The long-term durability of cytogenetic responses in patients with accelerated phase chronic myeloid leukemia treated with imatinib 600 mg: the GIMEMA CML Working Party experience after a 7-year follow-up

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ABSTRACT

Background

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

Design and Methods

A phase 2 multicenter trial of the use of imatinib 600 mg/daily in patients with accelerated phase chronic myeloid leukemia was sponsored and promoted by the Italian Cooperative Study Group on Chronic Myeloid Leukemia in 2001.

Results

One hundred and eleven patients were enrolled; the median follow-up of the 41 living patients is 82 months (range, 73-87). One hundred and seven patients (96%) returned to chronic phase and 79 patients (71%) achieved a complete hematologic response. Cumulative best rates of major cytogenetic response and complete cytogenetic response were 30% and 21%, respectively. All responses were maintained for a minimum of 4 weeks. At last follow-up, four patients were alive in complete remission after allogeneic transplant, 16 patients (14%) had switched to a second generation tyrosine kinase inhibitor and 21 patients (19%) were alive on imatinib therapy. No late toxicities were observed. Progression-free survival and event-free survival rates were 36.5% and 15%, respectively, at 7 years. The median survival time was 37 months, and was significantly associated with the achievement of a complete hematologic response or a complete cytogenetic response.

Conclusions

Imatinib may induce durable responses, associated with prolonged survival, in patients with accelerated phase chronic myeloid leukemia (*clinicaltrials.gov identifier: NCT00514969*).

Key words: chronic myeloid leukemia, accelerated phase, long-term results, imatinib.

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Introduction

Chronic myeloid leukemia (CML) is a clonal myeloproliferative disease characterized by a reciprocal t(9;22)(q34;q11) chromosomal translocation, which creates the Philadelphia chromosome and leads to the expression of the BCR-ABL fusion protein, whose deregulated constitutive tyrosine kinase activity is responsible for leukemogenesis.[1-3] Most patients present in the chronic phase, in which malignant progenitor cells proliferate rapidly but retain much of their ability to differentiate, with the disease later evolving into the accelerated phase (AP) and blastic crisis.

The AP is an intermediate stage in which patients show signs of disease progression and is characterized by increased refractoriness to standard therapy.[4-7] The acquisition of additional chromosome abnormalities (including trisomy 8 and 19, isochromosome 17q and Philadelphia chromosome duplication) is also a common feature.[8]

In 2000, the introduction of imatinib mesylate provided a new option for the treatment of advanced phase CML.[9,10,11-15] In AP patients, the reported complete hematologic response rates range from 40% to 82%, with major cytogenetic response rates between 24% and 49%.[16-18] These response rates are low, compared to those achieved in chronic phase CML, but significantly higher than those provided by interferon-α or any other agent.[19,20] Patients treated with imatinib also showed a better survival, with 38.8% patients alive at a 48-month follow-up.[16] However, the long-term outcome of these patients has not yet been fully described. In particular, it would be important to confirm whether responses in AP patients who do achieve a hematologic and/or cytogenetic response to imatinib are durable and associated with a significant benefit in terms of overall survival. For this purpose, we report the 7-year follow-up of 111 AP-CML patients, who were enrolled in a phase 2 prospective study of the Italian Cooperative Study Group on CML (now the GIMEMA Working Party on CML) and who were treated with imatinib 600 mg/day.

Design and Methods

Patients

From June 2000 to April 2001, 111 patients with confirmed Philadelphia-positive AP CML were enrolled in a prospective study (CML/003/STI571) which was designed, sponsored and implemented by the Italian Cooperative Study Group on CML according to good clinical practice and the principles of the Helsinki declaration. Informed consent was obtained according to institutional guidelines. The aims of this study were to study the effects of imatinib 600 mg/day in a population of adult patients with Philadelphia-positive CML in accelerated and blastic phase, and in particular to assess the rate of sustained hematologic responses and the duration of hematologic and cytogenetic responses. The safety profile of the drug and the survival of the patients were also evaluated. A total of 92 patients in blast crisis and 111 AP patients were enrolled. None of the patients had previously been treated with imatinib or participated in prior similar studies. The patients enrolled represented an estimated 50% of all new cases of AP-CML diagnosed in Italy in that period.

