Regular Article

CLINICAL TRIALS AND OBSERVATIONS

Bosutinib safety and management of toxicity in leukemia patients with resistance or intolerance to imatinib and other tyrosine kinase inhibitors

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Key Points

- Bosutinib had manageable toxicity and acceptable tolerability, with adverse events distinct from that of other tyrosine kinase inhibitors.
- Adverse events were primarily characterized by early-onset gastrointestinal events that were low grade, transient, and manageable.

Bosutinib is an oral, dual SRC/ABL tyrosine kinase inhibitor (TKI) with clinical activity in Philadelphia chromosome–positive (Ph+) leukemia. We assessed the safety and tolerability of bosutinib 500 mg per day in a phase 1/2 study in chronic-phase (CP) chronic myeloid leukemia (CML) or advanced Ph+ leukemia following resistance/intolerance to imatinib and possibly other TKIs. Patient cohorts included second-line CP CML (n = 286), third-/fourth-line CP CML (n = 118), and advanced leukemia (n = 166). Median bosutinib duration was 11.1 (range, 0.03-83.4) months. Treatment-emergent adverse events (TEAEs) in each cohort were primarily gastrointestinal (diarrhea [86%/83%/74%], nausea [46%/48%/48%], and vomiting [37%/38%/43%]). Diarrhea presented early, with few (8%) patients experiencing grade 3/4 events; dose reduction due to diarrhea occurred in 6% of affected patients. Grade 3/4 myelosuppression TEAEs were reported in 41% of patients; among affected patients, 46% were managed with bosutinib interruption and 32% with dose reduction. Alanine aminotransferase elevation TEAEs occurred in 17% of patients (grade 3/4, 7%); among patients managed with dose interruption, bosutinib rechallenge was successful in 74%. Bosutinib demonstrated acceptable safety with manageable toxicities in Ph+ leukemia. This trial (NCT00261846) was registered at www.ClinicalTrials.gov (this manuscript is based on a different data snapshot from that in ClinicalTrials.gov). (*Blood.* 2014;123(9):1309-1318)

Introduction

Tyrosine kinase inhibitors (TKIs) designed to inhibit the BCR-ABL oncoprotein are the backbone of treatment of all phases of Philadelphia chromosome–positive (Ph+) chronic myeloid leukemia (CML)[1,2] and acute lymphoblastic leukemia (ALL).[3] However, TKIs are associated with toxicity that may prevent patients from maintaining drug intensity, limiting therapeutic benefit. Indefinite TKI treatment duration makes tolerability and manageability of these adverse events (AEs) essential to therapeutic success. Familiarity with these AEs can aid monitoring and early identification of drug toxicity and appropriate intervention, including TKI dose modifications and concomitant medication support.

Imatinib, a TKI with specificity for BCR-ABL, as well as KIT and platelet-derived growth factor receptor (PDGFR), has been the standard of care for CML patients.[4,5] However, many patients cannot tolerate imatinib because of toxicities, including gastrointestinal symptoms, arthralgia/myalgia, rash, fatigue, and myelosuppression.[6-8] Intolerance also occurs with the second-generation TKIs dasatinib[9] and nilotinib[10] as first-line CML treatment. Thus, safety and tolerability of each TKI may influence treatment selection.

Bosutinib (SKI-606) is an oral, dual competitive SRC and ABL TKI with minimal activity against PDGFR or KIT.[11,12] In a phase 1/2 study, bosutinib demonstrated efficacy in all phases of CML previously treated with imatinib alone or imatinib followed by dasatinib and/or nilotinib.[13-15]

Bosutinib was associated with acceptable safety and tolerability across cohorts; mild or moderate gastrointestinal events and rash were the most common AEs.[14,15] Although myelosuppression is universally observed during TKI therapy for CML and Ph+ ALL,

There is an Inside *Blood* commentary on this article in this issue.

Table 1. Patient baseline demographic and clinical characteristics

Parameter	CP2L			CP3L				ADV (n = 166)	Total (n = 570)
	IM-R (n = 196)	IM-I (n = 90)*	Total (n = 286)	IM-R/I + D-R (n = 38)	IM-R/I + D-I (n = 50)*	IM-R/I + N-R (n = 26)	Total† (n = 118)		
Median age (range), y	51 (18-86)	55 (23-91)	53 (18-91)	56 (23-76)	57 (25-79)	53 (20-73)	56 (20-79)	50 (18-84)	53 (18-91)
Male sex, n (%)	114 (58)	36 (40)	150 (52)	18 (47)	19 (38)	14 (54)	53 (45)	97 (58)	300 (53)
Race, n (%)									
White	131 (67)	55 (61)	186 (65)	28 (74)	38 (76)	17 (65)	86 (73)	103 (62)	375 (66)
Asian	42 (21)	22 (24)	64 (22)	4 (11)	9 (18)	2 (8)	15 (13)	35 (21)	114 (20)
Black	11 (6)	5 (6)	16 (6)	1 (3)	1 (2)	3 (12)	6 (5)	19 (11)	41 (7)
Other	12 (6)	8 (9)	20 (7)	5 (13)	2 (4)	4 (15)	11 (9)	9 (5)	40 (7)
Median time since CML diagnosis (range), y	4.1 (0.6-15.1)	2.6 (0.1-13.6)	3.7 (0.1-15.1)	7.0 (1.2-17.6)	5.8 (0.6-18.3)	5.9 (1.2-16.3)	6.6 (0.6-18.3)	3.9 (0.1-22.1)	4.2 (0.1-22.1)
ECOG performance status, n (%)‡									
0	152 (78)	67 (74)	219 (77)	28 (74)	31 (62)	24 (92)	85 (72)	74 (45)	378 (66)
1	44 (22)	21 (23)	65 (23)	10 (26)	18 (36)	2 (8)	32 (27)	72 (43)	169 (30)
2	0	1 (1)	1 (<1)	0	0	0	0	20 (12)	21 (4)
No. of prior therapies, n (%)									
1	119 (61)	67 (74)	186 (65)	0	0	0	0	72 (43)	258 (45)
2	77 (39)	23 (26)	100 (35)	12 (32)	26 (52)	13 (50)	52 (44)	50 (30)	202 (35)
3	0	0	0	26 (68)	24 (48)	13 (50)	64 (54)	36 (22)	100 (18)
4	0	0	0	0	0	0	2 (2)	8 (5)	10 (2)
Prior TKI therapy, n (%)									
Imatinib only	196 (100)	90 (100)	286 (100)	0	0	0	0	98 (59)	384 (67)
Imatinib + dasatinib	0	0	0	38 (100)	50 (100)	0	88 (75)	40 (24)	128 (22)
Imatinib + nilotinib	0	0	0	0	0	26 (100)	27 (23)	12 (7)	39 (7)
Imatinib + dasatinib + nilotinib	0	0	0	0	0	0	3 (3)	16 (10)	19 (3)
Other prior therapies, n (%)									
Interferon	77 (39)	23 (26)	100 (35)	26 (68)	24 (48)	13 (50)	65 (55)	62 (37)	227 (40)
Stem cell transplant	6 (3)	2 (2)	8 (3)	2 (5)	5 (10)	0	9 (8)	14 (8)	31 (5)

CP, chronic-phase CML; 2L, second-line setting; 3L, third-/fourth-line setting; IM-R, imatinib resistant; IM-I, imatinib intolerant; IM-R/I, imatinib resistant/intolerant; D-R, dasatinib resistant; D-I, dasatinib intolerant; N-R, nilotinib resistant; ADV, advanced leukemia (accelerated-/blast-phase CML and acute lymphoblastic leukemia); ECOG, Eastern Cooperative Oncology Group.

