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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ORIGINAL ARTICLE

Phase I/II study of humanized anti-CD33 antibody conjugated with calicheamicin, gemtuzumab ozogamicin, in relapsed or refractory acute myeloid leukemia: final results of Japanese multicenter cooperative study

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Abstract The primary objective of this study was to investigate the tolerability, efficacy and pharmacokinetic profile of gemtuzumab ozogamicin (GO) in patients with relapsed and/or refractory CD33-positive acute myeloid leukemia (AML). Patients received 2-h infusions of GO twice with an interval of approximately 14 days. Tolerability was assessed using the National Cancer Institute Common Toxicity Criteria Version 2.0. Samples for pharmacokinetics were taken on day 1 and day 8 of the first treatment cycle. The dose was increased stepwise and, in each cohort, patients were treated at the same dose. Forty patients, median age 58 years (range 28–68) were treated; 20 and 20 patients were enrolled to the phase I and II parts, respectively. In the phase I part, dose-limiting toxicities (DLTs) were hepatotoxicities, and the recommended dose was established as 9 mg/m^2 given as two intravenous infusions separated by approximately 14 days. The pharmacokinetic study revealed that C_{max} and AUC were equivalent to those of non-Japanese patients. In the phase II

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part, complete remission was observed in 5 patients, and one patient had complete remission without platelet recovery. Four of these 6 in remission and one in the phase I are long-term survivors (alive for at least 44 months). GO is safe and effective as a single agent among Japanese CD33-positive AML patients. Remission lasted longer in a subset of patients than in non-Japanese patients in earlier studies. Further studies of this agent are warranted to establish standard therapy.

Keywords Gemtuzumab ozogamicin · AML · Pharmacokinetic study · Phase I/II study

1 Introduction

Gemtuzumab ozogamicin (GO) (CMA 676) is an immunoconjugate composed of a recombinant humanized murine anti-CD33 antibody linked to calicheamicin, a potent cytotoxic agent [1]. CD33 is expressed on the blast cells of approximately 80–90% of patients with acute myeloid leukemia (AML), but not on stem cell, normal granulocytes, or non-hematopoietic tissues. Leukemia cells rapidly internalize the antibody/calicheamicin complex, leading to cleavage of the toxic calicheamicin, which binds to DNA and induces double-strand breaks and subsequently cell death [2–4].

In a phase I dose escalation study with relapsed or refractory CD33-positive AML patients, eight of 40 (20%) treated with this agent had blast clearance from the blood and marrow [5]. In phase II efficacy and safety trials, a proceeding report indicated that 42 of 142 (30%) patients with CD33-positive AML in first relapse obtained remission after treatment with two doses of GO at 9 mg/m [5, 6]. Although severe myelosuppression was common, mucositis, and severe infections were not. Based on these data, GO was approved in the United States (US) for the treatment of patients with CD33-positive AML in first relapse who are 60 years of age or older and who are not considered candidates for any other cytotoxic chemotherapy.

In Japan, a multicenter study of GO was started in 1999. This is the summary of the treatment of Japanese CD33-positive AML patients. The long-term follow-up demonstrated unexpected longer second remission in a fraction of Japanese patients.

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2 Patients and methods

2.1 Patients

This was a single-arm, multicenter, open-label, phase I/II study. In the phase I part, patients with CD33-positive refractory and/or relapsed AML as well as relapsed AML after hematopoietic stem cell transplantation were eligible. Adequate bone marrow function; platelet level of 20,000/μl or more, neutrophil count of 500/μl or more and independence from transfusion also were required. In the phase II part, patients were limited to first relapse with minimum remission duration of 6 months. In both parts, the patients were required to be at least 18 and no more than 70 years of age and to have Eastern Cooperative Group (ECOG) performance status 0–2, serum creatinine level of 2.0 mg/dl or less, total bilirubin level of 1.5 mg/dl or less, and sterility or adequate contraception. All protocols were approved and monitored by central and institutional review boards, and the studies were conducted in a manner consistent with the Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided a written informed consent before treatment.

2.2 Treatment

Patients received 2 doses of GO, administered as a 2-h intravenous infusion with approximately 14 days between the doses. Acetaminophen at the dose of 400 mg and antihistamines (*d*-chlorpheniramine maleate) at the dose of 2 mg were administered before GO infusion, and two additional doses of acetaminophen were permitted after GO infusion in the phase I part. Corticosteroids (hydrocortisone sodium succinate) at the dose of 100 mg were given before infusion in the phase II part, and two additional doses were allowed after infusion. Before patients received the second dose of GO, they had to have recovered from all reversible, non-hematological toxicities and had no evidence of uncontrolled infection, disease progression, or detectable formation of antibodies to GO.

Patients were evaluated during the treatment period (from the initial dose of GO until 28 days after the last dose). After GO treatment, patients received the AML therapy that was most appropriate, as determined by their individual physicians. Survival data were collected until February 28, 2007.

