Dasatinib induces significant hematologic and cytogenetic responses in patients with imatinib-resistant or -intolerant chronic myeloid leukemia in accelerated phase

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Treatment options are limited for patients with imatinib-resistant or -intolerant accelerated phase chronic myeloid leukemia (CML-AP). Dasatinib is a novel, potent, oral, multitargeted kinase inhibitor of BCR-ABL and SRC-family kinases that showed marked efficacy in a phase 1 trial of patients with imatinib-resistant CML. Results are presented for 107 patients with CML-AP with imatinib-resistance or -intolerance from a phase 2, open-label study further evaluating dasatinib efficacy and safety. At 8 months' minimum follow-up, 81%, 64%, and 39% of patients achieved overall, major (MaHR), and complete hematologic responses, respectively, whereas 33% and 24% attained major and complete cytogenetic remission. Of 69 patients who achieved MaHR, 7 progressed. Seventy-six percent of patients are estimated to be alive and progression-free at 10 months. Response rates for the 60% of patients with baseline *BCR-ABL* mutations did not differ from the total population. Dasatinib was well tolerated: most nonhematologic adverse events (AEs) were mild to moderate; no imatinib-intolerant patients discontinued dasatinib because of AEs. Although common (76% of patients with severe neutropenia), cytopenias were manageable through dose modification. In summary, dasatinib induced significant hematologic and cytogenetic responses in patients with imatinib resistance or intolerance, was well tolerated, and may represent a potent new therapeutic option for CML-AP. Further follow-up is warranted. This trial was registered at www.clinicaltrials.gov as #CA180005. (Blood. 2007;109:4143-4150)

Introduction

Dasatinib (BMS-354825; Bristol-Myers Squibb, New York, NY) is a novel, oral, multitargeted kinase inhibitor of BCR-ABL and SRC family kinases (SFKs), that in vitro has demonstrated 325-fold greater potency compared with imatinib mesylate in cells transduced with unmutated BCR-ABL.[1] A recent phase 1 dose-escalation study has shown that dasatinib has considerable activity and an excellent safety profile in the treatment of patients with imatinib-resistant or -intolerant chronic myeloid leukemia (CML) in all disease phases.[2]

CML is a malignant clonal disorder of hematopoietic stem cells that results in increased numbers of myeloid cells, erythroid cells, and platelets in the peripheral blood, and myeloid hyperplasia in the bone marrow.[3] It is well established that the expression of a constitutively activated tyrosine kinase, BCR-ABL, which is sufficient to generate the CML phenotype in normal cells,[4,5] leads to the development of CML in humans. The *BCR-ABL* fusion gene occurs as a result of a reciprocal translocation between chromosomes 9 and 22, producing the shortened 22q known as the Philadelphia chromosome (Ph).[6] CML typically progresses via 3 phases: chronic, accelerated, and blast.[7] Definitions of accelerated phase (AP) vary, but the term is typically used to describe patients who show certain signs of disease progression and resistance to therapy, but who do not yet meet the criteria for blast phase.[8] Key features of AP include significant increases in peripheral blood and bone marrow blasts or basophils, development of extramedullary disease, extremes in platelet levels, increasing drug requirements, unresponsive splenomegaly, and persistent fever or bone pain.[8,9]

Although the current mainstay of CML treatment, imatinib, inhibits the BCR-ABL fusion protein, resistance to imatinib represents an important clinical problem, especially in later stages of CML. Forty percent to 50% of patients with accelerated phase CML (CML-AP) were estimated to have developed imatinib resistance after 2 years of treatment; that percentage increased to 75% after 4 years of treatment.[10,11] In addition to the problem of imatinib resistance, intolerance may be a concern

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among a small subset of patients. In a phase 2 study of imatinib, 4% of patients with CML-AP experienced adverse events (AEs) so severe that treatment was discontinued.[12] Treatment options for patients with CML-AP who have imatinib-intolerant or -resistant disease are extremely limited. Allogeneic stem cell transplantation is an alternative, but it is associated with significant early morbidity and mortality and is restricted by the availability of suitable donors.[13-15] Therefore, alternative therapies are needed for this patient group.

Resistance to imatinib is frequently associated with BCR-ABL point mutations, the majority of which prevent BCR-ABL from adopting the inactive conformation required for imatinib binding.[16] However, a number of other likely mechanisms of resistance exist, including BCR-ABL amplification and activation of alternative signaling pathways, such as those involving the SFKs.[17-22] Evidence suggests that these SFKs, functioning downstream and upstream of BCR-ABL and in BCR-ABL–independent pathways, may play a role in the progression of CML to the more aggressive phenotypes of advanced disease.[23-25] A number of genetic abnormalities have been identified that may be associated with progression from chronic to blast phases, including duplication of the Ph chromosome, trisomy of chromosome 8 or 19, isochromosome 17(q), and mutations in p53, p16/ARF, and Rb.[26] A recent microarray study identified a number of progression-associated events, including WNT/β-catenin pathway dysregulation, decreased Jun B and Fos expression, alternative kinase dysregulation, and increased PRAME expression.[27]

