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【 ORIGINAL ARTICLE 】

The Efficacy of Reduced-dose Dasatinib as a Subsequent Therapy in Patients with Chronic Myeloid Leukemia in the Chronic Phase: The LD-CML Study of the Kanto CML Study Group

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Abstract:

Objective The aim of this study was to prospectively investigate the efficacy and safety profiles of low-dose dasatinib therapy (50 mg once daily).

Methods Patients with chronic myeloid leukemia in the chronic phase (CML-CP) who were being treated with low-dose imatinib (≤200 mg/day), but were resistant to this agent were enrolled in the current study (referred to as the LD-CML study).

Results There subjects included 9 patients (4 men and 5 women); all were treated with dasatinib at a dose of 50 mg once daily. Among 8 patients who had not experienced major molecular response (MMR; *BCR-ABL1* transcript ≤0.1% according to International Scale [IS]) at study enrollment, 5 attained MMR by 12 months. In particular, 3 of 9 patients demonstrated a deep molecular response (DMR; IS ≤0.0069%) by 18 months. Five patients developed lymphocytosis accompanied by cytotoxic lymphocyte predominance. There was no mortality or disease progression, and all continue to receive dasatinib therapy at 18 months with only 2 patients requiring dose reduction. Toxicities were mild-to-moderate, and pleural effusion was observed in 1 patient (grade 1).

Conclusion Low-dose dasatinib can attain MMR and DMR without severe toxicity in patients with CML-CP who are unable to achieve MMR with low-dose imatinib. Switching to low-dose dasatinib should therefore be considered for patients in this setting, especially if they are otherwise considering a cessation of treatment.

Key words: low-dose dasatinib, chronic myeloid leukemia, LD-CML study

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Introduction

The outcomes for chronic myeloid leukemia (CML) patients have improved following the introduction of the tyrosine kinase inhibitor (TKI) imatinib, which is used widely nowadays (1, 2). Recent studies have shown that the majority of patients with CML in the chronic phase (CML-CP)

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were able to attain a major molecular response (MMR); their prognoses were generally favorable, with a CML-associated death rate below 10% (1, 2). When imatinib was the only available TKI, then imatinib-intolerant patients were managed with reduced doses that might have limited effect regarding the treatment response and prognosis (3). This was remedied with the advent of second-generation TKIs such as dasatinib, which is now considered the best available therapy for imatinib-intolerant/resistant patients. Dasatinib has been reported to be 325-fold more potent than imatinib against wild-type *BCR-ABL1*-expressing cells, and it effectively inhibits various imatinib-resistant *BCR-ABL1* mutants (4). Furthermore, dasatinib inhibits Src activity, which is associated with imatinib resistance (5). However, the starting treatment dose of dasatinib is uniform regardless of the reasons for switching (i.e., intolerance or resistance to the prior therapy) or patient background (age or comorbidity). Therefore, the safety of using the conventional dose of dasatinib (100 mg once daily) in clinical practice remains questionable because this drug often causes concomitant adverse events (e.g., pleural effusion [PE], platelet depletion, anemia, rash, or diarrhea) (6, 7). PE is particularly frequent in Japanese patients treated with dasatinib; 33% of patients experience PE by 18 months, and this rate generally increases over time. PE is thus a major reason for dasatinib cessation (8).

We and other groups recently reported the efficacy and safety profiles of the conventional dasatinib dose in the first- and second-line settings for patients with CML-CP in Japan (9-11). Furthermore, lymphocytosis has been well-studied (12, 13), and is believed to be a unique consequence of dasatinib treatment (14-16). In particular, a recent large-scale study demonstrated that the incidence of lymphocytosis was closely associated with a better treatment response regardless of the therapy setting (first- or second-line) (17). Multiple clinical studies evaluating the safety and efficacy of dasatinib therapy for patients with CML-CP revealed that nearly one-half of the patients required treatment dose reduction because of long-term adverse events. These findings suggest that it is a prudent treatment strategy to commence dasatinib administration at a reduced treatment dose. Notably, and despite increasing data regarding CML therapy using dasatinib, the consequences of reducing the dose of this agent have rarely been investigated to date.

