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IMATINIB 800MG DAILY INDUCES DEEPER MOLECULAR RESPONSES THAN IMATINIB 400MG DAILY: RESULTS OF SWOG S0325, AN INTERGROUP RANDOMIZED PHASE II TRIAL IN NEWLY DIAGNOSED CHRONIC PHASE CHRONIC MYELOID LEUKAEMIA

Michael W. Deininger^{1,2}, Kenneth J. Kopecky^{3,4}, Jerald P. Radich⁴, Suzanne Kamel-Reid⁵, Wendy Stock⁶, Elisabeth Paietta⁷, Peter D. Emanuel⁸, Martin Tallman⁹, Martha Wadleigh¹⁰, Richard A. Larson⁶, Jeffrey H. Lipton¹¹, Marilyn L. Slovak¹², Frederick R. Appelbaum⁴, and Brian J. Druker¹

¹Oregon Health and Science University, Portland, OR

²University of Utah Huntsman Cancer Institute, Salt Lake City, UT (current)

³SWOG Statistical Center, Seattle, WA

⁴Fred Hutchinson Cancer Research Center, Seattle, WA

⁵Ontario Cancer Institute/Princess Margaret Hospital, Toronto, Ontario, CAN

⁶University of Chicago, Chicago, IL

⁷Montefiore Medical Center, Bronx, NY

⁸University of Arkansas for Medical Sciences, Little Rock, AR

⁹Memorial Sloan Kettering Cancer Center, New York, NY

¹⁰Dana Farber Cancer Institute, Boston, MA

Correspondence: Michael Deininger MD PhD, University of Utah, Huntsman Cancer Institute, 2000 Circle of Hope, Room 4280, Salt Lake City, Utah 84112-5550, 801/581-6363 phone, 801/585-0900 fax, michael.deininger@hci.utah.edu.

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Author contributions

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Conflicts of Interest

MWD received honoraria (consulting) from Novartis, BMS, Pfizer, Ariad, Incyte and research support from Novartis, BMS and Gilead; KJK received salary support for this trial from Novartis as did the SWOG Statistical Center; JPR received honoraria (consulting) from Novartis, BMS, Pfizer, Ariad, and research support from Novartis; RAL received honoraria for consulting from Novartis and research support from Novartis; JHL received honoraria (consulting) from Novartis and BMS and research support from Novartis and BMS. BJD's institution received clinical trial support from Novartis and BMS. OHSU and BJD have a financial interest in MolecularMD. OHSU has licensed technology used in some of these clinical trials to MolecularMD. This potential individual and institutional conflict of interest has been reviewed and managed by OHSU. Authors not listed had no relevant conflicts of interest.

¹¹University Health Network-OCI/Princess Margaret Hospital, Toronto, Ontario, CAN

¹²City of Hope, Duarte, CA/Sonora Quest Laboratories/Laboratory Sciences of Arizona, Tempe, AZ (current)

Abstract

The standard dose of imatinib for newly diagnosed patients with chronic phase chronic myeloid leukemia (CP-CML) is 400mg daily (IM400), but the optimal dose is unknown. This randomized phase II study compared the rates of molecular, haematologic and cytogenetic response to IM400 vs. imatinib 400mg twice daily (IM800) in 153 adult patients with CP-CML. Dose adjustments for toxicity were flexible to maximize retention on study. Molecular response (MR) at 12 months was deeper in the IM800 arm (4-log reduction of BCR-ABL1 mRNA: 25% vs. 10% of patients, $P=0.038$; 3-log reduction: 53% vs. 35%, $P=0.049$). During the first 12 months BCR-ABL1 levels in the IM800 arm were an average 2.9-fold lower than in the IM400 arm ($P=0.010$). Complete haematologic response was similar, but complete cytogenetic response was higher with IM800 (85% vs. 67%, $P=0.040$). Grade 3–4 toxicities were more common for IM800 (58% vs. 31%, $P=0.0007$), and were most commonly haematologic. Few patients have relapsed, progressed or died, but progression-free ($P=0.048$) and relapse-free ($P=0.031$) survival were superior for IM800. In newly diagnosed CP-CML patients, IM800 induced deeper molecular responses than IM400, with a trend for improved progression-free and overall survival, but was associated with more severe toxicity.