Dasatinib was rationally designed to comprehensively target the underlying causes of imatinib resistance that have been identified to date.[16-22] Dasatinib has shown preclinical inhibitory activity against 21 of 22 imatinib-resistant mutants of BCR-ABL tested and potently inhibits the SFKs implicated in imatinib resistance.[1,28,29] In separate preclinical in vivo studies using mouse models of CML, dasatinib prevented the progression of CML from chronic to blast phase[30] and prolonged survival of animals bearing patient-derived CML cell lines grown at various sites, including the central nervous system.[31]

Here, we report the initial results for the first 107 treated patients enrolled in a phase 2, open-label, single-arm, multinational study designed to further evaluate the efficacy and safety of dasatinib in patients with imatinib-resistant or -intolerant CML-AP. Results are summarized in tabular format for a formal interim analysis conducted with a minimum follow-up of 6 months; a subsequent analysis extending the follow-up to at least 8 months forms the main focus for this present report.

Patients and methods

Objectives

The primary objective of the study was to determine the major hematologic response (MaHR) and overall hematologic response (OHR) rates to dasatinib in patients with imatinib-resistant CML-AP. Secondary objectives included: the determination of the durability of hematologic responses, the hematologic and cytogenetic response rates, and the assessment of the safety and tolerability of dasatinib. Baseline mutational analyses were also performed to assess responses to dasatinib in the context of specific BCR-ABL mutations.

Patients

Patients were recruited to the study at 40 clinical sites worldwide. Male and female patients, aged 18 years or older, were eligible for inclusion if they had Ph^+ or BCR-ABL–positive CML-AP with primary or acquired hematologic resistance or intolerance to imatinib therapy. Accelerated phase CML was defined by the occurrence of one or more of the following: (1) at least 15% to less than 30% blasts in peripheral blood (PB) or bone marrow (BM), (2) at least 30% blasts plus promyelocytes (summed) in PB or BM (but with $< 30\%$ blasts alone), (3) at least 20% basophils in PB or BM, (4) platelet counts less than 100×10^9/L ($100\,000/mm^3$) unrelated to drug therapy.[9]

The definition of resistance to imatinib differed depending on the initial CML diagnosis. Patients with an initial diagnosis of chronic phase CML were defined as having resistant disease if (1) progression to CML-AP occurred while receiving imatinib 400 or more mg/d or (2) no hematologic response was achieved after at least 4 weeks (or ≥ 2 weeks for patients who progressed rapidly) of imatinib 600 or more mg/d (or 400 to < 600 mg/d if the patient was intolerant of ≥ 600 mg/d). Patients with an initial diagnosis of CML-AP or blast crisis who had experienced a hematologic response were defined as having resistant disease if progression to CML-AP occurred while receiving imatinib 600 or more mg/d (or 400 to < 600 mg/d if the patient was intolerant of ≥ 600 mg/d). Patients were defined as having imatinib-intolerant CML-AP if they had toxicity which led to a discontinuation of therapy and was considered to be possibly related to imatinib at a dose of no more than 400 mg/d, or if they could only tolerate imatinib doses less than 400 mg/d.

Patients were also required to have adequate hepatic function, defined as total bilirubin no more than 2.0 times the institutional upper limit of normal (ULN), alanine aminotransferase and aspartate aminotransferase levels no more than 2.5 times the institutional ULN, in addition to adequate renal function defined as serum creatinine levels no more than 1.5 times ULN. Patients were excluded from the study if they had an Eastern Cooperative Oncology Group (ECOG) performance status of grade 3 or greater, uncontrolled or significant cardiovascular disease, or a history of a significant bleeding disorder unrelated to CML.

Study treatment

Following screening, eligible patients received dasatinib 70 mg twice daily (140 mg total daily dose), based on the previously reported outcome of a phase 1 dose-escalation study.[2] Treatment with dasatinib continued until progression of disease despite dose escalation or development of intolerable toxicity. Following the last dose of study therapy, all patients were followed for a minimum of 30 days or until recovery from all toxic effects, whichever was longer. Follow-up visits occurred at least every 4 weeks until all study-related toxicities resolved to baseline or National Cancer Institute Common Toxicity Criteria (NCI CTC) no greater than grade 1, stabilized, or were deemed irreversible.

Dose modifications were allowed for the management of disease progression or toxicity after one cycle of treatment, defined as 4 weeks (28 days). Dose escalation to 100 mg dasatinib twice daily was permitted for patients meeting any of the following criteria: rising percentage of blasts on 2 consecutive hematologic assessments at least 1 week apart, no complete hematologic response (CHR) within 1 month of dasatinib initiation, no complete cytogenetic response (CCyR) after 3 or more months of dasatinib treatment, or a loss of response.

