Phase II Study of Dasatinib in Philadelphia Chromosome–Negative Acute and Chronic Myeloid Diseases, Including Systemic Mastocytosis

Srdan Verstovsek,[1] Ayalew Tefferi,[2] Jorge Cortes,[1] Susan O'Brien,[1] Guillermo Garcia-Manero,[1] Animesh Pardanani,[2] Cem Akin,[3] Stefan Faderl,[1] Taghi Manshouri,[1] Deborah Thomas,[1] and Hagop Kantarjian[1]

Abstract

Purpose: Molecular characterization of Philadelphia chromosome–negative (Ph-) chronic myeloproliferative disorders, such as systemic mastocytosis (SM), has provided a clear rationale for investigating novel targeted therapies. The tyrosine kinase (TK) inhibitor dasatinib is 325-fold more potent against Bcr-Abl TK than imatinib *in vitro*, significantly inhibiting wild-type KIT and platelet-derived growth factor receptor β TKs, and is active against cells carrying the mutant *KIT-D816V* gene.

Experimental Design: In this phase 2, open-label study, the efficacy of dasatinib (140 mg/d) was investigated in 67 patients with various Ph- myeloid disorders, including SM (n = 33; 28 KIT-D816V positive).

Results: The overall response rate to dasatinib in patients with SM was 33%. Only two patients, one with SM-myelofibrosis and one with SM-chronic eosinophilic leukemia, achieved complete response (elimination of mastocytosis) lasting for 5 and 16 months, respectively. Both patients were negative for KIT-D816V mutation, had low tryptase levels, abnormal WBC counts, and anemia, and had failed prior therapy with erythropoietin. Additional nine SM patients had symptomatic response, lasting 3 to 18+ months. Complete responses were achieved in two other patients (acute myeloid leukemia and hypereosinophilic syndrome). No responses were observed among patients with myelodysplastic syndromes and primary myelofibrosis. The majority of adverse events were grade 1/2.

Conclusion: These data show that dasatinib therapy may benefit a selected group of SM patients, primarily by improving their symptoms, but it does not eliminate the disease in the patients with KIT-D816V mutation.

Despite clinical progress in leukemia therapy, notably the introduction of Bcr-Abl–targeted therapies for Philadelphia chromosome–positive chronic myeloid leukemia (Ph+ CML; ref. 1), most adult patients with advanced or refractory myeloid malignancies still die from their disease. For example, no generally effective therapy has been established for Ph-negative (Ph-) chronic myeloproliferative diseases (CMPD; ref. 2). Therefore, there is an urgent need to identify new targeted treatments for a range of potentially life-threatening myeloid diseases, including acute myeloid leukemia (AML), myelodysplastic syndromes (MDS), primary myelofibrosis (PMF), hypereosinophilic syndrome (HES), chronic eosinophilic leukemia (CEL), and systemic mastocytosis (SM).

Four main subcategories of SM are described by the WHO classification system for mast cell diseases: (3) indolent SM (ISM), SM with an associated clonal hematologic nonmast cell disorder (SM-AHNMD), aggressive SM (ASM), and mast cell leukemia. Although standard cytoreductive therapies for SM may provide symptomatic improvements, responses are transient and the overall prognosis, which is particularly poor for patients with ASM, SM-AHNMD, and mast cell leukemia, remains unchanged by treatment (4). Impetus for the clinical investigation of novel targeted agents for the treatment of CMPD has been provided by advances in molecular characterization of these diverse diseases. KIT is a 145-kDa transmembrane class III receptor tyrosine kinase (TK; ref. 5) required for human mast cell growth, differentiation, and functional activation (6, 7). Gain-of-function point mutations in the KIT kinase domain result in ligand-independent constitutive activation of KIT signaling, leading to uncontrolled mast cell proliferation and resistance to apoptosis (8). One of these KIT mutations (D816V) is present in >90% of patients with SM (9–11) and mutated KIT has also been described in patients

Authors' Affiliations: [1]Leukemia Department, M. D. Anderson Cancer Center, Houston, Texas; [2]Division of Hematology, Mayo Clinic College of Medicine, Rochester, Minnesota; and [3]University of Michigan, Ann Arbor, Michigan

Received 2/11/08; revised 3/5/08; accepted 3/5/08.

Grant support: Bristol-Myers Squibb.

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Requests for reprints: Srdan Verstovsek, Leukemia Department, M. D. Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 428, Houston, TX 77030. Phone: 713-792-7305; Fax: 713-794-4297; E-mail: sverstov@mdanderson.org.

doi:10.1158/1078-0432.CCR-08-0366

with AML (12). Additional genetic abnormalities have been identified in patients with SM-AHNMD (13, 14) in whom an associated CEL may be linked to the *FIP1L1-platelet-derived growth factor receptor α* (PDGFRα) fusion gene (14–17). A large body of data supports a role for PDGFR TKs in the pathophysiology of several subtypes of MDS and MPD (18). Mutated genes in molecularly defined CEL include those encoding for PDGFRα and PDGFRβ and fibroblast growth factor receptor 1.