Keywords

BCR-ABL; CML; imatinib

INTRODUCTION

The treatment of chronic myeloid leukaemia (CML) has been improved dramatically by imatinib, an inhibitor of BCR-ABL1, the tyrosine kinase causal to CML (Deininger, *et al* 2005, Sawyers 1999). Eight-year follow-up from the IRIS trial of newly diagnosed patients with CML in chronic phase (CP-CML) treated with 400mg imatinib orally once daily (IM400) showed an 83% cumulative complete cytogenetic response (CCyR) rate (Deininger, *et al* 2009). Estimated rates of freedom from progression to accelerated or blastic phase (AP/BP) and overall survival (OS) were 92% and 85%, respectively (Marin, *et al* 2012a). No patients with major molecular response (MMR, a 3-log reduction of BCR-ABL1 mRNA (Hughes, *et al* 2003)) at 12 months progressed to AP/BP. IM400 is considered an option for first-line treatment of CP-CML by the National Comprehensive Cancer Network (<http://www.nccn.org>) and the European LeukemiaNet (ELN) (Baccarani, *et al* 2009a). Despite imatinib's general efficacy there is a significant failure rate. In the IRIS trial ~40% of patients randomized to imatinib had discontinued therapy at 8 years, mainly for lack of efficacy or toxicity³. Another study reported 5-year event-free survival of only 63% (de Lavallade, *et al* 2008, Marin, *et al* 2012a) and a population-based report found that only half of newly diagnosed CP-CML patients were in CCyR and receiving imatinib at 2 years after starting therapy (Lucas, *et al* 2008). Reasons to consider imatinib doses >400mg daily

include the fact that no maximum tolerated dose was established in the initial phase 1 study (Druker, *et al* 2001), that higher plasma imatinib concentrations are associated with improved responses (Larson, *et al* 2008) and that dose escalation induces responses in some patients failing IM400 (Kantarjian, *et al* 2003). In 2004 four North American cooperative groups [Southwest Oncology Group/SWOG, Eastern Cooperative Oncology Group/ECOG, Cancer and Leukemia Group B/CALGB, National Cancer Institute (NCI) Canada Clinical Trials Group] initiated study S0325 (ClinicalTrials.gov identifier NCT00070499), a randomized phase II trial of IM400 vs. imatinib 400mg twice daily (IM800) in newly diagnosed CP-CML patients. S0325 consisted of 2 parts: In the first part patients were randomized between IM400 vs. IM800. In the second and separate part, patients were randomized between IM400 vs. dasatinib 100mg po daily; results from that part of the study were reported recently (Radich, *et al* 2012). We report here on the first part of S0325, which compared IM400 vs. IM800. We found that IM800 was more toxic than IM400, but superior in terms of molecular and cytogenetic responses at 12 months, with trends for improved progression free and overall survival. This study demonstrates that 'high dose' imatinib can produce responses similar to those seen with second-generation TKIs, if dose reductions are flexible and individualized.

PATIENTS AND METHODS

Patients

Eligible patients were ≥ 18 years, had adequate liver, kidney and cardiac function, a Zubrod performance status of ≤ 2 and a diagnosis of CP-CML (defined according to standard criteria (Radich, *et al* 2012)) < 6 months before enrollment. No prior CML therapy was allowed except hydroxyurea and/or anagrelide. This study was conducted in accordance with the Declaration of Helsinki. The ethics committee or institutional review board at each participating center was responsible for protocol review. All participants gave written informed consent prior to study entry according to institutional regulations.

Study Design and Treatment Arms

The objective of this randomized phase II trial was to test whether increasing the IM dose to 800mg daily would improve the molecular response at one year, to support a decision about a possible further definitive study of the IM dose. Patients were randomized 1:1 to IM400 or IM800, with stratification by Hasford risk category (Hasford, *et al* 1998) and were to remain on treatment until failure or unacceptable toxicity, for a maximum of one year. Failure was defined as reported (Radich, *et al* 2012). Patients with >95% Ph⁺ metaphases at 6 months could escalate imatinib to 600mg daily, which if tolerated for 2 weeks could be increased to 800mg daily. In case of grade (G) 2–4 non-haematologic or G3–4 haematologic toxicity, therapy was interrupted and resumed at the initial dose of 400mg or 800mg daily (or 300mg and 600mg for G3/4 non-haematologic toxicity) once the AE resolved to G1. If the AE recurred or persisted for >28 days, dose reductions were allowed to 600mg (IM800 arm) and 300mg (IM400 arm). For the IM800 arm, further reductions to 400mg and ultimately 300mg imatinib daily were allowed. In both arms, recurrence of any G3/4 non-haematologic toxicity despite dose reduction to 300mg daily was considered treatment intolerance. Dose

reductions to 200mg imatinib daily and management of AEs persisting for >28 days required guidance from the clinical trial leader.

