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Phase I Dose-Escalation and Pharmacokinetic Study of Dasatinib in Patients with Advanced Solid Tumors

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Abstract

Purpose: To determine the maximum tolerated dose, dose-limiting toxicity (DLT), and recommended phase II dose of dasatinib in metastatic solid tumors refractory to standard therapies or for which no effective standard therapy exists.

Experimental Design: In this phase I, open-label, dose-escalation study, patients received 35 to 160 mg of dasatinib twice daily in 28-day cycles either every 12 hours for 5 consecutive days followed by 2 nontreatment days every week (5D2) or as continuous, twice-daily (CDD) dosing.

Results: Sixty-seven patients were treated (5D2, $n = 33$; CDD, $n = 34$). The maximum tolerated doses were 120 mg twice daily 5D2 and 70 mg twice daily CDD. DLTs with 160 mg 5D2 were recurrent grade 2 rash, grade 3 lethargy, and one patient with both grade 3 prolonged bleeding time and grade 3 hypocalcemia; DLTs with 120 mg twice daily CDD were grade 3 nausea, grade 3 fatigue, and one patient with both grade 3 rash and grade 2 proteinuria. The most frequent treatment-related toxicities across all doses were nausea, fatigue, lethargy, anorexia, proteinuria, and diarrhea, with infrequent hematologic toxicities. Pharmacokinetic data indicated rapid absorption, dose proportionality, and lack of drug accumulation. Although no objective tumor responses were seen, durable stable disease was observed in 16% of patients.

Conclusion: Dasatinib was well tolerated in this population, with a safety profile similar to that observed previously in leukemia patients, although with much less hematologic toxicity. Limited, although encouraging, preliminary evidence of clinical activity was observed. Doses of 120 mg twice daily (5D2) or 70 mg twice daily (CDD) are recommended for further studies in patients with solid tumors. (Clin Cancer Res 2009;15(19):6232–40)

Dysregulated cell signaling through multiple kinases is associated with oncogenesis in many tumors. SRC family kinases (SFK), including SRC, YES, and FYN, are nonreceptor tyrosine kinases with a critical role in cellular proliferation. Together with YES and FYN, SRC has an ubiquitous distribution with particularly high levels in platelets, neurons, osteoclasts, and at epithelial cell-cell junctions (1, 2). Expression of the remaining SFKs is restricted primarily to hematopoietic cells. SFKs are basic components of the cell signaling machinery and are involved in pathways regulating growth, survival, motility, and adhesion (3). SFKs also promote several aspects of tumor progression and metastasis (4) and have a role in

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Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/.

Previous presentations and preliminary abstract publications: (*a*) Evans TRJ, Morgan JA, van den Abbeele AD, et al. Phase I dose-escalation study of the SRC and multi-kinase inhibitor BMS-354825 in patients (pts) with GIST and other solid tumors. J Clin Oncol 2005;23(16S):200s, 3034 (poster presented at the American Society of Clinical Oncology, 2005). (*b*) Luo FR, Luo FR, Barrett Y, et al. Dasatinib (BMS-354825) pharmacokinetics correlate with pSRC pharmacodynamics in phase I studies of patients with cancer (CA180002, CA180003). J Clin Oncol 2006;24 (18S):132s, 3046. (*c*) Morgan JA, Demetri G, Wang D, et al. A phase I study of dasatinib, a SRC and multi-kinase inhibitor, in patients (pts) with GIST and other solid tumors. Eur J Cancer Supplements 2006;4(12):118, abstract 383. Poster presented at the 18th European Organization for Research and Treatment of Cancer-National Cancer Institute-AACR International Conference on "Molecular Targets and Cancer Therapeutics" (7-10 November 2006, Prague).

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Translational Relevance

Dysregulated pathways of kinase signaling, including those involving c-KIT and SRC family kinases (SFK), play an important role in tumorigenesis. Dasatinib is an oral, small-molecule multikinase inhibitor of several SFKs as well as c-KIT, platelet-derived growth factor receptor, BCR-ABL, and ephrin receptor kinases. Although the benefits of dasatinib in patients with hematologic malignancies have been shown previously, its activity in patients with solid tumors has yet to be established. This work is relevant to current and future anticancer drug therapy because our results show that dasatinib, a multikinase inhibitor with activity against SFKs, is acceptably well tolerated in patients with solid tumors with encouraging preliminary evidence of efficacy in patients with advanced refractory disease. Importantly, the results of our study form the basis of dasatinib dosing for further clinical development in solid tumor oncology.

osteoclast function (5–7). SRC expression and/or activity are up-regulated in a variety of human tumors (8–16). Additionally, >90% of gastrointestinal stromal tumors (GIST) harbor activating mutations in either *KIT* or platelet-derived growth factor receptor-α (*PDGFRA*; ref. 17).

Dasatinib is a kinase inhibitor with potent activity against several kinases, including SFKs, KIT, PDGFRA, EPHA2, and BCR-ABL *in vitro* (18, 19). Dasatinib inhibits cellular SRC autophosphorylation and cellular proliferation in several cancer cell lines *in vitro* and has shown *in vivo* antitumor efficacy in mice against a range of human tumor xenografts (19–21). *In vitro* studies have shown that dasatinib potently inhibits both wild-type and mutated KIT (22). Dasatinib has proven clinical efficacy in patients with chronic myelogenous leukemia (CML) and Philadelphia chromosome–positive acute lymphoblastic leukemia (Ph+ALL; refs. 23–26).

Consequently, we have done a phase I study with dasatinib in patients with advanced solid tumors that were refractory to standard therapies or for whom no effective standard therapy existed. The primary objective of this study was to establish the maximum tolerated dose (MTD), dose-limiting toxicity (DLT), and recommended phase II dose of dasatinib. Secondary objectives included evaluation of the safety, tolerability, and plasma pharmacokinetics of dasatinib and assessing any preliminary evidence of antitumor efficacy.

Materials and Methods

Patients and eligibility criteria. This was a nonrandomized, open-label, phase I, dose-escalation study conducted in accordance with the International Conference on Harmonization Good Clinical Practice with the ethical principles of the current Declaration of Helsinki and approved by the Research Ethics Committee at each of the participating institutions. All patients provided written informed consent before doing any study-related procedures.