2.3 Dose escalation

In the phase I part, the initial dose of GO was 2 doses of 6 mg/m^2, which was one level less than the dose described in the product label, where approved [8]. After the initial three patients tolerated this dose, the dose was escalated to 9 mg/m^2, which is the dose described in the product label in the United States. However, the fifth patient treated with this dose experienced sudden death from pulmonary bleeding and accrual was suspended. The Safety Advisory committee recommended that the dose escalation be repeated. Again the starting dose of 6 mg/m^2 was to be given to three patients and, when this dose was demonstrated to be safe, an intermediate dose of 7.5 mg/m^2 was to be given to a second cohort. The dose was to be again escalated if the three patients did not experience toxicities of grade 3 or more. The third cohort was to be given 9 mg/m^2.

Toxicity was graded on a scale of 0–5 using the National Cancer Institute Common Toxicity Criteria Version 2.0. Dose-limiting toxicity (DLT) was defined as grade 3 or more non-hematological toxicity. If the first 3 patients in a cohort had no toxicities, the dose was escalated. If one patient had a DLT, another three patients were enrolled in the same cohort. When two or fewer patients among the six had DLTs, the dose was judged to be tolerable.

2.4 Pharmacokinetics and analysis for antibodies to GO

The plasma was collected at 0, 60, 120, 180, 240 and 360 min, when 0 is starting point of infusion. Maximum plasma concentration (C_{max}), area under the concentration-time curve from 0 to X h (AUC_{0-Xh}), elimination half life ($t_{1/2}$), elimination rate constant in terminal phase (λ_z), distribution volume calculated by λz (Vz), and distribution volume at steady state (Vss) were calculated as previously reported [6, 7]. All patients were screened for antibodies to the hP67.6 monoclonal antibody and the calicheamicin-linker portion of GO using enzyme-linked immunosorbent assays [6, 7].

2.5 Efficacy measures

The primary efficacy measure was complete remission (CR) rate. CR was defined as (1) the absence of leukemic blasts in peripheral blood (2) no more than 5% leukemic blasts in the bone marrow, as measured in bone marrow aspirates or biopsy samples (3) peripheral blood counts with hemoglobin 9 g/dl or more, absolute neutrophil count (ANC) 1,500/μl or more, and platelets 100,000/μl or more and (4) red blood cell transfusion independence for 2 weeks or longer and platelet transfusion independence for 1 week or longer. Determination of remission status was evaluated approximately 28 days after the last dose of GO. All bone marrow slides were evaluated by a central reviewer (S.N.), who was blinded to treatment outcomes.

Some patients had a morphological remission, which was defined as a CR with incomplete platelet recovery (CRp). These patients met all the criteria for CR (including freedom from platelet transfusion for 1 week), but platelet counts were less than 100,000/μl. CRp was included as a secondary efficacy measure in these studies, and the overall remission rate was based on the combined total of patients who had CR or CRp. For patients who had equal to or less than 5% blasts in the bone marrow, no blasts in the peripheral blood, and no extrameningeal leukemia evident, the effect was then defined as blast clearance (BC). Patients who did not meet the criteria for CR, CRp, or BC were categorized as no remission (NR).

To assess the durability of response and relapse-free survival (RFS), overall survival rates also were evaluated. RFS was measured from the first documentation of CR or CRp to the date of recurrence, death, or data cut-off. The overall survival was measured from the date of initial GO administration to the date of death or data cut-off. All survival data were analyzed using Kaplan–Meier estimates.

3 Results

3.1 Patient demographics and baseline clinical characteristics

In the phase I part, a total of 20 patients with CD33-positive relapsed or refractory AML were evaluated (Table 1). The patients' median age was 60 years, ranging from 34 to 68 years. Male/female ratio was 9/11. The median duration of the first CR was 11.8 months ranging from 0 (one patient) to 57 months. All the patients who had achieved CR had been given maintenance therapy. More than 80% of the cells were positive for CD33, which was required by the protocol. The positivity was more than 90% in the majority (19/20 in phase I and 20/20 in phase II part). Subtypes of AML included M0–M5 but no cases of M6 or M7. The number of times of relapse also varied; there were 15 patients with one relapse, 2 patients with two relapses, 1 patient with three relapses and 1 patient with five relapses, respectively.

