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ORIGINAL REPORT

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Dasatinib in the Treatment of Chronic Myeloid Leukemia in Accelerated Phase After Imatinib Failure: The START A Trial

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ABSTRACT

Purpose
Patients with chronic myelogenous leukemia in accelerated phase (CML-AP) that is resistant or intolerant to imatinib have limited therapeutic options. Dasatinib, a potent inhibitor of BCR-ABL and SRC-family kinases, has efficacy in patients with CML-AP who have experienced treatment failure with imatinib. We now report follow-up data from the full patient cohort of 174 patients enrolled onto a phase II trial to provide a more complete assessment of the efficacy and safety of dasatinib in this population.

Patients and Methods
Patients with imatinib-resistant (n = 161) or -intolerant (n = 13) CML-AP received dasatinib 70 mg orally twice daily.

Results
At a median follow-up of 14.1 months (treatment duration, 0.1 to 21.7 months), major and complete hematologic responses were attained by 64% and 45% of patients, respectively, and major and complete cytogenetic responses were achieved in 39% and 32% of patients, respectively. Responses were achieved irrespective of imatinib status (resistant or intolerant), prior stem-cell transplantation, or the presence of prior *BCR-ABL* mutation. The 12-month progression-free survival and overall survival rates were 66% and 82%, respectively. Dasatinib was generally well tolerated; the most frequent nonhematologic severe treatment-related adverse event was diarrhea (52%; grade 3 to 4, 8%). Cytopenias were common, including grade 3 to 4 neutropenia (76%) and thrombocytopenia (82%). Pleural effusion occurred in 27% of patients (grade 3 to 4, 5%).

Conclusion
Dasatinib is effective in patients with CML-AP after imatinib treatment failure.

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INTRODUCTION

Chronic myelogenous leukemia (CML) has an incidence of one to two cases per 100,000 adults.[1] The disease typically progresses through three phases: chronic, accelerated, and blast crisis. Most patients present in chronic phase, characterized by variable clinical symptoms, leukocytosis, and splenomegaly. Progression to accelerated phase (AP) is associated with increased symptoms, increases in blood and bone marrow (BM) blasts or basophils, persistent thrombocytopenia, and refractory splenomegaly.[2]

Current first-line therapy for all phases of CML is imatinib mesylate (Glivec [United States, Gleevec]; Novartis, Basel, Switzerland), which inhibits kinase activity of the causative BCR-ABL oncoprotein. Despite its efficacy in CML-AP, 45% of patients receiving imatinib developed resistance after a median of 2 years of treatment,[3] and median progression-free survival (PFS) was 8.8 months.[4] The estimated 4-year overall survival rate with imatinib was 53%.[5] Treatment options are limited after imatinib failure. Although allogeneic stem-cell transplantation (SCT) is potentially curative, it is restricted by donor availability, undesirable complications, and high mortality, and outcomes are better in newly diagnosed patients with early-stage disease.[6,7]

Dasatinib (SPRYCEL; Bristol-Myers Squibb, New York, NY) is a novel, potent, oral inhibitor of multiple tyrosine kinases, including BCR-ABL and SRC-family kinases (SFKs), which may contribute to CML disease progression and treatment resistance.[8-13] In vitro studies have demonstrated

that unlike imatinib, dasatinib inhibits multiple conformations of BCR-ABL,[14] and the majority of imatinib-resistant BCR-ABL mutants identified in patients.[15,16] Dasatinib has been investigated in a series of clinical trials in patients with CML or Philadelphia (Ph) chromosome–positive acute lymphoblastic leukemia (Ph-positive ALL) after resistance or intolerance to imatinib (the SRC/ABL Tyrosine Kinase Inhibition Activity Research Trials of Dasatinib [START] program).[17-21] Results demonstrated the efficacy and safety of dasatinib during an initial minimum follow-up of 6 to 8 months and led to rapid United States Food and Drug Administration approval of dasatinib for all phases of CML and Ph-positive ALL after imatinib failure. United States National Comprehensive Cancer Network guidelines indicate dasatinib as a treatment option in patients with CML after relapse, lack of response, or disease progression, while receiving imatinib therapy.[22]

Results from the initial 107 patients treated in the phase II study of dasatinib in CML-AP (START A) were previously reported.[18] This article updates initial findings, presenting data from the full study population (N = 174) with longer follow-up (median, 14.1 months compared with 8.8 months in the previous report), which confirm response durability within available follow-up.

