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ORIGINAL ARTICLE

Clinical profile of dasatinib in Asian and non-Asian patients with chronic myeloid leukemia

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Abstract Resistance and intolerance to imatinib are of particular clinical relevance to Asian patients because of their lower body surface area. Dasatinib is 325-fold more potent than imatinib in inhibiting BCR-ABL in vitro and is indicated for the treatment of chronic myeloid leukemia (CML) and Philadelphia chromosome-positive acute lymphoblastic leukemia resistant or intolerant to imatinib. Data from a series of phase I/II research trials were analyzed to compare the efficacy, safety and pharmacokinetic profile of dasatinib 70 mg twice daily in Asian and non-Asian patients. Results from 55 Asian and 615 non-Asian patients demonstrated that the efficacy and safety of dasatinib was comparable. Dasatinib was well tolerated, with no observed toxicities exclusive to Asian patients. A higher incidence of adverse events and lower rate of response observed among Asian patients with myeloid blast phase CML reflected the aggressive nature of the disease. Analyses of noncompartmental pharmacokinetics (5 Asian and 49 non-Asian patients) and population pharmacokinetics (17 Asian and 382 non-Asian patients) were also comparable. The efficacy, safety and pharmacokinetic profile of dasatinib 70 mg twice daily is similar in Asian and non-Asian patients with CML. Dasatinib is therefore an important therapeutic option for this patient population.

Keywords Dasatinib · Chronic myeloid leukemia · Asian · Pharmacokinetics · Cytogenetic response

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1 Introduction

Chronic myeloid leukemia (CML) is a common hematologic malignancy in Asia. CML has a worldwide incidence of 1–2 per 100,000 adults each year [1]. In the Asian population, the incidence of CML is lower with a rate of 1.3 per 100,000 men and 0.7 per 100,000 women [1]. Registry data from a number of Asian countries document a median age at diagnosis of 36–55 years of age, compared to 65 years in USA [2].

Treatment paradigms for CML in Asia are similar to those in other regions. Currently, the first-line therapy is imatinib (Glivec®; Gleevec®; Novartis, Basel, Switzerland). Resistance and intolerance to imatinib are important

clinical issues [3, 4]. Because of a lower body surface area (BSA) in Asian patients [5], there is a concern that the recommended imatinib dose of 400 mg/day will result in increased toxicity or will not be well tolerated. Because of this, lower doses than optimal are often used [5–7]. Previous studies have shown that plasma concentrations of imatinib correlate with both response and safety in patients with CML [8, 9]. Therefore plasma monitoring may be a useful approach to effectively determine imatinib dosing and schedules for Asian patients.

Dasatinib (SPRYCEL®, Bristol-Myers Squibb, New York, NY, USA) was the first agent approved to treat patients with CML who are intolerant or resistant to imatinib. In contrast to imatinib, which can only bind the inactive conformation of BCR-ABL, dasatinib binds both the inactive and active conformations [10]. Preclinical studies have demonstrated that dasatinib is 325-fold more potent than imatinib in inhibiting BCR-ABL in vitro [11], and also potently inhibits Src family kinases [12, 13].

The clinical benefits of dasatinib in imatinib-resistant or -intolerant CML or Philadelphia-chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) have been demonstrated in an extensive development program, including a phase I trial (CA180002) [14] and five phase II studies named START (Src/Abl Tyrosine kinase inhibition Activity Research Trials of dasatinib) [15–19]. The current report analyzes data obtained from these six trials to determine whether the efficacy, safety and pharmacokinetic (PK) profile of dasatinib is comparable in Asian and non-Asian patients.

2 Materials and methods

2.1 Study design

The design and methods of dasatinib trials have been reported previously [14–19]. Briefly, CA180002 was a phase I dose escalation study evaluating dasatinib 15–180 mg/day administered using either a once- (QD) or twice-daily (BID) schedule in patients with CML (chronic, accelerated or blast phase) or Ph+ ALL [14].

