Imatinib mesylate in Philadelphia chromosome-positive, chronic-phase myeloid leukemia after failure of interferon alpha

E. TÓTHOVÁ[1], A. KAFKOVÁ[1], M. FRIČOVÁ[1], B. BEŇOVÁ[1], G. KIRSCHNEROVÁ[2], A. TÓTHOVÁ[2]

[1]*Department of Hematology and Oncohematology, e-mail: etothova@post.sk, LF UPJŠ and University Hospital, Košice, Slovak Republic;* [2]*Cytogenetic Department of National Cancer Institute, Bratislava, Slovak Republic*

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Imatinib mesylate (STI 571; Glivec) is a potent and selective tyrosine kinase inhibitor. The introduction of imatinib has chanced the philosophy of mechanisms of cancer therapy and already changed current management of patients with chronic myeloid leukemia (CML).

A total of 49 patients with later chronic phase CML in whom previous therapy with interferon alpha had failed were treated with 400 mg of oral imatinib daily. Patients were evaluated for hematologic and cytogenetic responses. Time to progression, survival, and toxic effects were also evaluated.

Complete hematologic responses were reported for 48 of 49 patients studied (98 percent). The median time to a complete hematologic response was 1.2 month; 89% of patients who had a response did so within 4 months. Imatinib induced major cytogenetic responses in 73%; 62% had a complete responses. After a median follow-up of 18 months, CML had not progressed to the accelerated or blast phases in an estimated 98% of patients, and 100 percent of the patients were alive. Grade 3 or 4 nonhematologic toxic effects were manageable. No one of patients discontinued treatment due to of drug-related adverse events, and no treatment-related deaths occurred.

The results of current study indicate that imatinib has a significant therapy benefit in CML patients in whom treatment with IFN alpha had failed. Therefore, has favorably changed the prognosis for patients with chronic myelogenous leukemia.

Key words: chronic myeloid leukemia, cytogenetic response, imatinib mesylate

The causative agent of chronic myeloid leukemia (CML) is the Philadelphia (Ph) chromosome, a reciprocal genetic recombination that creates the acivated tyrosine kinase fusion gene and protein, *bcr/abl.*

The *bcr/abl* protein is a constitutively active protein tyrosine kinase with an important role in the regulation of cell growth [1–3, 6]. Therapy for Ph positive CML has induced strategies that simply control the leukocyte count (e.g., busulfan, hydroxyurea), eliminate Ph-positive cells by replacing them with allogeneic donor cells (e.g., allogenetic stem cell transplant-SCT), or suppress nonspecificaly the Ph-positive cells (e.g. interferon alpha) [10–12, 22]. Allogeneic SCT is reported to produce longterm, disease-free survival in aproximately 40–80% of patients (pts) treated in chronic phase (depending on patient age, donor source and degree of matching and other factors). However, it is linked to an inherent mortality risk (10–40%), as well as significant morbidities [7–9, 24, 25]. Treatment with interferon alpha can induce a complete cytogenetic response in 5 to 25 percent of pts and result in longer survival than that achievable with chemotherapy, but it is associated with serious toxic effects [23–25]. Imatinib mesylate (Glivec), formerly called STI 571, is a potent and selective competitive inhibitor of bcr/abl protein tyrosine kinase. After an initial phase I dose-escalation study of imatinib in pts with CML, a phase II study involving 532 pts with late chronic-phase, CML who had had an unsatisfactory response to interferon alpha was conducted that used a dose of 400 mg of oral imatinib once daily [4, 5, 7]. Imatinib was well tolerated, and 60 percent of pts had a cytogenetic response; 41 percent had a complete cytogenetic response [9, 13–15].

On the basis of the results of antileukemic activity of

imatinib in preclinical and clinical models, we conducted study of imatinib in pts with CML in whom treatment with interferon alpha had failed.

Material and methods

Characteristics of patients. Patients with CML in the chronic phase (defined by the presense of less than 15 percent blasts; less than 30 percent blasts plus promyelocytes in the peripheral blood and bone marrow and a platelet count of at least $100x10^9$/l) were eliglible if they were 18 years of age or older, if they tested positive for the Ph chromosome, and if treatment with interferon alpha had failed. Hematologic failure was defined as either hematological resistance (failure to achieve a complete hematologic response after at least six months of interferon treatment) or relapse after a complete hematologic response had been achieved. Cytogenetic failures were defined as either cytogenetic resistance (at least 65 percent of cells in metaphase were Ph chromosome positive after at least one year of interferon therapy), or relapse after a major cytogenetic response (MCR) had been achieved. A relapse was considered to have occured if the proportion of Ph chromosome positive cells in metaphase increased by at least 30 percent or to at least 65 percent [9, 17, 18]. Intolerance of IFN was defined by the presence of any nonhematologic toxic effect of grade 3 or higher (according to the National Cancer Institut's Common Toxicity Criteria) that persisted for more than one month during therapy with IFN alpha at a dose of 25 MIU units or more per week. Patients with a platelet count of less than $100x10^9$/l were excluded; adequate renal, hepatic, and cardiac function and performance status were required.