*The subgroups of patients with intolerance to prior TKI therapy.

†Includes patients (n = 4) in whom prior imatinib therapy failed and who were intolerant to prior nilotinib or resistant or intolerant to prior nilotinib and dasatinib therapy (because of low n, data not shown separately).

‡ECOG performance status at baseline was missing for 1 patient each in the CP2L and CP3L cohorts.

nonhematologic AEs associated with bosutinib appear distinct from those of imatinib, dasatinib, and nilotinib.[16-18] The current analysis from the same phase 1/2 study characterizes toxicities associated with bosutinib and describes toxicity management in Ph+ leukemia patients. Toxicity was assessed in patients receiving bosutinib as chronic-phase (CP) second-line (CP2L) or third-/fourth-line (CP3L) therapy and in patients with advanced (ADV) disease, including accelerated-phase (AP) or blast-phase (BP) CML and ALL.

Methods

Study design

This was an open-label, 2-part, multicenter, phase 1/2 study. Part 1 was a phase 1 dose-escalation study that determined a recommended dose of bosutinib 500 mg per day in primarily imatinib-resistant CP CML patients.[14] No dose-limiting toxicities occurred in the 400- and 500-mg cohorts; in the 600-mg cohort, 1 of 12 patients experienced a dose-limiting toxicity (grade 3 rash, nausea, and vomiting) and additional patients experienced grade 2 alanine aminotransferase (ALT) elevation, grade 2 rash, and grade 3 diarrhea.[14] Bosutinib 500 mg per day was selected as the part 2 starting dose, despite not reaching a protocol-defined maximum tolerated dose because of observed AEs with 600 mg per day. Clinical benefit was observed at all doses.

Part 2 is a phase 2 safety and efficacy evaluation of bosutinib 500 mg per day in CP, AP, or BP CML or Ph+ ALL patients with resistance or intolerance to imatinib and possibly dasatinib and/or nilotinib. Dose escalation to 600 mg per day was permitted for lack of efficacy (complete hematologic response not reached by week 8 or complete cytogenetic response not reached by week 12) if no drug-related grade 3/4 AE had occurred. Methodology and overall study results were reported previously for CP patients.[14,15]

The protocol was approved by the central or institutional review board for each study site, and informed consent was obtained in accordance with the Declaration of Helsinki.

Patients

Patients were aged 18 years or older with cytogenetic or polymerase chain reaction confirmation of Ph+ CML or ALL, resistant to full-dose imatinib (CP CML, ≥600 mg; ADV, ≥800 mg) or intolerant to any dose of imatinib. Patients in the CP3L cohort were resistant to dasatinib 100 mg per day or nilotinib 800 mg per day and/or intolerant to any dose of dasatinib; patients in the ADV cohort may also have been resistant or intolerant to dasatinib and/or nilotinib. Additional criteria included Eastern Cooperative Oncology Group performance status score of 0 or 1 (2 permitted for the ADV cohort); adequate bone marrow (CP2L and CP3L cohorts), hepatic, and renal function (defined previously[13,14]); ≥7 days since any antiproliferative treatment (except hydroxyurea and anagrelide); ≥3 months postallogeneic hematopoietic stem cell transplantation; and recovery to grade 0 or 1 or to baseline from any toxicities associated with prior anticancer treatment (except alopecia).

Table 2. Treatment modifications and discontinuations due to AEs

Parameter, n (%) or median (range)	CP2L			CP3L				ADV (n = 166)	Total (n = 570)
	IM-R (n = 196)	IM-I (n = 90)*	Total (n = 286)	IM-R/I + D-R (n = 38)	IM-R/I + D-I (n = 50)*	IM-R/I + N-R (n = 26)	Total† (n = 118)		
Patients with ≥1 dose reduction‡,§	87 (44)	52 (58)	139 (49)	13 (34)	32 (64)	13 (50)	59 (50)	57 (34)	255 (45)
No. dose reductions per patient‖									
1	45 (23)	33 (37)	78 (27)	10 (26)	16 (32)	10 (39)	36 (31)	32 (19)	146 (26)
2	37 (19)	15 (17)	52 (18)	2 (5)	13 (26)	2 (8)	18 (15)	21 (13)	91 (16)
≥3	5 (3)	4 (4)	9 (3)	1 (3)	3 (6)	1 (4)	5 (4)	4 (2)	18 (3)
Patients with ≥1 dose interruption	130 (66)	75 (83)	205 (72)	19 (50)	40 (80)	16 (62)	78 (66)	85 (51)	368 (65)
No. dose interruptions per patient									
1	51 (26)	34 (38)	85 (30)	11 (29)	14 (28)	6 (23)	32 (27)	40 (24)	157 (28)
2	33 (17)	21 (23)	54 (19)	3 (8)	11 (22)	5 (19)	19 (16)	21 (13)	94 (17)
3	21 (11)	7 (8)	28 (10)	1 (3)	5 (10)	2 (8)	9 (8)	10 (6)	47 (8)
≥4	25 (13)	13 (14)	38 (13)	4 (11)	10 (20)	3 (12)	18 (15)	14 (8)	70 (12)
Median cumulative duration of interruption (range), d	21.5 (1-582)	22.0 (1-429)	22.0 (1-582)	24.0 (1-144)	29.5 (1-181)	28.0 (1-150)	27.0 (1-181)	20.0 (1-257)	22.0 (1-582)
Early (≤4 wk) interruptions	53 (27)	38 (42)	91 (32)	8 (21)	19 (38)	5 (19)	32 (27)	52 (31)	175 (31)
Treatment discontinuation¶	30 (15)	34 (38)	64 (22)	6 (16)	20 (40)	3 (12)	29 (25)	30 (18)	123 (22)
Thrombocytopenia#	6 (3)	11 (12)	17 (6)	1 (3)	7 (14)	0	8 (7)	5 (3)	30 (5)
Increased ALT	3 (2)	4 (4)	7 (2)	0	1 (2)	2 (8)	3 (3)	3 (2)	13 (2)
Neutropenia#	2 (1)	6 (7)	8 (3)	3 (8)	1 (2)	1 (4)	5 (4)	0	13 (2)
Diarrhea	3 (2)	1 (1)	4 (1)	1 (3)	1 (2)	0	2 (2)	0	6 (1)
Vomiting	1 (1)	2 (2)	3 (1)	1 (3)	2 (4)	0	3 (3)	1 (1)	7 (1)
Increased AST	1 (1)	1 (1)	2 (1)	0	0	1 (4)	1 (1)	1 (1)	4 (1)
Cardiac failure	1 (1)	0	1 (<1)	0	2 (4)	0	2 (2)	0	3 (1)
Dyspnea	0	1 (1)	1 (<1)	0	1 (2)	0	1 (1)	2 (1)	4 (1)
Pleural effusion	0	1 (1)	1 (<1)	0	1 (2)	0	1 (1)	2 (1)	4 (1)
Pulmonary fibrosis	0	1 (1)	1 (<1)	0	0	0	0	2 (1)	3 (1)
Anemia#	0	2 (2)	2 (1)	1 (3)	1 (2)	0	2 (2)	1 (1)	5 (1)
Myocardial infarction	0	0	0	1 (3)	0	0	1 (1)	1 (1)	2 (<1)
Pneumonia	1 (1)	0	1 (<1)	0	0	0	0	1 (1)	2 (<1)
Rash	1 (1)	2 (2)	3 (1)	0	0	0	0	0	3 (1)
Pericardial effusion	0	0	0	0	1 (2)	0	1 (1)	3 (2)	4 (1)

Abbreviations are explained in Table 1.

