Response to treatment with imatinib mesylate in previously treated chronic-phase chronic myeloid leukemia patients in a hospital in Brazil

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ABSTRACT. We analyzed the results of treatment with imatinib mesylate in 70 patients with chronic-phase chronic myeloid leukemia who had previously been treated (with second-line or higher imatinib), many of them in a late chronic phase. The median follow-up period was 60.5 months (range 3-100 months). Our objective was to assess the efficacy and safety of treatment. The mean dose was 400 mg per day. The hematologic response rate was 92.1% at six months, while the cumulative rates of major and complete cytogenetic responses were 73.6 and 66.3%, respectively. Molecular response rate improved slowly and steadily over time, reaching 65.8% at 60 months, remaining stable for up to 96 months. The five-year progression-free survival and overall survival were 84 and 89%, respectively. Cytogenetic response by 12 months significantly correlated with overall survival ($P = 0.0007$) and progression-free survival ($P = 0.0280$). Sokal risk score did not differ significantly between subgroups. The medication was well tolerated, with only

16% of patients showing hematologic toxicity grades 3 and 4. At the end of the assessment, 57% of the patients were still on imatinib mesylate; most of those who discontinued treatment (17/30) did so because of unsatisfactory response. Treatment with imatinib mesylate in previously treated chronic-phase chronic myeloid leukemia induced durable responses in a high proportion of patients and was related to satisfactory long-term and event-free survival.

Key words: Chronic myeloid leukemia; Imatinib mesylate; Cytogenetic response

INTRODUCTION

Chronic myeloid leukemia (CML) is a chronic myeloproliferative disorder characterized by the presence of Philadelphia chromosome (Ph-positive CML), which is the result of a balanced translocation between chromosomes 9 and 22 (Sawyers, 1999; Vardiman et al., 2008). The molecular consequence of this translocation is the resulting hybrid BCR-ABL1 gene, which encodes the chimeric protein p210bcr-abl1 with constitutively and deregulated tyrosine kinase activity (Quintás-Cardama and Cortes, 2009).

The oncogenic potential of the BCR-ABL1 hybrid protein has been proven by its ability to transform hematopoietic progenitor cells *in vitro* and *in vivo* (Sawyers, 1999; Thijsen et al., 1999). CML occurs in three phases (chronic, accelerated and blast crisis) and is usually diagnosed during chronic phase (Bortolheiro and Chiattone, 2008).

The mechanism by which the p210bcr-abl1 protein promotes the transition from a benign state to a malignant state is not completely understood. However, the juxtaposition of sequences encoded by the BCR gene to the ABL1 gene results in critical functional changes that lead to increased cell proliferation, affect cellular differentiation and block apoptosis (Goldman and Melo, 2003).

Before imatinib mesylate (IM), the treatment of Ph-positive CML included hydroxyurea, interferon alpha (INF-α), and allogeneic hematopoietic stem cell transplantation (Silver et al., 1999). The advent of imatinib, which targets the tyrosine kinase activity of oncogenic proteins encoded by BCR-ABL1 (Druker et al., 1996), quickly and dramatically changed the treatment of CML (Druker et al., 2001) and led to major changes in its management (Baccarani et al., 2006). The most significant of these changes occurred after publication of the IRIS study (International Randomized Study of Interferon and STI571), which showed the clear superiority of imatinib compared to INF-α and cytarabine at low doses as initial treatment for CML (O'Brien et al., 2003). Currently, imatinib mesylate is considered to be the standard treatment for newly diagnosed CML (Baccarani et al., 2009). Nevertheless, the interest in previously treated chronic phase patients is still substantial, because IM may not be fully available as front-line treatment worldwide for economic reasons (Palandri et al., 2008).

Since March 2002, IM has been used in the hematology service at the Hospital de Base do Distrito Federal (Brasilia, Brazil). This article describes the results of second-line IM therapy for chronic-phase Ph-positive CML patients at this hospital, since there are no previous data on this population of patients. The main goal was to evaluate the efficacy and survival rate with the drug.

