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ORIGINAL REPORT

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Intermittent Target Inhibition With Dasatinib 100 mg Once Daily Preserves Efficacy and Improves Tolerability in Imatinib-Resistant and -Intolerant Chronic-Phase Chronic Myeloid Leukemia

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ABSTRACT

Purpose
Dasatinib is a *BCR-ABL* inhibitor, 325-fold more potent than imatinib against unmutated BCR-ABL in vitro. Phase II studies have demonstrated efficacy and safety with dasatinib 70 mg twice daily in chronic-phase (CP) chronic myelogenous leukemia (CML) after imatinib treatment failure. In phase I, responses occurred with once-daily administration despite only intermittent BCR-ABL inhibition. Once-daily treatment resulted in less toxicity, suggesting that toxicity results from continuous inhibition of unintended targets. Here, a dose- and schedule-optimization study is reported.

Patients and Methods
In this open-label phase III trial, 670 patients with imatinib-resistant or -intolerant CP-CML were randomly assigned 1:1:1:1 between four dasatinib treatment groups: 100 mg once daily, 50 mg twice daily, 140 mg once daily, or 70 mg twice daily.

Results
With minimum follow-up of 6 months (median treatment duration, 8 months; range, < 1 to 15 months), marked and comparable hematologic (complete, 86% to 92%) and cytogenetic (major, 54% to 59%; complete, 41% to 45%) response rates were observed across the four groups. Time to and duration of cytogenetic response were similar, as was progression-free survival (8% to 11% of patients experienced disease progression or died). Compared with the approved 70-mg twice-daily regimen, dasatinib 100 mg once daily resulted in significantly lower rates of pleural effusion (all grades, 7% *v* 16%; $P = .024$) and grade 3 to 4 thrombocytopenia (22% *v* 37%; $P = .004$), and fewer patients required dose interruption (51% *v* 68%), reduction (30% *v* 55%), or discontinuation (16% *v* 23%).

Conclusion
Dasatinib 100 mg once daily retains the efficacy of 70 mg twice daily with less toxicity. Intermittent target inhibition with tyrosine kinase inhibitors may preserve efficacy and reduce adverse events.

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INTRODUCTION

Leukemic cells from patients with chronic myeloid leukemia (CML) are characterized by the presence of the Philadelphia chromosome (Ph), which contains the oncogenic *BCR-ABL* fusion gene. The majority of patients with CML are diagnosed during the initial chronic phase (CP) and receive first-line treatment with imatinib mesylate (Gleevec; Novartis Pharma, East Hanover, NJ), an inhibitor of BCR-ABL tyrosine kinase activity.[1,2] Dasatinib (Sprycel; Bristol-Myers Squibb, New York, NY) is structurally unrelated to imatinib, 325-times more potent than imatinib in inhibiting the growth of *BCR-ABL*–expressing cells in vitro, and, unlike imatinib, able to bind to the *BCR-ABL* kinase in the functionally relevant, catalytically active conformation.[3-5] Dasatinib has been approved for the treatment of imatinib-resistant and -intolerant CML in all phases of the disease.[6-11]

Nearly all approved tyrosine kinase inhibitors are administered orally and have pharmacokinetic properties that result in continuous target inhibition when administered once daily. For example, the half-life of imatinib is 18 hours, and that of its primary active metabolite, *N*-desmethyl imatinib, is

40 hours.[12,13] Epidermal growth factor receptor tyrosine kinase inhibitors gefitinib, erlotinib, and lapatinib show in vivo half-lives of 48 hours, 36 hours, and 24 hours, respectively, and vascular endothelial growth factor receptor tyrosine kinase inhibitors sunitinib and sorafenib exhibit half-lives of 40 to 60 hours and 20 to 27 hours, respectively.[14-18] In contrast, the half-life of dasatinib is only 3 to 5 hours. The dasatinib 70-mg twice-daily regimen used for phase II studies and subsequently approved was selected on the basis of pharmacokinetic and pharmacodynamic studies on the phosphorylation of CRK-like protein (CRKL),[19-21] a substrate specific to BCR-ABL, which was previously used to guide imatinib dose selection.[22] In the dasatinib phase I program, BCR-ABL kinase inhibition was more sustained across a 24-hour period with the twice-daily schedule, consistent with pharmacokinetic analyses.

