The aim of this study was to investigate the effects of a non-standard, intermittent imatinib treatment in elderly patients with Philadelphia-positive chronic myeloid leukaemia and to answer the question on which dose should be used once a stable optimal response has been achieved. Seventy-six patients aged \( \geq 65 \) years in optimal and stable response with \( \geq 2 \) years of standard imatinib treatment were enrolled in a study testing a regimen of intermittent imatinib (INTERIM; 1-month on and 1-month off). With a minimum follow-up of 6 years, 16/76 patients (21\%) have lost complete cytogenetic response (CCyR) and major molecular response (MMR), and 16 patients (21\%) have lost MMR only. All these patients were given imatinib again, the same dose, on the standard schedule and achieved again CCyR and MMR or an even deeper molecular response. The probability of remaining on INTERIM at 6 years was 48\% (95\% confidence interval 35–59\%). Nine patients died in remission. No progressions were recorded. Side effects of continuous treatment were reduced by 50\%. In optimal and stable responders, a policy of intermittent imatinib treatment is feasible, is successful in about 50\% of patients and is safe, as all the patients who relapsed could be brought back to optimal response.

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**INTRODUCTION**

More than 80\% of patients with Philadelphia-positive (Ph+), BCR-ABL1+, chronic phase chronic myeloid leukaemia (CML) are alive after > 5 years and are projected to have a life expectancy very close or even identical to that of a non-leukaemic matched control population.\(^1\)–\(^5\) These results were obtained using the tyrosine kinase inhibitor (TKI) imatinib (Gleevec or Glivec, Novartis Pharmaceuticals), frontline.\(^1\)–\(^9\) Some of these patients, in a proportion estimated to range between 20\% and 40\%, achieve a deep molecular response (DMR), that is to say a BCR-ABL1 transcripts level \( \leq 0.01\% \) on the International Scale.\(^6\)–\(^12\) About 50\% of them were reported to maintain that remission status after discontinuation of imatinib and to achieve a stable treatment-free remission (TFR).\(^13\)–\(^16\) The introduction of the so-called second-generation TKIs, both in first and second line, is expected to fare even better, with up to 50\% or more of the patients achieving a DMR,\(^17\)–\(^20\) and up to \( \geq 50\% \) of them entering into a TFR status. If these expectations will be fulfilled, the proportion of patients who will be in TFR will range between 25\% and 50\%. However, about \( \geq 50\% \) of all patients will not be able to discontinue, and for them, the current policy is to continue the treatment with the same TKI, at the same dose and schedule, indefinitely and lifelong.\(^21\) Until today, the case of the chronic treatment of these patients has not received the same attention as the case of TFR policies. But the issue is important for obvious reasons of quality of life,\(^21\) treatment-related side effects and complications\(^22\)–\(^29\) and also because of drug and management costs.\(^30\)

For these reasons, we designed and initiated a pilot study testing the effect of a non-standard, dose-reduced, policy of imatinib treatment.\(^21\) We report here on the long-term results of that trial.

**PATIENTS AND METHODS**

The study (EUDRACT protocol number 2007-005102-42, approved by the Ethnic Committee of the Spedali Civili of Brescia, Italy and registered at...
ClinicalTrials.Gov with the number: NCT00858806) was limited to patients aged \(\geq 65\) years who had been treated first line with imatinib once daily (OD) for chronic phase CML, for a minimum of 2 years, and were in complete cytogenetic response (CCyR). One hundred and fourteen patients were screened in 24 GIMEMA (Gruppo Italiano Malattie Ematologiche dell'Adulto) centres. Nineteen patients (17%) did not fit the inclusion criteria, 19 (17%) did not consent and 76 were enrolled. The median age at enrolment was 72 years (range 65–83 years). The median duration of imatinib treatment was 5.75 years (range 2.0–6.6 years). Sokal risk distribution at diagnosis was 33% low risk, 55% intermediate risk and 12% high risk. At enrolment, all patients were in CCyR, and all but one were in major molecular response (MMR or MR3.0, BCR-ABL1 transcripts level \(\leq 0.1\%\) on the International Scale).