Four of the START trials were single-arm studies with the recruited patients in each disease status: chronic (START-C; CA180013) [15], accelerated (START-A; CA180005) [16], myeloid blast CML (START-B; CA180006) [17], or lymphoid blast phase CML or Ph+ ALL (START-L; CA180015) [19]. A fifth trial (START-R, CA180017) was a randomized trial that compared efficacy between dasatinib vs. high-dose imatinib (800 mg/day) [18]. In all five START trials, patients were treated with dasatinib 70 mg BID. Dose could be escalated to 90 mg BID [15, 18] or 100 mg BID [16, 17, 19] for lack of response, or reduced to 50 and then 40 mg BID for toxicity [15–19].

2.2 Efficacy

Standard efficacy assessments were used, which have been reported previously [14–19]. Hematologic responses were assessed through complete blood counts. Cytogenetic responses were assessed every 12 weeks using conventional cytogenetic analysis with at least 20 metaphase cells from bone marrow, and were classified according to the percentage of Ph+ cells. Responses are reported as the best response during the total follow-up period.

2.3 Safety

Adverse events (AEs) were graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0.

2.4 Non-compartmental pharmacokinetic (NC-PK) analysis

At the time of this analysis, PK data, available from patients in START-A and -B studies, were included in this report. Blood samples for PK analysis were collected during Cycle 1 following morning doses on day 1 and day 8 at the following time points: predose, 30 min post dose, and 1, 1.5, 2, 3, 4, 5, 6, 8, and 10 h post dose. Blood samples (3–5 mL) were collected from a peripheral vein using Becton Dickinson Vacutainers® containing potassium ethylenediaminetetraacetic acid (K_3 EDTA) as the anticoagulant. Samples were placed on crushed ice and centrifuged for 5 min at 2,000×g at 0–5°C within 30 min of collection. Plasma samples were transferred to separate polypropylene tubes and stored frozen at –20°C prior to analysis. Samples were assayed for dasatinib concentration using a cross-validated liquid chromatography tandem mass spectrometry method developed by Bristol-Myers Squibb and Cedra Corporation (Texas, USA). NC-PK parameters were derived from plasma concentration–time data with a non-compartmental method using Kinetica™ Basic Version 4.4.1 in the eToolbox (version 2.6.1; Thermo Electron Corporation, Pennsylvania, USA). Parameters included maximum plasma concentration (C_{max}), time of C_{max} (T_{max}) (both obtained from experimental observations), apparent plasma elimination half-life ($T_{1/2}$) (calculated as $\ln 2/L_z$, where L_z was the absolute value of the slope of the terminal log-phase), and the area under the curve (AUC) from baseline to the last time point where dasatinib plasma concentration was quantifiable [AUC_{0-T}].

2.5 Population pharmacokinetic (PPK) analysis

The characterization of dasatinib PPK has been described in detail elsewhere [20]. The PPK analysis dataset included data from the phase I study (CA180002), and the five START trials that were available as of 5 December 2005. The following covariates were examined in the PPK analysis: body weight, age, gender, race (Caucasian, black/African-American, Hispanic, Asian, Other), smoking status, disease status, prior imatinib treatment, nominal dose, and clinical laboratory indicators of baseline hepatic [alanine aminotransferase (ALT) and aspartate aminotransferase (AST)] and renal status (creatinine clearance calculated by the Cockcroft–Gault equation). Time-varying covariates tested included hemoglobin, white blood cell count, and concomitant medications. The PPK of dasatinib was characterized by a linear, two-compartment open model with first-order absorption. Individual estimates of dasatinib steady-state exposure (AUC_{SS}) at a given dose were obtained from individual estimates of apparent clearance (CL/F), and relative bioavailability (F_R), using: $AUC\text{-}ss = Dose/(CL/F)/F_R$.