AP was defined by either 15% to 29% blasts in blood or marrow, or 30% to 49% blasts plus promyelocytes in blood or marrow (provided that less than 30% blasts were present), or at least 20% basophils in the peripheral blood, or thrombocytopenia (platelet count no higher than 100×10^9/L, unrelated to therapy). The presence of chromosome abnormalities additional to the Philadelphia chromosome was an exclusion criterion. The main eligibility criteria were age 18 years or older; adequate performance status (0 to 2), normal renal and liver function and signed informed consent to participation in the study. December 31st, 2007 was the cut-off date for this analysis.

Therapy

Imatinib was given in oral doses of 600 mg/day to all patients. Treatment was continued until disease progression, death, intolerance to imatinib or allogeneic stem cell transplantation (SCT).

Response definitions

A complete hematologic response was defined as the normalization of platelet and white cell differential counts and absence of extramedullary involvement. The definition of return to chronic phase was less than 15% blasts and less than 30% blasts plus promyelocytes in blood or bone marrow and less than 20% peripheral basophils. The cytogenetic response was assessed by chromosome banding analysis (a minimum of 20 metaphases was required) at baseline, at 3-month intervals for the first 12 months and every 6 months thereafter. Depending on the percentage of Philadelphia-positive cells, the cytogenetic response was defined as complete (0%), partial (1-34%), major (0-34%), minor (35-65%), minimal (66-95%), or none (96-100%). Only sustained responses (lasting a minimum of 4 weeks) have been included im the analysis of the data.

Statistical analyses

Survival distributions were estimated by the method of Kaplan and Meier[21] and were compared using the log-rank test.[22] Overall survival was calculated from the start of imatinib treatment for AP-CML to the date of death from any cause or last follow-up, whichever came first. Progression-free survival was calculated from first imatinib intake to progression to blast crisis, death from any cause or last follow-up. Event-free survival was calculated from the first imatinib dose to progression to blast crisis, failure of imatinib therapy (covering the cases of loss/lack of the hematologic/cytogenetic response), death from any cause or last follow-up. Patients who were submitted to allogeneic SCT were censored at the date of transplant in all calculations. The association of hematologic and cytogenetic response with survival was assessed using a landmark at 3 months. Response duration was calculated from the date of the first assessment of the response until the date of response loss or last

contact. The associations of pre-treatment factors with survival were first assessed individually using log-rank test, and then significant factors ($p<0.05$) were included in the final model for multivariate analysis (Cox proportional hazards regression model) to adjust for their prognostic effects. Treatment response rates among subgroups were compared with a two-sided Fisher's exact test or χ^2 test, as appropriate.

Results

Patients' characteristics

The pre-treatment characteristics of the 111 patients are listed in Table 1. The median age of the patients at the start of imatinib treatment was 58 years (range, 26-82); 51 patients (46%) were 60 years of age or older at enrollment. Seventy (63%) were male and 41 female. Eighteen patients (16%) had a Performance Status of 2 on the WHO scale. Eleven patients (10%) presented in AP CML; for the remaining 100 patients, the median duration of the chronic phase prior to progression to AP was 60 months (range, 8-287). Prior to starting imatinib, 29 patients (26%) had received one or more courses of chemotherapy, including intensive induction chemotherapy (n=20), autologous SCT (n=4) or allogeneic SCT (n=5), whereas 82 patients had received interferon-α, hydroxyurea and/or busulfan.

Efficacy

Table 2 summarizes the hematologic and cytogenetic response rates (as best responses achieved, lasting at least 4 weeks) for all 111 patients and after stratification according to age and to treatment(s) before starting imatinib.

