminib (Novartis Pharma), a new BCR-ABL allosteric inhibitor, active also against the T315I mutation, is currently in advanced clinical development [73], and a trial of asciminib vs. bosutinib in third line is ongoing; therefore, asciminib may become a valid option in this setting in the near future.

10.6 Treatment Continuation or Discontinuation, Treatment-Free Remission (TFR), Cure

In the 2013 ELN recommendations, continuous treatment with TKIs at the approved dose was referred as the standard of care [3]. Indeed, this approach demonstrated that the life expectancy of newly diagnosed CML patients was similar to that of the age-matched general population [4, 74]. As a matter of fact, TKIs can induce deep and stable responses with up to a 5-log reduction of the BCR-ABL1 transcript levels. Experimental and clinical data strongly suggest that TKIs cannot eliminate all BCR-ABL1+ stem cells [75–89]. However, there is evidence from several clinical studies [90–100] that 40–60% of the patients who discontinue treatment, having been treated with TKI for at least 3–5 years and being in stable deep MR (MR4 or better for at least 2 years), remain in remission. Monitoring of genomic mesurable residual disease may help to identify true cures or very long lasting TFR [101]. The risk of molecular relapse is higher during the first 6–12 months after discontinuation, then the risk decreases progressively. Whether they will relapse much later is not yet known, but it is known that discontinuation does not increase the risk of progression: almost all patients who have a molecular relapse can regain a molecular remission upon reassumption of the same TKI used prior to discontinuation.

Given the several available studies and the vast experience with TFR gained in the recent years, the ELN 2020 recommendation [8] recognized TFR as a new significant goal of CML management and provided for the first time a set of requirements for TKI discontinuation, distinguishing mandatory, minimal (stop allowed) and optimal (stop recommended for consideration) criteria. However, the best treatment strategy, in first or subsequent lines, to drive patients toward a successful TFR is yet to be defined, and the 2020 ELN recommendations could not provide specific recommendations on that. Indeed, only a few trials are currently ongoing with TFR as a primary objective, including the GIMEMA SUSTRENIM trial and the German CML TIGER study, that is, however, a trial of nilotinib versus a combination of nilotinib and interferon-α. Waiting for the results of these trials, the GIMEMA published in 2019 a set of proposals specifically designed to optimize the treatment strategy for TFR.

The biological mechanisms underlying TFR are not well understood, but TFR probably represents an “operational cure” rather than a “true cure” (disease eradication). Indeed, residual BCR-ABL1+ stem cells are quiescent, no longer

BCR-ABL1 addicted and not sensitive to TKIs [76, 80, 81, 83, 85, 88, 89]. Other agents, targeting the stem cells [75, 78], may be necessary to attain CML eradication. Over the last 20 years, many studies have been dedicated to the identification of new targets in the stem cells [102], and many studies have shown that, experimentally, the combination of a TKI with anti-stem-cell agents can eliminate BCR-ABL1+ stem cells [103]. Regrettably, none of these combinations have been tested successfully in vivo, also because there is a legitimate concern of the use of potentially toxic agents in patients with minimal residual disease, with a normal life expectancy and a normal quality of life. For the time being, the search of a cure is theoretical and is addressed toward the immunologic control of minimal residual disease [104–108] which today mainly rely on the addition of IFNs to TKI treatment [109–111].

Certainly, TFR is a clinically relevant endpoint that influences on the well-being and the psychologic behavior of the patients because it limits the long-term toxicity of the treatment and spares the economical resources that are necessary for life-long TKI therapy.

With current treatment approaches it is expected that no more than 20–30% of all newly diagnosed CML patients will be able to achieve a stable TFR. The remaining 70–80% of patients. would need lifelong "standard" dose TKI as per current recommendation and guidelines. For these patients the main objectives are an improvement of quality of life [112] and minimization of long-term toxicities. With this regard, de-escalation of treatment through permanent dose reductions or even intermittent treatment has been investigated and results are promising [113, 114].

10.7 Conclusions

In the last 15 years ELN recommendations contributed to the improvement of the management of CML. Today the survival of CML patients is comparable to that of the general population; the next step is the achievement of a normal survival without continuous treatment. The ELN 2020 recommendations recognized TFR as an important goal of CML therapy and identified a set of requirements for TKI discontinuation. However, it was not possible to recommend specific treatment strategies, both in first or subsequent lines, to increase the proportion of patients reaching TFR. For these reasons, next prospective studies should be designed to consider TFR as the primary endpoint (instead of response rates at a time point). Hopefully, the next version of ELN recommendations will take advantage of the results of such trials to finally propose an evidence-based path to TFR.

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