

Brief report

Imatinib mesylate therapy in newly diagnosed patients with Philadelphia chromosome-positive chronic myelogenous leukemia: high incidence of early complete and major cytogenetic responses

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Fifty patients with Philadelphia chromosome-positive (Ph⁺) chronic myelogenous leukemia (CML) in early chronic phase received imatinib mesylate, 400 mg orally daily. After a median follow-up of 9 months, 49 patients (98%) achieved a complete hematologic response and 45 patients (90%) achieved a major cytogenetic response, complete in 36 patients (72%). Compared with similar patients

who received interferon- α with or without hydroxyurea or other interferon- α combination regimens, those receiving imatinib mesylate had higher incidences of complete and major (Ph < 35%) cytogenetic responses at 3 months (34% and 74% versus 1%-4% and 9%-24%, respectively), 6 months (52% and 80% versus 3%-7% and 11%-28%, respectively), and 9 months (60% and 77% versus 5%-11% and 14%-

30%, respectively; $P < .001$). Competitive quantitative polymerase chain reaction (QPCR) studies at 9 months showed a median QPCR value (ratio of BCR-ABL/ABL transcripts \times 100) of 0.59% overall and of 0.24% (range, 0.001%-29.5%) for complete cytogenetic response. (Blood. 2003;101:97-100)

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Introduction

The causal association between the Philadelphia chromosome (Ph) and BCR-ABL molecular events and the pathophysiology of chronic myelogenous leukemia (CML) has focused research on strategies that suppress the Ph⁺ cells or the expression of BCR-ABL.¹⁻⁴ These have included allogeneic stem cell transplantation (SCT), interferon α (IFN- α), cytosine arabinoside, and others.⁵⁻¹³ Achieving minimal residual disease (major or complete cytogenetic response) has been independently associated with survival prolongation and has become the therapeutic research goal. Imatinib mesylate (Gleevec, STI571), a selective Bcr-Abl tyrosine kinase inhibitor, has shown activity in all CML phases (blastic, accelerated, chronic after failure of IFN- α).¹⁴⁻²⁰ Herein, we summarize our results, previously reported in abstract form,²¹ in patients with newly diagnosed CML treated with imatinib mesylate 400 mg orally daily, demonstrating high early rates of major and complete cytogenetic responses.

Study design

Study group

Patients with Ph⁺ CML in early chronic phase (diagnosis to therapy < 12 months) were treated; informed consent was obtained according to institutional guidelines. Eligibility criteria were age 15 years or older; Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2; adequate renal (creatinine less than twice upper limit of normal), hepatic (bilirubin less than twice upper limit of normal), and cardiac functions (New York Heart Association cardiac disease grade 3-4 excluded); no prior imatinib mesylate therapy; and no more than 1 month of IFN- α therapy. Women of childbearing potential were required to have a negative

pregnancy test before starting imatinib mesylate; all patients at risk were required to use barrier contraception while on therapy. Chronic-phase CML was defined as less than 15% blasts, less than 20% basophils, and less than 30% blasts plus promyelocytes in the peripheral blood and bone marrow, and platelet counts of $100 \times 10^9/L$ or higher.

Therapy and monitoring

Patients received imatinib mesylate 400 mg orally daily. Patient monitoring and dose reductions of imatinib mesylate for nonhematologic or hematologic toxicities were detailed previously.¹⁸ When possible, patients were not reduced below a minimal daily dose of 300 mg daily. If therapy at this dose resulted in severe myelosuppression (not manageable with growth factors, eg, epoetin alfa [Procrit], granulocyte colony-stimulating factor [G-CSF]), the treatment was interrupted and resumed, rather than the dose reduced to less than 300 mg daily. Severe extramedullary toxicities with doses of 300 mg daily resulted in discontinuation of therapy.

Marrow studies including morphology and cytogenetics or interphase fluorescence in situ hybridization (iFISH) were performed every 3 months; iFISH used the Vysis BCR-ABL ES probe which, in normal controls has a positive mean value of $0.4\% \pm 1.2\%$ (2 SDs); the upper normal limit is 1.5%. The iFISH analysis is conducted on 200 interphases. Competitive quantitative polymerase chain reaction (QPCR) studies were conducted on marrow samples as previously described²²⁻²⁵ (Guo et al, manuscript submitted). The QPCR values were expressed as a ratio-percentage (BCR-ABL/ABL transcripts \times 100). Side effects were graded according to National Cancer Institute (NCI) Common Toxicity Criteria, version 2.0.

