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Achievement of complete molecular response by the switch from imatinib to dasatinib in a patient with chronic myeloid leukemia in chronic phase

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Abstract

The prognosis of chronic myeloid leukemia (CML) in chronic phase (CP) have been greatly improved by a tyrosine kinase inhibitor (TKI), imatinib. However, some patients show resistance or intolerance to imatinib. For such patients, more potent 2nd generation TKIs, nilotinib and dasatinib, were developed, and have been shown to be effective for imatinib resistant/intolerant cases. We here report a case with CML-CP, who had been treated with interferon (IFN) and hydroxycarbamide (HU) since 1999. Although complete hematologic response was achieved by IFN+HU, any cytogenetic response was not obtained. So, we changed IFN+HU to imatinib from 2002. She achieved complete cytogenetic response and major molecular response at 18 and 44 months from the start of imatinib, respectively. However, minimum residual disease (MRD) was still detected by the nested PCR at 94 months. In addition, she complained of side effects of imatinib, general fatigue and muscle clumps. So, we changed imatinib to dasatinib. Without any side effect of dasatinib, MRD became undetectable twelve months after the switch to dasatinib. This case suggests that the switch from imatinib to 2nd TKI would be a useful option for CML-CP patients with MRD and/or side effects in terms of both efficacy and quality of life.

Key words: chronic myeloid leukemia, 2nd-generation TKI, imatinib, dasatinib

Introduction

The treatment outcomes of chronic myeloid leukemia (CML) in chronic phase (CP) have been greatly improved by the advent of tyrosine kinase inhibitor (TKI), imatinib. In the IRIS trial, where the clinical efficacy of imatinib was prospectively and randomly compared with that of the conventional treatment, interferon-α (IFNα)+cytarabine (Ara-C) in 1,106 *de novo* CML-CP cases, imatinib showed more clinical efficacy in both cytogenetic and molecular effects than IFNα+Ara-C.[1] In the long-term follow-up, the 7-year overall survival (OS) rate was 86% and the rate of CML-related death was only 7% in the imatinib arm.[2] In addition, imatinib showed similar long-term efficacy in several other clinical trials and daily practice: OS rates at 5 years are 97% in the PETHMA study (n=210), 90% in the GIMEMA study (n=559), 88% in the German CML study IV (n=1551), and 83% in the Hammersmith Hospital.[3–6] However, after the long-term follow-up of the IRIS trial, 32% of patients in the imatinib arm showed resistance to imatinib and about 5% of the patients couldn't continue imatinib due to the side effects such as rash, liver toxicities, and edemas (judged as intolerance to imatinib).[2]

The 2nd generation TKIs (2nd TKIs), nilotinib and dasatinib, have been developed to treat

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CML-CP patients resistant and/or intolerant to imatinib as described above. These 2nd TKIs are more potent inhibitors of *BCR-ABL* than imatinib (inhibitory activities against *BCR-ABL in vitro*: nilotinib 20-30 fold; dasatinib 325 fold compared with imatinib).[7,8] Especially, they can overcome a variety of point mutations of the *BCR-ABL* gene, which are observed in 50-70% of secondary imatinib-resistant cases, whereas they are both ineffective for the gatekeeper mutation, T315I.[9,10] In accord with *in vitro* data, both 2nd TKIs have been shown to be effective for imatinib-resistant cases.[7,8] Also, as their non-hematologic side effects are rather different from those of imatinib, they can be safely given to most of patients intolerant to imatinib.[7,8] From these results, both 2nd TKIs were initially approved for CML patients resistant and/or intolerant to imatinib as 2nd line drugs. In addition, prospective randomized trials, DASISION and ENESTnd, in which the efficacy and safety of nilotinib and dasatinib were compared with imatinib in *de novo* CML-CP cases, respectively, demonstrated that both 2nd TKIs were more effective than imatinib in achieving complete cytogenetic response (CCyR) and major molecular response (MMR) (each definition is shown in Figure 1).[11,12] Based on these results, both TKIs were subsequently approved for de novo CML-CP cases as 1st line drugs.