PATIENTS AND METHODS

Patients

Entry criteria have been previously described in detail.[18] Briefly, patients aged at least 18 years with Ph-positive or *BCR-ABL*–positive CML-AP, plus primary or acquired hematologic resistance or intolerance to imatinib, were recruited at 39 sites worldwide. Exclusion criteria included Eastern Cooperative Oncology Group performance status of grade 3 or more, uncontrolled or significant cardiovascular disease, history of significant bleeding disorder unrelated to CML, or inadequate hepatic or renal function. CML-AP was defined by one or more of the following: peripheral blood (PB) or BM counts of $\geq$ 15% to less than 30% blasts, $\geq$ 30% blasts plus promyelocytes but with less than 30% blasts alone, or $\geq$ 20% basophils, or platelet counts less than 100×10^9/L unrelated to drug therapy.[23] The study was conducted in accordance with the Declaration of Helsinki and received ethical approval from each trial center. Written, informed consent was obtained from all patients.

Study Treatment

Patients received dasatinib 70 mg twice daily (140-mg total daily dose). Dose escalation to 100 mg twice daily was allowed for inadequate response, and dose reduction to 50 mg or 40 mg twice daily was permitted for toxicity.[18] All patients continued dasatinib on a twice-daily regimen throughout the reported follow-up. Dasatinib treatment continued until disease progression or intolerable toxicity. Patients were observed for 30 days after final dose of study therapy, or until recovery from all toxicity, whichever was longer. No treatment for CML other than dasatinib was permitted, except for anagrelide or hydroxyurea (each for a maximum of 2 weeks) to treat elevated platelet ($> 700 \times 10^9$/L) or WBC counts ($> 50 \times 10^9$/L), respectively.

Objectives

The primary study objective was to determine the hematologic response (HR) rate after dasatinib treatment in patients with imatinib-resistant CML-AP. Secondary objectives included assessment of HR rates in imatinib-intolerant patients; cytogenetic response (CyR) rates in all patients, time to and duration of HR and CyR, role of *BCR-ABL* mutations in responses, PFS and overall survival, and safety and tolerability of dasatinib during long-term treatment.

Efficacy Assessments

HRs were determined by assessing once-weekly CBC and were required to be maintained for at least 4 weeks. A major HR was defined as meeting the criteria for either a complete HR (CHR) or no evidence of leukemia (NEL). CHR was classified as WBCs no more than the institutional upper limit of normal; absolute neutrophil count at least 1×10^9/L; platelets at least 100×10^9/L; no blasts or promyelocytes in PB, BM blasts $\leq$ 5%; peripheral myelocytes plus metamyelocytes less than 5%; basophils in PB/BM less than 2%, and no extramedullary involvement. NEL was classified as no blasts or promyelocytes in PB, BM blasts $\leq$ 5%, and no extramedullary involvement.[18]

CyRs were classified according to the percentage of Ph-positive metaphases in BM aspirates/biopsies (complete [CCyR], 0%; partial [PCyR], 1% to 35%; minor, 36% to 65%; minimal, 66% to 95%; no CyR, $\geq$ 96%), as defined previously.[18] The major cytogenetic response (MCyR) rate was the sum of CCyR and PCyR rates. *BCR-ABL* mutations were analyzed in PB cells through exploratory assays, including reverse transcriptase polymerase chain reaction, followed by denaturing high-performance liquid chromatography and/or direct sequencing.

Disease progression was defined as loss of previous major or minor HR over a consecutive 2-week period, no decrease from baseline levels in percentage blasts in PB or BM on all assessments over a 4-week period, or confirmed blast phase disease, despite receiving the maximum tolerable dasatinib dose.

Safety Assessments

Adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria (version 3.0). Pleural effusions were graded as follows: grade 1, asymptomatic; grade 2, symptomatic, intervention such as diuretics or up to two thoracenteses indicated; grade 3, symptomatic and supplemental oxygen, more than two thoracenteses, tube drainage, or pleurodesis indicated; and grade 4, life-threatening (eg, causing hemodynamic instability or ventilatory support indicated). Chest x-ray, with or without chest computed tomography, was obtained at the investigator's discretion after occurrence of respiratory symptoms.

