making such a decision. In addition, the present protocol states that, if the decision is difficult due to equivocal findings, additional drugs should be given.

It was considered that the higher CR rates of previous JALSG studies for adult AML: AML87 [4], AML89 [5] and AML92 [6], were due to response-oriented individualized therapy, giving highly intensive but not too toxic doses of anti-leukemia drugs, especially IDR, to make the bone marrow severely hypoplastic, reduce the percentage of blasts to less than 5% within 10 days, and aim to obtain CR by the first course of induction therapy. For example, in the AML89 study, the primary objective of which was to compare Ara-C with BHAC in remission induction therapy, 130 (82%) of 159 patients in the DNR + Ara-C + 6MP + PSL group achieved CR by this individualized induction therapy [5]. It is clear that without a prospective randomized study, one cannot argue whether the individual therapy is superior to a standard fixed-schedule remission induction therapy. However, it is noteworthy, that in the 3 randomized studies in the USA mentioned in Sect. 1, which compared IDR plus Ara-C with DNR plus Ara-C, the fixed-schedule therapy with DNR plus Ara-C resulted in merely 57–58% CR rates, while IDA plus Ara-C regimens produced 70–80% CR rates [8–10].

Disappointingly, the present study could not demonstrate that response-oriented individualized therapy was superior to the fixed-schedule therapy. Both regimens resulted in almost the same CR rates: 79 and 82%, respectively. Actually, both therapies produced very good CR rates. The results were interpreted as follows: IDR is a good but very powerful drug, therefore, additional IDR and Ara-C on day 8 or later may not be necessary and gave too much myelosuppression. In fact, in the individualized group, leukocytopenia was significantly more severe and its duration was significantly longer, and early death within 30 days tended to occur more frequently. From the present study it is suggested that response-oriented individualized therapy could be successful in cases where DNR is used as a key drug. Usui et al. [12] reported that the optimal dose of DNR in the induction therapy for newly diagnosed adult AML was approximately 280 mg/m^2 (40 mg/m^2 for 7 days), which was more than its conventional dose of 40–60 mg/m^2 for 3 days.

It is very interesting that among patients of age 50 years or older, the individualized group had significantly lower RFS than the fixed group, but there was no such difference in younger patients. However, we cannot clearly explain the real reason of this observation. There may be potential sources of bias in our subset analysis of clinical data that have many confounding factors. Therefore, we must be cautious in drawing a conclusion from this observation.

So far, CR rates around 80% for newly diagnosed adults of age less than 65 years with non-M3 AML seems to be the upper limit by currently available anti-leukemia drugs in multi-institutional studies [7]. To increase the CR rates and improve treatment outcomes, novel drugs other than cytotoxic ones such as all-*trans* retinoic acid (ATRA) for acute promyelocytic leukemia (APL) are needed. With ATRA in combination with conventional cytotoxic drugs such as IDR and Ara-C, CR rates around 95% and more than 80% overall survival for APL with PML/RARα can be obtained [13, 14]. The remarkable success of molecule targeting therapy with ATRA against APL as well as imatinib mesylate against chronic myeloid leukemia [15] and Philadelphia chromosome-positive ALL [16] with BCR/ABL is a good example. Specific molecule targeting therapy should be developed against pathogenic molecules responsible for leukemogenesis. Meanwhile, it is necessary to explore separate treatment regimens for prognostically different subtypes of AML with conventionally available modalities in order to increase the cure rate of adult leukemia.

Acknowledgments We thank all participating physicians from the 79 institutions in the JALSG for their cooperation. This study was supported in part by a grant from the Ministry of Health, Labor, and Welfare of Japan.

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Int J Hematol (2009) 89:319–325
DOI 10.1007/s12185-009-0263-z

ORIGINAL ARTICLE

Long-term efficacy of imatinib in a practical setting is correlated with imatinib trough concentration that is influenced by body size: a report by the Nagasaki CML Study Group

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Received: 26 August 2008 / Revised: 9 January 2009 / Accepted: 27 January 2009 / Published online: 6 March 2009

Abstract Imatinib has dramatically improved long-term survival of chronic myelogenous leukemia (CML) patients. To analyze its efficacy in a practical setting, we registered most of CML patients in Nagasaki Prefecture of Japan. Of these, 73 patients received imatinib as an initial therapy. The overall survival rate of these patients was 88.7% at 6 years, and the cumulative complete cytogenetic response rate was 82.5% at 18 months. These results are comparable with the data of other reports including the IRIS study; however, the administered imatinib dose was smaller in our study than that in other reports. To address these discrepancies, we measured the trough concentration of imatinib among 35 patients. Although 39% of the patients were administered less than 400 mg/day, the trough level was comparable to those of previous reports. The trough level of imatinib showed a significant relationship with its efficacy, and was clearly related to dose of imatinib administrated and dose of imatinib divided by body surface area (BSA). Considering the smaller BSA of Japanese patients as compared to those of foreign origin, the results suggest that a lower dose of imatinib could maintain enough trough level and provided excellent results for the treatment of CML in our registry.

Keywords CML · Imatinib · Trough concentration

The affiliation details of the members of Nagasaki CML Study Group are given in Appendix.

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1 Introduction

Imatinib, an inhibitor of the BCR-ABL fusion protein, has dramatically changed the treatment of chronic myelogenous leukemia (CML) [1–3]. The International Randomized Interferon versus STI571 (IRIS) phase III clinical trial revealed that imatinib provided better long-term survival compared to interferon (IFN) plus cytosine arabinoside (AraC) for patients with CML in chronic phase [4–6]. Imatinib produces a complete cytogenetic response (CCR) by reducing the number of CML cells and enables the recovery of hematopoiesis without Philadelphia chromosome (Ph). Imatinib further reduces the volume of CML clone to the levels only detectable by molecular techniques [5]. Based on the results of several clinical trials including

the IRIS study, imatinib administration (400 mg/day) has become the standard treatment for CML patients in chronic phase. We previously conducted an analysis of registered CML patients in Nagasaki prefecture of Japan capturing more than 80% of patients in this prefecture (approximate population of 1.44 million) to determine imatinib efficacy in a practical setting rather than in a clinical trial situation [7]. Reflecting the practical situation of daily clinic, clinical features of patients in our registration were different from those reported in the IRIS study in some aspects: older age, advanced Sokal score at diagnosis, and lower daily dose of imatinib administered in the Nagasaki Study. However, interestingly the survival and cytogenetic/molecular responses of these patients were comparable to those of the IRIS study.

In 2008, after more than 6 years of imatinib use, we performed a survival analysis of our CML patients to identify the long-term effect of imatinib therapy in a practical setting. During this analysis, we again noticed a good survival in our series similar to the IRIS study despite lower dose of imatinib administered in the Nagasaki Study. Recently, some reports on plasma trough concentration of imatinib were published [8, 9]. In one report, the trough imatinib plasma levels were associated with both cytogenetic and molecular responses, demonstrating the importance of imatinib concentration above 1002 ng/ml for good responses [8]. In another report, which was a part of the IRIS study, the plasma imatinib level differed widely among patients administered with 400 mg/day, and showed a significant but not clinically meaningful relationship of imatinib concentration with body weight and body surface area (BSA) of the patients [9]. In the same study, there was a significant correlation between the imatinib trough level (day 29 of treatment) and the long-term response as judged by cytogenetic or molecular analysis [9]. With these reported data, we hypothesized that the plasma concentration of imatinib rather than the administered dose might explain the clinical results of imatinib in our registration that would represent the practical daily clinic for CML patients.

To address this issue, we measured the trough concentration of plasma imatinib in patients administered with different doses of imatinib, and tested the relationship between its concentration and efficacy. We found that the imatinib trough concentration was comparable or higher in our analysis compared to those reported in the IRIS study and the French group studies, and it was significantly related to the clinical efficacy in a practical setting. These results suggested that the imatinib trough level would be a useful marker to determine the dose of imatinib administered in each patient balancing its efficacy and adverse effects.