Several risk stratifications for CML-CP patients, such as Sokal, Hasford, and EUTOS scores, have been utilized at diagnosis.[13−15] However, after we start to treat CML-CP patients with TKI, the most important factor to prevent disease progression is clinical responses to TKI. By analyzing the relationship between the clinical responses and the prognosis, European LeukemiaNet (ELN) has published the recommendation when and how we should evaluate and interpret clinical responses to imatinib.[16] So, when we treat *de novo* CML-CP patients with standard dose of imatinib (400 mg, daily), we utilize these criteria and determine the following treatment according to the responses obtained at each time point after the start of imatinib (as shown in Figure 1).

We here report a case of CML-CP, who achieved CCyR at 18 months and MMR at 44 months as a late responder to imatinib. However, minimum residual disease (MRD) was still detected by the nested PCR even after 94-month treatment with imatinib. Because she had been

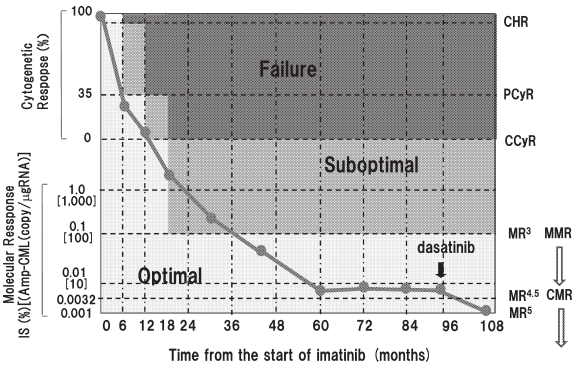

Fig. 1 Clinical course of the patient from the start of the imatinib. Hematologic responses are evaluated by the findings of the peripheral blood (PB) and clinical manifestation, cytogenetic responses by G-banding technique or FISH on the bone marrow (BM) cells, and molecular responses by RQ-PCR analysis or Amp-CML method.
Complete hematologic response (CHR): normalization of the PB findings and no extramedullary involvement; Partial cytogenetic response (PCyR): Ph+ cells ≦35% in the BM; Complete cytogenetic response (CCyR): Ph+ cells 0% in the BM; Major molecular response (MMR): BCR-ABL mRNA≦0.1% by the international scale (IS) or 100 copy/μgRNA by the Amp-CML method indicated in the parenthesis; Complete molecular response (CMR): BCR-ABL mRNA undetectable by highly sensitive RQ-PCR analysis, that is, BCR-ABL mRNA<0.0032% IS, which can't be evaluated by the Amp-CML method due to the lack of the internal control. Our nested PCR method can detect BCR-ABL mRNA 0.001% IS.

suffered from side effects of imatinib, we changed imatinib to dasatinib. As a result, MRD bacame undetectable twelve months after the switch to dasatinib without an apparent side effect of dasatinib. This case suggests that the switch from imatinib to 2nd TKI would be a useful option for CML-CP patients with MRD and/or side effects in terms of both efficacy and quality of life.

Case report

A 36-year-old woman was referred to our hospital because of leukocytosis found by chance in August 1999. She was free from clinical symptom and the physical findings were unremarkable. However, splenomegaly was detected by the abdominal ultrasound examination. The peripheral blood data were as follows: RBC $411\times10^4/\mu l$; hemoglobin (Hb) 10.7 g/dl (normal: 13.9-17.0); WBC 43,500/μl