Statistical Analysis

Efficacy analyses included all patients who received at least one dose of dasatinib. Although a minimum accrual of 60 patients was planned, no limit was imposed during the enrollment period. Two-sided 95% exact CIs were calculated for major and overall HR rates using Clopper-Pearson methodology.[24] Relapse-free survival (duration of major HR and MCyR), time to major HR and MCyR, PFS, and overall survival were estimated with Kaplan-Meier product-limit methodology. Relapse-free survival was calculated from date of initial response until loss of response, disease progression, or death. Two-sided 95% CIs were calculated for median values using Brookmeyer and Crowley methodology.[25] The study was not designed or powered to make statistical comparisons between patient subgroups.

RESULTS

Patient Demographics and Disease Characteristics

Overall, 174 patients with CML-AP were enrolled onto the study between December 2004 and July 2005 and received at least one dose of study medication. Demographic characteristics were representative of patients with CML-AP and were comparable between imatinib-resistant (n = 161) and imatinib-intolerant (n = 13) subgroups (Table 1). The age range was 22 to 86 years, with similar proportions of men and women (55% and 45%, respectively). Median time from initial diagnosis to start of dasatinib treatment was 82 months. Most patients had received therapies other than imatinib for CML disease, including interferon alfa (72%) and chemotherapy (59%). More than half of patients (59%) had been treated for more than 3 years with imatinib, and 52% had received escalated doses of imatinib (> 600 mg/d). Twenty-three patients (13%) had previously undergone SCT.

All 174 patients were observed for a median of 14.1 months, with 128 patients (74%) treated for a minimum of 6 months (median, 13.5 months; range, 0.1 to 21.7 months).

Table 1. Patient Baseline Characteristics

Characteristic	All Patients (N = 174)	Patients With Imatinib-Resistant Disease (n = 161)	Imatinib-Intolerant Patients (n = 13)
Age, years			
Median	57	56	61
Range	22-86	22-86	29-80
Male, %	55	57	31
Duration of CML at study entry, months			
Median	82	82	91
Range	4-359	4-359	4-206
Extramedullary involvement, %	23	22	31
Splenomegaly	21	21	31
Outside spleen	6	6	8
BCR-ABL mutation*			
No. of patients	88	87	1
Total patients analyzed	156	145	11
%	56	60	9
Prior therapy, %			
Interferon-α	72	73	62
Stem-cell transplantation	13	13	15
Chemotherapy	59	60	46
Hydroxyurea or anagrelide	94	94	92
Radiotherapy	4	4	8
Imatinib therapy duration, %			
< 1 year	10	7	46
1-3 years	31	30	39
> 3 years	59	63	15
Highest imatinib dose, %			
400-600 mg	48	45	77
> 600 mg	52	55	23

Abbreviation: CML, chronic myelogenous leukemia.
*Percentage based on number of patients with baseline mutation analysis available.

Hematologic and Cytogenetic Responses

Major HRs were achieved in 111 (64%) of 174 patients (95% CI, 56.2% to 70.9%), including 78 patients (45%) with a CHR (Table 2). For the primary target population of patients with imatinib-resistant disease, 63% had a major HR (CHR, 45%). In the total patient group, MCyRs were seen in 67 (39%) of 174 patients (95% CI, 31.2% to 46.2%), with 55 patients (32%) achieving a CCyR. In imatinib-resistant and -intolerant cohorts, CCyR rates were 32% and 38%, respectively. Because of the small number of intolerant patients (n = 13), no statistical comparison was performed between intolerant and resistant populations.

Median times to major HR and MCyR in responding patients were 64 days (95% CI, 57 to 83 days) and 58 days (95% CI, 57 to 85 days), respectively. With the extent of follow-up available, HRs and CyRs to dasatinib were mostly durable (Fig 1). Median durations of relapse-free survival after major HR and MCyR (duration of response until loss of response, progression, or death) could not be estimated with available follow-up. Of 111 patients who had achieved a major HR at the time of analysis, 18 patients lost their response (range of duration, 52 to 400 days). Of 67 patients attaining a MCyR, nine patients lost this response (range of duration, 14 to 299 days).

