Published in final edited form as:
*Cancer*. 2009 June 1; 115(11): 2482–2490. doi:10.1002/cncr.24257.

# Bleeding Diathesis in Patients With Chronic Myelogenous Leukemia Receiving Dasatinib Therapy

**Alfonso Quintás-Cardama, MD**[1], **Hagop Kantarjian, MD**[1], **Farhad Ravandi, MD**[1], **Susan O'Brien, MD**[1], **Deborah Thomas, MD**[1], **Gabriela Vidal-Senmache, MD**[2], **William Wierda, MD**[1], **Steven Kornblau, MD**[1], and **Jorge Cortes, MD**[1]

[1]Department of Leukemia, The University of Texas M. D. Anderson Cancer Center, Houston, Texas

[2]Department of Hematology, National Hospital Edgardo Rebagliati Martins, Lima, Peru

## Abstract

**BACKGROUND—**The most frequent nonhematologic side effects associated with dasatinib therapy in patients with chronic myeloid leukemia (CML) are gastrointestinal, rash, and fluid retention syndromes. However, bleeding has been observed in some patients receiving dasatinib. In the current study, the authors investigated the risk factors and management of bleeding associated with dasatinib therapy for CML after imatinib failure.

**METHODS—**The bleeding episodes associated with dasatinib therapy in 138 patients with CML who were consecutively treated at the study institution in clinical trials were evaluated.

**RESULTS—**Bleeding occurred in 32 (23%) patients (grade ≥3 in 9 [7%] patients [according to National Cancer Institute Common Toxicity Criteria]), including in 12% of patients treated in chronic phase, 31% of patients treated in accelerated phase (AP), and 35% of patients treated in blast phase (BP) ($P$ = .02). The majority of episodes (81%) affected the gastrointestinal tract. Basic coagulation studies were normal in 97% of patients who developed bleeding complications. Although 37% of episodes occurred with platelet counts >100 × $10^9$/L, multivariate analysis identified thrombocytopenia and advanced phase CML as risk factors for bleeding. A trend toward an increased risk with a twice-daily schedule was observed ($P$ = .17). Management included dasatinib interruption for a median of 17 days (range, 3–51 days) in 47%, of patients and transfusions in 72% of patients.

**CONCLUSIONS—**Bleeding occurs during dasatinib therapy, particularly in patients with AP or BP disease and low platelet counts. Appropriate clinical monitoring and the timely interruption of dasatinib therapy are warranted in this subset of patients.

### Keywords

bleeding diathesis; chronic myelogenous leukemia; dasatinib; risk factors; management



**Corresponding author:** Jorge Cortes, MD, Department of Leukemia, The University of Texas M. D. Anderson Cancer Center, Unit 428, 1515 Holcombe Boulevard, Houston, TX 77030; Fax: (713) 794-4297; jcortes@mdanderson.org.

***Conflict of Interest Disclosures***

The authors made no disclosures

The tyrosine kinase inhibitor (TKI) imatinib mesylate is the standard therapy for *BCR-ABL1*-positive chronic myeloid leukemia (CML), inducing complete cytogenetic responses (CCyR) in approximately 90% of newly diagnosed patients in chronic phase (CP).[1] Imatinib at a dose of 400 mg/day is associated with mild and manageable toxicities such as superficial edema, nausea, muscle cramps, and skin rash.[2] However, drug resistance secondary to BCR-ABL1 kinase point mutations or overamplification of the *BCR-ABL1* genomic locus[1,3] may limit long-term efficacy. Activation of SRC family kinases (SFKs) has been shown to be involved in *BCR-ABL1*-mediated leukemogenesis and in some cases of imatinib resistance.[4–7] Thus, targeting ABL and SFKs simultaneously represents a potential means with which to circumvent resistance induced by *BCR-ABL1* mutations and/or SFKs activation.

Dasatinib is a potent multikinase inhibitor that is highly active against BCR-ABL1 and SFKs.[8] Dasatinib is reported to be 325-fold more potent than imatinib against BCR-ABL1 and is active against a wide array of imatinib-resistant BCR-ABL1 kinase mutants, the exception being T315I.[9] In phase 2 studies in patients with CML in CP who had failed imatinib therapy, dasatinib rendered major cytogenetic and complete hematologic response (CHR) rates of 62% and 91%, respectively.[10] Although generally well tolerated, dasatinib therapy was not completely devoid of untoward side effects, with the most commonly observed toxicities being cytopenias, gastrointestinal symptoms, and peripheral edema.[10–12] The incidence of bleeding complications in dasatinib studies is reported to range from 8% in patients enrolled in the phase 1 dose escalation study to 24% among those patients with myeloid blast phase (BP) disease.[11,12]

The primary objective of the current study was to investigate the incidence, severity, management, and outcome of bleeding episodes associated with dasatinib therapy. To this end, we evaluated 138 patients with CML who had failed imatinib therapy who received treatment at The University of Texas M. D. Anderson Cancer Center (MDACC) in phase 1 and 2 studies of dasatinib.

