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REVIEW ARTICLE

A review of the European LeukemiaNet recommendations for the management of CML

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Abstract Several guidelines and recommendations on the management of chronic myeloid leukemia (CML) have been prepared by several scientific societies. The European LeukemiaNet (ELN) appointed a panel of experts who submitted their recommendations to peer-reviewed scientific journals in 2006, 2009, and 2013. Here, we make a critical review of the last, 2013, ELN recommendations, concerning the use of the five available tyrosine kinase inhibitors (TKIs), the evaluation of cytogenetic and molecular response, and the strategy of treatment. Three TKIs (imatinib, nilotinib, dasatinib) are recommended first-line. Bosutinib and ponatinib are available second-line; ponatinib is particularly indicated in case of the T315I mutation. Achieving an optimal response, not only for survival but also for a deeper, stable, treatment-free remission, requires a BCR-ABL transcripts level ≤10 % at 3 months, ≤1 % at 6 months, ≤0.1 % at 1 year, and ≤0.01 % later on. Molecular monitoring must include mutational analysis in every case of failure. A successful treatment of accelerated and blastic phase requires TKIs, and in many cases also allogeneic stem cell transplantation.

Keywords Chronic myeloid leukemia · Tyrosine kinase inhibitors · BCR-ABL1 · Philadelphia chromosome

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Introduction

Progress in treatment of chronic myeloid leukemia (CML) was so rapid, and is still marching so fast [1–3], that any recommendation on the management of CML can quickly become obsolete [4–7]. Information and data come from several different sources with several different missions and interests, particularly from independent investigators [8–17] and from pharma companies [18–27]. Both are sincerely interested in the progress of management and therapy, but both may have different motivations and some biases, mainly commercial for pharma companies and academic for independent investigators. Moreover, many other data come from a myriad of studies that are sometimes very important, and sometimes irrelevant or even deceiving (reviewed in ref. [6] and [7]). Therefore, the scientific and medical communities, as well as the patients, like, and to some extent ask for, and are willing to accept that the information coming from so many sources is collected, organized, ordered, and interpreted by experts, so as to help doctors and patients to find the best possible solution and a well-balanced one. The methodology may vary from the rigid principles that are required for true guidelines to the more flexible procedure of recommendations. Guidelines should be based on evidence and weighted evidence, mainly using prospective randomized studies with a long-term follow-up and only secondarily on phase 2 studies, on preliminary unconfirmed data and on the personal opinions of the experts. Recommendations can take into consideration also less powered, even non randomized, studies, preliminary reports at international meetings, and the personal opinion of the experts is even more important, particularly when the same opinion is shared and agreed upon by all the experts.

Several scientific societies and institutions in several countries have produced guidelines and recommendations for the management of CML. Two of them have acquired an international relevance: the European LeukemiaNet (ELN)

recommendations [4–6] and the so-called National Cancer Centre Network (NCCN) guidelines [7]. Though the latter are called "guidelines," they do not fit the methodological requirements of true guidelines and resemble much more a recommendation, where preliminary data and expectation count more than evidence. The ELN and NCCN recommendations differ under several aspects, particularly in the composition of the expert panel, with only US expert for NCCN and with experts from Europe, the USA, Canada, Korea, and Australia for ELN. Moreover, NCCN recommendations are published in the NCCN website [7] and are revised almost every year, while ELN recommendations were always published in peer-reviewed journals, at 3-year intervals [4–6].

This review will be based on the last, 2013, ELN recommendations [6], without a systematic comparison with the last version of the NCCN ones [7].

Importance of definition and recognition of the phase of CML

The clinical course of CML is divided into three phases, chronic, accelerated, and blastic (AP, CP, BP). The definitions of AP and BP that are recommended by ELN [6] are not the same that are recommended by the World Health Organizzation (WHO) [28], but are those that have been internationally shared, and used in almost all recent major studies of CML. According to ELN, AP is defined by 15 to 29 % blast cells or by 30 to 49 % blast cells plus promyelocytes in blood or marrow or by a platelet count $<100\times10^9$/L unrelated to treatment or by a clonal chromosome abnormality in Ph + cells (CCA/Ph+). BP is defined by a blast cells percentage ≥ ≥30 % in blood or marrow or by blast cells involvement of non hematopoietic tissues, excluding liver and spleen. The major difference with WHO definition is in blast cells percentage that for WHO is 15–19 % for AP and ≥20 % for BP.