Responses were achieved in patients with or without prior SCT or preexisting *BCR-ABL* mutations (Table 2). The number of patients with *BCR-ABL* mutations before study treatment was 88 (56%) of 156, and 29 different mutations were detected. As noted previously,[17] patients with a preexisting T315I mutation (n = 9) did not respond to dasatinib therapy (Table 3). Few CCyRs were observed in patients with F317L (0 of four) or E255K (one of eight) mutations.

PFS

The 12-month PFS rate was 66%, and the median duration could not be estimated with available follow-up (Fig 2).

Overall Survival

The 12-month overall survival on dasatinib was 82% (Fig 2). Reasons for death, as assigned by study investigators, were CML disease (n = 10; 6%); infection (n = 7; 4%); bleeding (n = 1; 1%); study drug toxicity (n = 1; 1%); pneumonia secondary to large granular lymphocytes (n = 1, 1%); respiratory insufficiency and CML complications (n = 1, 1%); graft-versus-host disease, gastrointestinal bleeding, and sepsis (n = 1, 1%); pulmonary embolism (n = 1, 1%); pulmonary edema (n = 1, 1%); CNS bleeding (n = 1, 1%); and unknown (n = 6, 3%).

Safety

Dasatinib was generally well tolerated. The majority of nonhematologic adverse events occurring during the course of the study were grade 1 to 2. The most common adverse event was diarrhea, which occurred in 52% of patients, and was grade 3 or 4 in 8% (Table 4). Grade 3 to 4 gastrointestinal bleeding was reported by 6% of patients (all grades, 9.5%).

Table 2. Hematologic and Cytogenetic Responses After a Median of 14 Months of Follow-Up

Response	All Patients (N = 174)		Imatinib Status: Patients With Imatinib-Resistant Disease (n = 161)		Imatinib Status: Imatinib-Intolerant Patients (n = 13)		Stem-Cell Transplantation: Prior SCT (n = 23)		Stem-Cell Transplantation: No Prior SCT (n = 151)		Prior *BCR-ABL* Mutation*: Any Mutation (n = 88)		Prior *BCR-ABL* Mutation*: P-Loop Mutation (n = 34)		Prior *BCR-ABL* Mutation*: No Mutation (n = 68)	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Hematologic	138	79	126	78	12	92	18	78	120	80	74	84	28	82	50	74
Major HR	111	64	102	63	9	69	15	65	96	64	64	73	24	71	38	56
95% CI, %	56 to 71		55 to 71		39 to 91		43 to 84		55 to 71		62 to 82		53 to 85		43 to 68	
CHR	78	45	72	45	6	46	12	52	66	44	48	55	20	59	23	34
95% CI, %	37 to 53		37 to 53		19 to 75		31 to 73		36 to 52		44 to 65		41 to 75		23 to 46	
NEL	33	19	30	19	3	23	3	13	30	20	16	18	4	12	15	22
No hematologic response	36	21	35	22	1	8	5	22	31	20	14	16	6	18	18	26
Cytogenetic																
MCyR	67	39	62	39	5	39	6	26	61	40	35	40	11	32	27	40
95% CI, %	31 to 46		31 to 46		14 to 68		10 to 48		32 to 49		29 to 51		17 to 51		28 to 52	
CCyR	55	32	50	31	5	39	4	17	51	34	28	32	9	26	22	32
95% CI, %	25 to 39		24 to 39		14 to 68		5 to 39		26 to 42		22 to 43		13 to 44		22 to 45	
PCyR	12	7	12	8	0	0	2	9	10	7	7	8	2	6	5	7
Minor CyR	10	6	10	6	0	0	1	4	9	6	4	5	2	6	5	7

Abbreviations: SCT, stem-cell transplantation; CCyR, complete cytogenetic response; CHR, complete hematologic response; CyR, cytogenetic response; HR, hematologic response; MCyR, major cytogenetic response; NEL, no evidence of leukemia; PCyR, partial cytogenetic response.
*Mutation data available in 156 patients.

Cytopenia was common, including grade 3 to 4 neutropenia (76%) or thrombocytopenia (82%). These were usually reversible and manageable through transient dose interruption or dose reduction. Similarly, infections that occurred in patients with or without neutropenia were manageable in the majority of all patients, although some developed severe life-threatening infections during dasatinib (at least nine deaths were attributable to infections).