PATIENTS AND METHODS

Inclusion criteria

Patients were eligible for the study if they were 18 years of age or older and had Ph-positive chronic phase CML and received IM as second-line or higher option of treatment in the period between March 2002 and January 2009. We included both patients previously monitored by the service and those who were admitted as of March 2002, if previously treated and naive to imatinib. The diagnosis of CML was suspected by clinical and hematological criteria and was established by conventional karyotype analysis, FISH (fluorescence *in situ* hybridization) or reverse transcriptase polymerase chain reaction (RT-PCR) for BCR-ABL. Chronic phase was defined by the presence of less than 15% blasts, less than 20% basophils, and less than 30% blasts and promyelocytes in peripheral blood and bone marrow, and platelet count exceeding 100,000/mm³ (Kantarjian et al., 2002a).

Exclusion criteria

The study excluded patients who were exclusively on IM or used it after hydroxyurea only, pregnant women, and patients diagnosed with CML admitted to the service and who had never taken imatinib because they were referred for other forms of treatment (allogeneic hematopoietic stem cell transplantation).

Treatment

Patients were treated with IM at 400 mg daily, orally and continuously with dose adjustments, either for toxicity (with decreasing the dose) or for unsatisfactory response (raising the dose to 600 or 800 mg daily), in accordance with guidelines provided in the literature so far valid (Baccarani et al., 2006; Goldman, 2007).

Study design and statistical analysis

This was a descriptive study based on institutional data. The aim was to evaluate the efficacy and safety of IM treatment in our institution. Patients were analyzed for overall survival, event-free survival, progression to accelerated-phase CML or blast crisis, and hematologic, cytogenetic and molecular responses. Hematologic response was defined as previously described (Kantarjian et al., 2002a). The cytogenetic response was defined according to the number of Ph chromosome-positive cells in metaphases and was categorized as complete (zero percent Ph chromosome-positive cells in metaphase in bone marrow), partial (1-35%), minor (36-65%), minimal (66-95%), and no response (>95%) (Kantarjian et al., 2002a). Response was defined as major if the patient had a complete or partial response. Molecular response was described as previously defined (Kantarjian et al., 2002a; Hughes et al., 2003; Funke et al., 2005). Occurrence of events in patient outcome was defined as: death (any cause), progression to advanced stages of disease (accelerated phase and/or blast crisis) (Cortes and Kantarjian, 2003; Giles et al., 2004) and loss of responses (hematologic, cytogenetic or molecular). Event-free survival was defined from the time of start of treatment to the first documentation of one

of the above-mentioned events, and it was censored at the time of treatment discontinuation or the last visit, whichever came first. Progression-free survival was defined as the time between start of therapy and the onset of an accelerated phase or blast crisis. Patients without progression were censored at the time of treatment discontinuation or at the time of the last visit. Overall survival was determined as the time from treatment initiation to death from any cause and was censored at the time of treatment discontinuation or on the date of the last visit. Hematologic failure was considered if patients failed to achieve complete hematologic response at six months or if they lost their hematologic remission at any time. Cytogenetic failure was considered if patients failed to achieve major cytogenetic response (MCR) at 12 months and complete cytogenetic response (CCR) at 18 months, as well as loss of MCR at any time. Overall survival, progression-free survival and event-free survival were all evaluated using the Kaplan-Meyer methods, with statistical significance (P value) assessed using the log-rank test.

Assessment of patients

Monitoring was performed according to the routine of the Hematology Department of Hospital de Base do Distrito Federal. In general, hematologic tests were done weekly, until stabilization, monthly during the first six months and every three months thereafter. Cytogenetic tests were scheduled for six, twelve and eighteen months of treatment and then annually or at any time according to discretion of the treating physician. Molecular tests by RT-PCR was scheduled every three months, from the eighteenth month of treatment or after obtaining a complete and confirmed cytogenetic response.

Ethical aspects

The study was approved by the Institutional Research Ethics Committee of the Secretaria de Estado de Saúde do Governo do Distrito Federal.

RESULTS

Seventy patients were eligible for the study. The median time between diagnosis and initiation of treatment was 16 months (range: 0-208). Overall, INF-α-based regimen was the principal first-line option of treatment. Two patients exhibited non-hematologic intolerance grades 3 and 4 to interferon and did not complete a month of use of this drug. Forty (57.1%) patients were on imatinib for more than 12 months after diagnosis (late chronic phase). The median follow-up was 60.5 months (range 3-100 months). The main clinical and hematologic features at diagnosis of the patients are summarized in Table 1.

