Chronic myeloid leukemia in blast crisis treated with imatinib 600 mg: outcome of the patients alive after a 6-year follow-up

Francesca Palandri,[1] Fausto Castagnetti,[1] Nicoletta Testoni,[1] Simona Luatti,[1] Giulia Marzocchi,[1] Simona Bassi,[2] Massimo Breccia,[3] Giuliana Alimena,[3] Ester Pungolino,[4] Giovanna Rege-Cambrin,[5] Riccardo Varaldo,[6] Maurizio Miglino,[6] Giorgina Specchia,[7] Eliana Zuffa,[8] Felicetto Ferrara,[9] Monica Bocchia,[10] Giuseppe Saglio,[5] Fabrizio Pane,[11] Daniele Alberti,[12] Giovanni Martinelli,[1] Michele Baccarani,[1] and Gianantonio Rosti[1] on behalf of the GIMEMA Working Party on Chronic Myeloid Leukemia

[1]Department of Hematology/Oncology "L. and A. Seràgnoli" S.Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy; [2]Division of Hematology, AIEOP, Milano, Italy; [3]Department of Cellular Biotechnology and Hematology, University "La Sapienza", Rome, Italy; [4]Division of Hematology, Ospedale Niguarda, Milano, Italy; [5]Department of Clinical and Biological Science, University of Turin at Orbassano, Torino, Italy; [6]Division of Hematology, San Martino Hospital, Genova, Italy; [7]Division of Hematology, Bari, Italy; [8]Division of Hematology, Ravenna, Italy; [9]Division of Hematology, Napoli, Italy; [10]Hematology Section, University of Perugia, Italy; [11]CEINGE Biotecnologie Avanzate and Department of Biochemistry and Medical Biotechnology, University of Naples Federico II, Napoli, Italy; [12]Novartis Pharmaceutical, East Hanover, NJ, USA

ABSTRACT

Background
Imatinib mesylate is the first line treatment for chronic myeloid leukemia. In patients with advanced phase of the disease, the advent of imatinib significantly increased survival. However, few long-term data, based on large, prospective and controlled trials are available on the outcome of these patients.

Design and Methods
We conducted a phase II trial of imatinib 600 mg daily in patients with chronic myeloid leukemia in blast crisis. The return to chronic phase was defined as <15% blasts and <30% blasts plus promyelocytes in blood or bone marrow and <20% peripheral basophils. A complete hematologic response required the normalization of platelet and white cell differential counts and absence of extramedullary involvement. Cytogenetic response was assessed by the standard banding technique and rated as usual.

Results
Ninety-two patients were enrolled (20 with lymphoid blast crisis and 72 with myeloid blast crisis). Forty-six patients (50%) returned to chronic phase, and 24 patients (26%) achieved also a complete hematologic response. Sixteen patients (17%) had a cytogenetic response (9 complete, 1 partial, and 6 minor or minimal). The complete cytogenetic response was subsequently lost by all but two patients between 2 and 12 months after first having achieved it: the median duration of complete cytogenetic response was 7 months. All responses were sustained for a minimum of 4 weeks. The median survival of all the patients was 7 months. After a median observation time of 66 months, seven (8%) patients are alive. Three of these patients are on imatinib treatment (1 in complete hematologic remission, 1 in partial cytogenetic response and 1 in complete cytogenetic remission). Three patients are in complete remission after allogeneic stem cell transplantation. One patient is alive in blast crisis, on therapy with a second-generation tyrosine kinase inhibitor.

Conclusions
Imatinib was effective and safe in the short-term treatment of chronic myeloid leukemia in blast crisis, but longer-term outcome was not significantly influenced (ClinicalTrials.gov identifier: NCT00514969).

Key words: chronic myeloid leukemia, blast crisis, imatinib, outcome, long-term.

