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Ibrahim C Haznedaroglu

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EXPERT OPINION

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Current concerns of undertreatment and overtreatment in chronic myeloid leukemia based on European LeukemiaNet 2013 recommendations

Ibrahim C Haznedaroglu
Hacettepe University Medical School, Department of Hematology, Ankara, Turkey

Introduction: The aim of this paper is to indicate optimal tyrosine kinase inhibitor (TKI) administration practices based on European LeukemiaNet (ELN) 2013 recommendations for chronic myeloid leukemia (CML). Likewise, current concerns of undertreatment and overtreatment with TKIs during the long-term clinical course of CML will be outlined.
Areas covered: Currently available TKIs for the management of CML are reviewed. The survival benefit of TKIs (imatinib, dasatinib, nilotinib, bosutinib, ponatinib) for the CML is excellent. The CML and TKI literature search was made in PubMed with particular focus on the clinical trials, recommendations, guidelines and expert opinions, as well as the ELN CML 2013 recommendations.
Expert opinion: Initial TKI treatment for low-risk chronic phase CML is imatinib 400 mg; high-Sokal risk and/or CML patients with complex karyotypic abnormalities would require more powerful second-generation TKIs (dasatinib 100 mg or nilotinib 600 mg). Absence of early molecular response after 6 months, complete cytogenetic response after 12 months and major molecular response after 18 months may require a more powerful TKI switch. If one of the two second-generation TKIs (nilotinib or dasatinib) was used as first-line therapy and failed, the other (dasatinib or nilotinib) could be administered.

Keywords: chronic myeloid leukemia, clinical trial, European LeukemiaNet 2013 recommendations, tyrosine kinase inhibitor

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1. Introduction

European LeukemiaNet (ELN) has recently proposed the ELN 2013 recommendations [1] for the management of chronic myeloid leukemia (CML) [1] replacing the previous ELN CML 2009 [2]. Current initial frontline therapy for CML is chronic oral administration of tyrosine kinase inhibitor (TKI). ELN 2013 recommendations [1] for CML are mainly based on the data obtained from the randomized clinical trials (RCTs) of TKI. Imatinib, dasatinib, nilotinib, bosutinib and ponatinib are the currently available TKIs for the management of CML [1]. The survival benefit of TKIs for the CML is excellent. However, disease progression, accelerated phase (AP) CML or blastic crisis (BC), under TKI is a great disaster. The survival after the progression into AP/BC is still significantly shorter even in the powerful TKI era. Nevertheless, the risk of progression has been decreased with the introduction of more powerful TKIs such as nilotinib and dasatinib. The efficacy of TKI

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Table 1. The comparative target end points of the ELN 2009 [2] and ELN 2013 [1] recommendations for CML.

	ELN CML 2009 [2]			ELN CML 2013 [1]		
	Optimal response	**Primary failure**	**Secondary failure**	**Optimal response**	**Primary failure**	**Secondary failure**
3 months	CHR and at least minor CyR (Ph+ ≤ 65%)	No CHR		CHR and BCR-ABL < 10% and/or at least PCyR (Ph+ < 35%)	No CHR and/or No CyR (Ph+ > 95%)	
6 months	At least PCyR (Ph+ < 35%)	No CyR (Ph+ > 95%)		BCR ABL < 1% and/or CCyR (Ph+ = 0%)	BCR-ABL > 10% and/or less than PCyR (Ph+ > 35%)	
12 months	CCyR (Ph+ = 0%)	Less than PCyR (Ph+ > 35%)		MMR (BCR-ABL ≤ 0.1%)	BCR-ABL > 1% and/or less than CCyR (Ph+ ≥ 1%)	
THEN (at any time)	MMR (MR 3) or better		Loss of CHR; loss of CCyR mutations CCA/ Ph+	MMR (MR 3) or better		Loss of CHR; loss of CCyR mutations CCA/Ph+ confirmed loss of MMR

treatment, TKI side effects, off-target drug complications, long-term morbidities due to the disease and drug are the current critical issues in the therapy of CML [1].