In preclinical studies, the TK inhibitor imatinib mesylate (Gleevec, Novartis) inhibited KIT, fibroblast growth factor receptor, and PDGFR, suggesting that it has a potential role in certain hematologic neoplasms expressing these kinases (19–21). Imatinib has shown activity against neoplastic mast cells exhibiting wild-type KIT and the spontaneously immortalized human mast cell line HMC-1.1 expressing mutant KIT-V560G, but it failed to inhibit HMC-1.2 cells expressing the mutant KIT-D816V (22, 23). Imatinib has also been investigated in several clinical studies of patients with CMPD, including SM (24–30). Durable hematologic and cytogenetic responses were achieved with imatinib in a recent study of 12 patients with PDGFRβ fusion-positive, Bcr-Abl–negative CMPD (31). Furthermore, 100 mg/d imatinib is the treatment of choice for FIP1L1-PDGFRα–positive SM-CEL or other clonal eosinophilia and induces a complete hematologic and molecular remission in almost all treated patients (15, 32). However, in FIP1L1-PDGFRα–negative HES, treatment with imatinib is unlikely to produce durable remissions (15). Similarly, therapy with imatinib does not usually benefit patients with SM in whom imatinib-sensitive molecular markers, such as FIP1L1-PDGFRα, are absent (24, 33) and imatinib is not indicated for those with KIT-D816V mutation. Because of the efficacy limitations of standard cytoreductive therapies, several new TK inhibitors and other novel therapeutic agents are under active clinical investigation in patients with CMPD (34–36).

Dasatinib (SPRYCEL, Bristol-Myers Squibb) is a dual Src/Abl kinase inhibitor with shown clinical activity in all stages of Ph+ CML after the failure of imatinib (37–40). Dasatinib is approved for the treatment of Ph+ CML and Ph+ acute lymphoblastic leukemia in patients resistant or intolerant to imatinib. Dasatinib is 325-fold more potent against Bcr-Abl than imatinib *in vitro* (41) and has significant inhibitory activity against wild-type KIT (IC_{50}, 5 nmol/L) and PDGFRβ (IC_{50}, 28 nmol/L; ref. 42). Preclinical studies have shown that dasatinib potently inhibits both the growth of HMC-1.2 cells carrying the mutant KIT-D816V (43) and primary mast cells with KIT-D816V mutation obtained from patients with SM (44). These preclinical studies suggested that dasatinib might be clinically effective in patients with SM that in >90% of cases carrying this KIT mutation.

In this phase 2, open-label study, the efficacy of dasatinib was investigated in patients with Ph- myeloid diseases, potentially expressing KIT and PDGFR. The primary objective was to determine the objective response rate to dasatinib according to disease-specific response criteria. The secondary objective was to evaluate the duration of response.

Materials and Methods

Patients. Patients included in the study were ages ≥18 years and had a confirmed diagnosis of one of the following Ph- acute or chronic myeloid diseases: (*a*) SM; (*b*) KIT-positive AML or MDS [≥10% bone marrow (BM) or peripheral blood mononuclear cells positive by flow for CD117], excluding acute promyelocytic leukemia [specifically refractory-relapsed AML or MDS, including those who failed to achieve complete response after the first cycle of induction, second or subsequent therapy, or newly diagnosed AML or MDS patients over 60 years of age with karyotype other than t(15:17), inv16, t(8:21), who did not want to receive chemotherapy] or chronic myelomonocytic leukemia (CMML), a subtype of MDS; (*c*) HES/CEL; and (*d*) PMF. All patients were required to have serum bilirubin level <2 mg%, serum creatinine level <2 mg% (unless the abnormality was considered by the investigator to be due to hematologic malignancy), Eastern Cooperative Oncology Group performance status <3, and adequate cardiac status (New York Heart Association grade <3). Patients with cardiac symptoms [uncontrolled angina within 3 months, congenital long QT syndrome, prolonged QTc interval on pre-entry electrocardiogram (>450 ms) on both the Fridericia and Bazett's correction, and clinically significant ventricular arrhythmias such as ventricular tachycardia, ventricular fibrillation, or torsades de pointes], uncontrolled hypertension, a history of significant bleeding disorder unrelated to cancer, acquired bleeding disorder within 1 year, and patients receiving drugs associated with a risk of torsades de pointes were not eligible. Women of child-bearing potential were required to have a negative pregnancy test and to use an effective contraceptive method. There were no exclusions of women or minorities based on the study objectives.

The protocol was approved by the research ethics board of the University of Texas M. D. Anderson Cancer Center; this was a single center study. Written informed consent was obtained according to institutional policy and the Declaration of Helsinki.

Treatment protocol. Dasatinib was administered orally at a starting dose of 70 mg twice daily or 140 mg as a single daily dose. One cycle was defined as 28 days. At the time of the study initiation, the 70 mg twice daily dose of dasatinib was recommended for use in patients with Ph+ CML; for that reason, we have treated most of our patients with it. In SM diagnostic group, after the accrual of first 24 patients, the protocol was modified to allow the accrual of an additional nine patients, treated with the alternative dose/schedule of dasatinib, 140 mg, as a single daily dose. Single daily dose was contemplated to deliver higher peak plasma levels of dasatinib, hypothesized to be possibly able to affect mast cells to greater extent. Treatment was administered at the same dose until disease progression or the occurrence of adverse events necessitating dose reduction or discontinuation. Adverse events were assessed and graded using the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.