Disease monitoring

Complete blood counts were performed at baseline, week 1, week 2, week 4, monthly until month 6 and every 3 months thereafter until end of study. Bone marrow metaphase cytogenetics was performed before therapy, then every 6 months. CHR and CCyR were defined as previously reported and based on best responses during the first 12 months (Radich, *et al* 2012). Relapse from CHR was defined as reported (Radich, *et al* 2012). Molecular response (MR) was based on quantitative RT-PCR (QPCR) on peripheral blood obtained at 3-months intervals, including time points of cytogenetic assessment. Conceptually similar to the IRIS trial (Hughes, *et al* 2003), the log-reduction of BCR-ABL1 mRNA was calculated by comparison to Group-specific BCR-ABL1 baseline level, defined as the Cooperative Group-specific median pretreatment mRNA level. A 3-log BCR-ABL1 reduction was referred to as MMR, and 4-log and 4.5-log reductions as MR^{4.0} and MR^{4.5}, respectively. Rates of CCyR and the three levels of molecular response were based on patients with evaluable cytogenetic and PCR studies, respectively. The central CALGB and NCI Canada labs performed the molecular studies on patients enrolled in their own cooperative groups; the central SWOG lab performed studies on all SWOG and ECOG patients. Cell line dilution experiments performed prior to the trial had intra-lab and inter-lab correlations of R>0.97. Results on exchanged CML samples had intra- and inter-lab correlations of R>0.92–0.96 (Radich, *et al* 2012).

Mutational analysis

Patients who failed to achieve CHR or lost CHR or CCyR were screened for mutations in the BCR-ABL1 tyrosine kinase domain by Sanger sequencing at the time of failure.

Statistical analyses

The primary endpoint of this study was MR^{4.0} at 12 months, although CHR, CCyR, MMR, MR^{4.5} and the variation of BCR-ABL1 mRNA levels over time were also investigated. Estimates of MR at discrete times, 3, 6, 9 and 12 months, were based on specimens collected during days 43–126, 127–210, 211–294 and 295–420, respectively (if a patient's molecular response was tested more than once within one of these intervals, only the result obtained closest to day 90, 180, 270 or 365, respectively, was included). Variation of BCR-ABL1 expression using all MR data over the entire 12-month period was analyzed using mixed models of the form $Y_i(T) = \alpha_i + \beta I(D_i) + \gamma(D_i, T)$, where $Y_i(T)$ is the log-transformed relative mRNA level of patient i at time T (days since randomization, treated as a continuous variable); α_i is a random coefficient reflecting patient-to-patient variability (and introducing within-patient correlation); $I(D_i) = 1$ for IM800, 0 for IM400; β is a nonrandom coefficient representing the treatment difference; and $\gamma(D_i, T)$ is a polynomial function to model the pattern of average relative mRNA levels as a possibly treatment-dependent function of time. mRNA levels reported as non-detected were left-censored at 10^{-6} . Follow-up after 12 months was not required for this study, however time-to-event outcomes included OS from the date of randomization until death from any cause, with observation censored at the date

of last contact for patients last known to be alive; progression-free survival (PFS) from the date of randomization until CML progression to AP/BC, relapse from CHR or death from any cause, with observation censored at the date of last contact for patients last known to be alive without report of progression or relapse; and relapse-free survival (RFS) from the date of CHR until relapse or death from any cause, with observation censored at the date of last contact for patients last known to be alive without report of relapse. In exploratory analyses of outcomes in relation to MR at 3 months, OS, PFS and RFS were measured from the date of the 3-month blood specimen. Analyses of CHR, OS and PFS were based on all eligible randomized patients (RFS was limited to patients who achieved CHR), while MMR and CCyR were based on patients with follow-up assessments. Distributions of OS, PFS and RFS were estimated using the Kaplan-Meier method (Kaplan 1958); treatment differences in time to event were evaluated by the log-rank test (Mantel 1966). The study plan called for randomization of 120 patients (60 per arm), for which a one-sided comparison of the 12-month MR^{4.0} rate at the 10% critical level would have 85% power if the true MR^{4.0} rates were 15% with IM400 and 35% with IM800, and 82% power if the true rates were 20% and 40%. The 10% critical level was appropriate for the trial's limited aim of informing a decision about whether to conduct a definitive trial of IM dose. Additional patients were enrolled to account for drop-outs before 12 months. Toxicity grades were compared between arms using the Wilcoxon test. All comparisons of treatment effects were based on one-sided tests for superior efficacy or higher toxicity in the IM800 arm, and exploratory analyses used one-sided tests for superior outcomes in patients with deeper 3-month MR; all other p-values are two-sided. Analyses were performed using SAS Version 9.2 (SAS Institute Inc., Cary, NC). Analyses were based on data available by June 24, 2012.