Ninety-six percent of the patients returned to chronic phase, and 79 patients (71%) also achieved a complete hematologic response (CHR). The median time to CHR was 2 months (range, 1-7 months), with 80% of the patients achieving the CHR within 3 months from starting imatinib. Forty-three out of 79 patients (54%) lost the CHR, 9 (17%) within 3 months from having first achieved it. Fifty-three patients (48%) obtained a cytogenetic response (23 complete, 10 partial, 6 minor and 14 minimal), for cumulative best rates of major cytogenetic response and complete cytogenetic response (CCgR) of 30% and 21%, respectively. The outcome of the 23 patients who achieved a CCgR is of particular interest: the median time to CCgR was 6 months (range, 1-42 months). The CCgR was subsequently lost by 6/23 patients (26%) 3 to 36 months (median, 10 months) after having first achieved it; 3/23 patients (13%) have died (two in CCgR from causes unrelated to CML, one because of disease progression). Two patients underwent allogeneic SCT (one patient while in CCgR and one after having lost a CCgR) and are in complete remission after their transplants. Three patients switched to therapy with a second generation tyrosine kinase inhibitor after losing their CCgR, while 15/23 (65%) are in continuous response and on imatinib therapy after a median observation time of 73 months (range, 63-83) and with a median CCgR duration of 66 months (range, 41-75). Figure 1 depicts the duration of the complete hematologic (Figure 1A) and cytogenetic (Figure 1B) responses by landmark analysis at 3 months.

Survival

After a median follow-up of 82 months (range, 73-87), 70 patients (63%) have died. Sixty-one (86%) patients died because of progression to blast crisis, 25 of them (41%) 1 to 22 months (median, 6 months) after discontinuing imatinib. Two patients died because of febrile neutropenia and two in chronic phase (car accident). A total of nine patients underwent allogeneic SCT (one in CCgR, one in chronic phase after losing the CCgR and seven in chronic phase in the absence of any cytogenetic response) and four of them are now alive in complete remission.

The overall survival rate of the entire study population was 43% at 7 years (95% CI 33%-53%), for a median survival time of 37 months (Figure 2A); as expected, the achievement of a CHR or a CCgR was predictive of a better outcome: for patients who had obtained a CHR and a CCgR, the median survival time had not been reached at the time of the analysis (versus 12 months and 25 months for patients without a

Table 1. Patient and disease characteristics at the start of imatinib treatment (n.=111 patients).

Parameter	
Age at start of imatinib therapy	
Median, yrs (range)	58 (26-82)
60 or older, (n.)	51 (46%)
Sex, n.	
Male	70 (63%)
Female	41 (37%)
Performance Status (WHO)	
0-1	93 (84%)
2	18 (16%)
Splenomegaly, (n.)[1]	
At least 5 cm below costal margin	35 (33%)
Peripheral blasts, (%)[2]	
Median (range)	4% (0-26%)
>10%	29 (30%)
Platelet count ($x10^9$/L)	
Median (range)	369 (10-3811)
< 100×10^9/L	22 (20%)
> 450×10^9/L	45 (41%)
Peripheral basophils (%)	
Median (range)	6% (0-33%)
≥ 20%	13 (12%)
Hemoglobin concentration	
Median (range)	11 (7-15.4)
< 10 g/dL	39 (35%)
Median chronic phase duration prior to AP, months (range)	60 (8-287)
Additional chromosomal abnormalities (yes), (n.)[2]	21 (22%)
Prior chemotherapy for AP CML	
None	82 (74%)
One line or more	29 (26%)

[1]*Data available for 106 patients;* [2]*data available for 98 patients.*

CHR or a CCgR, respectively, $p<0.0001$). The progression-free survival rate was 36.5% at 7 years (95%CI, 27%-45%), while the event-free survival rate was 15% at 7 years (95% CI, 7%-26.5%) (Figure 2B and 2C). Univariate (log-rank) and multivariate analyses were used to test for the effects of several baseline variables on survival (Table 3). Results of univariate log-rank analyses indicated that spleen enlargement more than 5 cm below the costal margin, a hemoglobin level greater than 10 g/dL and Performance Status lower than 2 on the WHO scale were associated with prolonged survival. In multivariate analysis, a Performance Status lower than 2 was the only independent prognostic factor for better survival.

