Effects and outcome of a policy of intermittent imatinib treatment in elderly patients with chronic myeloid leukemia

Running Head: Intermittent imatinib treatment in Ph+ CML

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Key points:

- Intermittent imatinib treatment affects cytogenetic and molecular response, but not the outcome.
- No patients treated with INTERIM progressed to AP or BP.

ABSTRACT

We report a study of an alternative treatment schedule of imatinib (IM) in chronic myeloid leukemia (CML). Seventy-six Philadelphia-positive (Ph+) - BCR-ABL - positive patients aged 65 years or older, who had been treated with IM for more than two years and who were in stable complete cytogenetic response (CCgR) and in major molecular response (MMR), were enrolled in a single-arm study to test the effects of a policy of intermittent imatinib (INTERIM) therapy, one month on and one month off. With a minimum follow-up of four years, 13 patients (17%) lost CCgR and MMR, and 14 (18 %) lost MMR only. All these patients resumed continuous imatinib, and all - but one (lost to follow-up) regained CCgR and MMR. No patients progressed to accelerated or blastic phase, or developed clonal chromosomal abnormalities in Ph+ cells, or BCR-ABL mutations. In elderly Ph+ CML patients carefully selected for a stable CCgR (lasting > 2 years), the policy of intermittent imatinib treatment affected the markers of residual disease, but not the clinical outcomes (overall and progression-free survival).

ClinicalTrials.gov number: NCT 00858806
INTRODUCTION

Over the last decade, the goals of the treatment of Philadelphia chromosome-positive (Ph+), BCR-ABL-positive chronic myeloid leukemia (CML) with tyrosine kinase inhibitors (TKIs) have become more and more ambitious: delayed progression, prolonged survival, normalization of survival, and treatment discontinuation without molecular recurrence, or cure (1-6). With imatinib (IM) at the standard dose of 400 mg daily, 80-90% of patients are alive at 8 years but only a small proportion of patients (about 5%) can discontinue the treatment without suffering a molecular recurrence (6). Thus, the great majority of responsive patients would be destined to continue the treatment indefinitely, at the same standard dose. Although elderly patients have cytogenetic and molecular responses comparable to younger ones, they tolerate imatinib worse and this may reduce the benefit of therapy by inducing higher rates of therapy discontinuation and lower adherence to chronic treatment. In this setting, it may be important to improve tolerability without impairing the benefit. Since the median age of CML patients at diagnosis is around 60 years, with a life expectancy of about 20 years, it is particularly important to devise and test age-related policies of treatment (3, 4). Results have been improved by the use of second generation TKIs, but their toxicity remains an issue and even if they prove to be very successful, the majority of patients are expected to undergo a lifelong treatment (7-12). Although the concept of cure remains more attractive, it is time to wonder whether the choice should still be restricted to either “white” (discontinuation) or ”black” (treatment for ever). Therefore, the issue is not only which of these two policies is better, but also if, between these two extremes (lifelong treatment vs treatment discontinuation), there are other potential or possible policies that can be affordable in specific settings, particularly in elderly CML patients. One such strategy could be the identification of schedule of imatinib that would be sufficient to maintain response and to avoid progression, but which might improve compliance.
We report here on a study – the INTERIM study - that was designed five years ago to investigate if an alternative policy of treatment, namely intermittent administration of imatinib, would effect the surrogate markers of outcome, namely the cytogenetic and molecular response, as well as the outcome itself (progression-free and overall survival).
PATIENTS AND METHODS

Patients

Patients with Ph+, BCR-ABL+ CML who were 65 years or older, who were treated with IM frontline, who had been on IM for two years or longer and who were in stable CCgR, were eligible for the study. The stability of CCgR had to be documented by negativity of a chromosome banding analysis (CBA) of at least 20 marrow cell metaphases within one year before enrollment, and again at enrollment. Written informed consent was requested. The study was conducted in accordance with the Declaration of Helsinki. The protocol a EudraCT number is 2007-005102-42 and it was approved by the Ethical Committee of the Spedali Civili Hospital in Brescia, Italy.