Complete hematological response (CHR), early complete cytogenetic response (CCyR), faster major molecular response (MMR) and the deeper, durable molecular responses (MR4, MR4.5 and MR5) are the ultimate goals of the TKI-receiving CML patients. Critical evaluations of the CML patients to hit those targets shall be made at the baseline and at the third, sixth, twelfth months and thereafter the TKI administration. MR4 can be achieved by a BCR-ABL expression < 0.01%, MR4.5 by < 0.0032% BCR-ABL^{IS} and MR5 by < 0.001% BCR-ABL^{IS}. Clinical response, the depth of response and the impact of TKI used on the disease outcome should always be focused during the long-term management of CML [1]. The comparative target end points of the ELN 2009 and ELN 2013 recommendations for CML are depicted in **Table 1**.

The aim of this paper is to indicate optimal TKI administration practices based on ELN 2013 recommendations for CML [1]. Likewise, current concerns of undertreatment and overtreatment with TKIs during the long-term clinical course of CML would be outlined. Those two unacceptable ways of therapy represent the deviations from the optimal management of CML and are described below:

Overtreatment: aggressive diagnostic/therapeutic clinical intervention during the management of CML disease course with TKI drugs, for instance, early/inappropriate decision of a very risky allografting in a CML patient receiving a given TKI and exhibiting suboptimal response, whereas a more powerful TKI would produce excellent outcome, and survival may be considered as 'overtreatment'.

Undertreatment: insufficient diagnostic/therapeutic clinical intervention during the management of CML disease course with TKI drugs, for instance, inability to detect ELN warnings in a CML patient receiving a given TKI, resulting in drug failure, and/or disease progression may be considered as 'undertreatment'.

2. Current initial frontline TKI therapy for CML: ELN 2013 recommendations and the arguments

Before the TKI decision, the baseline assessments of the *de novo* CML patient shall include exact medical diagnosis of CML, basic laboratory evaluation covering complete blood count (CBC) and peripheral blood smear (PBS), bone marrow histopathology, conventional cytogenetics and/or fluorescence *in situ* hybridization analyses for Philadelphia (Ph) chromosome and quantitative molecular analyses for the BCR-ABL1. Tumor load and disease phase should be defined [1,2]. Newly diagnosed chronic phase (CP) CML patients should be stratified based on the Sokal, Euro/Hasford and EUTOS CML prognostic scoring systems. Novel recent investigations for the *de novo* CML patients have searched the validity of gene expression profiling, genetic polymorphisms, next generation genomics, multidrug resistance genes (OCT1), fusion transcripts and pre-existing BCR-ABL kinase domain mutations [1].

ELN 2013 has acknowledged imatinib 400 mg or dasatinib 100 mg or nilotinib 600 mg as the initial TKI therapy for CML [1]. The most commonly prescribed initial TKI treatment for CP-CML is imatinib 400 mg p.o. [1,2].. Investigational efforts tried to improve the results of CML first-line therapy of imatinib obtained from the IRIS [3] trial. Those attempts include imatinib dose increase particularly in high-Sokal risk [4], imatinib-based combinations [5] and setting

Table 2. Major critical conclusions of the major clinical trials in the field of CML.

Clinical study	Major critical conclusion	CCyR 12 months with imatinib	MMR 12 months with imatinib
IRIS [3]	Imatinib is superior to IFN + Ara-C treatment with regard to hematological, cytogenetic and molecular responses (imatinib is the 'standard of care' in CML)	68%	38%
TOPS [16]	High-dose imatinib may obtain faster but not more responses	66% (w/400 mg) 70% (w/800 mg)	40% (w/400 mg) 46% (w/800 mg)
ELN/GIMEMA STUDY (only high-Sokal CML) [4]	High-dose imatinib could not increase responses in high-risk CML	58% (w/400 mg) 64% (w/800 mg)	36% (w/400 mg) 43% (w/800 mg)
GERMAN CML STUDY IV [5,8]	Imatinib dose optimization may obtain earlier and more molecular responses (addition of non-PEG IFN is not useful)	49% (w/400 mg) 63% (w/800 mg)	34% (w/400 mg) 46% (w/800 mg)
FRENCH SPIRIT [17]	PEG-IFN and imatinib combination may obtain earlier, deeper and more molecular responses (increasing the dose of imatinib is not useful)	58%	38%
ENESTnd [13]	Nilotinib is superior to imatinib with regard to cytogenetic and molecular responses	65%	22%
DASISION [12]	Dasatinib is superior to imatinib with regard to cytogenetic and molecular responses	72%	28%
BELA [18]	Bosutinib may obtain more molecular (but not cytogenetic) responses than imatinib	68%	27%
TIDEL [9]	CML treatment optimization with imatinib dosage, plasma level monitorization and convenient shift to nilotinib is possible with better responses	88%	47%

Those clinical studies have used the imatinib treatment as the research arm or the control arm for another TKI. Thus, the end points of CCyR and MMR at 12 months were depicted as an idea of comparison among the trials.