## MATERIALS AND METHODS

### Study Group

Patients received dasatinib in 1 phase 1 (n = 50 patients) and 4 phase 2 (n = 88 patients) studies sponsored by Bristol-Myers Squibb. Patients were required to have Philadelphia chromosome (Ph)-positive CML after imatinib failure because of hematologic or cytogenetic resistance or because of imatinib intolerance. Entry criteria included aged ≥18 years and adequate renal and hepatic function (creatinine, bilirubin, aspartate aminotransferase, and alanine aminotransferase levels of less than twice the upper limit of normal). Patients were excluded from the study if their Eastern Cooperative Oncology Group performance score was ≥3, or if they were in New York Heart Association functional class III through IV. Imatinib was required to be withdrawn at least 28 days before the initiation of dasatinib therapy in the phase 1 study and 7 days in phase 2 studies. Women of childbearing age were required to have a negative pregnancy test, and all patients were required to use barrier contraception during therapy. Studies were approved by the MDACC

Institutional Review Board and conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent before study entry.

### Study Design and Dose Modifications

The phase 1 dose escalation study used a classic "3 + 3 design" and used 7 dose levels ranging from 15 mg/day to 180 mg/day, administered as a single or as a divided dose.[11] Dasatinib was given according to 1 of the following schedules: 5 days on/2 days off, 6 days on/1 day off, or continuously. Only patients with advanced phase (accelerated phase [AP] or blast phase [BP]) CML or patients in CP with no steady improvement in their response parameters received dasatinib on a continuous schedule. In phase 2 and 3 studies, dasatinib was administered on 4 different schedules: 50 mg twice daily, 70 mg twice daily, 100 mg/day, and 140 mg/day in a continuous manner. Dasatinib dose escalation was allowed in patients who failed to achieve a CHR after 1 month or a CCyR after 3 months of therapy, or whenever loss of response was documented.

### Evaluation of Patients

Complete blood counts, serum chemistry, and targeted physical examination for the evaluation of adverse events were performed weekly during the first 12 weeks, every other week for the next 3 months, and every 6 weeks thereafter. Prothrombin time (PT), activated partial thromboplastin time (aPTT), and serum fibrinogen levels were obtained in all patients before the initiation of dasatinib treatment. Institutional normal limits for coagulation tests were as follows: PT, 10.6 to 13.3 seconds; aPTT, 22.6 to 35.7 seconds; and fibrinogen, 244 to 559 mg/dL. Coagulation studies were closely monitored in the event of bleeding. For the purposes of treatment interruptions and patient management, episodes of bleeding were graded according to the National Cancer Institute Common Toxicity Criteria (NCI CTC) (version 3.0) as follows: grade 1: mild, intervention (other than iron supplements) not indicated; grade 2: symptomatic and medical intervention or cauterization indicated; grade 3: transfusion, interventional radiology, endoscopic, or surgical intervention indicated; grade 4: life-threatening, major urgent intervention indicated; and grade 5: death.

### Statistical Analysis

Descriptive statistics were used to present the distribution of the measured parameters. A $P$ value <.05 was used as the criterion for statistical significance. Univariate and multivariate analyses were performed to identify potential prognostic factors associated with the development of pleural effusion. The Fisher exact or chi-square tests for categoric variables and the Mann-Whitney $U$ test for continuous variables were used to identify prognostic factors, which were subsequently included as variables in a multivariate regression model for the development of bleeding. Multivariate analysis used a logistic regression model.

## RESULTS

### Study Group and Dasatinib Therapy

From November 2003 through January 2006, 138 patients (69 males and 69 females) with Ph-positive CML in all phases were treated with dasatinib after imatinib failure or intolerance. The median age of the patients was 57 years (range, 15–81 years). Among 50

patients who were treated in the phase 1 study, 23 (46%) were in CP, 7 (14%) were in AP, and 20 (40%) were in BP at the time of the initiation of dasatinib treatment, whereas 88 patients (43 of whom [49%] were in CP, 25 of whom [28%] were in AP, and 20 of whom [23%] were in BP) received dasatinib in phase 2 studies. Fifteen (11%) patients initiated treatment with dasatinib at a dose <100 mg, 22 (16%) did so at 100 mg, 92 (67%) did so at 140 mg, and 9 (6%) did so at a dose >140mg daily. The median time on dasatinib therapy for the study group was 42 weeks (range, 4–120 weeks): 69 weeks (range, 18–120 weeks) for patients in the phase 1 study and 34 weeks (range, 4–61 weeks) for patients in the phase 2 studies.