Efficacy of imatinib

After six months, complete hematologic response was achieved in 92.1%, and it was achieved in 94.4% at some point during the study. The results of cytogenetic analysis at six months were available in 39 (55.7%) patients. The number of patients with MCR, CCR, partial cytogenetic response, and minor cytogenetic response were 26 (66.7%), 12 (30.8%), 14 (35.9%), and 9 (23.1%), respectively. The cumulative rates of MCR and CCR were 73.6 and

Table 1. Patients' characteristics at diagnosis.

Variables	
Median age, years (range)	44 (19-73)
Age ≥60 years	11 (15.7)
Gender (male/female)	34 (48.6)/36 (51.4)
Spleen size (cm)	
Available data	43 (61.4)
Spleen ≥10 cm bcm	15 (21.4)
Sokal risk group	
Available	35 (50.0)
Low risk	16 (45.7)
Intermediate risk	7 (20.0)
High risk	12 (34.3)
Hematologic variable: median (range)	
Hemoglobin level (g/dL)	12.2 (6.2-15.7)
White cell count (cells/mm^3)	115,600 (6300-651,000)
Platelet count (cells/mm^3)	473,000 (126,000-1,750,000)
Blasts in peripheral blood	0 (0-11)
Basophils in peripheral blood	0 (0-12)

Data are reported as number with percent in parentheses, unless otherwise reported. bcm = below costal margin.

66.3%, respectively. They are shown in Figure 1 and indicate a trend toward improvement over time both in MCR and CCR with stabilization of MCR rate from the 30th month on and CCR rate from the 40th month on. Seven of fifty-six patients with available data (12.5%) lost their cytogenetic response throughout the observation period. The median time to loss of cytogenetic response was 23 months (range: 12-60 months).
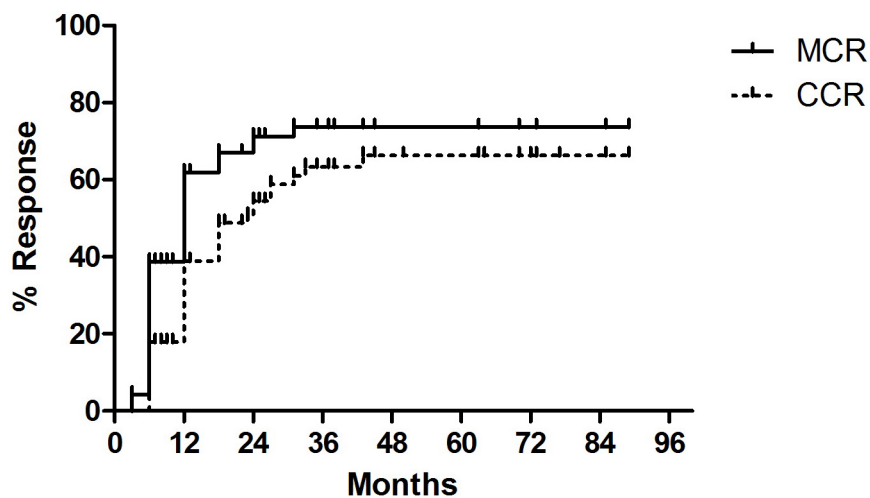

Figure 1. Time to cytogenetic responses: major (MCR) and complete (CCR).

The analysis of molecular response was performed in patients who achieved a CCR. The cumulative rate of major molecular response is shown in Figure 2. There was a tendency toward progressive improvement until the 60th month. The estimated 5-year cumulative rate of MCR was 65.8%. Only one patient (2.9%) showed loss of molecular response at the end of observation.
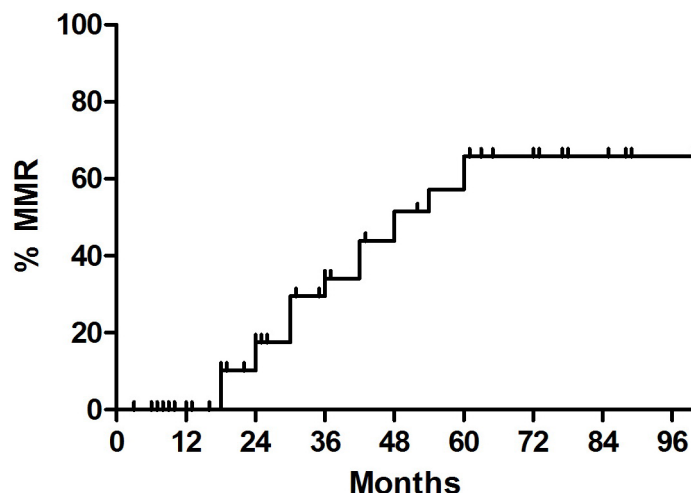
Figure 2. Cumulative rate of major molecular response (MMR).

