Leukemia Research xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Leukemia Research

journal homepage: www.elsevier.com/locate/leukres

Distinct predictive factors influence on achievement of early molecular response by frontline imatinib in chronic phase chronic myeloid leukemia

Sung-Eun Lee[a,b], Soo Young Choi[a], Yun Jeong Oh[a], Soo-Hyun Kim[a], Hye-Young Song[a], Hea-Lyun Yoo[a], Mi-Young Lee[a], Moon-Jung Chae[a], Ki-Hoon Kang[a], Hee-Jeong Hwang[a], Eun-Jung Jang[a], Dong-Wook Kim[a,b,*]

[a] Cancer Research Institute, The Catholic University of Korea, Seoul, Korea
[b] Department of Hematology, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, Korea

ARTICLE INFO

Article history:
Received 6 September 2014
Received in revised form 9 January 2015
Accepted 20 January 2015
Available online xxx

Keywords:
Chronic myeloid leukemia
Imatinib
Early molecular response

ABSTRACT

To explore the factors for achieving early molecular responses (EMR; BCR-ABL1 ≤10% at 3 months, ≤1% at 6 months) by imatinib (IM), baseline characteristics including individual BCR-ABL1 transcript level, dose intensity, and IM trough level on day 29 were analyzed in 286 chronic phase chronic myeloid leukemia patients. Distinct predictive factors for achieving EMR at 3 months and 6 months were noted. Blast count at diagnosis and IM trough level on day 29 were significantly associated with an achievement of 3-month EMR. Early decline of BCR-ABL1 transcript, low Sokal risk, and mean daily dose (≥350 mg/day) by 6 months were associated with an achievement of 6-month EMR. Understanding the predictive factors for EMR may provide additional information to guide clinical decisions on the changing therapies at each landmark.

1. Introduction

Imatinib (IM) has been the standard of care for chronic phase (CP) chronic myeloid leukemia (CML). Complete cytogenetic response (CCyR) has been established as a predictor for disease outcome by the International Randomized Study of Interferon and STI571 (IRIS) [1]. Recent studies have demonstrated that measurements of BCR-ABL1 transcript levels at 3 and 6 months were able to predict responses and survival, suggesting that the early switch to second-generation tyrosine kinase inhibitors (TKIs) may be beneficial for high-risk patients [2–4].

However, the factors that contribute to early molecular response have not been fully defined. The new European Leukemia Net (ELN) recommendations concluded that a single measurement of BCR-ABL1 transcripts level after 3 months of treatment is not sufficient to define failure necessitating a change of treatment. Instead, the ELN recommended that tests at 3 and 6 months, and supplementary tests in between, provide more support for the decision to change treatment [5].

Recently, Neelakantan *et al.* found that the prognostic value of the 3-month early molecular response (EMR) could be improved by combining the 3- and 6-month results, but suggested that the 3-month EMR had superior prognostic value than the 6-month EMR so early interventions could be determined based on the 3-month result [6]. However, this decision should be made with caution because various factors such as baseline biological characteristics, adherence to IM, IM dose intensity, and pharmacokinetics can be associated with the initial response to IM in CP CML. To date, factors associated with the achievement of EMR are not well-known.

This study was performed to identify the predictive factors for the achievement of 3- and 6-month EMRs. Thus, we explored contributing factors including the precise IM dose schedule. Additionally, the prognostic implications of EMR were analyzed in the same population.

2. Patients and methods

2.1. Study patients

A total of 286 newly diagnosed CP CML patients with follow-ups of more than 6 months who received IM with no prior treatment and had available molecular data at 3 months were included in the analysis. Patients who had atypical transcripts

* Corresponding author at: Department of Hematology, Seoul St. Mary's Hospital, The Catholic University of Korea, #222 Banpodaero, Seocho-Gu, Seoul 137-701, Republic of Korea. Tel.: +82 2 2258 7030; fax: +82 2 593 2522.
E-mail address: dwkim@catholic.ac.kr (D.-W. Kim).