Notably, cytogenetic responses were observed in phase I with both once-daily and twice-daily dosing (major cytogenetic response [MCyR]: once daily, 48%; twice daily, 42%), including cases treated with dasatinib once-daily 5 days per week.[23] Longer-term follow-up has indicated that pleural effusions were less frequent with once-daily than with twice-daily dosing. Because of dose reductions (initial dose, 70 mg twice daily), the median total daily dose across the phase II program in CP-CML was close to 100 mg/d.[6,8]

To confirm preliminary findings that intermittent BCR-ABL inhibition is efficacious and to test whether toxicity could be minimized with less frequent dosing, a randomized phase III study was performed investigating dasatinib administered as once-daily and twice-daily schedules at two total daily doses (100 mg and 140 mg) in patients with CP-CML after imatinib resistance or intolerance.

PATIENTS AND METHODS

Study Design and Patient Eligibility

This was a randomized, international, multicenter, open-label, phase III trial with a 2 × 2 factorial design. A permuted block design was used to randomly assign patients with a 1:1:1:1 ratio. The study was conducted in accordance with the Declaration of Helsinki and was approved by local ethical committees. Written, informed consent was obtained from every patient before participation.

Patients at least 18 years of age with Ph-positive CP-CML and primary or acquired hematologic resistance or intolerance to imatinib were enrolled. To meet inclusion criteria for Ph-positive CP-CML, patients were required to have less than 15% blasts in peripheral blood or bone marrow, less than 30% blasts and promyelocytes in peripheral blood or bone marrow, less than 20% basophils in peripheral blood, ≥ 100,000/μL platelets (or less if related to prior drug therapy), and no extramedullary involvement (except liver or spleen). Patients were stratified by imatinib resistance or intolerance. Primary resistance to imatinib (400 to 800 mg/d) was defined as no decrease in WBC count after ≥ 4 weeks of treatment, no complete hematologic response (CHR) after 3 months, no MCyR after 6 months, and no complete cytogenetic response

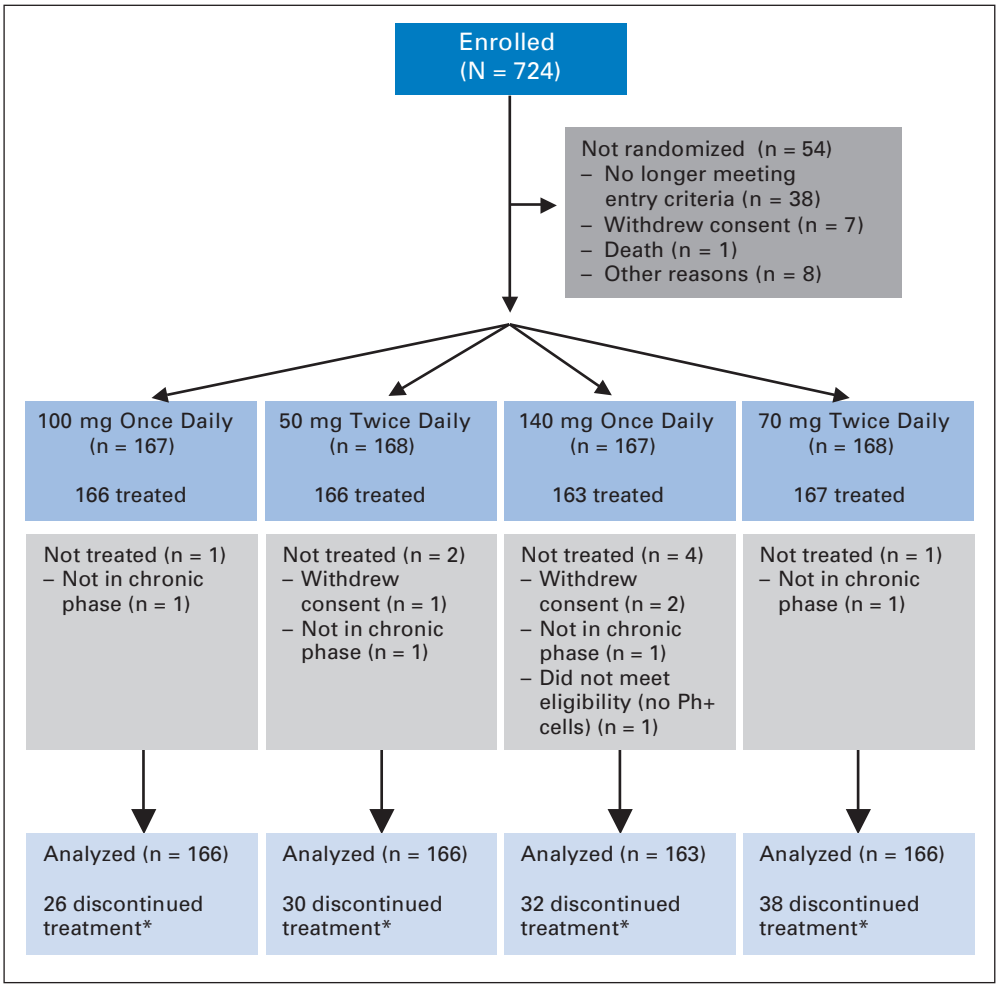

Fig 1. CONSORT diagram for the CA180-034 study. (*Reasons for discontinuation are listed in Table 4.) Ph+, Philadelphia chromosome positive.