In the phase II part, a total of 20 patients were evaluated (Table 1). The median age was 58 years, ranging from 28 to 68 years. Male/female ratio was 14/6. The median duration of the first CR was 16.5 months ranging from 6 to 87 months. Subtypes of AML included M1–M6 but no cases of M7. The number of times of relapse also varied; there were 12 patients with one relapse, 4 patients with two

Table 1 Summary of demographic and baseline characteristics

Characteristic	Phase I				Phase II ($N = 20$)
	6 mg/m^2 ($N = 6$)	7.5 mg/m^2 ($N = 3$)	9 mg/m^2 ($N = 11$)	Total ($N = 20$)	
Age					
Median (Min–Max)	57 (34–68)	62 (35–63)	55 (39–67)	60 (34–68)	58 (28–68)
Sex					
Female	4	1	4	9	6
Male	2	2	7	11	14
Number of times of relapse					
0	0	0	1	1	12
1	6	2	7	15	4
2	0	1	1	2	2
3	0	0	1	1	1
4	0	0	0	0	1
5	0	0	1	1	0
Laboratory data before study (median)					
BM Blast (%)	65	80	70	70	75
PB WBC	2900	1700	2900	2800	2000
PB Blast (%)	20	0	21	20	3
Hgb	9.5	9.5	10.6	9.8	11.3
Plt	7.0	7.9	4.5	5.5	5.6
Duration of first remission (months)					
Median				11.8	16.5
Mean	9.3	22.2	16.5	15.5	23.2
Max	21	24	57	57	87
Min	4	20	0	0	6
N	5[a]	3	11	19	20
FAB subtypes (at initial presentation)					
M0	1	1	0	2	0
M1	0	0	1	1	2
M2	2	0	4	6	6
M3	0	0	1	1	2
M4	1	2	4	7	2
M4E0	0	0	1	1	3
M5	2	0	0	2	4
M6	0	0	0	0	1
Prognostic category (at pre-study screening)					
Favorable	0	0	1	1	3
Intermediate	1	2	3	6	7
Poor	0	0	3	3	3
Notavailable	5	1	4	10	7
ECOG PS (at prestudy screening)					
0	4	2	6	12	15
1	1	1	5	7	3
2	1	0	0	1	2

[a] Another case was exempted from analysis object because its remission induction date is unknown

relapses, 2 patients with three relapses, 1 patient with four relapses and 1 patient with five relapses, respectively.

In the phase I part, seven patients did not receive the second infusion: three patients due to progressive disease, two due to toxicities, one due to central nervous system (CNS) invasion and one due to possible infection. In the phase II part, two patients did not receive the second infusion due to persisting toxicities.

3.2 Dose determination

The first dose level of 6 mg/m^2 for the 3 patients was judged to be tolerable based on the absence of toxicities of grade 3 or above. At the second dose level of 9 mg/m^2, one patient died on the day of the infusion due to grade 4 pulmonary hemorrhage. The safety monitoring committee determined that the adverse event was not judged unrelated to the infusion. The adverse event might have occurred due to the coagulopathy related to the disease. Thus, the protocol was amended and doses of 6, 7.5 and 9 mg/m^2 were to be used in the dose escalation. Collection of coagulation data was added for safety monitoring.

At the dose of 6 mg/m^2, 1 patient developed grade 3 toxicity of hyperglycemia, nausea, and infection. Combining with the first three cases at the dose of 6 mg/m^2, only 1 among 6 patients developed grade 3; hence, the next dose of 7.5 mg/m^2 was examined. At the dose of 7.5 mg/m^2, no patients had toxicity of grade 3 or above. At the dose of 9 mg/m^2, of the six patients, two showed toxicities of elevated hepatic enzymes, which were judged to be tolerable. Therefore, the dose level utilized in the subsequent phase II part was 9 mg/m^2.

3.3 Toxicities

The most commonly observed non-hematological toxicities during the treatment period were fever, nausea, vomiting, anorexia, and liver toxicities. Most were mild and below grade 3. In the phase I part, nausea of grade 3 or above was observed in two patients and elevated liver enzymes in two patients. In the phase II part, nausea of grade 3 or above occurred in six patients. In the treatment period of the phase II part, infections of grade 3 or above occurred in three patients, bleeding in 1 patient and elevated liver enzymes in four patients. No patients developed jaundice.

Hematological toxicities were more common during the treatment period. Anemia of grade 3 or above occurred in 13 patients in the phase I part and in 16 patients in the phase II part. In the phase I and II parts, granulocytopenia of grade 3 or above occurred in 16 and 9 patients, respectively; thrombocytopenia of grade 3 or above occurred in 19 patients in each part.

The toxicities that occurred on the day of infusion and the day after following the infusion were distinguished and categorized as infusion-related toxicities (Table 2). They included GI toxicities, which were the same for the other chemotherapeutic agents and not specific to the agents. However, fever, chilliness, headache and coagulopathy were notable and considered to be related to the infusion reactions. The coagulopathy might be related to tumor lysis and occurrence of disseminated intravascular coagulation. Fewer toxicities were observed following the second infusion than subsequent to the first one (tachyphylaxis), although this difference of frequency was not statistically significant. Fever occurred in 16/20 and 8/13 patients following the first and second infusions, respectively, in the phase I part; fever occurred in 15/20 and 5/18 patients in the phase II part, respectively. Nausea also showed tachyphylaxis. In the phase I part, grade 3 or more nausea occurred in two patients during course 1 and in the phase II part, four patients during course 1 and 1 patient during course 2.