(normal : 3,900-9,300) (Blast $<1\%$, Promyelo $<1\%$, Myelo 5%, Metamyelo 4%, Stab 3%, Seg 59%, Eosino 5%, Baso 15%, Mono 1%, Lym. 8%) with a neutrophil alkaline phosphatase (NAP) score 78 (normal : 167-367) ; Platelet (Plt) $98.3\times10^4/\mu$l (normal : 16.7-36.2$\times10^4$) (Table 1). The blood biochemistry data were almost normal excepting elevated LDH (450 IU/l : normal : 176-353). Bone marrow (BM) was hypercellular with a nucleated cells count (NCC) $60\times10^4/\mu$l (normal : 10-25$\times10^4$), which was mostly composed of maturating granulocytic cells with 3.2% myeloblast. Also, the number of megakaryocyte increased to 178/μl (normal : 30-90). Philadelphia (Ph) chromosome was detected by the G-banding chromosomal analysis in 20 out of 20 BM cells. Also, *BCR-ABL* fusion gene was detected in 73.1% of the analyzed cells by the FISH (fluorescent in situ hybridization) analysis. Based on these findings, we diagnosed this patient as having CML-CP with the intermediate risk by Sokal, and with the low risk by Hasford risk classifications. Interferon (IFN) therapy was started in August of the same year, and hematologic remission was achieved after one month. However, the leukocyte count subsequently increased. So, we controlled the leucocyte count by adding the oral anticancer agent hydroxyurea (HU) thereafter. However, any cytogenetic response was not achieved by IFN+HU. After imatinib was approved by the Japanese National Health Insurance, we switched IFN+HU to imatinib (400 mg, daily) from January 12, 2002. As shown in Fig. 1, partial cytogenetic response (PCyR) was achieved at 6 months from the start of imatinib. CCyR was not achieved at 12 months but was achieved at 18 months. However, MMR was not achieved at 18 months. So, this patient was classified as suboptimal response at 12 and 18 months by the ELN2009 criteria,[16] whereas it was originally made for *de novo* CML-CP patients treated with imatinib 400 mg, daily. Because this patient complained of several side effects of imatinib such as general fatigue and muscle clumps, we couldn't increase the dose of imatinib. Also, at that time, 2nd TKIs were not available. So, we continued imatinib 400 mg, daily, thereafter. Consequently, this patient achieved MMR at 44 months by the evaluation of the Amp-CML method (<100 copy/μgRNA). Also, minimum residual disease (MRD) became undetectable by the Amp-CML method, which can detect roughly 0.01% *BCR-ABL* mRNA by the international scale (IS), in the following period. However, MRD was still detected from the BM aspirate by the nested PCR even at 94 months, which is a more sensitive method than Amp-CML with the sensibility of 0.001% IS BCR-ABL mRNA conducted by the commercial laboratory, SRL INC (Tokyo, Japan). Around that time, 2nd TKIs were approved for CML cases resistant and/or intolerant to imatinib. Although it is not recommended to change imatinib to the 2nd TKI for the patients who already achieved MMR in daily practice, this patient desired to change imatinib to 2nd TKI due to the side effects as described above. So, we changed imatinib to dasatinib (100 mg, daily) in 2009. Then, the side effects of imatinib promptly dissolved, and an apparent side effect of dasatinib hasn't been observed. Twelve months after the switch to dasatinib, the nested PCR on the BM aspirate became negative, indicating the achievement of CMR.

Table 1 Laboratory findings on Aug 2 1999

WBC	43,500/μl	RBC	$411\times10^4/\mu$l	UA	5.2 mg/dl
Stab	3.0%	Hb	10.7 g/dl	Cre	0.5 mg/dl
Seg	59.0%	Ht	33.5%	T-cho	181 mg/dl
Lymph	8.0%	Plt	$98.3\times10^4/\mu$l	TG	84 mg/dl
Mono	1.0%	TP	7.7 g/dl	Na	142 mEq/l
Eosino	5.0%	Alb	4.8 g/dl	Cl	101 mEq/l
Baso	15.0%	T-Bil	0.6 mg/dl	K	4.6 mEq/l
Meta	4.0%	ALP	118 IU/l	Ca	9.1 mg/dl
Myelo	5.0%	GOT	22 IU/l	CRP	0.1 mg/dl
Pro	$<1\%$	GPT	9 IU/l	Bone marrow findings	
Blast	$<1\%$	LDH	450 IU/l	NCC	$60.0\times10^4/\mu$l
Erythroblast	$<1\%$	AMY	68 IU/l	MgK	780/μl
NAP score	78	BUN	12 mg/dl	46, XX, t(9 ; 22)(q34 ; q11)	20/20

