High-dose imatinib improves cytogenetic and molecular remissions in patients with pretreated Philadelphia-positive, *BCR-ABL*-positive chronic phase chronic myeloid leukemia: first results from the randomized CELSG phase III CML 11 "ISTAHIT" study

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ABSTRACT

Background
Imatinib 400 mg/day is the standard treatment for patients with chronic phase chronic myeloid leukemia. Recent reports suggested higher and more rapid cytogenetic and molecular responses with higher doses of imatinib.

Design and Methods
In this prospective international, multicenter phase III study, 227 patients with pre-treated Philadelphia chromosome-positive, *BCR-ABL*-positive chronic myeloid leukemia were randomized to a standard-dose imatinib arm (400 mg/day) or a high-dose imatinib arm (800 mg/day for 6 months followed by 400 mg/day as maintenance therapy). In this planned interim analysis hematologic, cytogenetic and molecular responses as well as toxicity were evaluated.

Results
Compared to the standard-dose, high-dose imatinib led to higher rates of major and complete cytogenetic responses at both 3 months (major: 21% *versus* 37%, P=0.01; complete: 6% *versus* 25%, P<0.001) and 6 months (major: 34% *versus* 54%, P=0.009; complete: 20% *versus* 44%, P<0.001). This was paralleled by a significantly higher major molecular response rate at 6 months in the high-dose imatinib arm (11.8% *versus* 30.4%; P=0.003). At 12 months, the rates of major cytogenetic response (the primary end-point) were comparable between the two arms (57% *versus* 59%). In contrast to non-hematologic toxicities, grade 3/4 hematologic toxicities were more common in the high-dose arm. Cumulative complete cytogenetic response rates were higher in patients without dose reduction in the high-dose arm (61%) than in the patients with no dose reduction in the standard-dose arm (36%) (P=0.014).

Conclusions
This is the first randomized phase III trial in patients with pre-treated chronic phase chronic myeloid leukemia demonstrating improvements in major cytogenetic response, complete cytogentic response and major molecular response rates with high-dose imatinib therapy (*ClinicalTrials.gov Identifier: NCT00327262).*

Key words: phase III study, chronic phase CML, high dose imatinib.

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Introduction

Based on the impressive results of the IRIS study comparing imatinib 400 mg/day with interferon-α plus low-dose cytarabine in patients with newly diagnosed chronic phase Philadelphia chromosome-positive (Ph+) *BCR-ABL*-positive chronic myeloid leukemia (CML),[1,2] imatinib 400 mg once daily became first-line, standard treatment for such patients. Recently published 7-year follow-up data showed that frontline therapy with imatinib 400 mg/day is capable of inducing durable cytogenetic and molecular responses. The estimated 7-year overall survival of patients receiving imatinib is 86% with only 6% CML-related deaths.[3] The initial phase I study revealed a clear dose-response relationship, and the maximal tolerated dose was not reached.[4] Moreover, higher doses of imatinib were able to improve or restore remissions that were not achieved with 400 mg.[5] Recently conducted phase II studies of the use of imatinib in patients with chronic phase CML receiving second-line therapy after failure of interferon-α treatment[6] or in newly diagnosed patients with chronic phase CML[7,8] suggest that a more aggressive dosing schedule (i.e. 800 mg/day) induces higher rates of cytogenetic and molecular responses and that the responses are achieved more rapidly. Early good responses have been shown to be associated with a better long-term progression-free survival.[2,9-12] Higher imatinib doses were generally well tolerated with the exception of myelosuppression, which necessitated dose reductions in 36% of the newly diagnosed CML patients after 6 months of therapy.[7] In the light of these observations, we initiated a prospective, international, multicenter, randomized, phase III study in which we compared imatinib 400 mg/day with imatinib 800 mg/day for a 6-month induction period followed by 400 mg/day imatinib as 'maintenance' therapy. This study was performed in a cohort of patients at high risk of disease acceleration including pretreated, but imatinib-naïve CML patients in late chronic phase who had not achieved a major cytogenetic remission at the time of enrollment into the study. The data presented are the results of a planned interim analysis that was performed on all patients after half of the patients had been treated for 12 months after randomization.

