Potent, transient inhibition of BCR-ABL with dasatinib 100 mg daily achieves rapid and durable cytogenetic responses and high transformation-free survival rates in chronic phase chronic myeloid leukemia patients with resistance, suboptimal response or intolerance to imatinib

Neil P. Shah,[1] Dong-Wook Kim,[2] Hagop Kantarjian,[3] Philippe Rousselot,[4] Pedro Enrique Dorlhiac Llacer,[5] Alicia Enrico,[6] Jorge Vela-Ojeda,[7] Richard T. Silver,[8] Hanna Jean Khoury,[9] Martin C. Müller,[10] Alexandre Lambert,[11] Yousif Matloub,[11] and Andreas Hochhaus[12]

[1]Division of Hematology and Oncology, University of California, San Francisco School of Medicine, San Francisco, CA, USA; [2]Division of Hematology, St Mary's Hospital, The Catholic University of Korea, Seoul, South Korea; [3]MD Anderson Cancer Center, Houston, TX, USA; [4]Hôpital Mignot and CIC Hôpital Saint Louis, Paris, France; [5]Hospital das Clinicas, Sao Paulo, Brazil; [6]Instituto de Trasplante de Medula Osea, La Plata, Argentina; [7]Centro Medico Nacional La Raza IMSS, Mexico; [8]Division of Hematology/Oncology, New York Presbyterian Hospital-Weill Cornell Medical College, New York, NY, USA; [9]Dept. of Hematology and Medical Oncology, Emory University, Atlanta, GA, USA; [10]III Medizinische Klinik, Universitätsmedizin Mannheim, Universität Heidelberg, Mannheim, Germany; [11]Bristol-Myers Squibb, Wallingford, CT, USA; [12]Dept. of Hematology/Oncology, Universitätsklinikum Jena, Jena, Germany

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Study Design

This was an international, randomized, open-label, phase 3 study (two x two factorial design) of patients with chronic phase chronic myeloid leukemia (CP-CML) with resistance, suboptimal response, or intolerance to imatinib. Randomization was in a 1:1:1:1 ratio to four treatment arms using a permuted block procedure. Patients were stratified by imatinib resistance/suboptimal response and intolerance. Written, informed consent was obtained from all patients. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice and was approved by the local Institutional Review Board or Independent Ethics Committee.

Enrolled patients were at least 18 years of age, had Philadelphia chromosome-positive (Ph^+) or BCR-ABL-positive CP-CML, primary or acquired imatinib resistance, or imatinib intolerance. These eligibility criteria encompassed inclusion of suboptimal responders to imatinib as defined by the European LeukemiaNet criteria.[1] Key exclusion criteria included, but were not limited to: history of a significant non-CML-related bleeding disorder, uncontrolled or significant cardiovascular disease, or prior diagnosis of accelerated or blast phase CML.

The primary study endpoint was the comparison of major cytogenetic response (MCyR) rates for once daily versus twice daily regimens in imatinib-resistant/suboptimal response patients after a minimum follow-up of 6 months. Secondary endpoints in imatinib-resistant/suboptimal response patients included comparison of MCyR rates between groups receiving different total daily doses (main secondary objective), MCyR rate, time to and duration of MCyR, complete hematologic response rate, time to complete hematologica response, progression-free survival, and overall survival. Other secondary endpoints included MCyR and complete hematologic response rates in imatinib-intolerant patients as well as analysis of *BCR-ABL* mutations, rates of specific adverse events, dose reductions due to toxicity, and safety in all treated patients.

Definitions of CP-CML, cytogenetic response, and complete hematologic response have been described previously.[2] Progression was a loss of complete hematologic response or MCyR while receiving the maximum dasatinib dose, conversion to accelerated or blast phase CML, no complete hematologic response after receiving the maximum dose with an increase in white blood cell count (previously defined[2]), or a 30% or greater absolute increase in the number of Ph^+ metaphases. Major molecular response was assessed by real-time quantitative polymerase chain reaction (RQ-PCR). The RNA isolated from 2.5 mL of whole blood collected in PAXgene™ (Preanalytix, Hombrechticon, Switzerland) reagent was reverse transcribed into cDNA, followed by the RQ-PCR assay for the absolute quantitation of *BCR-ABL* transcripts. *BCR-ABL/BCR* ratios were calculated and converted to the International Scale.[3] A major molecular response was defined as a 3-log reduction of *BCR-ABL* transcripts in peripheral blood leukocytes in comparison to the standardized baseline which is equivalent to 0.1% on the international scale.[3,4]

Assessment of BCR-ABL mutations was performed at baseline and at the end of treatment; data on baseline mutations are provided in this report. Peripheral blood RNA was collected and reverse transcriptase-polymerase chain reaction (RT-PCR) performed to amplify the *BCR-ABL* fusion transcript. The *BCR-ABL* point mutations were then analyzed by direct sequencing.