## Bleeding Associated With Dasatinib Therapy: Incidence and Outcome

The clinical and demographic characteristics of the patients who developed bleeding episodes while receiving dasatinib therapy are summarized in Table 1. Analysis of the frequency of bleeding associated with dasatinib therapy was based on all 138 patients. Bleeding was demonstrated in 32 (23%) patients: 11 (22%) who were treated in the phase 1 study and 21 (24%) who were treated in the phase 2 studies. Seven (5%) patients had grade 1, 16 (11.5%) patients had grade 2, and 9 (6.5%) patients had grade 3 bleeding. No grade 4 to 5 bleeding episodes were observed. The median time to the development of bleeding was 6 weeks (range, 0.5–38 weeks), and this occurred within the first 3 months of therapy in 22 (69%) patients. A total of 37 bleeding episodes were observed: lower gastrointestinal bleed (LGIB) in 22 patients, upper gastrointestinal bleeding (UGIB) in 8 patients, gingival bleeding in 4 patients, vaginal bleeding in 2 patients, and epistaxis in 1 patient. Six (19%) patients experienced different types of bleeding concomitantly: 4 patients with LGIB and UGIB; 1 patient with LGIB, gingival bleeding, and scalp hematoma; and 1 patient with gingival and vaginal bleeding. In addition, 12 (37.5%) patients (5 in CP, 2 in AP, and 5 in BP) had recurrent bleeding episodes: 8 cases of LGIB (in 2 separate occasions in 3 of these patients), 1 case of UGIB, 2 cases of gingival bleeding, and 1 case of vaginal bleeding. One additional patient in BP, who experienced LGIB, developed gingival bleeding at a later date. Among patients who developed bleeding while on study, dasatinib therapy was terminated in 7 (22%) patients because of LGIB (in 3 patients, recurrent in 2 patients), a combination of LGIB and UGIB (in 3 patients), or disease progression (in 1 patient). Five (71%) of these 7 patients died because of disease progression. Overall, 15 (47%) of the 32 patients with bleeding complications reported in the current study died because of disease progression.

## Correlation With CML Phase, Dasatinib Dose, and Hemostatic Status

Because patients in different CML phases were treated with different doses of dasatinib, we investigated the impact of these 2 variables on the development of bleeding associated with dasatinib therapy (Table 2). Eight of 66 (12%) patients treated in CP developed bleeding (5 with LGIB, 1 with UGIB, 1 with gingival bleeding, and 1 with vaginal bleeding). In contrast, 10 of 32 (31%) patients in AP (6 with LGIB, 1 with UGIB, 1 with epistaxis, 1 with vaginal bleeding, and 1 with gingival bleeding) and 14 of 40 (35%) in BP (11 with LGIB, 2 with UGIB, and 1 with gingival bleeding) developed this complication ($P = .02$). Because the initial dasatinib dose could be modified according to response and/or toxicity, we analyzed whether the dasatinib dose and dosing schedule at the onset of the first bleeding episode influenced the incidence of this complication. Of the 37 initial episodes of bleeding

reported, 5 (14%) occurred at dasatinib doses >140 mg/day, 26 (70%) occurred at a dose of 140 mg/day (all but 5 at a dose of 70 mg twice daily), 3 (8%) occurred at a dose of 100 mg/day, and 3 (8%) occurred at doses <100 mg/day. Thus, 31 (84%) bleeding episodes occurred in patients receiving ≥140 mg/day, whereas only 6 (16%) occurred at dasatinib doses ≤100 mg/day ($P = .001$). The time to the development of the first episode of bleeding did not appear to differ significantly among different dasatinib dosing schedules ($P = .82$).

Because advanced phase CML is frequently associated with abnormal platelet counts, we examined the relation between the development of bleeding during dasatinib therapy and platelet count in the study cohort (Table 3). Eighteen (49%) of the 37 episodes of bleeding occurred in patients with a platelet count $\leq 30 \times 10^9$/L (5 of them at a platelet count $< 10 \times 10^9$/L), 5 (14%) in patients with a platelet count of 31 to $100 \times 10^9$/L, and 14 (37%) in patients with a platelet count $> 100 \times 10^9$/L. The majority of episodes of bleeding in patients with a platelet count $> 100 \times 10^9$/L were grade 1 (3 patients) or grade 2 (9 patients), being grade 3 only in 2 instances. Coagulation studies were available at the onset of bleeding in 24 (75%) of the 32 patients. The median PT was 12.8 seconds (range, 10.3–21 seconds), the median aPTT was 28.8 seconds (range, 20.7–42 seconds), and the serum fibrinogen level was 540 mg/dL (range, 118–732 mg/dL). Only 1 patient with CML in BP and grade 3 LGIB presented with altered coagulation tests (PT of 21 seconds, aPTT of 42 seconds, serum fibrinogen of 118 mg/dL, and a D-dimer concentration of 5000 ng/mL), which is clinically compatible with sepsis-related disseminated intravascular coagulation. No patient was receiving anticoagulants at the time of the onset of the first episode of bleeding, but 2 patients in CP who developed LGIB had been receiving clopidogrel at a dose of 75 mg/day and aspirin at a dose of 81 mg/day for 3 months and 1 month, respectively, because of coronary events. Recently, lymphocytosis, resulting mainly from the expansion of clonal large granular lymphocytes (LGLs), has been reported to be associated with the development of colitis and pleural effusion in patients receiving dasatinib.[13] Although 9 (41%) patients with LGIB had relative lymphocytosis at the start of the bleeding episodes, only 1 (5%) patient demonstrated absolute lymphocytosis.