The dose of dasatinib could be increased by one level in patients showing evidence of progressive disease or no response after 8 weeks (Table 1). Treatment was interrupted for Common Terminology Criteria grade 2 nonhematologic toxicity (except alopecia and fatigue) and restarted at the original dose after resolution of the adverse event to grade ≤1 or return to baseline. The dose could be further reduced by one level each time the same adverse event recurred (maximum of three reductions). A similar dose modification scheme was used when grade 3 nonhematologic toxicity occurred, except that the dose was reduced by

Table 1. Dose modification levels for dasatinib

Dose level	Dose (mg) twice daily	Single daily dose (mg)
Escalation 1	100	200
Starting dose	70	140
Reduction 1	50	100
Reduction 2	40	80
Reduction 3	20	40

Table 2. Response criteria

A. Response criteria

Disease	Response criteria
ASM*	Major response: complete resolution of at least one clinical finding [C-Finding(s)] and no progression in other C-Findings Complete remission = disappearance of mast cell infiltrates in affected organs, decrease of serum tryptase levels to <20 ng/mL, and disappearance of SM-associated organomegaly Incomplete remission = decrease in mast cell infiltrates in affected organs and/or substantial decrease of serum tryptase level and/or visible regression of organomegaly Pure clinical response = without decrease in mast cell infiltrates, without decrease in tryptase levels, and without regression of organomegaly Partial response: incomplete regression of one or more C-Finding(s) without complete regression and without progress in other C-Findings Good partial response: >50% regression Minor response: ≤50% regression No response: C-Finding(s) persistent or progressive Stable disease: C-Finding variables show constant range Progressive disease: one or more C-Finding(s) show progression
AML and MDS	Complete remission: normalization of the peripheral blood and BM with ≤5% blasts; normocellular or hypercellular marrow; ANC >1.0 × 10^9/L, and platelet count >100 × 10^9/L Partial remission: as complete remission except for the presence of 6-25% marrow blasts, but reduction by >50% Complete remission marrow: as complete remission but platelet count <100 × 10^9/L All other responses were considered failures
PMF and CMML	Complete response: absence of signs or symptoms of the disease. WBC between 1 × 10^9/L and 10 × 10^9/L with no peripheral blasts, promyelocytes, or myelocytes and with normalization of BM (< 5% blasts in normocellular or hypercellular marrow) for at least 4 wk Resolution of pretreatment cytopenias: ANC ≥1.0 × 10^9/L without G-CSF or GM-CSF Hb ≥12.0 g/dL (≥11.0 g/dL for females) without erythropoietin or transfusion support Platelets ≥100 × 10^9/L without growth factor or transfusion support Resolution of pretreatment leukocytosis and/or thrombocytosis: WBC ≤10 × 10^9/L without peripheral blasts, promyelocytes, or myelocytes Platelets ≥100 × 10^9/L but <450 × 10^9/L Partial response: improvement of two or more of the following: ANC: Increase by 100% and to above 10^9/L for neutropenia WBC between 1 × 10^9/L and 10 × 10^9/L with persistence of immature cells (blasts, promyelocytes, myelocytes, and metamyelocytes) for pretreatment leukocytosis Hb: Increase by 2 g/dL if it was below 10 g/dL Decrease in transfusion requirements by at least 50% (decrease in frequency and/or volume) Platelet count: Below that level before therapy Persistent thrombocytosis >450 × 10^9/L but <50% of pretreatment Marrow blasts: Reduction of marrow blasts to ≤5% if it was >10% in normocellular or hypercellular marrow Organomegaly:

(*Continued on the following page*)

Table 2. Response criteria (Cont'd)

A. Response criteria

Disease	Response criteria
	Reduction in splenomegaly and/or hepatomegaly by 50% of pretreatment dimensions (measured as length below the left costal margin on palpation) confirmed by imaging in difficult cases All other responses were considered failures
HES/CEL	Complete response = disappearance of eosinophilia (≤10%) and disappearance of signs and symptoms of disease Partial response = reduction of eosinophilia by ≥50%; reduction of organomegaly by ≥50%