From April 2008 to November 2009, 114 Ph+, BCR-ABL+ CML patients were screened for the study. Nineteen patients (17%) denied consent, and another nineteen (17%) patients were not enrolled either because they had been pretreated with IFNα (7 patients) or because the CCgR status was not confirmed in the baseline sample (12 patients). Seventy-six patients were enrolled. The main characteristics of these patients are reported in Table 1. At least three of these characteristics are worth noticing: the long duration of IM treatment, with a median of more than 60 months; the high proportion (81%) of the patients on a 400 mg dose, in spite of the age and the long treatment duration; and the low proportion of high-risk patients, in spite of the advanced age. The great majority of the patients reported one or more comorbidities - cardiovascular in 72% of cases (Table 1). Also, 71% of patients were taking concomitant medications that in 28% of cases were drugs known to be metabolized by the CYP450 isoenzymes, CYP2D6 and CYP3A4.
INTERIM Treatment Plan

This was a multicenter, phase 2 study (EudraCT number 2007-005102-42; ClinicalTrials.gov number: NCT 00858806), aimed to investigate how an intermittent treatment with standard dose imatinib would modify the surrogate markers of outcome, namely the cytogenetic and molecular response, and how it would affect the treatment outcome, namely the progression free survival (PFS) and overall survival (OS).

The term “standard imatinib therapy” is used for daily administration of imatinib at any dose, whereas, “intermittent imatinib treatment” (INTERIM), is used to define a treatment where the same dose of imatinib was given according to the following intermittent schedule: one week on/one week off for the 1st month (weeks 1-4); two weeks on/two weeks off for the 2nd and the 3rd month (weeks 5-12); one month on/one month off from the 4th month (weeks 13) to the 12th month and thereafter. The patients who lost the CCgR resumed the pre-study, daily imatinib treatment. The patients who lost the MMR alone within the first year had to continue the intermittent schedule. After the first year, the patients who lost MMR alone were allowed to go back to the pre-study continuous treatment.

Objectives of the study

The first objective of the study was to evaluate the proportion of patients who remained in CCgR after one-year on INTERIM. The study was designed five years ago, when CCgR was universally recognized as the most solid surrogate marker of survival (13). Since we anticipated that a proportion of patients would lose CCgR, all patients were carefully monitored to evaluate if and when the standard continuous treatment had to be resumed. Other objectives were the proportion of patients who would lose MMR, who would lose complete hematologic response (CHR), who would develop BCR-ABL kinase domain (KD) point mutations, and who would progress to accelerated or blast phase (AP or BP). Progression free survival (PFS) and overall survival (OS)
were calculated for all patients, with a minimum follow-up of 48 months.

**Response monitoring**

Clinical evaluation, physical examination, blood counts and differential, together with relevant biochemical tests, were performed at the time of enrollment (baseline) and every 3 months during the study.

**Cytogenetics**

Karyotypes were performed at each participating Center and were examined after G or Q banding techniques, according to the International System for Human Cytogenetic Nomenclature (14). The evaluation of CCgR was based on CBA of marrow cell metaphases. CCgR was defined as the absence of the Ph chromosome in at least twenty marrow metaphases. CBA of marrow cell metaphases was performed at enrollment, then only in the patients who scored positive by fluorescence in situ hybridization (FISH) during the study.