On univariate analysis, variables found to be associated with bleeding risk included hemoglobin level, thrombocytopenia, peripheral blood and bone marrow blast percentage, CML duration, and CML phase (Table 4). Prior therapy with interferon-α was found to be associated with a trend toward an increased risk of bleeding ($P = .08$). In a multivariate analysis, thrombocytopenia and CML phase (AP/BP vs CP) were found to be associated with an increased risk of bleeding with dasatinib therapy (Table 5). It is interesting to note that neither dasatinib dose nor a history of gastrointestinal disorders were identified as variables associated with an increased probability of bleeding during dasatinib therapy.

## Management of Bleeding Episodes

Bleeding resulted in dasatinib therapy interruption in 15 (47%) patients: 8 with LGIB (2 of them also with concomitant UGIB), 6 with UGIB (2 of them also with concomitant LGIB), 2 with gingival bleeding, and 1 with vaginal bleeding. Dasatinib interruptions related to hemorrhagic episodes lasted for a median of 17 days (range, 3–51 days). The dasatinib dose was reduced in 11 (34%) patients: 6 with LGIB (1 of them also with UGIB), 4 with UGIB (1

of them also with LGIB), 1 with gingival bleeding, and 1 with vaginal bleeding. Three (9%) patients with UGIB (2 of them with concomitant LGIB) required treatment interruptions on >1 occasion because of recurrent bleeding. The median duration of the bleeding episodes was 8 days (range, 2–27 days).

Seventeen (65%) of 26 patients with gastrointestinal bleeding underwent either upper endoscopy (3 patients), lower endoscopy (7 patients), or both (7 patients). Upper endoscopic examination revealed mild distal esophagitis (2 patients), mild gastritis (3 patients), oozing from multiple sites at the duodenal bulb (1 patient), duodenal ulcer (1 patient), bleeding from an arteriovenous malformation at the greater gastric curvature (1 patient), or a normal examination (2 patients). Colonoscopies demonstrated severe colitis (2 patients), erythematous colon (2 patients), rectal ulcer (2 patients), a Dieulafoy lesion at the transverse colon (1 patient), or a normal examination (7 patients). Biopsies were obtained in 6 patients undergoing colonoscopy, revealing chronic inflammatory changes of varying severity characterized by cryptitis and apoptosis of the intestinal epithelium. The colon biopsy of a patient who had undergone allogeneic stem cell transplantation 4 months before bleeding revealed features consistent with graft-versus-host disease. Nevertheless, dasatinib was most likely the cause of bleeding in this patient because rechallenge with dasatinib immediately resulted in another LGIB episode.

Overall, 23 (72%) patients required transfusion of packed red blood cells (PRBC) or platelets; 17 patients received both and 6 received either PRBCs (3 patients) or platelets (3 patients). The median number of units of PRBCs and platelets transfused during the first week after the onset of bleeding was 4 (range, 2–11 units) and 16 (range, 2–49 units) units, respectively. Three patients with UGIB (2 of them also with LGIB) required admission to the intensive care unit for fluid resuscitation, hemodynamic monitoring, and endoscopic cauterization of bleeding lesions. These 3 patients were receiving dasatinib at a dose of 70 mg twice daily (2 patients) or 140 mg/day (1 patient) and had platelet counts of $216 \times 10^9$/L, $14 \times 10^9$/L, and $101 \times 10^9$/L, respectively. Proton pump inhibitors were administered intravenously to 14 (44%) patients.

## DISCUSSION

In the current study, we reported that dasatinib therapy was associated with bleeding episodes in 23% of patients with CML who were treated in clinical trials at the study institution. This complication was more frequent among those patients with advanced (AP or BP) disease who were receiving dasatinib at a dose ≥140 mg daily and affected the gastrointestinal tract in 81% of cases. There was a recurrence of bleeding in 37% of patients and led to the termination of dasatinib therapy in 22%. Although the majority of bleeding episodes were mild or moderate, 3 patients did require more aggressive management.

Despite this potential complication, dasatinib therapy is usually well tolerated. In the phase 1 study, the major adverse effect related to dasatinib was reversible cytopenia.[11] In the phase 2 studies, the most frequent nonhematologic side effects were diarrhea (37%) and rash (35%) among patients treated in CP,[10] and diarrhea (36%) and pleural effusion (28%) among those treated in myeloid BP.[12] In the above-mentioned phase 1 study, 7 (8%) of 84 patients