3 Results

3.1 Baseline patient characteristics

At the time of analysis, of the 911 patients enrolled in the phase I study and the five START trials, 64 were Asian. The Asian countries in which these patients resided included Korea (26 patients), Thailand (10 patients), Singapore (6 patients), Taiwan (5 patients), and Philippines (2 patients). The remaining 15 Asian patients resided in the US, Canada, EU, and Australia. Patients were enrolled in START-A ($n = 24$), START-B ($n = 18$), START-C ($n = 13$), START-R ($n = 6$), START-L ($n = 2$) and 002 ($n = 1$). The safety and efficacy analyses for Asian versus non-Asian subjects were conducted only on the 55 subjects who were enrolled and treated in the three single-arm phase II studies (START-A, START-B and START-C). Due to differences in experimental design and the small number of Asian patients, data from the START-R and -L trials and the phase I study were not included in the safety and efficacy analyses.

Compared with non-Asian patients enrolled in these trials, baseline characteristics of the Asian patients were broadly similar (Table 1). However, Asian patients were younger, had shorter duration of CML prior to entry, and were pre-treated less intensively compared with non-Asian subjects. Fewer Asian patients had received high-dose imatinib. The duration of dasatinib therapy was similar between Asian and non-Asian patients in START-A and -C (median duration: 6 months for Asian patients and 7 months for non-Asian patients), but shorter in START-B in the Asian group (2 vs. 5 months). In START-B, Asian patients had a higher incidence of abnormal hematologic parameters at baseline because of their disease phases which were more advanced at study entry.

3.2 Efficacy

Overall, hematologic and cytogenetic response rates in Asian patients with chronic phase CML appeared to be slightly higher than in non-Asian patients, while efficacy rates were similar in patients with accelerated phase CML (Table 2). Response rates in Asian patients with myeloid blast phase CML appeared to be lower than in the non-Asian group. However, efficacy data in Asian and non-Asian populations were not suitable for statistical comparison because of the study design.

3.3 Safety

In general, rates of treatment-related AEs in Asian patients were representative of those reported in all patients on dasatinib (Table 3). The most frequent AEs (experienced by more than 30% of Asian patients in any of the three trials) were headache, diarrhea, pyrexia, pleural effusion, acne and fatigue. The majority of AEs were mild to moderate. Across all three trials, more Asian patients experienced GI bleeding. None of the Asian patients from START-A and START-C experienced grade 3/4 pleural effusions, whereas in START-B there was a higher incidence of grade 3/4 pleural effusions in the Asian than the non-Asian population. Grade 3/4 cytopenias were common; compared to the non-Asian patients a higher proportion of Asian patients had thrombocytopenia, neutropenia and anemia across all disease phases, except for patients with chronic phase CML where the incidence of anemia was lower in the Asian subgroup (8 vs. 20%).

The death rate was low and there were fewer deaths in the Asian compared to the non-Asian population in the START-A and -C studies (Asian vs. non-Asian deaths: 4 vs. 7% [START-A]; 0 vs. 2% [START-C], respectively). Of the 12 Asian patients who died, 11 were from the START B study (myeloid blast phase CML). Reasons for death assigned by study investigators were disease progression ($n = 6$), infection ($n = 4$), and other causes ($n = 2$).

3.4 Non-compartmental pharmacokinetics

Pharmacokinetic data with intensive schedule are available for 5 Asian and 51 non-Asian patients who received 70 mg BID in START-A and START-B. The countries in which

Table 1 Demographics and baseline characteristics of Asian and non-Asian patients included in the efficacy and safety analyses