*The subgroups of patients with intolerance to prior TKI therapy.

†Includes patients (n = 4) in whom prior imatinib therapy failed and who were intolerant to prior nilotinib therapy or resistant or intolerant to prior nilotinib and dasatinib therapy (because of low n, data not shown separately).

‡Dose reduction defined as a decrease in the dose level from the previous dose level administered.

§For patients who started bosutinib treatment at a dose of 500 mg per day, dose could have been reduced to 400 mg per day because of toxicity and then subsequently escalated to 500 mg per day or reduced further to 300 mg per day. Patients whose dose was escalated to 500 mg per day could have had another dose reduction due to toxicity at another time; therefore, patients could have had multiple dose reductions to 400 or 300 mg per day.

‖Subcategory percentages may not add to the total due to rounding.

¶All AEs leading to treatment discontinuation in ≥1.0% of patients in the CP2L, CP3L, or ADV cohorts are shown in the table.

#Individual hematologic AEs were clustered with the related terms from investigations.

Safety evaluations

The safety population included patients from parts 1 and 2 who received ≥1 bosutinib dose. AEs were assessed continually and graded for severity according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0. Laboratory tests, electrocardiograms (ECGs), vital signs, and physical examinations were performed; in some instances, abnormalities may have been reported as AEs. Treatment-emergent AEs (TEAEs) were defined as any event increasing in severity from baseline or any new event starting during bosutinib therapy or within 30 days of the last bosutinib dose.

Results

Patients

Five hundred seventy patients received bosutinib and were evaluated for safety. Patients were grouped by disease phase and by prior therapy into 3 cohorts (Table 1). The CP2L cohort (n = 286) included patients with CP CML following resistance (n = 196) or intolerance (n = 90) to prior imatinib only (ie, no other TKIs). The CP3L cohort (n = 118) included patients with CP CML following resistance/intolerance to prior imatinib plus dasatinib resistance (n = 38), dasatinib intolerance (n = 50), nilotinib resistance (n = 26), or nilotinib intolerance or exposure to all 3 TKIs (n = 4). The ADV cohort (n = 166) included patients with AP CML (n = 78), BP CML (n = 64), or ALL (n = 24) following resistance/intolerance to prior imatinib or to multiple prior TKIs (ie, imatinib plus dasatinib and/or nilotinib).

Treatment summary

Median duration of bosutinib treatment across cohorts (analysis cutoff based on an interim unlocked database: May 15, 2013) was 11.1 (range, 0.03-83.4) months (CP2L, 24.8 [0.2-83.4] months; CP3L, 8.5 [0.2-78.1] months; ADV, 4.0 [0.03-77.9] months). The time from the last patient's first dose to the cutoff was ≥48 months for CP2L and ≥36 months for CP3L and ADV.

Table 3. TEAEs reported for ≥10% of patients

	CP2L			CP3L					
TEAE, n (%)	IM-R (n = 196)	IM-I (n = 90)*	Total (n = 286)	IM-R/I + D-R (n = 38)	IM-R/I + D-I (n = 50)*	IM-R/I + N-R (n = 26)	Total (n = 118)†	ADV (n = 166)	Total (n = 570)†
Diarrhea									
All grades	168 (86)	77 (86)	245 (86)	30 (79)	42 (84)	22 (85)	98 (83)	122 (74)	465 (82)
Grade 3/4	19 (10)	10 (11)	29 (10)	3 (8)	5 (10)	2 (8)	10 (9)	8 (5)	47 (8)
Nausea									
All grades	85 (43)	47 (52)	132 (46)	20 (53)	23 (46)	12 (46)	57 (48)	80 (48)	269 (47)
Grade 3/4	1 (1)	3 (3)	4 (1)	1 (3)	0	0	1 (1)	3 (2)	8 (1)
Vomiting									
All grades	73 (37)	34 (38)	107 (37)	14 (37)	24 (48)	7 (27)	45 (38)	72 (43)	224 (39)
Grade 3/4	3 (2)	8 (9)	11 (4)	1 (3)	0	0	1 (1)	6 (4)	18 (3)
Thrombocytopenia‡									
All grades	77 (39)	43 (48)	120 (42)	11 (29)	19 (38)	13 (50)	45 (38)	74 (45)	239 (42)
Grade 3/4	45 (23)	29 (32)	74 (26)	7 (18)	16 (32)	8 (31)	31 (26)	65 (39)	170 (30)
Rash									
All grades	63 (32)	39 (43)	102 (36)	10 (26)	18 (36)	3 (12)	32 (27)	51 (31)	185 (33)
Grade 3/4	15 (8)	11 (12)	26 (9)	0	3 (6)	0	3 (3)	6 (4)	35 (6)
Pyrexia									
All grades	57 (29)	17 (19)	74 (26)	6 (16)	8 (16)	3 (12)	18 (15)	64 (39)	156 (27)
Grade 3/4	1 (1)	1 (1)	2 (1)	0	0	0	0	5 (3)	7 (1)
Anemia‡									
All grades	51 (26)	25 (28)	76 (27)	8 (21)	7 (14)	6 (23)	22 (19)	64 (39)	162 (28)
Grade 3/4	23 (12)	9 (10)	32 (11)	3 (8)	4 (8)	1 (4)	8 (7)	42 (25)	82 (14)
Fatigue									
All grades	49 (25)	25 (28)	74 (26)	8 (21)	14 (28)	2 (8)	27 (23)	35 (21)	136 (24)
Grade 3/4	1 (1)	2 (2)	3 (1)	0	1 (2)	0	2 (2)	7 (4)	12 (2)
Abdominal pain									
All grades	50 (26)	25 (28)	75 (26)	9 (24)	12 (24)	7 (27)	28 (24)	35 (21)	138 (24)
Grade 3/4	3 (2)	2 (2)	5 (2)	0	1 (2)	0	1 (1)	4 (2)	10 (2)
Headache									
All grades	35 (18)	18 (20)	53 (19)	8 (21)	14 (28)	8 (31)	31 (26)	31 (19)	115 (20)
Grade 3/4	0	0	0	1 (3)	3 (6)	0	4 (3)	7 (4)	11 (2)
Cough									
All grades	44 (22)	19 (21)	63 (22)	7 (18)	11 (22)	4 (15)	23 (20)	34 (21)	120 (21)
Grade 3/4	0	0	0	0	0	0	0	0	0
Increased ALT									
All grades	41 (21)	23 (26)	64 (22)	6 (16)	6 (12)	5 (19)	18 (15)	17 (10)	99 (17)
Grade 3/4	15 (8)	10 (11)	25 (9)	0	4 (8)	3 (12)	7 (6)	7 (4)	39 (7)
Upper abdominal pain									
All grades	41 (21)	17 (19)	58 (20)	8 (21)	9 (18)	4 (15)	21 (18)	17 (10)	96 (17)
Grade 3/4	1 (1)	0	1 (<1)	0	0	0	0	3 (2)	4 (1)
Neutropenia‡									
All grades	29 (15)	17 (19)	46 (16)	9 (24)	7 (14)	7 (27)	24 (20)	36 (22)	106 (19)
Grade 3/4	16 (8)	11 (12)	27 (9)	6 (16)	7 (14)	4 (15)	18 (15)	33 (20)	78 (14)
Increased AST									
All grades	37 (19)	18 (20)	55 (19)	2 (5)	3 (6)	4 (15)	9 (8)	17 (10)	81 (14)
Grade 3/4	6 (3)	5 (6)	11 (4)	0	1 (2)	2 (8)	3 (3)	5 (3)	19 (3)
Arthralgia									
All grades	30 (15)	15 (17)	45 (16)	5 (13)	10 (20)	6 (23)	21 (18)	22 (13)	88 (15)
Grade 3/4	2 (1)	1 (1)	3 (1)	0	1 (2)	0	1 (1)	1 (1)	5 (1)
Decreased appetite									
All grades	30 (15)	11 (12)	41 (14)	3 (8)	7 (14)	4 (15)	14 (12)	21 (13)	76 (13)
Grade 3/4	2 (1)	0	2 (1)	0	1 (2)	0	1 (1)	0	3 (1)
Constipation									
All grades	22 (11)	18 (20)	40 (14)	2 (5)	8 (16)	3 (12)	15 (13)	27 (16)	82 (14)
Grade 3/4	0	1 (1)	1 (<1)	0	0	0	0	1 (1)	2 (<1)
Dyspnea									
All grades	23 (12)	10 (11)	33 (12)	2 (5)	10 (20)	1 (4)	13 (11)	32 (19)	78 (14)
Grade 3/4	4 (2)	0	4 (1)	0	1 (2)	0	1 (1)	9 (5)	14 (3)