2 Patients and methods

2.1 Patients

One hundred and thirty CML patients from 11 major hospitals were registered for the Nagasaki CML Study Group, Nagasaki Prefecture, Japan. As shown in our previous report, the registration included approximately 85% of the patients in the Nagasaki-Prefecture Tumor Registry [7]. The 130 patients included 74 newly diagnosed patients from December 2001 to March 2008 and 56 patients who were alive in December 2001, at the beginning of the registration when imatinib became widely available in Japan. Informed consent was obtained from 36 of the 130 patients to measure the trough concentration of imatinib, and it was measured in 35 patients (one sample was not suitable for the analysis). This study was approved by the Ethical Committees of the participating hospitals.

2.2 Measurement of plasma imatinib concentration

Peripheral blood was obtained from 36 patients within 24 ±2 h from the last imatinib administration. The plasma was immediately separated at 4°C by centrifugation and kept at −20°C until measurement. One sample was found not suitable for the analysis, so finally, 35 samples were analyzed. The plasma imatinib concentration of the 35 patients was measured at the Toray Research Center, Inc. (Nihonbashi, Tokyo, Japan) using liquid chromatography–tandem mass spectrometry method [10].

2.3 Clinical parameters including the response to the therapy

Overall survival (OS) was calculated from the day of diagnosis to the date of death (regardless of the cause of death), or the last follow-up date. The daily dose of imatinib was calculated as an average dose: total amount of imatinib taken was divided by the number of days of the certain period. Complete cytogenetic response (CCR) was defined as no Ph-positive metaphases in the sample. Real time reverse transcriptase-mediated quantitative polymerase chain reaction (RQ-PCR) was performed to identify the molecular response. In some cases, fluorescent in situ hybridization (FISH) analysis for bcr-abl fusion gene of peripheral blood neutrophils was also performed. In the cases only RQ-PCR or FISH results for bcr-abl fusion were available, CCR equivalent responses (bcr-abl/abl level <0.01 by RQ-PCR or below the detection limit of bcr-abl signal by FISH) were included in CCR. A threefold log reduction in the *bcr-abl* transcripts by RQ-PCR was determined to be a major molecular response (MMR). The

overall response to imatinib was evaluated using the criteria proposed by European LeukemiaNet [11].

2.4 Statistical analysis

Categorical parameters of the clinical characteristics were compared using the Chi-square or Fisher exact test, and the continuous parameters were compared using two-sample *t* test or the Wilcoxon rank-sum test. The imatinib dose between the two groups was treated as continuous or categorical data. The probabilities of CCR and OS were estimated by the Kaplan–Meier method. Linear regression was used to correlate baseline plasma trough concentration of imatinib with body weight, BSA, and imatinib dose divided by BSA. All statistical analyses were performed using JMP (SAS Institute, Inc., Cary, NC). A P values of <0.05 was considered statistically significant. All analyses were completed by April 30 2008.

3 Results

3.1 Characteristics of patients and long-term efficacy of imatinib as an initial treatment

The registration of CML patients started in December 2001. By March 2008, 130 patients were enrolled in this study including 99 patients who were registered before and 31 patients who were registered after July 2005 (Table 1).

Table 1 Clinical features of the patients

	All	Initial treatment	
		Imatinib	Others
Number of patients	130	73	57
Male/female	71/59	40/33	31/26
Age at diagnosis (median)	15–84 (56)	17–84 (57)	15–80 (55)
Clinical phase at diagnosis			
CP	105	61	44
AP	22	10	12
BC	2	2	0
Unknown	1	0	1
Time after diagnosis, years (median)	0.2–25.2 (5.5)	0.2–7 (3.2)	1.7–25.2 (9.6)
Sokal score at diagnosis			
Low	47	23	24
Intermediate	44	29	15
High	30	19	11
Unknown	9	2	7

CP Chronic phase, *AP* accelerated phase, *BC* blastic crisis

Imatinib was the first treatment for 73 patients, and 96% (70 out of 73 patients) including the 31 patients registered after July 2005, were still undergoing the imatinib treatment. Of the 130 patients 17 were died between 2001 and 2008 (12 patients by disease progression, 3 due to other malignancies, 1 by cerebral hemorrhage, and 1 by rhabdomyolysis).

The median daily dose of imatinib administered was 400 mg (range 0–600 mg) among 70 patients who were initially treated with and continued taking imatinib; 33% (23 of 70 patients) received less than 400 mg/day. To compare the long-term imatinib response between the IRIS study and the Nagasaki registry, a practical setting, we analyzed survival and cytogenetic response among 73 patients who received imatinib without prior treatment. The overall survival rate was 88.7% (95% CI = 79.3–98.1) at 5 years (Fig. 1a), and the accumulated rate of complete cytogenetic response was 82.5% (95% CI = 70.7–94.3) after 18 months of treatment (Fig. 1c). Data for cases in chronic and accelerated phase were also calculated separately (Fig. 1b, d).

The ELN has categorized the imatinib response as optimal, suboptimal, and failure based on the chronological monitoring of hematological, cytogenetic and molecular responses. We applied this response criterion to 70 patients (including those with other than chronic phase CML at diagnosis) who were initially treated with and also currently being treated with imatinib. Cytogenetic and molecular data were available for 51 out of 70 patients (death, 6 patients; lost follow-up, 4; insufficient data, 9). Imatinib response was judged as failure in 9 of these 51 patients, suboptimal in 6, and optimal in 36. Four of the 9 patients in the failure-response category had received imatinib 300 mg/day or less, but 8 out of 36 in the optimal response category had received less than 400 mg/day.

3.2 Trough concentration of imatinib and treatment response

Since the overall survival and cytogenetic response rate to imatinib was comparable to those observed in the IRIS study despite low dose of imatinib, we measured the plasma trough concentration of imatinib in 35 patients including 11 patients who had received IFN or other medication before imatinib was introduced (Table 1). Two patients were excluded from the analysis because of the additional IFN treatment and impaired renal function. The clinical features of the remaining 33 patients are listed in Table 2. Although 6 patients were in the accelerated phase at the time of diagnosis, all were in a chronic phase under imatinib for at least 6 months when the samples were obtained. The median dose of imatinib was 400 mg (range 100–600 mg), and 13 patients (39%) were treated with

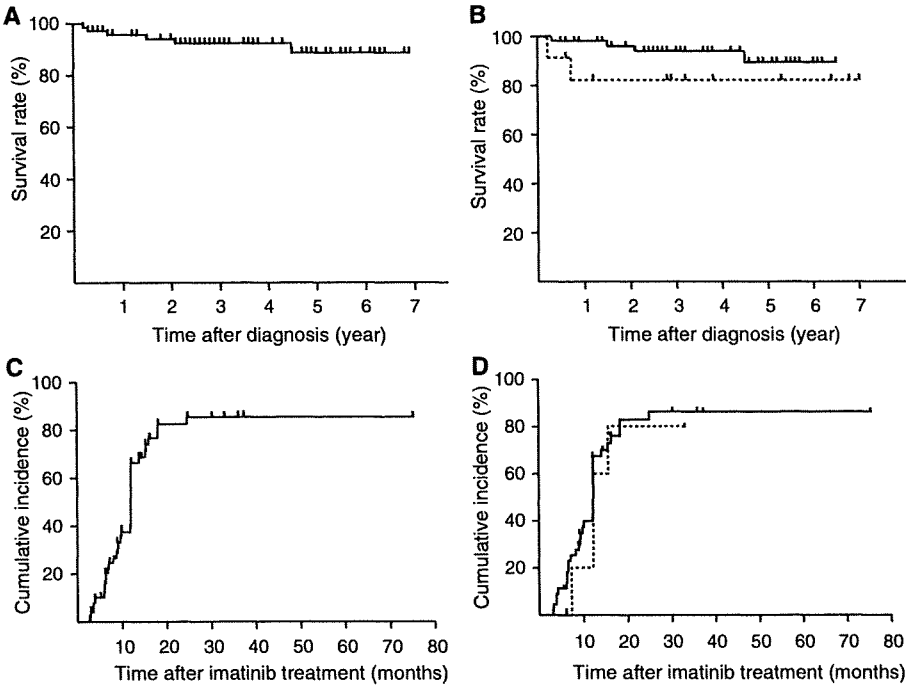

Fig. 1 Overall survival and cumulative cytogenetic response of patients whose initial treatment was imatinib. **a** Overall survival at 5 years was 88.7% in all cases ($n = 73$, 95% CI 79.3–98.1%), and (**b**) that of in chronic (*solid line*) and accelerated (*dotted line*) phases was 89.9 and 82.5%, respectively. **c** Cumulative cytogenetic response at 18 months was 82.5% in all cases ($n = 51$, 95% CI 70.7–94.3%), and (**d**) that of chronic (*solid line*) and accelerated (*dotted line*) phases was 82.9 and 80.0%, respectively