	Chronic phase CML (START-C)		Accelerated phase CML (START A)		Myeloid blast phase CML (START B)	
	Asian ($n = 13$)	Non-Asian ($n = 374$)	Asian ($n = 24$)	Non-Asian ($n = 150$)	Asian ($n = 18$)	Non-Asian ($n = 91$)
Median age, years (range)	44 (34–66)	58 (21–85)	47 (22–65)	58 (22–86)	48 (21–70)	55 (25–81)
Gender (%)						
Female	46	51	42	45	39	43
Male	54	49	58	55	61	57
Median time from diagnosis of CML to first dosing date, months (range)	41 (6–107)	63 (3–251)	58 (21–174)	85 (4–359)	29 (7–144)	50 (3–215)
Prior therapy (%)						
Chemotherapy	23	35	50	60	56	62
Interferon-a	46	66	75	72	28	53
Allogeneic SCT	8	10	0	15	22	12
Highest imatinib dose (%)						
<400 mg	0	<1	0	0	0	0
400–600 mg	62	44	67	45	61	47
>600 mg	38	56	33	55	39	52
Imatinib therapy duration (%)						
<1 year	23	19	4	11	22	19
1–3 years	38	27	54	27	56	36
>3 years	38	54	42	62	22	45
Response prior to imatinib failure (%)						
Complete hematologic response	77	82	71	81	78	75
Major cytogenetic response	38	37	29	33	39	45
Complete cytogenetic response	15	20	13	12	28	31
WBC count of at least 20,000 mm^3 (%)	8	29	33	46	56	44
Platelet count below 100,000/mm^3 (%)	23	6	21	40	83	60
Peripheral blasts at least 30% (%)	0	0	0	5	56	33
Marrow blasts at least 50% (%)	0	0	0	1	44	30

Table 2 Hematologic and cytogenetic responses to dasatinib

	Chronic phase CML (START-C)		Accelerated phase CML (START A)		Myeloid blast phase CML (START B)	
	Asian ($n = 13$)	Non-Asian ($n = 374$)	Asian ($n = 24$)	Non-Asian ($n = 150$)	Asian ($n = 18$)	Non-Asian ($n = 91$)
Complete hematologic response						
n (%)	13 (100)	336 (90)	6 (25)	53 (35)	2 (11)	25 (27)
95% CI	75.3–100	86.3–92.7	9.8–46.7	27.7–43.5	1.4–34.7	18.6–37.8
Major cytogenetic response						
n (%)	8 (62)	189 (51)	9 (38)	51 (34)	1 (6)	33 (36)
95% CI	31.6–86.1	45.3–55.7	18.8–59.4	26.5–42.2	0.1–27.3	26.4–47.0
Complete cytogenetic response						
n (%)	6 (46)	147 (39)	7 (29)	36 (24)	1 (6)	26 (29)
95% CI	19.2–74.9	34.3–44.5	12.6–51.1	17.4–31.6	0.1–27.3	19.6–39.0

these Asian patients were treated were Korea (three patients on day 1 and two patients on day 8), USA (one patient on days 1 and 8) and France (one patient on day 8). Out of these treated patients, PK data from four patients each on days 1 and 2 were evaluable. NC-PK parameters of Asian and non-Asian patients are summarized in Table 4.