Design and Methods

Study design

This multicenter randomized phase III study was performed in 13 centers in seven different countries (Austria, Bulgaria, Latvia, Lithuania, Macedonia, Ukraine and Serbia). Eligibility criteria included patients aged 18 years old or over with CML in late chronic phase pretreated for at least 12 months with no major cytogenetic remission at study entry. Pre-treatment with tyrosine kinase inhibitors was not allowed. Patients who were unable to tolerate interferon-α (defined by grade 3/4 non-hematologic toxicity persisting for more than 2 weeks) could be included. A World Health Organization (WHO) status of 0-2 was required, as was adequate organ function, defined as follows: total bilirubin less than 1.5 times the upper limit of normal, liver transaminases less than 2.5 the upper limit of normal, creatinine less than 1.5 times the upper limit of normal, an absolute neutrophil count greater than 1.5×10^9/L, and a platelet count greater than 100×10^9/L. Exclusion criteria were uncontrolled clinical disorders and serological evidence of infection by human immunodeficiency virus. Moreover, women who were pregnant, breast feeding, or premenopausal without a negative pregnancy test before the start of the study as well as patients in accelerated phase or blast crisis were excluded. All patients provided written informed consent to participation in the study, in accordance with the Declaration of Helsinki. The trial was reviewed and ethically approved at all participating centers and was registered at ClinicalTrials.gov, a service of the National Institutes of Health, with the identification code of NCT00327262. The trial was managed by the Central European Leukaemia Study Group (CELSG), and data were collected and processed at the CELSG trial center at the Medical University of Innsbruck (Austria). Overall, 227 patients were enrolled between February 2004 and December 2006. The patients' baseline characteristics, including pre-treatments, are summarized in Table 1.

Treatment and dose modifications

Patients were randomized, at a 1:1 ratio, into two treatment arms. Patients in arm A received a standard dose of imatinib (400 mg/day) for 24 months, whereas patients in arm B received the experimental, high dose of imatinib for 6 months (800 mg/day administered in two 400 mg doses each day), followed by 18 months of imatinib 400 mg/day. Dose modifications due to toxicity were planned if patients experienced grade 2 non-hematologic toxicity. In this case, the study drug was withheld until the toxicity resolved to grade 1 or less and was then resumed at the same daily dose. If the grade 2 toxicity recurred, imatinib was withheld until the toxicity had resolved to grade 1 or less, and the daily dose was then reduced to 300 mg/day for patients in arm A or to 600 mg/day for patients in arm B. If grade 2 toxicity recurred after a dose reduction to 600 mg/day in arm B, the dose was further decreased to 400 mg and if grade 2 toxicity recurred the dose was further decreased to 300 mg. In the case of recurring grade 2 toxicity while taking the 300 mg/day dose, the patient went off study. If the patient experienced grade 3/4 toxicity, the study drug was withheld until the toxicity had resolved to grade 1 or less and the daily dose was then reduced to 300 mg for patients in arm A or to 600 mg for patients in arm B. If grade 3/4 toxicity recurred in arm B, imatinib was withheld until toxicity had resolved to grade 1 or less, and the dose was further decreased to 400 mg and then, if grade 3/4 toxicity recurred with 400 mg, to 300 mg.

If patients experienced grade 3/4 hematologic toxicity, (i.e. absolute neutrophil count < 1×10^9/L or a platelet count < 50×10^9/L), imatinib was withheld until toxicity had resolved to grade 2 or less. If the toxicity resolved within 2 weeks, imatinib treatment was resumed at the same dose. If the grade 3/4 toxicity recurred or persisted for more than 2 weeks, imatinib was withheld and then recommenced at the dose of 300 mg/day in arm A and at 600 mg/day in arm B. If grade 3/4 toxicity recurred the dose was further decreased to 400 mg and then, if grade 3/4 toxicity recurred with 400 mg, to 300 mg. In the case of recurring grade 3/4 toxicity with 300 mg/day the patient went off study. No dose reductions were performed for grade 3/4 anemia. Patients who developed anemia were given red blood transfusions or recombinant human erythropoietin at the discretion of the investigator. Patients who progressed to accelerated phase or blast crisis went off study.