RESULTS

From March 2005 through January 2007, 153 patients with newly diagnosed CP-CML were randomized to IM400 or IM800. Eight patients were ineligible or not evaluable: 7 had a diagnosis other than CP-CML, and one could not afford protocol treatment. Pretreatment characteristics of the remaining 145 patients were balanced between the arms (Table 1). One patient randomized to IM800 was treated with IM400 and is included in the IM800 group for efficacy analysis.

Response

Outcomes are summarized in Table 2.

Molecular response—MR was deeper in the IM800 arm, judging by the proportion of patients achieving MMR, MR^{4.0} and MR^{4.5} during the first year (Table 2 and Figure 1). Regarding the study's primary endpoint, more patients on IM800 than on IM400 achieved MR^{4.0} at one year (26% vs. 9%, $p=0.023$). Moreover 53% of IM800 compared to 36% of IM400 patients achieved MMR ($P=0.065$), while MR^{4.5} was not significantly higher (19% vs. 9%, $p=0.13$). The median reduction of BCR-ABL1 mRNA at one year was 3.1-log for IM800 vs. 2.8-log for IM400 ($P=0.060$). In both arms, the most rapid decrease of BCR-ABL1 mRNA occurred during the first few months of treatment. In the mixed model analysis, therefore, average mRNA levels during the first 12 months were found to vary as a

quadratic function of time, and after accounting for this effect the levels were on average 0.466-log (2.9-fold) lower for IM800 than IM400 ($P=0.021$). This model was not significantly improved by allowing mRNA levels to vary as a cubic function of time ($P=0.45$) or allowing the treatment effect to vary over time ($P=0.94$).

Haematologic response—The CHR rate was 82% for IM400 and 85% for IM800 ($P=0.40$). Eight additional patients met CHR criteria but without confirmation of 28 days duration; inclusion of these unconfirmed CHRs increased the rates to 88% and 90% in the IM400 and IM800 arms, respectively ($P=0.38$). Seven patients (IM400 6%, IM800 4%, $P=0.49$) failed to achieve CHR.

Cytogenetic response was evaluable in 90 patients (62%), including 49 (68%) of IM400, and 41 (56%) of IM800 patients, with a higher CCyR rate for IM800 (85%) compared to IM400 (67%, $P=0.040$) within the first year.

Correlation between 3-month MR and outcome

MR at 3 months (i.e., between 43 and 126 days, Figure 1) was available for 111 patients. In thirty of these, BCR-ABL1 levels remained at 10%, and this tended to be more common for IM400 (19/55=35%) compared to IM800 (11/56=20%; $P=0.060$). Patients with 10% BCR-ABL1 at 3 months had poorer outcomes, including CCyR (43% vs. 89%, $P=0.0001$); 12-month MMR (5% vs. 60%, $P<0.0001$), MR^{4.0} (0% vs. 27%, $P=0.0058$) and MR^{4.5} (0% vs. 21%, $P=0.022$); and PFS (hazard ratio [HR] 4.02, $P=0.018$) and RFS (HR 3.27, $P=0.047$). Similar but non-significant effects were seen for CHR (90% vs. 95%, $P=0.28$) and OS (HR=2.89, $P=0.14$). Effects of similar direction and magnitude were seen in each treatment arm, except for CHR rates in the IM400 arm (Table 3). Importantly, all but one of the patients with MMR at 12 months had <10% BCR-ABL1 at 3 months; conversely no patient with 10% BCR-ABL1 at 3 months achieved MR^{4.0} at 12 months. Analysis of OS, PFS and RFS is limited by small numbers of events and limited follow-up beyond one year, which was not required for these patients (Radich, *et al* 2012). For IM400 these outcomes might be poorer for patients with 10% BCR-ABL1, but the differences do not reach statistical significance (OS: $P=0.27$, PFS: $P=0.045$, RFS: $P=0.11$). No conclusions are possible for IM800 due to the lack of events in the small group of patients with 10% BCR-ABL1 at 3 months.