http://dx.doi.org/10.1016/j.leukres.2015.01.011
0145-2126/

were excluded. Cytogenetic and molecular responses were assessed per the ELN recommendations [5]. All clinical data, including hematologic, cytogenetic, molecular response, baseline characteristics, IM trough levels on day 29 and the end of cycle 6, and the IM dose intensity were collected in the Asia CML Registry (ACR) database system. Measurements of IM plasma concentrations were performed in patients who permitted the test. Written informed consent was obtained from each patient. This study was approved by the Institutional Review Board of Seoul St. Mary's Hospital and was conducted in accordance with the Declaration of Helsinki.

2.2. Plasma trough levels of IM

Trough blood samples were collected on day 29 and at the end of cycle 6 (1 cycle = 28 days) prior to daily IM dosing. Plasma concentrations of IM were measured using liquid chromatography/mass spectrometry/mass spectrometry (LC/MS/MS). The limit of quantification was 5 ng/ml and the assay was tested in a fully validated laboratory (Bioanalytical Laboratory of Clinical Research Coordinating Center, The Catholic University of Korea, Seoul, Korea).

2.3. Molecular monitoring

Molecular responses were monitored using a qRT-PCR assay in 3-month intervals and then 6-month intervals after achieving a major molecular response (MMR). All qRT-PCR were tested with at least 4.5-log sensitivity in the central laboratory (Cancer Research Institute, The Catholic University of Korea, Seoul, Korea), as described previously [7]. The quality of RNA was assessed using Experion automated electrophoresis (Applied Bio-Rad, Hercules City, CA, USA), and only qRT-PCR results with more than 50,000 ABL1 copy numbers were analyzed. MMR was defined as a BCR-ABL1 transcript level of 0.1% or lower on the international scale (IS). Undetectable molecular residual disease (UMRD) was defined as negative PCR results with at least a 4.5-log sensitivity in both duplicated qRT-PCR and nested RT-PCR assays.

2.4. Statistical analysis

The study objectives were (1) to identify predictive factors for an achievement of BCR-ABL1 ≤10% at 3 months and BCR-ABL1 ≤1% at 6 months, and (2) to evaluate the clinical significance of EMR on the following outcomes. Potential predictive factors for an achievement of EMR were assessed using the logistic regression and included age, sex, transcript type, baseline BCR-ABL1 transcript, log reduction of the BCR-ABL1 transcript, Sokal risk, leukocyte count, platelet count, blast %, basophil %, spleen size, time from diagnosis to treatment initiation, and mean daily dose (MDD), which was calculated as the total amount of IM/total days of the specific duration. Covariates with a *P*-value of less than 0.1 in the univariate analyses were added to the multivariate analysis model. The impact of trough IM level on the achievement of EMR was separately analyzed.

Failure-free survival (FFS) was measured from the day of IM therapy initiation to death, progression to accelerated phase (AP) or blast phase (BP), and treatment failure according to the new ELN recommendations [5] or contact, whichever came first. In FFS, patients were censored at the time of permanent IM discontinuation. Overall survival (OS) included any death regardless of causes, and progression-free survival (PFS) included progression to AP or BP as well as death resulting from any cause. OS and PFS were also collected on patients who were treated with other TKIs after IM discontinuation.

3. Results

3.1. Patient characteristics and outcomes

Patient characteristics are summarized in Table 1. A total of 286 patients (173 men and 113 women) were analyzed. With a median age of 41 years (range, 15–75 years), the distribution of low, intermediate, and high Sokal risk scores were 36%, 40% and 20%, respectively, with 4% unknown risk. The median time from diagnosis to IM initiation was 0.5 months (range, 0–7 months). Most patients received 400 mg/day as a starting dose and 33 patients received higher doses (600 mg/day in 31 patients and 800 mg/day in 2 patients). By 3 and 6 months from IM therapy initiation, the median MDDs were 400 mg/day (range, 235.6–783.7 mg/day) and 400 mg/day (range, 177.8–783.7 mg/day), respectively.