All patients who entered into this study had a verified advanced solid malignancy, refractory to conventional therapy or for which there was no effective therapy. Eligible patients were ages ≥18 y with an Eastern Cooperative Oncology Group performance status of 0 to 1. They should not have received chemotherapy, immunotherapy, or radiotherapy within 4 wk of entering the study (6 wk for nitrosoureas, mitomycin C, and liposomal doxorubicin) and at least 2 wk must have elapsed since exposure to other kinase inhibitors. Eligibility criteria also included adequate hematologic, hepatic, and renal function[6]; serum potassium and magnesium within the institution's reference range; corrected serum calcium above the institution's lower limit of normal; and either a bleeding time that was less than the institution's upper limit of normal or a platelet aggregometry test within normal limits.

Patients were excluded if they had received prior radiotherapy to ≥25% of the bone marrow–containing skeleton or if they had uncontrolled or significant cardiovascular disease, known brain metastasis, prolonged QT syndrome or QT_c >450 ms, history of a significant bleeding disorder, vasculitis, or a significant bleeding episode from the gastrointestinal tract in the preceding 6 mo. Patients who were pregnant or breast-feeding or who were of childbearing potential but unwilling or unable to use adequate contraception were also excluded. Prohibited medications included those known to increase the risk of Torsades de Pointes, irreversible inhibitors of platelet function, and anticoagulants.

Treatment administration. Pretreatment evaluation included a complete history and clinical examination, vital signs, assessment of performance status, full blood count, biochemical profile, coagulation screen, bleeding time or platelet aggregometry, fasting cholesterol, triglycerides, and glucose, $CD4^+$ T-cell count, creatine kinase, creatine kinase myoglobin, troponin I and T, thyroid-stimulating hormone, urinalysis, chest X-ray, and pregnancy test. Electrocardiograms (EKG) were done in triplicate 1 to 3 d before study treatment. Relevant radiologic studies to evaluate sites of disease were done within 3 wk before dosing on day 1.

Dasatinib was administered orally on an empty stomach in 28-d treatment cycles either every 12 h for 5 consecutive days followed by 2 nontreatment days every week (5D2 schedule) or continuously, twice-daily (CDD schedule). No concomitant anticancer therapy was permitted. Hematopoietic growth factors and erythropoietin were permitted but not within the first 28 d of drug administration during which time DLTs were assessed.

The dasatinib starting dose [35 mg twice daily] was based on prior clinical experience from studies in hematologic malignancies (27) and was escalated in subsequent dose cohorts until the MTD was determined. Once the MTD was reached on the 5D2 schedule, subsequent patients were enrolled on the CDD schedule, with a starting dose two levels below the 5D2 MTD. Dose escalation on the CDD schedule continued until the CDD MTD was reached. Once the MTD had been defined, an additional cohort of up to 15 to 20 patients was recruited.

Study treatment continued until progressive disease, death, pregnancy, withdrawal of consent, or unacceptable toxicity. Patients initially treated on the 5D2 schedule had the option of crossing over to the CDD schedule at the investigator's discretion. All patients were followed for a minimum of 30 d after the last dose of study therapy or until recovery from any treatment-related toxicity.

Evaluation of toxicity. Toxicity was graded using the National Cancer Institute Common Toxicity Criteria version 3.0. Physical examinations and assessment of Eastern Cooperative Oncology Group performance status were done weekly. Laboratory assessments, similar to those done before treatment, were also done at regular intervals.[7] EKGs were done in triplicate 10 min before administration; 1, 2, 3, 4, 6, 8, and 10 h after administration on day 1; once between days 3 and 5; and once between days 24 and 26 of cycle 1. Toxicity assessments of subjects who remained on study with no dose reductions or interruptions ≥3 mo were subsequently done every 4 wk.

[6] Criteria for adequate organ function are provided in Supplementary Data.
[7] Full details of laboratory assessments are provided in Supplementary Data.

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Table 1. Baseline demographic and clinical characteristics

	Dasatinib schedule		Total (*N* = 67)
	5D2 (*n* = 33)	CDD (*n* = 34)	
Median age, y (range)	56 (32-81)	59 (31-82)	57 (31-82)
Gender			
Male	20 (60.6%)	18 (52.9%)	38 (56.7%)
Female	13 (39.4%)	16 (47.1%)	29 (43.3%)
Baseline ECOG score			
0	18 (54.5%)	14 (41.2%)	32 (47.8%)
1	15 (45.5%)	20 (58.8%)	35 (52.2%)
Tumor type			
GIST	17 (51.5%)	2 (5.9%)	19 (28.4%)
Colon	2 (6.1%)	6 (17.6%)	8 (11.9%)
Sarcoma	4 (12.1%)	4 (11.8%)	8 (11.9%)
Melanoma	3 (9.1%)	2 (5.9%)	5 (7.5%)
Rectum	2 (6.1%)	3 (8.8%)	5 (7.5%)
Gastric	1 (3.0%)	3 (8.8%)	4 (6.0%)
Mesothelioma	0	3 (8.8%)	3 (4.5%)
MPN sheath tumor	1 (3.0%)	1 (2.9%)	2 (3.0%)
Ovary	0	1 (2.9%)	1 (1.5%)
Other*	3 (9.1%)	9 (26.5%)	12 (17.9%)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; MPN, malignant peripheral nerve sheath tumor.
*Other tumors reported by study investigators were desmoid tumor, biliary tract, and small bowel (5D2) and adenoid cystic carcinoma, myoepithelioma, chordoma, squamous cell carcinoma of left pinna, meningioma, chromophobe renal cell carcinoma, medullary thyroid, and endometrial and breast (CDD).