Treatment was reduced or interrupted in response to hematologic or nonhematologic toxicity as defined by the NCI CTC Version 3.0. For patients with grade 2 to 4 nonhematologic toxicity considered to be at least possibly related to dasatinib, treatment was interrupted until recovery to no greater than grade 1 or baseline levels. Treatment was reinitiated at the original dose for the first grade 2 event but reduced by one dose level for a recurrence of the same event and reduced by a second dose level for a further recurrence. Dose reductions or interruption due to hematologic toxicity were only considered after 14 days of treatment for patients with grade 4 neutropenia (absolute neutrophil count [ANC] $< 0.5 \times 10^9$/L [$500/mm^3$]). Bone marrow aspirate and biopsy were performed, and if marrow cellularity was less than 10%, treatment was interrupted until ANC was greater than 1.0×10^9/L ($1000/mm^3$); treatment was interrupted regardless of biopsy results if grade 4 neutropenia persisted for 4 weeks. Treatment was reinitiated at the original dose for the first event and at a lower dose level for recurring events. If grade 4 neutropenia occurred for a fourth time a decision on further dose reductions or discontinuation was made by the investigator

Table 1. Hematologic response criteria

Major hematologic response (MaHR)
Complete hematologic response (CHR)
White blood cell (WBC) count no more than institutional ULN
Absolute neutrophil count (ANC) $\geq 1 \times 10^9$/L (1000/mm^3)
Platelet count $\geq 100 \times 10^9$/L (100 000/mm^3)
No blasts or promyelocytes in peripheral blood
Bone marrow blasts $\leq 5\%$
Less than 5% myelocytes plus metamyelocytes in peripheral blood
Basophils in peripheral blood $< 2\%$ and basophils in the bone marrow $< 2\%$
No extramedullary involvement (including no hepatomegaly or splenomegaly)
No evidence of leukemia (NEL)
WBC count no more than institutional ULN
No blasts or promyelocytes in peripheral blood
Bone marrow blasts $\leq 5\%$
Less than 5% myelocytes plus metamyelocytes in peripheral blood
No extramedullary involvement (including no hepatomegaly or splenomegaly)
Basophils in peripheral blood $< 2\%$ and at least one of the following:
20×10^9/L (20 000/mm^3) $\leq$ platelets $< 100 \times 10^9$/L (100 000/mm^3)
0.5×10^9/L (500/mm^3) $\leq$ ANC $< 1.0 \times 10^9$/L (1000/mm^3)
Minor hematologic response (MiHR)
Less than 15% blasts in bone marrow and in peripheral blood
Less than 30% blasts plus promyelocytes in bone marrow and $< 30\%$ blasts plus promyelocytes in peripheral blood
Less than 2% basophils in peripheral blood
No extramedullary involvement other than spleen and liver

and sponsor. Patients with interrupted therapy were required to reinitiate treatment within 21 days; failure to do so resulted in patients being removed from the study unless continuation of dasatinib was deemed to be in the best interests of the patient.

No treatment for CML other than dasatinib was permitted, with the exception of anagrelide and hydroxyurea (limited to a period of approximately 2 weeks for hydroxyurea) for the treatment of elevated platelet counts ($> 700 \times 10^9$/L [700 000/mm^3]) and white blood cell counts ($> 50 \times 10^9$/L [50 000/mm^3]), respectively.

Efficacy assessments

Hematologic response. Hematologic responses were determined by assessment of once-weekly complete blood counts (CBCs). Hematologic responses were scored as MaHR, minor (MiHR), or no response (Table 1). A patient with a MaHR was required to meet the criteria for either a CHR or no evidence of leukemia (NEL; see Table 1). The OHR was defined as the proportion of the treated population with a best response of MaHR or MiHR. Confirmed hematologic responses were required to be maintained for a minimum of 4 weeks (Table 1).

Cytogenetic response. Cytogenetic responses (CyRs) were evaluated by once-monthly BM aspirates/biopsies for the first 3 months and every 3 months thereafter. Cytogenetic responses were calculated from the percentage of Ph$^+$ cells in metaphase in the BM sample and defined as CCyR (0%), partial CyR (PCyR, 1%-35%), minor CyR (36%-65%), minimal CyR (66%-95%), or no CyR ($\geq 96\%$). Major cytogenetic response (MCyR) rate was the sum of the CCyR and PCyR rates.

Disease progression. Disease progression in patients who had achieved a MaHR or MiHR was defined as failure to meet the criteria for a MaHR or MiHR, respectively, on all assessments over a consecutive 2-week period after receiving the maximum dose of dasatinib. Progression was also defined as no decrease from baseline levels in percentage of blasts in PB or BM on all assessments over a 4-week period after receiving the maximum dose of dasatinib.

Analysis of BCR-ABL expression and mutational status. Data were collected from exploratory assays, including evaluation of mRNA from PB cells by quantitative polymerase chain reaction (PCR), to characterize changes in the level of expression of, and analysis of, point mutations in the *BCR-ABL* gene.