developed gastrointestinal hemorrhage, which was classified as grade 3 to 4 in 5 patients (6%).[11] Among patients with myeloid BP, gastrointestinal bleeding was reported in 9 (12%) of 74 patients (grade 3–4 in 8%).[12] However, none of these studies addressed the risk factors associated with bleeding complications during dasatinib therapy. In the current study, we observed that 49% of the bleeding episodes occurred in patients with platelet counts ≤30 × $10^9$/L. However, 37% of such episodes occurred in patients with platelet counts >100 × $10^9$/L. In addition, all but 1 (97%) of the patients who developed bleeding and for whom coagulation studies were available had PT, aPTT, and fibrinogen levels within normal limits. Using multivariate analysis, thrombocytopenia and advanced phase CML were found to be associated with an increased risk of bleeding during dasatinib therapy. Neither dasatinib dose nor an antecedent gastrointestinal disorder were identified as risks factors for bleeding diathesis ($P$ = .45). A trend toward an increased risk was observed with twice-daily versus once-daily administration ($P$ = .17) on univariate analysis, which suggests that patients with AP or BP disease receiving dasatinib twice daily, particularly at daily doses >140 mg, should be monitored for bleeding complications. In contrast to twice-daily schedules (especially those using ≥140 mg/day), a dose of 100 mg once daily has been shown to greatly reduce the incidence of adverse events in CP CML, including bleeding.[14] In keeping with these figures, only 8% of patients in the current study who were treated with 100 mg once daily developed bleeding, a rate that is similar to that of patients treated at a dose of <100 mg/day.

The pathophysiology of bleeding associated with dasatinib therapy remains poorly understood. In vitro, dasatinib inhibited collagen-induced platelet aggregation in human, cynomolgus monkey, and rat platelet-rich plasma at concentrations of 0.5 to 5 μg/mL. A concentration of 5 μg/mL (which is 5-fold higher than the peak concentration [Cmax] in humans) induced 94% inhibition of shear-induced platelet aggregation of human platelets.[15] The effect of dasatinib on human whole blood clot formation was limited to a 29% reduction in clot strength at a concentration of 5 μg/mL. In vivo, dasatinib at mean plasma concentrations ≥144 ng/mL prolonged cuticle bleeding time in rats.[16] It has been shown that dasatinib, while not interfering with secondary hemostasis, may disturb platelet aggregation through an as-yet unknown mechanism.[17] It is important to note that other TKIs such as imatinib, nilotinib, or the dual ABL1/SFK inhibitor bosutinib have not been associated with platelet aggregation defects.[17] Accordingly, all but 1 patient in the current study developed mucocutaneous bleeding with normal coagulation studies, strongly suggesting a primary hemostasis defect.

Inhibition of platelet-derived growth factor receptor (PDGFR) kinase may in part contribute to the development of bleeding associated with dasatinib.[8] The concentration that inhibits 50% ($IC_{50}$) for PDGFR-β inhibition in cell-based assays ranges between 3 nanomolar (nM) and 28 nM.[8,18] Dasatinib inhibits PDGF-stimulated migration and proliferation of human vascular smooth muscle cells.[18] PDGFR-β is involved in angiogenesis regulation,[19] and PDGFR-β-deficient mouse embryos are reported to exhibit severe pericyte deficiency in capillaries as well as smooth muscle hypoplasia, leading to microaneurysms and hemorrhage.[20,21]

The majority of bleeding episodes were circumscribed to the gastrointestinal tract, consisting of LGIB, UGIB, or both in 81% of patients. This anatomic predilection may be correlated with the oral administration of dasatinib. When a single $^{14}$C-dasatinib dose was administered to Long-Evans rats, the largest percentage of the radioactive dasatinib dose was detected in the gastrointestinal tract and liver,[15] which is consistent with the oral administration of dasatinib and a major route of elimination in the feces.[22] An exploratory repeat-dose study in dogs was discontinued after 2 days of the administration of dasatinib at a dose of 5 mg/kg because of bloody emesis and feces within 2 hours after dosing.[15] This gastrointestinal toxicity observed in animal models occurred at clinically relevant area-under-the-curve dasatinib levels. In cynomolgus monkeys that were euthanized after the development of dasatinib-induced gastrointestinal toxicity, intestinal villous blunting and nonspecific inflammatory signs were observed,[16] closely resembling the findings observed on endoscopic examination of patients with LGIB in the current study. Lymphocytosis secondary to marked expansion of clonal LGLs has been recently described in patients receiving dasatinib.[13] Dasatinib-induced complications (eg, colitis and pleural effusion) developed in a significant proportion of patients found to have LGL expansion.[13] In the current study, 41% of patients with LGIB had relative lymphocytosis, but only 5% had absolute lymphocytosis. The issue of whether clonal LGL expansion plays a significant pathogenetic role in dasatinib-induced bleeding will require prospective and systematic analysis of tissue samples obtained from dasatinib-treated patients who develop that complication.

In summary, bleeding complications occur during dasatinib therapy but are usually mild and manageable. Bleeding typically involves the gastrointestinal tract, particularly in patients with advanced phase CML and low platelet counts. Appropriate monitoring and early recognition of the signs of bleeding are warranted to prevent unwanted outcomes.

## Acknowledgments

FUNDING STATEMENT:

This article was supported by National Institute of Health (P30 CA016672).