(CCyR) after 12 months. Acquired resistance was defined as loss of MCyR (≥ 30% absolute increase in the percentage of Ph-positive metaphases), loss of molecular response (concomitant with a ≥ 10% Ph-positive metaphases at cytogenetic analysis), evidence of a new mutation in the *BCR-ABL* kinase domain, or loss of a confirmed CHR (WBC count > 10,000/μL on all assessments over at least a consecutive 2-week period). Intolerance to imatinib was defined as grade 3 or worse toxicity (considered at least possibly related to imatinib at a dose of ≥ 400 mg/d) which led to discontinuation of therapy. Patients who tolerated 400 mg/d imatinib but who did not achieve a CCyR and subsequently did not tolerate doses of ≥ 600 mg/d were considered to be resistant to imatinib.

Exclusion criteria included but were not limited to the following: treatment with imatinib, interferon alfa, cytarabine therapy, or any targeted small-molecule anticancer agent within 7 days of initiation; uncontrolled or significant cardiovascular disease (eg, myocardial infarction within 6 months, congestive heart failure within 3 months, congenital prolonged QT syndrome, or QTcF interval of more than 450 milliseconds on pre-entry ECG); history of a significant bleeding disorder unrelated to CML; eligibility for immediate autologous or allogeneic stem-cell transplantation; or concurrent incurable malignancy other than CML.

Treatment with Dasatinib

Four dasatinib treatment groups, to which patients were randomly assigned after stratification by imatinib resistance or intolerance, were defined according to schedule and total dose: 100 mg once daily; 50 mg twice daily; 140 mg once daily; and 70 mg twice daily. All doses were administered orally.

Dose escalation to 140 mg once daily (100-mg once-daily group), 70 mg twice daily (50-mg twice-daily group), 180 mg once daily (140-mg once-daily group), or 90 mg twice daily (70-mg twice-daily group) was allowed for inadequate response, defined as no decrease in WBC after 1 month of uninterrupted dasatinib treatment, no CHR after 3 months, no MCyR after 6 months, or no CCyR after 12 months. Dose interruption or reduction to 80 mg once daily (100-mg once-daily and 140-mg once-daily groups) or 40 mg twice daily (50-mg twice-daily and 70-mg twice-daily groups) was allowed after grade 2 or worse nonhematologic toxicity deemed to be drug related or grade 3 or worse hematologic toxicity. Treatment was administered until disease progression or intolerable toxicity, as determined by the treating physician. CML therapies other than dasatinib were prohibited, with the exception of hydroxyurea (for a maximum of 2 weeks) for elevated WBC counts (> 50,000/μL). Administration of myeloid growth factors or recombinant erythropoietin was permitted at the discretion of the investigator. Patients were supported with platelet transfusions as required.

Patient Evaluation

Treatment efficacy was evaluated on the basis of hematologic assessments and bone marrow cytogenetics.[6,8] Standard definitions of cytogenetic response according to number of Ph-positive metaphases in bone marrow were used (CCyR, 0%; partial cytogenetic response [PCyR], > 0% to 35%; minor cytogenetic response, > 35% to 65%; minimal cytogenetic response, > 65% to 95%; no cytogenetic response, > 95% to 100%). Patients with a CCyR or PCyR were considered to have a MCyR. Definitions of CHR and CML disease progression have been published previously[6,8]; the latter was defined as confirmed accelerated- or blast-phase disease, loss of a previous CHR or MCyR, ≥ 30% increase in Ph-positive metaphases, increasing WBC count (recorded by the investigator as a doubling from lowest value to > 20,000/μL or an increase by > 50,000/μL on two assessments performed at least 2 weeks