Safety assessments

Safety information was assessed for patients who received at least one dose of dasatinib. Patients were assessed by physical examination, performance status, vital signs, and 12-lead electrocardiogram at baseline. Adverse events (AEs; hematologic and nonhematologic) were evaluated throughout the study and graded according to the NCI-CTC Version 3.0.

Study conduct

The study was conducted in accordance with the Declaration of Helsinki and was consistent with International Conference on Harmonization Good Clinical Practice (ICH GCP) and applicable regulatory requirements. Written, informed consent was obtained from every patient prior to clinical trial participation. The protocol was reviewed and approved by a recognized ethics review committee at each trial center.

Statistical analysis

A minimum sample size of 60 treated patients with imatinib-resistant CML was required to give a maximum width of the exact 2-sided 95% confidence interval (CI) of 25% when the hematologic response rate was in the expected 5% to 30% range.

Efficacy analyses were performed for the treated population, which included all patients who received at least one dose of dasatinib. Two-sided 95% exact CIs were calculated for the primary endpoints MaHR and OHR using the Clopper-Pearson method.[32] Duration of hematologic response (overall and complete) was estimated with the Kaplan-Meier product limit method. A 2-sided 95% CI for the median duration of hematologic response was calculated using the Brookmeyer and Crowley method.[33] Kaplan-Meier estimates of progression-free survival (PFS) with the 95% CIs for the median time to progression were determined.

Analysis of all safety and laboratory observations and demographic characteristics were performed descriptively.

The lead author had open access to the primary data and was able to critically analyze the data collected.

Results

Patients and demographics

Results for the present report include 107 patients who were enrolled into the study between December 2004 and May 2005 and received at least one dose of study medication. Of these patients, 99 had imatinib-resistant CML-AP and 8 had CML-AP but could not tolerate imatinib. Reasons for imatinib intolerance included gastrointestinal symptoms (n = 1), arthralgia/myalgia (n = 2), rash (n = 1), and other (n = 6; other included pancytopenia, thrombocytopenia, and neutropenia). Intolerance could result from more than one toxicity symptom.

Demographic characteristics were representative of patients with CML-AP and were comparable between imatinib-resistant and -intolerant groups (Table 2). The age range in the study population was 23 to 86 years, with similar proportions of men and women (51% and 49%, respectively). Treated patients had a long history of CML: the median time from initial diagnosis to the start of dosing was approximately 91 months, although this value was markedly lower for patients with imatinib-intolerant CML-AP (69 months) than for patients with imatinib-resistant CML-AP (91 months). The patients in this study had been extensively pretreated; aside from imatinib, all had previously received other, and in some cases, multiple therapies for CML, including hydroxyurea or anagrelide (96%), interferon-α (75%), chemotherapy (67%), stem cell transplantation (18%), and radiotherapy (4%). They also had been treated at length and with high doses of imatinib; the majority of patients (68%) had received more than 3 years of imatinib

therapy, and 59% had been treated with doses of imatinib greater than 600 mg/d (Table 2).

Cut-off for 6 months' follow-up in the efficacy evaluation cohort was November 2005, with a median duration of study therapy of 5.5 months (range, 0.2-10.1 months) in the total treated population and 5.6 months (range, 2.0-10.1 months) among the 82 patients remaining on study at the time. Cut-off for 8 months' follow-up in the efficacy and safety evaluation cohorts was February 2006. Median duration of study therapy was 8.3 months (range, 0.2-12.9 months) in the total treated population and 8.6 months (range, 7.6-12.9 months) among the 67 patients remaining on study.

Efficacy

At 8 months' follow-up, a MaHR was achieved in 69 (64%) of 107 patients, with a CHR in 42 (39%) of 107 patients. For the primary target population of patients with imatinib-resistant CML-AP, a MaHR was achieved in 65% (CHR, 39%; NEL, 25%) of patients, whereas in the imatinib-intolerant CML-AP population, a MaHR was achieved in 63% (CHR, 38%; NEL, 25%) of patients. The median time to MaHR for the total population was 58 days (range, 26-252 days). MiHR was achieved by 17% of patients (16% and 25% of imatinib-resistant and -intolerant CML-AP patients, respectively). Table 3 summarizes the hematologic response rate to dasatinib treatment after 6 and 8 months' follow-up.

Of the 69 patients who achieved a MaHR, only 7 patients (all with imatinib-resistant CML-AP) progressed (Figure 1; Table 3).

At 8 months' follow-up, the OHR rate was 81% (87 of 107) of patients in the total population (CHR, 39%; NEL, 25%; MiHR, 17%). Comparable OHR rates of 81% (80 of 99) and 88% (7 of 8) were observed in the imatinib-resistant and imatinib-intolerant CML-AP populations, respectively (Table 3). Of the 87 patients who achieved an OHR with dasatinib, 15 progressed (13 with imatinib-resistant CML-AP and 2 with imatinib-intolerant CML-AP); median duration of OHR still had not been reached.