At diagnosis, a small but not irrelevant proportion of CML patients present in AP or even in BP. Other patients undergo acceleration and progression to BP after tyrosine kinase inhibitor (TKI) treatment failure [1]. Treatment recommendations are different when AP and BP are recognized at baseline, prior to any treatment, or during the treatment of CP [6, 29]. Patients presenting in AP are well responsive and should be treated with TKIs, better with the more potent second-generation TKIs; they are eligible for allogeneic stem cell transplantation (SCT) only if not achieving an optimal response. Patients presenting in BP are also well responsive to TKIs, but the risk of relapse is high, so that all of them should be considered eligible for a SCT procedure [29]. The patients who progress from CP to AP and BP are less sensitive to any subsequent treatment, they should be treated with a TKI, and they are all eligible for SCT [6, 29].

The definition of the risk, baseline

The definition of the risk, at baseline, is shown in Table 2. A high-risk score and a CCA/Ph+, so-called major route [30, 31], are significant predictors of a poorer response to TKIs and of a poorer outcome. There are three risk scores, Sokal [32], EURO [33], and EUTOS [34]. All the three scores have been validated. Patients with a high-risk score or with CCA/Ph + can probably benefit of a specific risk-adapted therapy, e.g., with a more potent second-generation TKI, but there are no data, no studies, showing that a specific treatment would be of benefit and, if so, how much.

Therefore, ELN includes these factors in the "warning" category, warning that the patients presenting either with a high risk or with CCA/Ph + should be monitored more carefully, suggesting that they are eligible for investigational therapies [6]. The ELN expert panel acknowledged that several studies have been reported suggesting that several other baseline factors may have a prognostic value, but recognized that the data were not yet sufficient and solid, and they could not be used to plan and modulate the treatment [6]. These factors are listed in Table 1. They should be considered still provisional, but some of them should be taken into due consideration if one wants to refine and to improve the already excellent treatment results.

Assessing and monitoring the response

ELN recommends to assess and monitor the response using both conventional cytogenetics (chromosome banding

Table 1 Several baseline factors and characteristics have been reported to influence the response to TKIs and the outcome

Baseline risk factors (warning)	
Established	High risk score (Sokal, or EURO, or EUTOS)
	Clonal chromosome abnormalities in Ph + cells (ACA/Ph+), major route: +8, +Ph, i(17)(q10), ider(22)(q10), +19
Provisional	Transcript type (B3A2 vs B2A2, atypical transcripts)
	Transcripts level
	Gene expression profile
	Polymorphisms of genes coding for proteins involved in drug metabolism and transport, and in apoptosis (BIM)
	Expression level of genes involved in drug transport (MDR,hOCT1)
	Low-level BCR-ABL1 mutations

A high-risk score, either by Sokal [32], or by EURO [33], or by EUTOS [34], and so-called major route CCA/Ph+, are recognized and confirmed, but it is not yet clear what it should be the optimal treatment in these cases. ELN recommends that such patients are monitored more frequently and suggests that they are eligible for investigational trials of therapy. All the other factors may have a prognostic value, but the data are not yet sufficient to mandate a different, specific treatment [6]

Table 2 ELN definition of the response to TKIs, first-line

Time	Optimal	Warning	Failure
Baseline	NA	High risk or CCA/Ph+, major route	NA
3 months	BCR/ABL1 ≤ 10 % or Ph + ≤35 %	BCR-ABL1 > 10 % or Ph + 36–95 %	Non CHR or Ph+ >95 %
6 months	BCR-ABL1 ≤ 1 % or Ph + 0 (CCyR)	BCR-ABL1 1–10 % or Ph + 1–35 % (PCyR)	BCR-ABL1 > 10 % or Ph+ >35 %
12 months	BCR-ABL 1 ≤ 0.1 % (MMR)	BCR-ABL1 0.1–1 %	BCR-ABL1 > 1 % or Ph + ≥1 %

NA not applicable

analysis (CBA) of at least 20 marrow cells metaphases) and real-time quantitative polymerase chain reaction (RT-Q-PCR) [6]. Cytogenetics should be performed at 3, 6, and 12 months, until a complete cytogenetic response (CCyR) is achieved.

CBA of marrow cell metaphases can be substituted by fluorescence-in-situ-hybridization (FISH) of at least 200 blood cells nuclei, only once a CCyR has been achieved. RT-Q-PCR should be performed on buffy coat blood cells every 3 months. ELN acknowledged that if RT-Q-PCR methodology is standardized and the results are expressed according to the International Scale (IS) as BCR-ABL1% [35–37], the response can be assessed using only RT-Q-PCR, not only after a CCyR has been achieved but also from the beginning because RT-Q-PCR is more sensitive and does not require marrow sampling. Once a major molecular response (BCR-ABL1 ≤ $0.1\%^{IS}$) has been achieved, RT-Q-PCR can be performed every 3 to 6 months, depending on baseline risk (warnings), transcripts level, and transcripts level fluctuations. In the patients who discontinue the treatment after a stable and deep molecular response, molecular monitoring must be ensured monthly for 1 year and at least every 3 months thereafter [6].