Response criteria and statistical considerations

Response criteria were as described.^{6,8} A complete hematologic response (CHR) was defined as white blood cell (WBC) count less than $10 \times 10^9/L$,

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platelets less than $450 \times 10^9/L$, no immature peripheral cells (blasts, promyelocytes, myelocytes), and disappearance of all signs and symptoms related to leukemia, including palpable splenomegaly, lasting for at least 4 weeks. This was further categorized by the best cytogenetic response: complete, Ph^+ 0%; partial, Ph^+ 1% to 34%; and minor, Ph^+ 35% to less than or equal to 90%. A major cytogenetic response included complete plus partial cytogenetic responses (Ph^+ less than 35%). At least 20 metaphases were analyzed for a cytogenetic response to be evaluable. If cytogenetic analysis was not successful, the ratio of iFISH on therapy to pretreatment iFISH was considered for cytogenetic response evaluation.

Historical control groups

These included patients with Ph^+ early chronic-phase CML (diagnosis to therapy < 12 months) treated with IFN- α alone or with hydroxyurea (Hydrea) or IFN- γ (n = 274), IFN- α and low-dose cytarabine (n = 257), or IFN- α with low-dose cytarabine and homoharringtonine (n = 90). These patients had similar follow-up studies as the patients on the current study.

Results and discussion

Study groups

The characteristics of the 50 patients in the study are detailed in Table 1. Their median age was 48 years (range, 15-79 years). The median time from diagnosis to therapy was 1.5 months (range, 0-11 months). Fifteen patients had no prior therapy; 35 patients had received short courses of hydroxyurea (33 patients) or IFN- α (less than 2 weeks; 2 patients).

Response

The median follow-up time is 9 months. One patient discontinued imatinib mesylate after 4 weeks because of recurrent severe hepatotoxicity; 49 patients (98%) achieved CHR (median time to CHR 2 weeks), and all 49 patients (98%) had a cytogenetic response: complete in 36 (72%), partial in 9 (18%), and minor in 4 (8%). The major cytogenetic response rate was thus 90% (45 of 50 patients). When only cytogenetic studies (without complementary iFISH studies) were considered, the cytogenetic response rates were complete in 34 (68%), partial in 9 (18%), and minor in 4 (8%). The complete cytogenetic response rate was 35% after 3 months

Table 2. Major and complete cytogenetic responses at 3, 6, and 9 months on different regimens

Regimen	No. of patients	% cytogenetic response, complete/major		
		3 mo	6 mo	9 mo
Imatinib mesylate for early chronic-phase CML	50	34/74	52/80	60/77
IFN- α	274	4/2	3/11	5/14
IFN- α + cytarabine	257	1/9	7/23	8/23
IFN- α + cytarabine + HHT	90	4/24	7/28	11/30
Imatinib mesylate for chronic phase after IFN- α failure (M. D. Anderson study group) ²⁶	261	26/44	31/49	35/53

and 53% after 6 months of therapy (Table 2). For interest, we also included the results of patients treated at our institution with imatinib mesylate for chronic-phase CML after IFN- α failure.²⁶ Response rates were higher (all values of $P < .001$) than those achieved with IFN- α regimens (Table 2). Currently, 44 patients continue on imatinib mesylate therapy; 6 patients are off study because of development of myeloid blastic phase (n = 2; at 6 and 6 months), hematologic relapse (n = 1; after 6 months of therapy), severe transient liver toxicities (n = 2; after 1 month and 9 months); and noncompliance (n = 1). The 2 patients who developed blastic phase had low risk by the Sokal model. The patient with hematologic relapse had high risk. All patients are alive.

QPCR studies

The QPCR values among patients treated with imatinib mesylate at 9 months on therapy are shown in Figure 1. The median overall QPCR value was 0.59%. Among 27 patients tested in complete cytogenetic response the median QPCR value was 0.24% (range, 0.001%-29.6%); 7 of them (26%) had a QPCR value less than 0.04%, and 21 (78%; 54% of 39 patients tested) had QPCR values less than 1%. Two patients in complete cytogenetic response had high QPCR values above 10%; the iFISH studies showed 1% and 3.5% positivity. The significance of this finding is unknown; it may be related to high BCR-ABL/ABL expression in resting nondividing cells and may be potentially predictive of relapse.

