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BCR-ABL Transcript Analysis of Patients (Pts) with Imatinib-Resistant or -Intolerant Chronic Myeloid Leukemia in Chronic Phase (CML-CP) Treated with Nilotinib

Dong-Wook Kim, Giuseppe Saglio, Giovanni Martinelli, Yaping Shou, Andrew M. Stein, Richard C. Woodman, Hagop M. Kantarjian, Timothy P. Hughes, Jerald P. Radich, Andreas Hochhaus

Background: CML patients with different types of BCR-ABL transcript may vary in disease prognosis and responses to therapy. An analysis was conducted to investigate the correlation between BCR-ABL transcript type and responses to nilotinib in the 2nd line setting.

Methods: CML-CP pts (N = 321) with imatinib resistance or intolerance were included. In order to determine if transcript type influenced response dynamics, BCR-ABL transcript types were analyzed in 301/321 (94%) of pts. In addition, the BCR-ABL transcript dynamics were modeled as previously described (Stein et al. *Blood*. 2009;114(22):209).

Results: Median nilotinib exposure was 561 days. The majority of pts (95%) were observed to have typical b3a2 (63%) and b2a2 (32%) BCR-ABL transcript types; 3% of pts had both typical transcripts and 2% had atypical transcripts (e1a2, e19a2, b3a3). The incidence of BL mutations was higher in patients with b3a2 transcripts compared with b2a2 (46% vs 32%, $P = .03$). Response to nilotinib was similar regardless of transcript type (Table). A two-sample $\chi 2$ test of the four endpoints (CHR, CyR, MMR, and PFS) did not show a significant difference ($P > .05$) between the b2a2 and b3a2 populations. Modeling results demonstrated no statistically significant difference in the response dynamics between the major BCR-ABL transcript types.

Conclusion: These data suggest that nilotinib is effective in patients with all BCR-ABL transcript types including those with atypical transcripts. Patients with typical b3a2 and b2a2 transcripts have similar patterns of response to nilotinib.

Best Response to Nilotinib by Transcript Type	Number	Hematologic Response,%	Cytogenetic Response, %		Molecular Response,%	Event Free Survival, %
Transcript type	n	CHR	CCyR	PCyR	MMR	EFS
b2a2	95	87.4	44.2	13.7	16.8	58.3
b3a2	190	80.5	34.2	10.0	15.3	51.4
b2a2 + b3a2	10	90.0	50.0	20.0	10.0	71.4
e1a2	2	100.0	0	50.0	--	100.0
e19a2	2	50.0	0	0	--	0
b3a3	2	100.0	100.0	0	--	100.0
P-value: comparing b2a2 vs b3a2 using χ^2 2-sample test		0.15	0.09		0.73	0.34

BCR-ABL Transcript Analysis of Patients With Imatinib-Resistant or -Intolerant Chronic Myeloid Leukemia in Chronic Phase Treated With Nilotinib

Dong-Wook Kim[1], Giuseppe Saglio[2], Giovanni Martinelli[3], Yaping Shou[4], Andrew M. Stein[4], Richard C. Woodman[5], Hagop M. Kantarjian[6], Timothy P. Hughes[7], Jerald P. Radich[8], Andreas Hochhaus[9]

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INTRODUCTION

- Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) is caused by the *BCR-ABL* fusion gene
- Ph+ CML arises from a reciprocal translocation of most of the cellular *ABL* gene on chromosome 9 to the *BCR* gene on chromosome 22
- Various breakpoints in the *BCR* and *ABL* genes have been described
  - Most cases are *BCR* exon 13 or 14 fused to the *ABL* exon 2 (a2), resulting in the b2a2 and b3a2 transcripts, respectively
- Variations in BCR-ABL transcript types may result in differences in disease prognosis and response to therapy

OBJECTIVE

- To investigate the correlation between BCR-ABL transcript type and responses to nilotinib in the second-line setting

METHODS

Study Design and Patient Population

- Open-label, multicenter, single-arm, phase 2 study of nilotinib (400 mg twice daily) in patients with imatinib-resistant or -intolerant Ph+ CML in chronic phase (N = 321)
- Median exposure to nilotinib was 561 days

Analysis Dataset Population

- Patients with a baseline BCR-ABL transcript type measurement were analyzed (n = 251)
  - Incidence of different BCR-ABL transcript types was described
  - Mutational status, clinical responses including complete hematologic response (CHR), cytogenetic response (CyR), and major molecular response (MMR), and event-free survival (EFS) were evaluated in patients with different BCR-ABL transcript types

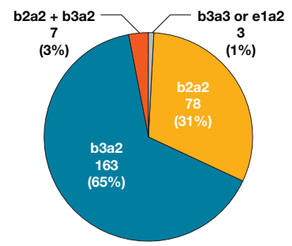
MODELING METHOD

- We analyzed the molecular response dynamics (BCR-ABL transcript by international scale [IS]) of a subset of the patient population (n = 107) with at least 3 PCR measurements and 90% dose intensity during the first 6 months of treatment, and a baseline BCR-ABL (IS) of >10%
- The time course of BCR-ABL transcript reduction (IS) was modeled as a biexponential function ($R(t) = Ae^{\alpha t} + Be^{\beta t}$), as found previously.[1] Patient parameters were estimated using nonlinear mixed effects modeling. The alpha parameter describes the initial decline in $\log_{10}$ (R) upon treatment start, while β describes the shallower slope of the subsequent $\log_{10}$ (R) dynamics in patients. It has been found among nilotinib second-line patients that α has a bimodal distribution, such that some exhibit a shallow decline (α > –5/year) and others exhibit a steep decline (α < –5/year). Steep decline has been shown to be associated with superior response