## References

1. Kantarjian H, Sawyers C, Hochhaus A, et al. Hematologic and cytogenetic responses to imatinib mesylate in chronic myelogenous leukemia. N Engl J Med. 2002; 346:645–652. [PubMed: 11870241]
2. O'Brien SG, Guilhot F, Larson RA, et al. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med. 2003; 348:994–1004. [PubMed: 12637609]
3. Schindler T, Bornmann W, Pellicena P, Miller WT, Clarkson B, Kuriyan J. Structural mechanism for STI-571 inhibition of abelson tyrosine kinase. Science. 2000; 289:1938–1942. [PubMed: 10988075]
4. Donato NJ, Wu JY, Stapley J, et al. BCR-ABL independence and LYN kinase overexpression in chronic myelogenous leukemia cells selected for resistance to STI571. Blood. 2003; 101:690–698. [PubMed: 12509383]
5. Donato NJ, Wu JY, Stapley J, et al. Imatinib mesylate resistance through BCR-ABL independence in chronic myelogenous leukemia. Cancer Res. 2004; 64:672–677. [PubMed: 14744784]

6. Dai Y, Rahmani M, Corey SJ, Dent P, Grant S. A Bcr/Abl-independent, Lyn-dependent form of imatinib mesylate (STI-571) resistance is associated with altered expression of Bcl-2. J Biol Chem. 2004; 279:34227–34239. [PubMed: 15175350]
7. Wu J, Meng F, Kong LY, et al. Association between imatinib-resistant BCR-ABL mutation-negative leukemia and persistent activation of LYN kinase. J Natl Cancer Inst. 2008; 100:926–939. [PubMed: 18577747]
8. Lombardo LJ, Lee FY, Chen P, et al. Discovery of N-(2-chloro-6-methyl-phenyl)-2-(6-(4-[2-hydroxyethyl]-piperazin-1-yl)-2-methylpyrimidin-4-ylamino)thiazole-5-carboxamide (BMS-354825), a dual Src/Abl kinase inhibitor with potent antitumor activity in preclinical assays. J Med Chem. 2004; 47:6658–6661. [PubMed: 15615512]
9. Shah NP, Tran C, Lee FY, Chen P, Norris D, Sawyers CL. Overriding imatinib resistance with a novel ABL kinase inhibitor. Science. 2004; 305:399–401. [PubMed: 15256671]
10. Mauro M, Baccarani M, Cervantes F, et al. Dasatinib 2-year efficacy in patients with chronic-phase chronic myelogenous leukemia (CML-CP) with resistance or intolerance to imatinib (START-C) [abstract]. Proc Am Soc Clin Oncol. 2008; 26:374s. Abstract 7009.
11. Talpaz M, Shah NP, Kantarjian H, et al. Dasatinib in imatinib-resistant Philadelphia chromosome-positive leukemias. N Engl J Med. 2006; 354:2531–2541. [PubMed: 16775234]
12. Cortes J, Rousselot P, Kim DW, et al. Dasatinib induces complete hematologic and cytogenetic responses in patients with imatinib-resistant or -intolerant chronic myeloid leukemia in blast crisis. Blood. 2007; 109:3207–3213. [PubMed: 17185463]
13. Mustjoki S, Laurinolli T, Ekblom M, et al. Clonal large granular lymphocyte (LGL) expansion associated with dasatinib therapy [abstract]. Blood. 2007; 110:863a. Abstract 2938.
14. Shah NP, Kantarjian HM, Kim DW, et al. Intermittent target inhibition with dasatinib 100 mg once daily preserves efficacy and improves tolerability in imatinib-resistant and - intolerant chronic-phase chronic myeloid leukemia. J Clin Oncol. 2008; 26:3204–3212. [PubMed: 18541900]
15. Sprycel Scientific Discussion. Available at: http://209.85.165.104/search?q=cache:KW1gSD1bwJQJ:www.emea.eu.int/humandocs/PDFs/EPAR/sprycel/H-709-en6.pdf+dasatinib+and+bleeding&hl=en&gl=us&ct=clnk&cd=1.
16. Wang, K.; Schumacher, W. BMS-Document Control No. 930004015. New York: Bristol-Myers Squibb Company; 2003. Effects of BMS-354825 on platelet function.
17. Quintas-Cardama A, Han X, Kantarjian H, Cortes J. Dasatinib-induced platelet dysfunction [abstract]. Blood. 2007; 110:864a. Abstract 2941.
18. Chen Z, Lee FY, Bhalla KN, Wu J. Potent inhibition of platelet-derived growth factor-induced responses in vascular smooth muscle cells by BMS-354825 (dasatinib). Mol Pharmacol. 2006; 69:1527–1533. [PubMed: 16436588]
19. Hellstrom M, Kalen M, Lindahl P, Abramsson A, Betsholtz C. Role of PDGF-B and PDGFR-beta in recruitment of vascular smooth muscle cells and pericytes during embryonic blood vessel formation in the mouse. Development. 1999; 126:3047–3055. [PubMed: 10375497]
20. Lindahl P, Johansson BR, Leveen P, Betsholtz C. Pericyte loss and microaneurysm formation in PDGF-B-deficient mice. Science. 1997; 277:242–245. [PubMed: 9211853]
21. Kaminski WE, Lindahl P, Lin NL, et al. Basis of hematopoietic defects in platelet-derived growth factor (PDGF)-B and PDGF beta-receptor null mice. Blood. 2001; 97:1990–1998. [PubMed: 11264163]
22. Christopher LJ, Cui D, Wu C, et al. Metabolism and disposition of dasatinib after oral administration to humans. Drug Metab Dispos. 2008; 36:1357–1364. [PubMed: 18420784]