B. Definition of responses in C-Findings for patients with ASM

C-Finding	MR (100%)	GPR (>50%)
BM/blood		
ANC <1.0 × 10^9/L	ANC >1.0 × 10^9/L	Decrease below 1,000 reverted by >50%† (e.g., 600-800 = 50%)
Anemia, Hb <10 g/dL	Hb >10 g/dL	Decrease below 10 reverted by >50%‡
Thrombocytopenia (platelets <100 × 10^9/L)	Platelets >100 × 10^9/L	Decrease to <100,000§ reverted by 50%
Liver		
Hepatomegaly with ascites	No ascites	Decrease of frequency of paracenteses
Abnormal liver tests		
Elevated enzyme levels	Decrease to normal	Increase reverted by >50%
Hypoalbuminemia	Increase to normal	Decrease reverted by >50%
Portal hypertension	Normal vein pressure	Increase in vein pressure improved by 50%
Spleen		
Palpable splenomegaly with hypertension-thrombocytopenia	No signs of hypertension, platelets >100 × 10^9/L	Variables indicating hypertension, platelets improved by >50%
Gastrointestinal tract		
Malabsorption with hypoalbuminemia and/or weight loss	Normal albumin	Decrease in albumin improved by >50%
	Normal weight	Weight loss reverted by >50%
Bones		
Huge osteolyses or/and severe osteoporosis with pathologic fractures	No osteolyses, normal bone density	Partial resolution of osteolyses, decreased bone density reverted by 50%

Abbreviations: G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte macrophage colony-stimulating factor; Hb, hemoglobin; MR, major response; GPR, good partial response.
*Response criteria for ISM and SM-AHNMD have not been established and are descriptive.
†A minimum increase of 0.1 × 10^9 ANC/L blood is required.
‡A minimum increase of 1 g/dL HB is required.
§A minimum increase of 10 × 10^9 platelets/L blood is required for good partial response.

one level on restarting therapy after the first occurrence of the adverse event. Dasatinib was generally discontinued in cases of grade 4 nonhematologic toxicity, although continuation with a dose reduction of at least one level was permitted at the investigators' discretion. Treatment was not modified or interrupted if neutropenia occurred during the first 14 days of treatment. Thereafter, if grade 4 neutropenia [absolute neutrophil count (ANC) <0.5 × 10^9/L] occurred and marrow cellularity was <10% or >10% and neutropenia persisted for 4 weeks, treatment was interrupted and restarted at the original dose after neutrophil recovery to >1.0 × 10^9/L. Doses were subsequently reduced by one level each time grade 4 neutropenia recurred. Dose modification was not applied in patients with AML and MDS when myelosuppression was attributable to disease.

No other therapies for the treatment of myeloid diseases were permitted except for anagrelide and hydroxyurea for initial reduction of platelet and WBC counts, and hematopoietic growth factors at the investigators' discretion. The administration of drugs that inhibit platelet function, prolong QT interval, or inhibit/induce CYP3A4 was prohibited or restricted.

Response assessment. Evaluation of patients during the study period included, at minimum, complete blood counts weekly for 4 weeks and then every 2 to 4 weeks, serum chemistry every 2 weeks for 2 weeks and then every month, BM biopsy and/or aspirate every 1 to 3 months, and an electrocardiogram between days 4 and 8 of cycle 1.

Patients were evaluated for hematologic response, when applicable, on an ongoing basis. Patients had to be off any supportive care therapy for 2 weeks, including hydroxyurea, anagrelide, transfusions, or hematopoietic growth factors, for a response to be documented. Patients were evaluated for BM response after a minimum of three treatment cycles (earlier evaluation was treating physicians choice). All patients who received any dasatinib were considered evaluable for efficacy analyses according to the response criteria shown in Table 2.

Table 3. Baseline demographic and clinical characteristics by patient diagnosis

	SM	AML
n	33 (9 ASM, 18 ISM, 6 SM-AHNMD)*	9
Median age, y (range)	57 (29-74)	70 (57-91)
Sex (M:F)	14:19	7:2
Cytogenetics	Diploid: 30 Complex (≥3 abn): 1 Unknown: 2 †	Diploid: 5 +(8): 1 -(7): 1 Other: 2 ‡
Performance status		
0	0	1
1	31	7
2	2	1
Number of prior therapies		
0	16	1
1	12	2
2	4	4
3	0	2
≥4	1	0
Prior therapies (no. patients indicated if >1)	Imatinib (8); denileukin diftitox (4), IFN (3); darbepoetin (4); cladribine (4); 17-AAG; PKC412	Idarubicin + cytarabine (5); fludarabine + cytarabine; high-dose cytarabine; cytarabine + tipifarnib; allo BMT; VNP40101M; perifosine; sapacitabine; thalidomide; azacitidine; hydroxyurea

Abbreviations: Abn, abnormalities; allo BMT, allogeneic BM transplantation; MPD, myeloproliferative disease; peg-IFN, pegylated IFN alfa; 17-AAG, 17-(allylamino)-17-demethoxygeldanamycin.
*CEL (1), MF (1), MDS/MPD (1), and CMML (3).
† Insufficient metaphase.
‡ 20q- and i(17q).
§ t(15;19).
‖ t(5;12)(q31;p13).

Patients were removed from the study if they developed progressive disease with no response to therapy despite increases of treatment doses or duration, experienced unacceptable toxicity despite dose reduction, did not comply with the treatment schedule, withdrew their consent, or died.

Statistical considerations. The primary objective of the study was to determine the activity of dasatinib. The response rate and duration of response were measured. Because dasatinib has a unique mode of action, a response rate as low as 10% was deemed to be of interest. The study sample size determination was based on a minimum-maximum of 14 to 25 patients in each diagnostic group, yielding an 82% posterior credibility interval for probability of response of width ~0.16. For each diagnostic group, an interim analysis was planned after 14 patients had been evaluated.