Discussion

The prognosis of the CML patients who progressed to accelerated phase (AP) and blastic crisis (BP) is poor. So, the most important point in the treatment of CML-CP is to prevent disease progression. Several risk factors that can predict disease progression have been identified. So, the risk stratification is totally performed at diagnosis by Sokal, Hasford, or EUTOS score each including these prognostic parameters.[13−15] However, the long-term follow-up data of the IRIS trial demonstrated that the most critical prognostic factor under the treatment with TKI is the clinical responses to TKI.[1,2] So, ELN published the recommendation to evaluate and interpret the clinical efficacy of imatinib in *de novo* CML-CP patients treated with imatinib 400 mg, daily in 2006, which was revised in 2009 and 2013.[16,17] According to the ELN2009 recommendation, the clinical responses to imatinib are evaluated by hematologic, cytogenetic and/or molecular analyses at 3, 6, 12, and 18 months, respectively, of which results are categorized into the following three criteria : "Optimal Response", "Suboptimal Response" and "Failure" (Figure 1). As the prognosis of "Optimal Response" is quite good[1,2], it is recommended to continue imatinib at the same dose. In contrast, the prognosis of "Failure" is poor, even if we continue imatinib at the same dose.[18] So, it is necessary to change the therapy. As the next therapeutic choice for patients categorized in "Failure", the switch to the 2nd TKI is recommended rather than high dose imatinib. Also, as far as the patients remain in CP without T315I mutation, there is no indication of allogeneic hematopoietic stem cell transplantation. Meanwhile, "Suboptimal Response" means that it may be possible to obtain benefit from continuing imatinib therapy at the same dose, but it may not be applicable to a substantial proportion of the patients.[18,19] As for the causes of "Suboptimal Response", pharmacological problems are more common than *BCR-ABL* point mutations, such as a low trough concentration of imatinib. In fact, mean trough imatinib plasma levels were significantly higher in patients with CCyR than in those without (1123 ± 617 ng/ml *vs*. 694 ± 556 ng/ml, $p=0.0312$).[20] Also, they were higher in patients with MMR than in those without (1452 ± 649 ng/ml *vs*. 869 ± 427 ng/ml, $p<0.001$).[20] In addition to trough levels, a low intracellular imatinib concentration due to the low OCT-1 activity, which acts in the uptake of imatinib into the cells, was reported to cause "Suboptimal Respnse".[21] Nonetheless, because the prognosis of the patients with "Suboptimal Response" varies among the cases,[18,19] ELN2009 recommended that we can choose any of the following therapeutic options according to the patient's situation : the continuance of the current imatinib treatment, imatinib dose escalation, and the switch to 2nd TKI.[16]

In the IRIS trial, the progression-free survival (PFS) rate at 5 years showed a tendency to be better in patients who achieved CCyR at 12 months from the start of imatinib than in those who achieved only PCyR, whereas there wasn't a statistically significant difference between the two groups (PFS rate at 5 years : 97% in patients with CCyR *vs*. 93% in those with only PCyR, $p=0.20$).[1] So, in the ELN2009 recommendation, the optimal timing of the achievement of CCyR was set at 12 months.[16] At 12 months, our patient achieved PCyR but not CCyR, which was judged as "Suboptimal Response". Among the patients assigned to the imatinib arm in the IRIS trial, CCyR was achieved in 69% at 12 months and in 87% at 60 months.1 These results indicate that roughly 50-60% (18% out of 31%) of the patients who didn't achieve CCyR at 12 months would subsequently achieve CCyR as observed in our case. However, it should be kept in mind that the remaining patients would not achieve CCyR, even if they continued imatinib at the same dose, falling into "Failure" from after 18 months. The PFS rate at 5 years of such patients is significantly poor compared with those who achieved CCyR by 18 months (PFS at 5 years : 87% in patients without CCyR *vs*. 98-100% in patients with CCyR, $p<0.001$).[1]