DLT was defined as grade 4 neutropenia for ≥5 consecutive days; febrile neutropenia (defined as absolute neutrophil count <1,000/mm^3 with temperature ≥38.5°C); thrombocytopenia (≤25,000 cells/mm^3 or bleeding requiring platelet transfusion); QT_c interval of ≥500 ms; grade 3 to 4 nausea, vomiting, or diarrhea despite maximal prophylaxis and intervention; any other grade ≥3 nonhematologic event except alopecia or fatigue (unless the fatigue was recurrent); drug-related toxicity that delayed scheduled retreatment for >14 d; and any grade of toxicity requiring dose reduction or discontinuation of study drug within the DLT assessment period. Description of DLTs, dose-escalation decisions, and determination of the MTD were based on toxicities occurring within the first 4 wk of drug administration. Cumulative toxicities were recorded at all dose cohorts.

At least three patients were enrolled at each dose cohort. If a DLT occurred, the cohort was expanded up to a maximum of six patients. The MTD was defined as the dose level below which more than one of three patients or two or more of six patients experienced a DLT. Intrapatient dose escalation was permitted if the maximum toxicity during prior cycles of therapy was grade ≤2 and if less than one or one DLT was observed in cycle 1 in three to six patients who had completed 4 wk of study drug at the next higher dose level.

Dose delays and modifications. Dose delays and modifications were done based on toxicity. Retreatment after dose interruption could be delayed for up to 14 d to allow recovery from any toxicity. Dose reductions were to the previous dose level or by 25%, whichever was larger. Following dose interruption for nonhematologic toxicities, dosing was recommenced when toxicities had resolved to grade 1 or baseline levels. Dosing was interrupted for any grade 2 nonhematologic toxicity (except alopecia or fatigue) thought to be related to the study drug, with dose reduction after recovery from the second occurrence. Dosing was interrupted, with subsequent reduction on recovery, following the first occurrence of grade 2 neuropathy and grade 3 nausea, vomiting, or diarrhea despite adequate/maximal intervention and/or prophylaxis. For QT_c prolongation ≥500 ms but <530 ms by both the Bazett and Fridericia methods, which resolved without any associated clinically significant arrhythmia, study drug was recommenced with a dose reduction after a minimum of 2 d of interruption of dosing. Dosing was also interrupted following grade 3/4 neutropenia or thrombocytopenia, with dose reductions implemented depending on time to recovery and severity. Patients who had their dose of dasatinib reduced due to toxicity did not have subsequent dose increases. Patients who developed recurrent toxicity despite dose reduction could remain on study after a second dose reduction at the discretion of the investigators. However, study drug was discontinued after the first occurrence of grade 4 nonhematologic toxicity, grade >3 neuropathy, or QT_c prolongation ≥530 ms.

Disease evaluation and objective response assessment. Tumor size was evaluated by computed tomography or magnetic resonance imaging, chest X-ray, and by physical examination in patients before starting study therapy. Assessments were repeated after every two cycles of treatment, after every 12 wk for patients who had been on study treatment for 24 wk, and at the end of treatment. Responses to treatment were defined using the modified WHO criteria (28), and all analyses done on an intention-to-treat basis.

Pharmacokinetics. Blood samples for pharmacokinetic analysis were collected before dose; 30 min, and 1, 1.5, 2, 3, 4, 5, 6, 8, and

Table 2. Overview of dasatinib treatment

Dasatinib cohort (*n*)	Treatment duration (mo), median (range)	Treatment duration excluding interruptions (mo), median (range)	Total dose (mg), median (range)	Net dose intensity (mg/d)*
5D2 schedule				
35 mg (*n* = 7)	0.9 (0.1-7.4)	0.9 (0.1-7.2)	1,400 (210.0-14,190)	54 (40-70)
50 mg (*n* = 3)	4.0 (1.1-5.0)	3.7 (1.1-5.0)	7,850 (2,450-14,110)	75 (71-93)
70 mg (*n* = 4)	2.8 (1.1-4.1)	2.8 (1.1-3.8)	8,750 (3,430-11,480)	103 (99-104)
90 mg (*n* = 6)	2.1 (0.7-3.6)	1.9 (0.7-3.6)	7,560 (3,330-14,400)	132 (126-180)
120 mg (*n* = 9)	1.1 (0.2-4.4)	0.9 (0.2-4.4)	4,800 (1,080-23,160)	182 (157-216)
160 mg (*n* = 4)	4.0 (1.3-23.8)	3.7 (0.8-21.6)	20,875 (3,970-84,720)	152 (129-225)
CDD schedule				
70 mg (*n* = 5)	1.0 (0.1-9.6)	0.8 (0.1-9.6)	3,500 (170-40,950)	140 (85-140)
90 mg (*n* = 7)	1.7 (0.6-18.3)	1.6 (0.3-16.9)	8,550 (1,710-90,630)	177 (149-182)
100 mg (*n* = 17)	1.2 (0.1-12.9)	0.8 (0.1-12.5)	4,700 (400-75,800)	197 (157-216)
120 mg (*n* = 5)	0.3 (0.2-1.8)	0.2 (0.2-1.8)	1,440 (1,080-21,720)	236 (197-240)

*Net dose intensity = cumulative total dose divided by treatment duration (excluding interruption) per patient.

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Table 3. Treatment-related nonhematologic toxicities occurring in ≥10% of patients on the 5D2 dosing schedule