Two recent retrospective analyses of the dynamics of the early molecular response have shown that it may be more important than the molecular response at 3 months [38, 39]. This requires an RT-Q-PCR every month and a different housekeeping, control gene, like GUS or β-2 microglobulin. Therefore the evaluation of the dynamics of early molecular response cannot yet be introduced and recommended in practice, but it is likely to become more and more important because it is quite logical that any response can be better evaluated with three points and a line, rather than with a single point evaluation.

Using molecular and cytogenetic tests together is recommended particularly in cases where the response is borderline or fluctuating. Cytogenetics is important and necessary in case of CCA/Ph−, as well as in patients with atypical BCR-ABL1 transcripts, where molecular quantitation is not standardized.

Mutational analysis is recommended in AP and in BP, prior to treatment and during any treatment. In CP, mutational analysis is mandatory only in case of failure, and it is recommended in case of warning [6, 40]. For clinical purposes, mutational analysis is performed with the Sanger sequencing technique that has a low sensitivity (it can detect a mutation only if the mutant clone account for more than 15 or 20 % of all Ph + cells) [40]. However, the detection of low-level mutations and of compound mutations (Ph + clones with more than one mutation) by ultradeep sequencing is likely to become more and more important [41–43].

Definition of the response

ELN distinguishes three grades of response (Table 2). These definitions are clinically important because they provide a guide to therapy. "Optimal" means that the treatment should be continued because the response predicts for an excellent outcome and an almost normal survival length. "Failure" means that the treatment should be changed because the response is such that the patient is at a significant risk of progression and death. Failures can be primary (Table 2) or secondary (Table 3). "Warning" defines an intermediate category of responses: on one hand, it is acknowledged that the response and the outcome could be better, but on the other hand, it is also acknowledged that there are no solid data to make a specific treatment recommendation on how the treatment should be changed to improve the response or the outcome. The definitions of the responses to first-line treatment (Tables 2 and 3) were based on solid data. The definitions of the responses to second-line treatment (Table 4) were provisional and were mainly based on dasatinib and nilotinib data [44–47]. The data on third-line treatment are still completely insufficient and do not allow a definition of the response (reviewed in ref. [6] and [7]). It is important to underscore that the patients who are or become resistant to one TKI are at a

Table 3 ELN definitions of secondary failures

Secondary failures
1. Loss of complete hematologic response
2. Loss of complete cytogenetic response
3. Confirmed loss of major molecular response (2 consecutive tests >0.1 %, of which one ≥1 %)
4. Any BCR-ABL1 mutation, detected by Sanger sequencing
5. Clonal chromosome abnormalities in Ph + cells, major route

Table 4 ELN definitions of the response to TKIs, second line

Time	Optimal	Warning	Failure
Baseline	NA	High risk CHR never achieved Loss of CHR CyR never achieved Mutations	NA
3 months	BCR-ABL1 ≤ 10 % or Ph + <65 %	Ph + 65–95 %	No CHR BCR-ABL1 > 10 % Ph+ >95 % New mutations
6 months	BCR-ABL1 ≤ 10 % or Ph + ≤ 35 % (MCyR)	Ph+35–65 %	BCR-ABL1 > 10 % Ph+ >65 % New mutations
12 months	BCR-ABL ≤1 % or Ph + 0 (CCyR)	BCR-ABL1 1–10 % or Ph + 1–35 % (PCyR)	BCR-ABL1 > 10 % Ph+ >35 % New mutations

These definitions are provisional and mainly applicable to the results of second-line treatment with dasatinib and nilotinib

NA not applicable

consistent risk of progression, a risk that becomes much higher in the patients who are resistant to two or three TKIs.

First-line treatment

Both ELN and NCCN recommend any one available and approved TKI, imatinib 400 mg once daily, or nilotinib 300 mg twice daily, or dasatinib 100 mg once daily. Although it is acknowledged that nilotinib and dasatinib are more potent and induce faster and deeper remissions, there is yet no solid evidence of a better outcome, if a second-generation TKI is used first-line. However, high-risk patients (warning) are eligible for trials of second-generation TKIs, and it is believed that patients in AP or BP may benefit more of a second-generation TKI.

Second-line treatment

A change of therapy is mandatory in case of failure (resistance) as well as in case of side or toxic effects that would prevent optimal dosing, or affect life quality, or threaten patient life.

If the change is required for side effects, any other available TKI can be used, including imatinib second-line after a second-generation TKI first-line.

