Clinical significance of dasatinib-induced pleural effusion in patients with *de novo* chronic myeloid leukemia

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Abstract

Dasatinib is currently approved for clinical use as a first-line treatment agent for newly diagnosed chronic myeloid leukemia (CML). However, only a few clinical trials have been performed to evaluate dasatinib-induced PE following first-line therapy. We investigated the incidence and clinical features of dasatinib-induced PE following first-line therapy in Japanese CML patients of real world clinical practice settings. Among 22 patients, the median age of PE-positive patients was higher than that of PE-negative patients. Major molecular response was achieved in 75% of PE-positive patients and 50% of PE-negative patients. Most patients developed PE more than 1 year after treatment. Appearance of PE is associated with better clinical response during dasatinib treatment, however it is developed at any time. Elderly and high-risk patients tend to develop PE. The clinical features of dasatinib-induced PE following first-line therapy might be late onset and might not immediately follow the increasing of large granular lymphocyte.

Introduction

Dasatinib, a second-generation tyrosine kinase inhibitor (TKI), is currently approved for clinical use as a first-line treatment agent for newly diagnosed chronic myeloid leukemia (CML). Despite the efficacy and safety of dasatinib, adverse events such as pleural effusion (PE) remain a serious concern. However, a paradoxical relationship between the development of PE and the efficacy of dasatinib has been reported. Patients who developed PE showed a better response rate than did patients without PE.[1] PE was reported in 15% to 30% of patients treated with dasatinib, with a median time to appearance of 5 to 26 weeks.[2-6] However, with the exception of the DASISION study,[7] which is the largest phase III trial to date comparing dasatinib to imatinib in patients with newly diagnosed CML, all previous studies of dasatinib-induced PE involved patients receiving dasatinib as second-line therapy. Few studies of dasatinib-induced PE following first-line therapy have been reported.[8,9] We anticipated that the clinical features of PE following initial use of dasatinib might differ from those associated with second-line use. We herein report the incidence and clinical features of dasatinib-induced PE following first-line therapy in patients with CML.

Materials and Methods

In total, 22 consecutive patients diagnosed with chronic-phase CML and treated with dasatinib as initial therapy at Kansai Medical University Hospital from June 2011 to December 2015 were included in this retrospective study. CML diagnosis and efficacy was assessed according to the European Leukemia Net (ELN) 2006 definition.[10] Molecular response was assessed by quantitative reverse-transcriptase PCR and converted to the International Scale (IS). Peripheral blood smears were examined under light microscopy by two certified hematology technicians. Lymphocytes with three or more large granules per cell were defined as large granular lymphocytes (LGLs), and 200 white blood cells were counted per smear. The LGL count and chest X-rays were monitored every 3 months. When patients developed PE, dasatinib was stopped or the dose was decreased. Patients were also given diuretics to control PE. The dasatinib was then restarted after the PE had diminished. The severity of adverse events was graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, v4.0.[11] This retrospective analysis was approved by the Ethics Committee of Kansai Medical University.

Results

The median age of the patients was 55 years (range, 19-75 years), and 95% were male. We used three major risk stratification scales to predict the outcome: the Sokal score, Hasford score, and EUTOS score. However, most patients were classified as having low-risk CML according to their Sokal and EUTOS scores (90% and 92%, respectively) and low- and intermediate-risk CML according to their Hasford score (low, 55%; intermediate, 45%). The results of a comparison between PE-positive and PE-negative patients are shown in Table 1. The median age of PE-positive patients was higher than that of PE-negative patients (66 *vs*. 42 years, respectively). Furthermore, all scores were higher in PE-positive patients. Molecular response 4 was achieved in 75% of PE-positive patients and 50% of PE-negative patients. The most frequent adverse event was grade 1/2 PE, which was observed in 36% of patients, followed by grade 1 rash (9%), grade 1 QT prolongation (5%), and grade 1/2 pancytopenia (5%). Failed treatment occurred in two patients because of poor treatment adherence.