Event, *n* (%)	35 mg (*n* = 7)		50 mg (*n* = 3)		70 mg (*n* = 4)		90 mg (*n* = 6)		120 mg (*n* = 9)		160 mg (*n* = 4)		Overall (*N* = 33)	
	Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4
Nausea	4 (57)	0 (0)	1 (33)	0 (0)	3 (75)	0 (0)	1 (17)	0 (0)	7 (78)	1 (11)	4 (100)	0 (0)	20 (61)	1 (3)
Fatigue	3 (43)	0 (0)	2 (66)	0 (0)	3 (75)	0 (0)	3 (50)	0 (0)	2 (22)	0 (0)	1 (25)	0 (0)	14 (42)	0 (0)
Diarrhea	3 (43)	1 (14)	1 (33)	0 (0)	1 (25)	0 (0)	1 (17)	0 (0)	4 (44)	0 (0)	3 (75)	0 (0)	13 (39)	1 (3)
Vomiting	2 (29)	0 (0)	1 (33)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	4 (44)	1 (11)	2 (50)	0 (0)	9 (27)	1 (3)
Anorexia	1 (14)	1 (14)	1 (33)	0 (0)	2 (50)	0 (0)	1 (17)	0 (0)	1 (11)	0 (0)	2 (50)	1 (25)	8 (24)	2 (6)
Lethargy	0 (0)	0 (0)	1 (33)	0 (0)	0 (0)	0 (0)	2 (33)	0 (0)	2 (22)	0 (0)	2 (50)	1 (25)	7 (21)	1 (3)
Headache	1 (14)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (17)	0 (0)	2 (22)	0 (0)	1 (25)	0 (0)	5 (15)	0 (0)
Pyrexia	1 (14)	0 (0)	1 (33)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (11)	0 (0)	1 (25)	0 (0)	4 (12)	0 (0)
Chills	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (11)	0 (0)	3 (75)	0 (0)	4 (12)	0 (0)
Proteinuria	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (11)	0 (0)	2 (50)	1 (25)	3 (9)	1 (3)

10 h after dose on the morning of day 1; once on days 3 to 5; and once on days 24 to 26 during cycle 1. Samples were assayed for dasatinib and BMS-606181, the *N*-oxide metabolite of dasatinib, concentrations by Bristol-Myers Squibb and Cedra Corp. using a cross-validated liquid chromatography tandem mass spectrometry method. Pharmacokinetic parameters were derived from plasma concentration-time data by a noncompartmental method using Kinetica Basic version 4.4.1 in the eToolbox (version 2.6.1; Thermo Electron Corp.). These included the maximal plasma concentration (C_{max}) and time of C_{max} (T_{max}; obtained from experimental observations), the apparent plasma elimination half-life ($t_{1/2}$; calculated as ln2/Lz, where Lz was the absolute value of the slope of the terminal log phase), the apparent oral clearance (CLo), the apparent volume of distribution in the terminal phase (Vz/F), and the area under the curve (AUC) within the dosing interval (12 h; AUC_{TAU}). AUC_{TAU} was calculated using the mixed log-linear trapezoidal algorithm in Kinetica. Dose proportionality was assessed by doing linear regression analyses on $\log_{AUC}$ versus $\log_{dose}$ for days 8 and 26 with combined data from 5D2 and CDD schedules.

Pharmacodynamic studies. The amount of phosphorylated SRC (pSRC) in peripheral blood cells was determined as a surrogate biomarker of kinase activity by ELISA as previously described (29). Additionally, ^{18}F-fluorodeoxyglucose positron emission tomography (PET) imaging analyses were done in a subset of 35 patients at baseline before treatment and periodically while receiving dasatinib. Metabolic response was assessed based on criteria established by the European Organization for Research and Treatment of Cancer (30). A quantitative analysis of the PET imaging as a pharmacodynamic readout for this study is beyond the scope of this report and will be presented in a separate article.

Results

Patient characteristics. Sixty-seven patients were enrolled (5D2, *n* = 33; CDD, *n* = 34). All 67 patients were included in the analysis of toxicity, with 48 patients evaluable for response. Patient baseline characteristics are summarized in Table 1; a large percentage of the trial consisted of patients with advanced GIST resistant to other kinase inhibitors. Two patients (3%), both in the CDD group, were alive with stable disease lasting >90 days at study closure and continuing to receive dasatinib. The median time from cancer diagnosis to study start was 43.1 months. Prior cancer treatment included surgery (*n* = 67), systemic therapy/chemotherapy (*n* = 63), radiotherapy (*n* = 19), hormonal/immunotherapy/biological therapy (*n* = 4), or other investigational agents (*n* = 8). Most patients had received more than one prior systemic therapy regimen, including 9 (13%) patients who had received two regimens, 13 (19%) three regimens, 19 (28%) four regimens, and 11 (16%) five or more regimens.

Table 4. Treatment-related nonhematologic toxicities occurring in ≥10% of patients on the CDD dosing schedule

Event, *n* (%)	70 mg (*n* = 5)		90 mg (*n* = 7)		100 mg (*n* = 17)		120 mg (*n* = 5)		Overall (*N* = 34)	
	Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4
Nausea	4 (80)	0 (0)	4 (57)	0 (0)	7 (41)	0 (0)	2 (40)	1 (20)	17 (50)	1 (3)
Anorexia	2 (40)	0 (0)	4 (57)	0 (0)	9 (53)	0 (0)	2 (40)	0 (0)	17 (50)	0 (0)
Fatigue	1 (20)	0 (0)	2 (29)	0 (0)	8 (47)	1 (6)	2 (40)	1 (20)	13 (38)	2 (6)
Diarrhea	1 (20)	0 (0)	3 (43)	0 (0)	6 (35)	0 (0)	1 (20)	0 (0)	11 (32)	0 (0)
Lethargy	2 (40)	0 (0)	3 (43)	0 (0)	2 (12)	1 (6)	0 (0)	0 (0)	7 (21)	1 (3)
Vomiting	1 (20)	0 (0)	3 (43)	0 (0)	3 (18)	0 (0)	0 (0)	0 (0)	7 (21)	0 (0)
Headache	2 (40)	0 (0)	0 (0)	0 (0)	3 (18)	0 (0)	1 (20)	0 (0)	6 (18)	0 (0)
Proteinuria	0 (0)	0 (0)	0 (0)	1 (14)	4 (24)	0 (0)	1 (20)	0 (0)	5 (15)	1 (3)
Rash	0 (0)	0 (0)	2 (29)	0 (0)	3 (18)	0 (0)	0 (0)	1 (20)	5 (15)	1 (3)
Pruritus	0 (0)	0 (0)	1 (14)	0 (0)	2 (12)	0 (0)	1 (20)	0 (0)	4 (12)	0 (0)
Anemia	0 (0)	0 (0)	1 (14)	0 (0)	2 (12)	0 (0)	1 (20)	0 (0)	4 (12)	0 (0)
Dyspnea	0 (0)	0 (0)	1 (14)	0 (0)	2 (12)	1 (6)	0 (0)	0 (0)	3 (9)	1 (3)