Interphase FISH analysis of buffy-coat blood cells was performed at each Center every 3 months during the first year (study core) and every six months thereafter. The Locus Specific Identifier BCR/ABL Dual Colour, Dual Fusion (DF) Translocation Probe (Abbott Molecular-Vysis) or the Double-Fusion Signal D-FISH BCR/ABL Probe (Oncor-QBiogene) was employed (15). FISH was defined as either negative or positive if the percent of BCR-ABL-positive nuclei was ≤ 1% or >1%, respectively, counting at least 200 nuclei (15). Therefore, in the patients who became FISH-positive during the study, a CBA of bone marrow metaphases was performed to confirm the loss of CCgR, and to detect if there were clonal chromosomal abnormalities in Ph+ cells (CCA/Ph+).
BCR-ABL transcript level

Real time quantitative reverse transcription-polymerase chain reaction (RT-Q-PCR) for BCR-ABL transcripts was performed at baseline and every 3 months during the study. Samples were collected at investigational sites and centralized in one of the reference laboratories (Bologna) of the “Gruppo Italiano Malattie Ematologiche dell’Adulsto” (GIMEMA) network. Leukocytes were isolated from 20 ml of peripheral blood after red blood cell lysis, and RNA was extracted and converted to cDNA according to conventional methods. RT-Q-PCR was performed with the TaqMan technology (Applied Biosystems, Foster City, CA) as previously set up and standardized within the framework of the Europe against Cancer program (16). Results were expressed as ratio of BCR-ABL/ABL% on the International Scale (IS) (17-19) using a laboratory-specific conversion factor (CF). The CF was derived by the reference laboratory in Bologna in the framework of the European Treatment and Outcome Study (EUTOS) standardization initiatives (16, 19). MMR, corresponding to a 3-log reduction in BCR-ABL transcripts level from the standardized baseline, was thus defined as BCR-ABL≤0.1%IS, and is also indicated as MR3.0.

In case of loss of CCgR or MMR, a BCR-ABL kinase domain (KD) point mutation analysis was also performed. The KD of the BCR-ABL transcript was amplified by nested RT-PCR and screened by denaturing-high performance liquid chromatography as previously described (20, 21).

Statistics

Based on previous studies showing that the CCgR rate during continuous treatment would range between 85% and 95%, and using the optimal Simon’s two stage procedure (22), we set p0 (as the proportion of responses below which the treatment would be considered ineffective) at 85% and p1 (as the proportion of responses above which the treatment would be considered effective) at 95%. With an alpha error of 0.05 and a power 1-beta of 80%, the number of patients to be enrolled was 65. To account of dropouts and withdrawals, the number of patients was adjusted to 76. The
study would have been stopped, if more than 2 of the first 13 patients (15.4%) had lost CCgR, within the first year (first stage), and more than 7 of 76 (9.2%) patients had lost CCgR in the second stage. Standard descriptive statistics, such as mean, median, range and proportions were used to summarize the patient sample. The χ²-test was used to compare differences in percentages, and the Mann-Whitney U test was used to compare continuous variables. The Kaplan-Meier method (23) was used to estimate PFS, OS, CCgR loss (CBA-positivity) and MMR (MR³.0) loss from the first day on INTERIM. Death by any cause and progression to A/BP were the events of interest for PFS. CCgR loss (CBA-positivity), MMR (MR³.0) loss and the probability of continuing INTERIM were calculated using the cumulative incidence procedure (24). Death was considered competing risk for CCgR and MMR loss, whereas death and refusal were the competing risks for the probability of continuing INTERIM. Cox proportional hazard regression model was used for univariate and multivariate analysis of factors associated with CCgR and MMR loss. The following variables were analyzed: age, sex, Sokal risk group, baseline BCR-ABL transcript level, duration of IM therapy before INTERIM and BCR-ABL transcript level. Variables found to be significant at the p<0.10 in univariate analysis were tested in multivariate analysis. All p values were 2-sided and p<0.05 was considered as statistically significant.
RESULTS

At the time of the start of the INTERIM study, the 76 enrolled patients were in CCgR and all but one were in MMR (MR $^{3.0}$). Table 2 shows the flow diagram of INTERIM study in which all the events occurring during the 48 months of intermittent treatment with imatinib are reported.