Eight patients developed PE. The characteristics of these patients are shown in Table 2. One patient developed PE 1.4 months after administration of dasatinib, while the others developed PE more than 1 year after treatment; the median time to the development of PE was 17.2 months (range, 1.4-38.7 months). All patients who developed PE achieved major molecular response (MMR). The median cumulative dose of dasatinib was 45.15 g, and all but one patient had an increased LGL count upon development of PE. The median LGL count of patients with PE was 1.980×10^9/L (range, $0.647\text{-}7.540\times10^9$/L). The timing of LGL elevation, appearance of PE and the relationship of response were revealed in Figure 1.

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Discussion and Conclusions

Dasatinib is a second-generation TKI that has been approved for clinical use in first-line therapy. Despite the efficacy and safety of dasatinib, adverse events such as PE remain a serious concern. Most previous studies that evaluated dasatinib-induced PE involved patients receiving dasatinib as second-line therapy, and they reported a PE frequency of 15% to 30% and median time to appearance of 5 to 26 weeks.[2-6] The DASISION study,[7] the largest phase III trial, recently reported the final results of a comparison of dasatinib with imatinib in patients with newly diagnosed CML.[12,13] In that study, the frequency of PE was 28%, and patients who developed PE tended to be older (>65 years). Patients with PE had a better prognosis, with 96% achieving a confirmed complete cytogenetic response and 82% achieving MMR. In another single-arm first-line study in Japan,[9] 33% of patients developed PE, and the MMR rates at 3 months were significantly higher in PE-positive than PE-negative patients (54% *vs*. 24%, respectively; P=0.013).

In this study, the median age of PE-positive patients was higher than that of PE-negative patients (66 *vs*. 42 years, respectively) (Table 1). As the DASISION study[7] also reported, age might therefore be a risk factor for PE. Using the risk scales described in the present study, patients with PE had a tendency to be categorized as having higher-risk CML than did PE-negative patients. However, PE-positive patients reached a deeper response than did PE-negative patients. The Sokal score and Hasford score were established before the TKI era. The EUTOS score was constructed using data from patients being treated with imatinib; however, it has not been sufficiently verified. Thus, these scales are necessary to evaluate the predictive potential in the TKI era.

Although the mechanism of PE development is unknown, most recent reports describe an association between an increased LGL count and PE.[14] Some studies have further suggested that dasatinib-induced PE may be immune-mediated.[5] Nagata *et al*.[6] reported that elevated LGL counts preceded the development of PE and that patients developed PE approximately 1 month after the appearance of a high LGL count. Mustjoki *et al*.[14] also described an elevated LGL count prior to PE, with a median 1.0- to 3.5-month interval from administration of dasatinib to development of PE. In the present study, most patients developed an elevated LGL count at an early stage of dasatinib treatment despite the late onset of PE (>1 year after starting treatment). The increase of LGL is seemed to precede MMR, but the appearance of PE did not necessarily follow increasing of LGL (Figure 1). In the DASISION study,[8] grade 3/4 pleural effusions was seen after 3 years from the start of treatment. On the other hand, in the CA 180-034 study[8] including second-line use, grade 3/4 PE was seen during the first year. In our study, most cases developed PE after 1 year from the treatment, suggesting the possibility of delayed onset of PE when dasatinib is used as the first-line. Although increasing of LGL is said to proceed before PE, in this study PE does not develop immediately after the increase in LGL. We assume that the presence of the time lag might be a characteristic of first-line treatment. Months might be required before increased LGL transit from blood to tissue. Thus, the onset of PE might be delayed in the first-line treatment.

Because previous reports have indicated that an elevated LGL count might be associated with PE, we examined the LGL counts

Table 1. Patients' characteristics.

	Patients with PE	Patients without PE
No. of patients	8	14
Median age, range (y/o)	66 (54-73)	42 (19-75)
Male sex (%)	100	95
Sokal score (%)		
Low	63	95
Intermediate	25	5
High	12	0
Hasford score(%)		
Low	25	79
Intermediate	75	21
High	0	0
EUTOS score(%)		
Low	88	95
High	12	5
Best response (%)		
MR 3.0	25	50
MR 4.0	25	7
MR 4.5	38	29
MR 5.0	12	14

PE, pleural effusion; MR, molecular response.