Study design. Doses of imatinib were administered orally once daily at a dose of 400 mg. No other cytoreductive agents were applied during the study. Complete blood counts were performed once a week during the first four weeks, and than once every two weeks. Assessments of bone marrow, including cytogenetic analyses, were performed after 4 weeks of therapy and then once every 3 months.

Asessment of toxicity. Safety assessments included the evaluation of adverse events, hematologic assessment, biochemical testing, urinalysis, and physical examination. Toxicity was graded in accordance with the common toxicity criteria of the National Cancer Institute [20].

Response criteria. The primary efficacy and point was the rate of major cytogenetic response (MCR), which was categorized as complete (CCR) (no cells positive for the Ph chromosome in metaphase in bone marrow) plus partial (PCR) 1 to 34 percent Ph-chromosome-positive cells in metaphase. Other categories of cytogenetic response were minor response (35 to 90 percent Ph-chromosome-positive cells in metaphase) (mCR), and no response (NR), more than 90 percent chromosome positive cells in metaphase. Evaluation of the cytogenetic response was based on the examination of at least 20 cells in metaphase in marrow by standard cytogenetic analysis, FISH and PCR [20].

Secondary efficacy and points were the rate of complete hematologic response (CHR), the time to progression, and overall survival (OS).

A complete hematologic remission required normalization for at least 4 weeks of the bone marrow (≤5% blasts) and peripheral blood (leucocytes $<10x10^9$/l and platelets $<450x10^9$/l, without peripheral blasts, promyelocytes, or myelocytes), in addition to the disappearance of all signs and symptoms of CML. Time to progression (TTP) was defined as the time from the start of treatment to the onset of an accelerated or blastic phase, discontinuation of therapy because of unsatisfactory therapeutic effect, or death. Survival (OS) was calculated from the time the treatment began until death from any cause or last follow-up [16].

Results

From January 1999 to April 2004, 49 patients in whom treatment with interferon alpha had failed, or who could not tolerante the drug, were enrolled at the study.

The characteristics of the pts are summarized in Table 1. Of the 49 pts, 16 had hematologic resistance or relapse, 25 had cytogenetic resistance or relapse, and 8 could not tolerante interferon alpha. The median time to a complete hematologic response was 1.2 months; 89 percent of pts who had response did so within 4 months. Imatinib induces major cytogenetic responses in 36 of 49 pts (73%) and 62% (30/49) of pts had a complete response tested negative for *bcr/abl* by fluorescence *in situ* hybridization, and 29 pts tested negative for bcr/abl messenger RNA (mRNA) by the polymerase chain reaction (Tab. 2). Cytogenetic response occured as early as 3 months and as late as 11 months after the initiation of treatment with imatinib. The median time to the best cytogenetic response (the lowest percentage of cells in metaphase that were positive for the Ph chromosome) was 146 days. After a median follow-up of 18 months, CML had not progressed to the accelerated or blast phase in an estimated 98% of patients, and 100% of the pts were alive. Patients who started therapy within 12 months of diagnosis and those with <90% Ph-positive cells before therapy had significantly higher response rates. Patients with IFN alpha intolerance or with hematological or cytogenetic relapse responded better than those with hematological or cytogenetic resistance.

Safety. Adverse events related to treatment with imatinib mesylate are in Table 3 and 4.

Grade 3 or 4 nonhematologic toxic effects were manage-

Table 1. Patients characteristics

Characteristics	Patients with confirmed diagnosis of CML			
	HF n=16	CF n=25	IFN-I n=8	All pts n=49
AGE (year)				
median	61	53	55	54
(range)	(24–66)	(20–54)	(31–59)	(20–66)
SEX				
male/female	9/7	14/11	4/4	27/22
Splenomegaly	5	1	3	9
Hemoglobin g/l				
median	96	124	123	125
(range)	(70–135)	(90–140)	(100–126)	(70–140)
Leukocytes $x10^9$/l				
median	18	8	11	15
(range)	(24–91)	(7–12)	(4–23)	(7–91)
Platelets $x10^9$/l				
median	375	361	296	303
(range)	(210–410)	(270–372)	(146–301)	(146–410)
BM basophilia ≥3%	2	0	1	3
Cytogenetic clonal evolution	2	0	1	3

