Discontinuation of imatinib in Japanese patients with chronic myeloid leukemia

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ABSTRACT

It was recently recognized that some chronic myeloid leukemia patients with a complete molecular response could sustain that response after discontinuation of imatinib. To characterize the clinical outcomes and profiles of chronic phase chronic myeloid leukemia patients who could discontinue imatinib, we conducted a nationwide survey in Japan. Among 3,242 imatinib-treated chronic myeloid leukemia patients, we identified 50 who had discontinued imatinib for at least six months; of these we analyzed 43. Molecular recurrence was detected in 19 patients, and a complete molecular response rate was estimated to be 47% following imatinib discontinuation. Based on multivariate regression analysis, imatinib dose intensity and prior interferon-α administration were independently predictive of molecular recurrence within 12 months. The depth of the molecular response should be a factor influencing long-term sustained complete molecular response after discontinuation of imatinib. Additionally, an immunological mechanism modified by interferon-α might control chronic myeloid leukemia stem cells.

Key words: chronic myeloid leukemia, molecular recurrence, imatinib, discontinuation.

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Introduction

Imatinib treatment dramatically improves survival in chronic myeloid leukemia (CML) patients and has made imatinib the standard-of-care for chronic phase CML. But whether the effects of imatinib can be considered a cure remains controversial. This may be because primitive, quiescent, Philadelphia-positive stem cells from patients with CML are insensitive to imatinib *in vitro*,[1] and residual BCR/ABL$^+$ hematopoietic progenitors are present in patients who achieve a complete cytogenetic response (CCyR) with imatinib.[2] Recently, it was recognized that some patients with a complete molecular response (CMR) are able to sustain this response after discontinuation of imatinib.[3] In a non-randomized prospective study, Mahon *et al.* reported that among patients with a CMR lasting at least two years, the CMR was sustained in 41% after discontinuation of imatinib. However, this strategy requires further validation and much longer follow up. At present, there appear to be no patients or disease characteristics that identify in advance those who can safely discontinue imatinib. Consequently, a cure has not yet been proven and life-long therapy with imatinib is still the consensus recommendation.[4] Discontinuing imatinib in CML should only be considered in a clinical trial with strict molecular monitoring.[3,5]

Nevertheless, the literature contains several case reports of CML patients in whom imatinib had to be discontinued for various reasons.[6-13] Some of these patients had molecular relapsed but others did not. This raises the question as to how deep does the molecular response to imatinib treatment need to be and how long must imatinib treatment be continued after achieving CMR before the drug can be safely discontinued. There has been no regional retrospective survey of the clinical outcomes of CML patients after discontinuation of imatinib.

To characterize the clinical outcomes and profiles of CML patients who have been off imatinib therapy for at least six months, we conducted a nationwide survey of CML patients in Japan.

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Design and Methods

Data collection

We first sent questionnaires to 780 hematologists in the Japanese Society of Hematology requesting information on the number of CML patients treated with imatinib between 2001 and 2010, and the number of patients who had been off therapy for at least six months due to any cause, except disease progression, transplantation or death. As dictated by the inclusion criteria, patients who relapsed and restarted imatinib within six months of its discontinuation were not included in the number of patients who had been off therapy. From among those contacted, 181 hematologists (23%) responded to the first questionnaire yielding a total of 3,242 CML patients who had been treated with imatinib. This is about one-third of Japanese CML patients. Among them, 50 patients (1.5%) were identified who discontinued imatinib therapy for at least six months. We then sent second questionnaires to the hematologists who treated those 50 patients, asking for information on the clinical features, treatments and clinical outcome in each patient. Forty-three CML patients were analyzed in this retrospective study. The other 7 patients among the 50 identified in the first questionnaire were not included because the hematologist either did not respond to the second questionnaire, the response was incomplete, or CMR was not confirmed at the time of imatinib cessation. All patients gave written informed consent in accordance with the Declaration of Helsinki, and this study was approved by the Akita University Research Ethics Board and Tokyo Medical University Research Ethics Board.

Molecular response

In general practice, the molecular response was assessed at least every three months. A major molecular response (MMR) was defined as a 3-log reduction in the BCR-ABL transcript (international scale <0.1%), and a complete molecular response (CMR) was defined as detection of no BCR-ABL transcript in a real-time quantitative-polymerase chain reaction (RQ-PCR) assay (n=24), nested reverse transcriptase-polymerase chain reaction (RT-PCR) assay (n=14), or a highly sensitive transcription-mediated amplification (TMA) method[14] (n=5). These PCR methods can detect at least a 4-log reduction in the BCR-ABL transcript (international scale <0.01%).