Patients were randomized to oral dasatinib 100 mg once daily, 50 mg twice daily, 140 mg once daily, or 70 mg twice daily. Dose modifications were permitted per protocol criteria for management of progression or toxicities.[2] Doses could be escalated for inadequate response (as previously defined[2]) up to 140 mg once daily, 70 mg twice daily, 180 mg once daily, or 90 mg twice daily. Treatment interruptions or dose reductions were permitted for bleeding or hemorrhage (per protocol criteria), grade 2 or greater non-hematologic toxicity considered treatment-related, or grade 3 or more hematologic toxicity. Doses could be reduced to 80 mg daily in both once daily treatment groups and to 40 mg twice daily in both twice-daily groups. Dasatinib was continued until progression or unaccept-

able toxicity. In accordance with a protocol amendment in 2007, 33 patients had their dose regimens changed by investigators from a twice daily to once daily regimen for specified adverse event criteria (fluid retention or cytopenias).

Additional definitions

Primary imatinib resistance/suboptimal response in patients receiving imatinib doses of 400 mg/day or more was defined as: no reduction in white blood cell count after at least 4 weeks, no complete hematologic response after 3 months, no MCyR after 6 months, or no complete cytogenetic response (CCyR) after 12 months of therapy.

Acquired imatinib resistance was a loss of MCyR, loss of molecular response with at least 10% Ph^+ metaphases, MCyR with a new *BCR-ABL* mutation, or loss of a confirmed complete hematologic response.

Patients who could not tolerate imatinib 600 mg/day or more, but had not achieved a CCyR on 400 mg were classified as imatinib-resistant.

Imatinib intolerant patients were defined as those who had experienced at least a grade 3 adverse event considered at least possibly related to imatinib at doses of 400 mg/day or less and subsequently discontinued therapy.

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Online Supplementary Table S1. Baseline Imatinib resistance and intolerance characteristics*

	Dasatinib			
	100 mg QD (n=167)	70 mg BID (n=168)	140 mg QD (n=167)	50 mg BID (n=168)
Median age (years)	56	55	54	55
Median time from disease diagnosis to randomization (months)	55	53	56	51
Prior treatment, n (%)				
Hydroxyurea or anagrelide	125 (75)	130 (77)	131 (78)	130 (77)
Interferon α	87 (52)	82 (49)	93 (56)	87 (52)
Chemotherapy	39 (23)	43 (26)	41 (25)	52 (31)
Radiotherapy	0	0	2 (1)	4 (2)
Stem-cell transplantation	10 (6)	7 (4)	5 (3)	13 (8)
Imatinib status, n (%)				
Primary imatinib resistance/suboptimal response, n (%)†	75 (45)	81 (48)	78 (47)	88 (52)
Inappropriate decrease in WBC ≥4 weeks	1 (1)	3 (2)	2 (1)	1 (1)
Less than CHR after ≥3 months	5 (3)	7 (4)	14 (8)	4 (2)
Less than MCyR (CCyR and/or PCyR) after ≥6 months	36 (22)	43 (26)	38 (23)	45 (27)
Less than CCyR after ≥12 months	60 (36)	63 (38)	54 (32)	67 (40)
Acquired imatinib resistance, n (%)	49 (29)	45 (27)	45 (27)	36 (21)
Loss of molecular response and ≥ ≥10% Ph-positive	7 (4)	6 (4)	12 (7)	6 (4)
Loss of MCyR (CCyR and/or PCyR) and new BCR-ABL mutation	2 (1)	7 (4)	4 (2)	4 (2)
Loss of CHR with WBC >10,000/μL	15 (9)	18 (11)	21 (13)	14 (8)
Loss of MCyR (CCyR and/or PCyR) with increase ≥30% Ph^+	27 (16)	24 (14)	21 (13)	17 (10)
Imatinib intolerance, n (%)	43 (26)	42 (25)	44 (26)	44 (26)