3.4 Pharmacokinetics

The plasma concentration of hP67.6, total calicheamicin, and unconjugated calicheamicin was measured (Tables 3, 4). Dose dependence was shown in C_{max} and AUC_{inf} of hP67.6 and total calicheamicin. AUC_{inf} of hP67.6 had tendency to increase; those for the first and second doses were 133 ± 94 and 223 ± 136 mg h/l, respectively. Half lives ($t_{1/2}$) of hP67.6 were variable and no tendency was shown during the subsequent dose periods.

C_{max}, half-lives and AUC_{inf} of total calicheamicin were calculated (Table 4). We found tendency to increase after the second infusion. For 9 mg/m^2, half-lives were 24 ± 16 and 48 ± 13 h for the first and second infusions, respectively. AUCs of total calicheamicin were 2.7 ± 2.0 and 6.2 ± 1.6 mg h/l, for the first and the second infusions, respectively. AUC_{inf} of unconjugated calicheamicin was also higher after the second infusion than after the first infusion.

3.5 Efficacy

In the phase I part, except for one patient who developed pulmonary bleeding, 19 patients were evaluable for efficacy. CR was obtained in two patients who were treated with 9 mg/m^2 (Table 5). Thus, of the patients treated with 9 mg/m^2 GO, 18.2% (2/11) achieved CR.

In the phase II part, among 20 evaluable patients, 5 achieved CR and 1 achieved CRp for an overall remission rate of 30.0% (6/20, 95% confidence interval [CI] 14.0–50.8%). Patients with multiple numbers of relapses or those who were in intermediate or poor prognostic groups achieved CR or CRp (Table 6). No patients who were 60 years of age or older achieved CR or CRp.

In a subset of patients, blasts disappeared in the bone marrow or peripheral blood, but did not fulfill the criteria of CR or CRp. Such responders were observed in 5 of 20 patients, and 3 of 20 patients in the phase I and II parts, respectively. The patients had been heavily pretreated: one patient had received three courses of induction therapy,

Table 2 Infusion related toxicities

	Phase I		Phase II	
	Course 1 ($N = 20$) G 3+4/G 1–4	Course 2 ($N = 13$) G 3+4/G 1–4	Course 1 ($N = 20$) G 3+4/G 1–4	Course 2 ($N = 18$) G 3+4/G 1–4
Gastro-intestinal				
Nausea	2/12	0/5	4/14	1/6
Vomiting	1/7	0/5	0/9	1/5
Hepatic				
Bilirubin	0/1	0/0	0/1	0/1
γ-GTP	0/1	0/0	0/0	0/0
GOT	1/3	0/0	1/1	0/0
GPT	12	0/0	1/1	0/0
Metabolic/laboratory				
Hyperglycemia	0/1	0/0	1/2	0/0
Elevated LDH	0/2	0/0	0/2	0/0
Hypoalbuminema	0/3	0/0	0/2	0/1
General conditions				
Chilliness	0/11	0/3	0/5	0/2
Headache	0/4	0/3	0/6	0/0
Fever	1/16	0/8	0/15	0/5
Hematological				
Leucopenia	4/4	1/1	1/1	0/0
Lymphopenia	2/5	0/2	3/4	0/1
Thrombocytopenia	4/4	0/0	6/6	0/0
Coagulopathy				
Elevated D-dimer	0/2	0/0	0/5	0/1
aPTT	0/1	0/0	0/2	0/0
PT	0/1	0/0	0/0	0/1

γ-GTP gamma-glutamyl transpeptidase, *GOT* glutamic-oxaloacetic transaminase, *GPT* glutamic pyruvic transaminase, *DH* lactose dehydrogenase

including high dose ara-C, and another patient had received five courses of induction therapy.

Responders were not limited to the first relapse. In the phase I part, a patient with an M3 subtype who was at the third relapsed and was resistant to all-trans-retinoic acid (ATRA) achieved blast clearance. A patient with an M4 subtype who relapsed after high-dose cytosine arabinoside (ara-C) and standard induction regimens achieved blast clearance. Another patient with an M4 subtype who failed standard induction therapy and relapsed five times also achieved blast clearance.

Cases with poor karyotype also responded. In the phase I part, a patient with an M4 subtype with complex karyotype (45, XY, -14, add(17)(p11), add(5)(q31)) achieved CR. In the phase II part, a patient with a M4 subtype with t(3;15)(p25;q22) achieved CRp and one with an M5 subtype who had an unfavorable karyotype (47, XX, +8) achieved blast clearance.

Overall survival (OS) was calculated using the Kaplan–Meier method (Fig. 1). The median OS was 305 days for the phase I part (not shown), and 420 days for the phase II part. The 95% confidence interval was from 74 days (lower limit) to 444 days (upper limit) for the phase I part. The lower limit of 95% confidence interval was 248 days and the upper limit has not been reached yet.