Table 1. Baseline Patient Demographics and Disease Characteristics

Characteristic	100 mg QD (n = 167)		50 mg BID (n = 168)		140 mg QD (n = 167)		70 mg BID (n = 168)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Age, years								
Median	56		55		54		55	
Range	20-78		21-84		20-84		18-83	
Male sex	84	50	85	51	70	42	77	46
Disease history, duration, months								
Median	55		51		56		53	
Range	1.6-251		4.4-212		0.9-227		1.2-246	
Duration of prior imatinib therapy, years								
< 1	36	22	40	24	39	23	37	22
1-3	55	33	68	40	58	35	60	36
> 3	76	46	60	36	68	41	71	42
Not reported	0		0		1	<1	0	
Prior imatinib ≥ 800 mg/d	61	37	55	33	55	33	56	33
Best response before imatinib failure								
CHR	136	81	146	87	138	83	141	84
MCyR	76	46	65	39	71	43	66	39
Resistance to imatinib	124	74	124	74	123	74	127	76
Primary	75	45	88	52	78	47	82	49
Acquired	49	29	36	21	45	27	45	27
Imatinib-resistant *BCR-ABL* mutation detected	49	34	60	41	51	37	45	31
Patients with samples available	144		145		138		143	
Other prior therapy								
Interferon-α	87	52	87	52	93	56	82	49
Chemotherapy	39	23	52	31	41	25	43	26
Stem-cell transplantation	10	6	13	8	5	3	7	4
Response status								
Patients in CHR at entry	85	51	70	42	69	41	64	38
Patients in MCyR at entry	34	20	23	14	28	17	31	18

Abbreviations: BID, twice daily; CHR, complete hematologic response; MCyR, major cytogenetic response; QD, once daily.

apart), or death from any cause. Calculations of hematologic or cytogenetic response rates did not exclude patients who had had responses at baseline.

Peripheral-blood cell mRNA was collected and analyzed for *BCR-ABL* gene point mutations by denaturing high-performance liquid chromatography and sequencing. Different *BCR-ABL* mutations were classified as being associated with imatinib resistance if supported by current literature.

Safety and tolerability were assessed using the National Cancer Institute's Common Terminology Criteria for Adverse Events version 3.0. In all patients, monitoring for pleural effusions included scheduled chest x-rays. Classifications of pleural effusions were as follows: grade 1, asymptomatic; grade 2, symptomatic, with intervention such as diuretics or up to two therapeutic thoracenteses indicated; grade 3, symptomatic and supplemental oxygen, more than two therapeutic thoracenteses, tube drainage, or pleurodesis indicated; grade 4, life-threatening (eg, causing hemodynamic instability or ventilatory support indicated).

The primary end point was the rate of MCyR in patients with imatinib resistance, with a minimum follow-up of 6 months. The primary analysis was the comparison between dosing schedules; the main secondary analysis was the comparison of daily doses (100 mg *v* 140 mg). Secondary end points included rates of MCyR in imatinib-intolerant patients, rates of CHR, time to and duration of MCyR and CHR, progression-free survival (PFS), overall survival, and safety evaluations.

Statistical Analysis

Efficacy data were analyzed for all randomly assigned patients as part of an intent-to-treat analysis. Noninferiority for the primary end point was assessed by determining whether the lower bound of the 95% CI of the difference between MCyR rates for once-daily and twice-daily schedules was $\geq -15\%$. Time to and duration of MCyR and CHR, PFS, and overall survival were estimated using Kaplan-Meier product-limit methodology. Fisher's exact test was used to compare the incidence of selected adverse events (AEs) using the worst Common Terminology Criteria for Adverse Events grade per patient.

RESULTS

Between July 2005 and March 2006, 670 patients were randomly assigned at 139 centers worldwide. A total of 662 patients were treated (Fig 1), including 491 patients (74%) with imatinib resistance and 171 patients (26%) with imatinib intolerance.

The analysis was performed 6 months after entry of the last patient, ensuring a minimum follow-up of 6 months. The median duration of treatment was 8 months (range, < 1 to 15 months). After discontinuing treatment, patients continued to be observed for disease progression and survival status.

Patient Demographics and Disease Characteristics

Patient demographics and baseline disease characteristics were well balanced (Table 1) and similar to cohorts of patients with CP-CML and imatinib resistance or intolerance from previous studies. Median age was 55 years and 47% of patients were male. Median time from CML diagnosis to randomization was 54 months. All patients received prior imatinib therapy, with 34% having received doses of 800 mg/d or more. The best previous hematologic response to imatinib was CHR in 84% of patients, and best previous cytogenetic response was MCyR in 41% (CCyR in 21%). The median duration of prior imatinib treatment was approximately 3 years. Prior treatment for CML included interferon alfa in 52%, chemotherapy in 26%, and stem-cell transplantation in 5% of cases.

Hematologic and Cytogenetic Responses

Dasatinib was associated with marked and consistent hematologic and cytogenetic response rates (CHR, 86% to 92%; MCyR, 54% to 59%; CCyR, 41% to 45%), irrespective of schedule (once daily or twice daily) or total daily dose (100 mg or 140 mg; Table 2). The primary objective was achieved: imatinib-resistant patients receiving once-daily therapy attained an MCyR rate that was noninferior to the twice-daily schedule (once daily, 52% [95% CI, 45.4% to 58.2%]; twice daily, 49% [95% CI, 42.7% to 55.4%]; treatment difference, 2.8% [95% CI, −6.0% to 11.6%]). The main secondary objective was also achieved: the 100-mg total daily dose was noninferior to the 140-mg total daily dose among imatinib-resistant patients (100 mg, 50% [95% CI, 43.6% to 56.4%]; 140 mg, 51% [95% CI, 44.4% to 57.2%]; treatment difference, −0.8% [95% CI, −9.6% to 8.0%]).

