

CHAPTER

High-dose imatinib versus high-dose imatinib in combination with intermediate-dose cytarabine in patients with first chronic phase myeloid leukemia: a randomized phase III trial of the Dutch-Belgian HOVON study group

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ABSTRACT

Despite the revolutionary change in the prognosis of chronic myeloid leukemia (CML) patients with the introduction of imatinib, patients with resistant disease still pose a considerable problem. In this multicenter, randomized phase III trial we investigate whether the combination of high-dose imatinib and intermediate-dose cytarabine compared to high-dose imatinib alone, improves the rate of major molecular response (MMR) in newly diagnosed CML patients. This study was closed prematurely because of declining inclusion due to the introduction of second generation tyrosine kinase inhibitors and only one third of the initially required patients were accrued. One hundred nine patients aged 18-65 years were randomly assigned to either imatinib 800 mg (n = 55) or to imatinib 800 mg in combination with 2 successive cycles of cytarabine 200mg/m² for 7 days (n = 54). After a median follow-up of 41 months, 67% of patients were still on protocol treatment. The MMR rate at 12 months was 56% in the imatinib arm and 48% in the combination arm ($p = 0.39$). Progression-free survival was 96% after 1 year and 89% after 4 years. Four-year overall survival was 97%. Adverse events grades 3 and 4 were more common in the combination arm. The addition of intermediate-dose of cytarabine to imatinib did not improve the MMR rate at 12 months. However, the underpowering of the study precludes any definitive conclusions.

This trial is registered at www.trialregister.nl (NTR674).

INTRODUCTION

The introduction of imatinib (Novartis, Basel, Switzerland) in 2001 revolutionized the treatment of chronic myeloid leukemia (CML). In the International Randomized Study of Interferon and STI571 (IRIS), imatinib demonstrated superior efficacy and safety compared to combination therapy with interferon-alpha and cytarabine (generic). In the 8-year follow-up of the IRIS study a major molecular response (MMR) was observed in 86% of the patients randomized to imatinib, which predicts for relatively long survival. The 8-year event-free survival (EFS) in these patients was 81% and freedom from progression to accelerated phase or blast crisis was 92%. Overall survival (OS) was 93% when considering only CML-related deaths.¹ The second generation tyrosine kinase inhibitors (TKIs) nilotinib and dasatinib show even deeper and faster cytogenetic and molecular responses, resulting in application as first-line therapy in several countries.^{2,3} Despite the increased OS and EFS attained with imatinib, patients with unsatisfactory responses due to imatinib resistance still pose a considerable challenge. In the 8-year follow-up of the IRIS study 16% of patients had discontinued imatinib because of unsatisfactory response.¹ Comparable results were observed in a large single center study, in which 23% of patients discontinued imatinib after failure or loss of response.⁴ Thus, development of new therapeutic approaches are needed to achieve better responses and overcome cell resistance. A strategy to increase the (molecular) response rate is the addition of conventional chemotherapeutic agents to imatinib, such as the pyrimidine nucleoside analogue cytarabine, used frequently in first-line therapy before the imatinib era. The addition of cytarabine to imatinib has already been shown to have synergistic effects in invitro studies in BCR-ABL expressing cell lines, mainly through inhibition of proliferation.^{5,6} Administration of higher doses of imatinib might be another strategy to achieve deeper responses. Indeed, dose escalation of imatinib to 600 or 800 mg has been shown beneficial in patients with suboptimal response to imatinib or in patients with advanced stage disease.⁷⁻¹¹ Moreover, more rapid and deeper responses to high-dose imatinib were seen in newly diagnosed chronic phase patients in most, but not all randomized and nonrandomized trials.¹²⁻¹⁶ To prospectively investigate whether combination therapy with imatinib and cytarabine would improve the molecular response rate, the Dutch-Belgian Cooperative Trial Group for Hematology Oncology (HOVON) conducted a recently published phase I/II feasibility and efficacy study (HOVON 51) in which escalated doses of imatinib and cytarabine were combined. All dose levels were feasible, and the efficacy results of the combination of imatinib and cytarabine were encouraging.¹⁷⁻¹⁸ In order to assess whether combination therapy results in a higher MMR rate and a lower incidence of disease progression compared to high-dose imatinib alone, we conducted this open-label, investigator-initiated, randomized, multicenter, phase III trial (HOVON 78) comparing arm A: high-dose imatinib with arm B: high-dose imatinib combined with two successive cycles of intermediate-dose cytarabine in newly diagnosed CML patients.