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Correspondence:
Gianantonio Rosti,
Institute of Hematology and Medical Oncology "L. and A. Seràgnoli",
S. Orsola-Malpighi University Hospital, via Massarenti, 9
40138 Bologna, Italy.
E-mail: gianantonio.rosti@unibo.it

Introduction

Blast crisis (BC) is the terminal phase of chronic myeloid leukemia (CML), a clonal myeloproliferative disease characterized by a reciprocal t(9;22)(q34;q11) chromosomal translocation, which creates the Philadelphia chromosome (Ph) and leads to the expression of the BCR-ABL fusion protein, whose deregulated constitutive tyrosine kinase activity is responsible for leukemogenesis. In more than 95% of the patients, blast crisis is preceded by an initial period of chronic phase CML. While *BCR-ABL* gene expression is sufficient to promote the chronic phase phenotype, progression to blast crisis depends on genomic instability, with accumulation of additional genetic changes, which leads to loss of differentiation and to a more aggressive clinical presentation. Treatment of BC-CML with chemotherapy regimens inherited from therapeutic experience in acute leukemias, produces only temporary benefits, if any.[1,2] Allogeneic stem cell transplantation induces a durable remission in less than 10% of patients, with overall survival at 2 years ranging from 16% to 22%.[3]

In 2000, the introduction of imatinib mesylate (Glivec; Novartis Pharmaceuticals, NJ, USA), a small molecule that selectively inhibits the BCR-ABL tyrosine kinase, provided a new option for the treatment of BC-CML.[4] In the light of the favorable results of the phase I/II studies on imatinib, in 2001 the Italian Cooperative Study Group on CML (now GIMEMA Working Party on CML) conducted a phase II trial to confirm the activity and safety of imatinib 600 mg in the treatment of BC-CML. The reported 6-year follow-up is the longest in this setting of patients. This cohort of patients is consequently a valuable source of data for the assessment of the very long-term compliance to and efficacy of imatinib therapy, covering response duration and survival, and for the characterization of the prognostic factors associated with a favorable outcome.

Design and Methods

Patients

From June 2000 to April 2001, 92 patients with confirmed Ph-positive BC-CML were enrolled into a prospective study (CML/003/STI571) which was designed, sponsored and carried out by the Italian Cooperative Study Group on CML according to good clinical practice and the principles of the Helsinki declaration. Informed consent was obtained from the participants according to institutional guidelines. The primary end-point of the study was to determine the rate of sustained hematologic responses in adult patients with Ph-positive CML in accelerated and blast phase; the secondary end-point was the assessment of the duration of hematologic and cytogenetic responses and overall survival, and the safety of the study drug. To be eligible, patients had to (i) have morphologic and cytogenetic evidence of Ph-positive BC-CML; (ii) be 18 years or older; (iii) have an adequate performance status (level 0 to 2 on the World Health Organization Scale); (iv) have normal renal function; and (v) normal hepatic function. Exclusion criteria included: (i) childbearing potential wihout a negative pregnancy test prior to initiation of the treatment; (ii) previous treatment with antileukemic agents, if sufficient time had not elapsed for potential recovery of the nadir in blood counts to have occurred; (iii) grade 3/4 cardiac disease; (iv) a history of non-compliance to medical regimens or patients considered potentially unreliable. All patients were naïve to imatinib treatment, and represented an estimated 50% of all the new cases of CML in blast crisis diagnosed in Italy in this period.

Chromosome banding analysis was used to confirm the presence of Ph-positive metaphases and to identify other chromosomal abnormalities. Blast crisis was defined as the presence of 30% blasts in blood or marrow and/or the presence of extramedullary disease (other than liver or spleen enlargement). The definition of the myeloid or lymphoid phenotype was confirmed by flow cytometry. Imatinib was given at a starting dose of 600 mg daily. Treatment was continued until disease refractoriness or progression, death, or treatment failure from other causes.

Response definitions and statistics

The return to chronic phase was defined as less than 15% blasts and less than 30% blasts plus promyelocytes in blood or bone marrow and less than 20% peripheral basophils. A complete hematologic response required the normalization of platelet and white cell differential counts and the absence of extramedullary involvement. The cytogenetic response was assessed by chromosome banding analysis prior to treatment and at 1-3 month intervals thereafter, and rated as described elsewhere.[5] Hematologic and cytogenetic responses needed confirmation after a minimum period of 4 weeks (sustained responses). Survival analysis was based on the Kaplan-Meier method.[6] Differences among groups were compared by the log-rank test.[7] Comparison of frequencies were calculated with the χ^2 test or the Fisher's exact test, as appropriate.

Results

Patients' characteristics

The pre-treatment characteristics of the 92 patients are listed in Table 1. The median age at the start of imatinib was 55 years (range 18-88); 59 patients (64%) were male and 33 female.