Table 2 Characteristics of patients whose imatinib concentration was measured

Male/female (number)	22/11
Initial imatinib treatment (yes/no)	22/11
Age at diagnosis, years (median)	17–82 (50)
Clinical phase at diagnosis	
CP	27
AP	6
BC	0
Time after diagnosis, years (median)	1.6–25.2 (4.9)
Duration of imatinib, years (median)	0.5–7.4 (4.2)
Dose of imatinib (mg/day)	
<200	3
200	1
300	9
400	19
600	1

CP Chronic phase, *AP* accelerated phase, *BC* blastic crisis

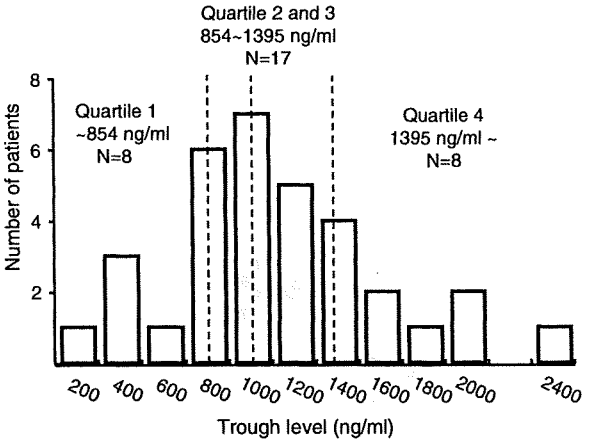

Fig. 2 Distribution of imatinib trough levels ($n = 33$). The *vertical dashed lines* represent the 25th, median, and 75th percentiles within quartiles 2 and 3

300 mg/day or less. As shown in Fig. 2, the median concentration was 1040 ng/ml (range 233–2420 ng/ml). We divided the patients into quartile groups (Q1–Q4) based on their imatinib trough level. The average of trough level of the lowest quartile (Q1) was 845 ng/ml, and that of upper quartile (Q4) was 1395 ng/ml. Trough concentration did not exhibit correlation with body weight of patients ($r^2 = 0.004$), or BSA ($r^2 < 0.001$), but it demonstrated significant correlation with the imatinib dose divided by BSA (dose/BSA, $r^2 = 0.28$, Fig. 3a–c) or by BW (dose/BW, $r^2 = 0.23$). However, even among those taking the same dose of 400 mg/day, the imatinib concentration was widely distributed (582–2420 ng/ml). Interestingly, the influence of body size on the plasma concentration of imatinib seemed stronger among those taking lower dose of imatinib: r^2 value in the concentration and dose/BSA among those with 200 mg was 0.65 ($P = 0.1922$) and those with 300 mg or more was 0.008 and 0.018 ($P = 0.8158$ and 0.5910, respectively, Fig. 3c). The similar tendency was observed in the relationship between BW

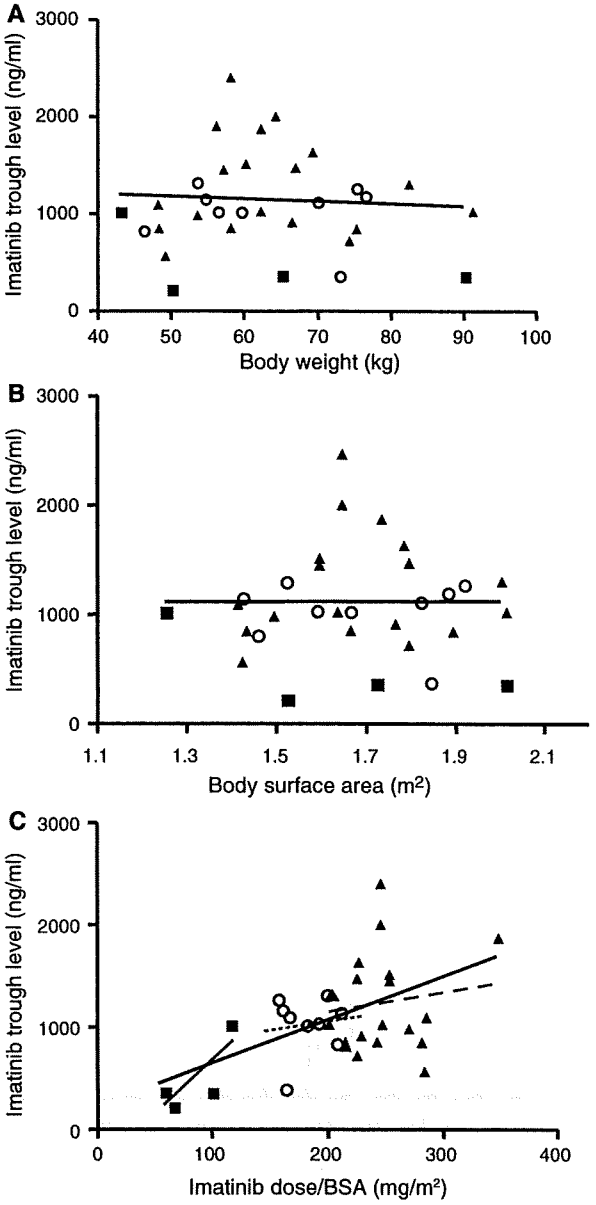

Fig. 3 Imatinib trough levels by body weight (**a**), body surface area, BSA (**b**), and daily imatinib dose divided by BSA (**c**). Imatinib trough and (**a**) body weight, $r^2 = 0.004$; **b** BSA, $r^2 < 0.001$; **c** imatinib dose/BSA, $r^2 = 0.28$. *Filled rectangles* represent cases taking imatinib 200 mg/day or less, *open circles* those taking 300 mg/day, *filled triangles* those taking 400 mg/day or more. *Bold line* represents a fit line in each figure. In **c**, *thin line* represents a fit line for those taking 200 mg/day or less, *dotted line* for those taking 300 mg/day, and *broken line* for those taking 400 mg/day or more. The imatinib trough level was significantly correlated with imatinib dose/BSA as total ($P = 0.0021$)

or BSA and imatinib concentration although not statistically significant (data not shown). There were eight out of thirteen patients (61.5%) whose imatinib concentration was higher than 1000 ng/ml despite taking 300 mg/day of imatinib or less. As shown in Fig. 4a, patients in the optimal-response category showed a significantly higher trough concentration than those in the suboptimal or failure categories ($P = 0.0087$). Similarly, 41% (10 out of 17) of the patients in the lower two quartiles (Q1 and Q2) and 94% (15 out of 16) in the upper two quartiles (Q3 and Q4) had an optimal response, demonstrating a significantly superior response (Table 3, $P = 0.04$) in the groups with a high-trough concentration. We also found a significant relationship between dose/BSA and the response ($P = 0.01$, Fig. 4b), and the dose and response ($P = 0.01$, Fig. 4c). These tendencies did not change even cases were divided into chronic and accelerated phases ($P = 0.0272$, Fig. 4d, e). Of note, there was no difference in the trough imatinib levels between patients with or without prior treatment (data not shown).

4 Discussion

We analyzed the long-term results of 73 CML patients initially treated with imatinib in a practical clinical setting, and confirmed its excellent long-term efficacy as in our previous report [7]. Despite administration of a lower dose of imatinib as compared to the IRIS study (400 mg/day of imatinib or more in 92% of patients), the OS and CCR of our patients were comparable to those observed in the IRIS study [6]. These results were surprising considering that our patients were older and in a more advanced stage (i.e., 12 out of 73 were not in the chronic phase at diagnosis) than those in the IRIS study. To address why smaller amount of imatinib could provide an excellent response for patients in the Nagasaki Study, we measured the trough concentration of imatinib and found that it was comparable or higher than those reported in foreign studies (mean = 1058 and 1119 ng/ml in the French and Nagasaki Study, respectively, median = 979 and 1040 ng/ml in the IRIS and Nagasaki study, respectively) [8, 9]. Although our results are based on a relatively small number of patients, the mean imatinib trough concentration of patients administered with 400 mg/day was higher in our analysis (1244 ± 494 ng/ml) than that reported from a French group study (1058 ± 557 ng/ml) [8]. The trough imatinib concentration had the strongest relationship with imatinib dose/BSA compared to that with body weight or BSA alone, which might explain the paradoxical median trough concentration in patients taking 300 mg/day (1130 ng/ml) or 400 mg/day (1040 ng/ml).