PATIENTS AND TREATMENT

Patients with newly diagnosed CML in first chronic phase were eligible if they were between 18 and 65 years of age and if they were registered within 2 months after diagnosis. Other eligibility criteria included the presence of the Philadelphia chromosome or *BCR-ABL* fusion transcript and a World Health Organization performance status of 2 or less. Previous treatment for CML was not allowed with the exception of hydroxyurea for less than 2 months or imatinib for less than 1 month. Exclusion criteria included accelerated phase or blast crisis, hepatic or renal dysfunction, severe cardiac dysfunction or severe pulmonary or neurological disease, a history of active malignancy the past 5 years, except for basal carcinoma of the skin and stage 0 cervical carcinoma, HIV positivity and active uncontrolled infections. Patients of reproductive potential not willing to practice effective means of protection and pregnant or lactating women were also excluded. Patients were randomized 1:1 between both arms and stratified by center and Sokal score with a minimization procedure, ensuring balance within each stratum and overall balance. All patients provided written informed consent. The study was approved by the ethics committees of the participating institutions and informed consent was obtained from all patients in accordance with the Declaration of Helsinki.

Following registration and randomization, preceding therapy with hydroxyurea or imatinib was stopped and imatinib was started at a total dose of 800 mg daily, preferably twice daily 400 mg. When randomized to combination therapy (arm B), the first cycle of intravenous cytarabine was started as soon as possible, preferably within 14 days from the start of imatinib, and at the latest 4 weeks from the start of imatinib. Cytarabine was given at a dose of 200 mg/m²/day in 500 ml NaCl 0.65% or 0.9% as a 1-2 h infusion, once daily for 7 days. The second cycle started if there was evidence of hematopoietic recovery (platelets > 100 × 10⁹/l and WBC > 2.0 × 10⁹/l) and when all toxicities had resolved to grade ≤ 1. Cycle II had to be started within 8 weeks from the start of cycle I. If start of cycle II within 8 weeks from start of cycle I was not possible, patients just continued with imatinib monotherapy. Imatinib was continued during the phase of cytopenia following combination therapy. Combination therapy was administered on an outpatient basis. However, it was advocated to admit patients clinically in case of grade 4 hematologic toxicity (e.g., ANC < 0.5 × 10⁹/l). Alternatively, patients were followed up frequently (three times per week) in the outpatient clinic, with immediate clinical admittance in case of fever. When giving combination therapy, antibacterial and antifungal prophylaxis was given from the start of neutropenia. Following full hematologic recovery of cycle II, patients continued with imatinib at a dose of 800 mg until progression of disease or intolerance of treatment. Dose modifications and interruptions of imatinib and cytarabine, management and required evaluations are described in the supplemental file (online resource: <http://link.springer.com/article/10.1007/s00277-013-1730-4>). Reasons for going off protocol were disease progression, excessive toxicity, including toxic death, intolerance of treatment,

intercurrent death, noncompliance of the patient and major protocol violation. Disease progression was defined as progression to accelerated phase or blast crisis, progression with or without prior complete hematologic response (CHR), progression from major cytogenetic response (MCR) or clonal evolution.

METHODS

The primary endpoint of the study was the MMR rate at 12 months from randomization. MMR was defined as ≥ 3 log decrease of BCR-ABL mRNA by real time quantitative RT-PCR, a complete molecular response as ≥ 4.5 log decrease (MR^{4.5}) of BCR-ABL mRNA by real time quantitative RT-PCR. Definition of the molecular responses and the full PCR method are described in the supplemental file at the online resource (<http://link.springer.com/article/10.1007/s00277-013-1730-4>). Secondary endpoints of this study included the rate, the time to and the duration of MMR, MR^{4.5}, MCR, complete cytogenetic response (CCR) and CHR, progression-free survival (PFS), OS and toxicity.

