Imatinib Mesylate Discontinuation in Patients with Chronic Myelogenous Leukemia in Complete Molecular Remission for More Than Two Years.

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On behalf of the Intergroupe Français des Leucémies Myéloïdes Chronique (FlφLMC)

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Running title: Imatinib mesylate discontinuation in complete molecular response

Keywords: Imatinib, Chronic Myelogenous Leukemia, Discontinuation

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Abstract word count: 140
Total word count: 1380
ABSTRACT

In the present study, we address the issue of the discontinuation of imatinib in chronic myelogenous leukaemia with undetectable residual disease for more than 2 years. Twelve patients were included. The median duration of RTQ-PCR negativity and imatinib therapy were respectively 32 months (24-46) and 45 months (32-56) before imatinib interruption. Six patients displayed a molecular relapse with a detectable BCR-ABL transcript at respectively 1, 1, 2, 3, 4 and 5 months. Imatinib was then re-introduced and led to a novel molecular response in most patients. Six other patients (50%) have still an undetectable level of BCR-ABL transcript after a median follow up of 18 months (9-24). We hypothesize that relapses observed within 6 months reflects the kinetic of undetectable dividing CML cells. Those cells may be eradicated or controlled in long term non relapsing patients described in our study.
INTRODUCTION
The BCR-ABL tyrosine kinase inhibitor imatinib mesylate (Gleevec®) induces complete cytogenetic responses (CCR) in more than 85% of patients with chronic myelogenous leukemia (CML). However, patients in CCR relapse after imatinib interruption in case of detectable residual disease ¹. In fact, less than 10% of patients achieve a molecular remission, defined by an undetectable residual disease using real time quantitative polymerase chain reaction (RTQ-PCR) ². We previously reported the outcome of CML patients in CCR after cessation of interferon-alpha during the pre-imatinib era. Seven (all with a negative PCR) out of 15 patients did not relapse ³. Here, we have discontinued imatinib in CML patients with undetectable residual disease for more than 2 years, under strict monitoring of the reappearance of BCR-ABL transcript, using monthly RTQ-PCR. Relapses, i.e. positivity of RTQ-PCR, were observed early after imatinib discontinuation in 6 patients. Six patients previously exposed to interferon for more than 6 months are still in molecular remission with a median follow up of 18 month (9-24) after imatinib discontinuation.

PATIENTS AND METHODS

Patients
Consecutive patients from the five participating centers with a confirmed diagnosis of CML (Philadelphia (Ph) chromosome positive) were included in this pilot study after informed consent. Inclusion criteria were the following: CCR and undetectable BCR-ABL transcript for more than 2 years under imatinib. All eligible patients were included from March 2004 to July 2005 whether or not they had already been treated before imatinib initiation.

Evaluation and criteria for response
CCR was defined according to standard criteria, i.e. 0 % Ph+ metaphases among at least 25 metaphases in a bone marrow aspirate. Molecular remission was defined by a BCR-
ABL/ABL below of the threshold detection of PCR. The cut-off value for the determination of positivity of PCR was the lowest BCR-ABL plasmid dilution run in parallel, i.e. 4 molecules. The quantification of ABL was also used to check the quality of mRNA and the results were considered reliable when the mean cycle threshold (CT) was below 25.4.

**Study design and treatment**

Imatinib was administered at 400-600 mg/day until molecular remission was reached and then pursued during at least 2 years, with BCR-ABL/ABL ratio measurements every 3 months in blood samples. At the time of imatinib discontinuation, the absence of detection of the BCR-ABL transcript was ultimately confirmed in the second laboratory participating to the study on the same cDNA. Imatinib was then discontinued after informed consent of the patient and BCR-ABL/ABL ratio was monitored by RTQ-PCR monthly during the first 6 months and every 2 months thereafter. Molecular relapse defined as RTQ-PCR positivity was taken into account if confirmed in two successive assessments. In case of molecular relapse, patients were re-treated with imatinib at 400 mg daily.

**Statistical analysis**

Descriptive statistics and Kaplan Meier analysis (to estimate event-free survival (EFS)) were performed using the Statview 5.0 software (SAS Institute, Cary, NC).
RESULTS AND DISCUSSION

Twelve patients were enrolled from March 2004 to July 2005. During the same period of time, the prevalence of patients with an undetectable BCR-ABL transcript was 9.5%. Median age was 70 year-old (42–83) and sex ratio was 0.5. Sokal score at diagnosis was low in 5 patients, intermediate in 5 patients and high in 1 patient. Eleven patients had chronic phase (CP)-CML and 1 patient had accelerated phase (AP)-CML. All patients except 1 had been previously treated before imatinib initiation. Previous therapies comprised interferon in 10/12 patients including 2 patients treated with interferon and cytarabine and 2 patients with autologous hematopoietic stem cell transplantation, 1 after interferon failure and 1 as part as a prospective trial. Median duration of interferon therapy was 33 months (9-152). Median interval from diagnosis to imatinib initiation was 60 months (2-154). Imatinib was started at 400 mg/day in CP-CML and at 600 mg/day in AP-CML. The median interval from imatinib to molecular remission was 10 months (4-16). Imatinib therapy was then maintained during a median of 32 months (24-45), which corresponds to a median of 45 months (32-56) of treatment (Table 1).