Thirteen patients (17%) lost CCgR and MMR and all but one (a patient who was lost to follow-up) regained CCgR and MMR after they had discontinued intermittent imatinib (INTERIM) and resumed continuous imatinib. The monitoring and outcome of these patients are detailed in the supplemental data (Table 3 and 4). The first loss of CCgR (CBA-positivity) was detected after 6 months. Six patients (8%) lost CCgR during the first 12 months and the remaining 7 patients lost CCgR between the 13th and the 27th month. Thus, at 12 and 48 months, the probabilities of maintaining CCgR were 92% (95% CI 86-98%) and 81% (95% CI 71-90%), respectively (Figure 1). The loss of MMR occurred 3 to 9 months before the loss of CCgR in 9 cases. All 13 patients discontinued INTERIM and resumed continuous IM treatment at the same dose and, with the exception of one patient lost to follow-up, all of them regained the CCgR and MMR after a median of 7 and 6 months from resuming IM daily, respectively; they are still in chronic phase, in CCgR and in MMR after a median follow-up of 48.5 months (range 39-66) (see Supplemental Table 3).

Fourteen patients (18%) lost MMR alone. Nine of these discontinued INTERIM and resumed daily imatinib; all regained MMR (Table 2). The first loss of MMR alone was detected after 3 months. Seven patients (9%) lost MMR during the first 12 months and the remaining 7 patients lost MMR between the 13th and the 36th month (see Supplemental Table 4). Thus, at 12 and 48 months the probabilities of maintaining MMR (MR$^{3.0}$) were 80% (95% CI 71-89%) and 63% (95% CI 52-74%) respectively (Figure 2). The intermittent schedule of treatment was discontinued in 9 patients who had lost MMR alone; all of these regained a MMR after a median of 3 months
from resuming daily imatinib. All the 14 patients who lost MMR alone are still in the chronic phase, and in MMR after a median follow-up of 48 months (range 33-60) (see Supplemental Table 4).

Neither age nor sex, Sokal risk group, baseline BCR-ABL transcript level or duration of IM therapy before INTERIM were found to be associated with loss of CCgR or MMR when they were examined by univariate and multivariate analyses.

One patient developed atrial fibrillation at 15 months, one refused to continue INTERIM at 24 months, but all the patients were in CCgR and in MMR when the events occurred. No patients developed CCA in Ph+ cells or BCR-ABL point mutations; moreover, none of the patients progressed to AP-BP, but two died at 24 and 36 months because of acute myocardial infarction and of intracranial hemorrhage, respectively (Table 2). Therefore, the probabilities of continuing INTERIM were 92% (95% CI 86-98%) and 70% (95% CI 60-80%) at 12 and 48 months, respectively (Figure 3), while the estimated PFS was 100% at 12 months and 96% (95% CI 91-100) at 48 months (Figure 4).

No patient complained of new or more severe side effects during the months “on”. Three patients reported grade 2 side effects (adverse events) at enrolment into INTERIM. In one of these, fluid retention, muscle cramps and skin erythema disappeared after 10 months. In the second patient, skin erythema disappeared after 8 months. The third patient continued to complain of fluid retention and skin erythema and this remained stable during INTERIM. Seventeen patients reported grade 1 side effects at enrolment in INTERIM (see Supplemental Table 5). Muscle pain or cramps and fluid retention disappeared in 4 of 5 patients. Fluid retention disappeared in 2 of 8 patients. Overall, the side effects disappeared in 11 of 20 patients (see Supplemental Table 5).
DISCUSSION

This is a report of a phase 2, single-arm study, testing prospectively, for the first time, the effects of a policy of TKI treatment reduction in patients who were optimal responders to imatinib but who did not fit the current requirements for a trial of treatment discontinuation. The first selection was based on age, and the study was limited to patients who were 65 years old or older (the median age was 72 years). Elderly patients respond to imatinib as well as young patients (25), but they have more comorbidities, take more concomitant drugs and tolerate TKI worse. Furthermore, in comparison to younger patients, elderly patients may suffer less from living with leukemia, have fewer problems related to family planning and career, but may have more financial problems in those countries where the cost of TKI cannot yet be completely covered by a public health system or by private insurance. These reasons can be more or less general, but in many diseases treatment is modulated according to age and there are no good reasons why CML should be an exception.