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Table 5. Summary of pharmacokinetic parameters

Dasatinib schedule (twice daily dose)	Day	*n*	C_{max} (ng/mL), geometric mean (CV %)	AUC (ng·h/mL), geometric mean (CV %)	T_{max} (h), median (minimum, maximum)	$t_{1/2}$ (h), mean (SD)	CLo (L/h), mean (SD)	Vz/F (L), mean (SD)
5D2 (35 mg)	8	6	25 (99)	85 (73)	1.5 (0.5, 4.0)	3.0 (1.1)	642 (651)	3,083 (3,866)
	26	4	19 (84)	84 (30)	1.4 (0.5, 1.6)	3.0 (0.9)	433 (146)	1,842 (602)
5D2 (50 mg)	8	3	38 (45)	140 (22)	1.0 (0.5, 3.0)	3.8 (0.6)	402 (74)	2,144 (205)
	26	3	43 (100)	158 (4)	0.5 (0.5, 2.0)	4.4 (2.2)	317 (13)	2,034 (1,052)
5D2 (70 mg)	8	3	46 (91)	165 (78)	0.5 (0.5, 2.0)	4.9 (1.5)	1,188 (1,716)	9,464 (14,175)
	26	4	25 (80)	161 (8)	2.0 (1.0, 6.0)	4.3 (1.6)	488 (37)	3,649 (94)
CDD (70 mg)	8	3	78 (90)	245 (57)	1.0 (0.5, 6.0)	4.0 (0.8)	327 (210)	2,039 (1,715)
	26	3	50 (86)	325 (19)*	3.1 (1.1, 6.1)	2.5 (1.0)*	217 (42)*	739 (162)*
5D2 (90 mg)	8	5	89 (44)	251 (37)	1.0 (0.5, 4.0)	3.2 (0.7)	438 (311)	1,922 (1,204)
	26	5	83 (58)	492 (33)†	3.0 (1.0, 8.0)	2.3 (0.7)†	191 (64)†	600 (82)†
CDD (90 mg)	8	6	52 (84)	204 (68)	1.6 (0.0, 3.1)	4.1 (1.3)	545 (364)	3,516 (2,894)
	26	5	72 (59)	274 (45)	1.5 (0.5, 5.0)	3.1 (1.2)	409 (360)	2,176 (2,727)
CDD (100 mg)	8	12	56 (118)	218 (102)	1.5 (0.5, 3.6)	4.3 (1.7)	667 (538)	4,224 (3,549)
	26	7	52 (96)	207 (79)	2.0 (0.5, 5.0)	3.2 (1.7)	697 (793)	2,740 (2,541)
5D2 (120 mg)	8	5	77 (73)	298 (66)	1.0 (0.5, 2.0)	3.2 (0.8)	511 (326)	2,223 (1,079)
	26	7	98 (82)	396 (74)	1.0 (0.5, 2.0)	3.3 (1.5)	368 (234)	1,679 (1,145)
CDD (120 mg)	8	5	131 (48)	526 (49)	0.5 (0.0, 2.0)	3.4 (0.7)	270 (195)	1,401 (1,336)
	26	1	60 (n/a)	207 (n/a)	1.5 (1.5, 1.5)	2.2 (n/a)	590 (n/a)	1,877 (n/a)
5D2 (160 mg)	8	2	203 (53)	436 (56)	0.8 (0.5, 1.0)	2.7 (0.6)	411 (224)	1,523 (549)
	26	1	178 (n/a)	502 (n/a)	1.5 (1.5, 1.5)	2.6 (n/a)	319 (n/a)	1,195 (n/a)

Abbreviations: CV, coefficient of variation; n/a, not available.
*n = 2.
†n = 4.

Patients received dasatinib in nine dose cohorts, 35, 50, 70, 90, 120, and 160 mg twice daily (5D2) and 70, 90, and 120 mg twice daily (CDD), with a subsequent expanded dose cohort enrolled at an intermediate dose level (100 mg twice daily, CDD; Table 2). Duration of therapy was greater for patients on the 5D2 schedule compared with those on the CDD schedule for all dose cohorts. In contrast, dose intensity was greater for patients on the CDD schedule.

Toxicity. DLTs were observed in 6 of 26 evaluable patients with the 5D2 schedule and in 11 of 27 evaluable patients with the CDD schedule. On the 5D2 schedule, one of seven evaluable patients enrolled at 35 mg twice daily reported a DLT of grade 3 dehydration and anorexia, one of six patients enrolled at 90 mg twice daily reported grade 3 dehydration and hyponatremia, and one of nine patients enrolled at 120 mg twice daily reported grade 3 tumor lysis syndrome. None of the patients enrolled at 50 or 70 mg twice daily had a DLT. Of four evaluable patients enrolled at 160 mg twice daily, three reported DLTs: grade 2 rash that required dose interruption, grade 3 lethargy, and one patient with both grade 3 prolonged bleeding time and grade 3 hypocalcemia.

On the CDD schedule, none of the three patients enrolled at 70 mg twice daily reported DLTs. At the 90 mg twice daily dose level, DLTs were observed in two of seven patients (grade 3 proteinuria and grade 2 rash in one patient, and grade 1 cognitive impairment with grade 2 somnolence, altered taste, slurred speech, and unsteady gait). During the dose-escalation part of the study, it had been unclear if the grade 1 cognitive impairment with grade 2 somnolence was related to the study drug and this patient was therefore replaced and the subsequent dose escalation proceeded as per protocol. However, based on the observed toxicities at 100 and 120 mg twice daily (CDD), it was concluded retrospectively that this event had been drug related and was dose limiting. The first four patients at the intermediate (100 mg twice daily) dose level reported no DLTs. However, when this cohort was further expanded, 6 of the 13 patients reported DLTs, including 1 patient who developed grade 2 myocardial toxicity and EKG T-wave inversion and grade 4 elevation of cardiac troponin. The myocardial toxicity and elevated cardiac troponin resolved following appropriate treatment. Other DLTs in this cohort included grade 3 dyspnea, grade 3 constipation, grade 2 proteinuria, grade 4 fatigue, and grade 3 lethargy. At the 120 mg twice daily dose level, three of four patients reported DLTs, which were grade 3 nausea, grade 3 fatigue, and one patient with both grade 3 rash and grade 2 proteinuria. Consequently, the MTDs (and recommended doses) were defined as 120 mg twice daily on the 5D2 schedule (DLT in one of six patients) and 70 mg twice daily on the CDD schedule (no DLTs).