Results

Patient characteristics

The characteristics of 67 patients included in the study are detailed in Table 3. Patients with SM comprised approximately half (49%) of the study population. The next most common diagnosis was PMF (16%) followed by AML (13%), HES/CEL (12%), and MDS/CMML (10%).

Among the group with SM, there were 9 patients with ASM, 18 with ISM, and 6 with SM-AHNMD, including 1 case each of CEL, PMF, and MDS/MPD and 3 cases of CMML. Sixteen patients had not received prior treatment for SM. KIT-D816V mutation status was positive in 28 patients, negative in 4 patients, and unknown in 1 patient. There was no correlation between the percentage mast cells in patients' BMs, or blood tryptase level, and the subtype of SM. The percentage of mast cells in the BM in patients was ≤10% in 14, 10% to 20% in 6, 25% to 35% in 5, 40% to 65% in 4, and >65% in 4. Tryptase blood levels (n = 32) were >200 ng/mL (upper limit of quantitation) in 11 patients, ≤20 ng/mL in 5 patients, 21 to 60 ng/mL in 8 patients, 61 to 100 ng/mL in 4 patients, and 101 to 199 ng/mL in 4 patients. Testing for FIP1L1-PDGFRα yielded negative results in all patients with SM and HES/CEL.

Efficacy

Systemic mastocytosis. The overall response rate to dasatinib in patients with SM was 33% (11 of 33 patients treated). Two patients, one with SM-PMF {KIT-D816V negative, FIP1L1-PDGFRα negative, JAK2 V617F positive; complex abnormalities on cytogenetic analysis [47,XY,+1,der(1;7)(q10;p10),+9]} and one with SM-CEL (KIT-D816V negative, FIP1L1-PDGFRα negative, JAK2 V617F negative, insufficient metaphases on cytogenetic analysis), achieved a complete response lasting for 5 and 16 months, respectively (Table 4). Specifically, in SM-PMF patient, we recorder the elimination of SM but PMF persisted. In SM-CEL patient, on the other hand, the BM completely normalized. Both patients started dasatinib therapy at 70 mg orally twice daily. Both patients had low tryptase level, abnormal WBC count differential, and anemia, and had failed prior therapy with erythropoietin. The patient with SM-PMF progressed to AML after 8 months on dasatinib therapy and died, whereas the patient with SM-CEL died, while off therapy due to intercurrent medical problems, after 18 months.

Table 3. Baseline demographic and clinical characteristics by patient diagnosis (Cont'd)

MDS/CMML	HES	CEL	PMF
6 (3 MDS, 3 CMML)	5	3	11
68 (61-75)	48 (23-71)	68 (62-75)	63 (43-77)
4:2	3:2	2:1	10:1
Diploid: 5 +(8): 0 -(7): 0 Other: 1[§]	Diploid: 5	Diploid: 0 +(8): 1 Complex (≥3 abn): 1 Other: 1[‖]	Diploid: 9 Complex (≥3 abn): 2
2	2	0	1
4	2	2	8
0	1	1	2
3	0	1	2
1	4	0	4
1	0	1	3
0	1	1	1
1	0	0	1
Peg-IFN, lenalidomide, PTK787 + imatinib; thalidomide; decitabine (2); hydroxyurea; clofarabine + cytarabine	Imatinib (2); peg-IFN; nilotinib	Epoetin; hydroxyurea; idarubicin + cytarabine; decitabine + valproic acid; imatinib	PTK787 (3); lenalidomide (2); IFN, thalidomide; etanercept, imatinib, RAD001, hydroxyurea (5); azacitidine (3); peg-IFN, anagrelide

Importantly, in the patient with SM-CEL, the cytogenetic analysis done on the BM done 1 year after the start of dasatinib therapy (while on therapy in complete response and with normal BM findings) revealed cytogenetic abnormality 46,XY,t(5;12)(q33;q13) in 9 of 20 analyzed cells. This is a cytogenetic abnormality known to involve the gene for PDGFRβ on chromosome 5q33, sensitive to dasatinib, and therefore a likely reason for a response in these patients.

Nine patients (six with ISM and three with ASM) had symptomatic improvement, as recorded by treating physicians. One patient with ISM was KIT-D816V negative, whereas others were positive; none had cytogenetic abnormality. The duration of symptomatic responses ranged from 3 to 18+ months and five responses were ongoing at the time of analysis. The types of improvements in symptoms related to SM included improvement in rash, diarrhea, bone pain, headaches, itching, fatigue, shortness of breath, indigestion, and decrease or elimination of anaphylactic reactions. Although one patient with ASM had a reduction in the spleen size (from 7 to 1 cm below the left costal margin, on physical examination), this patient did not fulfill predetermined response criteria for ASM (Table 2B).

There were no significant, sustained (for at least 3 months) responses in blood tryptase levels and, with the exception of the two patients achieving complete response, there were no significant, sustained (evident at least in two consecutive BM biopsies done 3 months apart) responses in the percentage of BM mast cells.