TEAEs were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.

Abbreviations are explained in Table 1.

*The subgroups of patients with intolerance to prior TKI therapy.

†Includes patients (n = 4) for whom prior imatinib therapy failed and who were intolerant to prior nilotinib therapy or resistant or intolerant to prior nilotinib and dasatinib therapy (because of low n, data not shown separately).

‡Individual hematologic TEAEs were clustered with the related terms from investigations.

Table 3. (continued).

	CP2L			CP3L				ADV	Total
TEAE, n (%)	IM-R (n = 196)	IM-I (n = 90)*	Total (n = 286)	IM-R/I + D-R (n = 38)	IM-R/I + D-I (n = 50)*	IM-R/I + N-R (n = 26)	Total (n = 118)†	(n = 166)	(n = 570)†
Asthenia									
All grades	25 (13)	16 (18)	41 (14)	2 (5)	1 (2)	4 (15)	8 (7)	20 (12)	69 (12)
Grade 3/4	6 (3)	0	6 (2)	0	0	0	0	1 (1)	7 (1)
Back pain									
All grades	22 (11)	17 (19)	39 (14)	5 (13)	5 (10)	3 (12)	14 (12)	15 (9)	68 (12)
Grade 3/4	1 (1)	0	1 (<1)	0	2 (4)	1 (4)	3 (3)	3 (2)	7 (1)
Dizziness									
All grades	17 (9)	9 (10)	26 (9)	5 (13)	8 (16)	2 (8)	16 (14)	21 (13)	63 (11)
Grade 3/4	0	0	0	0	0	0	0	1 (1)	1 (<1)
Leukopenia‡									
All grades	21 (11)	14 (16)	35 (12)	4 (11)	0	0	4 (3)	23 (14)	62 (11)
Grade 3/4	8 (4)	7 (8)	15 (5)	0	0	0	0	18 (11)	33 (6)
Peripheral edema									
All grades	18 (9)	13 (14)	31 (11)	1 (3)	5 (10)	4 (15)	11 (9)	17 (10)	59 (10)
Grade 3/4	1 (1)	0	1 (<1)	0	0	0	0	1 (1)	2 (<1)
Nasopharyngitis									
All grades	24 (12)	13 (14)	37 (13)	4 (11)	5 (10)	4 (15)	14 (12)	7 (4)	58 (10)
Grade 3/4	0	0	0	0	0	0	0	0	0
Extremity pain									
All grades	26 (13)	5 (6)	31 (11)	1 (3)	5 (10)	3 (12)	9 (8)	18 (11)	58 (10)
Grade 3/4	2 (1)	0	2 (1)	0	0	0	0	1 (1)	3 (1)
Pleural effusion									
All grades	18 (9)	5 (6)	23 (8)	5 (13)	12 (24)	1 (4)	18 (15)	16 (10)	57 (10)
Grade 3/4	4 (2)	2 (2)	6 (2)	2 (5)	2 (4)	0	4 (3)	7 (4)	17 (3)

TEAEs were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.

Abbreviations are explained in Table 1.

*The subgroups of patients with intolerance to prior TKI therapy.

†Includes patients (n = 4) for whom prior imatinib therapy failed and who were intolerant to prior nilotinib therapy or resistant or intolerant to prior nilotinib and dasatinib therapy (because of low n, data not shown separately).

‡Individual hematologic TEAEs were clustered with the related terms from investigations.

Across cohorts, dose reductions and interruptions due to AEs occurred in 45% and 65% of patients, respectively, and were more common in CP2L (49% and 72%) and CP3L (50% and 66%) cohorts vs the ADV cohort (34% and 51%) (Table 2), likely reflecting differences in bosutinib exposure and treatment duration. More CP2L and CP3L patients intolerant vs resistant to prior TKIs had dose reductions and interruptions; intolerant patients were more likely to discontinue bosutinib treatment because of AEs, particularly thrombocytopenia (Table 2). Treatment interruptions due to AEs occurring ≤4 weeks after bosutinib initiation were comparable among the overall CP2L, CP3L, and ADV cohorts but were more common in CP2L and CP3L patients intolerant vs resistant to prior TKIs (Table 2).