Cumulative toxicity. Cumulative toxicity (worse grade per patient, all cycles) is summarized in Tables 3 and 4. Hematologic toxicity was reported in four patients. Two patients on the 5D2 schedule who had grade 1 to 2 anemia at baseline developed grade 3 anemia while on study drug (50 mg twice daily, 70 mg twice daily). On the CDD schedule, one patient had grade 4 neutropenia (120 mg twice daily) and another grade 3 anemia (100 mg twice daily).

On the 5D2 schedule, the most common treatment-related nonhematologic toxicities were nausea (64%) and fatigue (42%; Table 3). One patient on the 5D2 schedule (50 mg twice daily) experienced moderate QT_c prolongation and EKG ST segment changes (grade 2). On the CDD schedule, the most common treatment-related nonhematologic toxicities were nausea (53%) and anorexia (50%; Table 4). Pleural effusion considered by the study investigator to be related to dasatinib treatment was observed in three patients on the CDD schedule. All were grade 1 to 2 and occurred at the 70 mg (n = 2) or

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90 mg (n = 1) twice daily dose level. The majority of nonhematologic events were grade 1 to 2. However, three grade 4 events were observed (suicidal depression, 35 mg twice daily, 5D2; fatigue, 100 mg twice daily, CDD; and elevated cardiac troponin, 100 mg twice daily, CDD). The occurrence of nonhematologic toxicities did not seem to be dose related with either the 5D2 or CDD schedules (Table 5).

Thirteen patients discontinued treatment due to drug-related toxicity: 3 patients on the 5D2 schedule (suicidal ideation with depression, vomiting, and prolonged bleeding time) and 10 patients on the CDD schedule (nausea, headache, vomiting, gait disturbance, cognitive disorder, dysarthria, dysgeusia, somnolence, fatigue, proteinuria, cardiotoxicity, constipation, EKG T-wave inversion, increased troponin, and anorexia).

Ten patients died during the study or within 30 days of their last dose of dasatinib, and 8 died >30 days after their last dose of dasatinib. All of these deaths were due to disease progression; one patient died from vomiting and gastrointestinal bleeding, which was considered to be most likely due to disease progression, although a possible contribution from the study drug could not be excluded.

Dose interruptions and dose modifications. Dose reductions were necessary for 19% of patients and were more frequent in the CDD group (n = 9, 27%) than in the 5D2 group (n = 4, 12%). The most common reason for first dose reduction was hematologic (3%; 5D2, n = 1; CDD, n = 1) or nonhematologic (8%; 5D2, n = 3; CDD, n = 2) toxicity. Hematologic toxicities requiring first dose reduction were thrombocytopenia in the 5D2 group (160 mg twice daily) and anemia in the CDD group (100 mg twice daily). Nonhematologic toxicities reported by the investigators requiring first dose reduction in the 5D2 group were elevated serum glutamic pyruvic transaminase (alanine aminotransferase) levels (35 mg twice daily) and rash and grade 3 hypocalcemia (160 mg twice daily). Nonhematologic toxicities in the CDD group were grade 2 rash (n = 1; 90 mg twice daily) and fatigue (n = 1; 100 mg twice daily).

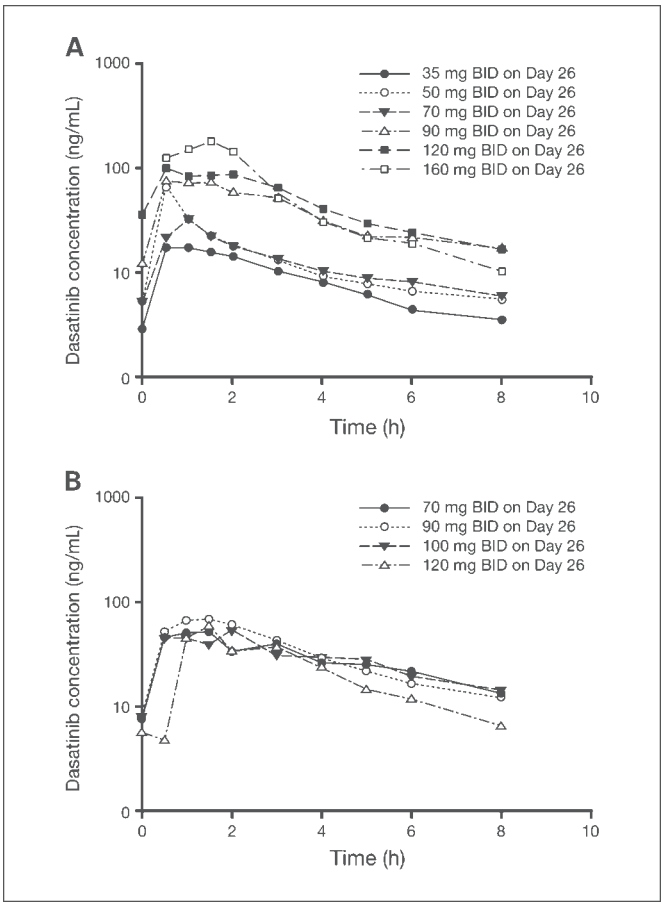

Fig. 1. Mean plasma concentration time profiles of dasatinib at steady state (day 26): 5D2 schedule (*A*) and CDD schedule (*B*).