Twenty-seven out of the 92 (29%) patients had received intensive chemotherapy prior to imatinib; eight patients presented evidence of extramedullary disease and 36 (39%) had a performance status of 2. Clonal evolution with additional chromosomal aberrations was observed in 20 patients (22%), including trisomy 8 (1 patient), a second Ph chromosome (2 patients), isochromosome 17 (1 patient), deletion 9 (1 patient), and single additional alterations (4 patients). Variant translocations were discovered in one case and ten patients had a complex karyotype with at least three additional chromosomal aberrations (4 of whom carried trisomy 8).

Safety

Non-hematologic grade 3-4 side effects included nausea and vomiting (3%), liver dysfunction (6%), skin rash (4%) and fluid retention and edema (9%). Hematologic reactions were difficult to separate from the pre-treatment degree of myelosuppression: febrile episodes due to grade 3-4 neutropenia were recorded in 13 patients (17%), 30 patients required platelet transfusions and one patient died because of cerebral hemorrhage, while severely thrombocytopenic.

Efficacy

All 92 patients were included in the efficacy analysis. Eighteen (20%) patients were previously untreated; 57 (62%) patients had received therapy with interferon-α, hydroxyurea and/or cytarabine, whereas 27 (29%) patients had previously received intensive chemotherapy (including conventional induction chemotherapy, autologous and/or allogeneic stem cell transplantation). Table 2 shows a summary of the hematologic and cytogenetic responses of all 92 patients and after stratification according to prior treatment. Forty-six patients (50%) returned to chronic phase, and 24 patients (26%) also achieved a complete hematologic remission. Responses usually occurred early after the start of treatment: of the 46 patients with a return to chronic phase, 31 (68%) achieved their first response within 1 month of imatinib therapy. The return to chronic phase was subsequently lost by 22 patients, for a median duration of the second chronic phase of 11 months (range, 1-67). Sixteen patients lost the complete hematologic response, for a median duration of the hematologic response of 6 months (range 1-43). Sixteen patients (17%) had a cytogenetic response (9 complete, 1 partial, and 6 minor or minimal). The median time to complete cytogenetic response was 3 months (range, 1-11 months). The complete cytogenetic response was subsequently lost by all but two patients between 2 to 12 months after it had first been achieved, for a median complete hematologic response duration of 7 months. No patient underwent dose escalation to 800 mg.

Survival

Overall survival for the entire group and patients divided according to the type of blast crisis (myeloid, 72 patients; lymphoid, 20 patients) is shown in Figure 1A. The Kaplan-Meier[5] median survival time was 7 months, and the survival rates were 53% at 6 months (95% CI, 43%-63%), 29% at 12 months (95% CI, 19%-39%), 23% at 18 months (95% CI, 14% to 33%) and 11% at 36 months (95% CI, 4%-18%). There were no differences in terms of survival between patients in myeloid or lymphoid blast crisis (p=0.4); however, the number of patients with lymphoid blast crisis was small (n=20).

Eighty-five patients (92%) have died: 78 (92%) because of BC-CML after 0.5 to 58 months of imatinib treatment (median, 6 months), 6 patients from complications after allografting and 1 patient while in chronic phase (myocardial infarction). Nine patients underwent allogeneic stem cell transplantation: eight patients in blast crisis, after 1 to 37 months of imatinib therapy (median, 2.5 months) and one patient after 3 years of

Table 1. Patient and disease characteristics at the start of imatinib treatment.

Characteristics	*All patients*	*Myeloid BC*	*Lymphoid BC*
Total, n.	92	72	20
Male/female, n.	59/33	45/27	14/6
Age at start of imatinib therapy			
median, yrs. (range)	55 (18-88)	57 (18-88)	52 (31-74)
60 or older, n.	41 (45%)	33 (46%)	8 (40%)
Median time from first diagnosis of CML to BC, months (range)	36 (0-307)	39 (0-307)	24 (0-161)
Median time from diagnosis of BC to start of imatinib, months (range)	2 (0-25)	2 (0-25)	3 (1-22)
Median hemoglobin value, gr/dL (range)	9.5 (6.3-13.6)	9.2 (6.3-13.6)	10.8 (7.6-13.3)
Median platelet count, 10^9/L (range)	109 (4-1000)	137 (4-1000)	76 (10-1000)
Median peripheral blast, % (range)	28.5% (0-96%)	26.5% (0-92%)	33% (0-96%)
Other chromosomal abnormalities at start of imatinib, no. (%)	20 (22%)	17 (24%)	3 (15%)
Extramedullary involvement	8 (9%)	5 (7%)	3 (15%)
Performance Status (WHO)			
0-1	56 (61%)	42 (58%)	14 (70%)
2	36 (39%)	30 (42%)	6 (30%)
Prior chemotherapy (conventional chemotherapy, autologous and allogeneic stem cell transplantation)			
none	65 (71%)	53 (74%)	12 (60%)
1 or more	27 (29%)	19 (26%)	8 (40%)

Table 2. Hematologic and cytogenetic responses according to immunophenotype and to previous treatment.