Cytogenetic responses were also seen in a notable proportion of patients (Table 4). At 8 months' follow-up, MCyR was achieved in 33% of the total treated population (CCyR, 24%; PCyR, 8%), 34% of patients in the imatinib-resistant group (CCyR, 25%; PCyR, 9%), and 13% of patients in the imatinib-intolerant group (CCyR, 13%; PCyR, 0%). The median time to achieve MCyR for the total population was 57 days (range, 28-263 days) (Table 4).

Figure 2 shows the progression-free survival (PFS) for the total patient population and the imatinib-resistant subgroup. With a minimum of 8 months' follow-up, 76% of patients in the total population remained progression free. The median PFS had not yet been reached. Fourteen deaths were recorded, 5 of which were as a result of documented disease progression. Six of the 14 deaths occurred more than 30 days after dasatinib was discontinued (Figure 2).

Table 2. Patient baseline characteristics

	Total	Imatinib-resistant	Imatinib-intolerant
No. patients	107	99	8
Median age, y (range)	57 (23-86)	57 (23-86)	67 (54-74)
Male sex, %	51	54	25
Median duration of CML, mo	90.9	91.2	68.7
Extramedullary involvement, no. (%)			
Spleen	18 (17)	16 (16)	2 (25)
Outside spleen	5 (5)	5 (5)	0 (0)
Median WBC count, mm^3 (range)	16.8 (1.0-243.4)	17.5 (1.0-243.4)	5.6 (3.2-68.4)
WBC count of at least 20 000/mm^3, %	42	42	38
Median marrow blasts	9.0	8.9	15.0
Marrow blasts at least 15%, %	33	31	50
Median peripheral blasts	2.5	2.0	7.0
Peripheral blasts at least 15%, %	13	13	13
Median platelet count, no. (range)	165 (8-3580)	165 (8-3580)	166 (54-1463)
Platelet count below 100 000/mm^3, no. (%)	44 (41)	40 (40)	4 (50)
Basophils at least 20%, no. (%)	20 (19)	20 (20)	0 (0)
BCR-ABL mutation, no. (%)*	56/98 (57)	55/90 (61)	1/8 (13)
Imatinib therapy duration, %			
Less than 1 y	8	4	50
1-3 y	24	24	25
Longer than 3 y	68	72	25
Highest imatinib dose, %			
400-600 mg	41	39	63
More than 600 mg	59	61	38
Prior chemotherapy, %	67	69	50
Prior interferon-α, %	75	77	50
Prior SCT, %	18	17	25
Baseline grade 3-4 hematologic toxicity, %			
Leukopenia	5	5	0
Thrombocytopenia	25	25	0
Neutropenia	7	7	0
Anemia	5	5	0

WBC indicates white blood cell; SCT, stem cell transplantation.
Percentage is based on number of patients with baseline mutation analysis available.

Table 3. Hematologic response to dasatinib

	Follow-up for 6 mo, no. (%)			Follow-up for 8 mo, no. (%)		
	Total	Imatinib-resistant	Imatinib-intolerant	Total	Imatinib-resistant	Imatinib-intolerant
All patients	107 (100)	99 (100)	8 (100)	107 (100)	99 (100)	8 (100)
CHR	35 (33)	33 (33)	2 (25)	42 (39)	39 (39)	3 (38)
NEL	28 (26)	25 (25)	3 (38)	27 (25)	25 (25)	2 (25)
Major hematologic response (CHR and NEL)	63 (59)	58 (59)	5 (63)	69 (64)	64 (65)	5 (63)
Minor hematologic response	23 (22)	22 (22)	1 (13)	18 (17)	16 (16)	2 (25)
Overall hematologic response*	86 (80)	80 (81)	6 (75)	87 (81)	80 (81)	7 (88)
No response	21 (20)	19 (19)	2 (25)	20 (19)	19 (19)	1 (13)

CHR indicates complete hematologic response; NEL, no evidence of leukemia.
*Overall hematologic response is defined as the sum of CHR, NEL, and minor hematologic response rates.

Response to dasatinib by baseline BCR-ABL mutational status

Baseline mutational analysis of the ABL kinase domain was available for 100 of the 107 patients in the treated population (94 with imatinib-resistant CML-AP and 6 with imatinib-intolerant CML-AP). Mutations were identified in 60 (60%) of these patients (all with imatinib-resistant CML-AP).