Among patients with <10% BCR-ABL1 at 3 months, IM800 was associated with higher 12-month molecular response (MMR 74% vs. 41%, $P=0.0078$; MR^{4.0} 40% vs. 11%, $P=0.011$; MR^{4.5} 29% vs. 11%, $P=0.085$). Meaningful analyses of OS, PFS and RFS in these patients were not possible due to the small numbers of events.

Similar analyses of the effects of molecular response at 6 and 9 months were also performed. Since few patients had BCR-ABL1 10% at these times, the effect of BCR-ABL1 1% was examined. In general, these analyses showed that failure to achieve <1% at these times was associated with lower 12-month molecular response rates. In addition BCR-ABL1 1% at 6 months was associated with poorer PFS ($P=0.0088$) and RFS ($P=0.0067$), and BCR-ABL1 1% at 9 months was associated with poorer OS ($P=0.012$) and PFS ($P=0.0017$).

BCR-ABL1 kinase domain mutations

At the time of failure samples for mutation analysis were available for 9/12 IM400 and 4/5 IM800 patients with primary (7 patients) or acquired resistance (10 patients). T315I was detected in a patient on IM400 and F359C in a patient on IM800 (both lost CHR). The remaining samples showed native BCR-ABL1.

Toxicity

Among the 144 patients who received their assigned regimens, 14% (10/72) and 13% (9/72) of IM800 and IM400 patients, respectively, experienced G4 toxicities ($P=0.50$ by Fisher's exact test). Five IM400 patients had G4 non-haematologic toxicities (bone pain, head/neck edema, urinary tract infection, depression, and elevated creatine phosphokinase, as did two IM800 patients (rash, and elevated liver enzymes). Altogether 58% of IM800 patients and 31% of IM400 patients had G3/4 toxicities ($P=0.0007$), most commonly haematologic (thrombocytopenia in 19% and 8%, respectively, $P=0.045$). Non-haematologic toxicities were consistently more frequent for IM800 (Table 4). In particular, the IM800 patients had significantly higher grades of diarrhea (Wilcoxon $P=0.0088$), fatigue ($P=0.0006$) and rash ($P=0.0012$). The IM800 patient treated with IM400 had no G3/4 toxicities.

Dose escalations and reductions

Thirty-nine patients [IM400: 22(31%), IM800: 17(23%)] permanently discontinued protocol treatment before completing 12 months, including six in each arm due to toxicity and 11 patients (6 IM400, 5 IM800) who discontinued at their own choice. Sixty-one percent of IM400 patients completed 12 months of treatment without dose reduction, interruption or discontinuation, compared to only 32% of IM800 patients. An additional 45 patients had treatment interruptions (6 IM400, 13 IM800), or dose reductions (4 IM400, 22 IM800) in the first year. In the IM400 arm, imatinib was reduced to 300mg daily and 200mg daily permanently for one patient each, and temporarily for one patient each. In the IM800 arm, imatinib was permanently reduced to 600mg daily, 400mg daily, and 300mg daily in nine, eight, and two patients, respectively, and was temporarily reduced to 600mg daily in two patients and to 400mg daily in one. Two IM400 patients were escalated, one to 600mg and the other to 800mg. The IM800 patient who received the IM400 regimen completed one year of protocol treatment without dose change.

Survival

There have been few deaths, relapses or progressions, and consequently OS, PFS and RFS cannot differ widely between the two arms (Figure 2). Eight patients have died), and the other 137 were last known to be alive between 3 months and 6.5 years (median 1.4 years) after entering the study. One patient in each arm died from progression, and 3 from complications of allogeneic stem cell transplant (all in the IM400 arm). OS at 4 years was 95% (95% CI 80–99%) for IM800 and 90% (75–96%) for IM400. The estimated mortality hazard ratio (HR) for IM400 relative to IM800 is 2.24 but with a very wide 95% CI (0.44–11.6, $P=0.16$) due to the small number of deaths. In the PFS analysis, 11 patients had CML relapse (7 IM400, 1 IM800) or progression to BP (1 IM400, 2 IM800), and 5 (4 IM400, 1 IM800) died without report of progression. PFS at 4 years was 92% (77–97%) for IM800

and 80% (65–89%) for IM400 (HR 2.51, 95% CI 0.80–7.90, $P=0.048$). Of 129 patients who achieved CHR, nine (7 IM400, 2 IM800) relapsed and four (3 IM400, 1 IM800) died in CHR. RFS at 4 years after achieving CHR was 93% (76–98%) and 80% (64–90%) in the IM800 and IM400 arms, respectively (HR 3.40, 95% CI 0.94–12.4, $P=0.031$).