		Blast type[a]		*Previous treatment with intensive chemotherapy*[b]	
Type of response	*Total n.*	*Myeloid*	*Lymphoid*	*No*	*Yes*
Total n.	92	72	20	65	27
Hematologic response, n.					
RTC	46 (50%)	34 (47%)	12 (60%)	33 (51%)	13 (48%)
CHR	24 (26%)	17 (24%)	7 (35%)	17 (26%)	7 (26%)
Cytogenetic response, n.					
Complete	9 (10%)	5 (5%)	4 (20%)	6 (9%)	3 (11%)
Partial	1 (2%)	0	1 (5%)	0	1 (3.5%)
Minor–Minimal	6 (5%)	3 (4%)	3 (15%)	4 (6%)	2 (7%)
Overall	16 (17%)	8 (11%)	5 (25%)	10 (15%)	6 (22%)

Responses were confirmed for a minimum of 4 weeks. RTC: return to chronic phase. CHR: complete hematologic response. [a]Patients treated in myeloid and lymphoid blast crisis had the same rates of hematologic (p=0.44, Fisher's exact test) and of cytogenetic (p=0.14) responses. [b]Patients who received imatinib after intensive chemotherapy (induction chemotherapy, autologous and/or allogeneic stem cell transplantation) had the same rates of hematologic (p=1) and cytogenetic (p=0.54) responses as the other patients.

continuous complete cytogenetic remission. The other patients were not submitted to allogeneic transplantation because of fully active disease (56 patients), age older than 60 (14 patients), or unavailability of a donor (13 patients). At a median observation time of 66 months, seven (8%) patients are alive: three patients are still on treatment with imatinib at the scheduled dose (1 in complete hematologic remission, 1 in partial cytogenetic remission and 1 in complete cytogenetic remission). Three patients are in complete remission after allogeneic stem cell transplantation. One patient is alive in blast crisis, on therapy with a second-generation tyrosine kinase inhibitor, initiated because of loss of the hematologic response 51 months after the start of imatinib therapy.

Univariate (log-rank) analyses[7] were used to test for the effects of several baseline variables on survival. Results of those log-rank analyses indicated that a lower percentage of peripheral blasts (<50%) and better performance status (<2) were associated with prolonged survival. As expected, patients who achieved a hematologic response or a major cytogenetic response benefited most from imatinib therapy. The median survival time for the 46 patients achieving a hematologic response was 12 months (*vs.* 5 months in patients without any hematologic response, p=0.0001, Figure 1B), whereas the median survival was 20.5 months for the ten patients who achieved a major cytogenetic response and 6 months for patients without such a response (p=0.001, Figure 1C).

