Brief report

Imatinib mesylate discontinuation in patients with chronic myelogenous leukemia in complete molecular remission for more than 2 years

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In the present study, we address the issue of the discontinuation of imatinib mesylate (Gleevec) in chronic myelogenous leukemia with undetectable residual disease for more than 2 years. Twelve patients were included. The median duration of real-time quantitative–polymerase chain reaction (RTQ-PCR) negativity and imatinib therapy were, respectively, 32 months (range, 24-46 months) and 45 months (range, 32-56 months) before imatinib interruption. Six patients displayed a molecular relapse with a detectable BCR-ABL transcript at 1, 1, 2, 3, 4, and 5 months. Imatinib was then reintroduced and led to a novel molecular response in most patients. Six other patients (50%) still have an undetectable level of BCR-ABL transcript after a median follow-up of 18 months (range, 9-24 months). We hypothesize that relapses observed within 6 months reflect the kinetics of undetectable dividing chronic myelogenous leukemia (CML) cells. Those cells may be eradicated or controlled in long-term nonrelapsing patients, as described in our study. (Blood. 2007;109:58-60)

Introduction

The BCR-ABL tyrosine kinase inhibitor imatinib mesylate (Gleevec) induces complete cytogenetic responses (CCRs) in more than 85% of patients with chronic myelogenous leukemia (CML). However, patients in CCR relapse after imatinib interruption in the case of detectable residual disease.[1] In fact, fewer 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 patients with CML in CCR after cessation of interferon-alpha during the pre-imatinib era. Seven (all with a negative PCR) of 15 patients did not relapse.[3] Here, we discontinued imatinib in patients with CML with undetectable residual disease for longer than 2 years, under strict monitoring of the reappearance of BCR-ABL transcript, using monthly RTQ-PCR. Relapses (ie, 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 months (range, 9-24 months) after imatinib discontinuation.

Patients, materials, and methods

Patients

Consecutive patients from 5 participating centers with a confirmed diagnosis of CML (Philadelphia chromosome positive [Ph^+]) were included in this pilot study after informed consent. Inclusion criteria were CCR and undetectable BCR-ABL transcript for longer 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; that is, 0% Ph^+ metaphases among at least 25 metaphases in a bone marrow aspirate. Molecular remission was defined by a BCR-ABL/ABL below 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 (ie, 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 mg/d to 600 mg/d until molecular remission was reached, and then pursued during at least 2 years, with BCR-ABL/ABL ratio measurements taken 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 in 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 2 successive assessments. In case of molecular relapse, patients were retreated with imatinib at 400 mg daily.

Submitted March 21, 2006; accepted July 6, 2006. Prepublished online as *Blood* First Edition Paper, September 14, 2006; DOI 10.1182/blood-2006-03-011239.

The online version of this article contains a data supplement.

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Table 1. Patient characteristics

Pt no.	Age, y	Sex	CML phase	Sokal score	Previous therapy	IFN duration, mo	Best response to IFN	Last response at start of IM	IM treatment duration for undetectable BCR-ABL transcripts, mo	IM treatment duration with a negative RTQ-PCR, mo	Reappearance of BCR-ABL transcripts (level, %*)	Duration of undetectable BCR-ABL transcripts, mo	IM treatment duration after molecular relapse, mo/last RTQ-PCR result, %
1	42	F	CP	L	IM + Ara-C	0	—	No Resp	10	26	Yes (0.02)	3	7/undetec
2	54	M	CP	L	IM + Ara-C	0	—	No Resp	17	30	Yes (0.3)	2	4/0.015
3	75	F	CP	H	HU + IFN	9	No Resp	No Resp	11	45	Yes (0.015)	1	9/0.001
4	83	F	CP	I	HU + IFN	29	No Resp	No Resp	11	45	Yes (0.01)	2	6/0.002
5	73	M	AP	—	IFN	63	mCR	mCR	14	42	Yes (0.002)	1	8/undetec
6	58	F	CP	L	IFN	71	CCR	No Resp	5	27	Yes (0.03)	5	1/0.03
7	76	M	CP	I	IFN + Ara-C	29	mCR	No Resp	14	32	No	22†	—
8	68	M	CP	I	IFN	29	CCR	No Resp	4	44	No	9†	—
9	58	F	CP	I	IFN + Ara-C and AHSCT	32	mCR	No Resp	16	24	No	24†	—
10	71	M	CP	L	HU + IFN and AHSCT	33	CCR	PCgR	11	34	No	21†	—
11	66	F	CP	L	IFN	67	CCR	PCgR	5	32	No	15†	—
12	78	M	CP	I	IFN	152	CCR	No Resp	6	32	No	9†	—