Table 2. Best Hematologic and Cytogenetic Response

Response	100 mg QD (n = 167)			50 mg BID (n = 168)			140 mg QD (n = 167)			70 mg BID (n = 168)		
	No. of Patients	Total Patients	%	No. of Patients	Total Patients	%	No. of Patients	Total Patients	%	No. of Patients	Total Patients	%
Complete hematologic response	150	167	90	154	168	92	143	167	86	146	168	87
95% CI		84.2 to 94.0			86.4 to 95.4			79.4 to 90.6			80.8 to 91.6	
By status												
Imatinib resistant	107	124	86	113	124	91	105	123	85	111	127	87
Imatinib intolerant	43	43	100	41	44	93	38	44	86	35	41	85
Major cytogenetic response	98	167	59	90	168	54	93	167	56	93	168	55
95% CI		50.8 to 66.2			45.7 to 61.3			47.8 to 63.4			47.5 to 63.0	
By status												
Imatinib resistant	66	124	53	58	124	47	62	123	50	65	127	51
Imatinib intolerant	32	43	74	32	44	73	31	44	70	28	41	68
Complete cytogenetic response	69	167	41	70	168	42	74	167	44	75	168	45
By status												
Imatinib resistant	42	124	34	43	124	35	44	123	36	50	127	39
Imatinib intolerant	27	43	63	27	44	61	30	44	68	25	41	61

NOTE. "No. of Patients" indicates number of patients with response; "Total Patients" indicates number of patients in a given category.
Abbreviations: BID, twice daily; QD, once daily.

A greater depth of response was evident for imatinib-intolerant patients (MCyR, 68% to 74%; CCyR, 61% to 68%) than for the imatinib-resistant cohort (MCyR, 47% to 53%; CCyR, 34% to 39%).

With the current minimum follow-up of 6 months, disease progression for patients who experienced an MCyR is minimal, with similar rates observed across the four treatment groups (100 mg once daily, 1%; 50 mg twice daily, 1%; 140 mg once daily, 3%; 70 mg twice daily, 3%; Fig 2A). Time to CHR and MCyR were similar between treatment groups.

BCR-ABL *Mutations*

CHR and MCyR rates in patients classified according to mutation status were similar across all four treatment groups (Table 3).