As for the molecular responses, the 7-year follow-up data of the IRIS trial suggested that event-free survival (EFS) rate (the definition of events were disease progression, loss of CCyR, and death) was better in patients who achieved MMR at 18 months compared with those who failed (EFS rate at 7 years : 94.9% in patients with MMR *vs*. 86.4% in patients with CCyR but not without MMR, $p<0.01$).[2] Based on this result, the optimal timing of the achievement of MMR was set at no later than 18 months after the start of imatinib in the ELN2009 recommendation.[16] However, there are some reports suggesting that the achievement of CCyR but not of

MMR was sufficient to prevent disease progression.[22–24] In our case, CCyR but not MMR was achieved at 18 months, which was again judged as "Suboptimal Response". For "Suboptimal response" at 12 and 18 months, we couldn't increase the dose of imatinib due to its side effects. Furthermore, 2nd TKI was not available at that time. So, we continued imatinib at the same dose, and she could achieve MMR at 44 months. However, several recent studies suggest that the achievement of early and deep molecular responses would improve the prognosis of CML-CP patients.[25–27] Based on these results, recently published ELN2013 recommendation revised the response criteria to fasten the molecular response.[17] For example, the optimal timing of the achievement of MMR was changed from 18 months to 12 months. From these revised concepts, if we treat this patient now, it would be better to change imatinib to 2nd TKI at 12 or 18 months.

Landmark analysis of the IRIS trial showed that the PFS rate at 7 years was 100% in the patients who achieved MMR within 18 months.[2] Also, in the other study, landmark analyses at 18- and 24-month showed that patients achieving CMR have no advantage in PFS and OS compared to those achieving MMR.[28] These results suggest that MMR but not CMR within 18 or 24 months is sufficient to prevent disease progression. However, it was also reported that about 10% of the patients who achieved MMR but without CMR consequently lost MMR in the long-term follow up.[29] Furthermore, the other report emphasized the importance of CMR rather than MMR. In this report, the PFS rate at 7 years was 96% in the patients with CMR, while it was 86% in those with MMR but without CMR ($p=0.01$).[30] Also, when we consider the discontinuation of TKI, the achievement of CMR and its maintenance for a certain period are prerequisite to keep treatment-free remission (TFR),[31] which means no recurrence after the discontinuation of TKI in spite of the persistence of CML stem cells. However, at present, the survival benefit of CMR over MMR is not certain. So, it is not recommended by the ELN2009 recommendation to change the therapy in daily practice if the patients achieved and maintained MMR.[16] However, a recent randomized ENESTcmr trial showed that the switch to nilotinib was more effective in achieving CMR (undetectable MRD, less than 0.032% IS in this trial) than the continuance of imatinib in patients who couldn't achieve CMR despite the over 2-year imatinib treatment (CMR rate at 12 months : switch to nilotinib 20.8% *vs*. imatinib continuance 10.0%, $p=0.0387$; CMR rate at 24 months : switch to nilotinib 31.7% *vs*. imatinib continuance 17.0%, $p=0.0106$).[32] Also, the ENRICH study showed that QOL was greatly improved by switching to nilotinib in the patients who had mild (Grade 1/2) side effects on imatinib.[33] In addition, molecular responses were apparently improved by the switch to nilotinib in most of the patients in this study. Furthermore, it was noted that only about 10% of the patients show the intolerance to 2nd TKI and couldn't continue it in the ENESTcmr and ENRICH trials. Our patient couldn't achieve CMR regardless of the 94-month imatinib treatment. Because imatinib treatment was accompanied by general fatigue and muscle clumps with Grade 1/2, we changed imatinib to dasatinib after informed consent was given. As a result, she was relieved from side effects of imatinib and no new side effect related with dasatinib emerged. Also, she could achieve CMR twelve months after the switch to dasatinib.

Together, our case suggests that switch from imatinib to 2nd TKI would be useful for CML-CP patients with MRD and/or some side effects related with imatinib in terms of both efficacy and QOL.

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