RFS of the two patients who achieved CR in the phase I part was 104 days and 62 months plus, in which "plus" means the patient lived longer than the follow-up interval. RFS for the six patients who achieved CR or CRp in the phase II part was 142 days, 161 days, 71 months, 50-plus months, 47-plus months, 47-plus months, and 44-plus months. The five long-term survivors in the phase II part included three with an M3 subtype, one with an M4 subtype, and one with an M5 subtype.

4 Discussion

In this study, the recommended dose of GO for Japanese patients with AML was 9 mg/m^2, given as two intravenous infusions separated by approximately 14 days, and is the

Table 3 Summary of hp67.6 pharmacokinetic parameters by dose group for dose periods 1 and 2

GO (mg/m^2)	Dose period	N	C_{max} (ng/ml)	$AUC_{0\sim t}$ (mg h/l)	AUC_{inf} (mg h/l)	$t_{1/2}$ (h)	λ_2 (1/h)	CL (l/h)	V_z (l)	V_{ss} (l)
6.0	1	6	1837 ± 237	63.5 ± 15.6	67.1 ± 16.6	62.78 ± 7.90	0.0112 ± 0.0014	0.151 ± 0.045	13.64 ± 4.29	7.54 ± 2.02
	2	5	1934 ± 569	90.0 ± 44.1	109.1 ± 42.9	310.51 ± 514.76	0.0084 ± 0.0055	0.097 ± 0.037	37.58 ± 54.98	23.23 ± 29.75
7.5	1	3	2497 ± 832	103.2 ± 79.8	108.7 ± 81.1	54.08 ± 28.38	0.0151 ± 0.0068	0.152 ± 0.089	11.73 ± 8.66	6.93 ± 4.84
	2	2	2808	170.0	180.9	52.24	0.0136	0.084	5.91	3.79
9.0	1	11	3248 ± 1195	123.6 ± 95.5	133.4 ± 94.0	50.94 ± 24.72	0.0164 ± 0.0078	0.188 ± 0.139	12.89 ± 11.78	6.71 ± 4.99
	2	6	3640 ± 859	217.4 ± 134.4	223.1 ± 135.9	59.06 ± 36.03	0.0140 ± 0.0046	0.082 ± 0.037	5.99 ± 2.00	3.95 ± 1.13

(Mean ± SD)

Table 4 Summary of total and unconjugated calicheamicin pharmacokinetic parameters by dose group for dose periods 1 and 2

GO (mg/m^2)	Dose period	N	C_{max} (ng/ml)		$AUC_{0\sim t}$ (mg h/l)		AUC_{inf} (mg h/l)		$t_{1/2}$ (h)		λ_2 (1/h)	
			Total	Unconjugated	Total	Unconjugated	Total	Unconjugated	Total	Unconjugated	Total	Unconjugated
6.0	1	6	45 ± 8	4 ± 3	0.95 ± 0.24	0.17 ± 0.28	1.07 ± 0.27	0.28 ± 0.51	15.31 ± 4.34	54.76 ± 69.94	0.0481 ± 0.0123	0.0306 ± 0.0212
	2	5	40 ± 5	5 ± 4	1.53 ± 0.69	0.49 ± 0.57	1.79 ± 0.77	1.52 ± 1.65	60.31 ± 46.85	1880.56 ± 1836.56	0.0224 ± 0.0191	0.0021 ± 0.0031
7.5	1	3	56 ± 20	5 ± 0	2.23 ± 1.99	0.14 ± 0.07	2.35 ± 2.05	0.15 ± 0.08	21.70 ± 14.49	23.49 ± 19.92	0.0408 ± 0.0199	0.0435 ± 0.0248
	2	2	59	7	3.60	0.25	4.05	0.27	42.46	28.15	0.0208	0.0310
9.0	1	11	83 ± 25	6 ± 4	2.50 ± 1.91	0.21 ± 0.16	2.72 ± 1.98	0.35 ± 0.32	24.39 ± 15.88	169.86 ± 270.02	0.0463 ± 0.0445	0.0272 ± 0.0321
	2	6	107 ± 18	9 ± 5	5.83 ± 1.45	0.43 ± 0.19	6.16 ± 1.57	0.79 ± 0.78	48.67 ± 13.40	609.51 ± 1221.08	0.0151 ± 0.0035	0.0088 ± 0.0061

(Mean ± SD)

Table 5 Number of CR, CRp and blast clearance: phase I and II

	Phase I (mg/m^2)			Phase II	Total
	6	7.5	9		
CR	0	0	2	5	7
CRp	0	0	0	1	1
Blast clearance	1	2	2	3	8
No remission	5	1	7	11	13
Total	6	3	11	20	40

same as that described in the product label, where approved [8]. In the phase I part, the dose level of 9 mg/m^2 was tolerable and two CRs were achieved.

