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REVIEW

How we will treat chronic myeloid leukemia in 2016

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ABSTRACT

Imatinib will become generic in 2016; assuming that its price will decrease precipitously, we expect that the economic forces will change our current practice habits. We reviewed the literature on the current recommendations to treat chronic myeloid leukemia and highlight how we plan to deal with these changes. Specifically, we propose to better characterize patients according to prognostic scores, to allow more attention to those at high risk for disease progression, e.g., 3-month guidelines and *BCR/ABL1* message half-time, emphasize compliance by using contemporary technologies, and increase the importance of early monitoring. We hope that our message will open communication between providers, insurance companies and healthcare authorities to offer the best care for our patients.

1. Introduction

Imatinib was approved for chronic myeloid leukemia (CML) in the United States of America (USA) by the Food and Drug Administration (FDA) in 2001 [1]. Since its approval, two other tyrosine kinase inhibitors (TKIs), nilotinib and dasatinib, were approved by the FDA as frontline treatment for CML based on two separate randomized trials comparing these second-generation TKIs to imatinib [2,3]. Both trials showed "faster" cytogenetic and molecular responses at 12 months with the second-generation TKIs, which persisted up to three years (Fig. 1, A and B). Dasatinib's improved cytogenetic outcome at 12 months was also confirmed by an independent trial [4]. Interestingly, high-dose imatinib improved cytogenetic and molecular responses in one randomized study [5] but not in another [6]. Those effects were mainly observed in patients with a higher risk for disease progression based on the Sokal [7], the Hasford [8], or the European Treatment and Outcome Study (EUTOS) [9] prognostic systems (Tables 1 and 2). Progression to accelerated/blastic phases was statistically less frequent with the use of nilotinib compared to imatinib (ENESTnd, Fig. 1C). No such data are available for dasatinib or high-dose imatinib. Yet none of these differences translated into longer disease-free or overall survival. Despite these facts, the second-generation TKIs have been adopted in the first line setting for all patients by many practitioners in the USA. Their long-term safety data are summarized in Table 3.

2. How will we treat these patients in 2016?

Imatinib's patent expires on February 1, 2016. Currently, imatinib sells in the USA for $92,000 per year [10]. The second-generation TKIs are even more expensive; nilotinib costs $115,500 per year and dasatinib $123,500 per year [10]. The prices for these drugs vary in other countries. For example, in the United Kingdom, imatinib and nilotinib cost the same ($33,500) while dasatinib is more expensive ($48,500). In South Africa, nilotinib is less expensive than imatinib ($28,000 vs. $43,000) and dasatinib is more expensive than imatinib ($54,500). It is logical to assume that given a broad cost differential after patent expiration, insurance companies, and healthcare authorities in the USA will favor generic imatinib as of 2016. The question for clinicians in the face of this anticipated change in drug coverage is how to optimize or codify the upfront use of second-generation TKIs for patients at higher risk of progression on imatinib.

3. Clinical parameters for evaluation of treatment response

Clinical response to TKIs is measured by three main parameters which are acknowledged by the European Leukemia Net (ELN) [11] and the National Comprehensive Cancer Network (NCCN) [12]. Complete hematologic response (CHR) is defined as reduction in white blood cell count to less than 10×10^9/L, reduction in platelet count to less than 450×10^9/L, disappearance of immature cells in the peripheral blood, no signs or symptoms of disease, and disappearance of splenomegaly. Cytogenetic response is divided into complete, partial, and minor responses. Complete cytogenetic response (CCyR) is defined as 0% Philadelphia-positive (Ph^+) metaphase cells upon evaluation of a minimum of 20 cells; partial cytogenetic response is ≤35% Ph^+ metaphase cells, and minor cytogenetic response is >35% Ph^+ metaphase

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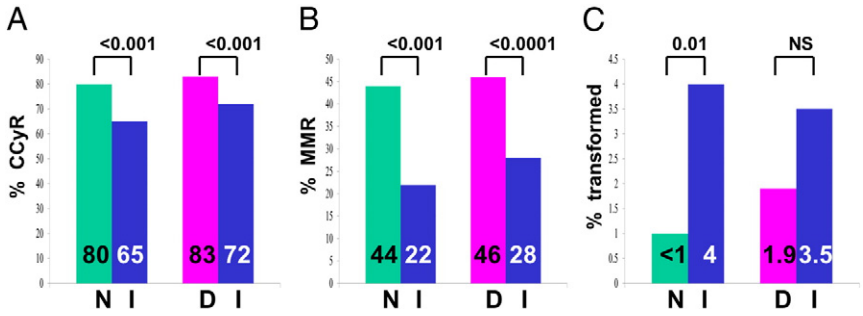

Fig. 1. Response to nilotinib and dasatinib compared to imatinib. Panels A and B demonstrate complete cytogenetic response (CCyR) and major molecular response (MMR) achieved at 12 months in ENESTnd [nilotinib (N) vs. imatinib (I)] and DASISION [dasatinib (D) vs. imatinib (I)] trials. Panel C shows progression to accelerated/blastic phase with nilotinib (N) and dasatinib (D) in comparison to imatinib (I), at the conclusion of the first 12 months of follow-up. Numbers at the top represent P values.

cells. Major cytogenetic response applies only to large studies and combines complete and partial cytogenetic responses (0% to 35% metaphase cells with the Ph + chromosome) [13].