*BID indicates twice daily; Ph-positive: Philadelphia chromosome positive; QD: once daily; WBC,: white blood cells. *Some baseline characteristics previously reported by Shah et al.[12] †The reason for primary resistance was unknown for 1 patient (0.6%) on the 140 mg once-daily arm.*

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Online Supplementary Table S2. **Treatment-associated adverse events.**

	Dasatinib 100 mg QD (n=165)		70 mg BID (n=167)		140 mg QD (n=163)		50 mg BID (n=167)		*P* value
	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)	
Cytopenia †									
Neutropenia†	106 (64)	58 (35)	125 (77) ‡	74 (45)‡	119 (73)	71 (44)	128 (77)	78 (47) 0.127‖	0.034§
Thrombocytopenia†	107 (65)	38 (23)	123 (75)	62 (38)	122 (75)	66 (41)	115 (69)	60 (36) 0.003‖	0.129§
Leukocytopenia†	100 (61)	29 (18)	120 (73)	39 (24)	120 (74)	35 (22)	124 (75)	44 (27) 0.254‖	0.017§
Anemia†	150 (91)	22 (13)	156 (95)	30 (18)	147 (91)	31 (19)	159 (96)	30 (18)	–
Fluid retention	50 (30)	6 (4)	64 (38)	16 (10)	66 (40)	12 (7)	58 (35)	8 (5)	–
Superficial edema	28 (17)	0	31 (19)	1 (1)	27 (17)	1 (1)	30 (18)	0	–
Pleural effusion	23 (14)	4 (2)	38 (23)	9 (5)	41 (25)	8 (5)	39 (23)	6 (4)	0.049§
Other fluid-related events									
Pericardial effusion	3 (2)	2 (1)	4 (2)	2 (1)	10 (6)	3 (2)	9 (5)	3 (2)	–
Generalized edema	5 (3)	0	1 (1)	0	8 (5)	0	0	0	
CHF/cardiac dysfunction	0	0	9 (5)	4 (2)	6 (4)	2 (1)	2 (1)	1 (1)	
Pulmonary hypertension	0	0	2 (1)	1 (1)	1 (1)	0	2 (1)	0	
Pulmonary edema	0	0	5 (3)	1 (1)	0	0	2 (1)	1 (1)	
Other non-hematologic adverse events¶									
Diarrhea	42 (25)	2 (1)	45 (27)	7 (4)	47 (29)	6 (4)	52 (31)	4 (2)	–
Headache	54 (33)	1 (1)	50 (30)	5 (3)	48 (29)	3 (2)	38 (23)	0	–
Bleeding	18 (11)	2 (1)	26 (16)	4 (2)	22 (13)	1 (1)	18 (11)#	6(4)	–
GI Bleeding	3 (2)	1 (1)	6 (4)	3 (2)	3 (2)	0	9 (5)	5 (3)	0.225§
Other	17 (10)	2 (1)	20(12)	1 (1)	19(12)	1 (1)	9(5)	1 (1)	–
Nausea	30 (18)	1 (1)	48 (29)	1 (1)	39 (24)	1 (1)	33 (20)	1 (1)	–
Fatigue	39 (24)	4 (2)	34 (20)	7 (4)	41 (25)	4 (2)	31 (19)	0	–
Rash	28 (17)	3 (2)	39 (23)	3 (2)	46 (28)	1 (1)	40 (24)	2 (1)	–
Abdominal pain	19 (12)	1 (1)	17 (10)	2 (1)	22 (13)	1 (1)	20 (12)	0	–
Arthralgia	20 (12)	1 (1)	15 (9)	4 (2)	17 (10)	0	16 (10)	1 (1)	–
Constipation	15 (9)	1 (1)	4 (2)	0	5 (3)	0	16 (10)	0	
Cough	9 (5)	0	19 (11)	0	11 (7)	0	12 (7)	0	–
Dyspepsia	8 (5)	0	11 (7)	0	17 (10)	0	5 (3)	0	
Dyspnea	31 (19)	3 (2)	33 (20)	8 (5)	41 (25)	11 (7)	40 (24)	10 (6)	–
Infection	20 (12)	1 (1)	17 (10)	3 (2)	17 (10)	2 (1)	13 (8)	1 (1)	–
Musculoskeletal pain	31 (19)	3 (2)	23 (14)	6 (4)	28 (17)	2 (1)	19 (11)	2 (1)	–
Myalgia	21 (13)	0	11 (7)	1 (1)	21 (13)	1 (1)	6 (4)	0	–
Pain	16 (10)	1 (1)	17 (10)	1(1)	12 (7)	1 (1)	9 (5)	1 (1)	–
Pruritus	16 (10)	1 (1)	12 (7)	0	12 (7)	0	6 (4)	0	–
Pyrexia	8 (5)	1 (1)	19 (11)	1 (1)	24 (15)	0	15 (9)	1 (1)	–
Vomiting	12 (7)	1 (1)	21 (13)	0	16 (10)	2 (1)	17 (10)	2 (1)	–