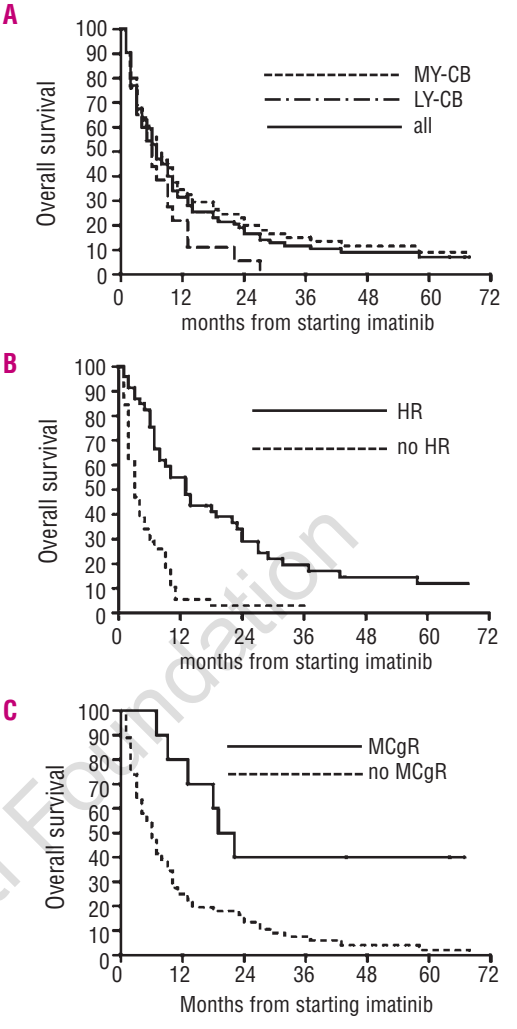

Figure 1. Overall survival of patients according to the phenotype (A) and to the hematologic (B) and the cytogenetic (C) response. Survival was calculated from the initiation of treatment for BC-CML until death or last follow-up, whichever came first. Patients who underwent allogeneic stem cell transplantation were censored at the date of transplantation. Overall survival was comparable for patients treated in lymphoid blast crisis (LY-BC) and in myeloid blast crisis (MY-BC), but was significantly better for patients achieving a hematologic response (HR) or a major cytogenetic response (MCgR).

Discussion

Imatinib was first tested for the treatment of CML in advanced phase 8 years ago, to determine whether this drug could induce higher rates of hematologic and cytogenetic responses than those induced by conventional chemotherapy. The reported outcome of these patients, treated with imatinib alone at variable doses, showed an incidence of hematologic improvement ranging from 52% to 62%, with 16% to 30% of patients obtaining a complete hematologic response and 3% to 16% of the patients also achieving a major cytogenetic response,[8-11] with a median survival ranging from 6 to 7.5 months.

We report the long-term outcome of 92 BC-CML patients homogeneously treated with imatinib 600 mg/daily. Response rates were comparable to those reported in the literature, with 50% and 12% of the patients obtaining a hematologic or major cytogenetic response, respectively. Among the baseline characteristics tested for association with survival, only better performance status (<2) and lower peripheral blast count (<50%) had significant impacts on survival in multivariate analysis, probably reflecting the severity of the disease. Imatinib treatment in this setting of patients was associated with several adverse events, as expected, because BC-CML is burdened by a considerable morbidity. Non-hematologic side-effects were, however, generally mild and manageable with temporary dose-reductions; no treatment-related deaths occurred. However, after a median follow-up of more than 5 years, only 7% of the study population were still alive, with 3% of the patients continuing imatinib therapy at the scheduled dose, without toxicity.

Since 2001, the mechanisms of resistance to imatinib have been at least partially elucidated[5,12,13] and many studies are ongoing, investigating combinations of imatinib with other drugs[14-17] and the role of second-generation tyrosine kinase inhibitors.[18-21] Unfortunately, we have no data on the mutational status of *BCR-ABL* before and during imatinib therapy, which might have shed some light on the causes of primary and secondary resistance, since this study accrued patients at a time when mutational status was still highly experimental and not available in most of

the molecular biology labo-ratories collaborating with the Italian Cooperative Study Group. This final analysis of a multicenter experience confirms that imatinib as monotherapy provides hematologic control in BC-CML with an acceptable level of toxicity. However, the relapse rate was high and the longer term clinical outcome was not significantly influenced, comparing the present results (median and long-term survival) with previous results obtained with conventional chemotherapy. Further studies are warranted to investigate induction treatment of BC-CML based on combination therapy or sequential use of second-generation tyrosine kinase inhibitors with other agents, and to explore new strategies for patients who initially respond but do not have a suitable donor for transplantation.

Authorship and Disclosures

FP: collected data and wrote the manuscript; MB, GR: designed and supervised the study and gave final approval of the manuscript; FC, NT, SB, AML, MM, MB, EP, RV, GS, GR-C, EZ, FF, MB, GS, FP, GM: contributed to the development of the study and to data collection. GR-C: speaker bureau Novartis and Bristol Myers Squibb; FP: research grant from Novartis, honoraria from Novartis, Bristol Myers Squibb and Roche; GS: advisory board and speaker bureau Novartis and Bristol Myers Squibb, research grant from Novartis; GR: grant and speaker bureau (Novartis), speaker bureau (Bristol Myers Squibb); MB: research grants and honoraria as speaker and consultant from Novartis Pharma. DA is an employee of Novartis.

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