## Table 1

Characteristics of Patients Who Developed Bleeding While Receiving Dasatinib Therapy

| | All Patients With Bleeding | CP | AP | BP |
|---|---|---|---|---|
| **Sex, no.** | | | | |
| **Male** | 13 (41%) | 2 (6%) | 5 (16%) | 6 (19%) |
| **Female** | 19 (59%) | 6 (19%) | 5 (16%) | 8 (25%) |
| **Age, y** | | | | |
| **Median** | 63 | 61 | 63 | 63 |
| **Range** | 19–81 | 36–81 | 33–76 | 19–74 |
| **No. of prior therapies (range)** | 3 (1–7) | 4 (1–5) | 3 (2–8) | 3 (2–7) |
| **Imatinib** | 32 | 8 | 10 | 14 |
| **Nilotinib** | 9 | 0 | 6 | 3 |
| **SCT** | 5 | 2 | 0 | 3 |
| **Chemotherapy** | 16 | 4 | 6 | 6 |
| **Time on imatinib, mo** | | | | |
| **Median** | 40 | 47 | 34 | 39 |
| **Range** | 5–69 | 5–69 | 5–55 | 10–58 |
| **Reason off imatinib, no.(%)** | | | | |
| **Resistance** | 28 (88%) | 6 (19%) | 8 (25%) | 14 (44%) |
| **Intolerance** | 4 (13%) | 2 (6%) | 2 (6%) | 0 |
| **Time on dasatinib, mo** | | | | |
| **Median** | 11 | 15 | 9 | 7 |
| **Range** | 2–30 | 5–30 | 2–23 | 1–23 |
| **Time from dasatinib to bleeding, wk** | | | | |
| **Median** | 6 | 10 | 5 | 6 |
| **Range** | 0.5–38 | 1.5–37 | 1–37 | 0.5–34 |

CP indicates chronic phase; AP, accelerated phase; BP, blast phase, SCT, stem cell transplantation.

## Table 2

Incidence of Bleeding Episodes During Dasatinib Therapy by CML Phase, Dasatinib Dose, and Daily Schedule

| | | No. of Patients (%) | |
|---|---|---|---|
| | Total, n=138 | Bleeding Any Grade*, n=32 (23) | Bleeding Grade ≥3, n=9 (6.5) |
| **CML phase** | | | |
| **CP** | 66 | 8 (12) | 2 (3) |
| **AP** | 32 | 10 (31) | 3 (9) |
| **BP** | 40 | 14 (35) | 4 (10) |
| **Daily dose** | | | |
| **>140 mg/d** | 9 | 4 (44) | 1 (11) |
| **140 mg/d** | 92 | 23 (25) | 7 (8) |
| **100 mg/d** | 22 | 3 (14) | 1 (5) |
| **<100 mg/d** | 15 | 2 (13) | 0 (0) |
| **Schedule** | | | |
| **Once daily** | 39 | 6 (16) | 2 (5) |
| **Twice daily** | 99 | 26 (26) | 7 (7) |

CML indicates chronic myelogenous leukemia; CP, chronic phase; AP, accelerated phase; BP, blastic phase.

*Grading was according to the National Cancer Institute Common Toxicity Criteria (version 3.0).

## Table 3

Frequency of Bleeding Episodes in Patients Receiving Dasatinib Therapy According to Anatomic Location, CML Phase, and Platelet Count

| Characteristic | Total No. (%) | No. of Bleeding Episodes (%) CML Phase | | |
|---|---|---|---|---|
| **Location** | | **CP** | **AP** | **BP** |
| UGIB | 8 (22) | 3 (8) | 2 (5) | 3 (8) |
| LGIB | 22 (59) | 5 (14) | 7 (19) | 10 (27) |
| Gingival | 4 (11) | 1 (3) | 2 (5) | 1 (3) |
| Vaginal | 2 (5) | 1 (3) | 1 (3) | 0 (0) |
| Epistaxis | 1 (3) | 0 (0) | 1 (3) | 0 (0) |
| **Platelet count ($\times 10^9$/L)** | | | | |
| **<30** | 18 (49) | 0 (0) | 8 (22) | 10 (27) |
| **30–100** | 5 (14) | 2 (5) | 0 (0) | 3 (8) |
| **>100** | 14 (37) | 8 (22) | 5 (14) | 1 (3) |

CML indicates chronic myelogenous leukemia; CP, chronic phase; AP, accelerated phase; BP, blastic phase; UGIB, upper gastrointestinal bleeding; LGIB, lower gastrointestinal bleeding.