Statistical analysis

Statistical analyses were carried out using SPSS statistical software (SPSS Japan Inc., Tokyo, Japan, version 17.0). Non-parametric values or numbers were compared between two groups using the Mann-Whitney test, the χ^2 test or Fisher's exact test. Time to molecular relapse was measured from the date of imatinib discontinuation to the date of molecular recurrence, or the date of last molecular examination for patients who did not relapse. Relapse-free survival was estimated using the Kaplan-Meier method. Survival rate was compared between two groups using the log rank test. Stepwise forward selection multiple logistic analysis for molecular recurrence by 12 months was performed to determine the effect of the variables examined in a univariate analysis. $P<0.05$ was considered significant.

Results and Discussion

This is the first survey of outcomes after imatinib discontinuation in Japan. The survey is estimated to cover about one-third of Japanese CML patients. One question we asked was how many patients are able to sustain CMR after imatinib discontinuation. Only 50 patients (1.5%) who had discontinued imatinib therapy for at least six months were identified, and 43 patients were analyzed in this retrospective study. The median age at diagnosis of CML was 57 years (range 18-80). The male:female ratio was 19:24. All patients were in chronic phase, with no history of progression to the accelerated phase or blast crisis (AP/BC), and all had achieved CMR before imatinib discontinuation. Based on their Sokal scores, 25 patients were classified as low risk, 15 patients as intermediate risk, and 3 patients as high risk. The reasons for which imatinib was discontinued were adverse events (n=18), patient's request due to cost (n=14), patient's desire to become pregnant (n=3), and long undetectable residual disease (n=8). In this study, the male:female ratio was the inversion of that commonly observed. This might indicate that women are more likely than men to want to stop imatinib because of some adverse event (e.g. facial edema, skin rash), and could also reflect their desire to become pregnant.

Seventy-two percent of patients were treated with the standard or a higher dose of imatinib (<400 mg, n=12; 400 mg, n=22; >400 mg, n=9; median daily dose 400 mg; range 100-700 mg). The median duration of imatinib treatment was 45.2 months (range 4.5-92.7 months) and the estimated median total dose of imatinib was calculated to be 541 g (range 53.6-1,112.8 g). Twenty-five patients (58%) had prior IFN-α treatment, and 12 (28%) received IFN-α in combination with imatinib. Among the patients who received combination therapy, 8 had also received prior IFN-α treatment. However, no patients received maintenance therapy with IFN-α after cessation of imatinib. The median duration of imatinib treatment needed to achieve CMR was 12.6 months (range 2.0-83.3 months). The median duration of CMR before cessation was 27.4 months (range 0.9-79.6 months). The median period of cessation was 22.4 months (range 6.2-97.9 months).

Molecular recurrence was detected in 19 patients (44%); it was not associated with cytogenetic relapse in any patient. Among them, TKI treatment was restarted in 17 patients who all then recovered to CMR (13 patients) or MMR (4 patients). The remaining 2 patients had shown sustained MMR (<0.1%) for 98 months or near MMR (0.175%) for 24 months, respectively, with no therapy. No progression to AP/BC was seen after restarting TKI treatment, and all patients are still alive. The relapse-free survival (RFS) rate at five years was estimated to be 47% while median RFS was determined to be 41 months using the Kaplan-Meier method. Twenty-four patients among the 43 (56%) analyzed also showed sustained CMR without a molecular recurrence after discontinuation. Although the sample size was small, it seems clear that imatinib treatment could be stopped in some patients.

We also asked, what is the profile of patients who can sustain CMR without a molecular recurrence after discontinuation of imatinib, and how long after achieving CMR should imatinib treatment be continued before attempting cessation? Comparison of patients who did and did not show molecular recurrence within 12 months after stopping imatinib therapy revealed several significant differences between them (Table 1). First, the median duration of imatinib therapy before cessation was 51.7 months in patients without molecular recurrence, which is significantly (P=0.0228) longer than the 26.3 months of

therapy received by patients with molecular recurrence. Second, the estimated dose of imatinib before cessation was 576.8 g in patients without molecular recurrence, which is significantly (P=0.0042) greater than the 275.4 g in patients with molecular recurrence. Third, IFN-α was administered prior to cessation significantly (P=0.0102) more frequently in patients without molecular recurrence within 12 months. On the other hand, no significant differences were found with respect to age, sex, Sokal risk, imatinib daily dose, combination with IFN-α, or time to CMR. In the STIM study, the probability of a sustained CMR at 12 months differed between Sokal risk groups (P=0.008).[3] In our study, a molecular recurrence by 12 months occurred in only one of 3 patients in the high risk group, 7 of 13 patients in the intermediate risk group, and 6 of 24 patients in the low risk group. Because of the sample size in this study, the effect of the Sokal score was not significant (P=0.2135).