If the change is required for failure (resistance), there is no longer space for imatinib, and the logic sequence is as follows: [1] from imatinib to any other available and approved TKI (dasatinib, nilotinib, bosutinib, ponatinib), [2] from nilotinib to other TKIs (dasatinib, bosutinib, ponatinib), and [3] from dasatinib to other TKIs (nilotinib, bosutinib, ponatinib).

Regrettably, there are no studies comparing different TKIs in second-line. Therefore, the choice of the second-line TKI is guided by some patient characteristics, mainly age and comorbidities, by the type of side effects with the first TKI, and by the presence of BCR-ABL1 kinase domain point mutations, and also by drug availability and cost, and by doctor experience. Some mutations are poorly sensitive to dasatinib, some are poorly sensitive to nilotinib, and some are poorly sensitive to bosutinib, and even to ponatinib (reviewed in ref. [6] and [7]) (Table 5). The T315I mutation is sensitive only to ponatinib.

Table 5 Provisional list of the more critical BCR-ABL1 mutations

BCR-ABL1 mutation	Poorly sensitive to	Resistant to
G250E	Bosutinib	
Q252H	Dasatinib	
Y253H	Nilotinib	
E255K/V	Bosutinib, dasatinib, nilotinib, ponatinib	
T3151		Bosutinib, dasatinib, nilotinib
F317L	Dasatinib	
F355V	Nilotinib	
H396R	Ponatinib	

The assessment of sensitivity was based on in-vitro data (the inhibitory concentration 50 %) and on clinical data. All these mutations, as well as many other mutations, are poorly sensitive or resistant also to imatinib

The problem of second-line treatment is much more complex and questionable in case of warning, when a change of treatment is expected to improve the response, but there are no data showing that the change would be useful, and if so how much, and at which cost. The concept of warning has been introduced by ELN to categorize the cases where the response is not optimal, but a failure is not observed. Warning was not taken into consideration by NCCN, where responses are either "white" (continue the treatment) or "black" (change the treatment). The major difference between ELN and NCCN is at 3 months. For NCCN, the patients who have not achieved a major cytogenetic response (MCyR, Ph + <35 %) or have a BCR-ABL1 transcripts level >10 % should change the treatment, either increasing imatinib dose, or switching to second-generation TKIs, or even considering SCT. For ELN, the same patients should be monitored more carefully and frequently, even monthly, and are eligible for experimental trials. For these patients, the NCCN recommendations are based on the demonstration that early molecular response (BCR-ABL1 ≤ 10 %) that is achieved more frequently with second-generation TKIs is a significant predictor of subsequent responses and outcome [48–53] and on the expectation that a switch to a second-generation TKI may be convenient. ELN acknowledged the value of early molecular response, but pointed out that no studies have shown so far that the early switch would be convenient, for how many patients, and how much, also taking into account that the use of second-generation TKIs has some clinical and financial problems [6].

Third-line treatment

There are no evidence-based, reliable, specific recommendations for the patients who fail two or even three TKIs. These patients form a heterogeneous group where several different causes of failure recur, from low compliance and side effects to true cell resistance. In these cases, a study of cell karyotype, a study of BCR-ABL1 kinase domain point mutations, a bone marrow biopsy, and a stringent monitoring are necessary, in preparation of SCT. Ponatinib is likely to be more efficient than any other TKI [54, 55], but there are no comparative studies. Chemotherapy is likely more cosmetic than useful.

Management of CML, evolution of goals and strategies

Current recommendations for the management of CML are basically addressed to the goal of achieving an at least MMR, with a life quality and a life duration close to normality, as much as possible. To achieve and to maintain these goals, it is possible to choose among several TKIs, and a chronic, lifelong treatment is required. However, the scenario is changing, the goal is moving from survival to cure, and the treatment policies are moving towards discontinuation [1, 6, 7, 56–58]. The next goal is to achieve a condition of treatment-free remission (TFR) [59–61]. It is not yet known how many patients will achieve that condition, and it is not yet clear which drugs and which treatment policies will be more successful. It is likely that an extended use of second-generation TKIs that are more potent and induce faster and deeper molecular remissions will bring more patients into TFR, and it is likely that the earlier and the deeper the early molecular response, the higher will be the number of patients in TFR. The early surrogate markers of TFR will be a rapid decline of BCR-ABL1 transcripts, a BCR-ABL1 transcripts level ≤1 % within 3 months, ≤0.1 % within 1 year, and ≤0.01 % later on. Taking into account these goals, a revision of the ELN recommendations will be undertaken in 2015.

Conflict of interest The authors declare that they have no conflict of interest.

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