A total of 90 patients (81%) discontinued imatinib, after a median time of 25 months (range, 1-86 months). Seven patients (6%) discontinued imanitib because of adverse events: skin rash (2 patients), fluid retention (1 patient), gastric intolerance (1 patient), and febrile neutropenia (3 patients). Eighty patients (72%) discontinued imatinib because of lack or loss of the hematologic or cytogenetic response (40 patients) or because of progression to blast crisis (40 patients). Sixteen patients have switched to a second generation tyrosine kinase inhibitor, after 41 to 86 months (median, 71 months) of imatinib therapy. Among these patients, 11 switched to dasatinib (nine because of absence of a partial cytogenetic response, one after the loss of the CCgR and one after the loss of the hematologic response). Five patients were treated with nilotinib (one because intolerant to imatinib, two because of absence of a partial cytogenetic response, two after progression to blast crisis). All these patients were alive in chronic phase at last contact.

After a median follow-up of 82 months (range, 73-87 months), 21 patients were still on imatinib treatment (14 in complete, 5 in partial, 2 in minor or null cytogenetic response). No additional serious safety concerns were identified with longer term follow-up, and no treatment-related deaths occurred. In particular, no cases of heart failure or left ventricular dysfunction were documented throughout the follow-up.

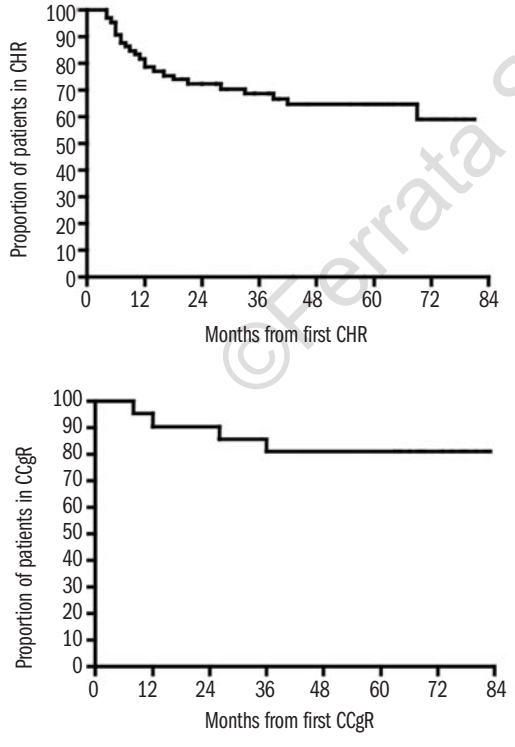

Figure 1. (A) Duration of complete hematologic response (CHR) and of (B) complete cytogenetic response (CCgR) by landmark analysis at 3 months. Fifty-six percent and 81% of the patients who had achieved a CHR or a CCgR, respectively, maintained the response during follow-up.

