Leukemia Research 70 (2018) 100–105

Contents lists available at ScienceDirect

Leukemia Research

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

Research paper

Comparative analyses of nilotinib versus high-dose imatinib versus sustained standard-dose imatinib in patients with chronic phase chronic myeloid leukemia following suboptimal molecular response to first-line imatinib

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ARTICLE INFO

Keywords:
Chronic myeloid leukemia
Suboptimal response
Nilotinib
Imatinib

ABSTRACT

The aim of this study was to investigate the efficacy of nilotinib (NIL) versus high-dose imatinib (IM) versus sustained standard-dose IM for patients with chronic myeloid leukemia (CML) with suboptimal molecular response to first-line IM therapy. Patients with CML who achieved complete cytogenetic response (CCyR) but not major molecular response (MMR) after 18–24 months on first-line IM therapy were enrolled and divided into three treatment cohorts: NIL 800 mg/day (Cohort 1, n = 28) and IM 800 mg/day (Cohort 2, n = 28) in the RENICE study, and sustained IM 400 mg/day (Cohort 3, n = 52) in clinical practice. The primary efficacy variable of cumulative rate of MMR by 12 months was not different among the three cohorts. However, the cumulative incidence of MMR by 36 months was significantly higher in Cohort 1 than Cohort 3 (83.1% vs. 57.1%, P = 0.021), but there were no significant differences in Cohort 1 vs. 2 (P = 0.195) and Cohort 2 vs. 3 (P = 0.297). Different profile for adverse events was observed between NIL and high-dose IM therapy. In conclusion, our data suggested that switching to NIL may provide more effective long-term response than sustaining standard-dose IM for patients with suboptimal molecular response to first-line IM.

1. Introduction

Imatinib (IM) treatment is one of the standards of care for chronic phase (CP) chronic myeloid leukemia (CML). Its generic form is currently widely available as a cost-effective frontline treatment [1]. Although IM treatment has improved outcomes for CML patients, resulting in a 6-year progression-free survival of 93% [2], patients who experience treatment failure at milestones are at increased risk of disease progression to accelerated phase (AP), blast phase (BP), and death due to CML [3–6].

The 2009 European Leukemia Net (ELN) recommendations suggest that some patients who do not achieve optimal responses to tyrosine kinase inhibitor (TKI) therapy may still sustain a suboptimal response, which that means a long-term benefit from continuing a specific treatment may be achieved but the chances of an optimal outcome are reduced [7]. Of note, patients who show treatment failure are unlikely to achieve a favorable long-term outcome and should receive a different treatment. This intermediate zone, which was previously referred to as suboptimal response, has been designated as warning the ELN recommendations in 2013 [8].

It has been reported that suboptimal responders to IM therapy have a less favorable prognosis with a reduced likelihood of achieving future

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https://doi.org/10.1016/j.leukres.2018.06.002
Received 29 January 2018; Received in revised form 1 June 2018; Accepted 2 June 2018
Available online 07 June 2018

optimal responses and poor outcomes compared with optimal responders to IM therapy [7,9,10]. However, there is insufficient evidence for the decision to change treatment for patients with suboptimal responses [11]. Several studies have shown that IM dose escalation may provide additional benefit in some patients with suboptimal response or treatment failure on standard-dose IM [12–14], but high-dose IM is associated with an increased risk of adverse events (AEs) [15,16] and poor tolerability [17]. The safety and efficacy of nilotinib (NIL) in patients with IM-resistant or IM-intolerant CML have been established [18–22]. A few studies have evaluated the benefits of switching patients with suboptimal response on front-line IM to NIL as a treatment strategy for patients with suboptimal response [21,23,24].

We conducted this study to compare the impact of switching to NIL, IM dose escalation, and sustaining standard-dose IM in patients in complete cytogenetic response (CCyR) with suboptimal molecular response to first-line IM therapy.

2. Patients and methods

2.1. Patients and study design

Three cohorts of 108 patients in total were analyzed in this study. Patients in Cohort 1 and 2 were enrolled in a phase 3 multi-center, open-label, randomized study of the efficacy of NIL versus IM in adult patients with Philadelphia chromosome–positive CML in early CP who had a suboptimal molecular response to IM (RE-NICE study) between 2 April 2009 and 13 January 2014. Patients in Cohort 3 were selected from the Asia CML registry (ACR) database system using the same inclusion and exclusion criteria as the RE-NICE study. The RE-NICE study protocol was registered with the National Institutes of Health clinical trial registry at www.clinicaltrials.gov as #NCT01400074.