BELA: Bosutinib Efficacy and Safety in Chronic Myeloid Leukemia; CCyR: Complete cytogenetic response; CML: Chronic myeloid leukemia; DASISION: Dasatinib versus Imatinib Study in Treatment-naive CML patients; ELN: European LeukemiaNet; ENESTnd: Evaluating Nilotinib Efficacy and Safety in Clinical Trials – Newly Diagnosed Patients; IFN + Ara-C: Interferon plus cytosine arabinoside combination; IRIS: The International Randomized Study of Interferon and STI571; MMR: Major molecular response; PEG-IFN: Polyethylene glycol-added interferon; TIDEL: Therapeutic Intensification in *De-novo* Leukemia; TOPS: Tyrosine Kinase Inhibitor Optimization and Selectivity.

the second-generation TKIs as first-line therapy [6,7]. Dose optimization studies of TKI such as German CMLIV [8] and TIDEL [9] have been taken into account for the increments in the safety, efficacy, tolerability, adherence and acceptable manageable drug toxicity (**Table 2**). Second-generation TKIs, namely dasatinib [6] 100 mg p.o. and nilotinib [7] 600 mg p.o. have also been registered for the first-line therapy of CML. There is a tendency for the prescription of more powerful TKIs in high-Sokal risk CML patients and high-risk patients with complex karyotypic abnormalities (CCA) at the beginning of the disease for the prevention of disease progression. Likewise young and low prognostic risk CML patients are candidates of second-generation TKIs for the sake of drug discontinuation in the future. However, heterogeneous presentation and course of CML, individual characteristics, compliance and preferences of the patients, comorbidities, different toxicity profile of the drug and the physician-clinical center experience shall all be considered during the initial decision making for first-line TKI of the newly diagnosed CP-CML [2,6,7]. Careful consideration of those critical issues would prevent overtreatment and undertreatment at the initial decision making in CML.

3. Critical early disease management at the third and sixth months after the initiation of TKI: ELN 2013 recommendations for CML and the arguments

Standard disease assessments at the third month following the TKI treatment of the CP-CML patient include critical clinical evaluation and CBC/PBS to reveal CHR, cytogenetic analyses to search the cytogenetic response and quantitative molecular BCR-ABL analyses to identify molecular response at the third month of oral TKI administration [2]. Optimal response at the third month of imatinib is CHR and minor cytogenetic response. However, particularly after the introduction of the powerful second-generation TKIs, namely nilotinib and dasatinib, to the first-line therapy of CML, the expectations in response became higher. Recent data indicated that the critical BCR-ABL transcript level (10% cut-off value) at the third month following the TKI treatment (early molecular response [EMR]) may have a prognostic significance in CML patients. This scientific observation has been made with imatinib in GIMEMA [10], German CML IV [5], Hammersmith [11],

DASISION [12] and ENESTnd [13]; with dasatinib in DASISION [14] and with nilotinib in ENESTnd [13] trials. The challenges for the widespread routine use of the 10% BCR-ABL transcript cut-off at the third month of TKI are present. First, the estimated ratio of BCR-ABL:ABL is highly technique-dependant. Many laboratories in the world are still not qualified for the international harmonization of scale (IS). High ratio values on IS scale, housekeeping control gene problem, variations in the samples, delays in the exact molecular assessment time after TKI and early unexpected variation kinetics of response in individual CML patients complicate the universal decision of the 10% BCR-ABL transcript cut-off at the third month of TKI. Furthermore, the tumor burden at diagnosis, prognostic scoring, gene profile, cytoreduction with TKI dosage, treatment adherence and numerous confounding effects may obscure the real-life decision at the third month of TKI outside the clinical trials [1]. Therefore, ELN 2013 recommendations suggested that any CML patient who does have a BCR-ABL over 10% after the 3 months of TKI presents a strong warning requiring a more careful and more frequent monitoring. If the CML patient exhibits no CHR and/or no minor cytogenetic response, the failure of the first-line TKI is evident. If the initial failed TKI treatment for CML was imatinib, nilotinib or dasatinib shall be given. If one of the two second-generation TKIs (nilotinib or dasatinib) was used as the first-line therapy and failed, the other one (dasatinib or nilotinib) could be administered. Increasing the dose of imatinib [4] has been tried in the literature (**Table 2**) but seems to be a dying art in the era of stronger TKIs. Drug tolerability and adherence to the treatment should always be sought. Effective management of the treatment-related adverse effects is a vital part of the CML care [2].