HF – hematologic failure, CF – cytogenetic failure, IFN-I – intolerance of on IFN based therapy, pts – patients, n – number of patients

Table 2. Response to imatinib mesylate therapy

Response	percent (95% CI)			
	HF	CF	IFN-I	All pts
Complete hematologic[1]	96.3	98.6	97.6	98
Major cytogenetic[2]	67.3	73.1	77.2	73
complete cytogenetic	56	61	69.2	62
partial cytogenetic	11.3	12.1	8	10.5

[1]The level of cytogenetic response was defined by the percentage of Philadelphia-chromosome-positive cells in metaphase: Complete response, 0 percent; partial response, 1 to 35 percent. [2]A major cytogenetic response was defined as a complete and partial response. CI – confidence interval, HF – hematologic failure, CF – cytogenetic failure, IFN-I – intolerance of on IFN based therapy, pts – patients

able. Grade 3 or 4 neutropenia was noted during the study in 17.1 percent of the pts, and thrombocytopenia was found in 19 percent of patients (Tab. 4). The median time to a first grade 3 or 4 episode of neutropenia was 59 days (range, 9 to 216); the median time to a first grade 3 or 4 episode of thrombocytopenia was 54 days (range, 8 to 272). No one of pts discontinued treatment because of drug-related adverse events, and no treatment-related deaths occurred.

Table 3. Adverse events* (hematologic)

Adverse event	All grades %	Grade 3 or 4 %
Anemia	41	4.2
Neutropenia	35	17.1
Trombocytopenia	37	19

*Adverse events include conditions that worsened from base line or developed during initial treatment in more than 10 percent of the patients and were graded according to the common toxicity criteria of the National Cancer Institute.

Table 4. Adverse events (nonhematologic)

Adverse event	All grades %	Grade 3 or 4 %
Superficial edema	57	0.6
Nausea	4.1	3
Muscle cramps	31	0.2
Musculosceletal pain	21	0.4
Fatigue	11	0.7
Diarrhea	2	1.2
Headache	13	3.1
Joint pain	26	4.4
Myalgia	21	0.7
Upper respiratory tract infection	14.1	0.4
Weight gain	20	0.4
Depression	10.1	0.3
Anxiety	8.4	1.1
Influenza-like illnes	7	1.1
Stomatitis	2.1	0.2
Dry mounth	2.2	0

Discussion

The presence of the *bcr/abl* fusion protein in virtualy all pts with CML and its required tyrosine kinase (TK) activity, make CML ideal for testing a specific inhibitor of this enzyme. KANTARJIAN et al [14] published results of a large multicenter trial including 454 patients with CML who had failed prior therapy with interferon alpha. At the latest update, 65% patients achieved a major cytogenetic, most of these (48%) constitued complete cytogenetic response with the other 17% being partial response. One important observation was that patients with an earlier response (MCR at 3 months) had a significantly longer progressions-free survival. In our study the rates of major and complete cytogenetic responses were 73% and 62%, respectively. Treatment was well tolerated; serious drug-related adverse events ocurred in less than 5 percent of pts, and hematologic toxic effects were manageable.

The rates of major and complete cytogenetic responses we observed were higher than those reported in patients treated with interferon (15 percent and 5 to 7 percent, respectively) or in combination with low-dose cytarabine [20, 21, 24].

The estimated 18-months progression-free survival rate of 89 percent is also higher than in trials of interferon.

Our results cannot be attributed to a bias in favor of patients with a favorable prognosis, since the factors associated with a poor prognosis in this trial were similar to those of other studies of pts with CML in the late chronic phase. In these published series, the failure of interferon therapy was also predictive of a poor subsequent outcome, with an annual mortality rate of 10 to 20 percent [15, 16, 20, 25].

Higher cytogenetic response rates to imatinib mesylate therapy were observed in patients who had experienced relapse or had been intolerant to IFN alpha therapy than in those treated for cytogenetic or hematological resistance. Similarly, better responses were noted in pts with less aggressive form of disease (normal platelet count, low blast and basophil levels, and no cytogenetic clonal evolution) or those treated within 12 months from diagnosis.

The results of the current study indicate that imatinib offer a significant therapy benefit in CML pts in whom treatment with IFN alpha had failed.

Combinations of imatinib mesylate with IFN alpha, cytarabine, homoharringtonine, decitabine, or other compounds hopefully will further improve the complete cytogenetic and molecular response rates and thus the long-term prognosis for patients with this disease.

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