It was demonstrated that the trough concentration of imatinib relates to the cytogenetic and molecular responses from two different groups [8, 9]. In accordance with these reports, despite the possibility of inappropriate inclusion of late responders, the clinical and molecular efficacy of

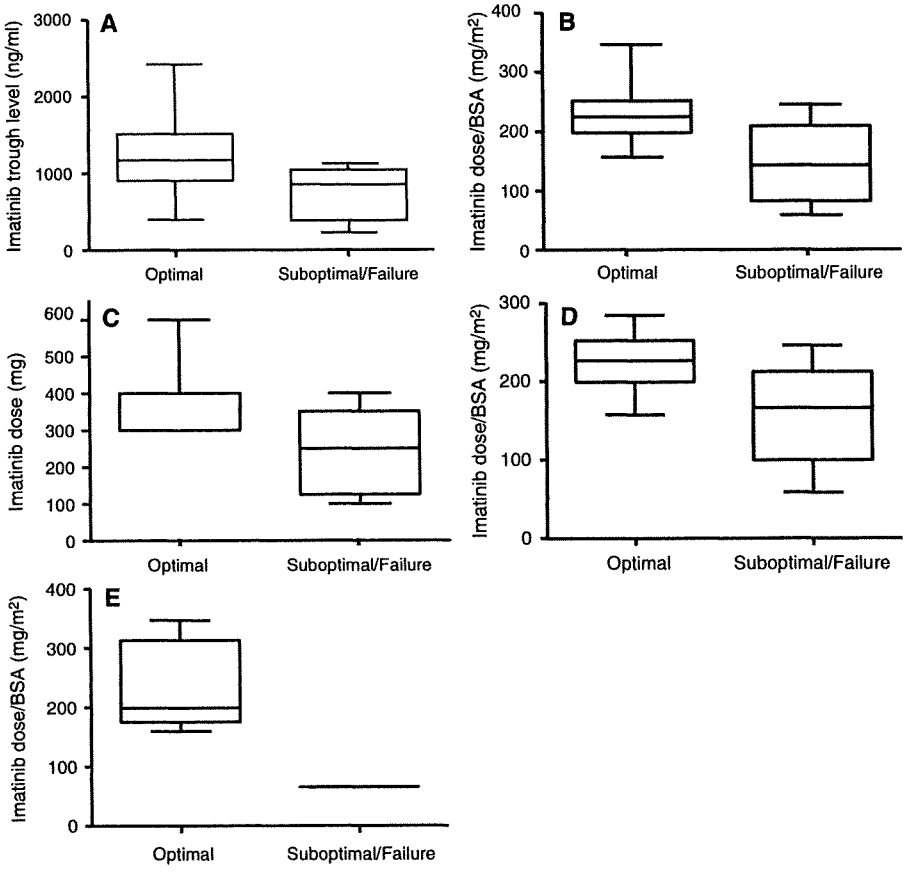

Fig. 4 Imatinib trough levels (**a**), imatinib dose/BSA (**b**), and imatinib dose (**c**) categorized as optimal response, and suboptimal response or failure based on European LeukemiaNet criteria. The trough level of cases with optimal response, mean = 1242 ng/ml, $n = 25$; suboptimal response/failure, mean = 736 ng/ml, $n = 8$; $P = 0.0087$. There were also significant differences in imatinib dose/BSA (**b**, $P = 0.01$) and in imatinib dose (**c**, $P = 0.01$) between the two response categories. This tendency remained even after cases were divided into chronic (**d**, Optimal, 18 cases; suboptimal/failure, 7 cases, $P = 0.0272$) and accelerated phase (**e**, Optimal, 5 cases; suboptimal/failure, 1 case). BSA was not available in 2 cases

Table 3 Number of patients in each quartile group

Quartile group	Total	Average dose (mg/day) of imatinib (range)	Response category[a]	
			Optimal	Suboptimal/ failure
Q1	8	275 (100–400)	4	4
Q2	9	361 (150–400)	6	3
Q3	8	325 (300–400)	7	1
Q4	8	425 (400–600)	8	0

[a] Distribution of patients in Q1/Q2 and Q3/Q4 is significantly different ($P = 0.04$)

imatinib as judged by the ELN criteria, was related to its trough concentration in the current analysis. These results strongly suggest that the high trough level in our patients resulted in an excellent imatinib response. Although body weight and BSA per se were not clinically significant determinants of the trough concentration [12, 13], the smaller body size of the Japanese population as compared to foreign populations might have influenced the results. The similar trough concentration despite smaller dose could be explained, at least in part, by the difference in the BSA between the IRIS (male 2.0 m^2, female 1.8 m^2) and the Nagasaki (male 1.77 m^2, female 1.45 m^2) studies [9].

The imatinib trough concentration is dependent on a variety of factors including prescribed dose, compliance, drug–drug interaction, serum-binding proteins, genetic differences in enzymatic pathways, and concomitant diseases [11–13]. Although not clearly mentioned previously, BSA might also affect trough imatinib concentration, in particular when BSA is small. It is well known that molecular monitoring of the *bcr-abl* fusion transcripts is necessary to manage CML patients for the appropriate choice of treatment: the conversion of tyrosine kinase inhibitors, or the indication of other treatment including IFN or stem cell transplantation [11, 14–17]. Because a plasma level above 1040 ng/ml (or 1000 ng/ml suggested by the IRIS study, or 1002 ng/ml reported from French study) seemed necessary to obtain a significant effect from imatinib, our results suggest that monitoring trough imatinib concentration in addition to molecular monitoring would be useful for the management of CML patients. For example, patients with an imatinib blood concentration lower than the optimal level could be candidates for an increased imatinib dose or for other treatment than imatinib

such as a second generation of BCR-ABL inhibitor. Given the fact that more than 30% of patients are treated with less than 400 mg/day in a practical setting, it would be useful to measure trough concentration of imatinib when it might be necessary to make a dosage change, such as to consider increase of imatinib with an unsatisfactory response, or to consider decrease of imatinib with a fair response but intolerable side effects. Maximizing the efficacy and minimizing the side effects of imatinib could be achieved by the dose adjustment based on its trough data, reducing the cost of treatment at the same time. Further research should include an evaluation of imatinib-binding proteins and genetic differences in metabolic enzymes, such as CYA3A5 [12, 13]. These types of studies would provide clinically important information for the prediction of imatinib efficacy in CML patients.

Acknowledgments We would like to thank Dr. T Matsuo for his support and Ms. N Shirahama for her assistance.

Appendix

Members of the Nagasaki CML Study Group are as follows: S. Atogami, and H. Kawaguchi (Nagasaki Municipal Medical Center), M. Yamamura (Nagasaki Municipal Hospital), T. Joh, Y. Takasaki, and M. Tawara (The Japanese Red Cross Nagasaki Atomic Bomb Hospital), H. Tsushima (St. Francis Hospital), Y. Moriuchi, Y. Onimaru, R. Yamasaki, and Y. Sawayama (Sasebo Municipal General Hospital), S. Yoshida, Y. Inoue, and Y. Moriwaki (National Hospital Organization, Nagasaki Medical Center), D. Ogawa (Nagasaki Prefectural Shimabara Hospital), H. Soda (Health Insurance, Isahaya General Hospital), H. Nonaka (Japan Labour Health and Welfare Organization, Nagasaki Rosai Hospital), S. Ikeda (Hirado Municipal Hospital), I. Jinnai (Saitama Medical School), K. Kuriyama (University of the Ryukyus), M. Kusano (Senju Hospital), S. Koida (Gotoh Central Hospital), Y. Matsuo (Sankoukai Obama Hospital) and other authors in Nagasaki University.