In our previous study of patients administered 100 mg dasatinib as a subsequent therapy, some patients who had been treated with low-dose imatinib were excluded by virtue of the study design. Given the lack of data regarding the treatment efficacy of reduced-dose dasatinib as a subsequent therapy in patients with CML-CP, we devised this independent 'LD-CML' study to investigate the clinical efficacy and safety profiles of low-dose dasatinib administered to patients who are unable to tolerate sufficient doses of imatinib (≥300 mg/day). Furthermore, the incidence of lymphocytosis was also prospectively investigated in this study.

Materials and Methods

Patients

The LD-CML study was an open-label, multicenter, prospective study. Patients were enrolled between April 2010 and March 2012. The inclusion criteria were as follows: those who are treated with imatinib at a dose of less than or equal to 200 mg (reduced dose due to any adverse event), age ≥15 years, diagnosis with Philadelphia chromosome-positive CML-CP, an Eastern Cooperative Oncology Group performance status ≤2, and a corrected QT interval ≤450 ms on electrocardiography. Imatinib resistance was defined as the lack of a complete hematologic response at 3 months of imatinib treatment, the lack of a partial cytogenetic response at 6 months, the lack of a complete cytogenetic response at 12 months, or persistence of more than 100 copies/μg RNA of the *BCR-ABL1* transcript (which was considered equivalent to MMR at the time of study planning) at 18 months or later. The exclusion criteria included double cancers, pregnancy, breastfeeding, having PE, a history of severe or uncontrolled cardiovascular failure, myocardial infarction within 6 months, angina or congestive heart failure within 3 months, or any reason considered to render the patient ineligible for the therapy protocol. The study was approved by the research ethics boards of all participating institutions, and was conducted in accordance with the Declaration of Helsinki. All patients provided their written informed consent prior to enrollment in the study.

Assessment of treatment response and molecular analysis

Quantification of *BCR-ABL1* transcripts by real-time quantitative real-time polymerase chain reaction (RT-PCR) analysis was performed to assess the molecular response. Patient peripheral blood samples were obtained before and at 1, 3, 6, 9, 12, 15, and 18 months after starting dasatinib treatment, and an analysis of the *BCR-ABL1* transcripts was performed by Biomedical Laboratories (BML; Tokyo, Japan) as described previously (18). The values were normalized to the reference gene *GAPDH* and converted to the International Scale (IS). An MMR was defined as ≤0.1% and a deep molecular response (DMR) was ≤0.0069%, as our laboratory equipment was only capable of reliably measuring depths of 0.0069% (18). The primary endpoint was the MMR rate at 12 months.

Lymphocytosis and immunophenotyping

Complete blood cell counts were routinely obtained before the initiation of dasatinib treatment and every month thereafter. The absolute lymphocyte count was expressed as the total blood cell count and the percentage of lymphocytes. Lymphocytosis was defined as a peripheral blood lymphocyte count of greater than 3,000/μL on at least 2 occasions at any point after 4 weeks of commencing dasatinib

Table 1. Patient Characteristics at the Time of Study Enrollment.

Patient number	Age (years)	Sex	Body weight (kg)	PS	IS at study enrollment	Antecedent imatinib therapy (months)	Prior interferon therapy (months)
1	73	F	48	0	116.54	95	No
2	75	F	47	0	36.57	84	No
3	83	M	60	0	1.42	53	No
4	64	F	51	0	27.53	10	No
5	66	F	63	0	0.663	97	No
6	78	M	64	0	10.58	66	Yes (65)
7	73	F	49	1	0.807	22	No
8	87	M	63	0	27.858	NA	No
9	68	M	71	0	0.025	17	No

PS: performance status, IS: International Scale, F: female, M: male, NA: not available

therapy (12). Immunophenotyping of lymphocyte fractions was performed before and 1, 3, 6, 9, 12, 15, and 18 months after commencing dasatinib treatment at a centralized laboratory (BML), as described previously (12, 13).

Safety assessment

Adverse events were evaluated via blood tests, including blood cell counts, liver and renal function tests, and measurements of serum mineral levels including magnesium. Additionally, chest radiographs were obtained at 2 weeks and at 1, 2, 3, 6, 9, 12, 15, and 18 months after initiation of dasatinib treatment, although some of these time points could be omitted at the discretion of the physician if abnormal symptoms or findings were not observed. Toxicities were graded according to the Common Terminology Criteria for Adverse Events version 4.0.