Cytogenetic response on bone marrow was classified on the basis of G-, R-, or Q-banding in at least 20 metaphase cells per sample. Fluorescent in situ hybridization (FISH) analysis on metaphase or interphase cells with specific BCR-ABL probe sets was performed for patients with a cryptic Ph translocation at diagnosis and follow-up, and in addition, during follow-up when cytogenetic analysis failed. If cytogenetic results were not available during follow-up, BCR-ABL with values below 1% was used as a surrogate for complete cytogenetic response.¹⁹ Cytogenetic and hematologic response criteria are defined in the supplemental file (online resource: <http://link.springer.com/article/10.1007/s00277-013-1730-4>). Cumulative incidences of response are expressed as the time from registration to CHR, MCR, CCR, MMR and MR^{4.5}. Loss of CHR was defined as a WBC of more than $20 \times 10^9/L$, or progression to accelerated phase or blast crisis; loss of MCR as an increase of Ph-positive metaphases by at least 30 points to 35% or more Ph-positive metaphases; loss of CCR by the detection of one or more Ph-positive metaphases; loss of MMR as a 0.5 log increase of BCR-ABL to a BCR-ABL level greater than 0.1%; and loss of MR^{4.5} as BCR-ABL level greater than 0.0032%. All molecular losses were confirmed by a second RQ-PCR, preferably within 4 weeks after the first measurement. Patients were considered a failure in case of loss of hematological, cytogenetic or molecular response, accelerated phase, blast crisis, clonal evolution, death before 12 months and no achievement of MMR at 12 months. PFS was defined as time from randomization until acceleration phase, blast crisis or death from any cause. OS was measured from randomization until death from any cause. Patients alive at the date of last contact were censored.

Assessment of toxic effects and response are described in the supplemental file (online resource: <http://link.springer.com/article/10.1007/s00277-013-1730-4>).

STATISTICAL METHODS

The primary objective of the study was to evaluate whether addition of two 7-days' cycles of cytarabine 200 mg/m²/day to daily imatinib 800 mg treatment, would improve the 1-year MMR rate as compared to treatment with 800 mg imatinib daily alone. In order to detect with 80% power an improvement in 12-months' MMR rate (MMR₁₂) from 60 to 75%, with a two-sided significance level $\alpha = 0.05$, 330 patients were required. All analyses were performed according to the intention to treat principle. The primary analysis of MMR₁₂ between the two treatment arms was performed using univariate logistic regression, and the odds ratio (OR) and 95% confidence interval (CI) were determined. In addition, an exploratory logistic regression with adjustment for baseline Sokal score was planned.

The cumulative incidences of MMR, CHR, CCR and MR^{4,5} were calculated using competing risk analysis. Competing risks were disease progression, death without previous response, and other events leading to discontinuation of protocol treatment before achieving response. PFS and OS were estimated by the Kaplan-Meier method, and 95% CI were determined. Survival endpoints were analyzed with Cox regression analysis. Hazard ratios (HR) with 95% CI were determined. Kaplan-Meier curves were generated to illustrate survival.