Importantly, the median duration of CMR before cessation was 32.5 months in patients without molecular recurrence, which was significantly (P=0.0025) longer than the 6.0 months in patients with molecular recurrence. Furthermore, there was a significant difference in the estimated RFS rates following discontinuation between patients in whom CMR was sustained for more than 24 months prior to imatinib discontinuation and those sustaining a CMR for less than 24 months (78% *vs.* 15%, P=0.0002 by log rank test, Figure 1). The duration of CMR was one of the eligibility criteria for the STIM trial.[3] Because patients who relapsed and restarted imatinib within six months after its discontinuation were not included in this study, as dictated by the inclusion criteria, we are able to show that the estimated RFS rates at five years were much higher (78%) among patients who sustained a CMR for more than 24 months before cessation of therapy in this series than in the STIM study. However, in a multivariate regression analysis, only imatinib dose intensity and prior IFN-α administration were independently predictive of a molecular recurrence within 12 months (Table 2). The identified prediction formula was: Y= -0.0061 × dose intensity of imatinib (g) -3.17171 × prior IFN-α (Yes=1/No=0) + 4.0124. If 1/(1+exp(-1 × Y)) was more than 0.5, a molecular recurrence was predicted; the total accuracy rate of this formula was 82.5%.

In our series, although 56% of patients showed a sustained CMR after discontinuation of imatinib, some molecular recurrences occurred much later after cessation. The longest period between cessation and recurrence was 42 months, which suggests that there was a residual CML stem cell that was induced to begin cycling.

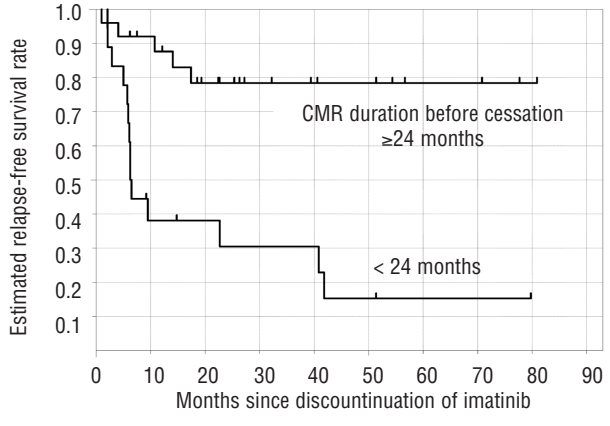

Figure 1. Relapse-free survival (RFS) plotted against CMR duration. The estimated RFS rates at five years were 78% and 15% among patients who did and did not sustain a CMR for more than 24 months before cessation of therapy (P=0.0002, log rank test).

Table 2. Multivariate regression analysis: factors predictive of a molecular recurrence within 12 months.

	Estimate	SE	P	OR (95% CI)
Imatinib dose intensity (g)	-0.0061	0.0021	0.0035	0.9940 (0.9899-0.9980)
Prior IFN-α (Yes=1/No=0)	-3.1717	1.1551	0.0060	0.0419 (0.0044-0.4035)
Intercept	4.0124	1.4810	0.0067	

SE: standard error; OR: odds ratio; CI: confidence interval.

Table 1. Patients' characteristics as related to molecular recurrence within 12 months after discontinuation of imatinib therapy.

Molecular recurrence by 12 months	Yes (14)	No (26)*	P value
Age (y.o)	61.0 (56.3-65.4)	46.6 (34.5-67.6)	0.1164
Sex (male/female)	7/7	11/15	0.6409
Sokal risk (low/intermediate/high)	6/7/1	18/6/2	0.2135
Imatinib daily dose (mg)	400 (300-400)	400 (300-500)	0.2543
≥400/<400 (yes/no)	9/5	19/7	0.4089
Duration of imatinib therapy (months)	26.3 (13.3-63.9)	51.7 (31.0-70.6)	0.0228
Imatinib dose intensity (g)	275.4 (159.2-541.5)	576.8 (364.0-846.8)	0.0042
Prior IFN-α (yes/no)	5/9	20/6	0.0102
Combination IFN-α (Yes/no)	2/12	10/16	0.1076
Time to achieve CMR (months)	11.5 (6.4-17.3)	13.1 (7.4-33.8)	0.4852
CMR duration before cessation (months)	6.0 (2.0-19.3)	32.5 (24.6-39.7)	0.0025
PCR method (RQ-PCR/nested PCR/TMA)	6/7/1	17/5/4	0.1234

** Three patients without a molecular recurrence were excluded from this group because the duration of cessation was less than 12 months. Data are medians (quartile 1- quartile 3) or number. Non-parametric values were compared between two groups using the Mann-Whitney test. CMR: complete molecular response.*

The depth of the molecular response should be one of the factors influencing long-term sustained CMR, but other factors, for example an immunological mechanism that could be modified by IFN-α, might eradicate CML stem cells in a quiescent state. Interestingly, 2 patients in the present study experienced molecular recurrence after sustaining MMR or near MMR for an extended period with no therapy. This finding is consistent with the notion that other factors might control CML stem cells. As suggested by Hochhaus *et al.*, induction of a proteinase-3-specific cytotoxic T-cell response by IFN-α may contribute to sustained remissions.[15]

Although it is still a small subset of CML patients, our data also suggest that imatinib could achieve a clinical 'cure'.

Authorship and Disclosures

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