The schedule of “one month on” and “one month off” was selected from several different possibilities. For the sake of simplicity, the cycle was set to one month, but, a posteriori, this choice looks fairly reasonable and appropriate, since the discontinuation studies have shown that most molecular relapses occur rapidly (6, 26). Dose reduction instead of the intermittent administration was not taken into consideration, as prolonged exposure to a low imatinib concentration may favor the emergence and selection of resistant clones (27-29). When the study was designed, we anticipated that some patients could lose the molecular and cytogenetic responses, that were the most reliable surrogate markers of survival, at least at that time. Therefore, all patients were carefully monitored, and the protocol required that resuming the continuous schedule of treatment was always mandatory if CCgR was lost and was advisable if MMR was lost, after the completion of the first year of INTERIM. With these recommendations and stringent cytogenetic and molecular monitoring, all the patients who had lost CCgR or MMR regained CCgR or MMR.
with daily imatinib treatment. No BCR-ABL kinase domain point mutation emerged, and all patients remained free from progression to AP or BP - the ultimate goal of the study protocol.

This study cannot prove that a policy of intermittent imatinib treatment was better or worse than the standard policy of continuing treatment. Furthermore, it cannot lead to the recommendation to extend this policy either to the patients who are believed to be ineligible for treatment discontinuation, or to patients undergoing less stringent conventional monitoring of cytogenetic and/or molecular response. However, these results help to open a small door to alternative and yet unexplored policies of treatment. Currently, the internationally shared standard policy of treatment of CML with TKI is to continue the treatment, at the same dose, indefinitely, with the goal of ensuring survival close to that of the general population. More recently, a more ambitious policy is gaining support, with the goal of achieving a condition of minimal residual disease (MRD) such that remission can even be maintained after treatment discontinuation (6, 26). This latter policy requires sensitive molecular assessment of MRD, and foresees that the depth of molecular response is the best surrogate marker of outcome, but the major obstacle to its success is the small proportion of patients who can achieve and maintain a deep molecular response and do not relapse after treatment discontinuation (6, 26). In the patients who have been treated with imatinib for years, the probability of achieving a MMR or better is high, but the proportion of patients who maintain a MR$^4.0$ or more for a sufficiently long period is lower. There are not many data, but a recent analysis of a multicentric series by the GIMEMA CML WP has shown that the proportion of patients who maintained a stable MR$^4.0$ or better for one year or more was of about 22% (30). A similar analysis of a single center series reported that the proportion of patients who would have fitted the requirements for entering the STIM study was 21% (31). Although it is believed, and expected, that the introduction of second generation TKI as first-line treatment will mark a significant improvement, that proportion would hardly exceed 20-30%, leaving the majority of responders to a policy of chronic treatment at the same standard schedule and dose.
In conclusion, it has been shown that in the setting of optimal responders to imatinib, a 50% dose reduction of the drug results in loss of CCgR in 17% of patients and in loss of MMR alone in 18% of patients, but that all patients can achieve the same level of response again by reassuming continuous imatinib. What is particularly striking is that, with a follow-up of 48 months, no patient has progressed, or died of leukemia. In elderly CML Ph+ patients carefully selected for a stable CCgR (long lasting i.e. > 2 years) and carefully monitored, the policy of intermittent imatinib treatment affected the markers of residual disease, but not the clinical outcomes (overall and progression-free survival). The results of this study do not allow us definitively to conclude that intermittent treatment can be offered to optimal and stable responders, but opens a window to alternative treatment policies, even in the patients for whom a very deep molecular response cannot be achieved.
Acknowledgments: This work was supported in part by EuropeanLeukemiaNet (contract LSHC-CT-2004-503216) through the European Treatment and Outcome Study (EUTOS) supported by Novartis Oncology Europe, and COFIN 2009. Special thanks to the following Authors for their participation in the development of the Manuscript: Francesco Albano (Bari), Miriam Fogli (Bologna), Chiara Colombi (Brescia), Giovanni Quarta and Mariella Girasoli (Brindisi), Emilio Usala and Emanuele Angelucci (Cagliari), Alberto Bosi and Valeria Santini (Firenze), Gianluca Gaidano and Monia Lunghi (Novara), Giuseppe Visani and Giuseppina Nicolini (Pesaro), Giuseppe Fioritoni and Roberto Di Lorenzo R (Pescara), Monica Bocchia and Francesco Lauria (Siena), Francesco Rodeghiero and Anna D’Emilio (Vicenza). Many thanks to Multilingue Srl Translations Services, Brescia, Italy for English Revision.