However, one patient who received 9 mg/m^2 GO during the initial dose escalation developed pulmonary bleeding after infusion. This could be a manifestation of the infusion-related syndrome, which already has been reported in a post-marketing study performed in the US. It has been reported that eight patients experienced pulmonary events immediately after or within 24 h of the GO administration; six of the eight had high leucocyte counts of more than 60,000/μl. This manifestation appears to be similar to the presentation of pulmonary leukostasis or to the acute pulmonary events that have been reported after administration of other monoclonal antibodies [8].

To examine this hypothesis, other patients were monitored for coagulopathy after the fatal hemorrhage occurred and we found a subset of patients who developed coagulopathy upon infusion of GO. In the phase II part, in which collection of coagulation data was required, thrombocytopenia (six patients), hyperfibrinogenemia (two patients), and increased levels of fibrinogen degradation product (five patients) were observed. The pulmonary toxicity we observed could be the combined effects of these two toxicities, infusion-related toxicity and coagulopathy after infusion of GO. Patients with high leucocyte counts should be given GO with caution.

Including this pulmonary toxicity, all the toxicity profiles observed in our study were comparable to the earlier papers [6, 8, 9]. Among them hepatic toxicities were reported. In the earlier phase II studies [6], 23% of patients treated with the 9 mg/m^2 doses experienced grade 3–4 bilirubin elevation; however, this elevation was transient. Although cases with prior HSCT were not excluded from our study, all the patients lacked history of HSCT, and had chance to observe the incidence of hepatic toxicities attributed to the agent alone. And in patients with no history of HSCT, we observed such hepatic toxicities. Grade 3–4 elevations of GOT and GPT were observed in two cases in the phase I part, which was judged to be DLT, and four cases in phase II part. Despite these elevations of hepatic enzymes, they were transient and no cases developed jaundice. It has been reported that the incidence of sinusoidal obstructive syndrome/veno-occlusive disease is not specific to GO, and the rate of this toxicity was the same as that of conventional therapy [10].

The patterns of pharmacokinetic data of Japanese patients were almost the same as those of earlier studies [8]. Regarding the half-lives ($t_{1/2}$) of hP67.6, the data as well as the tendency to prolongation of clearance during the subsequent dose periods were the same as the earlier study. In our study of 9 mg/m^2, half-lives were 51 ± 25 and 59 ± 36 h from the first dose to the second dose. In earlier studies, half-lives were 67 ± 37 and 88 ± 58 h, respectively [8]. In our study, AUC_{inf} for the first and second doses was 133 ± 94 and 223 ± 136 mg h/l, respectively, while it was 132 ± 136 and 243 ± 198 mg h/l, respectively, in earlier studies [8].

The parameters of half-lives and AUC_{inf} of total calicheamicin also showed the same pattern (Table 4). In our study, for 9 mg/m^2, half-lives were 24 ± 16 and 48 ± 13 h for the first and second infusions, respectively. In earlier studies, they were 39 ± 25 and 63 ± 63 h for the first and second infusions, respectively [8]. Again, in our study, for 9 mg/m^2, AUCs of total calicheamicin were 2.7 ± 2.0 and 6.2 ± 1.6 mg h/l, for the first and the second infusions, respectively; in the earlier studies, they were 2.1 ± 1.8 and 4.7 ± 4.1 mg h/l for the first and the second infusions, respectively. The AUC_{inf} of unconjugated calicheamicin was also higher after the second infusion than after the first infusion (Table 4), and it was again comparable with the earlier studies.

This observation suggests that there are no race-specific differences in the pharmacokinetics of GO. Similarly, it has been reported that no age or gender differences exist in the pharmacokinetics of this agent [11]. The similarity of the pharmacokinetic data for Japanese and non-Japanese patients might translate into similar efficacy of GO. In the phase I part, two patients had CRs at the dose level of 9 mg/m^2, whereas none had CR or CRp at the dose levels of 6 and 7.5 mg/m^2. In the phase II part, at the dose level of 9 mg/m^2, the overall remission rate was 30.0% (95% CI, 14.0–50.8%). In the earlier phase II studies, the overall remission rate was 30% (95% CI, 22–38%). Thus, there was reproducible efficacy of GO in Japanese and non-Japanese patients and this result contributed to the approval of this agent in Japan.

This study included cases with multiple relapses, and even in those patients we were able to observe responses. Our study showed that relapse cases are likely to achieve responses as compared with the refractory cases; patients with earlier longer remission prior to this study responded better than with the shorter one; the number is small, and parameters contributing to the response should be obtained

Table 6 Summary of remission rates by demographic and baseline characteristics: Phase II