End-points

The primary end-point for evaluation in the study was the proportion of patients who achieved a major cytogenetic remission after 12 months of therapy. Secondary end-points were the achievement of complete cytogenetic response and molecular responses as well as the tolerability of the two imatinib regimens.

Definitions of responses and response monitoring

Blood counts and biochemical and clinical evaluations were performed at baseline and at 1.5, 3, 6, 12, 18 and 24 months. Hematologic responses were analyzed according to the criteria estab-

lished by the European LeukemiaNet.[13] Bone marrow morphology, cytogenetic analyses and quantitative real-time polymerase chain reaction analyses of peripheral blood were performed at baseline and at 1.5, 3, 6, 12 and 24 months. Cytogenetic responses were assessed locally, whereas molecular monitoring was done centrally at the European LeukemiaNet-certified reference laboratory at the Children's Cancer Research Institute/Labordiagnostik in Vienna, Austria. For molecular monitoring, peripheral blood was collected into four Paxgene RNA-stabilization tubes (PreAnalytiX, Hombrechtikon, Switzerland), each containing 2.5 mL of blood. The tubes were stored locally at -20°C until shipment on dry ice every 3-6 months to the reference laboratory. Total RNA was extracted using the PAXgene Blood RNA kit (PreAnalytiX, Hombrechtikon, Switzerland) according to the manufacturer's instructions. Reverse transcription and real-time polymerase chain reaction analyses were carried out as described elsewhere.[14] Quantitative analysis of *BCR-ABL* expression was performed in relation to the *ABL* gene. Assessment of the molecular response was performed on the basis of the international scale.[15-17]

Table 1. Patients' characteristics including pre-treatments.

	Arm A (400 mg)	Arm B (800/400 mg)
Male	42.5%	46.6%
Female	57.5%	53.5%
Age (mean)	46.5±12.3*	45.5±13.4*
Age (median)	46.3 (20.2-68.2)§	46.6 (18.4-76.4)§
CML duration before study entry (Mean)	38.2 months	33.6 months
CML duration before study entry (Median)	27 months (2-199)§	26 months (1-192)§
Pretreatments		
Hydroxyurea	97% (109)#	96% (109)#
Interferons	70% (79)	74% (84)
Busulfan	20% (23)	14% (15)
Others (mainly AraC ± additional drug)	24% (27)	27% (31)

*SD, §Range, #Numbers.

Table 2. WHO grade 3 and 4 hematologic toxicities during the first 6 months of treatment and WHO grade 3 and 4 non-hematologic toxicities reported up to the time of the interim analysis.

	Arm A (400 mg)	Arm B (800/400 mg)
Anemia	2% (2/86)	14% (11/80)*
Leukopenia	24% (21/86)	46% (37/80)*
Thrombocytopenia	15% (13/86)	39% (31/80)§
Infections	2% (2/113)	3% (3/114)
Liver	1% (1/113)	2% (2/114)
Fluid retention	< 1% (0/113)	< 1% (0/114)
Gastrointestinal	< 1% (0/113)	< 1% (0/114)
Muscle	< 1% (0/113)	3% (3/114)
Renal	3% (3/113)	3% (3/114)
Cardiac	< 1% (0/113)	< 1% (0/114)
Neurologic	< 1% (0/113)	1% (1/114)
Pulmonary	< 1% (0/113)	< 1% (0/114)
Others	< 1% (0/113)	7% (8/114)

*P=0.02; §P=0.003.