Table 3 Treatment-related adverse events

	Patients, *n* (%)					
	Chronic phase CML (START-C)		Accelerated phase CML (START A)		Myeloid blast phase CML (START B)	
	Asian ($n = 13$)	Non-Asian ($n = 374$)	Asian ($n = 24$)	Non-Asian ($n = 150$)	Asian ($n = 18$)	Non-Asian ($n = 91$)
Non-hematologic*						
Headache						
All grades	3 (23)	111 (30)	9 (38)	38 (25)	1 (6)	9 (10)
Grade 3–4	0	4 (1)	0	1 (1)	1 (6)	1 (1)
Rash						
All grades	3 (23)	82 (22)	7 (29)	22 (15)	2 (11)	13 (14)
Grade 3–4	0	2 (1)	1 (4)	0	0	0
Diarrhea						
All grades	5 (38)	119 (32)	6 (25)	73 (49)	7 (39)	33 (36)
Grade 3–4	0	8 (2)	0	11 (7)	0	7 (8)
Pyrexia						
All grades	1 (8)	51 (14)	6 (25)	32 (21)	6 (33)	14 (15)
Grade 3–4	0	3 (1)	0	5 (3)	2 (11)	3 (3)
Dizziness						
All grades	1 (8)	21 (6)	5 (21)	13 (9)	1 (6)	0
Grade 3–4	0	1 (<1)	0	0	0	0
Myalgia						
All grades	1 (8)	24 (6)	5 (21)	13 (9)	1 (6)	3 (3)
Grade 3–4	0	0	0	1 (1)	0	0
Nausea						
All grades	1 (8)	87 (23)	5 (21)	39 (26)	2 (11)	18 (20)
Grade 3–4	0	2 (1)	0	0	0	4 (4)
Petechiae						
All grades	0	8 (2)	5 (21)	16 (11)	4 (22)	6 (7)
Grade 3–4	0	1 (<1)	1 (4)	1 (1)	0	1 (1)
Pleural effusion						
All grades	0	67 (18)	5 (21)	32 (21)	9 (50)	24 (26)
Grade 3–4	0	11 (3)	0	3 (2)	6 (33)	8 (9)
Weight decrease						
All grades	0	14 (4)	5 (21)	8 (5)	1 (6)	4 (4)
Grade 3–4	0	0	1 (4)	1 (1)	0	0
Arthralgia						
All grades	1 (8)	25 (7)	4 (17)	12 (8)	2 (11)	7 (8)
Grade 3–4	0	2 (1)	0	0	0	2 (2)
Cough						
All grades	1 (8)	39 (10)	4 (17)	10 (7)	3 (17)	7 (8)
Grade 3–4	0	0	0	1 (1)	0	1 (1)
Fatigue						
All grades	2 (15)	102 (27)	4 (17)	37 (25)	6 (33)	13 (14)
Grade 3–4	0	6 (2)	1 (4)	6 (4)	0	1 (1)
GI hemorrhage						
All grades	1 (8)	5 (1)	4 (17)	12 (8)	5 (28)	6 (7)
Grade 3–4	1 (8)	1 (<1)	2 (8)	7 (5)	2 (11)	4 (4)
Upper abdominal pain						
All grades	0	18 (5)	4 (17)	7 (5)	2 (11)	4 (4)
Grade 3–4	0	1 (<1)	0	0	0	0

Table 3 continued

	Patients, *n* (%)					
	Chronic phase CML (START-C)		Accelerated phase CML (START A)		Myeloid blast phase CML (START B)	
	Asian ($n = 13$)	Non-Asian ($n = 374$)	Asian ($n = 24$)	Non-Asian ($n = 150$)	Asian ($n = 18$)	Non-Asian ($n = 91$)
Vomiting						
All grades	0	35 (9)	4 (17)	26 (17)	3 (17)	19 (21)
Grade 3–4	0	1 (<1)	1 (4)	2 (1)	0	2 (2)
Acne						
All grades	4 (31)	13 (3)	3 (13)	6 (4)	2 (11)	1 (1)
Grade 3–4	0	1 (<1)	0	0	0	0
Anorexia						
All grades	1 (8)	43 (11)	2 (8)	22 (15)	3 (17)	9 (10)
Grade 3–4	0	0	0	1 (1)	0	1 (1)
Mucosal inflammation						
All grades	0	2 (1)	2 (8)	2 (1)	3 (17)	1 (1)
Grade 3–4	0	0	0	0	0	0
Paresthesia						
All grades	3 (23)	8 (2)	0	2 (1)	2 (11)	2 (2)
Grade 3–4	0	0	0	1	0	0
Purpura						
All grades	0	1 (<1)	0	4 (3)	3 (17)	4 (4)
Grade 3–4	0	0	0	0	0	1 (1)
Hematologic						
Thrombocytopenia						
All grades	1 (8)	75 (20)	4 (17)	18 (12)	3 (17)	11 (12)
Grade 3–4	1 (8)	63 (17)	4 (17)	18 (12)	3 (17)	11 (12)
Neutropenia						
All grades	1 (8)	48 (13)	3 (13)	11 (7)	2 (11)	11 (12)
Grade 3–4	1 (8)	46 (12)	3 (13)	11 (7)	2 (11)	10 (11)
Anemia						
All grades	0	38 (10)	1 (4)	16 (11)	2 (11)	9 (10)
Grade 3–4	0	17 (5)	1 (4)	10 (7)	2 (11)	8 (9)
Leukopenia						
All grades	0	5 (1)	1 (4)	2 (1)	1 (6)	3 (3)
Grade 3–4	0	3 (1)	1 (4)	2 (1)	0	2 (2)