Among the 60 patients with mutations, 26 unique imatinib-resistant mutations were identified, of which G250E was the most common (n = 9) (Table 5). Of these 60 patients, 30 (50%) carried mutations located within the P-loop of the kinase domain. Despite the presence of imatinib-resistant *BCR-ABL* mutations and their association with poor prognosis, at 8 months' follow-up, 73% of patients with an imatinib-resistant BCR-ABL mutation had achieved MaHR following treatment with dasatinib. Moreover, 73% and 86% of patients with an imatinib-resistant mutation in the kinase P-loop or activation loop, respectively, had achieved MaHR. In addition, MaHR was achieved in 70% of patients with mutations known to confer mild to very high resistance to imatinib. Similarly, MCyR was achieved in 30% of patients with imatinib-resistant mutations, 23% of patients with an imatinib-resistant mutation in the kinase P-loop, 57% of patients with an imatinib-resistant mutation in the activation loop, and 24% of patients with mutations known to confer mild to very high resistance to imatinib (Table 5).

Safety

Nonhematologic AEs related to treatment that occurred with an incidence of at least 10% at 8 months' follow-up are shown in Table 6. Most nonhematologic AEs were mild to moderate. The most frequently reported drug-related AE were diarrhea (50%), headache (28%), pyrexia (23%), fatigue (23%), nausea (22%), and peripheral edema (22%). Pleural effusion occurred in 25 (23%) patients; this was grade 3 to 4 in 3 (3%) patients. Three patients (3 of 25, 12%) underwent thoracentesis, and no patient required pleurodesis. In general, most pleural effusions were uncomplicated, resolving with temporary dose interruption, diuretics, and, in some cases, pulse steroids. The most common (≥ 5%) grade 3 to 4 nonhematologic AEs related to treatment were diarrhea (6%) and gastrointestinal bleeding (7%).

As would be expected in this population of pretreated patients with CML-AP, a proportion of patients had severe (grades 3-4) pancytopenia at baseline: 5% had severe leukopenia, 7% had severe neutropenia, 23% had severe thrombocytopenia, and 5% had severe anemia (Table 2). Overall, the majority of patients in the safety population had experienced some degree of pancytopenia at 8 months' follow-up (Table 7). Cytopenias were reversible and could be managed effectively by dose interruption and/or reduction. Among treated CML-AP patients at 8 months' follow-up, 91 (85%) had received packed red blood cell transfusions (including all 8 patients with imatinib-intolerant CML-AP) and 65 (61%) had received platelet transfusions. Plasma was administered to 3 (3%) patients. Of the 107 patients treated, 13 (12%) were hospitalized for febrile neutropenia (fever with an ANC < 1000) (Table 7).

Discussion

This phase 2 study was conducted to evaluate the ability of dasatinib to produce sustained hematologic and cytogenetic responses in patients with imatinib-resistant or -intolerant CML-AP.

The results presented here with relatively short follow-up show that dasatinib induced an overall hematologic response in 81% of patients, including 64% with an MaHR. In addition, an MCyR was achieved by 33% of patients, including 24% who achieved a CCyR. Importantly, only 7 of the 69 patients who achieved an MaHR had progressed at 8 months. Seventy-six percent of patients in the total treated population are estimated to be alive and progression free at 10 months. Overall, dasatinib response rates were comparable between imatinib-resistant and -intolerant subgroups.

It is important to put these results in the context of the extent to which patients in this study population had been pretreated. The median time from original diagnosis of CML to study entry was more than 5.5 years, and patients had been heavily pretreated with imatinib and other therapies.

For patients with CML-AP that is imatinib-resistant or -intolerant, as in this study, there are few effective therapeutic options currently available. Imatinib resistance is particularly

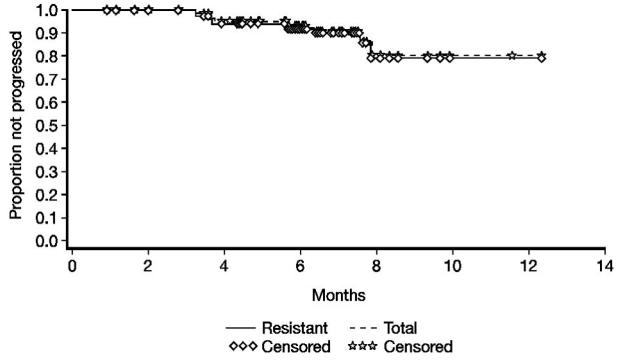

Figure 1. Duration of major hematologic response with dasatinib for the total treated population and for the imatinib-resistant CML-AP subgroup at 8 months' follow-up.

Table 4. Cytogenetic response to dasatinib

	Follow-up for 6 mo, no. (%)			Follow-up for 8 mo, no. (%)		
	Total	Imatinib-resistant	Imatinib-intolerant	Total	Imatinib-resistant	Imatinib-intolerant
All patients	107 (100)	99 (100)	8 (100)	107 (100)	99 (100)	8 (100)
CCyR	23 (22)	23 (23)	0 (0)	26 (24)	25 (25)	1 (13)
PCyR	10 (9)	9 (9)	1 (13)	9 (8)	9 (9)	0 (0)
MCyR (CCyR and PCyR)	33 (31)	32 (32)	1 (13)	35 (33)	34 (34)	1 (13)
Minor CyR	6 (6)	6 (6)	0 (0)	6 (6)	6 (6)	0 (0)
Minimal CyR	19 (18)	16 (16)	3 (38)	20 (19)	17 (17)	3 (38)
No CyR	37 (35)	34 (34)	3 (38)	33 (31)	30 (30)	3 (38)
Unable to determine	12 (11)	11 (11)	1 (13)	13 (12)	12 (12)	1 (13)

Data are provided as number (%) of patients. Cytogenetic response was defined by the prevalence of Ph^+ metaphases: CCyR, 0% Ph^+; PCyR, 1% to 35% Ph^+; minor CyR, greater than 35% to 65% Ph^+; minimal CyR, greater than 65% to 95% Ph^+; no response, greater than 95% Ph^+.