Acute myeloid leukemia

One complete response was observed in an 80-year-old male with cytogenetic abnormality [+8] who had CD117 (i.e., KIT) expressed on 66% BM blasts. Testing for a mutation in *KIT* gene was not done. He previously achieved a short complete response with cytarabine and daunorubicin chemotherapy (Table 4). He relapsed on dasatinib therapy after 60 weeks (15 months). Eight patients had no response (four stopped therapy within the first month).

HES/CEL. One 48-year-old woman with HES, previously treated with imatinib without response, achieved a complete response (Table 4), with normalization of blood and BM findings and disappearance of symptoms related to the disease (rash, indigestion/nausea/diarrhea, and shortness of breath). Tests for KIT-D816V and PDGFRα were negative. She relapsed after 58 weeks (14.5 months) while off therapy because of toxicity. Other patients did not respond (one stopped therapy within the first month).

Other chronic myeloid diseases

No objective clinical responses were observed among the patients with MDS and PMF.

Treatment received during study

The initial dose of dasatinib was administered as 70 mg twice daily to 58 patients and as 140 mg once daily to 9 patients with SM (Table 5). The median number of treatment cycles administered ranged from <1 to 20. Dasatinib treatment was continued without dose modification in 38% of patients overall. Dose reduction by one level was required in 34% of patients and by two levels in 9% of patients. No patient received a dose escalation either due to noted toxicity or due to either physician or patient decision not to pursue therapy at higher dose. Dasatinib was discontinued within the first month in 12 patients (due to toxicity in 9 patients). The most common reasons for patients discontinuing the study after the first month of therapy were no response (n = 17), toxicity (n = 14), and disease progression (n = 6).

Safety and tolerability

Treatment-related adverse events among the 67 patients included in the study are detailed in Table 6. No grade 4 adverse events were reported. The majority of adverse events were mild-moderate (Common Terminology Criteria grade 1 or 2).

Grade 3 adverse events were reported in all disease groups. Pleural effusion was the most common grade 3 adverse event, occurring in 7 of 67 patients overall (similar to prior experience with dasatinib in CML). Grade 3 nonhematologic adverse events occurring in the subgroup of patients with SM comprised headache (four cases), pain (three cases), dyspnea and pleural effusion (two cases each), and ascites, fatigue, hyperuricemia, nausea/vomiting, palpitations, and hemorrhage (1 case each). There were two cases of grade 3 hematologic toxicity (low platelets and anemia) in patients with SM, with six cases overall. Twenty-three patients discontinued dasatinib therapy because of toxicity (9 stopped early and 14 discontinued after at least 1 month on treatment).

Discussion

This open-label, phase 2 study was designed to determine the objective response rate to dasatinib in patients with Ph- acute and chronic myeloid diseases. Disease-specific response criteria were used. The response rate to dasatinib in patients with SM

Table 4. Complete responses to dasatinib

	SM		AML	HES
	SM-PMF	SM-CEL		
Patient characteristics	61-y-old white male, diagnosed with SM-PMF in 6/2005 Anemia, SOB, fatigue, back pain	64-y-old African-American male, diagnosed with SM-CEL in 9/2005 Anemia, SOB, fatigue, low-grade fever, sweating, loss of weight	80-y-old white male, diagnosed with AML in 11/2005	48-y-old white female, diagnosed with HES in 1/2001 Rash, SOB, diarrhea, fatigue
Prior therapy	Darbepoetin × 5 mo without result	Epoetin alfa × 4 mo without result	Daunorubicin + cytarabine with short complete response (1 mo)	Prednisone, imatinib, hydroxyurea
Baseline laboratory values	Hb: 9.4 g/dL	Hb: 9.4 g/dL	Hb: 11.8 g/dL	Hb 13.3 g/dL
	Platelets: 90 × 10^9/L WBC: 4.4 × 10^9/L 6% blasts	Platelets: 150 × 10^9/L WBC: 8.3 × 10^9/L Eosinophils: 13%, AEC: 1.08 ×10^9/L	Platelets: 604 × 10^9/L WBC: 6.9 × 10^9/L No blasts	Platelets: 299 × 10^9/L WBC: 9.4 × 10^9/L Eosinophils: 28%, AEC: 2.63 × 10^9/L
	Tryptase 22 ng/mL	Tryptase 13 ng/mL		
Baseline BM, cytogenetics, and gene analysis	4% blasts	20% eosinophils	13% blasts	20% eosinophils
	10-15% MC on biopsy	10-20% MC on biopsy; insufficient metaphases on cytogenetic analysis, but t(5;12) (q33;q13) after 1 y of therapy	Cytogenetics: +8 [2/20]	Diploid cytogenetics
	Reticulin 2+ (scale 0-3)	KIT-D816V negative, PDGFRα negative, JAK2-V617F negative		KIT-D816V negative, PDGFRα negative
	Cytogenetics: 47, ×Y, +1, der(1;7) (q10;p10), +9 [10/20] KIT-D816V negative JAK2-V617F positive			
Dasatinib dose	70 mg twice daily	70 mg twice daily; -1 level due to pleural effusion; -2 level due to fatigue	70 mg twice daily; -1 level due to rash; -2 level due to rash	70 mg twice daily; -1 level due to nausea/vomiting, headache and rash; stopped therapy due to pleural effusion
Response to dasatinib	Starting at 3 wk: Platelets ≥148 × 10^9/L Starting at 6 mo: Hb: ≥10.1 g/dL BM at 3 and 6 mo: Hypocellular No SM Reticulin 4+ Blasts 4%	Starting at 2 mo: Hb: 13.0 g/dL WBC: 7.4 × 10^9/L Eosinophils: 3.9% BM at 3, 6, 9, 12, and 15 mo: Eosinophils ≤4% No SM Normal cellularity	At 2 mo: BM: 3% blasts Normal cytogenetics Hb: 13.7 g/dL Platelets: 223 × 10^9/L WBC: 6 × 10^9/L	Starting at 1 wk: ≤4% eosinophils in blood At 3, 6, and 12 mo: ≤4% eosinophils in BM
Outcome	Died after 8 mo due to AML	Died off therapy (due to other medical reasons) after 18 mo	Cytogenetic relapse after 6 mo (+8 [16/20]); AML relapse after 15 mo (BM: 10% blasts)	Relapsed after 14.5 mo while off therapy