Based on ELN 2013 recommendations (**Table 1**), CCyR at 6 months and/or BCR-ABL < 1% following 6 months of second-generation TKIs are considered as optimal. Any CML patient who does have a BCR-ABL over 10% (absence of EMR) and/or Ph chromosome > 35% after the 6 months of TKI (particularly nilotinib and dasatinib) may be accepted as failure and the treatment strategy may be changed. Those higher treatment milestones could be applied to the first-line imatinib receiver CML patients and the switch to second-generation TKIs may be performed. Cumulative incidence of MMR is higher with both nilotinib and dasatinib. Early switch from imatinib to second-generation TKI is rational, since the RCTs indicated the higher probability to obtain better responses as well as the progression-free survival and overall survival [6,7]. Prevention of disease progression seems to be better achieved with more powerful second-generation TKIs. Specific long-term drug adverse effects (such as pleuropulmonary syndrome for dasatinib and metabolic syndrome for nilotinib) as well as the increased treatment costs shall be considered. Careful consideration of those critical issues would prevent overtreatment and undertreatment at the early management stages of CML.

4. Critical early disease management at the twelfth month after the initiation of TKI: ELN 2013 recommendations for CML and the arguments

Based on ELN 2013 recommendations (**Table 1**), MMR (BCR-ABL < 0.1%) following 12 months of second-generation TKIs are considered as optimal response. Any CML patient who does have a BCR-ABL > 1% and/or Ph chromosome > 1% after the 12 months of TKI (particularly nilotinib and dasatinib) may be accepted as failure and the treatment strategy may be changed. Those higher treatment milestones could be applied to the first-line imatinib receiver CML patients and the switch to second-generation TKIs may be performed. Drug tolerability and adherence to the treatment should always be sought [1,2].

5. Evaluation and management thereafter following the initiation of TKI in CML patients

Based on ELN 2013 recommendations (**Table 1**), optimal response obtained from TKI in CML is, at least, the continuation of MMR. Quality of life is especially a matter of concern in CML patients receiving long-term maybe lifetime TKI drugs [2]. Evaluation for the discontinuation of TKI in the superior-TKI responder CML patient shall be performed in long-term, for instance, after 2 years. The deeper molecular responses (MR4, MR4.5 and MR5) are candidates for the TKI discontinuation [15] MR4 can be achieved by a BCR-ABL expression < 0.01%, MR4.5 by < 0.0032% BCR-ABL^{IS} and MR5 by < 0.001% BCR-ABL^{IS}. [3,8]. Pregnancy represents a way of TKI discontinuation because of the negative impact of any TKI to the organogenesis. Treatment-free remissions and reinduction of the remission with the same TKI seem to be possible based on the data from the STIM trial [15].

In case of the intolerance to any TKI and/or multi-TKI-resistant CML cases with or without mutations, third-line treatment includes bosutinib, ponatinib, allogeneic stem cell transplantation and experimental therapies [1]. Mutations detected during the TKI therapy may result in drug alterations and entire treatment strategy based on the nature of the mutation. T315I, Y253H, E255K, E255V, F359V, F359C and F359I are the mutations that are poorly sensitive to nilotinib; whereas T315I, T315A, F317L, F317V, F317I, F317C and V299L are the mutations that are poorly sensitive to dasatinib. T315I is a unique mutation that makes the CML patients irresponsive to many TKIs and allografting may be an option in the case. Combination treatments such as TKI plus interferon are still a matter of research (**Table 2**) and rarely used outside clinical trials. Patients with AP/BC CML would be treated with the most powerful TKI available (dasatinib or ponatinib) and with multi-agent chemotherapy before