RESULTS

Accrual in this trial started in June 2006. Due to excellent evolving results of imatinib monotherapy and the introduction of second generation tyrosine kinase inhibitors, this study was closed prematurely in April 2010 because of declining inclusion. Therefore, the number of patients included was substantially lower than initially expected. Ultimately, 111 patients from 19 Dutch and 2 Belgian centers were enrolled in the study. One ineligible patient and one patient who withdrew informed consent within a few days after randomization were excluded from all analyses. The remaining 109 patients were randomly assigned to imatinib alone (arm A, n = 55), or cytarabine plus imatinib (arm B, n = 54). Data available as of April 12, 2012 were used for this manuscript, resulting in a median follow-up of 41 months (range, 12-66 months).. Patient baseline characteristics were equally divided between the two groups (Table 1). Table 2 shows the number of the cytarabine cycles given and the median daily doses of imatinib taken in both arms. The dose of cytarabine was given as scheduled except for one patient who received a reduced dose for one cycle because of non-hematologic toxicity. Until now, in 65% of all patients the daily dose of imatinib was reduced at least once, to levels between 200 and 600 mg. From the patients still on protocol, 36 (49%) are on the scheduled daily dose of 800 mg imatinib. Currently, 73 (67%) patients are still on protocol, and 36 (33%) went off protocol and discontinued imatinib therapy, 17 patients (31%) in the monotherapy arm and 19 patients (35%) in the combination arm (Figure 1). Reasons for going off protocol included

unsatisfactory response (8), progression to blast crisis (1), progression from major cytogenetic response (2), hematologic progression after prior complete hematologic response (2), excessive toxicity (18), major protocol violation (1) and other reasons (4). Thirty-two patients were treated with one or more of the second- and third-line TKIs (Table 2).

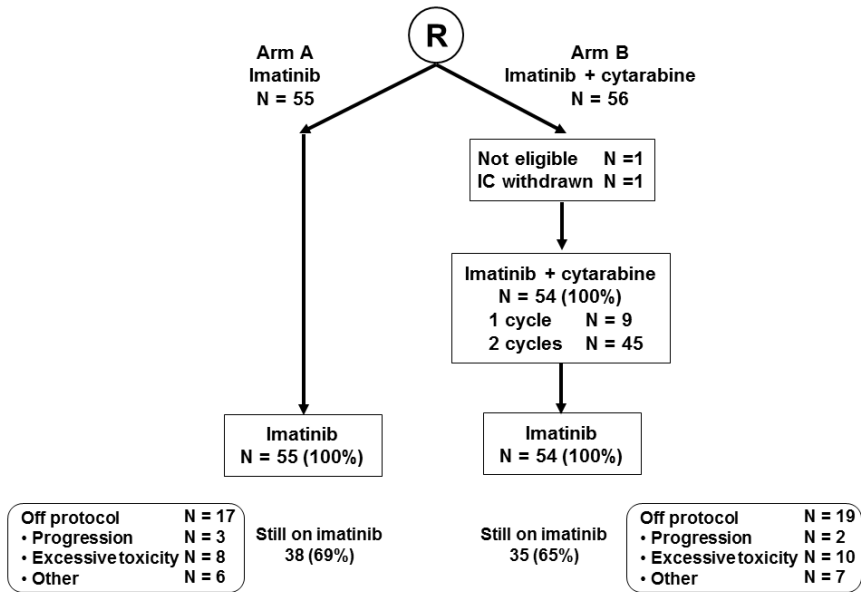


Figure 1. Flow diagram of randomly assigned and evaluable patients after a median follow-up of 37 months

Table 1. Patient characteristics of the 2 study arms

	Imatinib	Imatinib/Cytarabine	Total
Total (no)	55	54	109
Age (years)			
median	46	45	45
range	17-65	23-65	17-65
WHO performance status (no,%)			
WHO 0	43 (78)	40 (74)	83 (76%)
WHO 1	12 (22)	14 (26)	26 (24%)
Sokal score (no, %)			
low	16 (29)	20 (37)	36 (33)
intermediate	24 (44)	21 (39)	45 (41)
high	12 (22)	11 (20)	23 (21)
unknown	3 (5)	2 (4)	5 (5)

EFFICACY

Considering the primary endpoint of this study, the MMR_{12} was 56% (95% CI 42-70%) in the monotherapy arm and 48% (95% CI 34-62%) in the combination arm (OR = 0.72, 95% CI 0.34-1.53, $p = 0.39$). After adjustment for baseline Sokal score, the outcome remained very similar (OR = 0.69, 95% CI = 0.31-1.53, $p = 0.37$).