DISCUSSION

Although IM400 is effective in newly diagnosed CP-CML, a considerable proportion of patients will require alternative treatments due to intolerance or resistance (de Lavallade, *et al* 2008, Lucas, *et al* 2008). Several strategies have been explored to improve on IM400, including drug combinations, higher doses of imatinib, and the more potent TKIs nilotinib and dasatinib (Castagnetti, *et al* 2009, Cortes, *et al* 2010, Hehlmann, *et al* 2011, Kantarjian, *et al* 2010, Kantarjian, *et al* 2004, Preudhomme, *et al* 2010, Saglio, *et al* 2010). As most progression events on imatinib occur within the first 3 years of therapy (Druker, *et al* 2006), the overarching rationale for these approaches is that a more rapid reduction of leukaemia burden may prevent early progression, and that improved CCyR and MMR rates will translate into improved PFS and OS. Two single-armed studies of IM800 observed higher CCyR and MMR rates compared to historical controls of IM400, and suggested that ‘high dose’ imatinib may be superior to IM400 (Cortes, *et al* 2009, Kantarjian, *et al* 2004). Similarly, a study of IM800 in intermediate Sokal risk patients reported 88 and 91% CCyR rates at 12 and 24 months, respectively (Castagnetti, *et al* 2009), higher than the 83% at 60 months in the IRIS study (Druker, *et al* 2006). Several randomized studies subsequently compared IM400 vs. higher doses and/or combinations with IFN- α or cytarabine. In the TOPS trial IM800 induced MMR more rapidly than IM400, but at 12 months the difference had lost statistical significance (Cortes, *et al* 2010). A similar trial of high Sokal risk patients also found no significant difference in CCyR or MMR rates (Baccarani, *et al* 2009b). In contrast, the German CML IV study reported 12 months MMR rates of 59% and 44% for IM800 vs. IM400, respectively ($p<0.001$) (Hehlmann, *et al* 2011) and the SPIRIT showed MMR rates of 49% and 38% for imatinib 600mg vs. IM400 ($p<0.001$) (Preudhomme, *et al* 2010), although neither trial found a difference in OS or PFS. In line with the latter reports we demonstrate a higher 12 months MMR rate for IM800 vs. IM400 (53% vs. 36%, $P=0.065$), although only 98 rather than the planned 120 patients were evaluable (Table 2 and Figure 1). Moreover, BCR-ABL1 transcript levels with IM800 were on average 2.9-fold lower throughout the first 12 months of treatment. Notably, the second and separate part of this study reported 12-month MMR rates of 44 and 59% for IM400 and dasatinib 100mg daily, respectively, despite having fewer Hasford high risk patients (30% versus 49%), suggesting that IM800 and dasatinib 100mg daily have similar efficacy (Radich, *et al* 2012). In our study OS (95% vs. 90% at 4 years, $P=0.16$) and PFS (92% vs. 80%, $P=0.048$) were somewhat higher for IM800. These differences should be interpreted with caution in view of the large 95% confidence intervals and the considerable rate of drop-out during the first year.

In both arms BCR-ABL1 levels $\geq 10\%$ at 3 months were associated with a lower likelihood of achieving MMR at 12 months. In the IM400 arm there was also a trend toward lower PFS and RFS, while the number of events in the IM800 arm is too small to draw conclusions. These data validate the predictive value of the 10% BCR-ABL1 cutoff at three

months(Hanfstein, *et al* 2012, Hughes, *et al* 2010, Marin, *et al* 2012a, Marin, *et al* 2012b). However among patients with BCR-ABL1 levels <10% at 3 months, IM800 was still associated with higher molecular response rates, suggesting that even amongst the patients with an optimal 3-month response, a higher imatinib dose was able to improve subsequent molecular response.

IM800 was associated with more G3/4 toxicity compared to IM400 (58% vs. 31%, $P=0.001$), similar to data from the TOPS trial (64% vs. 33%)(Cortes, *et al* 2010), and more IM800 patients required a transient or permanent dose reduction (IM400: 4; IM800: 22). However, permanent discontinuation due to toxicity or refusal (15% vs. 17%) and early (<12 months) discontinuation (23% vs. 31%) were similar for IM400 and IM800, suggesting that IM800 is a feasible regimen.