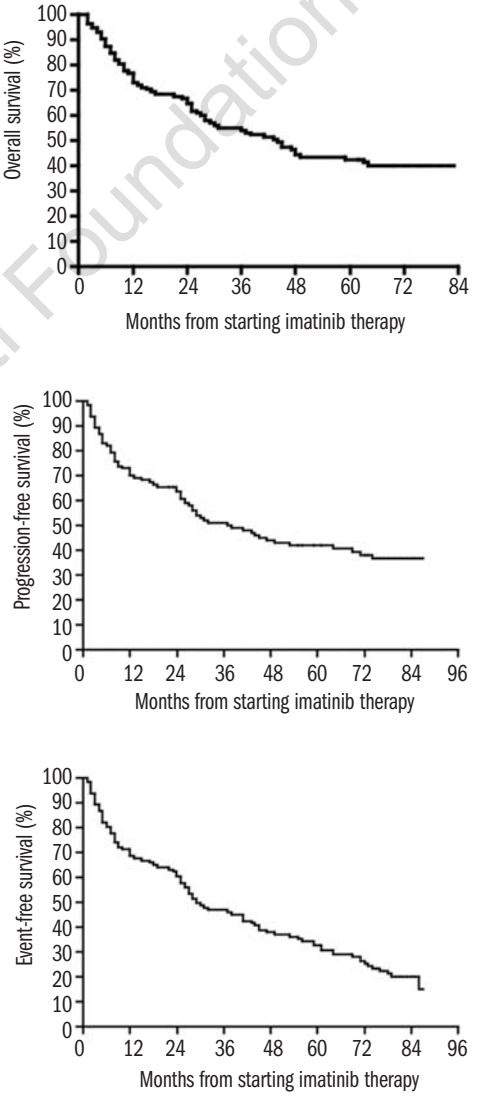

Figure 2. (A) Overall survival, (B) progression-free survival and (C) event-free survival. At 7 years, the overall survival rate of the entire study population was 43% (95% CI 33%-53%), the progression-free survival rate was 36.5% (95%CI, 27%-45%), and the event-free survival rate was 15% (95% CI, 7%-26.5%).

Additional cytogenetic abnormalities

Conventional cytogenetic analysis was not available at the start of imatinib therapy for 13 patients (12%) because the number of evaluable metaphases was lower than 20. Among the 98 patients evaluable by conventional cytogenetics, 21 (22%) showed additional cytogenetic abnormalities, and specifically: a single additional translocation (4 patients), trisomy of chromosome 8 (3 patients); duplication of the Philadelphia chromosome (3 patients); monosomy of chromosome 21 (1 patient); trisomy of chromosome 13 (1 patient), trisomy of chromosome 19 (1 patient). Eight patients had a com-

Table 2. Best hematologic and cytogenetic responses according to previous treatment and to age at starting imatinib.

Type of response	Total n.	Previous treatment with intensive chemotherapy*		Age older than 60 years**	
		No	Yes	No	Yes
Patients, n. (%)	111	82 (74%)	29 (26%)	60 (52%)	51 (46%)
Hematologic response					
RTC	107 (96%)	80 (98%)	27 (93%)	59 (98%)	48 (94%)
CHR	79 (71%)	59 (72%)	20 (69%)	43 (72%)	36 (70%)
Cytogenetic response					
Complete	23 (21%)	18 (22%)	5 (17%)	14 (23%)	9 (18%)
Partial	10 (9%)	7 (9%)	3 (10%)	6 (10%)	4 (8%)
Minor – Minimal	20 (18%)	16 (20%)	4 (14%)	10 (17%)	10 (20%)
Overall	53 (48%)	41 (50%)	12 (41%)	30 (50%)	23 (45%)

*Responses were confirmed for a minimum of 4 weeks. RTC: return to chronic phase. CHR: complete hematologic response. *Patients who received imatinib after intensive chemotherapy (induction chemotherapy, autologous and/or allogeneic SCT) had the same CHR (p=0.7, χ^2) and cytogenetic response rate (p=0.4) as the other patients. **Patients younger than 60 years had the same CHR (p=0.9) and cytogenetic response rate (p=0.6) as older patients.*

Table 3. Prognostic baseline factors tested for association with survival and response in univariate analysis.

	N. of patients	Median survival months (95% CI)	p (log-rank)	N. of patients obtaining a CHR (%)	p (χ^2)	N. of patients obtaining a MCgR (%)	p (χ^2)
Age at start of IM							
<60 yrs	58	48 (39-59)	0.1	41 (71%)	0.9	19 (33%)	0.6
60 yrs or more	53	27 (17-37)		37 (71%)		13 (25%)	
Sex							
Male	70	45 (35-55)	0.72	52 (74%)	0.9	21 (30%)	0.9
Female	41	36 (21-51)		27 (66%)		12 (29%)	
Splenomegaly >5 cm bcm							
No	71	64 (51-69)	0.02	53 (75%)	0.86	25 (35%)	0.7
Yes	35	26 (15-35)		21 (62%)		7 (21%)	
Platelets							
$<100\times10^9$/L	22	Not reached	0.31	19 (86%)	0.1	9 (41%)	0.2
$>100\times10^9$/L	89	41 (30-52)		60 (67%)		24 (27%)	
Hemoglobin,							
<10 g/dL	39	26 (15-35)	0.002	26 (67%)	0.6	8 (21%)	0.1
>10 g/dL	72	Not reached		51 (73%)		24 (34%)	
Peripheral blasts							
<10%	69	38 (28-48)	0.32	56 (73%)	0.7	24 (31%)	0.9
>10%	29	29 (15-37)		20 (65%)		8 (26%)	
Performance status (WHO)							
0-1	93	49 (37-57)	0.0003	72 (78%)	0.001	30 (32%)	0.4
2	18	15 (3-28)		7 (40%)		4 (20%)	
Additional chromosomal abnormalities							
Yes	21	16 (5-35)	0.1	14 (68%)	0.78	5 (26%)	0.79
No	77	44 (25-63)		55 (72%)		23 (30%)	
Prior chemotherapy							
Yes	29	48 (31-65)	0.71	20 (69%)	0.9	8 (27%)	0.9
No	82	41 (24-58)		59 (72%)		25 (30%)	
CML duration prior to imatinib							
<60 months	63	64 (54-74)	0.08	41 (64%)	0.1	16 (25%)	0.2
>60 months	48	29 (17-43)		38 (79%)		17 (35%)	