Hematologic, cytogenetic and molecular responses are presented in figure 2. At 12 months the corresponding rates of CHR, MCR, CCR and $MR^{4,5}$ in the imatinib arm and combination arm, were 100 and 94%, 87 and 93%, 69 and 80% and 22 and 11% respectively (p -values between 0.06 and 0.82). $MR^{4,5}$ at 24 and 36 months in the imatinib arm and the combination arm were 26 and 19% and 40 and 34% respectively. Median time to CHR was 3 months, median time to CCR was 6 months and median time to MMR was 9 months. With a median follow-up of 41 months, six patients lost their CHR, five patients lost their MCR, four patients lost their CCR and one patient lost his MMR.

PROGRESSION-FREE SURVIVAL AND OVERALL SURVIVAL

After a median follow-up of 41 months, ten patients had progressive disease, five patients in both arms, and one patient died without progression. Four patients progressed to blast crisis, three patients had hematologic progression with prior CHR and three patients had cytogenetic progression. This resulted in a PFS of 96% at 1 year and 89% at 4 years, with similar results in both arms ($p = 0.83$) (Figure 3), also applying for the time to progression. Six patients underwent allogeneic stem cell transplantation as second- or third line therapy because of intolerance of imatinib (1), primary resistance (1), secondary resistance (1) and blast crisis (2). The 4-year OS is 97% ($HR = 2.34$, 95% CI 0.21-25.9, $p = 0.47$) (Figure 4). In total, 3 patients died: one patient in the monotherapy arm died after 49 months due to a cardiac arrest after allogeneic stem cell transplantation. One patient in the combination arm died after 6 months following an intracerebral bleeding during blast crisis and one patient in the combination arm died after 39 months due to an aspergillus pneumonia accompanying chronic graft versus host disease after allogeneic stem cell transplantation.

ADVERSE EVENTS

Adverse events are shown in figure 5. Adverse events occurred most frequently in the combination arm during cytarabine therapy. As expected, there were much more infectious complications Common Terminology Criteria for Adverse Events (CTCAE) grades 3-4 in the combination arm compared to the imatinib arm (39 vs 4%). During imatinib maintenance therapy in both arms, the most frequent adverse events CTCAE grade 2 or more included constitutional symptoms (39%), gastrointestinal complaints (31%), pain (21%) and dermatologic symptoms (15%). Toxicity of CTCAE grade 3 and 4 occurred infrequently.

Ten patients in arm B discontinued therapy because of side effects compared with 7 patients in arm A.

Serious adverse events (SAEs) were significantly more frequent in the combination arm (time to first SAE: HR = 4.32, 95% CI 1.84-10.52, $p < 0.001$). Forty-three SAEs occurred in 30 patients, 10 in the monotherapy arm and 33 in the combination arm, of which 26 occurred during cytarabine therapy.

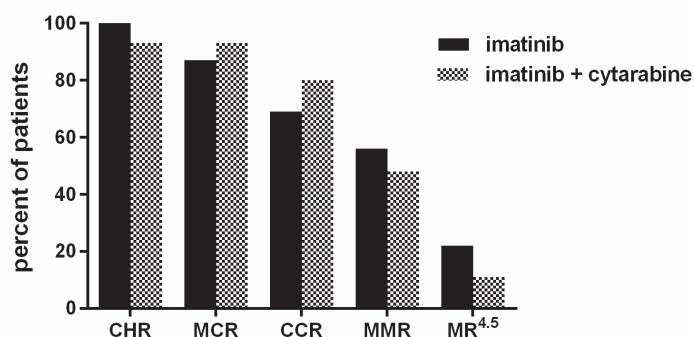


Figure 2. Actuarial responses at 12 months of complete hematologic response (CHR), major cytogenetic response (MCR), complete cytogenetic response (CCR), major molecular response (MMR) and complete molecular response (MR^{4.5})

Table 2. Imatinib and cytarabine dose and use of second and third generation TKIs. Only patients who went off protocol were eligible for these TKIs