The daily dose of imatinib was not modified (400 mg OD in 81% of patients, 200–300 mg OD in 17% of patients and 600 mg in one patient), but imatinib was given 1 week on/1 week off for 1 month, 2 weeks on/2 weeks off for another 2 months and then on a 1 month on/1 month off schedule. The protocol originally mandated to proceed with the intermittent schedule as long as the CCyR was maintained so that the return to continuous daily treatment was mandatory only in case of CCyR loss. After 2 years, an amendment allowed a return to the continuous daily schedule also in case of MMR loss.

The cytogenetic response was assessed by chromosome banding analysis of marrow cell metaphases or by interphase fluorescence in situ hybridization analysis of peripheral blood cell nuclei, as described elsewhere. The cytogenetic test was performed every 6 months for the first 2 years, and then only in case of loss of MMR. A CCyR was defined either by the absence of Ph+ metaphases out of at least 20 metaphases or by < 1% BCR-ABL1+ nuclei out of > 200 nuclei. The molecular response was evaluated every 3 months and was reported according to the International Scale by reverse transcriptase-PCR of peripheral blood leukocytes. The tests were performed at one GIMEMA reference laboratory for 4 years, then also at other laboratories that had received their conversion factor through the EUTOS project and were certified by the Labnet GIMEMA network. A mutational analysis, by Sanger sequencing technique, was performed in the Bologna reference laboratory in all cases of loss of CCyR or MMR. The definition of the phases of the disease and of response was those recommended by EuropeanLeukemiaNet 2013.

Figure 1. Flow diagram of INTERIM study—update at 72 months.
Statistics
The Kaplan–Meier method was used to estimate overall survival. Death by any cause was the event of interest for overall survival. CCR loss (CBP-positivity), MMR (MR3.0) loss and the probability of continuing INTERIM were calculated using the cumulative incidence procedure. Death was considered competing risk for CCR loss and MMR loss, whereas death and refusal were the competing risks for the probability of continuing INTERIM.

RESULTS
The results of intermittent imatinib treatment, with a median follow-up of 5.75 years (range 2.0–6.6 years) are shown in the flow diagram (Figure 1). Sixteen patients (21%) lost CCR and MR3.0, 11 of them during the first 2 years and 5 later on. One of these patients was lost to follow-up. All the remaining 15 patients recovered a CCR, with MR3.0 in 13 patients and MR3.0 in one. Sixteen patients (21%) lost MR3.0 after the second year. All these patients recovered an MR2.0, and two of them achieved a DMR (MR4.0 in one case and MR4.5 in one case). One patient went off the study because of an atrial fibrillation. He was back on standard imatinib, then switched to nilotinib and is in MR. Four patients withdrew their consent after 24–70 months. They went back to standard daily imatinib; 3 are in MR3.0, the fourth achieved a MR4.0 and is currently in TFR. Nine patients (12%) died after 24–60 months, being in MR3.0, of the causes that are listed in the flow diagram, namely another cancer (five patients), chronic pulmonary obstructive disease (two patients) and cardiovascular events (two patients). The median age at death was 75 years (range 72–80). No patients progressed to accelerated phase or blastic phase. No BCR-ABL1 kinase domain point mutations were detected at the time of CCR or MR3.0 loss.

The distribution over time of the loss of CCR and of MR3.0 is shown in Figures 2a and b, respectively. The probability of maintaining the intermittent treatment schedule is shown in Figure 3a, where events were the return to the continuous, daily treatment, whatever the reason for that. At 6 years, 48% of patients were still on the intermittent schedule. Overall survival is shown in Figure 3b, where it should be noticed that all deaths occurred in remission. There were no progressions.

With a median follow-up of about 6 years, 30 patients are still on intermittent treatment taking the same imatinib dose as at baseline, 1 month on/1 month off. Four of them are in CCR, 4 are in MR3.0, 20 are in MR3.0 and 2 are in MR4.5.