As shown in Fig. 1A, patients with CML in early CP who had been treated with first-line IM therapy with 400 mg IM daily for at least 18 months and achieved CCyR but not MMR were enrolled in this study. Patients in Cohorts 1 and 2 (Fig. 1B) were randomized 1:1 between high-dose IM (400 mg twice daily) and NIL (400 mg twice daily) and were followed for the study duration of up to 3 years. Crossover to the alternative treatment arm was allowed at 12 months for patients who failed to achieve a MMR and for patients who could not tolerate treatment and were receiving less than 400 mg of IM or NIL once daily. The patients who experienced crossover were followed for up to 3 years post-crossover. Patients in Cohort 3 (Fig. 1C) continued IM therapy with 400 mg daily in clinical practice. This analysis was approved by the Institutional Review Board of each participating institution and conducted in accordance with the Declaration of Helsinki.

2.2. Evaluation of cytogenetic and molecular response

For all patients, eligibility due to CCyR and lack of MMR after first-line IM therapy with 400 mg daily for at least 18 months was confirmed. To evaluate the cytogenetic response a minimum of 20 metaphases were examined in bone marrow samples; FISH analysis was not accepted for evaluation of cytogenetic response. For all screening and subsequent follow-up of molecular response, duplicate qRT-PCR and nested RT-PCR with at least 4.5-log sensitivity was performed in the central laboratory (Leukemia Research Institute, The Catholic University of Korea, Seoul, Korea). Major molecular response (MMR) was defined as a *BCR-ABL1* transcript level of 0.1% or lower on the international scale (IS). Deep molecular response (DMR) was defined as 0.0032% or lower in duplicated qRT-PCR assays with 5-log sensitivity. To monitor molecular response under each treatment, peripheral blood was obtained from all patients at baseline, at the end of cycles 1, 3, 6, 9, and 12, and at the end of every 3 cycles thereafter. All baseline samples were analyzed for *BCR-ABL1* mutation.

2.3. End points and statistical analysis

The primary objective was the cumulative rate of MMR by 12 months, which was plotted using the Kaplan–Meier method and compared between treatment cohorts using the log-rank test. The secondary objectives included the cumulative rates of DMR, time to MMR, time to DMR, rate of loss of MMR, and rate of loss of DMR. These end points were calculated on an intention-to-treat basis; patients with missing values and those who withdrew from study were scored as failures. Exploratory objectives included investigation of the presence of *BCR-ABL1* mutations at initiation and during the course of treatment. Safety evaluation, consisting of adverse events and biochemical abnormalities, was only performed for patients enrolled in Cohorts 1 and 2.

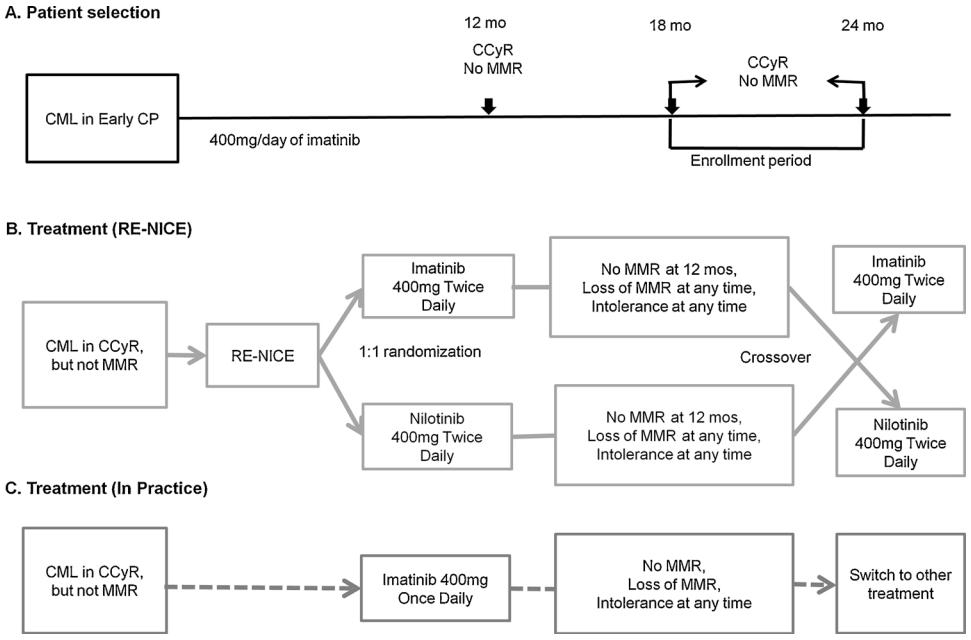

Fig. 1. Study Scheme. Patients with chronic myeloid leukemia (CML) in early chronic phase (CP) who had been treated with first-line IM therapy with 400 mg once daily for at least 18 months and achieved a complete cytogenetic response (CCyR) but did not achieve a major molecular response (MMR) were enrolled (A). This analysis included patients who received IM 800 mg/day or NIL 800 mg/day in the RE-NICE study (B) and patients who continued IM therapy with 400 mg once daily in clinical practice (C).