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Int J Hematol (2009) 89:332–341
DOI 10.1007/s12185-009-0260-2

ORIGINAL ARTICLE

Phase 1/2 clinical study of dasatinib in Japanese patients with chronic myeloid leukemia or Philadelphia chromosome-positive acute lymphoblastic leukemia

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Received: 22 July 2008 / Revised: 24 December 2008 / Accepted: 9 January 2009 / Published online: 5 March 2009

Abstract A phase 1/2 study was conducted to assess the safety and efficacy of dasatinib in Japanese patients with chronic myelogenous leukemia (CML) or Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph^+ ALL) resistant or intolerant to imatinib. In phase 1, 18 patients with chronic phase (CP) CML were treated with dasatinib 50, 70, or 90 mg twice daily to evaluate safety. Dasatinib $\leq$ 90 mg twice daily was well tolerated. In phase 2, dasatinib 70 mg was given twice daily to CP-CML patients for 24 weeks and to CML patients in accelerated phase (AP)/blast crisis (BC) or Ph^+ ALL for 12 weeks. In the CP-CML group ($n = 30$) complete hematologic response was 90% and major cytogenetic response (MCyR) 53%. In the AP/BC-CML group ($n = 11$) major hematologic response (MaHR) was 64% and MCyR 27%, whereas in the Ph^+ ALL group ($n = 13$) MaHR was 38% and MCyR 54%. Dasatinib was well tolerated and most of the nonhematologic toxicities were mild or moderate. Dasatinib therapy resulted in high rates of hematologic and cytogenetic response, suggesting that dasatinib is promising as a

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new treatment for Japanese CML and Ph+ ALL patients resistant or intolerant to imatinib.

Keywords CML · Ph+ ALL · Dasatinib · Imatinib resistant · Imatinib intolerant

1 Introduction

Chronic myeloid leukemia (CML) is a disease attributable to abnormalities of hematopoietic stem cells involving uncontrolled proliferation of cells originating from the bone marrow. The Philadelphia (Ph) chromosome is formed by translocation between chromosomes 9 and 22. The *BCR-ABL* fusion gene on this chromosome produces BCR-ABL, which constitutively activates ABL tyrosine kinase and is thus responsible for CML and 20–30% of adult patients with acute lymphoblastic leukemia (ALL) [1]. Imatinib (Glivec®) is a selective BCR-ABL inhibitor effective against CML and Ph-positive (Ph+) ALL. Currently, imatinib is the only tyrosine kinase inhibitor indicated in newly diagnosed CML and Ph+ ALL [2–4]. However, resistance to imatinib gradually develops in many patients with CML and Ph+ ALL, particularly those with advanced disease. Among CML patients treated with imatinib, 31% discontinue the drug within 5 years because of insufficient responses or unacceptable toxicity [5]. As a major factor responsible for development of resistance to imatinib, numerous point mutations in BCR-ABL have been reported [6–8]. Additional factors including *BCR-ABL* gene amplification [6, 9], excretion of the drug through a P-glycoprotein efflux pump [10, 11], and activation of the signal transduction pathway for SRC family kinase and other signals [12, 13] have also been implicated. Therefore the development of new treatments is desirable for patients with insufficient response to imatinib and in whom imatinib cannot be continued at effective doses due to toxicity.

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Dasatinib (BMS-354825) is a novel oral tyrosine kinase inhibitor that exerts inhibitory activity against BCR-ABL and SRC family kinase. In vitro, dasatinib binds to both active and inactive BCR-ABL and is 325 times more potent than imatinib and 16 times more potent than nilotinib against wild-type BCR-ABL-expressing cells [14]. Dasatinib has demonstrated activity against all reported types of imatinib-resistant mutant BCR-ABL, except for T315I [14–18]. Five phase 2 studies collectively known as START (SRC/ABL Tyrosine kinase inhibition Activity Research Trials of dasatinib) studies demonstrated that dasatinib is safe and elicits hematologic and cytogenetic response at all stages of CML and Ph+ ALL resistant or intolerant to imatinib [18–22]. Against chronic phase (CP)-CML, dasatinib was highly effective with 91% of patients showing complete hematologic responses (CHR) and 62% major cytogenetic responses (MCyR). Efficacy for CP-CML was durable and duration of MCyR was 88%, progression-free survival was 80% and overall survival was 94% at 2-year follow-up [23]. Dasatinib (Sprycel®) was initially approved in the United States in June 2006 and has received marketing approvals in numerous other countries world-wide.

We conducted an open-label phase 1/2 study of dasatinib in Japanese patients with CP-CML, accelerated phase (AP)/blast crisis (BC)-CML or Ph+ ALL resistant or intolerant to imatinib. This study comprised two parts. Phase 1 evaluated the safety of dasatinib at escalating doses in patients with CP-CML. Phase 2 evaluated the efficacy and safety of dasatinib in patients with all-stage CML or Ph+ ALL.

2 Methods

2.1 Patients

Adult CML or Ph+ ALL patients aged 20–75 years who were resistant or intolerant to imatinib were conducted from 2005 to 2007. Because imatinib had no registered indication for Ph+ ALL in Japan at the start of this study, patients with Ph+ ALL resistant to or intolerant of prior therapies were eligible. Treatment and analysis were conducted in three cohorts with CP-CML, AP/BC-CML and Ph+ ALL (Table 1).

CP-CML was considered to be resistant to imatinib when given at a dose level ≥ 400 mg/day if the following occurred: (1) white blood cell count (WBC) showed a ≥2-fold increase from nadir to >20000/mm^3 or rose from nadir to ≥50000/mm^3; (2) CHR was not achieved despite ≥3-month treatment with imatinib; (3) cytogenetic response was not achieved despite ≥6-month treatment with imatinib; (4) MCyR was not achieved despite ≥12-month

Table 1 Definition of CML phases

Phase	Description
	Patients satisfying all the following requirements:
CP	• Percentage of blasts in peripheral blood and bone marrow <15%
	• Percentage of basophils in peripheral blood or bone marrow <20%
	• Total percentage blasts and promyelocytes in peripheral blood and bone marrow <30%
	• Platelet count ≥100,000/mm^3 (rated at chronic stage if thrombocytopenia due to prior therapy is present)
	• Extramedullary leukemia absent
AP	• Nonacute patients satisfying ≥1 of the following requirements:
	• Percentage blasts in peripheral blood or bone marrow ≥15 and <30%
	• Percentage basophils in peripheral blood or bone marrow ≥20%
	• Total percentage blasts and promyelocytes in peripheral blood or bone marrow ≥30% and percentage blasts <30%
	• Platelet count <100,000/mm^3 (not associated with treatment)
BC	• Patients satisfying ≥1 of the following requirements:
	• Percentage blasts in peripheral blood or bone marrow ≥30%
	• Extramedullary leukemia, excluding that affecting liver or spleen

treatment with imatinib; (5) relapse after MCyR or CHR; or (6) mutation in *ABL* gene suggestive of resistance to imatinib (L248V, G250E, Q252H/R, Y253H/F, E255K/V, T315I/D, F317L or H369P/R) was noted in patients of chronic CML. AP-CML was considered as resistant to imatinib if the following occurred in patients treated with imatinib at a dose level ≥600 mg/day, or ≥400 mg/day if the initial diagnosis was CP-CML intolerant to imatinib: (1) progressed to BC; (2) hematologic response was not achieved in ≤4 weeks; or (3) progressed to AP after hematologic response. BC-CML was considered as resistant to imatinib if the following patients occurred: (1) the condition progressed into BC after hematologic response; or (2) the condition remained BC-CML despite ≥4-week treatment. Ph$^+$ ALL was considered as resistant to prior therapies if the following occurred: (1) CHR was not achieved at least 2 weeks after the start of treatment; or (2) progressed from CHR.

Patients with CP-CML were assessed as intolerant to imatinib if grade ≥3 nonhematologic toxicity was observed or grade 4 hematologic toxicity persisted ≥7 days. Patients with AP/BC-CML were considered intolerant to imatinib if treatment had to be discontinued or the dosage kept <400 mg/day for reasons of toxicity. Ph$^+$ ALL patients were considered intolerant to prior therapy if grade ≥3 nonhematologic toxicity was noted, grade 4 hematologic toxicity persisted ≥7 days, or existing therapy could not be given for other reasons. This study was carried out in accordance with the principles of the Declaration of Helsinki, ICH-GCP, and requirements set forth by Japanese Good Clinical Practice. Prior to the study, written informed consent was obtained from each subject. The study was approved by the Institutional Review Board at each participating institution. The study was designed by academic investigators in conjunction with representatives from the sponsor, Bristol-Myers K.K. Both parties contributed to the collection and analysis of the data. This study was registered at http://www.clinicaltrials.gov as NCT00227454.