Median cumulative duration of dose reduction to 400 mg per day was 88 days (range, 1-2323 days) (CP2L: 169 days; CP3L: 63.5 days; ADV: 59.5 days) and 127 days (range, 1-1480 days) to 300 mg per day (CP2L: 115 days; CP3L: 180 days; ADV: 158 days). Among patients with bosutinib dose reduction to 400 mg per day in the CP2L and CP3L cohorts, 18 of 130 (14%) and 4 of 52 (8%), respectively, had a major cytogenetic response (MCyR) before and after reduction, and an additional 56 of 130 (43%) and 15 of 52 (29%) patients first achieved MCyR after reduction; 3 CP2L patients and 2 CP3L patients lost their previously attained MCyR after reduction. Among those with dose reduction to 300 mg per day in the CP2L and CP3L cohorts, 17 of 49 (35%) and 4 of 21 (19%) patients had MCyR both before and after reduction; 8 of 49 (16%) and 4 of 21 (19%) patients first achieved MCyR after reduction; 2 and 0 patients lost their previously attained MCyR after reduction. For ADV patients with bosutinib dose reduction to 400 or 300 mg

per day, 11 of 50 (22%) and 4 of 23 (17%) patients had an overall hematologic response (OHR) before and after first reduction; 15 of 50 (30%) and 3 of 23 (13%) first achieved OHR after reduction; 3 and 7 lost their previously attained OHR after reduction. Of 558 patients who received an initial dose of bosutinib 400 or 500 mg per day, 92 (17%) had dose escalation to 600 mg per day due to lack of efficacy; median treatment duration at 600 mg per day was 159 (range, 4-1811) days.

At the time of analysis, 147 (26%) patients were receiving treatment. Disease progression was the most common reason for treatment discontinuation (25%), followed by AEs (22%). Rates of discontinuation due to AEs did not substantially differ across patient cohorts (Table 2); median time to bosutinib discontinuation due to AEs was 5.1 (range, 0.2-75.3) months. Of those who discontinued treatment because of an AE, 29% and 28% had their AE managed with bosutinib dose reduction to 300 or 400 mg per day, respectively, before discontinuation; 42% were not reduced to <500 mg per day before discontinuation. Of patients reduced to bosutinib 300 or 400 mg per day because of an AE, 12 of 93 (13%) and 41 of 232 (18%), respectively, later discontinued bosutinib because of progressive disease and 8 of 93 (9%) and 17 of 232 (7%) discontinued due to unsatisfactory response/lack of efficacy. Among 272 patients who had achieved/maintained an MCyR, treatment was discontinued for 139 (51%); more patients discontinued treatment in the ADV (84%) vs CP2L (38%) or CP3L (60%) cohorts. The most common reasons for treatment discontinuation among patients who had achieved/maintained an MCyR were disease progression (CP2L, 13%; CP3L, 15%; ADV, 46%) and AEs (10%, 23%, 18%).

Overall safety

Bosutinib toxicities were generally of mild to moderate severity and managed with concomitant medication, dose interruption and/or dose reduction, or resolved spontaneously. The most frequently reported TEAEs were gastrointestinal events (diarrhea, nausea, and vomiting) and thrombocytopenia; incidences did not substantially differ across cohorts overall (Table 3). Although diarrhea was common (82%), maximum severity was grade 1 (45%) or 2 (28%) in most patients; few experienced maximum grade 3 (8%) or 4 (<1%; 1 ADV patient) diarrhea. Based on differences of ≥10% for TEAEs occurring in ≥10% of patients, rash was more common and pyrexia less common in patients intolerant vs resistant to prior imatinib treatment in the CP2L cohort (Table 3). In the CP3L cohort, vomiting, rash, dyspnea, and pleural effusion were more common and neutropenia was less common in patients intolerant to prior dasatinib therapy vs patients resistant to prior TKI therapy (Table 3). Thrombocytopenia was most common in CP3L resistant to nilotinib. Grade 3/4 TEAEs reported in ≥10% of all patients were hematologic events, including thrombocytopenia (30%), anemia (14%), and neutropenia (14%; Table 3). Among 92 patients who were dose escalated to bosutinib 600 mg per day, generally no increases >5% were observed in the frequency or severity of individual TEAEs following dose escalation.

Serious AEs occurred in 248 (44%) patients, more commonly in the ADV cohort (58%) vs CP2L (39%) and CP3L (34%) cohorts. The most frequently reported serious AEs (≥16 patients) were pneumonia (n = 29), pleural effusion (n = 23), pyrexia (n = 21), and thrombocytopenia (n = 16).

On-treatment grade 3/4 hematologic laboratory abnormalities were reported frequently, particularly in the ADV cohort (Table 4). Grade 3/4 nonhematologic laboratory abnormalities reported on treatment in ≥5% of patients included hypermagnesemia (10%), increased ALT (8%), hypophosphatemia (8%), and increased lipase (7%; Table 4). Grade 3/4 hypermagnesemia was more common in patients intolerant vs resistant to prior TKIs (CP2L or CP3L); hematologic laboratory abnormalities were more common in CP2L patients intolerant vs resistant to prior TKIs.

Forty-four deaths (including 32 deaths in the ADV cohort) occurred within 30 days after the last bosutinib dose (supplemental Table A1, available on the *Blood* Web site). Common reasons included CML disease progression (n = 25 [4%]) and AEs considered unrelated to bosutinib by the investigators (n = 16 [3%]), most frequently pneumonia/pneumonitis (n = 5) and cardiac events (n = 6). Three deaths were attributed to an AE considered bosutinib-related by the investigator (lower gastrointestinal hemorrhage with thrombocytopenia [CP3L cohort], myocardial infarction [ADV], and acidosis [with respiratory failure complicated by sepsis; ADV]). All deaths in the CP2L cohort occurred in patients with resistance (not intolerance) to prior imatinib treatment; all deaths in the CP3L cohort occurred in patients with resistance or intolerance to prior dasatinib (not nilotinib) treatment (supplemental Table A1).

Characteristics and management of individual toxicities

Diarrhea occurred in 82% of all patients with little variability across patient cohorts. Diarrhea TEAEs were noted soon after bosutinib initiation, with a median time to first event of 2.0 days (Table 5). Diarrhea incidence decreased over time on treatment (supplemental Figure A1). Diarrhea TEAEs were predominantly of low severity and were typically transient, with a median duration of 1 to 2 days per event across cohorts. Diarrhea TEAEs were considered bosutinib-related in 455 (80%) patients, with <2% of bosutinib-related diarrhea

AEs considered serious (n = 8). Concomitant antidiarrheal medication was used in 65% of patients who experienced diarrhea, representing the primary management strategy. Loperamide (58%; Imodium) was used most frequently. Less commonly, diarrhea was managed by bosutinib interruption (14%) and reduction (6%), allowing most affected patients to maintain their bosutinib dose. Few patients (1%) in the safety population discontinued treatment because of diarrhea, emphasizing the manageability of this toxicity in the majority of patients. Nearly all (97%) patients whose diarrhea was managed with temporary interruption of bosutinib dosing and who were subsequently rechallenged did not discontinue bosutinib because of diarrhea. Diarrhea characteristics were generally consistent across the 3 cohorts.