DISCUSSION
The current policies of TKI treatment of chronic phase CML mandate using TKIs at their respective approved or maximum tolerated doses lifelong, with the possibility of opening a window for treatment discontinuation when a DMR has been achieved and maintained for an as yet unspecified period of time. The window for treatment discontinuation can be enlarged in some of the patients who received imatinib first line, by switching early or late to a second-generation TKI, as well as using second-generation TKIs first line. Other policies have not been tested prospectively, particularly for treatments alternative to discontinuation, when discontinuation is not possible. The importance of the compliance to the treatment dose is highlighted by studies reporting that poor compliance is associated with a poorer molecular response. However, it is time to open a debate not on compliance but on which dose should be used for chronic treatment, once a stable, optimal response has been achieved.

The concept of dose adaptation for chronic treatment can be tested in many different ways. Different schedules, such as a continuous daily treatment with a reduced dose or 1 day on/1 day off or 1 week on/1 week off, could be tested. In this exploratory study, it was decided to maintain the standard daily dose on a 1 month on/1 month off schedule. No pharmacokinetic studies were performed, but it is conceivable that the plasma concentration of imatinib fell to zero during the month off. This study shows that a policy of imatinib reduction to 50% of the initial standard dose was associated with a substantial loss of response in 42% of patients but had no negative effects on outcome, particularly on progression and leukaemia-related deaths. It should be noted that at baseline all patients were in MMR, while after 6 years of intermittent treatment 22 of the original 76 patients (29%) were in DMR and could be eligible for a trial of treatment discontinuation. Therefore, even an intermittent schedule can improve the response, with time. A systematic, prospective study of the quality of life was not designed and performed. All these patients were tolerating imatinib well. Only 20 of them were complaining of minor side effects. In all, 50% of them reported the disappearance of the side effects, particularly of muscle pain and cramps, and of fluid retention. No evidence of a ‘discontinuation syndrome’ was found, as it was reported in patients discontinuing imatinib in the EUROSKI study. In this exploratory study, only elderly patients (≥65 years) were selected and enrolled, because elderly patients tolerate TKIs less well, have
and TFR, a policy that is more radical and more appealing.\textsuperscript{11,12,16} However, the point is not only which policy is ‘better’. The point is to acknowledge that a policy of TFR cannot be always successful, because at least 50\% of patients are estimated to never reach a TFR, even with the largest use of second-generation TKIs. For the patients who do not achieve a TFR, it is necessary to reconsider some current concepts of treatment and to begin to look for a ‘minimum effective therapy’.\textsuperscript{25}

On these bases, we continue to work on the intermittent schedule with a standard daily dose, and we are now testing a progressive increase of the off-treatment period, up to 1 month on/3 months off.

CONFLICT OF INTEREST

Domenico Russo, Patrizia Pregno and Simona Soverini receive compensation as a consultant for Novartis, Bristol-Myers Squibb and Ariad. Elisabetta Abruzzese receives compensation as a consultant for Ariad, Bristol-Myers Squibb, Novartis, Takeda and Pfizer. Giovanni Martinelli receives compensation as a consultant for Novartis, Bristol-Myers Squibb and Pfizer. Gianantonio Rosti, Fausto Castagnetti and Michele Baccarani receives compensation as a consultant for Novartis, Ariad, Bristol-Myers Squibb and Pfizer, Mario Tiribelli receives compensation as a consultant for Novartis, BMS and Ariad. The remaining authors declare no conflict of interest.

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AUTHOR CONTRIBUTIONS

Domenico Russo and Michele Baccarani designed the study; all the authors collected the data; Domenico Russo, Michele Baccarani, Gianantonio Rosti, Michela Malagola, Cristina Skert, Antonio De Vivo and Bruno Mario Cesana analysed the data; all the authors wrote the manuscript and gave final approval of the manuscript.

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Figure 3. (a) Probability of remaining in the intermittent imatinib schedule (INTERIM). In all, 46/76 patients (61\%) discontinued the intermittent schedule, of whom 24 during the first 2 years and 22 later on. The probability of maintaining the intermittent treatment schedule was 74\% (95\% CI 62–82) at 2 years, 59\% (95\% CI 46–69) at 4 years and 48\% (95\% CI 35–59) at 6 years. (b) Overall survival. No patients progressed and died of leukaemia. Nine patients (median age at death, 75 years) died in MMR for an overall survival of 87\% (95\% CI 78–95\%) at 6 years.

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