CyR indicates cytogenetic response; MCyR, major cytogenetic response; CCyR, complete cytogenetic response; PCyR, partial cytogenetic response.

problematic in advanced CML, because the incidence of both primary and acquired resistance are greater in the accelerated and blast phasescompared with chronic phase.[11,34] One possible explanation for this is the involvement of pathways involving SFKs in the progression of the disease. Preclinical studies in mice have shown that SFKs are required for the induction of an acute leukemia phenotype but are not required to induce a model of chronic phase CML, and blocking pathways involving SFKs with dasatinib prevents CML progression from chronic to blast phase.[24,35] Furthermore, in mice with acute leukemia, targeting BCR-ABL alone with imatinib has little effect, but targeting both BCR-ABL and SFK activity with dasatinib results in a marked prolongation of survival.[35] In light of these preclinical findings, the clinical activity of dasatinib observed in this phase 2 study may be partly due to dasatinib's potent inhibition of SFKs. Other possible mechanisms of imatinib resistance include amplification of the *BCR-ABL* gene,[17,18] and overexpression of the P-glycoprotein efflux pump, for which imatinib, but not dasatinib, is a substrate.[19,20] Dasatinib's ability to overcome these forms of resistance may also account for the efficacy seen in this study.

The best-understood mechanism of imatinib resistance involves mutations in *BCR-ABL* that preclude binding of imatinib to the BCR-ABL kinase domain.[18] In this study, 60% of patients had *BCR-ABL* mutations at baseline. Despite this, response rates to dasatinib in this group were similar to those in the study population as a whole. In addition, comparable response rates to dasatinib were observed in patients with mutations in the *BCR-ABL* P-loop compared with mutations located elsewhere, a significant finding given that previous studies have shown that P-loop mutations may be associated with a lower life expectancy in patients treated with imatinib.[36] The activity of dasatinib in these patients is likely due to its less stringent binding requirements, because dasatinib has the ability to bind to both active and inactive BCR-ABL conformations.[1] Recent crystal structure studies support this hypothesis, showing a more significant role for the P-loop in imatinib binding compared with dasatinib binding.[37] In confirmation of preclinical findings,[1,28] the only *BCR-ABL* mutation resistant to dasatinib in the current study is the ATP binding site mutation T315I. Mutations of this residue, sometimes termed the "gatekeeper" residue, are relatively uncommon, affecting only 5% of patients in this study, but they appear to be critical for binding of all ATP-competitive BCR-ABL kinase inhibitors, because the T315I mutation also prevents the activity of imatinib and nilotinib.[1]

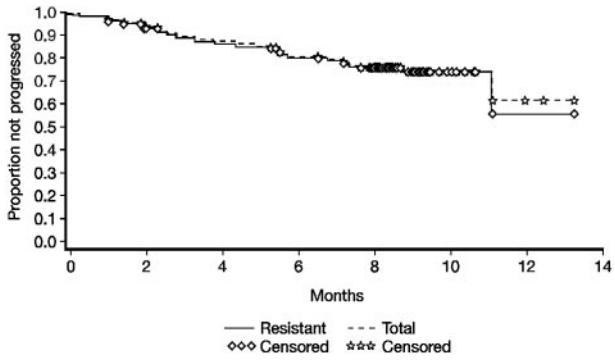

Figure 2. Progression-free survival with dasatinib for the total treated population and for the imatinib-resistant CML-AP subgroup at 8 months' follow-up.

Table 5. Response by baseline BCR-ABL mutation analysis of patients with imatinib-resistant and -intolerant CML-AP at 8 months' follow-up

	Total*	Patients with MaHR	Patients with MCyR
No mutation, no. (%)	40 (40)	22/40 (55)	15/40 (38)
Any mutation, no. (%)	60 (60)	44/60 (73)	18/60 (30)
P-Loop,† n (%)	30 (30)	22/30 (73)	7/30 (23)
A-Loop,‡ n (%)	7 (7)	6/7 (86)	4/7 (57)
Other regions, no. (%)	24 (24)	17/24 (71)	8/24 (33)
Mutations documented in at least 2 patients, no. patients			
M244V	5	4	2
L248V	3	3	1
G250E	9	6	1
Y253H	6	5	2
E255K	6	4	0
E255V	2	2	1
T315I	5	0	0
F317L	4	4	0
M351T	6	3	1
E355G	4	2	2
F359C	2	2	2
F359V	7	5	1
V379I	4	3	2
A397P	2	2	1
E459K	3	1	3

MaHR indicates major hematologic response; MCyR, major cytogenetic response.