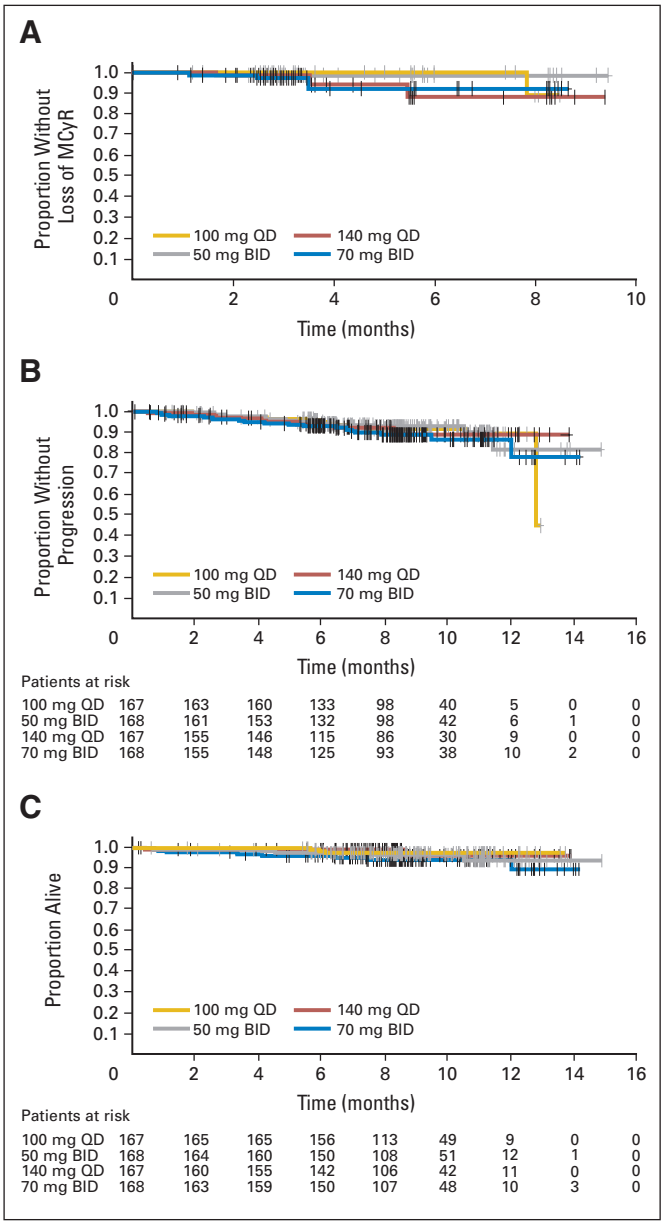

Fig 2. Kaplan-Meier analyses. (A) Duration of major cytogenetic response. (B) Progression-free survival (progression was defined as confirmed accelerated- or blast-phase disease, loss of previous complete hematologic response or major cytogenetic response, or increasing WBC count [see Patients and Methods for definition]). (C) Overall survival. QD, once daily; BID, twice daily.

PFS

No differences in PFS were evident across the treatment groups; to date, few patients have either experienced disease progression or died (100 mg once daily, 8%; 50 mg twice daily, 8%; 140 mg once daily, 8%; 70 mg twice daily, 11%). The Kaplan-Meier PFS curve is presented in Figure 2B.

Overall Survival

Rates of overall survival were also similar across the various treatment groups, with few patients having died (100 mg once daily, 2% [n = 3]; 50 mg twice daily, 4%, [n = 6]; 140 mg once daily, 2% [n = 4]; 70 mg twice daily, 5% [n = 8]; Fig 2C). Other than CML disease (n = 6), reasons for death assigned by study investigators were as follows: infection (n = 4), cardiovascular disease (n = 1), bleeding (n = 1), study drug toxicity (n = 1), other (n = 5: idiopathic pneumonia syndrome, secondary to stem-cell transplantation, suicide, relapse of tuberculosis/liver insufficiency, and left ventricular diastolic dysfunction), not reported (n = 2), and unknown (n = 1).

Adverse Events

Rates of key treatment-related AEs (ie, cytopenia and pleural effusion) were consistently lower in patients receiving dasatinib 100 mg once daily than for the other treatment groups (Table 4). Overall, significantly fewer patients treated with 100 mg once daily experienced grade 3 to 4 AEs than patients receiving the currently approved 70-mg twice-daily dose (30% *v* 48%; $P = .001$), particularly grade 3 to 4 thrombocytopenia (22% *v* 37%; $P = .004$). In general, cytopenia was reversible and could be managed effectively through dose interruption or reduction and/or with the addition of growth factors or transfusions.

Significantly fewer patients experienced pleural effusions (of any grade) with dasatinib 100 mg once daily than with 70 mg twice daily (7% *v* 16%; $P = .024$). In general, pleural effusions resolved with temporary dose interruption, diuretics, and/or pulse corticosteroids. Grade 3 to 4 pleural effusions were reported in 1% to 2% of patients in each treatment group. Grade 2 pleural effusions (also symptomatic) were reported in 4% (100 mg once daily), 7% (50 mg twice daily), 10% (140 mg once daily), and 11% (70 mg twice daily) of patients. Grade 1 pleural effusions (asymptomatic and detected by routine chest x-rays) were reported in 2% (100 mg once daily, 50 mg twice daily, 140 mg once daily) or 4% (70 mg twice daily) of patients.

Drug-related nausea (15% *v* 25%) and vomiting (5% *v* 10%) of any grade occurred in fewer patients receiving 100 mg once daily than 70 mg twice daily. Rates of other treatment-related nonhematologic AEs were similar between treatment groups. The most commonly reported grade 3 to 4 nonhematologic AEs among all four treatment groups were diarrhea (2% to 5%), dyspnea (1% to 5%), fatigue (0% to 3%), and headache (0% to 3%).

Dose Adjustments and Treatment Discontinuations

Fewer patients in the 100 mg once daily group required dose interruption or reduction as compared with 70 mg twice daily (Table 5). In particular, the 100-mg once-daily regimen was associated with lower rates of treatment interruptions (27% *v* 35%) and dose reductions (22% *v* 32%) because of hematologic toxicity than was the 70-mg