Results

Patient characteristics

Nine patients (4 men and 5 women) were enrolled in the study, all of whom were eligible for assessment. The patient characteristics are presented in Table 1. All patients were followed for a minimum of 18 months; the median age at study enrollment was 73 years (range, 64-87 years). Dasatinib was initiated 10-97 months after imatinib therapy (data from one of the patients were not available) and all patients initially received 50 mg/day of dasatinib. The IS before dasatinib initiation was >10% in 5 patients, 1-10% in 1, and <1% in 3. Notably, the depth of the molecular response at study enrollment was equivalent to MMR in 1 patient (#9); the molecular assessment was validated and a conversion factor was obtained. The formal threshold of *BCR-ABL1* transcript expression for MMR was revised from 100 to 731 copies/μg RNA after study completion.

Efficacy of dasatinib treatment

No mortality or disease progression was observed among the enrolled patients during the observation period. With respect to the primary endpoint, 5 of 8 patients (excluding 1 who was already in MMR at dasatinib initiation) attained MMR (#3-6 and #8) by 12 months, and 3 patients reached DMR during the treatment period (#4, #6, and #9, Figure and Table 2). Two patients (#4 and #7) had their doses reduced owing to adverse events (platelet depletion and anemia), but none required dasatinib cessation. Furthermore, none of the patients had a dose escalation of dasatinib.

Toxicity profiles

The toxicities observed in this study are shown in Table 3. The drug-related adverse events were generally mild and tolerable. PE rarely occurred among our patients; there was only 1 patient at 15 months with grade 1 PE (#7). Regarding non-hematologic toxicities of grades ≥3, only 1 patient had hyperkalemia and increased amylase (#6, grade 3) and lipase (#6, grade 4) levels. As for hematologic toxicities, anemia was observed in 2 patients (#3 and #7, grade 3), platelet depletion in 1 (#2, grade 3), and neutropenia in 1 (#1, grade 3). Other grade ≤2 non-hematologic toxicities observed in 2 or more patients included liver dysfunction (n=4), renal dysfunction (n=3), rash (n=2), edema (n=2), muscle pain (n=2), and arrhythmia (n=2); however, none developed gastrointestinal symptoms suggestive of colitis, such as diarrhea or melena.

Development of lymphocytosis and analysis of lymphocyte subsets

Of all 9 patients, 5 had lymphocytosis during their affliction periods (#2 and #6-9). The results of a flow cytometric analysis of each lymphocyte subset are shown in Table 4. The majority of lymphocytes were natural killer (NK) cells (CD3-CD56+) and/or cytotoxic T lymphocytes (CTL; CD3+ CD8+). The increased number of cytotoxic lymphocytes mostly comprised a differentiated phenotype (CD57+); on the other hand, an expansion of γδ T-cells was not prevalent in these patients.