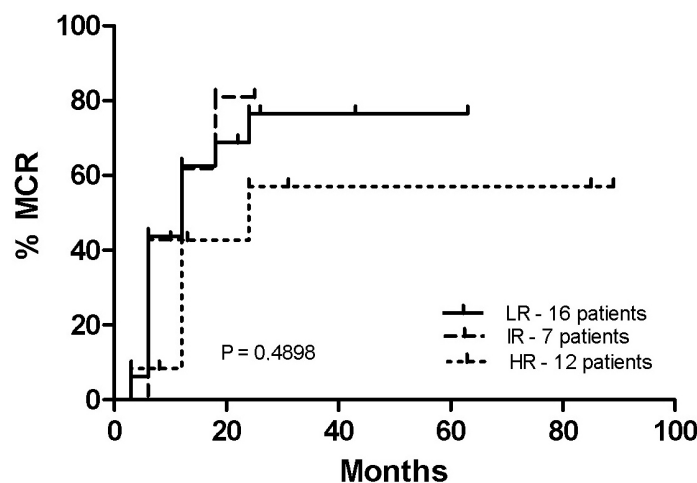Sokal score (Sokal et al., 1984) was not associated with achievement of cytogenetic response (P = 0.4898) (Figure 3).

Figure 3. Sokal risk score and probability of achieving major cytogenetic response (MCR). LR = low risk; IR = intermediate risk; HR = high risk.

Long-term outcomes

The estimated progression-free survival (PFS) rate at 60 months was 84.2% (Figure 4). Sixty-four (91.4%) among the 70 patients were alive at the end of the observation period. There were six deaths: five related to progression of the disease and one related to sepsis after skin infection. Overall survival rate was 89.1% (Figure 5).
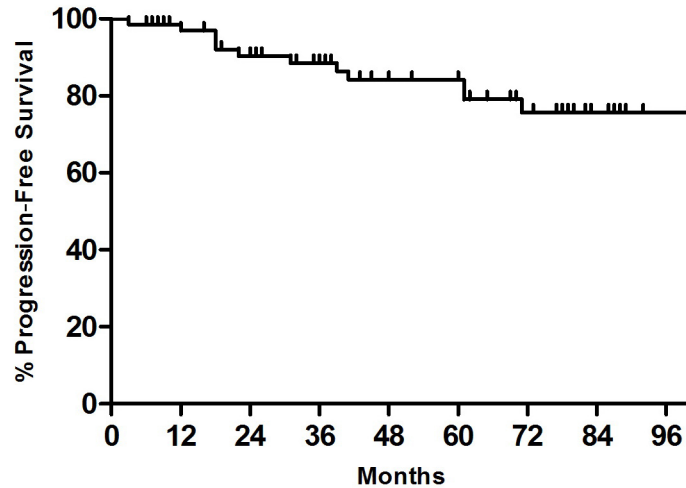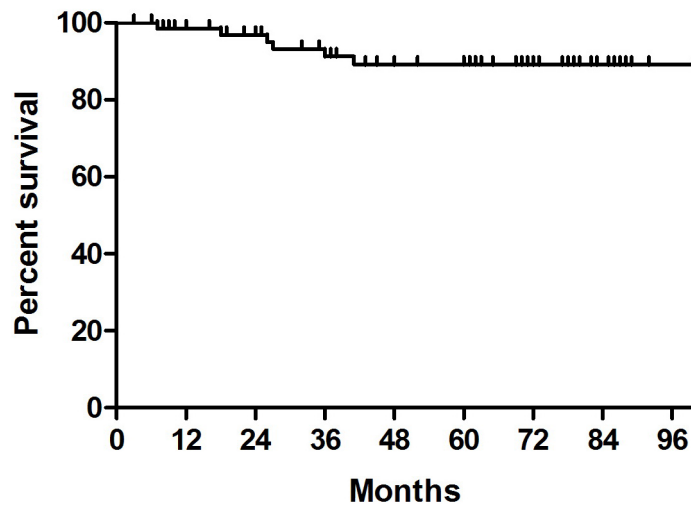
Figure 4. Progression-free survival.