Grade 3 to 4 pleural effusions occurred in eight patients (5%; all grades, n = 47, 27%; grade 1, n = 5, 3%; grade 2, n = 34, 20%). Median time to appearance of grade 2 to 4 pleural effusions was 124 days (range, 15 to 500 days).

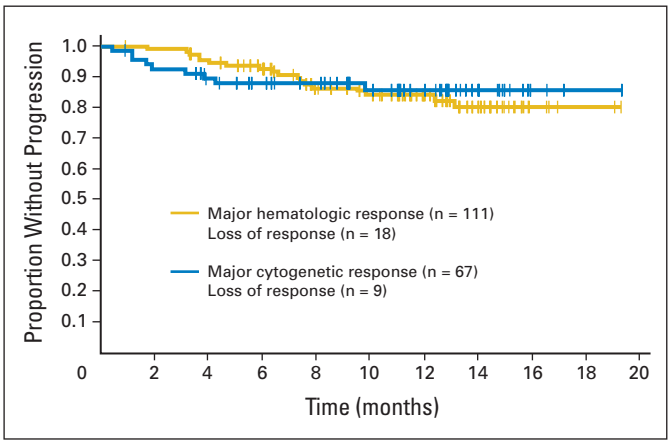

Fig 1. Kaplan-Meier analysis of duration of response after a median of 14 months of follow-up. Major hematologic and major cytogenetic responses are shown.

Few patients experienced cardiac events. One patient (< 1%) had a grade 1 ECG change, and another patient (< 1%) had a grade 2 arrhythmia. There were no reports of QT interval prolongation.

Dose reductions were required by 65% of patients (imatinib-resistant, 63%; imatinib-intolerant, 85%). Reasons for first dose reduction were hematologic toxicity in 30% (imatinib-resistant, 29%; imatinib-intolerant, 46%), nonhematologic toxicity in 22% (imatinib-resistant, 22%; imatinib-intolerant, 23%), and other reasons in 13% (imatinib-resistant, 12%; imatinib-intolerant, 15%). In imatinib-resistant and -intolerant subgroups, median time to first dose reduction was 47 days (range, 1 to 367 days) and 36 days (range, 15 to 169 days), respectively. Dose interruptions were necessary for 85% (imatinib-resistant, 84%; imatinib-intolerant, 100%). Dose escalations (> 140 mg) occurred in 35% of patients (imatinib-resistant, 36%; imatinib-intolerant, 15%). Ninety patients (52%) discontinued treatment (imatinib-resistant, n = 82). The most common reason for discontinuation, as assigned by study investigators, was disease progression (n = 38; imatinib-resistant, n = 38; further data are in Appendix Table A1, online only). Six patients (3%) underwent SCT after discontinuing dasatinib treatment. Median total daily doses were as follows: all patients, 126 mg (range, 32 to 196 mg); imatinib-resistant, 127 mg (range, 32 to 196 mg); imatinib-intolerant, 110 mg (range, 49 to 140 mg).

DISCUSSION

Both primary and acquired resistance to imatinib are more common in patients with advanced CML (AP or blast phase disease) than with chronic-phase disease.[3,26] The aim of this phase II study was to evaluate the ability of dasatinib to produce durable HRs and CyRs in