Table 1
Patient characteristics.

Parameters	Total (*n* = 286)
Age (years), median (range)	41 (15–75)
Sex, male, *n* (%)	173 (61)
Transcript type, *n* (%)	
b3a2/b2a2/b3a2 + b2a2	115(40)/167(59)/4(21)
Baseline BCR-ABL1^{IS} transcript (%), median (range) (NA = 105)	85.98 (23.77–881.37)
Sokal risk, *N* (%)	
Low/INT/High/NA	104(36)/114(40)/57(20)/11(4)
Leukocyte count ($\times 10^9$/l), median (range) (NA = 21)	82.1 (2–1834)
Platelet count ($\times 10^9$/l), median (range) (NA = 44)	420 (73–3365)
Percentage of blast (%), median (range) (NA = 51)	1 (0–14)
Percentage of eosinophil (%), median (range) (NA = 55)	2 (0–25)
Percentage of basophil (%), median (range) (NA = 59)	4 (0–20)
Spleen size from costal margin (cm), median (range) (NA = 65)	3.2 (0–22)
Time from Dx to IM therapy initiation (mos),median (range)	0.5 (0–7)
Mean daily dose by 3 month (mg), median (range)	400 (235.6–783.7)
Mean daily dose by 3 month (mg), *n* (%)	
≤200	0 (0)
>200 to ≤300	5 (2)
>300 to ≤400	220 (77)
400	61 (21)
Mean daily dose by 6 month (mg), median (range)	400 (177.8–783.7)
Mean daily dose by 6 month (mg), *n* (%)	
≤200	1 (0)
>200 to ≤300	5 (2)
>300 to ≤400	219 (77)
400	61 (21)

Abbreviations: Dx, diagnosis; IM, imatinib; INT, intermediate; mos, months; NA, not available; Q1, quartile 1; Q2, quartile 2; Q3, quartile 3; Q4, quartile 4.

3.2. Predictive factors for an achievement of 3-month EMR

286 patients with available 3-month qRT-PCR on IM therapy were evaluated and the results were as follows: BCR-ABL1 ≤10% (*n* = 225) and >10% (*n* = 61). Among 61 patients with BCR-ABL1 >10%, 2 patients failed to achieve complete hematologic response (CHR). Of the potential predictive factors for an achievement of 3-month EMR on univariate analyses, multivariate analyses reveal that higher blast count (*P* = 0.052) was associated with a lower 3-month EMR (Table 2 and Supplementary Fig. 1).

To analyze the impact of the pharmacokinetics of IM on the achievement of EMR, we performed separate analyses. The day 29 trough IM level data were available from 95 patients. The median trough concentrations of IM were 1252 ng/mL (range, 439-3491) and the cut-off IM levels for the lower Q1, Q2, and Q3 quartiles were 958.2, 1252, and 1767 ng/mL on day 29, respectively. Patients in Q1 of the plasma IM trough level on day 29 had a lower 3-month EMR compared with those in Q2-4 [relative risk (RR) of 5.03, *P* = 0.015].

3.3. Subsequent change of molecular responses at 3 months

Subsequent changes in molecular responses at 3 months are shown in Fig. 1. Among 225 patients with BCR-ABL1 ≤10% at 3 months, 154 of the patients who achieved a 3-month EMR had a reduction to BCR-ABL1 ≤1% at 6 months, while 61 patients failed to achieve a BCR-ABL1 ≤1% at 6 months. The other 8 patients were permanently discontinued from IM treatment and switched to an alternate TKI due to intolerance (*n* = 3), warnings according to the new ELN recommendations with adverse events (*n* = 4), and primary IM failure (*n* = 1) between 3 and 6 months. After switching to an alternative TKI, all of 8 patients achieved an MMR. Two patients

Please cite this article in press as: Lee S-E, et al. Distinct predictive factors influence on achievement of early molecular response by frontline imatinib in chronic phase chronic myeloid leukemia. Leuk Res (2015), http://dx.doi.org/10.1016/j.leukres.2015.01.011