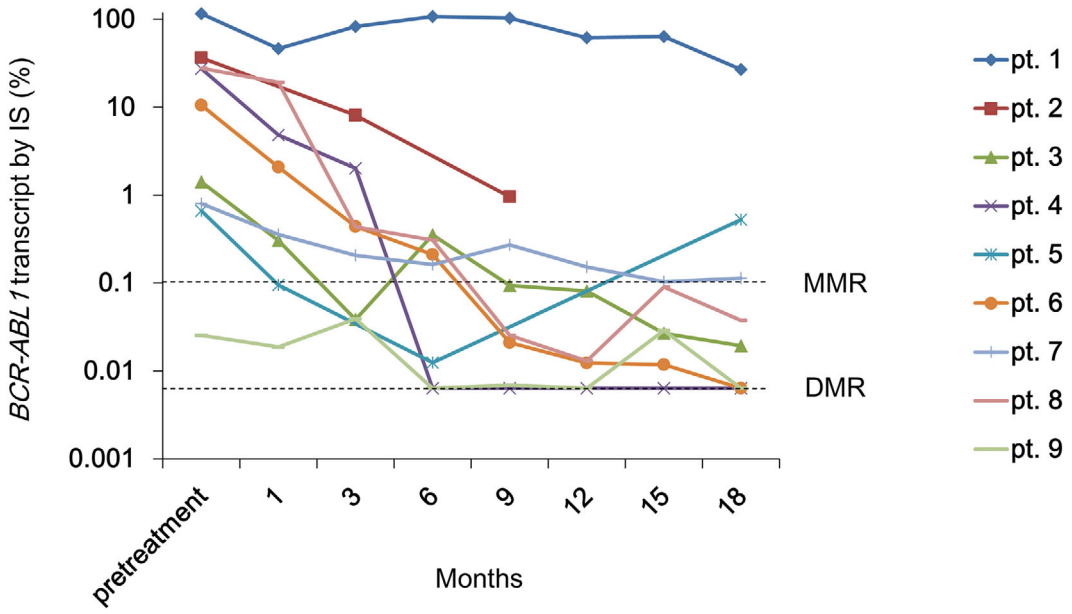

Figure. **Dynamics of the *BCR-ABL1* transcripts according to the International Scale (IS) in the study cohort. One patient (#9) had already achieved major molecular response (MMR) at the time of dasatinib initiation. An MMR was defined as ≤0.1%, while a deep molecular response (DMR) was 0.0069%, according to the IS.**

Table 2. **Outcomes of Patients Treated with Dasatinib.**

Patient number	MMR achieved (month)	DMR achieved (month)	Treatment interruption	Treatment dose reduction (mg)	Lymphocytosis (/μL)
1	No	No	Yes	No	No
2	No	No	Yes	No	3,400
3	3	No	Yes	No	No
4	6	6	Yes	20	No
5	1	No	No	No	No
6	9	18	Yes	No	3,871
7	No	No	No	20	7,473
8	9	No	No	No	3,760
9*	-	6	No	No	3,101

*Patient #9 had already achieved MMR at the time of dasatinib initiation.
MMR: major molecular response, DMR: deep molecular response

Discussion

To our knowledge, this study is the first to investigate the efficacy and safety profiles of patients with CML-CP treated with low-dose dasatinib (50 mg once daily). We found that the patients were able to attain MMR, which is a critical threshold for evaluating the patient prognosis, even after reducing the treatment doses. Ultimately, 3 of our patients attained DMR, which may allow for TKI discontinuation. Although our patient population was not homogeneous, our findings showed that switching to dasatinib appears to be more effective for achieving molecular responses than maintaining imatinib treatment. Recently, we demonstrated the efficacy of 100 mg dasatinib for imatinib-intolerant or -resistant CML-CP, with an MMR rate of 76% and a DMR rate of 38% by 18 months (10). The current study showed a similar dasatinib efficacy, although our cohort included more patients with less favorable statuses (e.g., IS>10% in 5 of 8 patients). These results suggest that patients who are prescribed continued low-dose imatinib treatment owing to unattained MMR and/or DMR, as well as patients who are imatinib-resistant, have an alternative method to improve their outcomes by switching to low-dose dasatinib. However, the dose escalation of dasatinib or switching to other TKIs for patients who are unable to achieve MMR with reduced-dose dasatinib should also be considered.

Additionally, we found that low-dose dasatinib actually induced lymphocytosis, which is recognized to confer an immune-mediated effect against CML cells based on evidence of better treatment response in patients with lymphocytosis (12, 14, 15, 17). Lymphocytosis occurred in 5 pa-

tients, with an increase in the number of cytotoxic lymphocytes. The lymphocytosis incidence trend was similar to that in patients treated with the conventional dose of dasatinib, although the degrees were relatively mild (12, 13).

The increased number of lymphocytes comprised either NK cells or CTLs with differentiated immunophenotypes (CD57+), which was consistent with previous findings (14-16). The increase in NK cells produced higher cytotoxicity against CML cells (14). Indeed, CD57+ NK cells are known to produce high amounts of interferon-γ and show a more potent cytolytic activity when stimulated by the activating receptor CD16 (19); however, the role of CD57+ T cells in cancer immunity has not yet been elucidated (20). Importantly, an increase in the number of NK cells is reported to be closely associated with a favorable treatment response or successful treatment-free remission in patients with CML-CP (13, 21, 22). Thus, even low-dose dasatinib therapy with an increased number of cytotoxic lymphocytes is deemed to be advantageous for eradicating CML cells, although the association between lymphocytosis and the treatment response in our study was unclear owing to the limited number of patients.