Author Contributions: Domenico Russo and Michele Baccarani designed the study; Domenico Russo, Giovanni Martinelli, Gianantonio Rosti, Michele Malagola, Cristina Skert, Simona Soverini, Ilaria Iacobucci, Antonio De Vivo, Nicoletta Testoni, Fausto Castagnetti, Gabriele Gugliotta, Diamante Turri, Michela Bergamaschi, Patrizia Pregno, Ester Pungolino, Fabio Stagno, Massimo Breccia, Bruno Martino, Tamara Intermesoli, Carmen Fava, Elisabetta Abruzzese, Mario Tiribelli M, Catia Bigazzi Bruno Mario Cesana, and Michele Baccarani collected the data; Giovanni Martinelli, Ilaria Iacobucci, Simona Soverini and Nicoletta Testoni performed the molecular and cytogenetic analysis; Domenico Russo, Michele Baccarani, Giannatonio Rosti, Michele Malagola, Crisitna Skert, Antonio De Vivo and Bruno Mario Cesana analysed the data; Domenico Russo and Michele Baccarani wrote the manuscript.

Conflict-of-interest disclosure: Domenico Russo received research funding from Celgene and Gilead, is a paid expert testimony for Novartis and serves on the speakers’ bureaus of Novartis. Giovanni Martinelli serves on the speakers’ bureaus of Novartis, Bristol-Myers Squibb, and Pfizer. Gianantonio Rosti is a consultant for Novartis, Bristol-Myers Squibb and ARIAD, serves on the
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Table 1. Main characteristics, comorbidities and concomitant medications of the patients who have been enrolled into INTERIM study. All patients were aged 65 years and more, and were in CCgR for at least 2 years.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>76</td>
</tr>
<tr>
<td>Gender, M/F</td>
<td>41/35</td>
</tr>
<tr>
<td>Age at enrollment, years, median (range)</td>
<td>72 (65-83)</td>
</tr>
<tr>
<td>No. of patients more than 80 years old</td>
<td>8 (11%)</td>
</tr>
<tr>
<td>Time from diagnosis, months, median (range)</td>
<td>64 (25-98)</td>
</tr>
<tr>
<td><strong>Sokal risk (at diagnosis)</strong></td>
<td></td>
</tr>
<tr>
<td>- Low (&lt; 0.80)</td>
<td>25 (33%)</td>
</tr>
<tr>
<td>- Intermediate (0.80 – 1.20)</td>
<td>42 (55%)</td>
</tr>
<tr>
<td>- High (&gt; 1.20)</td>
<td>9 (12%)</td>
</tr>
<tr>
<td><strong>Imatinib therapy duration, months</strong></td>
<td></td>
</tr>
<tr>
<td>- Median (range)</td>
<td>60 (24-94)</td>
</tr>
<tr>
<td>- No. of patients with more than 48 months</td>
<td>51 (67%)</td>
</tr>
<tr>
<td>Imatinib dose, mg, median</td>
<td>400</td>
</tr>
<tr>
<td>- No. of patients at 200 mg</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>- No. of patients at 300 mg</td>
<td>11 (14%)</td>
</tr>
<tr>
<td>- No. of patients at 400 mg</td>
<td>62 (81%)</td>
</tr>
<tr>
<td>- No. of patients at 600 mg</td>
<td>1 (1%)</td>
</tr>
<tr>
<td><strong>No. of patients with comorbidities</strong></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>55 (72%)</td>
</tr>
<tr>
<td>Prostatic</td>
<td>14 (18%)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>14 (18%)</td>
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<tr>
<td>Kidney</td>
<td>12 (16%)</td>
</tr>
<tr>
<td>Arthritis</td>
<td>7 (9%)</td>
</tr>
<tr>
<td>Respiratory</td>
<td>6 (8%)</td>
</tr>
<tr>
<td>Neurological</td>
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</tr>
<tr>
<td>Diabetes mellitus</td>
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<tr>
<td>Thyroid</td>
<td>5 (7%)</td>
</tr>
<tr>
<td>Other</td>
<td>20 (26%)</td>
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<tr>
<td><strong>No. of patients with concomitant medications</strong></td>
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<tr>
<td>1-2 drugs</td>
<td>20 (26%)</td>
</tr>
<tr>
<td>3-4 drugs</td>
<td>24 (31%)</td>
</tr>
<tr>
<td>&gt; 4 drugs</td>
<td>10 (13%)</td>
</tr>
<tr>
<td>Cy3A4 drugs metabolized</td>
<td>21 (28%)</td>
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</tbody>
</table>
Table 2: flow diagram of INTERIM study