Table 3. Response by Baseline *BCR-ABL* Mutation

Mutation Status	Total	Patients With Major HR	Patients With MCyR
No mutation			
No. of patients	68	38	27
Total patients	156	68	68
%	44	56	40
Any mutation			
No. of patients	88	64	35
Total patients	156	88	88
%	56	73	40
Mutations associated with an increased IM IC_{50} of at least 5-fold			
No. of patients	58	39	20
Total patients	156	58	58
%	37	67	34
Specific *BCR-ABL* point mutations, n*†			
L248V (NR)	3	3	2
E355G (NR)	4	2	2
V379I (IC_{50} IM: 1,630 nmol/L; DA: 0.8 nmol/L)†	6	4	4
S417Y (NR)	3	1	0
E459K (NR)	3	1	3
M351T (IC_{50} IM: 880 nmol/L; DA: 1.1 nmol/L)†	11	9	3
F317L (IC_{50} IM: 1,050 nmol/L; DA: 7.4 nmol/L)†	4	4	0
G250E (IC_{50} IM: 1,350 nmol/L; DA: 1.8 nmol/L)†	10	6	2
H396R (IC_{50} IM: 1,750 nmol/L; DA: 1.3 nmol/L)†	6	4	2
F359V (IC_{50} IM: 1,825 nmol/L; DA: 2.2 nmol/L)†	8	6	2
M244V (IC_{50} IM: 2,000 nmol/L; DA: 1.3 nmol/L)†	6	5	4
E255K (IC_{50} IM: 5,200 nmol/L; DA: 5.6 nmol/L)†	8	5	1
Y253H (IC_{50} IM: > 6,400 nmol/L; DA: 1.3 nmol/L)†	9	8	4
T315I (IC_{50} IM: > 6,400 nmol/L; DA: > 200 nmol/L)†	9	0	0

Abbreviations: HR, hematologic response; MCyR, major cytogenetic response; IM, imatinib; IC_{50}, half maximal inhibitory concentration; NR, not reported by O'Hare et al[15]; DA, dasatinib.

*Reported in three or more patients.

†Cellular imatinib and dasatinib IC_{50} values taken from O'Hare et al.[15]

patients with CML-AP after imatinib failure. In the previous report from this study, based on the initial 107 patients who received treatment, dasatinib was associated with early efficacy after 6 and 8 months.[18] Here, we report data from the full patient cohort (N = 174) with double the duration of follow-up (median, 14.1 months), providing a more complete assessment of dasatinib in CML-AP. With the extended follow-up now available, rates of HR and CyR have increased compared with the earlier 6-month analysis, from 33% to 45% for CHR, 31% to 39% for MCyR, and 22% to 32% for CCyR. This suggests that continued treatment with dasatinib may result in an increasing proportion of responding patients and/or an increasing depth of response and/or that larger numbers of patients provided a more accurate picture of the true response rate. Median durations of relapse-free survival after major HR and MCyR in responding patients and median values for PFS and overall survival could not be estimated with available follow-up. In a study of patients with CML-AP treated with imatinib for a median of 10 to 11 months (including 34% who received imatinib as first-line therapy), response rates were 34% CHR, 24% MCyR, and 17% CCyR,[4] although any comparisons with dasatinib treatment should be made with caution because of differences between the patient populations. Results from the current dasatinib study are particularly notable given the median time from original diagnosis of CML to study entry of more than 6.5 years and the significant pretreatment with imatinib and other therapies.

Responses in this trial were achieved for both imatinib-resistant and -intolerant cohorts. Responses were also observed in patients with prior SCT, suggesting that dasatinib therapy can successfully be administered after previous imatinib treatment and/or SCT.

Responses also occurred among patients carrying a wide range of *BCR-ABL* mutations, except T315I. In this study, limited responses were observed in patients with F317L or E255K mutations, suggesting that some mutations may not be highly responsive to dasatinib. No assessment of alternative resistance mechanisms was performed in mutation-negative patients. Patients with mutated *BCR-ABL* may respond to dasatinib because of its 325-fold higher potency for inhibiting BCR-ABL kinase activity in vitro compared with imatinib.[16] Because dasatinib can bind to multiple conformations of BCR-ABL,[14] the large number of mutations that cause imatinib resistance by destabilizing the inactive conformation required for imatinib binding are predicted to be sensitive to dasatinib. Treatment with dasatinib may produce additional effects through inhibition of SFKs, which are postulated to play a role in CML disease progression. In a mouse model of acute leukemia, SFKs LYN, HCK, and FGR, activated by *BCR-ABL* in lymphoid leukemic cells, were required for CML progression to lymphoid-blast crisis and development of Ph-positive ALL.[13] In this model, simultaneous inhibition of both BCR-ABL and SFK activity by dasatinib, but not sole inhibition of BCR-ABL by imatinib, resulted in disease remission. Another potential mechanism of imatinib resistance that might be overcome by dasatinib is *BCR-ABL* amplification.[27,28] However, a considerable proportion of the patients in this study demonstrated clinical resistance without evidence of