Characteristic	CR	CRp	Neither CR nor CRp	Indeterminable	Total	OR[a] (%)
Sex						
Male	3	1	10	0	14	4/14 (28.6)
Female	2	0	4	0	6	2/6 (33.3)
Age						
<60	5	1	9	0	15	6/15 (40.0)
≥60	0	0	5	0	5	0/5 (0.0)
Number of relapse times						
0	3	0	9	0	12	25.0 (3/12)
1	0	1	3	0	4	25.0 (1/4)
2	1	0	1	0	2	50.0 (1/2)
3	1	0	0	0	1	100.0 (1/1)
4	0	0	1	0	1	0.0 (0/1)
FAB subtypes (at initial presentation)						
M1	0	0	2	0	2	0/2 (0.0)
M2	0	0	6	0	6	0/6 (0/0)
M3	2	0	0	0	2	2/2 (100.0)
M4	0	1	1	0	2	1/2 (50.0)
M4E0	2	0	1	0	3	2/3 (66.7)
M5	1	0	3	0	4	1/4 (25.0)
M6	0	0	1	0	1	0/1 (0.0)
FAB subtypes (at prestudy screening)						
M1	0	0	3	0	3	0/3 (0.0)
M2	0	1	5	0	6	1/6 (16.7)
M3	2	0	0	0	2	2/2 (100.0)
M4	1	0	2	0	3	1/3 (33.3)
M4E0	1	0	1	0	2	1/2 (50.0)
M5	1	0	2	0	3	1/3 (33.3)
M6	0	0	1	0	1	0/1 (0.0)
Prognostic category (at initial presentation)						
Favorable	3	0	3	0	3	0/3 (0.0)
Intermediate	2	0	10	0	12	2/12 (16.7)
Poor	0	0	3	0	3	3/3 (100.0)
Not available	0	1	1	0	2	1/2 (50.0)
Prognostic category (at prestudy screening)						
Favorable	20	0	1	0	3	0/3 (0.0)
Intermediate	2	1	4	0	7	3/7 (42.9)
Poor	0	0	3	0	3	2/3 (66.7)
Not available	1	0	6	0	7	1/7 (14.3)
Duration of first remission						
<1 year	1	0	5	0	6	1/6 (16.7)
≥1 year	4	1	9	0	14	5/14 (35.7)
Disease status at pretreatment						
Relapse	5	1	12	0	18	6/18 (33.3)
Refractory	0	0	2	0	2	0/2 (0.0)
HiDAC						
Without	2	0	9	0	11	2/11 (18.2)
With	3	1	5	0	9	4/9 (44.4)

HiDAC high dose ara-C

[a] Overall remission (%) = (CR plus CRp)/*N* × 100

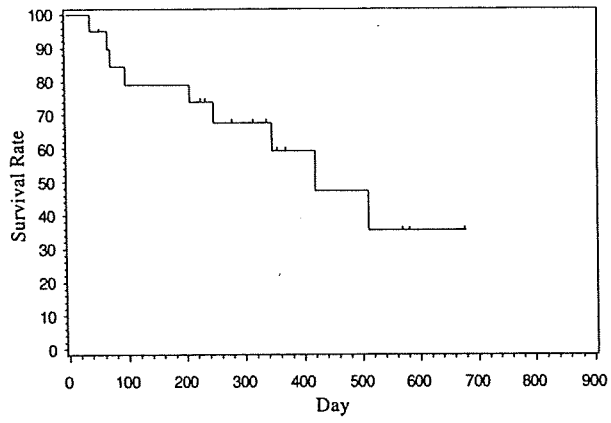

Fig. 1 Overall survival in the phase II part

in the future. Patients who achieved CR also had included those cases poor karyotypes. It has been reported that there is no correlation between karyotype and achievement of CR [12].

Three long-term survivors had the M3 subtype. It should be noted that all of 3 M3 patients achieved CR. This marker is unique as blasts containing M3 on their surface are abundant with CD33. Due to the availability of other highly effective agents (ATRA, arsenic trioxide), relatively few M3 patients have been treated thus far with GO, and their follow-up is still short [13]. As the earlier study did not include M3 cases, this is the first report of GO benefit to M3 patients.

In conclusion, our study confirmed the efficacy and safety of GO when administered as monotherapy. Further studies of GO used in combination with other agents are warranted.

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ORIGINAL ARTICLE

A Phase I/II study of nilotinib in Japanese patients with imatinib-resistant or -intolerant Ph+ CML or relapsed/refractory Ph+ ALL

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Abstract Nilotinib is a second-generation BCR-ABL kinase inhibitor with improved potency and selectivity compared to imatinib. A Phase I/II dose-escalation study was designed to evaluate the efficacy, safety, and pharmacokinetics of nilotinib in Japanese patients with imatinib-resistant or -intolerant Philadelphia chromosome-positive (Ph+) chronic myelogenous leukemia (CML) or relapsed/refractory Ph+ acute lymphoblastic leukemia (ALL). A total of 34 patients were evaluated in this analysis and had a median duration of drug exposure of 293 (range 13–615) days. All 6 CML-CP patients without complete hematologic response (CHR) at baseline rapidly achieved CHR. A major cytogenetic response was achieved in 94% of patients with CML-CP, including a complete cytogenetic response in 69%. A major molecular response was achieved by 56%. These responses were also observed in patients with CML in advanced stages and Ph+ ALL. Non-hematologic adverse events were mostly mild to moderate. Grade 3 or 4

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neutropenia and thrombocytopenia occurred in 50 and 28% of patients, respectively. Overall, the results of this study suggest that nilotinib induced significant responses in imatinib-resistant or -intolerant patients with CML-CP and CML in advanced stages and Ph+ ALL. The results of this study confirmed the efficacy and safety of nilotinib in Japanese patients.