The dropout rate during the first 12 months of this study (31% for IM400 and 23% for IM800) was high compared to other studies, particularly for IM400. In both arms, approximately half of the dropouts were due to patient's refusal or other reasons, probably a reflection of the fact that keeping patients on a stringent protocol is challenging in a situation where no free study drug is provided. Although these dropouts reduced the statistical power of the study, with 104 rather than the planned 120 patients evaluable for 12-month molecular response, molecular response was significantly higher in the IM800 arm.

The use of higher dose imatinib for frontline treatment of CP-CML has seen considerable evolution from early enthusiasm based on single-armed studies through disappointment from randomized trials to renewed interest based on European multicenter studies. The exact reasons for the discrepant results are unknown, but it is likely that dosing flexibility is required to fully exploit the therapeutic potential of higher imatinib doses and that the optimal dose may be closer to 600mg than to 800mg daily. For example, the CML IV study used an initial 6-week wash-in of 400mg daily to avoid excessive cytopenias, which was followed by dose escalation. The median maintenance dose was 628mg daily, similar to the 600mg daily of the SPIRIT study(Preudhomme, *et al* 2010). Our study allowed for successive dose reductions to 300mg in case of recurrent toxicity and required feedback from the trial leader in case of persistent toxicity, keeping the drop-out rate in the IM800 arm low and producing overall superior results for this arm.

The therapeutic options for newly diagnosed CML patients continue to evolve. Nilotinib and dasatinib were approved for frontline therapy. Despite impressive improvements in the rates of MMR and a reduction of progression events, OS is thus far comparable to IM400, suggesting that salvage therapy is effective for patients who fail IM400, at least in the short term(Kantarjian, *et al* 2011, Kantarjian, *et al* 2012). This emphasizes the importance of considering CML management as a multi-tiered strategy rather than a question of individual agents, and it is possible that the patients who failed IM400 when no second-generation inhibitors were available, would have been salvaged more efficiently with dasatinib or nilotinib. In any case the expectation that the price differential between imatinib and second-generation TKIs will increase dramatically with the availability of generic imatinib in 2015 suggest that imatinib will maintain a significant role in frontline CML therapy, and our data suggest that higher doses may become part of the treatment algorithm.

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Figure 1.

Molecular responses of CML-CP patients, by treatment arm and approximate time on study, during the first 12 months on treatment. Changes of Bcr-Abl mRNA level, relative to Group-specific median baseline values, are shown on a common log ($\log_{10}$) scale for patients randomized to IM800 (solid line) or IM400 (dashed line) therapy. Boxplots showing the 25th and 75th percentiles are connected at the median values. Horizontal dashed lines indicate no change, 3-log (MMR) and 4-log (MR^{4.0}) reduction from baseline. Month 3: days 43–126; month 6: days 127–210; month 9: 211–294; month 12: days 295–420 (if a patient's molecular response was tested more than once within a month's range of days, only the result obtained closest to day 90, 180, 270 or 365, respectively, was included in this Figure).

Figure 2.

Kaplan-Meier estimates of treatment outcomes for patients randomized to IM400 (1) or IM800 (2). Tickmarks indicate censored observations. Number of patients remaining at risk are shown beneath each plot. (A) Overall survival; (B) Progression-free survival; (C) Relapse-free survival of patients who achieved complete haematologic response.

Table 1

Characteristics of 145 CML-CP patients by treatment arm

	IM400 (N=72)			IM800 (N=73)			P*
	Median	Min-Max	Median	Min-Max	Median	Min-Max	
Age (yrs)	50	23-80	52	19-82	52	19-82	0.76
WBC ($10^9/L$)	74.8	5.3-393	64.7	1.1-474	64.7	1.1-474	0.57
Basophils (%) [N=143]	3	0-17	2	0-19	2	0-19	0.12
Platelets ($10^9/L$)	398	128-2168	370	140-2485	370	140-2485	0.57
BM blasts (%) [N=142]	2	0-8	2	0-8	2	0-8	0.55
	Pts	%	Pts	%	Pts	%	P*
Sex							
Female	27	38%	26	36%	26	36%	0.86
Male	45	63%	47	64%	47	64%	
Hasford Risk Category							
Low	15	21%	15	21%	15	21%	1.00
Inter.	22	31%	22	30%	22	30%	
High	35	49%	36	49%	36	49%	
Performance Status							
0	49	68%	44	61%	44	61%	0.48
1	22	31%	25	35%	25	35%	
2	1	1%	3	4%	3	4%	
Unknown	0	---	1	---	1	---	
Palpable Splenomegaly							
Yes	30	42%	34	48%	34	48%	0.50
No	42	58%	37	52%	37	52%	
Unknown	0	----	2	---	2	---	
Palpable Hepatomegaly							
Yes	2	3%	3	4%	3	4%	0.68

	IM400 (N=72)		IM800 (N=73)		P*
	Median	Min-Max	Median	Min-Max	
No	69	97%	65	96%	
Unknown.	1	---	5	--	

* Two-sided p-value from Wilcoxon test (continuous variables) or Fisher's exact test (sex, organomegaly). P-value from Pearson's chi-square test for Hasford risk category and performance status. Unknowns were excluded from significance tests. Pts=patients.