Statistical analyses

This paper presents an interim analysis of a multi-center, randomized, open-label, two-arm, parallel group, phase III clinical trial comparing standard-dose imatinib with high-dose imatinib in patients with pretreated CML. The demographic characteristics, diagnosis, extent of cancer, disease history, toxicity, adverse events and medication administered were summarized applying Fisher's exact test, a χ^2 test, t-test or Mann-Whitney U test, as appropriate. Response rates at different time-points were summarized using contingency table analyses and compared between treatment groups using Fisher's exact test. According to the protocol for this interim analysis, *P* values less than 0.005 were considered statistically significant. All tests performed were two-sided. Event-free and progression-free survival were compared applying the Kaplan-Meier estimator together with the log-rank test. The following were considered events: death from any cause during treatment, progression to accelerated phase or blast crisis, loss of a complete hematologic response, and loss of a major cytogenetic response.

Results

Patients' characteristics

Of a total of 243 patients screened, 227 patients were randomized to one of the two treatment arms. The median follow-up at the time of the interim analysis was 12.75 months (range, 3-24 months). The distributions of age and sex and median duration of CML before study entry were not significantly different between the two treatment arms (Table 1). Almost all patients had received hydroxyurea during the course of their disease (96%). Other pretreatments included interferon (72%), busulfan (17%) and "others" (26%; mainly cytarabine with or without an additional drug).

Remission rates

Rates of complete hematologic responses did not differ significantly between the two arms at 1.5, 3, 6 and 12 months (54% in arm A and 59% in arm B at 3 months; 92% in arm A and 85% in arm B at 6 months; 82% in arm A and 90% in arm B at 12 months). In contrast, more patients in the high-dose arm achieved major and complete cytogenetic remissions at both 3 months (major: 21% in arm A, 37% in arm B, *P*=0.01; complete: 6% in arm A, 25% in arm B, *P*<0.001) and 6 months (major: 34% in arm A, 54% in arm B, *P*=0.009; complete: 20% in arm A, 44% in arm B, *P*<0.001) (Figure 1A and B). At 12 months, following dose reduction of imatinib to 400

Table 3. Comparison of the cumulative complete cytogenetic response (CCyR) rate if the intended dose of imatinib (i.e. 400 mg in arm A and 800 mg in arm B) was either continuously taken or if dose interruptions or dose reductions were performed.

	Cumulative achievement of CCyR	
Therapy within first 6 months	Arm A (400 mg)	Arm B (800 mg)
No change	20/56 (35.7%)	25/41 (61.0%)
Interruption/dose reduction	6/25 (24.0%)	15/43 (34.9%)
Discontinued	0/3 (<33%)	0/6 (<17%)

In the case of toxicity in arm A, the dose was reduced to 300 mg, otherwise patients went off study. In arm B, 35% of the patients in whom the dosse had to be reduced received 600 mg/day, 63% 400 mg/day and 2% 300 mg/day.

mg/day for 'maintenance' at month 6 in arm B, the rates of major cytogenetic response (the primary end-point of the study) were comparable in the two arms (59% in arm A, 57% in arm B). There was still a tendency towards a higher rate of complete cytogenetic responses in the high-dose arm (37% in arm A, 48% in arm B), but at the time of the interim analysis, this difference was not statistically significant (P=0.29).

The median *BCR-ABL* values at 3 and 6 months (Figure 2) were in agreement with the significantly better cytogenetic response rates during the high-dose imatinib induction phase. The proportion of patients who achieved major molecular remission was significantly higher at 6 months in the high-dose arm than in the standard-dose arm (Figure 1C). Progression-free and event-free survival rates were not significantly different at the time of the interim analysis (progression-free survival: 97.3% in arm A, 93.9% in arm B, P=0.191; event-free survival: 93.8% in arm A, 85.1% in arm B, P=0.027; Figure 3). After the first 6 months of therapy, loss of response was common. Notably, loss of major or complete cytogenetic response was less frequent in the high-dose arm (53.5% and 54.3%, respectively) than in the standard-dose arm (72.4% and 82.4%, respectively) (P=0.14 and P=0.07, respectively).