Table 3. Best Treatment Responses by Baseline *BCR-ABL* Mutation Status

Response	100 mg QD (n = 144)*			50 mg BID (n = 145)*			140 mg QD (n = 138)*			70 mg BID (n = 143)*		
	No. of Patients	Total Patients	%	No. of Patients	Total Patients	%	No. of Patients	Total Patients	%	No. of Patients	Total Patients	%
CHR												
No mutation	90	95	95	79	83	95	77	86	90	83	94	88
Any mutation	42	49	86	54	60	90	42	51	82	40	45	89
Mutations associated with an increased imatinib IC_{50} of at least 5-fold†	26	31	84	26	32	81	23	31	74	22	25	88
MCyR												
No mutation	59	95	62	50	83	60	54	86	63	57	94	61
Any mutation	24	49	49	23	60	38	22	51	43	20	45	44
Mutations associated with an increased imatinib IC_{50} of at least 5-fold†	15	31	48	10	32	31	10	31	32	10	25	40

NOTE. "No. of Patients" indicates number of patients with response; "Total Patients" indicates number of patients in a given category.
Abbreviations: BID, twice daily; QD, once daily; CHR, complete hematologic response; IC_{50}, concentration that achieves 50% of the maximum possible cell growth inhibition; MCyR, major cytogenetic response.
*Patients with baseline samples available for testing.
†Cellular IC_{50} compared with unmutated *BCR-ABL*.

twice-daily regimen. The 100-mg once-daily group was also associated with a higher rate of dose escalation as compared with the 70-mg twice-daily group (15% *v* 7%).

Median total daily doses administered across the four treatment groups were as follows: 100 mg once daily, 100 mg; 50 mg twice daily, 93 mg; 140 mg once daily, 126 mg; and 70 mg twice daily, 108 mg,

Table 4. Treatment-Related Adverse Events Occurring During the Study

Event	100 mg QD (n = 166)				50 mg BID (n = 166)				140 mg QD (n = 163)				70 mg BID (n = 167)				*P* (100 mg QD *v* 70 mg BID)
	All Grades		Grade 3/4		All Grades		Grade 3/4		All Grades		Grade 3/4		All Grades		Grade 3/4		
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	
Cytopenia																	
Anemia	147	89	16	10	151	92	27	16	146	90	28	17	154	93	27	16	.074*
Leukocytopenia	98	59	27	16	119	72	42	25	116	72	33	20	114	69	38	23	.130*
Neutropenia	105	63	55	33	124	75	72	44	119	73	68	42	121	74	68	42	.112*
Thrombocytopenia	100	60	37	22	110	67	52	32	122	75	64	40	122	74	61	37	.004*
Fluid retention	35	21	2	1	36	22	4	2	43	26	7	4	46	28	7	4	—
Superficial edema	23	14	0	0	21	13	0	0	19	12	1	< 1	23	14	0	0	—
Pleural effusion	12	7	2	1	19	11	3	2	24	15	4	2	26	16	2	1	.024†
Other fluid-related events																	
Pericardial effusion	1	< 1	0	0	2	1	1	< 1	5	3	1	< 1	2	1	1	< 1	—
Pulmonary edema	0	0	0	0	1	< 1	0	0	0	0	0	0	2	1	1	< 1	—
CHF/cardiac dysfunction	0	0	0	0	2	1	1	< 1	2	1	1	< 1	5	3	4	2	—
Pulmonary hypertension	0	0	0	0	0	0	0	0	0	0	0	0	2	1	1	< 1	—
Other adverse event‡																	
Headache	49	30	1	< 1	32	19	0	0	43	26	2	1	46	28	5	3	—
Diarrhea	39	23	1	< 1	40	24	4	2	38	23	3	2	36	22	6	4	—
Fatigue	33	20	2	1	22	13	0	0	29	18	4	2	27	16	5	3	—
Nausea	25	15	1	< 1	30	18	1	< 1	30	18	1	< 1	42	25	1	< 1	—
Rash	19	11	2	1	25	15	1	< 1	32	20	0	0	27	16	2	1	—
Myalgia	19	11	0	0	5	3	0	0	19	12	1	< 1	10	6	1	< 1	—
Dyspnea	17	10	2	1	25	15	7	4	24	15	8	5	19	11	5	3	—
Peripheral edema	16	10	0	0	9	5	0	0	9	6	0	0	17	10	0	0	—
Vomiting	9	5	1	< 1	12	7	2	1	13	8	2	1	17	10	0	0	—
Pyrexia	5	3	1	< 1	12	7	1	< 1	20	12	0	0	12	7	1	< 1	—

NOTE. Cytopenia was determined from laboratory evaluations and rates are stated according to available samples.
Abbreviations: QD, once daily; BID, twice daily; CHF, congestive heart failure.
*Grade 3/4.
†All grades.
‡Adverse events experienced by ≥ 10% of patients in any group.