Abbreviations: AEC, absolute eosinophil count; MC, mast cells; SOB, shortness of breath.

Table 5. Summary of dasatinib treatment received, dose modifications, and discontinuations

	SM (*n* = 33)	AML (*n* = 9)	MDS/CMML (*n* = 6)	HES (*n* = 5)	CEL (*n* = 3)	PMF (*n* = 11)
Initial dose schedule (*n*)						
70 mg twice daily	24	9	6	5	3	11
140 mg once daily	9					
Median number of treatment cycles (range)	4 (1-20)	1 (1-18)	1 (1-2)	3 (0-17)	3 (1-4)	6 (1-19)
No. dose modifications						
0	11	2	2	2	2	7
-1	13	2	2	2	1	3
-2	5	1				
Early (<1 mo) discontinuation of therapy (*n*)	4 (toxicity)	4 (toxicity 2, progression 1, death 1)	2 (toxicity 1, comorbid condition 1)	1 (toxicity)		1 (toxicity)
Off-study due to (*n*):						
Relapse	4	1				
Progression	0	2	2	1	1	
Toxicity	6	2	2	2	1	1
Death	2	1	1			
No response	16	3	1	2	1	10

was 33%, including two complete responses and nine patients with symptomatic improvement. Objective responses to dasatinib were also achieved in one AML and one HES patient (complete response in each) but not in those with MDS and MF.

Cytoreductive therapy is indicated for patients with ASM and selected patients with less aggressive forms of SM to control mast cell burden and improve quality of life. IFN-α and cladribine have been beneficial in this setting. A phase 2 trial of IFN-α in 20 adult patients with SM resulted in seven (35%) partial responses and no major responses (45). In another small study, 10 patients with SM with severe symptoms were treated with cladribine and all experienced symptomatic responses and improvements in mast cell variables (serum tryptase and urinary histamine metabolite excretion), but none achieved a complete response (46). Lack of complete responses and relatively short duration of partial responses to IFN-α and cladribine justify investigations of novel targeted therapies for SM. The first such agent, imatinib, was proven ineffective against KIT-D816V carrying mast cells. The failure of imatinib to inhibit cells expressing KIT-D816V (22, 23) is probably because of an allosteric clash within the activation loop caused by the structural change at residue 816, which is key for maintaining the inactive conformation needed for imatinib binding. Preclinical data, on the other hand, have shown that dasatinib is active against the KIT-D816V mutation (44) at clinically achievable concentrations. Interestingly, KIT-D816Y–bearing cells were found to be 10-fold more sensitive to dasatinib than were KIT-D816V/F–carrying cells, suggesting that conformational changes within the KIT activation loop may also influence the inhibitory activity of dasatinib (43). The broad spectrum of activity of dasatinib against many mutations of a given TK may override possible mutational resistance and increase efficacy compared with other small-molecule TK inhibitors that bind more specifically to a target (KIT in this case; ref. 47). In the present study, 28 of 33 patients with SM were positive for KIT-D816V mutation. However, only two SM patients achieved a complete response, and both tested negative for the KIT-D816V mutation. This result is rather disappointing as our expectations for a significant reduction in the mast cell burden in these patients were high based on the preclinical results with dasatinib against cells carrying KIT-D816V mutation. We do not have an explanation for this clinical result.