* Adverse events experienced by >15% of Asian patients in any one study

PK parameters were comparable among Asian and non-Asian patients, with the exception that the AUC on day 8 was approximately twofold higher in Asian compared to non-Asian patients (Table 4). The distribution of individual AUCs observed among Asian patients on day 8 was all within the range observed in non-Asian patients (Fig. 1). As stated in the dasatinib prescribing information, concomitant medications such as CYP3A substrates, inducers, inhibitors, H_2-blocker antagonist and proton pump inhibitors have been found to influence the exposure of dasatinib [21]. The distribution of individual AUCs on day 8 for Asian and non-Asian subjects after excluding subjects on concomitant medications showed that AUCs observed among non-Asians were comparable to those observed among Asian patients (the difference in AUC on day 8 was $\sim$ 1.5-fold; Fig. 2).

3.5 Population pharmacokinetics

Data from 399 patients were included in the population PK analysis [20]. Of these, 17 patients (4.3%) were Asian: 9 enrolled in clinical sites in Asia (Korea, Singapore, and Thailand) and 8 in Europe or USA. None of the covariates examined (including age, gender, and race) had statistically significant (likelihood ratio test, $P < 0.001$ to account for multiplicity) and clinically relevant (greater than 20%

Table 4 Summary of pharmacokinetics parameter in Asian and non-Asian patients (START-B/-C)

Patient population	Study day (n)	C_{max} (ng/mL) Geometric mean (CV%)	$AUC_{(0-T)}$ (ng h/mL) Geometric mean (CV%)	T_{max} (h) Median (min, max)	$T_{1/2}$ (h) Mean (SD)
Asian	1 ($n = 4$)	51.5 (68)	145.8 (80)	1.0 (0.5, 5.0)	2.67 (0.81)
	8 ($n = 4$)	115.1 (46)	472.2 (16)	2.3 (0.5, 4.8)	6.55 (3.43)
Non-Asian	1 ($n = 49$)	45.2 (76)	143.1 (74)	1.0 (0.4, 6.0)	3.45 (1.38)
	8 ($n = 46$)	75.0 (63)	206.7 (69)	0.8 (0.0, 3.0)	4.77 (2.02)

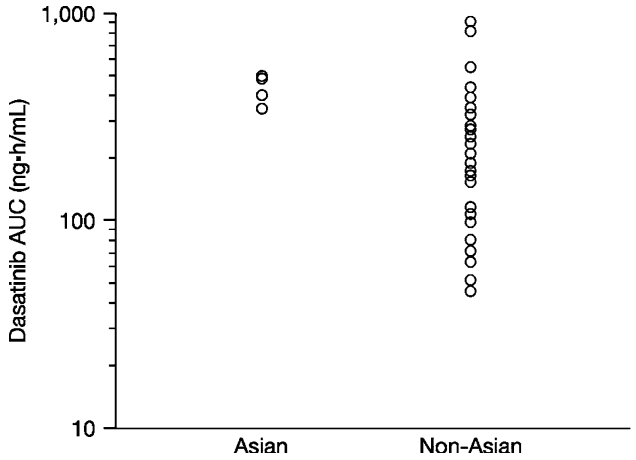

Fig. 1 Individual AUC values of dasatinib in Asian versus non-Asian patients at steady state (day 8) after administration of 70 mg BID dose