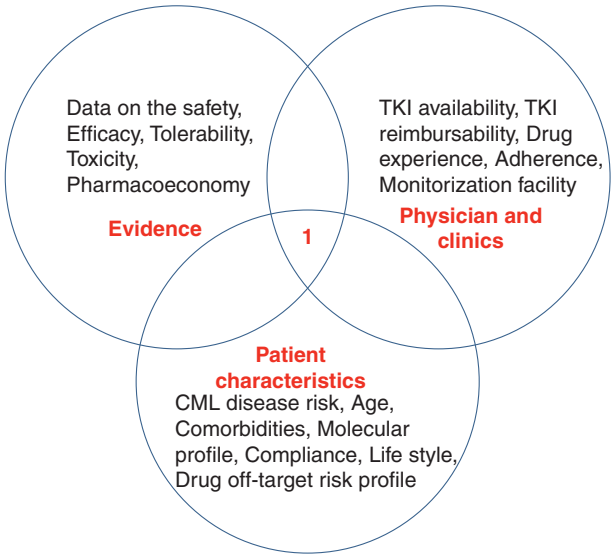

Figure 1. Illustration of clinical decision making for any TKI drug in CML. Number one [1] clinical decision should be reached based on the optimization of the best available evidence, individual patient/disease characteristics and the clinical experience.

allografting. Nilotinib has not been approved for the treatment of advanced phase (AP/BC) CML. Since those patients with advanced phase CML still do have a worse prognosis, prevention of disease progression is the most significant aspect of CML disease management [1].

6. Gray zone of ELN 2013 recommendations for CML management

ELN 2013 recommendations [1] provided clear practical suggestions for the physicians dealing with CML management, based on the best available evidence without disregarding clinical realities and expectations. On the other hand, several points of criticism are discussed below to underline the gray unclear zones of ELN 2013 mainly because of the lack of solid data in the given issue:

- ELN 2013 cannot be applied to all of the CML patients and cannot cover all of the possibilities during the long-term CML disease course. Response levels at 3 months, 6 months and 12 months are useful but could fail to predict long-term survival, morbidity, sudden BC and probability of disease acceleration.
- ELN 2013 recommendations indicate the targets (response, time to response and outcomes), but not the TKI drug itself. However; pharmacobiological function, BCR-ABL inhibitory activity, side effects, tolerability, off-target complications and pharmacoeconomy of the TKI drugs are quite different. Therefore, expected end points of the TKI treatment may not be exactly similar in all cases.
- ELN 2013 recommendations tried to establish a balance between scientific research and real-life practice in CML. Study populations in RCTs are younger than usual CML population. Likewise, in-study patients usually do not have significant comorbidities, associated diseases and concurrent medications and are closely monitored with standardized molecular techniques. Therefore, the results of RCTs cannot be directly applied to the out-study patients with distinct individual risk profiles.
- Early surrogate markers (CCyR and MMR) of the recommendations predict the clinical outcome but the relationship between the timing of deeper response based on those markers and survival is still not clear. Particularly the effect of an early switch from one TKI to a superior one is not certain or is evidence-based.
- There is still a suspicion whether an 'optimal TKI drug' and an 'optimal TKI dose' exists in all CML patients listed in the recommendations. Alternatively, CML treatment may be modeled on the individual disease and patients' characteristics (risk, molecular profile, age, comorbidities, aggressive clinical course, etc.). The dose of TKI (imatinib 400 vs 600 mg; dasatinib 100 vs 140 mg; nilotinib 600 vs 800 mg) could also be tailored based on the tolerability and organ functions of the patient. Otherwise, late, off-target complications of TKI (lung toxicity, cardiac toxicity, metabolic syndrome, bone toxicity, arterial occlusive events, pancreas toxicity and others) may limit the benefits of the given TKI.

7. Expert opinion in the TKI treatment of CML

Current optimal management of CML is chronic oral TKI administration. Initial TKI treatment for low-risk CP-CML is imatinib 400 mg; high-Sokal risk and/or CML patients with CCA would require more powerful second-generation TKIs (dasatinib 100 mg or nilotinib 600 mg). Absence of EMR after 6 months, CCyR after 12 months and MMR after 18 months may require a more powerful TKI switch. If one of the two second-generation TKIs (nilotinib or dasatinib) was used as the first-line therapy and failed, the other one (dasatinib or nilotinib) could be administered. Optimal clinical decision making is depicted in **Figure 1**. The cessation of the TKI therapy with the aim of cure, stem cell depletion, stem cell exhaustion and immunological control of the disease will be the future therapeutic tools of CML.

Declaration of interest

IC Haznedaroglu is a member of ELN and has received research grants and honoraria from Novartis.

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Affiliation

Ibrahim C Haznedaroglu MD
Hacettepe University Medical School,
Department of Hematology, Ankara, Turkey
E-mail: haznedar@yahoo.com