*BID: twice daily; QD: once daily; CHF congestive heart failure * Comparison across all four treatment arms (Fisher's exact test). †Based on laboratory evaluations with available samples: 100 mg QD arm n=165; 70 mg BID arm n=165 with the exception of neutropenia for which n = 163; 140 mg QD arm n=162; 50 mg BID arm n=166. ‡n=163 for 70 mg BID arm neutropenia; §All grades, ‖Grade 3/4 ¶Non-hematologic treatment-related adverse events occurring in ≥10% of patients. Patients could have had more than one adverse event. #One (1%) patient with central nervous system (CNS) bleeding; no grade 3 to 4 CNS bleeding reported.*

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Online Supplementary Table S3. **Dose modifications.**

	Dasatinib			
	100 mg QD n=165	70 mg BID n=167	140 mg QD n=163	50 mg BID n=167
Average median daily dose, mg/day (range)	98 (18-161)	101 (10-169)	117 (18-173)	91 (21-160)
Median treatment duration, months (range)	22 (1-30)	22 (0.1-31)	22 (0.2-30)	22 (0.2-31)
Dose interruption, n (%)	103 (62)	128 (77)	128 (79)	121 (72)
Key reasons for first interruption, n (%)				
Hematologic toxicity	45 (27)	59 (35)	63 (39)	64 (38)
Non-hematologic toxicity	41 (25)	65 (39)	51 (31)	44 (26)
Reasons (≥11 across groups)				
Pleural effusion	7 (4)	14 (9)	14 (9)	14 (9)
Pain	6 (4)	8 (5)	1 (1)	4 (2)
Rash	2 (1)	6 (4)	7 (4)	1 (1)
Diarrhea	1 (1)	4 (2)	4 (2)	5 (3)
Headache	1 (1)	5 (3)	4 (2)	1 (1)
Dose reductions, n (%)	65 (39)	103 (62)	101 (62)	77 (46)
Key reasons for first reduction, n (%)				
Hematologic toxicity	39 (24)	54 (32)	58 (36)	47 (28)
Non-hematologic toxicity	21 (13)	42 (25)	40 (25)	26 (16)
Reasons (≥7 across groups)				
Pleural effusion	6 (4)	9 (5)	10 (6)	12 (7)
Pain	2 (1)	7 (4)	4 (2)	3 (2)
Rash	4 (2)	3 (2)	3 (2)	1 (1)
Diarrhea	0	3 (2)	4 (2)	2 (1)
Dyspnea	2 (1)	0	2 (1)	3 (2)
Headache	0	2 (1)	4 (2)	1 (1)
Dose escalation, n (%)	37 (22)	20 (12)	22 (13)	32 (19)
Key reasons- for first escalation, n (%)				
No CCyR after 12 months	8 (5)	3 (2)	2 (1)	6 (4)
No CHR after 3 months	5 (3)	2 (1)	6 (4)	3 (2)
Inappropriate decrease in WBC after 1 month	6 (4)	2 (1)	2 (1)	3 (2)
No MCyR after 6 months	14 (9)	7 (4)	8 (5)	18 (11)
Time to first reduction/interruption due to toxicity (days)				
n (%)	95 (58)	127 (76)	123 (75)	114 (68)
Median (range)	71 (4-652)	38 (4-606)	44 (4-742)	37.5 (4-724)
≥2 months	52 (32)	39 (23)	51 (31)	42 (25)
Length of first interruption due to toxicity (days)				
n (%)	92 (56)	125 (75)	119 (73)	114 (68)
Median (range)	16 (2-99)	14 (2-227)	14 (1-76)	14 (1-91)

Abbreviations: as in Online Supplementary Table S1.

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