Figure 5. Overall survival.

Achievement of cytogenetic response by 12 months significantly correlated with PFS. The estimated 60-month PFS rate was 87.6% with MCR and 40.4% without MCR by 12 months (P = 0.0280) (Figure 6). Cytogenetic response by 12 months also significantly correlated with overall survival. The estimated 60-month overall survival rate was 97% for patients with MCR and 47.4% for those who did not achieve MCR by 12 months (P = 0.0007).

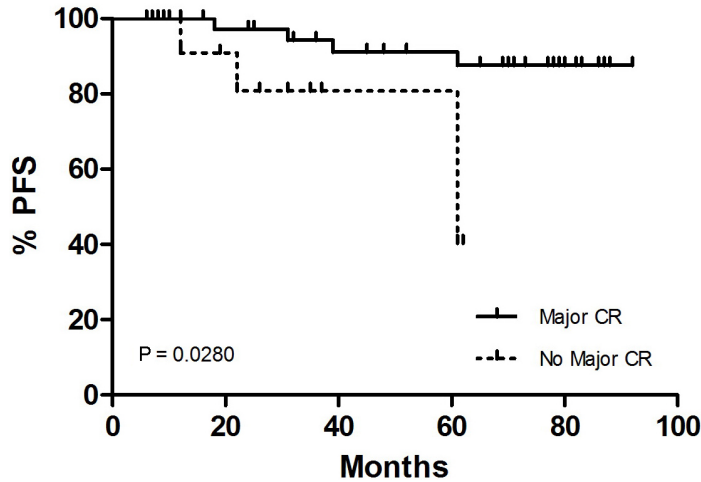Analysis of survival according to Sokal risk score was not significant, as shown in Figure 7 (P = 0.1189).

Figure 6. Progression-free survival (PFS) according to cytogenetic response (CR) by 12 months.
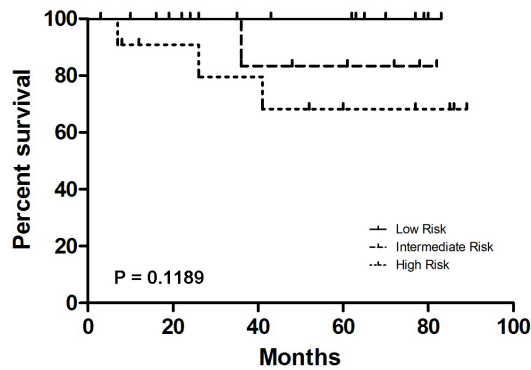

Figure 7. Overall survival according to Sokal risk score.

Events

The rates of events occurred as depicted in Table 2. The 60-month event-free survival rate was 65.5%.

Table 2. Events considered to be adverse outcomes.

Event	No. (%)	Time in months (median/range)
Death	6 (8.6)	26.5 (7-41)
Progression	12 (17.1)	
Accelerated phase	10 (14.3)	35 (3-71)
Blast crisis	2 (2.9)	18 (16-18)
Loss of response		
Hematologic	10 (14.3)	23 (8-63)
Cytogenetic	5 (8.9)	23 (12-60)
Molecular	1 (2.7)	42

Treatment and toxicity

At the end of the assessment, 40 patients (57.1%) were still on the drug, while it had been discontinued in 30 (42.9%). The main reasons for discontinuation were: 17 (56.6%) failure or disease progression, 6 (20%) death, 3 (10%) loss of follow-up, 2 (6.7%) patient decision, and 2 (6.7%) toxicity. Thirty-three patients needed drug dose adjustment: eleven (15.7%) required dose reduction; 6 (8.6%) increase to 600 mg; 4 (5.7%) increase to 800 mg, and 12 (17.1%) increase to 600 mg initially and then to 800 mg. Eleven patients (15.7%) developed hematologic toxicity grades 3 or 4.