Dose interruptions for toxicity were necessary for 28 patients (42%) and were more frequent in the CDD group (n = 17) compared with the 5D2 group (n = 11). Dose interruptions were most commonly the result of nonhematologic (31%; 5D2, n = 6; CDD, n = 15) rather than hematologic (3%; 5D2, n = 1; CDD, n = 1) toxicity. Nonhematologic toxicities reported by the investigators requiring first dose interruption in the 5D2 group included rectal bleeding/pain (70 mg twice daily) and grade 3 hypocalcemia (160 mg twice daily). Nonhematologic toxicities reported by the investigators requiring first dose interruption in the CDD group included patient undergoing laser therapy (70 mg twice daily), dyspnea, shortness of breath, proteinuria, and fatigue (100 mg twice daily), and rash (120 mg twice daily).

The median time to first dose reduction/interruption due to toxicity was 12 days [5D2 = 10 (2-208) days; CDD = 12 (2-56) days]. The median length of dose interruptions due to toxicity was 7 days [5D2 = 8 (3-12) days; CDD = 5.5 (3-19) days].

Antitumor activity. There were no observed objective tumor responses. Eleven patients [including GIST (3 patients), colon, melanoma, biliary tract, epithelial sarcoma, small bowel carcinoma, myoepithelioma, thigh sarcoma, and renal cell cancer; 16%] had Response Evaluation Criteria in Solid Tumors–defined stable disease as their best response, including 7 of 33 (21%) patients on the 5D2 schedule and 4 of 34 (12%) on the CDD schedule. The median duration of stable disease in these patients was 3.6 months (range, 1.7-23.6).

Similar findings were observed when comparing the metabolic response on ^{18}F-fluorodeoxyglucose PET imaging of individual lesions and the overall metabolic response of patients. Only four patients (12.9%) showed an early metabolic partial response (PR) during the first week of treatment with dasatinib. However, by the end of cycle 1, the proportion of patients with metabolic PR was nearly twice as large (23.8%). A similar proportion of patients with metabolic PR was observed at the end of cycle 2 (25%).

There was high variability in the pSRC assay using peripheral blood cells, and although pSRC inhibition was observed, a dose-response trend could not be determined (data not shown).

Pharmacokinetic analyses. The plasma concentration-time curves at steady state (day 26) are shown in Fig. 1. Dasatinib was detectable in plasma 30 minutes after oral administration and reached C_{max} at median T_{max} values of 0.5 to 3.1 hours. The AUC_{TAU} increased approximately proportionally with dose, the slope (90% confidence interval) being 1.08 (90% confidence interval, 0.63-1.54) on day 8 and 1.07 (90% confidence interval, 0.63-1.51) on day 26. The C_{max} and AUC_{TAU} values on days 8 and 26 were similar, suggesting no clinically relevant accumulation on repeated dosing. Across the range of 35 to 160 mg twice daily, the mean $t_{1/2}$ of dasatinib was consistent on days 8 and 26. Although consistent across the dose groups, there was considerable variability in both CLo and Vz/F.

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BMS-606181 was rapidly formed in subjects with metastatic tumors and is considered a minor metabolite of dasatinib. The metabolite-to-parent ratio unadjusted for molecular weight difference (which was <10%) ranged from <1% to 13%.

Discussion

Dasatinib potently inhibits several kinases, including KIT, PDGFRA, EPHA2, and BCR-ABL, in addition to SFKs *in vitro*. Specific somatic mutations in the *KIT* gene resulting in kinase activation are implicated in the pathogenesis of GIST (31), and KIT dysregulation is also implicated in the pathobiology of several other tumor types, including small cell lung carcinoma and certain melanomas. Similarly, dysregulation of expression and activation of the PDGF ligand and receptor systems is implicated in many forms of solid tumors, including glioblastoma and prostate cancer (32). Furthermore, EPHA2 may promote angiogenesis (33); enhance tumor cell motility, invasion, and metastasis (34, 35); and is overexpressed in melanoma and in several solid tumors.

In this study, the recommended doses of dasatinib for phase II development seemed to be schedule dependent: 120 mg twice daily for the 5D2 schedule and 70 mg twice daily for the CDD schedule. A dose of 70 mg twice daily on a continuous administration schedule is currently approved for second-line treatment of patients with accelerated-phase CML (CML-AP), myeloid or lymphoid blast-phase CML (CML-BP), or Ph+ALL and is well tolerated in these patients (23, 24, 26).

The DLTs in this study were recurrent grade 2 rash requiring dose modification, grade 3 lethargy, grade 3 prolonged bleeding time, and grade 3 hypocalcemia with the 5D2 schedule and grade 3 nausea, grade 3 fatigue, and one patient with both grade 3 rash and grade 2 proteinuria with the CDD schedule. The most frequent cumulative toxicities in this present study were nonhematologic, including diarrhea, nausea, fatigue, and lethargy. Other toxicities included anorexia, although this may have been secondary to nausea or other gastrointestinal toxicities in several cases, proteinuria, and dyspnea. These toxicities were manageable with dose interruption and reduction. However, hematologic toxicity was uncommon in this study with only one episode of grade 4 neutropenia and no evidence of thrombocytopenia, although prolonged bleeding time was observed as a DLT in one patient. In contrast, in the phase I study of dasatinib in patients with CML or Ph+ALL intolerant or resistant to imatinib (27), grade 3 or 4 neutropenia occurred in 45% of patients with chronic-phase disease (CML-CP) and in 89% of patients with CML-AP, CML-BP, or Ph+ALL, although 55% of the latter group had grade 3 or 4 myelosuppression at study entry. Similarly, grade 3 or 4 thrombocytopenia occurred in 35% of patients with CML-CP and in 80% of patients with CML-AP, CML-BP, or Ph+ALL (27). However, the contrasting hematologic toxicities observed between this study and that reported by Talpaz and colleagues is most likely due either to the result of the action of dasatinib against Ph+ leukemia cells or to the disease-related compromised bone marrow function in the patients in the latter study. Dose interruptions and dose reductions (42% and 19% of patients, respectively) were also less common in this study and mostly due to nonhematologic toxicities.