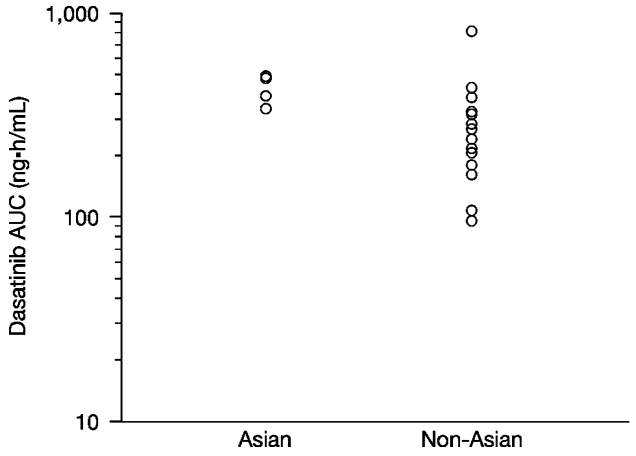

Fig. 2 Individual AUC values of dasatinib in Asian versus non-Asian patients with exclusion of subjects who received concomitant medications at steady state (day 8) after administration of 70 mg BID dose

effect) effects on dasatinib PK parameters. The AUC_{ss} for dasatinib 70 mg BID in Asian patients ($n = 13$) was within the AUC_{ss} range in non-Asian ($n = 322$) patients (Fig. 3). The geometric mean AUC_{ss} for Asian and non-Asian populations were comparable (315.0 vs. 248.3 ng h/mL).

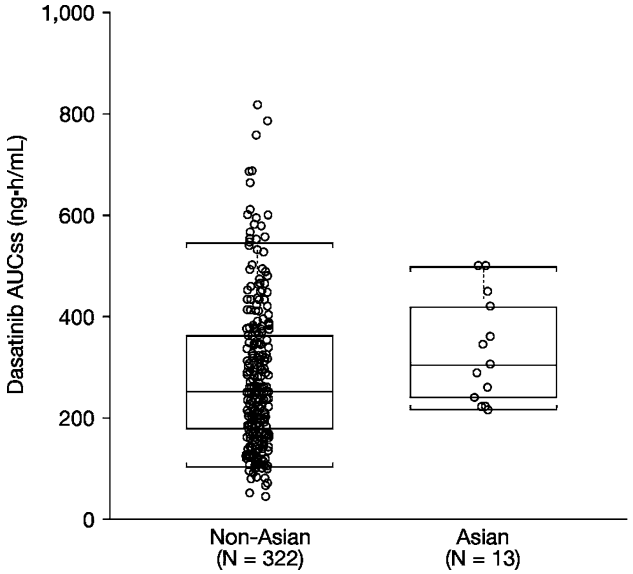

Fig. 3 Individual estimates of dasatinib AUCss for a dosage regimen of 70 mg BID in Asian and non-Asian patients. The *dots* are individual estimated AUCss and the median for each group is indicated by the *center line* within the box. The *box* represents inter-quartile range (25–75%) and whiskers are 5 and 95%. Geometric mean AUCss for non-Asian and Asian patients are 248 and 315 ng h/mL, respectively

4 Discussion

Dasatinib provides effective treatment for adults with all phases of CML or Ph+ ALL following resistance or intolerance to imatinib. The results reported here show that in Asian patients dasatinib has similar efficacy, safety and PK profile compared to those of dasatinib in non-Asian patients. Dasatinib provides an important therapeutic option in Asian patients, many of whom have no alternatively approved treatment options.

Although this study was not designed to allow statistical comparisons between patient populations, we observed comparable results between the Asian and non-Asian patients. Among the 13 Asian patients with chronic phase CML (START-C), hematologic and cytogenetic response rates appeared to be higher than in non-Asian patients, In the 24 Asian patients with accelerated phase CML (START-A), responses were similar, whereas in 18 patients

with myeloid blast phase CML (START-B), response rates were lower than in non-Asian patients.

During this analysis, dasatinib had a favorable tolerability profile, and no unexpected toxicities exclusive to Asian patients were observed. Safety results between Asian and non-Asian patients with chronic or accelerated phase CML (START-C and -A) were comparable. Asian patients with myeloid blast phase CML (START-B) had a higher incidence of pleural effusions and GI bleeding. Most treatment-related AEs were grade 1/2. As reported previously, grade 3/4 cytopenias observed during dasatinib treatment were generally reversible with dose interruptions or reductions [15–19]. Similarly, pleural effusions were manageable through dose reductions or interruptions and use of supportive care such as diuretics and/or pulse steroid therapy [22].