DISCUSSION

Imatinib mesylate was initially introduced into clinical practice in patients resistant or intolerant to INF-α (Kantarjian et al., 2002a,b; Cervantes et al., 2003; Goldman, 2007). Since then, several publications have shown the results of treatment in similar groups (Kantarjian et al., 2004a,b; Funke et al., 2005; Lahaye et al., 2005). In this study, we analyzed patients at our institution who were treated with second-line IM and called them "pre-treated", as some were in late chronic phase (over a year since diagnosis) and others not. The treatment achieved similar results compared to those of some groups (Cervantes et al., 2003; Palandri et al., 2008) and better than others (Hocchaus et al., 2008), with reasonable tolerability and without observed adverse effects of greater severity.

The clinical characteristics of our group at diagnosis showed the presence of some variables related to worse prognosis. The proportion of patients with spleen size larger than 10 cm below the costal margin was around 21%, while this has been observed by others at lower rates; the median number of leukocytes was higher when compared with other studies (Kantarjian et al., 2002a,b). These two features are clearly indicative of large tumor mass. Also, the prognostic stratification according to the Sokal risk score (Sokal et al., 1984) showed a smaller proportion of patients in the low-risk group (46%), when compared to groups of high risk and intermediate risk, analyzed together (54%). In other studies, however, there was a larger number of patients classified as low risk (Cervantes et al., 2003; Kantarjian et al., 2004a). Some reasons for these worse features may include delay in seeking medical help or no regular screening tests in many hospitals of the country. In spite of the unfavorable factors described, the good results observed could be explained by the lower median age of our group, with probably less associated diseases and possibly better compliance, since in younger patients we could see less severe or more tolerable adverse events.

Response rates to imatinib therapy in this long-term follow-up population were high and durable. Overall, 73.6% of patients achieved a major cytogenetic response, which was complete in 66.3%. Thirty-four (85%) patients still on treatment had achieved CCR, a substantial rate for late chronic-phase patients. These results are similar to some international studies (Kantarjian et al., 2004b). However, the continuous trend in improving responses was not seen in our group, which showed a stabilization rate around 48 months (Figure 1). This was probably seen because of the fewer number of cytogenetic analyses performed after achievement of CCR and start of molecular monitoring. Long-term outcomes were satisfactory. The estimated 5-year progression-free survival (84.2%) and overall survival (89.1%) were close to that observed in many series (Cervantes et al., 2003; Kantarjian et al., 2002b, 2004a,b; Lahaye et

al., 2005), which may be due to reasonable cytogenetic control at the beginning of treatment.

We showed that the degree of cytogenetic response at 12 months was significantly associated with progression-free survival (Figure 6) according to findings by Hochhaus et al. (2008). However, it was not possible to show significant differences according to Sokal risk score in either major cytogenetic response (P = 0.4898) (Figure 3) or overall survival (P = 0.1189) (Figure 7). One possible explanation is the small number of patients in which the score was available (50% of the entire group), or the fact that data of general population groups could not be equivalent to those observed in clinical trials, as observed by Lucas et al. (2008). Our data were insufficient to evaluate a difference in treatment outcomes with imatinib-intolerant patients and those who had failed treatment with interferon.

In regard to safety, the patients exhibited lower rates of hematologic toxicity (15.7% grades 3 and 4) in relation to a phase 2 study that evaluated IM (Kantarjian et al. 2002a), in which up to 35% of patients showed grades 3 and 4 neutropenia. There were no reports of severe non-hematologic toxicity, and adverse effects were handled according to usual recommendations.

We share the opinion of Palandri et al. (2008) that the interest in the fate of the patients treated in late chronic phase tended to vanish over time. However, we also agree with the view that our patients and many living in other countries still in treatment may benefit from observations made in several centers, with respect to rates of recurrence or progression to more advanced forms of the disease or even the long-term stability of their responses.

In conclusion, treatment with imatinib mesylate of previously treated chronic-phase Ph-positive CML patients induced durable responses in a high proportion of patients, despite producing adverse clinical and laboratory features at presentation. Sokal risk score was not applicable in our patients as a tool for stratification.

ACKNOWLEDGMENTS

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