Toxicity and cumulative median doses

Grade 3 and 4 non-hematologic toxicities were uncommon and did not occur with statistically significant different frequencies between the two treatment arms (Table 2). In contrast, grade 3/4 hematologic toxicities were more common in the high-dose arm (anemia: 2% in arm A, 14% in arm B, P=0.02; leukopenia: 24% in arm A, 46% in arm B, P=0.02; thrombocytopenia: 15% in arm A, 39% in arm B; P=0.003) (Table 2). In spite of higher rates of grade 3/4 leukopenia in the high-dose arm, grade 3/4 infections were uncommon and their frequency was not statistically different between the two treatment arms. The cumulative median dose of imatinib during the first 6 months was 400 mg in the standard-dose arm and 767 mg in the experimental, high-dose arm.

Correlation between the administered dose and response rates

A higher proportion of patients (65.1%) remained on the initial dose of 400 mg of imatinib in arm A, whereas only 45.6% remained on the initial 800 mg dose in the high-dose arm (P=0.009). The cumulative rate of major cytogenetic response among patients who did not require a dose reduction/interruption during the first 6 months was higher in arm B (71%) than in arm A (59%) (P=0.232). Likewise, the cumulative rate of complete cytogenetic responses among patients who did not require a dose reduction/interruption was higher in arm B (61%) than in arm A (36%) (P=0.014) (Table 3). In addition, within the high-dose arm, the cumulative rate of complete cytogenetic responses was higher among the patients who did not require a dose reduction/interruption than among patients in whom the dose was reduced or interrupted (61% *versus* 34.9%; P=0.017) (Table 3). Interestingly, the complete cytogenetic response rates among patients not requiring a dose reduction/interruption in the standard arm (35.7%) and those among patients not able to maintain high dose imatinib therapy in the experimental arm (34.9%) were comparable.

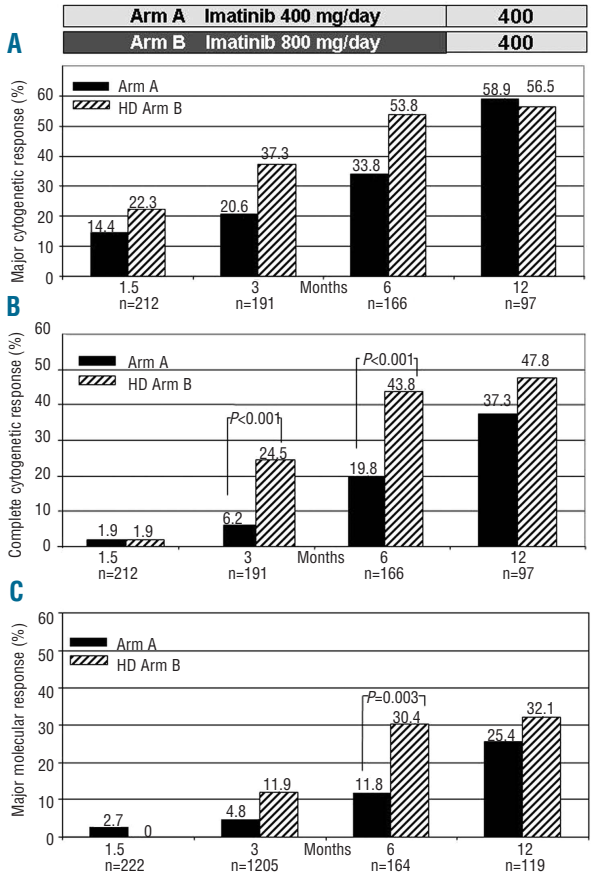

Figure 1. (A) Major cytogenetic response; (B) complete cytogenetic response, and (C) major molecular response rates analyzed at 1.5, 3, 6 and 12 months after randomization.