*n = 100. Seven of the 107 treated patients had no mutational analysis performed at baseline.

†P-loop mutations are those in location 244 through 255.

‡Activation loop mutations are those in location 379 through 398.

Dasatinib was generally well tolerated in this study; at 8 months' follow-up, only 6% of patients in the entire safety population had withdrawn from therapy as a result of drug-related toxicities. Nonhematologic AEs were mostly mild to moderate in intensity, with the most common side effects being GI events (diarrhea, nausea, vomiting, abdominal pain, and GI bleeding), headache, pyrexia, fatigue, and peripheral edema. Among the subset of patients who experienced episodes of pleural effusion while on dasatinib therapy, temporary dose interruption as well as diuretic and/or pulse steroid therapy typically led to resolution of these events. Resumption of dasatinib at a lower dose enabled most patients to continue treatment without recurrence of the complication.

Of the 8 patients in the treated population who had imatinib-intolerant disease, 2 had discontinued dasatinib treatment at 8 months' follow-up, but neither instance was due to dasatinib-related toxicity. These findings suggest minimal cross-intolerance between dasatinib and imatinib.

Given the paucity of normal blood cell progenitors in patients in this phase of CML, the observed frequency of cytopenia may reflect the potent activity of dasatinib against leukemic cells. Despite the relatively frequent occurrence of rapid-onset and severe neutropenia, no patients had discontinued therapy as a result of infection related to dasatinib therapy by the time of this analysis. Nevertheless, it will be important to carefully monitor patients for complications related to cytopenia, as is the case with most forms of treatment for advanced phase CML.[38,39] As would be expected for heavily pretreated patients with accelerated phase disease, many patients on this study began dasatinib treatment with severe baseline cytopenias, including 25% of patients with severe thrombocytopenia.

The results of this study demonstrate that dasatinib induces significant hematologic and cytogenetic responses in patients with imatinib-resistant or -intolerant CML-AP. Moreover, dasatinib efficacy and safety have been consistently observed in studies of patients with other phases of imatinib-resistant or -intolerant CML.[40-42] Clinical trials of dasatinib in patients with earlier stages of CML, and other Ph^+ leukemias, are ongoing. Dasatinib represents a potent new therapeutic option for patients with accelerated phase CML.

Table 6. Drug-related toxicity events in the total treated population at 8 months' follow-up (n = 107)

Nonhematologic adverse events*	Grades 1-4, no. (%)	Grades 3-4, no. (%)
Diarrhea	53 (50)	6 (6)
Nausea	24 (22)	0 (0)
Vomiting	17 (16)	1 (1)
Abdominal pain	12 (11)	0 (0)
GI bleeding	12 (11)	9 (7)
Pyrexia	25 (23)	4 (4)
Fatigue	25 (23)	4 (4)
Peripheral edema	24 (22)	0 (0)
Asthenia	20 (19)	4 (4)
Rash	16 (15)	1 (1)
Pleural effusion	25 (23)	3 (3)
Dyspnea	17 (16)	4 (4)
Epistaxis	12 (11)	0 (0)
Headache	30 (28)	1 (1)
Dizziness	12 (11)	0 (0)
Pain in extremity	15 (14)	0 (0)
Arthralgia	11 (10)	0 (0)
Myalgia	11 (10)	1 (1)
Anorexia	14 (13)	1 (1)

GI indicates gastrointestinal.
*Nonhematologic adverse events occurring with a frequency of at least 10%.

Table 7. Hematologic adverse events

Cytopenias grade 3-4	Total, no. (%)	Imatinib-resistant, no. (%)	Imatinib-intolerant, no. (%)
All patients	107 (100)	99 (100)	8 (100)
Leukopenia	65 (61)	59 (60)	6 (75)
Thrombocytopenia	88 (82)	81 (82)	7 (88)
Neutropenia	83 (76)	75 (76)	8 (100)
Anemia	74 (69)	67 (68)	7 (88)

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Authorship

Contribution: F.G. performed research, analyzed data, and wrote the paper; J.A., D.-W.K., E.O.B., G.J.R., S.A., D.H., and S.B. performed research; M.B., C.A.S., and J.H.L. performed research and analyzed data; A.H. designed research, performed research, analyzed data, and wrote the paper; R.A.L. performed research and wrote the paper; M.C.M. performed research and contributed vital new reagents or analytical tools; P.A. analyzed data; A.G. designed research and analyzed data; M.T. designed research, performed research, and analyzed data.

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Dasatinib induces significant hematologic and cytogenetic responses in patients with imatinib-resistant or -intolerant chronic myeloid leukemia in accelerated phase

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