After discontinuation, a molecular relapse (without cytogenetic nor hematological relapse) occurred in 6 patients respectively at 1, 1, 2, 3, 4 and 5 months. Imatinib was re-introduced in all 6 patients with a new decline in residual disease. Two of them obtained a second molecular remission after respectively 7 and 8 months of imatinib while the other are still decreasing their BCR-ABL transcript level. Six patients (50%) are in persistent molecular remission after a median follow up of 18 months (9-24) (Table 1).

We then sought factors associated with persistent molecular remission after imatinib discontinuation. No significant difference between relapsing and non-relapsing patients was found (clinical presentation, imatinib therapy, best and last response to interferon), except a trend for a shorter time to BCR-ABL negativity (8.5 months in non relapsing patients versus
11 months in relapsing patients, p=0.05), taking into account the small number of patients. The absence of relapse was also not significantly associated with the length of interferon exposure prior imatinib. However, it is noticeable that most of our patients (10 out of 12) were exposed to interferon alpha before imatinib therapy. This could be explained by a selection bias due to an early access to imatinib for patients after interferon failure and also to a potential long term benefit of interferon exposure (median duration: 30.5 months; 0-152).

Previous experience of patients in molecular remission who stopped imatinib has already been published, but the duration of molecular remission before imatinib discontinuation was shorter than in our study\(^5\). Overall, imatinib was stopped in 9 cases after a median duration of molecular remission of 14 months (0-19) and 6 patients (66 %) relapsed. In our study, the median duration of molecular remission before imatinib interruption was longer (32 months; 24-45) and the relapse rate was lower (50%). In all reported cases including ours, the reintroduction of imatinib was followed by a new molecular response.

In CML patients treated by imatinib and in CCR, it becomes now clear that the molecular response improves over time \(^8\). Thus, we assume that a time-dependent decrease of the residual disease continues to occur even when BCR-ABL transcripts become undetectable by RTQ-PCR, and that the residual disease, although no longer measurable, is lower after 24 months than after 12 months of complete molecular remission. With the assumption that the doubling time of a proliferative CML cell is 8 days, it will take a maximum of 6 months if only one leukemic cell persists and proliferates to reach \(10^7\) cells i.e corresponding to a residual disease detectable by RTQ-PCR \(^9\). This kinetic may be an explanation for the early relapses observed in our study. In the absence of molecular relapse after 6 month, it could be hypothesized that either there is no more residual disease, or that the undetectable residual cells are no longer in a proliferating state.
To conclude, imatinib discontinuation in case of complete molecular response is feasible and does not automatically lead to relapse. As shown in our study, 50% of patients in complete molecular remission for more than 2 years remain in molecular remission after 18 months of follow up. However, we do not widely recommend imatinib discontinuation at the present time. We have initiated a large prospective study to better characterize patients with undetectable BCR-ABL transcript. We aim to assess biological and immunological endpoints before and after imatinib discontinuation. Such studies may lead to therapeutic strategies based on immune modulation in patients with minimal residual disease.
REFERENCES.


Table 1. Patients’ characteristics.

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<th>Patients</th>
<th>Age</th>
<th>Sex</th>
<th>CML phase</th>
<th>Sokal score</th>
<th>Previous therapy</th>
<th>IFN duration (months)</th>
<th>Best response to IFN</th>
<th>Last response at start of IM</th>
<th>IM treatment duration for undetectable BCR-ABL transcripts (months)</th>
<th>IM treatment duration with a negative RTQ-PCR (months)</th>
<th>Reappearance of BCR-ABL transcripts (level*)</th>
<th>Duration of undetectable BCR-ABL transcripts (months)</th>
<th>IM treatment duration after molecular relapse (months) / last RTQ-PCR result</th>
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<td>-</td>
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<td>No Resp</td>
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CML: chronic myelogenous leukemia; CP: chronic phase CML; AP: accelerated phase CML; Sokal score high (H), intermediate (I), low (L); IM: imatinib mesylate; Ara-C: cytarabine; IFN: recombinant interferon alpha; HU: hydroxyurea; AHSCT: autologous hematopoietic stem cell transplantation; PCgR: partial cytogenetic response; mCR: minor cytogenetic response; No Resp: absence of cytogenetic response; * normalized level of BCR-ABL/ABL ratio; undetect: undetectable BCR-ABL transcript; +: last follow-up with undetectable BCR-ABL transcript.
Imatinib mesylate discontinuation in patients with chronic myelogenous leukemia in complete molecular remission for more than two years

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