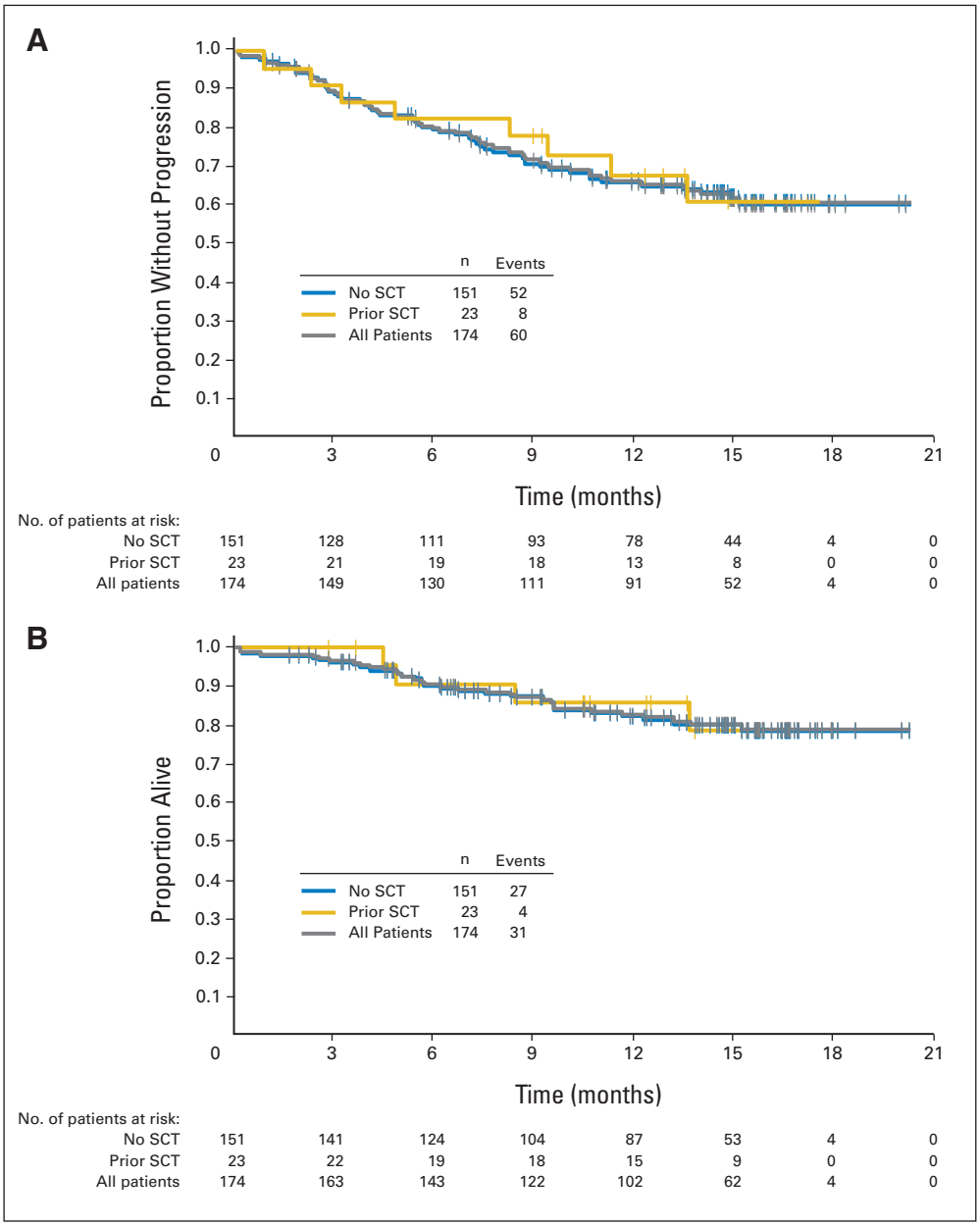

Fig 2. Kaplan-Meier analysis of outcomes after a median of 14 months of follow-up in all patients and in subgroups defined by prior stem-cell transplantation (SCT). (A) Progression-free survival. (B) Overall survival. Progression was defined as loss of major or minor hematologic response, no decrease from baseline levels in percentage blasts, or confirmed blast-phase disease.

clonal evolution or kinase mutations. Although the mechanism(s) of resistance in these patients is unknown, clearly some are clinically responsive to dasatinib.