	Imatinib	Imatinib/Cytarabine	Total
Total (no)	55	54	109
Cytarabine cycles given (no)			
only one cycle		9	9
both cycles		45	45
Daily imatinib dose (mg)			
median	600	727	681
range	395-800	174-800	174-800
2nd generation TKI given (no)			
yes	15	17	32
no	40	37	77
Nilotinib	5	7	12
Dasatinib	14	13	27
Ponatinib	0	1	1

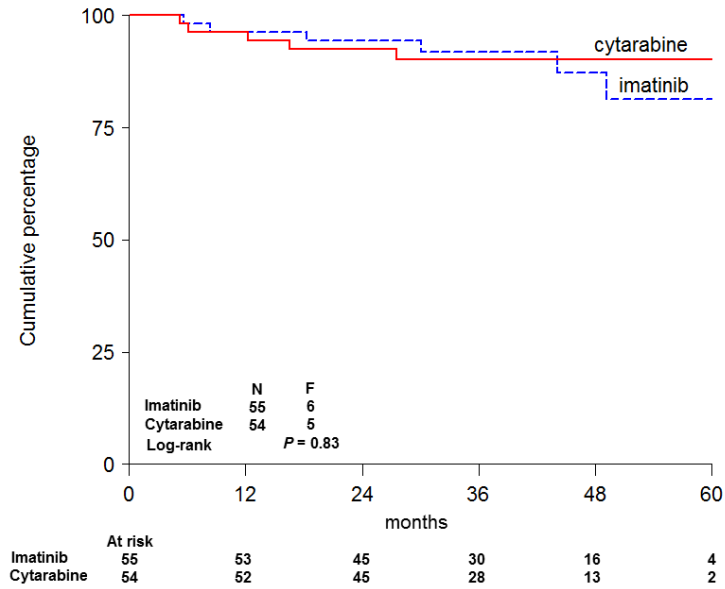


Figure 3. Progression-free survival

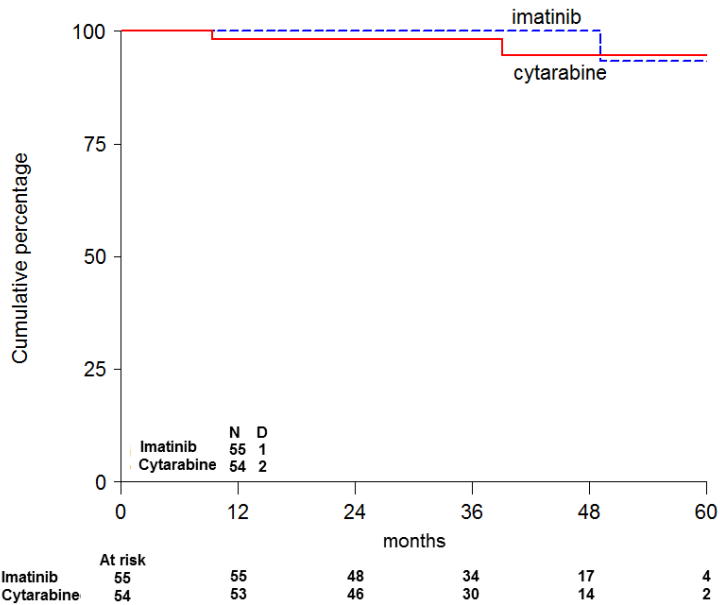


Figure 4. Overall survival

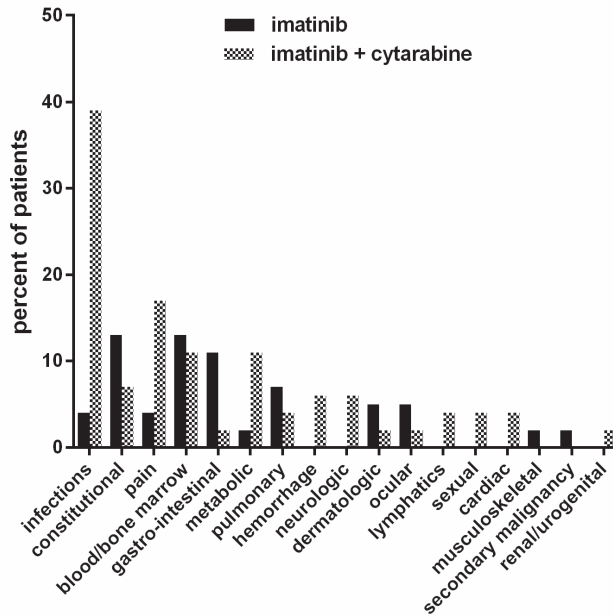


Figure 5. Adverse events grade 3-4. Note that AE events for arm B include all events occurring during both 2 cytarabine cycles and imatinib maintenance therapy

DISCUSSION

Treatment of CML patients with a standard dose of 400 mg imatinib is currently associated with high rates of hematologic, cytogenetic and molecular responses.²⁰

A number of studies have stressed the importance of achieving a MMR as a molecular endpoint associated with overall outcome.^{14,21,22} Since achieving a MMR at 1 year is clearly associated with absent progression and better overall outcome¹, we chose MMR rate at 12 months as the primary endpoint of this study.

The rationale for our study was based on the results of the HOVON 51 study and was focused on whether high-dose imatinib in combination with cytarabine would induce higher molecular response rates and less disease progression in newly diagnosed CML patients. In that study high-dose imatinib (800 mg) was associated with significantly higher MMR rates ($p = 0.03$) and a trend towards better MR^{4.5} rates ($p = 0.07$) compared with standard dose imatinib (400 mg). Moreover, a significant dose-dependent effect of cytarabine on MR^{4.5} ($p = 0.04$) was observed.¹⁸ Despite our hypothesis that combination therapy might result in better and faster molecular responses rates, intensification of treatment in the present study, did not lead to an improved MMR rate at 12 months compared to imatinib high-dose alone. It should be noted that due to premature closure of our study, statistical power was insufficient to detect the projected difference, originally outlined in our