Pleural effusion TEAEs occurred in 57 patients (10%) in the safety population, including 17 (3%) with maximum toxicity grade of 3 (n = 15), 4 (n = 1), or 5 (n = 1; CP2L, death on study day 2290 due to congestive heart failure and pleural effusion, both unrelated to bosutinib). Twenty-one patients (4%) experienced a serious pleural effusion TEAE. Among the 3 cohorts, pleural effusions were more common in the CP3L (all grades, n = 18 of 118 [15%]; grade 3/4/5, 4 of 118 [3%]) vs CP2L (n = 23 of 286 [8%] and n = 6 of 286 [2%], respectively) and ADV (n = 16 of 166 [10%] and 7 of 166 [4%]) cohorts. Median time to onset of the first pleural effusion was 541 (range, 3-1993) days; median event duration was 21 (range, 1-421) days. Of patients who experienced pleural effusion, 26% had dose reductions, 47% had dose interruptions, and 58% were managed with concurrent medications. Four (1%) patients discontinued bosutinib because of pleural effusion.

Of 57 patients with pleural effusion during bosutinib treatment, 22 (39%) had a history of pleural effusion, of whom 16 attributed prior TKI discontinuation to pleural effusion (dasatinib, n = 14; imatinib and nilotinib, n = 1 each). Of 17 CP3L patients with prior dasatinib treatment who experienced pleural effusion during bosutinib treatment, 11 (65%) indicated pleural effusion as the reason for dasatinib intolerance. Most patients (n = 33 of 57 [58%]) with pleural effusions during bosutinib treatment had never been exposed to dasatinib.

The collective incidence of cardiac-related TEAEs (combined analysis of MedDRA system organ class Cardiac Disorders and Investigations [cardiac and vascular terms]) was relatively low (18% of patients experienced any cardiac event, of whom most presented with prior or ongoing cardiac disorders at screening), with most patients (10%) experiencing maximum grade 1 or 2 events, 5% maximum grade 3 events, 2% maximum grade 4 events, and 1% grade 5 events (including death due to myocardial infarction [n = 3], congestive cardiac failure [n = 2], and cardiac failure and coronary artery disease [n = 1 each]). The most common cardiac events were pericardial effusion (3%), atrial fibrillation, congestive cardiac failure, tachycardia, and palpitations (2% each). In the overall population, 33 of 570 (6%) patients experienced cardiac events considered bosutinib-related; 13 patients (2%) had treatment-related grade 3/4 events. Management of cardiac TEAEs included bosutinib dose interruption (24%) or reduction (7%); 40% received concomitant medication. Few patients (n = 12 [2%]) in the safety population discontinued treatment due to cardiac events. Of patients whose cardiac TEAE was managed with dose interruption, 19 of 24 (79%) were rechallenged with bosutinib; only 4 rechallenged patients subsequently discontinued bosutinib due to a cardiac event.

Based on ECG laboratory data, only 1 patient experienced on-treatment grade 3 Fridericia corrected QT interval prolongation (patient had eligibility violation of grade 2 prolongation at baseline). Based on echocardiogram/multiple gated acquisition scan analysis, 1

Table 4. Maximum on-treatment grade 3 and 4 laboratory abnormalities reported for ≥5% of patients

Laboratory abnormality, n (%)	CP2L			CP3L				ADV (n = 166)	Total (n = 570)
	IM-R (n = 196)	IM-I (n = 90)*	Total (n = 286)	IM-R/I + D-R (n = 38)	IM-R/I + D-I (n = 50)*	IM-R/I + N-R (n = 26)	Total† (n = 118)		
Hematologic									
Thrombocytopenia									
Grade 3	30 (15)	19 (21)	49 (17)	7 (18)	8 (16)	3 (12)	18 (15)	32 (19)	99 (17)
Grade 4	14 (7)	9 (10)	23 (8)	1 (3)	7 (14)	5 (19)	13 (11)	67 (40)	103 (18)
Lymphopenia									
Grade 3	23 (12)	15 (17)	38 (13)	5 (13)	4 (8)	3 (12)	13 (11)	27 (16)	78 (14)
Grade 4	5 (3)	1 (1)	6 (2)	1 (3)	2 (4)	3 (12)	6 (5)	16 (10)	28 (5)
Neutropenia									
Grade 3	20 (10)	16 (18)	36 (13)	5 (13)	4 (8)	2 (8)	11 (9)	25 (15)	72 (13)
Grade 4	7 (4)	6 (7)	13 (5)	2 (5)	6 (12)	4 (15)	13 (11)	42 (25)	68 (12)
Anemia									
Grade 3	15 (8)	16 (18)	31 (11)	4 (11)	0	1 (4)	5 (4)	41 (25)	77 (14)
Grade 4	9 (5)	1 (1)	10 (3)	1 (3)	4 (8)	0	5 (4)	16 (10)	31 (5)
Leukopenia									
Grade 3	13 (7)	10 (11)	23 (8)	1 (3)	4 (8)	0	5 (4)	28 (17)	56 (10)
Grade 4	0	0	0	0	0	0	0	20 (12)	20 (4)
Nonhematologic									
Hypermagnesemia									
Grade 3	14 (7)	17 (19)	31 (11)	1 (3)	13 (26)	0	14 (12)	14 (8)	59 (10)
Grade 4	0	0	0	0	0	0	0	0	0
Increased ALT									
Grade 3	19 (10)	10 (11)	29 (10)	0	2 (4)	4 (15)	6 (5)	9 (5)	44 (8)
Grade 4	1 (1)	2 (2)	3 (1)	0	0	1 (4)	1 (1)	0	4 (1)
Hypophosphatemia									
Grade 3	20 (10)	7 (8)	27 (9)	0	3 (6)	1 (4)	4 (3)	12 (7)	43 (8)
Grade 4	1 (1)	0	1 (<1)	0	0	0	0	1 (1)	2 (<1)
Increased lipase									
Grade 3	19 (10)	7 (8)	26 (9)	2 (5)	3 (6)	2 (8)	7 (6)	4 (2)	37 (6)
Grade 4	1 (1)	1 (1)	2 (1)	0	1 (2)	0	1 (1)	1 (1)	4 (1)
Hyperglycemia									
Grade 3	4 (2)	5 (6)	9 (3)	0	1 (2)	0	1 (1)	10 (6)	20 (4)
Grade 4	1 (1)	0	1 (<1)	0	0	0	0	0	1 (<1)
Hyponatremia									
Grade 3	2 (1)	3 (3)	5 (2)	1 (3)	0	0	1 (1)	10 (6)	16 (3)
Grade 4	4 (2)	0	4 (1)	0	0	0	0	0	4 (1)

Abbreviations are explained in Table 1.

*The subgroups of patients with intolerance to prior TKI therapy.

†Includes patients (n = 4) for whom prior imatinib therapy failed and who were intolerant to prior nilotinib therapy or resistant or intolerant to prior nilotinib and dasatinib therapy (because of low n, data not shown separately).

patient had a shift in left ventricular ejection fraction (LVEF) decrease from normal (baseline) to grade 3 (on treatment); 3 patients had grade 3 LVEF at baseline that continued on therapy; 1 patient had on-treatment grade 3 LVEF with no available baseline results.

Overall, cardiac-related toxicities on bosutinib were infrequent, occurred mostly in patients with preexisting cardiac conditions reported at baseline, and were manageable with dose interruption and/or reduction and concomitant medication.