**BASELINE**
76 pts on INTERIM
- 7 patients lost MMR alone
- 6 pts lost CCgR and MMR from 0 to 12th mo
- 6 pts regained IM daily
- 6 pts regained CCgR and MMR

@ 1st YEAR
70 pts on INTERIM
- 6 pts lost CCgR and MMR from 13th to 24th mo
- 6 pts resumed IM daily
- 5 pts regained CCgR and MMR
- 1 pt was lost to follow-up
- 6/7 pts who lost MMR alone from 0 to 12th mo resumed IM daily
- 6 pts regained MMR
- 3 pts regained MMR
- 1 pt discontinued INTERIM because of atrial fibrillation @ 15th mo
- 1 pt died because of myocardial infarction in CCgR and MMR @ 24th mo
- 1 pt refused to continue INTERIM @ 24th mo

@ 2nd YEAR
52 pts on INTERIM
- 1 pt lost CCgR and MMR from 24th to 36th mo
- 1 pt resumed IM daily
- 1 pt regained CCgR and MMR
- 2 pts lost MMR alone from 24th to 36th mo
- 1 pt died because of intracranial hemorrhage in CCgR and MMR @ 36th mo

@ 3rd YEAR
50 pts on INTERIM

@ 4th YEAR
50 pts on INTERIM
Figures’ Legends

**Figure 1. Probability of maintaining the CCgR on INTERIM.** Estimated CCgR loss was 92% (95% C.I., 86-98) at 12 months and 81% (95% C.I., 71-90) at 48 months.

**Figure 2. Probability of maintaining the MMR on INTERIM.** Estimated MMR loss was 80% (95% C.I., 71-89) at 12 months and 63% (95% C.I., 52-74) at 48 months.

**Figure 3. Probability of maintaining INTERIM treatment.** The estimated probability of maintaining INTERIM treatment was 92% (95% CI 86-98%) at 12 months and 70% (95% CI 60-80%) at 48 months.

**Figure 4. Progression free survival.** Estimated PFS was 100% at 12 months and 96% (95% C.I. 91-100) at 48 months. The events were 2 deaths in remission (CCgR and MMR). No patients progressed to accelerated or blastic phase.
Figure 1.
Figure 2.
Figure 3.
Figure 4.
Effects and outcome of a policy of intermittent imatinib treatment in elderly patients with chronic myeloid leukemia

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