Bcm: below costal margin; CHR: complete hematologic response; MCgR: major cytogenetic response.

plex karyotype with at least three additional chromosomal abnormalities, including trisomy 8 (1 patient).

Evidence of clonal evolution was not associated with poorer outcome, nor with worse response to imatinib therapy. However, although the difference is not statistically significant, the outcome of patients with clonal evolution was poor: none of the patients with trisomy 8, Philadelphia chromosome duplication or a complex karyotype obtained a major cytogenetic response, and 15 out of 21 patients carrying additional chromosomal abnormalities (71%) progressed to blast crisis, after 3 to 48 months of imatinib therapy (Table 4).

Discussion

We describe the long-term outcome of 111 AP-CML patients, treated with imatinib 600 mg/day, with particular focus on the long-term efficacy and safety of this drug.

In this setting, imatinib 600 mg/day revealed noteworthy activity in the short term. The achievement of a CHR (71% of the patients), mainly (79%) within 3 months, once again documents the marked antiproliferative effect of imatinib, which is exerted preferentially on the late progenitor cell compartment,[23] leading to rapid debulking of the leukemic cell population. Moreover, half of the patients had a cytogenetically normal cell population (major cytogenetic response rate 30%, CCgR 21%). Cytogenetic responses were achieved later with respect to CHR, but mainly (88% of responders) within 12 months of starting treatment.

As expected, these results are significantly inferior to those obtained in analogous trials promoted by the GIMEMA CML Working Party in the same years (2000-2001), investigating the efficacy of imatinib 400 mg/day in early[24] and in late[25] chronic phase patients, in whom CCgR rates were 87% and 55%, and overall survival rates at 5 to 6 years 96% and 77%, respectively.

However, these results are in the same range of those reported in other experiences in the setting of AP-CML.[16-18] In particular, in the pivotal STIA109 study, 20.4% of AP-CML patients treated with imatinib (400 to 600 mg daily) achieved a CCgR and 7.2% a partial cytogenetic response, for a major cytogenetic response rate of 28.1% at 48 months.[16] The overall long-term outcome, the durability of the responses and the definition of variables influencing the prognosis, given the particularly long period of observation, add new information on the efficacy of imatinib in this setting. The main finding is the durability of the CCgR, maintained by 81% of the patients who achieved the response after a median follow-up period of 82 months (Figure 1B). Once more, the achievement of CCgR was confirmed to be a surro-

Table 4. Responses and outcomes in patients with additional cytogenetic abnormalities at the time of starting imatinib therapy.