Relatively few vascular disorders (MedDRA system organ class) were observed (overall, 76 [13%]; treatment related, 18 [3%]). Hypertension was the most frequent TEAE (any grade, 37 [6%]; grade 3/4, 11 [2%]); for all other vascular events, frequency was ≤2%. Notably, 1 event of peripheral arterial occlusive disease (grade 2) was reported in a CP3L patient with prior nilotinib exposure; the event was considered serious, unrelated to bosutinib, and resolved within 10 days.

Myelosuppression (ie, anemia, neutropenia, and thrombocytopenia) was reported frequently; thrombocytopenia was the most commonly observed grade 3/4 TEAE (Table 3) and grade 3/4 laboratory abnormality (Table 4). Several patients with grade 3/4 laboratory abnormalities on treatment had baseline grade 3/4 hematologic laboratory abnormalities (thrombocytopenia, n = 56 of 202 [28%];

neutropenia, n = 30 of 140 [21%]; anemia, n = 15 of 108 [14%]; supplemental Table A2).

Median time to first myelosuppression TEAE was 22.0 days across cohorts (Table 6). Myelosuppression TEAEs were generally transient; median event duration was 14.0 days (range, 1-1373 days). Myelosuppression events were managed primarily with bosutinib treatment modifications; 46% of affected patients temporarily stopped treatment, 32% underwent dose reduction. Across cohorts, 10% of affected patients received growth factor support; 1% underwent transfusion for management of ≥1 event. Although these events represented the most severe toxicities, only 7% of patients in the safety population discontinued treatment because of a myelosuppression TEAE, suggesting overall manageability and tolerability of these events.

Across cohorts, ALT and aspartate aminotransferase (AST) elevation TEAEs were reported in 99 patients (17%) and 81 patients (14%), respectively; 112 patients (20%) had either or both types of elevation. Maximum grade 3 ALT/AST TEAEs were reported in 39 patients (7%); maximum grade 4 TEAEs were reported in 2 patients (<1%). Median time to first ALT/AST TEAE was 33.5 days; median event duration was 21.0 days. Despite the relative frequency of ALT and AST elevations, relatively few patients (13 [2%])

Table 5. Characteristics and management of diarrhea TEAEs

Parameter	Total (n = 465)
Median time to first event (range), d	2.0 (1-1330)
Median duration of an event* (range), d	2.0 (1-1510)
Diarrhea resolved, n (%)	387 (83)
Diarrhea management, n (%)	
Received dose reduction	26 (6)
Received dose interruption	65 (14)
No rechallenge	1 (2)
Rechallenge	64 (99)
Successful rechallenge†	62 (97)
Unsuccessful rechallenge‡	2 (3)
Received concurrent medication	304 (65)
Permanent treatment discontinuation due to diarrhea§	6/570 (1)

*Event defined based on start to stop of diarrhea with no grade change; any change in grade represents a new event.

†Successful rechallenge includes patients who did not experience subsequent/persistent diarrhea (n = 8) or experienced subsequent diarrhea that did not lead to treatment discontinuation (n = 54).

‡Unsuccessful rechallenge indicates treatment discontinuation due to diarrhea following rechallenge with bosutinib.

§Includes patients with no rechallenge or unsuccessful rechallenge following dose interruption, as well as those who discontinued treatment because of diarrhea without dose interruption.

discontinued treatment because of these events (Table 7). The incidence of ALT events decreased over time on treatment (supplemental Figure A2). ALT and AST TEAEs were primarily managed with bosutinib dose reduction or temporary interruption (18% and 35%, respectively, of affected patients). Among patients who required a temporary dose interruption for ALT and/or AST elevation and were subsequently rechallenged with bosutinib, 9 of 35 (26%) discontinued bosutinib due to ALT/AST elevation. ALT and AST elevation TEAEs were managed with concomitant medication in 13% of affected patients.

Discussion

This analysis comprehensively assessed toxicities and toxicity management associated with long-term bosutinib therapy (CP2L, 4-year minimum follow-up [unless discontinued earlier]: CP3L and ADV, 3-year minimum follow-up [unless discontinued earlier]) in patients with Ph$^+$ leukemia resistant or intolerant to prior TKI therapy. Overall, bosutinib tolerability did not differ substantially among Ph$^+$ leukemia patients, regardless of disease phase and treatment line. Within second-line and third-/fourth-line CP CML cohorts, dose reductions/interruptions and treatment discontinuation due to AEs, particularly thrombocytopenia, were more common in patients intolerant vs resistant to prior TKIs; in the CP2L cohort, patients intolerant to prior TKI therapy had 0 deaths in 90 patients within 30 days of last dose vs 7 in 196 for patients resistant to prior TKI therapy. Among all cohorts, the percentage of patients discontinuing bosutinib because of AEs in this analysis (CP2L, 22%; CP3L, 25%; ADV, 18%) was similar to that reported for first-line bosutinib therapy in the phase 3 Bosutinib Efficacy and Safety in Newly Diagnosed Chronic Myeloid Leukemia (BELA) trial (19%) with a median bosutinib treatment duration of 13.8 months.[19]

Gastrointestinal events, particularly diarrhea, were the most commonly reported TEAEs (all grades, grade 3/4). Although diarrhea occurred in most patients (CP2L, 86%; CP3L, 83%; ADV, 74%), events were typically transient and of mild to moderate severity, with most patients experiencing diarrhea early after treatment initiation (median time to first event, 2.0 days) and few treatment-related events reported as serious. Gastrointestinal AEs (diarrhea/nausea/vomiting) were less frequently reported in patients with imatinib-resistant/intolerant CP CML previously treated with dasatinib 100 mg per day (25%/18%/7%, respectively)[19] or nilotinib (12%/25%/13%).[20] These gastrointestinal AEs occurred more frequently in the CP2L (86%/46%/37%) and CP3L (83%/48%/38%) CML cohorts in the present analysis than in patients receiving first-line bosutinib treatment (68%/31%/32%).[19] Diarrhea AEs associated with bosutinib in all lines of therapy were manageable with concurrent medications and dose interruptions and/or reductions. No patients discontinued therapy primarily because of diarrhea in the first-line setting,[19] and only 1% of patients receiving bosutinib second-line (or later) discontinued due to diarrhea. Among patients who had dose interruption due to diarrhea and were subsequently redosed, 97% were successfully rechallenged with bosutinib. These data suggest bosutinib remains well tolerated despite the relatively high incidence of gastrointestinal events. With proper management, these events are transient and mild for most patients.