Safety results reported here are consistent with earlier dasatinib studies in patients with other phases of imatinib-resistant or imatinib-intolerant CML and confirm that dasatinib-related nonhematologic adverse events are most frequently grade 1 to 2 and that dasatinib-related AEs are usually manageable.[17-21] Compared with the previous report from this study, no unexpected toxicity was observed with longer-term treatment.[18] Grade 3 to 4 cytopenia was generally reversible with dose interruption and/or reduction. In a study of patients with chronic-phase CML treated at a single institution who developed grade 3 to 4 cytopenia while being treated with dasatinib, it was reported that growth factor therapy, including granulocyte colony-stimulating factor, interleukin-11, and erythropoietin, enabled more continuous dasatinib administration.[29] In some patients, severe life-threatening infections occurred. These were probably a result of neutropenia, which in turn was related to the underlying disease and/or its treatment, although an additional effect of dasatinib on the immune system cannot be excluded. Most patients required dose adjustments during the study (dose reductions in 65%, interruptions in 85%, and escalations in 35%), and 52% of patients discontinued treatment, although this was most commonly because of disease progression (42% of discontinuations).

In this study, the incidence of grade 3 to 4 pleural effusion was 5%. An analysis of 48 patients with pleural effusions after dasatinib therapy showed that early identification, temporary dose interruption/reduction, and diuretic and/or pulse corticosteroid therapy ensured rapid and timely resolution of such events.[30] Nonhematologic AEs with dasatinib are typically grade 1 to 2.

Table 4. Drug-Related Adverse Events

	All Patients (N = 174)				Patients With Imatinib-Resistant Disease (n = 161)				Imatinib-Intolerant Patients (n = 13)			
	All Grades		Grade 3/4		All Grades		Grade 3/4		All Grades		Grade 3/4	
Adverse Event	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Nonhematologic events*												
Diarrhea	90	52	13	8	81	50	11	7	9	69	2	15
Headache	51	29	1	< 1	49	30	1	< 1	2	15	0	0
Nausea	48	28	1	< 1	45	28	1	< 1	3	23	0	0
Pleural effusion	47	27	8	5	44	27	8	5	3	23	0	0
Fatigue	46	26	7	4	42	26	6	4	4	31	1	8
Pyrexia	42	24	7	4	38	24	6	4	4	31	1	8
Peripheral edema	39	22	1	< 1	35	22	1	< 1	4	31	0	0
Dyspnea	37	21	7	4	34	21	7	4	3	23	0	0
Rash	36	21	2	1	33	21	2	1	3	23	0	0
Vomiting	35	20	4	2	29	18	4	3	6	46	0	0
Anorexia	27	16	1	< 1	25	16	1	< 1	2	15	0	0
Asthenia	24	14	4	2	22	14	4	3	2	15	0	0
Petechiae	24	14	2	1	22	14	2	1	2	15	0	0
Arthralgia	22	13	0	0	22	14	0	0	0	0	0	0
Pain in extremity	21	12	0	0	20	12	0	0	1	8	0	0
Abdominal pain	19	11	0	0	17	11	0	0	2	15	0	0
Myalgia	20	12	1	< 1	19	12	1	< 1	1	8	0	0
Cough	18	10	1	< 1	18	11	1	< 1	0	0	0	0
Dizziness	18	10	0	0	17	11	0	0	1	8	0	0
Cytopenia												
Thrombocytopenia	167	97	141	82	155	97	131	82	12	92	10	77
Neutropenia	159	92	131	76	146	91	118	74	13	100	13	100
Anemia	172	99	120	69	159	99	109	68	13	100	11	85
Leukocytopenia	152	88	102	59	140	88	91	57	12	92	11	85

*Nonhematologic adverse events occurring with a frequency ≥ 10% are listed.

In summary, this trial demonstrates that dasatinib is associated with encouraging rates of response (both hematologic and cytogenetic) that are usually maintained for more than 12 months in patients with CML-AP after imatinib failure. This has the potential to alter the natural history of the disease and to increase the life expectancy of patients with poor prognoses. Evaluation is warranted in patients with previously untreated CML-AP.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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