A recent phase III dose optimization trial has investigated the effects of dasatinib administered at a dose of 100 mg QD in patients with imatinib-resistant or -intolerant chronic phase CML. Compared with the approved 70 mg BID schedule, dasatinib 100 mg QD was associated with equivalent efficacy and a significantly lower incidence of key AEs, including pleural effusion and grade 3/4 thrombocytopenia [23]. A subsequent PK analysis demonstrated that the 100 mg QD dose was associated with a low dasatinib steady-state trough plasma concentration, which correlated with a reduced incidence of key toxicities and fewer dose interruptions [24]. Based on these results the recommended daily dose of dasatinib for patients with chronic-phase CML was recently changed from 70 mg twice daily to 100 mg QD in several countries, including Korea, Hong Kong, Malaysia, India and the Philippines. Dasatinib 100 mg QD dosing is likely to further improve tolerability in Asian patients compared to the safety data reported here.

The lower efficacy and safety among the Asian patients with myeloid blast phase CML (START-B) may reflect the aggressive nature of this disease phase. Myeloid blast phase CML represents an advanced stage of leukemia with a median survival of only 2–6 months [25]. Although the Asian patients were generally younger, had shorter disease duration, and had received less amounts of imatinib than their non-Asian counterpoints, baseline hematology characteristics suggested that these patients had more advanced disease at study entry. Clinical features associated with a poor prognosis in myeloid blast phase include clonal evolution, bone marrow blasts >50%, and platelet counts $<50 \times 10^9$/L [26]. However, other factors that were not evaluated in this analysis, namely, presence of T315I mutation may also have affected outcomes.

The favorable safety profile of dasatinib in Asian patients reported here is supported by an ongoing Japanese phase I/II dose-finding study. In the phase I portion of the trial, treatment was generally well tolerated [27]. Of the 16 patients treated with dasatinib (50–90 mg BID, $n = 16$), only two patients (treated with 50 and 70 mg) had dose-limiting toxicity (both grade 4 thrombocytopenia). Major cytogenetic responses were reported in all three cohorts. Thirty-six patients with different phases of CML or Ph+ ALL were included in the phase II portion of the trial. Further results from the trial are eagerly awaited.

The results of both noncompartmental and population PK analyses between Asian and non-Asian patients were generally comparable, except for an increased exposure to dasatinib in Asian patients on day 8. However, exposure to dasatinib in non-Asian patients was more variable, which may have contributed to the lower mean AUC. One possible source of variability is the use of a broader range of concomitant medications (because of the variety of participating sites) by non-Asian patients, such as CYP substrates/inhibitors/inducers and gastric pH modulators (H_2-blockers/proton pump inhibitors). CYP3A4 is the major enzyme involved in the metabolism of imatinib and dasatinib [28]. In an investigation to determine the influence of rifampicin, a potent inducer of CYP3A4, on dasatinib exposure, following co-administration of dasatinib and rifampicin, the C_{max} and AUC of dasatinib decreased by approximately 80% [21, 29]. Exposure of dasatinib is increased by approximately four- to fivefold in the presence of the potent CYP3A4 inhibitor, ketoconazole. Genetic polymorphism in Asian breast cancer patients has been associated with altered pharmacokinetics, of doxorubicin resulting in significantly increased exposure levels and reduced clearance [30]. However, because CYP3A4 is not known to have genetic polymorphisms; this is unlikely to cause exposure differences among Asian and non-Asian CML patients treated with dasatinib.

In conclusion, the results of this analysis demonstrate that the efficacy and safety of dasatinib 70 mg BID is similar in Asian and non-Asian patients with CML. Additional analyses are warranted to assess the longer-term benefits of dasatinib in the Asian population and possible tolerability improvements associated with the dasatinib 100 mg once-daily dose.

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