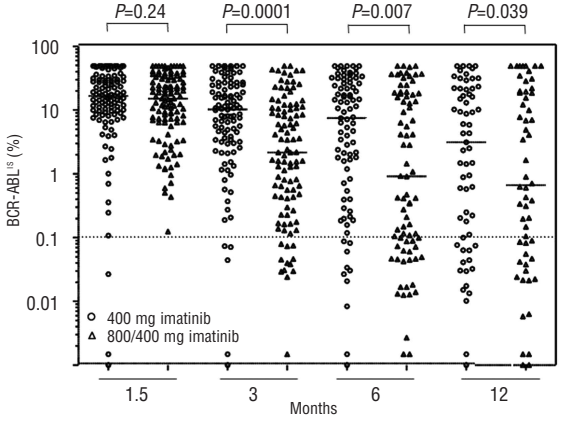

Figure 2. Molecular response (*BCR-ABL*) at different time points after randomization. Each symbol represents an individual patient at the respective time-point. Horizontal bars represent the median values for each study arm at the respective time points. The indicated *P* values are for the differences between median molecular responses observed in individual treatment arms at defined time points. The dashed line at 0.1% represents the cut-off value for definition of a major molecular response.

Discussion

The results presented here are the first published phase III data from a randomized multicenter study in pretreated chronic phase CML patients comparing the standard dose of 400 mg/day imatinib with a high dose of imatinib (i.e. 800 mg/day). It is worth noting that the majority of patients included in this trial were in late chronic phase and had already received various lines of previous therapies, thus representing a high-risk population. In addition, patients could not be in major cytogenetic remission at the time of entering the study. As this is a planned interim analysis, we primarily focused on interesting biological events (i.e. differences in cytogenetic and molecular responses at different time points). Survival data (event-free survival and progression-free survival) are also reported, but should be considered with caution, as only limited numbers of patients were evaluable after 12 months of therapy (i.e. a total of 54 patients at 18 months, 1 patient at 24 months). Our data clearly show that better cytogenetic and molecular responses can be achieved earlier with higher doses of imatinib. This might be of importance because delayed achievement of cytogenetic and molecular response was reported to be associated with an increased risk of disease progression.[1,10,18] The primary end-point of the study (i.e. the achievement of a significantly higher major cytogenetic response rate at 12 months in the high-dose arm) was not, however, achieved. Of note, only half of the patients have been included in the 12-month analysis so far, suggesting that the statistical power may be limited to detect statistically significant differences between the two treatment arms. The complete cytogenetic response rate at 12 months was clearly higher, albeit not statistically so, in the high-dose arm, despite the fact that at this time point imatinib had already been reduced to a 'maintenance' dose of 400 mg/day for 6 months in the high-dose arm. In contrast to findings of previous studies,[1-3,6,8] loss of responses was common in this high-risk population of patients. Interestingly, and in favor of the higher imatinib dose, a lower proportion of patients in the high-dose arm lost a major or complete cytogenetic remission after the first 6 months of therapy. One could speculate that these late chronic phase CML patients might have benefited from continuous treatment with high-dose imatinib. The reasons for having chosen a strategy of 6 months of high-dose imatinib at 800 mg/day followed by 400 mg/day as 'maintenance' therapy were based on a concept of "hit hard and early" and concerns of hematologic toxicity in the long-term with high-dose imatinib, considering the inclusion of heavily pre-treated patients in late chronic phase CML.

There are two additional reports on phase III trials comparing the same two different doses of imatinib in chronic phase CML patients.[18,19] Both trials were, however, performed in newly diagnosed CML patients and both tested continuous administration of high-dose imatinib (i.e. 800 mg) throughout the whole study period.