Type of additional cytogenetic abnormality	Karyotype	Best hematologic response	Best cytogenetic response	Follow-up (months)	Outcome
Complex	48XY,t(9;22),t(17;18),-10	RTC	None	10	Dead BC
Complex	46,XX,t(9;22),del 2(p23),add 3(q28)	CHR	None	6	Dead BC
Complex	Tetraploidism	CHR	Minimal	36	Dead BC
Complex	48,XY,t(9;22),+14,+20,t(8;22)	RTC	None	3	Dead BC
Complex	49,XY,t(9;22),der(17)t(1;17)(q21;p11),+6,+8,+21	RTC	None	5	Dead BC
Complex	45,X,-Y,t(9;22),dupl(1)(q21 q32)	RTC	None	8	Dead BC
Complex	46,X,-X,t(9;22),-3,+7,+20	RTC	None	36	Dead after alloSCT
Ph duplication	47,XY,t(9;22),+der(22)t(9;22)	CHR	Minimal	59	Dead after alloSCT
Ph duplication	47,XY,t(9;22),+der(22)t(9;22)	RTC	None	7	Dead BC
Ph duplication	47,XY,t(9;22),+der(22)t(9;22)	RTC	None	12	Dead BC
Trisomy 8	47,XY,+8,t(9;22)	CHR	Minimal	48	Dead BC
Trisomy 8	47,XY,+8,t(9;22)	CHR	Minor	12	Dead BC
Trisomy 8	47,XY,+8,t(9;22)	CHR	Partial	86	Alive on IM in partial CgR
Additional translocation	46,XX,t(9;22),t(1;12)(q21;p13)	CHR	Complete	47	Dead BC
Additional translocation	46,XX,t(9;22),t(12;13)	CHR	None	16	Dead BC
Additional translocation	46,XY,t(9;22),t(11;16)(q13,q2 4)	RTC	None	6	Dead BC
Additional translocation	46,XX,t(9;22),t(1;3;4) (p32;p21;q31)	CHR	None	48	Dead BC
Monosomy	45,XY,t(9;22),-21	CHR	None	45	Dead BC
Trisomy	47,XY,t(9; 22),+13	CHR	Complete	75	Alive on IM in CCgR
Trisomy	47,XY,t(9; 22),+22	CHR	Complete	85	Alive on IM in CCgR
Trisomy	47,XY,t(9; 22),+19	CHR	Complete	73	Alive on IM in CCgR

RTC: return to chronic phase; CHR: complete hematologic response; BC: blast crisis; CgR: cytogenetic response; alloSCT: allogeneic stem cell transplantation; CCgR: complete cytogenetic response; Data were available for 98/111 (88%) patients on study.

gate marker of long-term survival, being a feasible and reliable indicator even in a subset of patients at high risk of further progression.

After progression to advanced phase disease, the eligibility for and feasibility of allogeneic SCT is generally discussed for all patients below a certain age limit. In our experience, only one out of 23 patients who achieved a CCgR underwent allogeneic SCT while in CCgR. The other patients did not undergo allogeneic SCT because of: donor unavailability (2 patients), age older than 55 years (16 patients), or physicians' decision (3 patients). Allogeneic SCT remains a therapeutic option to be considered for all eligible cases. However, particularly for those patients achieving an early CCgR and eligible for allogeneic SCT, it may be advised to monitor the response carefully, proceeding to transplant in case of response loss, particularly if the risk of transplant-related mortality is high.[26] Phase II studies investigating the efficacy of second-generation tyrosine kinase inhibitors in AP-CML are currently underway and results in AP-CML seem to be promising.[27,28] Clearly, to confirm the role of second generation tyrosine kinase inhibitors as a therapeutic alternative to allogeneic SCT,[29,30] the durability of the responses to such inhibitors, which might not be long-lasting in a substantial proportion of patients with AP-CML, should be weighed against the risk of transplant-related mortality for that specific patient and against the higher risk of subsequent relapse due to more advanced disease according to the EBMT risk score.[26] Although our data showed that, for initially responding patients, responses to imatinib were durable, the event-free survival rate was only 15% at 7 years, suggesting that it is appropriate to consider allogeneic SCT in all eligible patients, also taking into account the continuous improvements in transplant procedures.

Our results show that a stable and confirmed CCgR to a tyrosine kinase inhibitor treatment policy, even when the disease has progressed to AP, constitutes an affordable surrogate marker of long-term overall and event-free survival.

Authorship and Disclosures

FP, MB, and GR designed and supervised the study, collected data, wrote (FP) and revised (MB, GR) the manuscript; NT and SL performed cytogenetic analyses; FC, AG, BM, GRC, SF, SG, MB, LL, MS, LAM, PF, GS, AD, and MG contributed to data collection.

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