The prognosis of patients who are unable to be treated with the appropriate dose of imatinib is presumed to be unfavorable, based on the results of a clinical study previously performed in Japan (3). Although dasatinib has been shown to be a more effective therapy than imatinib, adverse events are generally frequent in Japanese patients in the first-line treatment setting (23). In the current study, general toxicity profiles were less severe than, or equivalent to, those of previous studies that tested the efficacy and safety of dasatinib at a dose of 100 mg or more in Japanese patients with CML-CP (10, 11, 23, 24). In particular, the prevalence of PE was previously shown to be frequent, with an incidence rate of 33% by 18 months in patients treated with a dose of 100 mg once daily (8). Importantly, the incidence rate of PE was higher in patients at an advanced age in the same study (8). Because our cohort consisted of relatively older patients (the median age was 73 years), a higher incidence rate of PE was therefore expected. However, none of the patients, except for 1, developed PE; and that patient did not require a dose reduction to control it. Some patients with CML-CP who are treated with dasatinib are actually required to optimize its treatment dose. Indeed, the occurrence of PE is the major reason for dasatinib cessation (25), and is closely associated with higher trough concentrations, treatment schedules (e.g., once or twice daily), and/or higher daily doses of dasatinib (26-28). Therefore, a treatment strategy of starting dasatinib at a lower dose may be an appropriate management route. Our results provide evidence to sanction the use of low-dose dasatinib as a subsequent therapy.

This study is associated with some limitations. We were unable to enroll the target number of patients (n=30); therefore, our smaller cohort size could weaken the reliability of our outcomes regarding the clinical significance of reduced-dose dasatinib therapy. There were 3 patients who actually attained DMR after switching to dasatinib; in contrast, 3 other patients did not achieve MMR; thus, dose escalation

Table 3. Non-hematologic and Hematologic Drug-related Adverse Events during 18 Months of Treatment with Low-dose Dasatinib.

Adverse events	All grades (n)	Grade 3/4 (n)
Non-hematologic		
Pleural effusion	1	0
Fatigue	1	0
Edema	2	0
Nausea	1	0
Muscle pain	2	0
Rash	2	0
Cardiac	2	0
Increased liver enzyme	4	0
Increased amylase/lipase	1	1
Increased creatinine	3	0
Hyperkalemia	1	1
Hypoalbuminemia	2	0
Hematologic		
Neutropenia	4	1
Anemia	6	2
Thrombocytopenia	7	1

Table 4. Lymphocyte Fraction Analysis in Patients Enrolled to the Study.

Patient number	Time point (month)	Lymphocytes ($\times 10^9$/L)	CD3-CD56+ ($\times 10^9$/L)	CD3+CD56+ ($\times 10^9$/L)	CD3-CD57+ ($\times 10^9$/L)	CD3+CD57+ ($\times 10^9$/L)	CD3+CD8+ ($\times 10^9$/L)	CD8+TCRγδ+ ($\times 10^9$/L)
1	6	2,288	142	664	103	1,137	879	373
2	9	3,150	772	488	939	964	1,017	72
3	6	1,284	544	50	488	225	182	72
4	6	2,440	390	66	576	649	639	49
5	6	2,370	649	168	647	301	415	33
6	18	3,096	1,149	180	972	641	551	15
7	6	4,930	764	207	1,114	1,933	2,007	281
8	9	3,302	819	234	829	1,486	1,030	155
9	6	2,538	376	292	345	670	538	195

Data showing the maximal lymphocyte counts per flow cytometric analysis are presented for each patient.

or switching to other TKIs should be considered in poor responders. However, since no patient underwent dose escalation, the small cohort size makes it difficult to conclude whether the dose escalation of dasatinib (from 50 to 100 mg) would effectively improve the treatment response.

In conclusion, our study demonstrated that low-dose dasatinib treatment may be safe and effective for patients with CML-CP who are resistant to low-dose imatinib therapy. We showed that low-dose imatinib-treated patients without MMR may be able to improve their outcomes by switching to dasatinib at a dose of 50 mg. While these results are encouraging, our overall findings require further validation in larger cohort studies going forward.

Author's disclosure of potential Conflicts of Interest (COI).
Noriyoshi Iriyama: Honoraria, Bristol-Myers Squibb. Shinya Kimura: Honoraria, Bristol-Myers Squibb, Pfizer and Otsuka Pharmaceutical. Chiaki Nakaseko: Honoraria, Bristol-Myers Squibb and Pfizer; Research funding, Bristol-Myers Squibb. Satoshi Morita: Honoraria, Bristol-Myers Squibb. Koiti Inokuchi: Honoraria, Bristol-Myers Squibb, Pfizer and Novartis Pharma; Research funding, Bristol-Myers Squibb.

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