Pt indicates patient; CML, chronic myelogenous leukemia; IFN, recombinant interferon alpha; IM, imatinib mesylate; CP, chronic-phase CML; L, low Sokal score; Ara-C, cytarabine; —, not applicable; No Resp, absence of cytogenetic response; undetec, undetectable BCR-ABL transcript; H, high Sokal score; HU, hydroxyurea; I, intermediate Sokal score; AP, accelerated-phase CML; mCR, minor cytogenetic response; CCR, complete cytogenetic response; AHSCT, autologous hematopoietic stem cell transplantation; PCgR, partial cytogenetic response.

*Normalized level of BCR-ABL/ABL ratio.

†Last follow-up with undetectable BCR-ABL transcript.

Statistical analysis

Descriptive statistics and Kaplan-Meier analysis (to estimate event-free survival [EFS]) were performed using 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 years (range, 42-83 years) 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 treated before imatinib initiation. Previous therapies comprised interferon in 10 of 12 patients, including 2 patients treated with interferon and cytarabine, and autologous hematopoietic stem cell transplantation in 2 patients, 1 after interferon failure and 1 as part of a prospective trial. Median duration of interferon therapy was 33 months (range, 9-152 months). Median interval from diagnosis to imatinib initiation was 60 months (range, 2-154 months). Imatinib was started at 400 mg/d in CP-CML and at 600 mg/d in AP-CML. The median interval from imatinib to molecular remission was 10 months (range, 4-16 months). Imatinib therapy was then maintained during a median of 32 months (range, 24-45 months), which corresponds to a median of 45 months (range, 32-56 months) of treatment (Table 1).

After discontinuation, a molecular relapse (without cytogenetic or hematologic relapse) occurred in 6 patients at 1, 1, 2, 3, 4, and 5 months. Imatinib was reintroduced in all 6 patients with a new decline in residual disease. Two of those patients obtained a second molecular remission after 7 and 8 months of imatinib, respectively, while the others are still decreasing their BCR-ABL transcript levels. Six patients (50%) are in persistent molecular remission after a median follow-up of 18 months (range, 9-24 months; Table 1).

We then sought factors associated with persistent molecular remission after imatinib discontinuation. No significant difference between relapsing and nonrelapsing 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 nonrelapsing patients versus 11 months in relapsing patients, $P = .05$), taking into account the small number of patients. The absence of relapse was also not significantly associated with the length of interferon exposure prior to imatinib. However, it is noticeable that most of our patients (10 of 12) were exposed to interferon alpha before imatinib therapy. This could be explained by a selection bias due to early access to imatinib for patients experiencing interferon failure and also to a potential long-term benefit of interferon exposure (median duration, 30.5 months; range, 0-152 months).

The 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 that in our study.[5-7] Overall, imatinib was stopped in 9 cases after a median duration of molecular remission of 14 months (range, 0-19 months), and 6 patients (66%) relapsed. In our study, the median duration of molecular remission before imatinib interruption was longer (32 months; range, 24-45 months) and the relapse rate was lower (50%). In all reported cases including those in our study, the reintroduction of imatinib was followed by a new molecular response.

In patients with CML treated by imatinib and in CCR, it is 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 (ie, 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 months, 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 biologic and immunologic endpoints before and after imatinib discontinuation. Such studies may lead to therapeutic strategies based on immune modulation in patients with minimal residual disease.

Authorship

Contribution: F.-X.M. and P.R. collaborated in the conception and design of the study, and performed data analysis. F.H., D.R., L.L., G.M., E.G., J.R., M.G., F.-X.M., and P.R. followed the patients. J.M.C., O.M., O.B., and F.-X.M. performed molecular investigations. P.R., D.R., and F.-X.M. wrote the article.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

A complete list of the participating members of the Intergroupe Français des Leucémies Myéloïdes Chronique appears as a data supplement to the online version of this article.

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2007 109: 58-60
doi:10.1182/blood-2006-03-011239 originally published online September 14, 2006

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Blood (print ISSN 0006-4971, online ISSN 1528-0020), is published weekly by the American Society of Hematology, 2021 L St, NW, Suite 900, Washington DC 20036.