The role of SRC-dependent signaling on lymphovascular permeability is of great interest, and pleural effusion has been reported previously with dasatinib (27). In leukemic patients, pleural effusion is adequately managed by dose interruption/reduction and appropriate medical intervention (36). Moreover, findings from a trial comparing 70 mg twice daily dosing with 100 mg once-daily dosing in patients with CML-CP showed that the once-daily schedule improved tolerability, including reducing the occurrence of pleural effusion, while maintaining efficacy (37). In the present study, pleural effusion was infrequent with only two patients developing pleural effusion and both were grade 1/2. It seems that pleural effusions are observed less frequently with dasatinib in patients with solid tumors than in patients with hematologic malignancies (35%; grade 3 or 4 in 17%; ref. 38), although the reasons for this observation are unclear.

Preliminary evidence suggests that dasatinib is not directly cardiotoxic per se, unlike other kinase inhibitors such as imatinib, sunitinib, and nilotinib, which have more profound *in vitro* effects on cardiac tissue (39). Although QT prolongation has been reported with dasatinib (27), extensive serial electrocardiographic monitoring showed only one case of QT_c prolongation (grade 2) in this study. The increase was moderate (≥455 ms and ≤490 ms by the Bazett method) and resolved with a temporary dose reduction. Nevertheless, screening for patients at risk of QT prolongation is recommended before starting dasatinib therapy. Dose-limiting cardiac toxicity was observed in one patient in this study (grade 2 myocardial toxicity and EKG T-wave inversion and grade 4 elevated cardiac troponin), which was reversible. Asymptomatic grade 1 or 2 hypocalcemia was noted in ~60% of the patients treated with dasatinib for hematologic malignancies (27). We observed one episode of grade 3 hypocalcemia in this current study (dose limiting at 160 mg twice daily 5D2 schedule). This is most likely due to the key role of SRC in osteoclast formation, activation, and survival (reviewed in ref. 40), raising the intriguing notion that dasatinib might justifiably be studied for the management of metastatic bone disease.

Although studies suggest an immunosuppressant effect for dasatinib (41), there have been no indications of an increased susceptibility to infection following dasatinib in patients with CML. In this study, hematologic toxicity was rare. Lymphopenia (grade 2) was reported for one patient (120 mg twice daily, 5D2) and was resolved by dose interruption.

The pharmacokinetic data suggest that there is no long-term drug accumulation. Although the small number of evaluable patients used for this analysis resulted in substantial variance, the data suggest rapid absorption and dose proportionality. *In vitro* studies of the activity of dasatinib metabolites, including BMS-606181, against SRC and BCR-ABL suggest that dasatinib metabolites do not contribute significantly toward *in vivo* activity (42). Further pharmacokinetic modeling will be required to determine whether the levels of drug achieved in this study are sufficient to inhibit specific kinases.

No objective responses were observed in this study. However, this study was done in patients with advanced, treatment-refractory solid tumors, in whom objective responses might not be observed despite an optimal biological effect on the proposed drug targets. The observation of stable disease in 16% of patients is encouraging, particularly as disease stabilization seemed durable, lasting for >90 days in several patients, including stable disease for ~2 years in a patient with refractory metastatic melanoma. In addition, stable disease was observed in 3 of the 19 patients with GIST, lasting for >3 months in one of

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these patients. Two of these three patients with GIST had also received prior treatment with imatinib. These preliminary observations suggest that dasatinib may have differential activity in patients with GIST compared with other available kinase inhibitors, similar to the distinctive clinical activity of dasatinib observed in CML patients (25). Gain-of-function mutations of KIT are a critical oncogenic contributing factor to the malignant phenotype of most GISTs (43). *In vitro* data with dasatinib show that it potently inhibits both wild-type and mutated KIT, including inhibiting imatinib-resistant KIT activation loop mutants (22). It is unclear why more patients on the 5D2 schedule had stable disease than patients on the CDD schedule.

PET scan changes and biomarkers may act as additional indicators of a pharmacodynamic and meaningful biological response with dasatinib. A metabolic PR was observed in 23.8% of a subset of 35 patients at the end of cycle 1 and in 25% at the end of cycle 2. These results will be discussed more fully in a separate communication. The preliminary effects of dasatinib on levels of the biomarker pSRC were reported by Luo et al. (29) using data from the study reported here and from a phase I study in patients with CML. The results showed that with twice daily dosing, pSRC inhibition was dose dependent across the dosing range (25-160 mg twice daily). Inhibition also directly correlated with dasatinib plasma concentration, with maximal inhibition achieved at ~2.5 hours (29). On database closure and data analysis of the study reported herein, there was a higher variability of the assay than previously found, and although pSRC inhibition was observed, a dose-response trend could not be determined.

In conclusion, this is the first clinical study of an inhibitor of SFKs in patients with solid tumors. Dasatinib was well tolerated and hematologic toxicities were infrequent. Doses of 120 mg twice daily on the 5D2 schedule or 70 mg twice daily on a continuous administration schedule are recommended for future studies. Encouraging preliminary evidence of efficacy was observed, and further studies are required in patients with solid tumors.

Disclosure of Potential Conflicts of Interest

S. Agrawal, P. Paliwal, and M. Voi are employed by Bristol-Myers Squibb. P. Lo Russo has received research grants from the National Cancer Institute, Amgen, Array Biopharma, Ariad, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Endocyte, Exelixis, Genentech, GlaxoSmithKline, ImClone, Merck, Nereus, Novartis, Nereus, Pfizer, Roche, Sanofi Aventis, and Ziopharm; is a consultant for Takeda, AstraZeneca, Pfizer, and Genentech; and is a member of the speakers' bureau for Aventis, Genentech, and GlaxoSmithKline. G.D. Demetri is a consultant for Novartis, Pfizer, Ariad, Genentech, Infinity Pharmaceuticals, Ziopharm, Alnylam, Idera, Bayer, EMD-Serono, Amgen, PamGene, Plexxikon, N-of-One, and Kolltan Pharmaceuticals; has received honoria from Novartis and Pfizer; and is a member of the advisory board of Ziopharm, PamGene, N-of-One, and Kolltan Pharmaceuticals. The other authors have no conflicts to disclose.

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Clinical Cancer Research

Phase I Dose-Escalation and Pharmacokinetic Study of Dasatinib in Patients with Advanced Solid Tumors

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