statistical plan. High-dose imatinib alone resulted in a 12-months' MMR rate of 56%. That response is much higher than that obtained in the IRIS study, where imatinib 400 mg daily resulted in a 39% MMR rate at 12 months, but comparable with MMR rates in several large randomized and nonrandomized studies using 800 mg imatinib.^{12-14,23} As expected, the combination therapy was more toxic than imatinib alone. However, this did not result in a higher number of patients going off protocol because of excess toxicity in arm B. This is possibly due to the relatively short treatment period of cytarabine whereby the adverse event profile did not appear to preclude its use.

A few other cooperative groups have tested the additive value of cytarabine to imatinib in first chronic phase CML patients. One phase II study showed promising results with respect to cytogenetic response, in line with the HOVON 51 study results.²⁴ Another randomized trial using low-dose cytarabine suggested a significantly higher CCR rate for combination therapy. However, molecular responses were not determined.²⁵ In the randomized Spirit trial, the imatinib plus cytarabine arm was prematurely closed due to superiority of the interferon arm and toxic effects of cytarabine.²⁶ However, the results of all these studies cannot be easily compared with our data, because of the difference in dosing and administration of cytarabine. These studies used low-dose cytarabine given subcutaneously during 14 days of each 28-day cycle while in our study intermediate-dose cytarabine was given intravenously during 2 cycles directly after diagnosis. Furthermore, our patients received high-dose imatinib (800 mg), while patients in the abovementioned studies received imatinib 400 mg.²⁴⁻²⁶

In conclusion, we could not demonstrate an advantage of the addition of cytarabine to imatinib in this randomized study. However, the underpowering of the study precludes any definitive conclusions. Furthermore, the rate of severe toxicity was significantly higher in patients receiving the combination of imatinib and intermediate-dose cytarabine. Since second line TKIs already show results superior to imatinib alone, the value of adding high-dose chemotherapy to TKIs is highly questionable in patients in first chronic phase CML. The use of cytostatic drugs in patients with accelerated phase and/or blast crisis, however, remains to be determined.

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