In line with our observation of a faster response to high-dose imatinib, the Tyrosine Kinase Inhibitor Optimization and Selectivity (TOPS) study showed significantly better complete cytogenetic and major molecular response rates during the first 6 months of therapy and a trend towards better cytogenetic and molecular remissions at 12 months in favor of the group receiving the 800 mg/day schedule.[18] The primary end-point (major molecular response at 12 months) was not, however, different between the different dosing schedules. A prospective trial of the European LeukemiaNet, whose results were presented by Baccarani *et al.*,[19] included only newly diagnosed CML patients with a high-risk Sokal score.[20] Interestingly, this study failed to demonstrate significant differences in terms of cytogenetic and molecular remissions, even at early time points. The primary end-point of the study (the achievement of a statistically significant improvement of the complete cytogenetic response rate at 12 months) was not attained. In contrast to these findings, a sub-analysis of high-risk Sokal patients in the TOPS trial revealed an increased rate of patients in major molecular remission at 12 months in the high-dose arm although the difference did not reach statistical significance.[18]

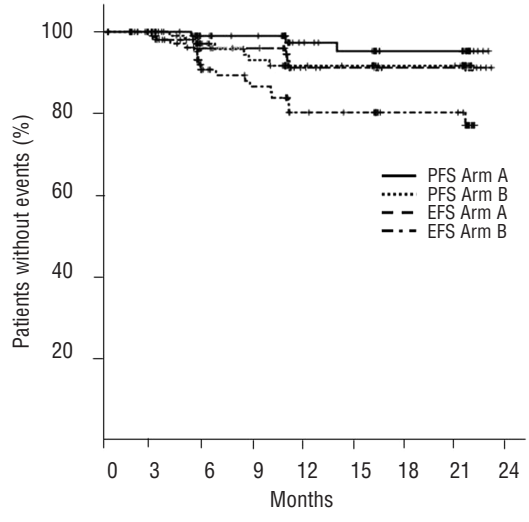

Figure 3. Kaplan-Meier estimates of the rates of event-free survival (EFS) and progression free from accelerated phase or blast crisis (PFS) for patients in arm A and arm B.

In terms of toxicity, it is noteworthy that in this ISTAHIT study the higher dose of imatinib (800 mg/day) appeared to be generally well tolerated although dose reductions or interruptions were more frequent in the high-dose arm than in the standard-dose one. It was interesting to note that complete cytogenetic response rates were higher among the patients who were able to take the intended high dose of 800 mg/day over a 6-month period than among either the patients who were intended to take the dose of 400 mg/day or the patients in the high-dose arm who required a dose reduction. This observation highlights the possibly more efficient anti-leukemic activity of high-dose imatinib, supporting the idea that the anti-tumor activity of imatinib is dose-dependent. However, our data as well as the findings of the TOPS and the ELN trial suggest that, in the long-term, the absolute anti-leukemic effect (i.e. the depth of the response) under high-dose imatinib might not be increased.

In conclusion, this first randomized, phase III trial in

pretreated late chronic phase CML patients showed that, in comparison to continuous standard-dose imatinib, induction with high-dose imatinib (i.e. 800 mg/day) produces higher cytogenetic and molecular response rates and the responses are achieved more rapidly. High-dose imatinib was tolerable even in these heavily pre-treated patients. Although grade 3 and 4 hematologic toxic side effects occurred more frequently in the high-dose treatment arm, relevant infectious or bleeding complications were not seen. Whether the earlier and better responses will lead to a reduction in *BCR-ABL* mutations and fewer events in the long-run (leading to reduced rates of progression into accelerated phase and blast crisis) and, subsequently, to improved overall survival remains to be determined. Our study is of particular relevance for those countries in which imatinib is not currently available but with a prospective of obtaining approval for its use in the near future.

Authorship and Disclosures

ALP, DW, DF TL, MK, FR and GG designed the study, performed research and wrote the manuscript; ID, ZM, AB, LG, SL, SG, LG, AS, DP, NT, RG and RO performed research and reviewed the manuscript. HU performed statistical analyses and reviewed the manuscript.

ALP, DW, TL, AB and GG have received lecture fees. ALP, TL, AB, LG and GG have received research support from Novartis. DW and AB have acted as consultants for Novartis. ALP, TL have acted as consultants for BMS. AB has acted as an expert witness for Novartis. MK and FR are Novartis employees. FR: ownership of stocks, honoraria from companies, expert testimony, lecture fees from companies, institutional research support by commercial firms, patents or patent applications.

No other potential conflicts of interests relevant to this article were reported.

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