Treatment outcomes of 145 CML-CP patients by treatment arm.

*** Based on blood specimens collected 295–406 days after randomization (if a patient's molecular response was tested more than once during that interval, only the result obtained closest to day 365 was included in this analysis).

Table 3
Treatment outcomes of 111 patients with CML-CP according to molecular response at 3 months

	IM400						IM800							
	10% (N=19)			<10% (N=36)			10% (N=11)			<10% (N=45)				
	Pts	%	95% CI	Pts	%	95% CI	P*	Pts	%	95% CI	Pts	%	95% CI	P*
CHR **	18	95%	74–100%	33	92%	76–98%	0.83	9	82%	48–98%	44	98%	88–100%	0.095
Not evaluable	0			3				1			1			
	N=15			N=27				N=6			N=28			
CCyR ***	6	40%	16–68%	23	85%	66–96%	0.0038	3	50%	12–88%	25	93%	76–99%	0.031
	N=10			N=27				N=9			N=35			
MR at 1 year ****														
3-log (MMR)	1	10%	0–45%	11	41%	22–61%	0.080	0	0%	0–34%	26	74%	57–86%	0.0001
4-log (MR ^{4.0})	0	0%	0–31%	3	11%	2–29%	0.38	0	0%	0–34%	14	40%	24–58%	0.020
4.5-log (MR ^{4.5})	0	0%	0–31%	3	11%	2–29%	0.38	0	0%	0–34%	10	29%	15–46%	0.074

* One-sided p-value for poorer outcome in patients with <10% reduction in transcript at 3 months, based on Fisher's exact test.

** Includes 84 CHR (40 IM400, 44 IM800) achieved on or before collection of 3-month specimen.

*** All CCyRs were achieved after day 90 specimen collection, except one IM400 patient 4 with 10% Reduction.

**** Based on blood specimens collected 295–406 days after randomization (if a patient's molecular response was tested more than once during that interval, only the result obtained closest to day 365 was included in this analysis).

Table 4

Toxicities of 144 CML-CP patients who received assigned therapy, by treatment arm

	IM400 (N=72)		IM800 (N=72)		P*
	All grades	Grade 3-4	All grades	Grade 3-4	
Haematologic toxicities					
Hemoglobin	47 (65%)	5 (7%)	59 (82%)	8 (11%)	0.0067
Neutrophils	23 (32%)	8 (11%)	33 (46%)	12 (17%)	0.043
Febrile neutropenia	1 (1%)	1 (1%)	1 (1%)	1 (1%)	0.75
Platelets	24 (33%)	6 (8%)	46 (64%)	14 (19%)	<0.0001
Fluid retention					
Edema (any)	42 (58%)	3 (4%)	50 (69%)	2 (3%)	0.15
Pleural effusion	0 (0%)	0 (0%)	2 (3%)	0 (0%)	0.25
Gastrointestinal toxicities					
Diarrhea	28 (39%)	1 (1%)	40 (56%)	6 (8%)	0.0088
Nausea	36 (50%)	2 (3%)	42 (58%)	2 (3%)	0.043
Vomiting	11 (15%)	1 (1%)	20 (28%)	0 (0%)	0.036
Anorexia	11 (15%)	0 (0%)	16 (22%)	0 (0%)	0.16
Other non-haematologic toxicities					
Fatigue	47 (65%)	0 (0%)	57 (79%)	11 (15%)	0.0006
Musculoskeletal pain (any)	33 (46%)	2 (3%)	42 (58%)	8 (11%)	0.011
Rash	19 (26%)	1 (1%)	36 (50%)	4 (6%)	0.0012
Headache	9 (13%)	1 (1%)	9 (13%)	1 (1%)	0.49
Prolonged QTc interval	3 (4%)	0 (0%)	7 (10%)	0 (0%)	0.14

* One sided p-value for higher AE grades in the IM800 arm, based on Wilcoxon test.