**Table 4**

Disease and Patient Characteristics in Association With Bleeding During Dasatinib Therapy

| Variable | | Median (Range) | No. | No. Bleeding (%) | *P* |
|---|---|---|---|---|---|
| Age, y | Bleed | 60 (18–78) | | | .33 |
| | No bleed | 55 (15–78) | | | |
| WBC, × 10 g/L | Bleed | 7.6 (0.7–144.4) | | | .15 |
| | No bleed | 13.7 (0.8–160.8) | | | |
| Hemoglobin, g/dL | Bleed | 10.2 (7.6–13.2) | | | .007 |
| | No bleed | 11.1 (6.3–16.6) | | | |
| Platelet, × 10 g/L | Bleed | 77 (3–681) | | | .001 |
| | No bleed | 255 (10–1615) | | | |
| PB basophil % | Bleed | 4 (0–44) | | | .29 |
| | No bleed | 2 (0–45) | | | |
| PB blast % | Bleed | 6 (0–63) | | | .049 |
| | No bleed | 0 (0–99) | | | |
| BM blast % | Bleed | 13 (0–88) | | | .002 |
| | No bleed | 3 (0–98) | | | |
| BM basophil % | Bleed | 3 (0–41) | | | .21 |
| | No bleed | 2 (0–57) | | | |
| CML duration, mo | Bleed | 77 (1–216) | | | .049 |
| | No bleed | 60 (1–207) | | | |
| Sex | Female | | 76 | 20 (26) | .34 |
| | Male | | 62 | 12 (19) | |
| Pulmonary history | Yes | | 16 | 2 (13) | .28 |
| | No | | 122 | 30 (25) | |
| Diabetes history | Yes | | 10 | 2 (20) | .80 |
| | No | | 128 | 30 (23) | |
| Cardiac history | Yes | | 18 | 5 (28) | .62 |
| | No | | 120 | 27 (22) | |
| Renal history | Yes | | 12 | 1 (8) | .20 |
| | No | | 126 | 31 (25) | |

*Cancer*. Author manuscript; available in PMC 2014 October 01.

| Variable | | Median (Range) | No. | No. Bleeding (%) | *P* |
|---|---|---|---|---|---|
| Gastrointestinal history* | Yes | | 25 | 7 (25) | .53 |
| | No | | 113 | 25 (22) | |
| HTN | Yes | | 37 | 8 (22) | .79 |
| | No | | 101 | 24 (24) | |
| Prior SCT | Yes | | 11 | 3 (27) | .74 |
| | No | | 127 | 29 (23) | |
| Prior IFN-α | Yes | | 81 | 23 (28) | .08 |
| | No | | 57 | 9 (16) | |
| **CML phases** | | | | | **.007** |
| **CP** | | | 63 | 7 (11) | |
| **AP** | | | 38 | 13 (34) | |
| **BP** | | | 35 | 12 (34) | .002 (CP vs AP/BP) |
| **Dose schedule** | | | | | **.17** |
| **QD** | | | 39 | 6 (15) | |
| **BID** | | | 99 | 26 (26) | |
| **Dose, mg/day** | | | | | **.45** |
| **<100** | | | 15 | 2 (13) | |
| **100** | | | 21 | 3 (14) | |
| **105–140** | | | 93 | 24 (26) | |
| **>140** | | | 9 | 3 (33) | |

WBC indicates white blood cell; PB, peripheral blood; BM, bone marrow; CML, chronic myelogenous leukemia; HTN, hypertension; SCT: stem cell transplantation; IFN-α, interferon-α; CP, chronic phase; AP, accelerated phase; BP, blast phase; QD, daily; BID, twice daily.

*Gastrointestinal history included gastroesophageal reflux disease, hiatal hernial, esophagitis, peptic ulcer disease, gastritis, Mallory-Weiss syndrome, duodenitis, and diverticulitis.

## Table 5

Multivariate Logistic Regression Model*

| Variable | Risk of Bleeding | *P* Value (Univariate Analysis) | *P* Value (Multivariate Analysis) | Risk Ratio |
|---|---|---|---|---|
| Anemia, g/dL† | Higher | .007 | NS | |
| Thrombocytopenia, $\times 10^9$/L | Higher | .001 | .02 | 1.002 |
| PB blast %, higher | Higher | .049 | NS | |
| BM blast %, higher | Higher | .002 | NS | |
| Longer CML duration | Higher | .049 | NS | |
| CML phase: AP/BP (vs CP) | Higher | .002 | .03 | 1.69 |
| Prior IFN-α (yes) | Higher | .08 | NS | |

NS indicates not significant; PB, peripheral blood; BM, bone marrow; CML, chronic myelogenous leukemia; AP, accelerated phase; BP, blast phase; CP, chronic phase; IFN-α, interferon-α.

*Estimation of the association between disease and patient characteristics and the development of bleeding, considering other covariates in the model.

†Anemia denotes a hemoglobin level <10 g/dL.