We were particularly cautious to account, in our assessment of possible responses, for known variability in the percent mast cells (in the BM), and tryptase level (in blood) in patient samples from time to time, while not on any therapy. Durability of a response is currently not accounted for in published response criteria for ASM (Table 2A) and the hope is

Table 6. Treatment-related adverse events

Adverse event	Grade 1	Grade 2	Grade 3
Anorexia	1	1	
Ascites			1
Atrial fibrillation			1
Confusion		1	
Diarrhea	3	2	
Dysphagia	1		
Dyspepsia	1		
Dyspnea	4	11	3
Edema	1	4	
Fatigue	1	4	3
Fever	1		
Flushing	1	2	
Headache	4	3	5
Hemorrhage			1
Hyperuricemia			1
Nausea/vomiting	9	9	3
Pain	2	2	3
Palpitations	1		1
Pericardial effusion	1		
Platelets/Hb			6
Pleural effusion	1	6	7
Pleural pain		1	
Pulmonary edema	1	1	
Rash	1	3	
Tachycardia	1		
Tinnitis		1	
Urticaria	1	1	
Weight gain	2		
Weight loss	1		

that this oversight will be corrected in very near future. We required a record of a sustained improvement in these variables for a response to be assigned, and this did not happen in other SM patients.

The complete responses achieved with dasatinib were durable, lasting for 5 months in the patient with SM-MF and for 16 months in the patient with SM-CEL. Two other patients in the study achieved durable complete responses: 15 months in one patient with AML previously treated with intensive chemotherapy and 14.5 months in one patient with HES previously treated with prednisone, imatinib, and hydroxyurea. The patient with SM-CEL exhibiting a complete response was found, on a later testing, to harbor a cytogenetic abnormality involving PDGFRβ, a TK sensitive to dasatinib and likely responsible for a response in this patient. Molecular abnormalities possibly sensitive to dasatinib and responsible for responses in other patients achieving a complete response are currently unknown.

A further nine patients (six with ISM and three with ASM) had symptomatic improvement lasting for 3 to 18+ months. Patients with mast cell diseases can exhibit a myriad of symptoms, ranging in severity from bothersome to life threatening. In this study, improvements were documented by treating physicians in terms of rash, diarrhea, bone pain, headaches, itching, fatigue, shortness of breath, indigestion, anaphylactic reactions, and spleen size. It is possible that this positive effect of dasatinib therapy was a result of nonspecific inhibition of many kinases in the malignant cells. Symptom improvement is an important therapeutic goal for all forms of SM and can enhance patients' quality of life. However, our expectation was to observe significant elimination of mast cell burden in treated SM patients and, therefore, our evaluations during therapy focused on the BM and blood (e.g., tryptase) testing rather than on the proper documentation of symptom improvement. This is a limitation of our study and a good learning point for a design of future studies in SM.

Chronic therapy is required to maintain symptomatic responses in patients with SM, and therefore, tolerability is an important issue affecting treatment strategy. The safety profile of dasatinib has been well established in patients with Ph+ CML (37–40). No new or unexpected adverse events emerged in patients with Ph- myeloid diseases treated with dasatinib in the present study. The majority of adverse events were mild-moderate and no grade 4 toxicities were observed. None of the patients discontinued therapy early because of toxicity. Grade 3 adverse events leading to dose interruption or dose reduction were observed in all disease subgroups. Grade 3 pleural effusions were reported in 10% of patients. Previous clinical studies of dasatinib have also reported pleural effusions, which can be managed by dose interruption and reduction, and with the administration of diuretics and steroids (48, 49). The majority of dose reductions were by one level, from 140 to 100 mg/d, administered as 50 mg twice daily or 100 mg once daily. Data from a dose optimization trial in patients with Ph+ CML have suggested that the incidence and severity of pleural effusions may be lower with 100 mg dasatinib administered once daily leading to a very recent change in the recommended starting dose for CML patients (50). It is possible that the 100 mg once daily starting dose in this trial would have resulted in less toxicity.

All of the patients achieving a complete response were initially treated with 70 mg dasatinib twice daily. Three of the four patients with a complete response required a dose reduction by one or two levels because of toxicity; one patient (with HES) stopped therapy due to toxicity and then relapsed. It is not possible to draw any conclusions from these preliminary data about potential differences in therapeutic ratio between once-daily and twice-daily schedules of dasatinib.

In conclusion, dasatinib therapy is beneficial in a proportion of SM patients, mainly by improving disease-related symptoms, but it does not eliminate the disease in the patients with KIT-D816V mutation. Dasatinib therapy is associated with side effects that may prevent desirable long-term therapeutic use of this agent for patients with SM. Therefore, whether its use in patients with SM provides any advantage over other conventional therapies is questionable. Dasatinib therapy does not seem to have significant activity in patients with AML, MDS, PMF, and HES/CEL.

Disclosure of Potential Conflicts of Interest

H. Kantarjian has commercial research grants with Bristol-Myers Squibb, MGI Pharma, and Novartis. D. Thomas has received honoraria from Bristol-Myers Squibb. S. O'Brien has minor commercial research support from Genentech, Berlex, Biogen Idec, Eli Lilly, Novartis, Bristol-Myers Squibb, GeminX, and Genta and is a consultant with Genta and the Scientific Advisory Boards of GeminX, Biogen Idec, and Eli Lilly.

Acknowledgments

We thank Tim Kelly and Andrew Richardson for providing professional writing and editorial support.

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Clin Cancer Res 2008;14:3906-3915.