Table 2. Characteristics of patients with pleural effusion

No.	Sex	Age	Months to PE	LGL (/l) at PE	Cumulative dose of dasatinib (g)	Best response
1	M	73	12.0	1.798	42.7	MR 4.5
2	M	66	13.3	1.858	30.4	MR 4.0
3	M	72	26.9	2.089	67.6	MR 4.5
4	M	54	1.4	0.647	2.1	MR 3.0
5	M	66	18.5	2.460	55.5	MR 4.5
6	M	66	22.7	3.850	27.2	MR 5.0
7	M	71	38.7	1.872	116.2	MR 3.0
8	M	61	15.9	7.540	47.6	MR 4.0

M, male; LGL, large granular lymphocytes; PE, pleural effusion; MR, molecular response.

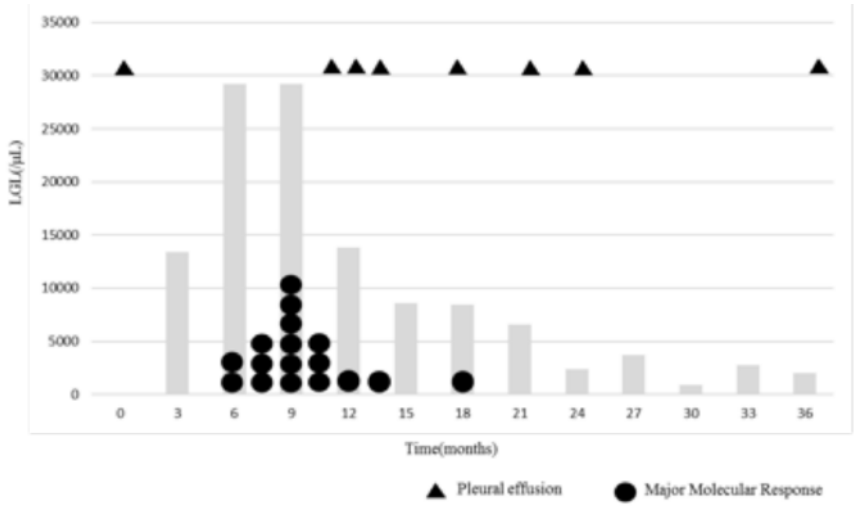

Figure 1. The timing of large granular lymphocytes (LGL) elevation, appearance of pleural effusion (PE) and the relationship of response. MR, molecular response. The increase of LGL is seemed to precede MMR, but the appearance of PE did not necessarily follow increasing of LGL. PE is developed at any time during dasatinib treatment.

in patients who developed PE and found that the median count was 1.980×10^9/L, which is elevated. In previous studies, the median LGL count ranged from 2.8 to 17.4×10^9/L.[15] However, the lower limit associated with the development of PE is unclear. The LGL count might be correlated with the development of PE, although elevated LGL has also been reported in patients without PE. We also evaluated the cumulative dose of dasatinib but found no correlation between the cumulative dose and LGL count (correlation coefficient, 0.0348; P=0.935).

Some reports from Asian countries have described differences between Asian and non-Asian patients with CML, with the prevalence of PE slightly higher in patients in Asian countries. In a subset analysis of the DASISION trial with a 2-year follow-up, PE was reported in 27% of Japanese patients compared with 13% of the total patient population.[11] In the Korean study, PE was observed in 54% of patients.[16] Thus, differences might be expected according to the patients' ethnicity and location. Furthermore, Epstein-Barr virus (EBV) infection might be associated with PE because some reports have described EBV-associated PE.[17]

This study had some limitations. It was performed retrospectively, had a small sample size, and involved a single treatment center in Japan. Although our aim was to compare the characteristics of patients treated with dasatinib as a first- versus second-line agent, most patients were conventionally treated with nilotinib as a second-line agent in our facility. Therefore, comparison was not possible in these patients.

Although the etiology of PE is unknown, the clinical features of dasatinib-induced PE following first-line therapy might differ from those of second-line therapy. Thus, the clinical significance of PE following first-line therapy warrants further investigation because it appears to represent a long-term adverse event that should be monitored in patients receiving dasatinib.

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