2.2 Two-part study design: phases 1 and 2

Phase 1 was designed as a dose-escalation study in patients with CP-CML, evaluating the safety of dasatinib. Phase 2 was designed as a fixed-dose study in patients with CP or AP/BC-CML resistant or intolerant to imatinib and Ph$^+$ ALL resistant or intolerant to prior therapies, evaluating the efficacy and safety of dasatinib. In this phase, the primary endpoint was cytogenetic response in patients with CP-CML and hematologic response in those with AP/BC-CML and Ph$^+$ ALL.

2.3 Dasatinib treatment

During phase 1, dasatinib was orally administered twice daily at 50, 70, or 90 mg/dose for 24 weeks. Dose-limiting toxicity (DLT) defined as grade ≥3 nonhematologic toxicity, grade 3–4 QTc interval prolongation, grade 4 neutropenia lasting ≥7 days, grade 4 thrombocytopenia, bleeding requiring platelet transfusion, and other toxicity requiring discontinuation of the drug was evaluated during the first 4 weeks of treatment.

Phase 2 was started after the safety of 70 mg twice daily was confirmed. During phase 2, dasatinib was orally administered at 70 mg twice daily for 24 weeks in the CP-CML group and for 12 weeks in the AP/BC-CML and Ph$^+$ ALL groups. Upon completion of the observation period, an extension study involving continued treatment was planned.

The dose level of dasatinib was reduced if the following occurred: (1) grade ≥2 nonhematologic toxicity (grade ≥3 nonhematologic toxicity in patients of CP-CML); or (2) grade 4 neutropenia in patients of AP/BC-CML and Ph$^+$ ALL when bone marrow cell density and percentage of blasts were checked ≥15 days after the start of treatment. The dose level of dasatinib for CP-CML patients was increased if: (1) progression of disease (PD) was noted; (2)

Table 2 Criteria for efficacy evaluation

Hematologic response[a]	
(1) CP-CML	
CHR	
• WBC count less than or equal to institutional upper limit of normal	
• Platelet count <450,000/mm^3	
• Absence of blasts or promyelocytes in peripheral blood	
• Total percentage myelocytes and metamyelocytes in peripheral blood <5%	
• Percentage basophils in peripheral blood <20%	
• Absence of extramedullary leukemia (including hepatomegaly and splenomegaly)	
(2) AP/BC-CML and Ph+ ALL	
Major HR	
(a) CHR	
• WBC count less than or equal to institutional upper limit of normal	
• Neutrophil count ≥1000/mm^3	
• Platelet count ≥100,000/mm^3	
• Absence of blasts/promyelocytes in peripheral blood	
• Percentage of blasts in bone marrow <5%	
• Total percentage myelocytes and metamyelocytes in peripheral blood <5%	
• Percentage basophils in peripheral blood <20%	
• Absence of extramedullary leukemia (including hepatomegaly and splenomegaly)	
(b) NEL	
• WBC count less than or equal to institutional upper limit of normal	
• Absence of blasts or promyelocytes in peripheral blood	
• Percentage blasts in bone marrow <5%	
• Total percentage myelocytes and metamyelocytes in peripheral blood <5%	
• Percentage basophils in peripheral blood <20%	
• Absence of extramedullary leukemia (including hepatomegaly and splenomegaly)	
• Platelet count ≥20,000/mm^3 and <100,000/mm^3 and/or neutrophil count ≥500/mm^3 and <1000/mm^3	
Minor HR	
• Percentage blasts in bone marrow/peripheral blood <15%	
• Total percentage blasts/promyelocytes in peripheral blood <30%	
• Percentage basophils in peripheral blood <20%	
• Absence of extramedullary leukemia other than in spleen and liver	
Cytogenetic response	
Percentage Ph+ cells in bone marrow	
MCyR	
(a) CCyR	0%
(b) PCyR	>0 and ≤ 35%
Minor CyR	>35 and ≤65%
Minimal CyR	>65 and ≤95%
No response	>95 and ≤100%

CHR Complete hematologic response, *NEL* no evidence of leukemia, *MCyR* major cytogenetic response, *CCyR* complete cytogenetic response, *PCyR* partial cytogenetic response

[a] Hematologic response is confirmed if the remitted state lasts ≥4 weeks

CHR was not achieved despite ≥8 weeks of treatment; and (3) MCyR was not achieved despite ≥12 weeks of treatment. For AP/BC-CML and Ph+ ALL patients, the dose level of dasatinib was increased if: (1) PD was noted; (2) the percentage of blasts in peripheral blood showed an increase from that recorded ≥1 week previously; and (3) CHR was not achieved despite ≥4-week treatment. During the study period, concomitant use of anticancer drugs other

than dasatinib was prohibited in both CML and Ph^+ ALL patients, except for short term (≤14 days) use of hydroxycarbamide in patients in whom WBC was >50000/mm^3.

2.4 Patient evaluation

Evaluation of peripheral blood findings was performed every week during the first 4 weeks in phase 1, every other week during the first 4 weeks in phase 2, and every 4 weeks thereafter. Evaluation of bone marrow findings was made at the end of the study. Table 2 shows the criteria for efficacy evaluation. Cytogenetic response was evaluated in bone marrow by G-band test and in bone marrow and peripheral blood samples by fluorescence in situ hybridization (FISH) for *BCR-ABL* at baseline and at week 12 in AP/BC-CML and Ph^+ ALL patients and at week 24 in those with CP-CML. *BCR-ABL* point mutation was assessed by direct sequencing of PCR products of peripheral blood cells before the start of treatment. Adverse events were graded according to NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0.

3 Results

3.1 Patient demographics and dasatinib treatment

A total of 55 patients were registered for this trial, of whom dasatinib was administered to 54 (18 and 36 patients during phases 1 and 2, respectively). Median age was 43 (range 27–66) and 60 (29–73) years in patients entered in phases 1 and 2, respectively. Of the 54 patients, 35 were males and 19 females. Thirty-five patients were resistant to imatinib at daily dose of 400 mg or more, and 19 patients were intolerant to imatinib. Table 3 shows patient characteristics. Phase 1 involved 18 patients of CP-CML (12 resistant/6 intolerant); phase 2 involved 12 patients of CP-CML (6 resistant/6 intolerant), 11 AP/BC-CML (8 resistant/3 intolerant), and 13 Ph^+ ALL (9 resistant/4 intolerant). Major causes for intolerance to imatinib were rash ($n = 6$), myalgia and vomiting ($n = 3$ each), and hepatic dysfunction ($n = 2$). Although prior treatment with imatinib was not a requirement for enrollment in the Ph^+ ALL group, all patients enrolled had a history of imatinib therapy and were either resistant or intolerant to imatinib.

The duration of prior imatinib therapy was 1–3 years in 19 patients (35%), and >3 years in 19 patients (35%). The dosage of imatinib during prior therapy was ≥400 mg/day in all patients. Forty-three patients (80%) had previously received therapy other than imatinib, seven patients (13%) had undergone hematopoietic stem cell transplantation.