Table 5. Dose Adjustments and Treatment Discontinuations During the Study

Factor	100 mg QD (n = 166)		50 mg BID (n = 166)		140 mg QD (n = 163)		70 mg BID (n = 167)	
	No.	%	No.	%	No.	%	No.	%
Daily dose, mg								
Median	100		93		126		108	
Range	18-150		21-158		42-166		13-167	
Interruption	85	51	102	61	105	64	114	68
Hematologic toxicity*	44	27	60	36	60	37	59	35
Nonhematologic toxicity*	30	18	35	21	30	24	54	32
Reduction	49	30	68	41	77	47	92	55
Hematologic toxicity*	36	22	44	27	55	34	53	32
Nonhematologic toxicity*	11	7	20	12	22	13	31	19
Escalation	25	15	20	12	15	9	11	7
Still on therapy	140	84	136	82	131	80	129	77
Discontinued therapy	26	16	30	18	32	20	38	23
Disease progression	9	5	8	5	11	7	7	4
Study drug-related toxicity	7	4	11	7	12	7	19	11
Adverse event unrelated to study drug	1	< 1	2	1	3	2	4	2
Investigator request	1	< 1	0	0	0	0	0	0
Patient request	2	1	4	2	2	1	3	2
Other	6	4	5	3	4	3	5	3

Abbreviations: QD, once daily; BID, twice daily.
*Reason for first dose modification (interruption or reduction).

suggesting that patients receiving once-daily treatment required fewer dose reductions.

Discontinuation rates were lower for the dasatinib 100-mg once-daily group than for the 70-mg twice-daily group (16% *v* 23%). In particular, discontinuation owing to toxicity occurred in only 4% of patients treated with 100 mg once daily as compared with 11% of patients treated with 70 mg twice daily. Overall, 536 patients (80%) remain on the trial, with most discontinuations attributable to disease progression or toxicity.

DISCUSSION

Dasatinib 100 mg once daily offered the most favorable overall benefit-risk assessment in this study evaluating dose and schedule optimization in patients with CP-CML that is resistant or intolerant to imatinib. This finding is noteworthy, given that the target kinase, BCR-ABL, is inhibited only intermittently. In comparison with the approved 70-mg twice-daily regimen, dasatinib 100 mg once daily was associated with improved tolerability, with significantly reduced incidences of key treatment-related AEs (grade 3 to 4 thrombocytopenia and pleural effusions). Other treatment-related nonhematologic AEs were generally mild to moderate in nature. The 100-mg once-daily regimen also resulted in the lowest incidence of treatment interruption and discontinuation, and once-daily treatment groups (100 mg or 140 mg) received higher median total daily doses than did corresponding twice-daily groups. These findings support the concept that some toxicities associated with kinase inhibitors may be driven by persistent exposure to inhibitory drug concentrations. However, peak levels must also be relevant, as patients in the 100-mg once-daily cohort experienced fewer adverse effects as compared with patients in the 140-mg once-daily cohort. All four dasatinib treatment arms displayed marked and comparable levels of hematologic and cytogenetic efficacy. Notably, no major differences in durability of response (CHR or MCyR) or in the rates of PFS and overall survival were reported.

Laboratory studies have revealed that transient exposure of three CML cell lines to clinically relevant dasatinib concentrations (100 nmol/L) results in apoptosis of the majority of cells when assessed 48 hours later.[24] Similar findings were observed when a non–small-cell lung cancer cell line harboring an activating epidermal growth factor mutation was transiently exposed to high concentrations of erlotinib.[24]

The findings described in this study have important implications for the emerging field of kinase inhibitor treatment for human malignancies. Specifically, compounds with pharmacokinetic properties requiring intravenous administration may retain significant efficacy, and tyrosine kinase inhibitor development should not be abandoned if promising compounds are found to have short half-lives. Of particular interest is the promise of intermittent high-dose kinase inhibitor therapy for malignancies that have developed resistance after an initial response, because this phenomenon is frequently mediated by kinase domain mutations within the target that result in a relative degree of resistance.

Response rates to dasatinib reported here after a median of 8 months' treatment are notable (MCyR, 54% to 59%; CCyR, 41% to 45%) and consistent with the responses observed after 8 months in START-C, a phase II, single-arm study of dasatinib in CP-CML (MCyR, 52%; CCyR, 39%).[6]

The rapid clinical development and approval of dasatinib enabled prompt access to an effective and potentially life-saving treatment for patients with CML and imatinib treatment failure. Dose

optimization may now improve the safety profile of dasatinib in clinical practice. Patients in this study will continue dasatinib therapy according to their randomly assigned treatments, and longer-term follow-up results will be reported.

Treatment with dasatinib 100 mg once daily provides the most favorable overall benefit-risk profile, with improved tolerability and consistent efficacy to the recommended 70-mg twice-daily dose in patients with CP-CML. On the basis of these findings, the 100-mg once-daily regimen should be used for patients with CP-CML who are initiating dasatinib treatment.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).