Molecular response is the most sensitive measure currently used to monitor the disease. It is determined by quantifying the *BCR/ABL1* transcript level through quantitative real-time reverse-transcriptase polymerase chain reaction of a sample from either the peripheral blood or the bone marrow. Major molecular response (MMR), a term that arose from the International Randomized study of Interferon and STI571 (IRIS) [14], is defined as greater than 3 log reduction (<0.1%) in *BCR/ABL1* transcript level based on the International Standard (IS) [13]. The sensitivity of this assay allows for a new treatment goal of a "deep molecular response" described as 4.5-log fold reduction ($MR^{4.5}$) of *BCR/ABL1* transcript with prognostic value for overall survival [5]. Fluctuation of *BCR/ABL1* transcript levels at the very low end of the detection level has a poor accuracy in defining a relapse risk [15,16]. Complete molecular response denotes inability to detect the transcript.

Imatinib data indicate that timing and degree of CCyR and MMR achieved have prognostic significance. For instance, attainment of CCyR or MMR within the first 12 months of imatinib treatment predicts a low risk for disease progression (Fig. 2) [13,17]. Furthermore, achievement of MMR in the first year indicates long-lasting CCyR [13]. However, waiting for 12 months is not appropriate and therefore several groups have looked at earlier time points. The 3-month time point was chosen by the ELN [11] and the NCCN [12] as a decision point based on imatinib data showing better outcome if patients achieved 10% or less *BCR/ABL1* transcript by IS at the 3-month time point (Fig. 3A) [18,19]. Others have challenged this time point and proposed the 6-month time point, especially when using second-generation TKIs because of their more robust response [20]. When one compares nilotinib to imatinib data from ENESTnd, (Fig. 3B) one can clearly notice that 33% of patients on imatinib did not achieve the 10% *BCR/ABL1* message level by IS at the 3-month time point and those patients are at risk for disease progression [21], especially if they had intermediate or high Sokal or Hasford Scores at diagnosis [3]. However, no data showing that a change in treatment will modify the prognosis of these patients are available. A study offering nilotinib (400 mg orally twice daily) for patients with suboptimal response by ELN [11] showed improved responses in some patients but many did not achieve CCyR [22]. It is possible that patients with suboptimal responses inherently have worse disease and therefore are likely to progress regardless of change in treatment [19]. We propose the 3-month time point as a decision point because we predict that generic imatinib will become the drug of choice based on insurance coverage after 2016, and we therefore should be monitoring these patients more closely for disease progression. Alternatively, though with minimal data on longer disease-free or overall survival, insurance companies, and healthcare authorities should be encouraged to pay for the use of second-generation TKIs for all patients with intermediate and high Sokal, Hasford, or EUTOS scores at the time of diagnosis given their higher risk of disease progression and imatinib failure.

Two randomized studies, ENESTnd and dasatinib vs. imatinib (DASISION), have taught us that patients at low risk by either Sokal or Hasford prognostic systems are less likely to progress to accelerated/blastic phase when treated with either imatinib or the second-generation TKIs. However, patients at the intermediate- and high-risk groups (Table 2) are less likely to benefit from imatinib [23,24]. These prognostic systems (Table 1) should therefore be calculated on all newly diagnosed CML patients [7–9]. Such applications currently exist for free on the web (e.g., http://bloodref.com/myeloid/cml/sokal-hasford).

4. Adherence and compliance to therapy

Adherence to treatment is a challenge for many of the patients who are on chronic therapy for any medical condition. The ADAGIO study [25] was the first to demonstrate that only 14.2% of CML patients were perfectly adherent with 100% of prescribed imatinib. That study covered only 90 days. A study covering a 2-year period in patients with CML or gastrointestinal stromal tumors showed 78% adherence to imatinib [26]. Furthermore, this study showed that adherence decreased with

Table 1
Current prognostication systems for chronic myeloid leukemia.

Parameters	Sokal risk score	Hasford risk score	EUTOS score
Age (years)	*0.116 (age–43.4)*	0.666 when Age ≥50	
Spleen (cm)	0.0345 (spleen–7.51)	0.042 × Spleen	0.0402 × Spleen
Platelet Count ($x10^9$/L)	0.188 [(Plt/700)^2-0.563]	1.0956 when Platlet ≥1500	
Blood Myeloblasts (%)	0.0887 (Myeloblasts −2.10)	0.0584 × Myeloblasts	
Blood Basophils (%)	–	0.20399 when Basophils >3%	0.07 × Basophils
Blood Eosinophils (%)	–	0.0413 × Eosinophils	
Relative Risk	Exponential of the Total	Total × 1000	
Low Risk	<0.8	≤780	≤87
Intermediate Risk	0.8–1.2	781–1480	
High Risk	>1.2	>1480	<87

Abbreviations: EUTOS, EUropean Treatment and Outcome Study.