Treatment-related pleural effusion is associated with dasatinib (all grades, 14%) in patients with imatinib-resistant/intolerant CP CML,[20] but not nilotinib (all grades, 1%).[21] In our study, pleural effusion TEAEs occurred in relatively few CP CML patients with

Table 6. Characteristics and management of myelosuppression TEAEs

Parameter	All grades				Grade 3/4
	CP2L (n = 157)	CP3L (n = 56)	ADV (n = 106)	Total (n = 319)	Total (n = 231)
Median time to first event (range), d	29.0 (1-1767)	28.0 (1-1202)	14.0 (1-899)	22.0 (1-1767)	29.0 (1-1767)
Median duration of an event (range), d	15.0 (1-1373)	15.0 (1-454)	8.0 (1-889)	14.0 (1-1373)	9.0 (1-889)
Myelosuppression resolved, n (%)	85 (54)	34 (61)	52 (49)	171 (54)	163 (71)
Myelosuppression management, n (%)					
Received dose reduction	56 (36)	21 (38)	25 (24)	102 (32)	60 (26)
Received dose interruption	74 (47)	33 (59)	38 (36)	145 (46)	138 (60)
Received concurrent medication	22 (14)	13 (23)	26 (25)	61 (19)	46 (20)
Received transfusion(s)	0	1 (2)	1 (1)	2 (1)	1 (<1)
Received growth factor(s)	10 (6)	10 (18)	13 (12)	33 (10)	26 (11)
Permanent treatment discontinuation due to myelosuppression*	20/286 (7)	14/118 (12)	6/166 (4)	40/570 (7)	33/570 (6)

Myelosuppression events include anemia, hemoglobin decreased, neutropenia, neutrophil count decreased, thrombocytopenia, and platelet count decreased.

Abbreviations are explained in Table 1.

*Includes patients with no rechallenge or unsuccessful rechallenge following dose interruption as well as those who discontinued treatment due to myelosuppression without dose interruption.

Table 7. Characteristics and management of ALT and AST TEAEs

Parameter	ALT elevation (n = 99)	AST elevation (n = 81)	ALT or AST elevation (n = 112)
Median time to first event (range), d	30 (6-841)	33 (1-1400)	33.5 (1-1400)
Median duration of event (range), d	21 (1-1714)	20 (1-803)	21.0 (1-1714)
Events resolved, n (%)	84 (85)	69 (85)	94 (84)
Event management, n (%)			
Received dose reduction	17 (17)	7 (9)	20 (18)
Received dose interruption	39 (39)	28 (35)	39 (35)
No rechallenge	4 (10)	7 (25)	4 (10)
Rechallenge	35 (90)	21 (75)	35 (90)
Successful rechallenge*	26 (74)	19 (90)	26 (74)
Unsuccessful rechallenge†	9 (26)	2 (10)	9 (26)
Received concurrent medication‡	12 (12)	10 (12)	14 (13)
Permanent treatment discontinuation due to event§	12/570 (2)	4/570 (1)	13/570 (2)

*Successful rechallenge includes patients who did not experience subsequent ALT or AST AEs (n = 4 and n = 6, respectively) or experienced subsequent ALT and AST AEs that did not lead to treatment discontinuation (n = 22 and n = 13).

†Unsuccessful rechallenge indicates treatment discontinuation due to ALT or AST elevation following rechallenge with bosutinib.

‡Concurrent medications used for management of ALT and/or AST elevations included essential phospholipids, ursodiol, steroids, S-adenosylmethionine, milk thistle extract, and glycyrrhizic acid. Patients may have received ≥1 medication.

§Includes patients with no rechallenge or unsuccessful rechallenge following dose interruption, as well as those who discontinued treatment due to ALT or AST elevation without dose interruption.

imatinib resistance/intolerance (CP2L cohort, 8%) and overall (10%) during bosutinib treatment. The proportion of patients experiencing pleural effusion was highest in the CP3L cohort (n = 18 [15%]), and the majority (17 of 18) of affected patients received prior dasatinib. Furthermore, 11 of these 17 patients reported pleural effusion as the reason for dasatinib intolerance. Notably, pleural effusions rarely led to bosutinib discontinuation (1%).

Cardiac and vascular events were observed at relatively low frequency in this study (any cause, 18% and 13%, respectively; treatment-related, 6% and 3%), with low incidences of individual events (≤3% and ≤6%). The majority of patients requiring dose interruption for cardiac toxicity were successfully rechallenged; 2% of patients discontinued bosutinib for cardiac-related events. Notably, the incidence of drug-related cardiac AEs in first-line CP CML patients was also low (4%).[19]

In our study, the most common grade 3/4 TEAEs and laboratory abnormalities were myelosuppression events, which is unsurprising because myelosuppression is commonly associated with other BCR-ABL TKIs (dasatinib and nilotinib) as second-line CML treatment.[16-18] In a phase 3 trial of dasatinib in patients with imatinib-resistant/intolerant CP CML, reported rates of grade 3/4 treatment-related myelosuppression laboratory abnormalities were 35% for neutropenia, 23% for thrombocytopenia, and 13% for anemia after a median treatment duration of 22 months.[20] Similarly, a phase 2 trial of nilotinib in imatinib-resistant/intolerant CP CML reported incidences of grade 3/4 laboratory abnormalities of 31% for neutropenia, 30% for thrombocytopenia, and 11% for anemia.[21] Rates of grade 3/4 laboratory abnormalities of neutropenia were lower with bosutinib in both the CP2L (17%) and CP3L (20%) cohorts vs dasatinib and nilotinib, whereas rates of thrombocytopenia (CP2L, 25%; CP3L, 26%) and anemia (CP2L, 14%; CP3L, 8%) were fairly similar. The incidences of grade 3/4 myelosuppression laboratory abnormalities with bosutinib were higher in ADV patients (thrombocytopenia, 60%; neutropenia, 41%; anemia, 35%) than in CP CML

patients. Myelosuppression was managed with bosutinib dose modifications and less frequently with transfusions and growth factors; myelosuppression events were the primary reason for treatment discontinuation in 7% of patients. Myelosuppression grade 3/4 laboratory abnormalities with bosutinib were lower (14% for thrombocytopenia, 11% for neutropenia, 6% for anemia) with first-line therapy.[19]

ALT and AST elevation TEAEs in our study were typically well tolerated; few patients (2%) discontinued treatment because of these TEAEs. The percentage of affected patients with bosutinib dose interruptions (35%) or reductions (18%) due to ALT or AST elevation was lower in our analysis vs first-line therapy (57% and 36%, respectively).[19] In our analysis, the majority (74%) of patients subsequently rechallenged with bosutinib following dose interruption due to ALT and/or AST elevation did not discontinue treatment because of ALT/AST elevation, again suggesting that these toxicities, while notable and requiring monitoring, were manageable.

Generally, bosutinib demonstrated acceptable tolerability in patients with Ph⁺ CML and ALL, with an AE profile distinct from that of other TKIs. Toxicities observed with bosutinib treatment were generally manageable with treatment modification and/or concomitant medication. Additional experience with bosutinib treatment may further improve the management of observed toxicities. Our findings support the continued clinical development of bosutinib as monotherapy for the treatment of Ph⁺ CML patients.

Acknowledgments

Authorship

Contribution: J.E.C., H.J.K., and C.G.-P. contributed to the study design; J.E.C., D.-W.K., T.H.B., G.M., N.B., and K.T. collected and assembled the data; H.M.K., J.E.C., D.-W.K., H.J.K., T.H.B., K.P., G.M., S.D., E.L., V.K., K.T., N.B., and C.G.-P. contributed to the analysis and/or interpretation of data; H.M.K., J.E.C., D.-W.K., H.J.K., T.H.B., K.P., G.M., S.D., and C.G.-P. provided study materials and/or enrolled patients in the study; E.L. performed statistical analyses; and all authors assisted in the writing and/or critical review of the manuscript and approved the final version of the manuscript for submission.

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