Table 1. Characteristics of the study groups

	Imatinib (N = 50) (%)	IFN- α (N = 274) (%)	IFN- α + ara-C (N = 257) (%)	IFN- α + ara-C + HHT (N = 90) (%)	P	P for imatinib versus all IFN- α regimens
Patient characteristics						
Age older than 60 y	13 (26)	34 (12)	28 (11)	4 (4)	.002	.004
Male	26 (52)	166 (61)	146 (57)	46 (51)	NS	NS
Splenomegaly	11 (22)	116 (42)	72 (28)	26 (29)	.001	NS
Hemoglobin less than 12g/dL	19 (38)	107 (39)	95 (37)	28 (31)	NS	NS
WBC count more than $50 \times 10^9/L$	11 (22)	143 (52)	86 (33)	20 (22)	<.001	.02
Platelets more than $450 \times 10^9/L$	17 (34)	122 (44)	81 (32)	29 (32)	.01	NS
Peripheral blasts (any)	14 (28)	94 (34)	66 (26)	17 (19)	.02	NS
Marrow blasts more than 5%	0 (0)	11 (4)	11 (4)	2 (2)	NS	NS
Peripheral basophils 7% or higher	10 (20)	46 (17)	42 (16)	16 (18)	NS	NS
Marrow basophils 4% or higher	12 (24)	63 (23)	28 (11)	19 (21)	.02	NS
Cytogenetic clonal evolution	0 (0)	5 (2)	20 (8)	4 (4)	NS	NS
Risk group (Sokal model)						
Good	25 (51)	124 (52)	111 (56)	34 (53)	NS	NS
Intermediate	13 (26)	58 (24)	52 (26)	24 (37)		
Poor	11 (22)	54 (23)	34 (17)	6 (9)		
Unknown	9	38	60	26		

HHT indicates homoharringtonine; and NS, not significant.

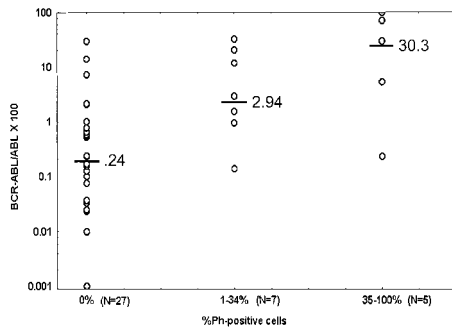


Figure 1. Competitive quantitative PCR values at 9 months on imatinib mesylate therapy by cytogenetic response. Horizontal markings on graphs are median values.

Side effects

Side effects of imatinib mesylate were similar to those reported in previous trials.¹⁸ Grade 3 to 4 toxicities were skin rashes in 6%, muscle cramps or aches in 2%, fatigue in 2%, and liver function abnormalities in 4%. Myelosuppression-associated complications were granulocytopenia less than $0.5 \times 10^9/L$ in 20%, thrombocytopenia less than $50 \times 10^9/L$ in 8%, and anemia less than 9 g/dL in 8%. These required dose interruptions ($n = 1$) or reductions to 300 mg daily ($n = 2$), but no patient had to discontinue therapy permanently because of myelosuppression.

This study demonstrates the superior efficacy of imatinib mesylate compared with IFN- α regimens in relation to previously defined early surrogate end points for long-term prognosis with IFN- α therapy³⁻¹¹ but not yet convincingly with imatinib mesylate therapy^{18,19} (Table 2). The incidence of complete cytogenetic response with imatinib mesylate was 72% overall and 60% at 9 months of therapy (versus 4% to 11% with IFN- α). A randomized study of imatinib mesylate versus IFN- α plus cytosine arabinoside (ara-C) in early chronic phase showed better cytogenetic response rates (major 63% versus 10%, complete 40% versus 2%, respectively, at 6 months; $P < .001$), lower failure rates, and fewer side effects with imatinib mesylate therapy.²⁷

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