In phase 1, dose reduction was performed for 3 of 7 patients in the 70 mg group and 3 of 4 patients from the 90 mg group because of hematologic toxicity in 5 patients and nonhematologic toxicity in one patient. In phase 2, dose reduction was performed for 10 of 12 patients in the CP-CML group, 3 of 11 patients in the AP/BC-CML group, and 5 of 13 patients in the Ph^+ ALL group because of hematologic toxicity in 10 patients and nonhematologic toxicity in 8 patients. Dose increase was performed in one

Table 3 Patients' baseline characteristics

	CP-CML, phase 1 ($n = 18$)	CP-CML, phase 2 ($n = 12$)	AP/BC-CML ($n = 11$)	Ph^+ ALL ($n = 13$)
Median age, range (years)	43 (27–66)	60 (30–68)	57 (31–73)	64 (29–70)
Median time after diagnosis, range (years)	6.9 (0.3–19)	3.6 (0.7–15)	1.6 (0.0–14)	1.1 (0.2–6.3)
Imatinib resistant, *n* (%)	12 (67)	6 (50)	8 (73)	9 (69)
Imatinib intolerant, *n* (%)	6 (33)	6 (50)	3 (27)	4 (31)
Length of prior imatinib therapy, *n* (%)				
<1 years	3 (17)	4 (33)	2 (18)	7 (54)
1–3 years	4 (22)	3 (25)	6 (55)	6 (46)
>3 years	11 (61)	5 (42)	3 (27)	0
Prior imatinib dosage, *n* (%)				
400–600 mg/day	16 (89)	11 (92)	5 (45)	13 (100)
>600 mg/day	2 (11)	1 (8)	6 (55)	0
Prior chemotherapy, *n* (%)	12 (67)	9 (75)	9 (82)	13 (100)
Prior IFN therapy, *n* (%)	9 (50)	6 (50)	3 (27)	0
Prior HSCT, *n* (%)	0	1 (8)	3 (27)	3 (27)
BCR-ABL mutation, *n* (%)	4 (22)	1 (8)	2 (18)	4 (31)

IFN Interferon, *HSCT* hematopoietic stem cell transplantation

patient with Ph+ ALL because of insufficient response. The median treatment period was 24 weeks in phase 1 and 24, 12, and 11 weeks in the CP-CML, AP/BC-CML, and Ph+ ALL groups, respectively, in phase 2. Median dose was 96.20 (range 46.5–179.5) mg/day in phase 1 and 99.05 (44.7–141.8) mg/day in phase 2.

Forty-four patients completed the trial (17 in phase 1 and 27 in phase 2). One patient in phase 1 and 9 patients (2 patients of AP/BC-CML and 7 of Ph+ ALL) in phase 2 discontinued study treatment prematurely, because of insufficient response in 6 patients and adverse events in 4 patients.

3.2 DLT evaluation: phase 1

In phase 1, DLT was evaluated in 15 patients (6 each in the 50 and 70 mg groups and 3 in the 90 mg group). One patient in the 50 mg group was not evaluated who was diagnosed as AP-CML after registration, one in the 70 mg group had violated the protocol, and one in the 90 mg group reduced dosage. One patient in each of the 50 and 70 mg groups developed grade 4 thrombocytopenia as DLT, whereas no patient in the 90 mg group developed DLT. Two patients in the 50 mg group exhibited grade 3 elevation of ALT, but this change was not deemed DLT since it was transient and subsided without requiring treatment. There was no dose level at which DLT appeared in ≥ 2 patients; thus dasatinib was well tolerated at dose levels ≤ 90 mg twice daily.

Following this finding, dasatinib 70 mg twice daily, which was previously demonstrated safe and effective in an overseas phase 1 and 2 studies, was adopted as the regimen for the second phase of this study.

3.3 Efficacy: phases 1 and 2

3.3.1 CP-CML

Table 4 shows the efficacy results for 30 patients with CP-CML in phase 1 ($n = 18$) and 2 ($n = 12$). A high response rate was achieved, with 90% of CP-CML patients achieving a CHR (83% in imatinib-resistant and 100% -intolerant). CHR was achieved rapidly and median time to CHR was 10 days. Fifty-three percent of CP-CML patients exhibited a MCyR following dasatinib therapy. The rate of CCyR was 43%. MCyR was achieved in 33% of imatinib-resistant and 83% of -intolerant patients. In phase 1, CHR, MCyR and CCyR were 89, 50 and 44%, respectively. In phase 2, CHR, MCyR, and CCyR were 92, 58 and 42% respectively. Dasatinib therapy was not discontinued in any CP-CML patient due to insufficient response.

3.3.2 AP/BC-CML

MaHR was achieved in a high percentage (64%) of AP/BC-CML patients (63% imatinib-resistant, 67% -intolerant). Median time to MaHR was 34 days. MCyR was achieved in 27% of AP/BC-CML patients, whereas CCyR was observed in 9%. MCyR was achieved in 38% of imatinib-resistant and 0% -intolerant patients. Dasatinib therapy was not discontinued in any AP/BC-CML patient due to insufficient response.

3.3.3 Ph+ ALL

MaHR was achieved in 38% of Ph+ ALL patients (33% imatinib-resistant, 50% -intolerant). Median time to

Table 4 Treatment response

	CP-CML			AP/BC-CML			Ph+ ALL		
	Imatinib resistant $n = 18$	Imatinib intolerant $n = 12$	Total $n = 30$	Imatinib resistant $n = 8$	Imatinib intolerant $n = 3$	Total $n = 11$	Imatinib resistant $n = 9$	Imatinib intolerant $n = 4$	Total $n = 13$
Hematologic response, *n* (%)									
Major	–	–	–	5 (63)	2 (67)	7 (64)	3 (33)	2 (50)	5 (38)
Complete	15 (83)	12 (100)	27 (90)	2 (25)	0	2 (18)	0	1 (25)	1 (8)
NEL	–	–	–	3 (38)	2 (67)	5 (45)	3 (33)	1 (25)	4 (31)
Minor	–	–	–	1 (13)	0	1 (9)	2 (22)	2 (50)	4 (31)
Cytogenetic response, *n* (%)									
Major	6 (33)	10 (83)	16 (53)	3 (38)	0	3 (27)	3 (33)	4 (100)	7 (54)
Complete	5 (28)	8 (67)	13 (43)	1 (13)	0	1 (9)	2 (22)	4 (100)	6 (46)
Partial	1 (6)	2 (17)	3 (10)	2 (25)	0	2 (18)	1 (11)	0	1 (8)
Minor	3 (17)	1 (8)	4 (13)	2 (25)	0	2 (18)	0	0	0
Minimal	3 (17)	1 (8)	4 (13)	1 (13)	1 (33)	2 (18)	0	0	0

CHR + NEL = Major hematologic response, CCyR + PCyR = major cytogenetic response, NEL = no evidence of leukemia

MaHR was 57 days. CCyR was achieved in 46% of Ph^+ ALL patients. MCyR was seen in 33% of imatinib-resistant and 100% -intolerant patients. Dasatinib treatment was discontinued because of insufficient response in 6 patients.

3.3.4 Efficacy by baseline BCR-ABL mutation status

Of the 54 subjects, 11 (20%; 5 CP-CML; 2 AP/BC-CML; 4 Ph^+ ALL) showed 8 different *BCR-ABL* point mutations (L248V, G250E, Y253H, E255K, F311I, T315I, E355A, and H396R) at baseline. All these 11 patients were resistant to imatinib (Table 3). Seven patients (64%) had mutation of kinase domain P-loop (amino acids 244–255) and one that of T315I, which are highly resistant mutations to imatinib. Nonetheless, even in patients with various BCR-ABL point mutations, dasatinib conferred a MaHR in 5 (45%; 3 CP-CML; 1 AP/BC-CML; 1 Ph^+ ALL) of 11 patients and MCyR in 4 patients (36%; 2 CP-CML; 1 AP/BC-CML; 1 Ph^+ ALL), comparable to the MaHR and MCyR rates for patients without *BCR-ABL* mutation. Six patients had no hematologic or cytogenetic response; 2 patients early discontinued dasatinib due to adverse events, 1 patient had T315I mutation at baseline and 2 patients had additionally emerging T315I mutation during dasatinib treatment period.

3.4 Safety

Overall, dasatinib was well tolerated. Most of the nonhematologic adverse events were mild or moderate and required no intervention or disappeared following dose interruption or reduction of dasatinib. Frequently observed adverse events possibly related to dasatinib were headache (41%), fever (33%), diarrhea (33%), rash (31%), edema (31%), and malaise (30%) (Table 5). Pleural effusion was seen in 14 patients (26%), but was mostly mild or moderate except for one patient with grade ≥3. In all patients, the adverse events recovered to a level that allowed resumption of study treatment upon administration of diuretics or dose interruption/reduction of dasatinib. Hematologic toxicity was observed in a high percentage of patients, as expected, but was often reversible and subsided following dose interruption or reduction. Grade ≥3 thrombocytopenia was seen in 50% of CP-CML, 64% of AP/BC-CML, and 62% of Ph^+ ALL patients. Neutropenia was observed in 47, 73, and 77%, respectively (Table 6). The incidence of grade >3 anemia was highest in Ph^+ ALL patients.