1. Stein A, et al. *Blood.* 2009;114(22):209 [abstract 506].

RESULTS

Figure 1. Patient Population Breakdown Based on Transcript Type



Breakpoint Type (N = 251)	n	%
b3a2	163	65
b2a2	78	31
b2a2 + b3a2	7	3
b3a3 or e1a2	3	1

- 99% of patients had typical b2a2 or b3a2 transcripts
- 1% of patients had atypical transcripts

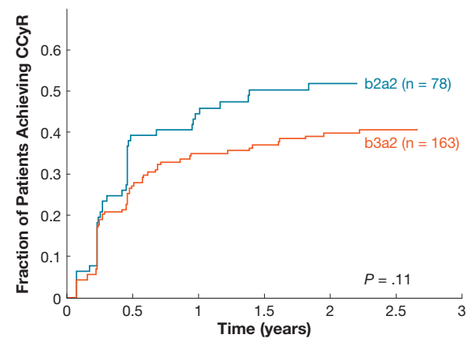
RESULTS

Table 1. Best Response to Nilotinib by Transcript Type

		Best Response					
	All Patients	Complete Hematologic Response (CHR) n (%)	Complete Cytogenetic Response (CCyR) n (%)	Partial Cytogenetic Response (PCyR) n (%)	Major Molecular Response (MMR) n (%)	Progression-Free Survival (PFS) at 24 Months n (%)	Baseline Mutation n (%)
b3a2	163	131 (80.4%)	52 (31.9%)	18 (11.0%)	39 (23.9%)	56 (34.4%)	76 (46.6%)
b2a2	78	70 (89.7%)	34 (43.6%)	9 (11.5%)	20 (25.6%)	32 (41.0%)	23 (29.5%)
P value: comparing b2a2 vs b3a2 using χ^2 2-sample test		.07	.17		.77	.31	.01

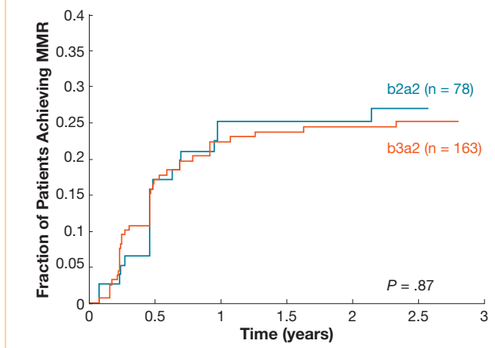
- Transcript type (b3a2 or b2a2) did not influence the response or PFS in patients receiving nilotinib
- The incidence of baseline mutations was higher in patients with b3a2 transcripts compared with b2a2 (*P* = .01)
- Of the three patients with atypical transcripts (b3a3 or e1a2), all achieved CHR, one achieved CCyR, and one achieved PCyR

Figure 2. Time to Complete Cytogenetic Response Based on Transcript Type



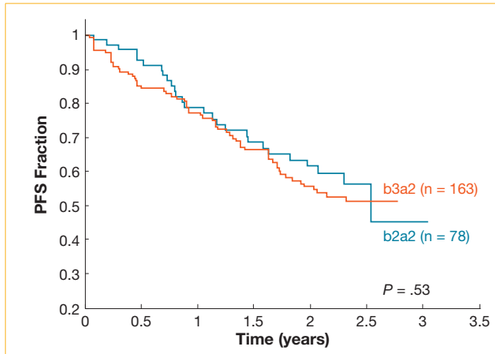
- Cytogenetic response to nilotinib did not exhibit a statistically significant difference between b2a2 and b3a2 transcript types

Figure 3. Time to Major Molecular Response for Different Transcript Types



- Molecular response to nilotinib was similar regardless of transcript type

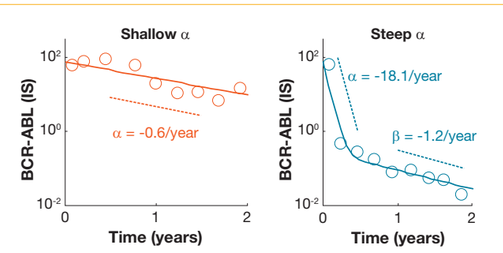
Figure 4. Progression-Free Survival for Different Transcript Types*



* No patient with b3a3 or e1a2 (n = 3) progressed.

- Progression-free survival was similar for b2a2 and b3a2

Figure 5. Mathematical Modeling of BCR-ABL % (IS) Dynamics



	All Patients	Shallow α	Steep α
b3a2	64	44 (68.8)	20 (31.3)
b2a2	38	27 (71.1)	11 (28.9)

- Dynamics of response in patients with b2a2 and b3a2 transcripts were similar

CONCLUSIONS

- The b3a2 and b2a2 BCR-ABL transcript types were observed in the majority of patients
- Regardless of transcript type, hematologic, cytogenetic, and molecular responses were similar in nilotinib-treated patients
- The incidence of baseline mutations was higher in patients with b3a2 transcripts compared with b2a2 (*P* = .01)
- Patients with b3a2 and b2a2 had similar patterns of response to nilotinib and long-term outcomes
- CHR, CyR, MMR, and EFS were not significantly different between the b3a2 and b2a2 patient populations
- Data indicate that nilotinib therapy was effective in patients with imatinib intolerance and resistance with all transcript types, including the atypical transcripts (e1a2, b3a3)

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