Keywords Nilotinib · CML · BCR-ABL · Imatinib resistant · Ph+ ALL

1 Introduction

The Philadelphia chromosome (Ph), which results from a reciprocal translocation between the long arms of chromosomes 9 and 22, is detected in more than 90% of chronic myeloid leukemia (CML) and 20–30% of adult acute lymphoblastic leukemia (ALL). The Philadelphia chromosome carries the *BCR-ABL* fusion gene, which encodes a constitutively active protein tyrosine kinase [1, 2]. Without BCR-ABL-targeted therapy, CML generally progresses within several years from a stable chronic phase (CP) to an accelerated phase (AP), and terminates in blast crisis (BC) [3]. Ph+ ALL is the most aggressive form of ALL and carries a poor prognosis comparable to CML-BC [4].

Imatinib (Gleevec®, Glivec®; Novartis Pharmaceuticals, Florham Park, NJ), a BCR-ABL tyrosine kinase inhibitor (TKI), has greatly improved the outcome in CML. In newly diagnosed CML patients, treatment with imatinib has shown a complete cytogenetic response (CCyR) rate of 87%, a progression rate to AP or BC of 7%, and an estimated 5-year survival rate of 89% [5, 6]. At the 6-year follow-up, the CCyR rate was 82% with 0% transformation to AP or BC between years 5 and 6, and an estimated 6-year overall survival of 88% [7]. However, resistance and intolerance to imatinib does occur in some patients and, therefore, additional treatment options are necessary to address these unmet medical needs.

Nilotinib (Tasigna®; Novartis Pharmaceuticals) is a second-generation TKI with improved potency and target specificity [8]. Like imatinib, nilotinib binds to and stabilizes an inactive conformation of the kinase domain of the ABL protein, thus preventing the enzyme from adopting the catalytically active conformation and blocking the tyrosine phosphorylation of proteins involved in BCR-ABL signal transduction [8, 9]. Nilotinib has been approved for the treatment of patients with CML-CP and -AP resistant to or intolerant of prior therapy, including imatinib, in 50 countries, including the United States and Europe based on the pivotal Phase II registration study. Responses to nilotinib were rapid and durable, with the vast majority of patients with CML-CP or -AP remaining alive at 12 months. Nilotinib is generally well tolerated, with a minimal occurrence of grade 3/4 drug-related adverse events and a favorable hematologic adverse event profile compared to other second-generation TKIs. Nilotinib also displayed significant activity in imatinib-resistant or -intolerant CML-BC, and relapsed/refractory Ph+ ALL, with significant rates of complete hematologic response (CHR), major cytogenetic response (MCyR), and CCyR [10–14].

This Phase I/II dose-escalation study, including an extension portion of the study, was conducted to confirm the efficacy, safety, and pharmacokinetic profiles of nilotinib in Japanese patients with imatinib-resistant or -intolerant CML or relapsed/refractory Ph+ ALL.

2 Methods

2.1 Study design and patient population

A Phase I/II dose-escalation study with an extension portion of the study was designed to evaluate the efficacy, safety, and pharmacokinetics of nilotinib. Patients who completed at least three 28-day cycles of treatment in the Phase I/II study without discontinuation were enrolled into the extension study. Tolerability up to the dose levels 400 mg BID, clinical dose approved in the US and Europe was confirmed in Japanese patients in a Phase I component [15].

Japanese patients were eligible for this multi-center, open label study when having imatinib-resistant/intolerant Ph+ CML or relapsed/refractory Ph+ ALL who were at least 20 years of age. Patients also needed to have adequate performance status (World Health Organization [WHO] Performance Score [PS] ≤ 2) and normal hepatic, renal, and cardiac functions.

CML-CP, -AP, -BC, Ph+ ALL and Ph+ ALL with minimal residual disease (MRD) were defined as previously described [10–14]. Imatinib resistance in patients with CML-CP was defined as failure to achieve CHR after 3 months, cytogenetic response (CyR) after 6 months, MCyR after 12 months, or loss of a hematologic or cytogenetic response at any time during treatment with imatinib following a minimum of 3 months of imatinib therapy with at least 600 mg/day. Imatinib resistance for CML-AP and -BC was defined by one of the following criteria during treatment with at least 600 mg/day of imatinib: (1) disease progression from chronic phase to accelerated or blast phase occurring during imatinib therapy; (2) disease progression defined as at least a 50% increase in peripheral white blood cell count, blast count, basophils, or platelets during imatinib therapy for accelerated or blast phase; or (3) lack of hematologic response (HR) in the bone marrow following a minimum of 4 weeks of imatinib therapy for