Treatment was discontinued in 4 (7%) of the 54 patients because of adverse events; pneumonia in 2 patients, neutropenia in 1 patient and arrhythmia and heart failure in 1 patient.

Table 5 Cumulative possibly dasatinib related adverse events in the total treated population ($n = 54$) at 24 weeks (CP-CML) or 12 weeks (AP/BC-CML, Ph^+ ALL) of follow-up

Adverse event	Cumulative incidence rate, *n* (%)	
	All grade	Grades 3–4
Headache	22 (41)	0
Fever	18 (33)	0
Diarrhea	18 (33)	1 (2)
Rash	17 (31)	1 (2)
Edema	17 (31)	0
Malaise	16 (30)	0
Pleural effusion	14 (26)	1 (2)
Weight gain	14 (26)	0
Nausea	11 (20)	0
Constipation	11 (20)	0
Anorexia	10 (19)	0
Cough	10 (19)	0
Stomatitis	7 (13)	0
Weight loss	7 (13)	0
Pain in extremity	6 (11)	1 (2)
Vomiting	6 (11)	0
Arthralgia	6 (11)	0

4 Discussion

This two-part study was designed to evaluate the safety of escalating doses of dasatinib in Japanese patients with CP-CML (phase 1) and its safety and efficacy in patients with CP-CML, AP/BC-CML, and Ph^+ ALL (phase 2).

Although the results shown in this paper cover relatively short treatment periods of 6 and 3 months in CP-CML and AP/BC-CML or Ph^+ ALL, respectively, dasatinib demonstrated clinical efficacy in Japanese patients in all stages of CML and Ph^+ ALL resistant or intolerant to imatinib. Among patients with CP-CML, more than half achieved MCyR and most retained their cytogenetic response throughout the study period. These observations are clinically significant in view of reports that long-term prognosis may be improved in patients with CP-CML achieving MCyR [24, 25]. Also, in patients with AP/BC-CML and Ph^+ ALL, dasatinib monotherapy resulted in rapid achievement of a high rate of MaHR (64 and 38%, respectively) and the percentage of patients showing hematologic response among imatinib-resistant patients was comparable to that of imatinib-intolerant patients. The rate of cytogenetic response seemed to be higher in imatinib-intolerant patients than in imatinib-resistant patients in this study. Most patients enrolled in this study had a history of long-term imatinib therapy and of many other therapies such as interferon and chemotherapy, and were therefore expected to have a poor prognosis.

Table 6 Hematologic adverse events grade 3–4

	Cumulative incidence rate, *n* (%)		
	CP-CML ($n = 30$)	AP/BC-CML ($n = 11$)	Ph+ ALL ($n = 13$)
Leukopenia	8 (27)	5 (45)	10 (77)
Neutropenia	14 (47)	8 (73)	10 (77)
Thrombocytopenia	15 (50)	7 (64)	8 (62)
Anemia	5 (17)	2 (18)	4 (31)

However, these patients without effective treatment options showed favorable responses to dasatinib. The observation period was short in this study to be able to fully assess the efficacy of dasatinib in CML and Ph+ ALL patients and it would be expected that the response rate would be higher than the result in the present study.

At baseline, 20% of the subjects had *BCR-ABL* point mutations reported associated with resistance to imatinib [26]. Moreover, 64% of mutations observed were P-loop mutations, which are associated with high resistance to imatinib. Even these highly resistant patients achieved hematologic and cytogenetic responses. It is known that mutations associated with imatinib resistance reduce the potential of imatinib to bind to the ATP-binding site of BCR-ABL. Since the mode of binding by dasatinib differs from that by imatinib, dasatinib retains its activity even in the presence of mutation associated with imatinib resistance.

Although 35 (65%) of the 54 subjects in the present study were resistant to imatinib, mutation associated with imatinib resistance was seen in only 31% of the 35 imatinib-resistant subjects. This finding suggests that resistance to imatinib involves not only BCR-ABL point mutation but also other mechanisms. Since dasatinib exerted clinical efficacy even in patients without *BCR-ABL* point mutation, treatment with dasatinib is expected to overcome resistance to imatinib attributable not only to BCR-ABL mutation but also to other mechanisms.

In phase 1 of this study, dasatinib was shown to be safe in patients with chronic CML with dose escalations up to 90 mg twice daily. The only DLT observed in this study was grade 4 thrombocytopenia in 2 patients. Cytopenia is common adverse events in leukemia patients who have long-term and intensive prior therapy. Although cytopenia following dasatinib treatment could be controlled by dose interruption or reduction, close monitoring of blood cell counts is advisable during use of this drug.

Treatment had to be discontinued in 4 (7%) of the 54 patients because of adverse events. These results indicate that dasatinib is safe in patients with all phases of CML and Ph+ ALL resistant or intolerant to imatinib. Pleural effusion was noted in 14 (26%) patients, but the incidence of edema (a frequent toxicity of imatinib) was low in the present study. Grade ≥3 pleural effusion was seen in only one patient, and treatment did not have to be discontinued. The mechanism by which dasatinib induces pleural effusion is likely related to off-target kinase inhibition, platelet-derived growth factor receptor beta (PDGFRβ) in particular [27]. Pleural effusion was successfully treated by interruption of dasatinib and was reversible. There was low incidence of rash, muscle cramp, and nausea, which are frequent toxicities associated with imatinib. There was no apparent difference in the safety profile of dasatinib among Japanese and non-Japanese CML and Ph+ ALL patients [18–22]. It was rare that patients who had been intolerant to imatinib experienced the same severe nonhematologic toxicity following treatment with dasatinib. Therefore it is possible to treat imatinib-intolerant patients safely with dasatinib.

It has been reported that most Japanese CML patients are treated with lower dosages of imatinib than the standard recommended dosage, because of toxicities [28–31]. Imatinib treatment at low dosage is related with low rate of cytogenetic response [30]. Dasatinib is a meaningful option for those patients intolerant to the standard dosage of imatinib.

In the overseas phase 3 study designed to determine the optimal dose level and dosing method of dasatinib in patients with CP-CML [32], the efficacy of dasatinib 100 mg once daily in terms of hematologic response and cytogenetic response was comparable to that of 70 mg twice daily while the incidence of adverse events was lower. Dasatinib 100 mg once daily is currently being evaluated in Japanese patients with CP-CML. A multinational study (including Japan) is underway to access the efficacy and safety of dasatinib in newly diagnosed CML patients. In the past, only limited options were available for the treatment of imatinib-resistant or -intolerant CML and Ph+ ALL and patients often had a poor prognosis. The results of the present study indicate that dasatinib is promising as a new treatment for Japanese CML and Ph+ ALL patients resistant or intolerant to imatinib.

Conflicts of interest statement The authors indicated no potential conflicts of interest. T. S. is employee of Bristol-Myers K.K.

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Int J Hematol
DOI 10.1007/s12185-009-0483-2

ORIGINAL ARTICLE

Allogeneic stem cell transplantation versus chemotherapy as post-remission therapy for intermediate or poor risk adult acute myeloid leukemia: results of the JALSG AML97 study

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Received: 13 May 2009 / Revised: 4 December 2009 / Accepted: 22 December 2009

Abstract We prospectively compared allogeneic hematopoietic stem cell transplantation (allo-HSCT) with chemotherapy as a post-remission therapy in a multicenter trial (JALSG AML97) of adult patients with intermediate or poor risk acute myeloid leukemia (AML). Of 503 patients aged 15–50 years old registered between December 1997 and July 2001, 392 achieved complete remission (CR). CR patients classified in the intermediate or poor risk group using a new scoring system were tissue typed. Seventy-three with and 92 without an HLA-identical sibling were assigned to the donor and no-donor groups. Of 73 patients in the donor group, 38 (52%) received allo-HSCT during CR1 and 17 (23%) after relapse. Intention-to-treat analysis revealed that the relapse incidence was reduced in the donor group (52 vs. 77%; $p = 0.008$), and the disease-free survival (DFS) improved (39 vs. 19%; $p = 0.016$), but overall survival (OS)

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Published online: 09 January 2010