

## Original Article

# Six-Year Follow Up of Imatinib Therapy for Newly Diagnosed Chronic Myeloid Leukemia in Iranian Patients

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## Abstract

**Background:** The present study reported a six-year follow up of patients with chronic myeloid leukemia who were on imatinib therapy.

**Methods:** We performed a retrospective study on a total of 417 patients diagnosed with chronic-phase, Philadelphia-positive (Ph+) chronic myeloid leukemia within six months before study entry. Patients were eligible for the study if they were between 18 and 70 years of age. Enrolled patients were treated at an initial dose of 400 mg of imatinib.

**Results:** The mean age of 417 patients was 40.9±14.5 years; 220 (52%) were men and 197 (47.2%) were women. Complete hematologic response at three months occurred in 99% of patients, 221 (53%) before four weeks and 196 (47%) after four weeks. Adverse events occurred in 17 (4.1%) of patients, relapse in 46 (11%) and death in 31 (7.4%) of our studied population. At 72 months, the estimated rate of overall survival rate was 89%.

**Discussion:** Our findings showed the efficacy and safety of imatinib mesylate among Iranian patients with chronic myeloid leukemia by hematological and molecular response.

**Keywords:** BCR-ABL positive, chronic myeloid leukemia, imatinib mesylate

## Introduction

Chronic myeloid leukemia (CML) is a myeloproliferative disorder characterized by the expansion of pleuripotent hematopoietic stem cells.<sup>1</sup> Philadelphia chromosome, the result of t(9; 22) reciprocal translocation, is identified in over 90% of patients with CML.<sup>2</sup> This translocation results in a BCR-ABL gene that encodes an active tyrosin kinase, with leukemogenesis properties. Imatinib is a selective competitive inhibitor of tyrosine kinase that potentially prevents the growth and production of CML cells.

Many studies have substantially noted an excellent clinical efficacy of imatinib in patients with newly diagnosed CML as well as those with chronic phase CML who were either resistant or intolerant to interferon plus cytarabine. Based on these studies, imatinib was approved as first line therapy in patients with CML and has been available in clinical practice since December 2001.<sup>1</sup> To date, we are unaware of any study that has demonstrated the efficacy and tolerability of imatinib among Iranian patients with CML. The present study reports on the six-year follow up of CML patients on imatinib therapy.

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## Patients and Methods

### Patients

This was a multicenter uncontrolled observational retrospective study of 417 patients with confirmed Philadelphia-positive (Ph+) CML. Patients were eligible for the study if they were between 18 and 70 years of age and received a diagnosis of chronic-phase CML within six months before study entry. All patients' confirmative diagnoses, treatment, and follow up were performed at Imam Khomeini, Artesh, and Arad Hospitals in Tehran, some of the patients referred from other cities for treatment to these hospitals. Chronic phase was defined by the presence of less than 20% basophils, and 15% blasts in the peripheral blood and marrow.<sup>3</sup> Patients were recruited from June 2003 to January 2004 and received Indian type imatinib mesylate (imatinib) at a dose of 400 mg orally per day. Patients with initial WBC counts  $\geq 50 \times 10^9$  received hydroxyurea 2 g daily until WBC counts were below  $50 \times 10^9$ , then hydroxyurea was held and patients continued on imatinib. Dose escalation to 600 mg was implemented if patients failed to achieve a complete hematologic response at three months. Exclusion criteria were serum bilirubin or serum creatinine levels three times higher than the upper limit of the normal, serum liver aminotransferases levels five times higher than the upper limit of the normal, the presence of chromosome abnormalities additional to the Philadelphia chromosome, and pregnancy.

### End points

Overall survival was defined as the percentage of people on treatment who survived until the end of the study. Event-free survival was defined as the date of diagnosis until locoregional or systemic recurrence, second malignancy, or death from any cause. The pri-

mary end point was defined by the first occurrence of death from any cause during treatment, progression to the accelerated phase or blast crisis of CML, and the occurrence of any type of side effects during treatment. Signs of molecular response were determined 12 months after a complete hematologic response with the use of real time polymerase chain reaction.<sup>4</sup> A complete hematologic response was defined as a platelet count  $150 - 450 \times 10^9/L$ ; white blood cell count  $<10 \times 10^9/L$ ; differential without immature granulocytes with less than 5% basophils and less than 5% blasts in blood or bone marrow; and nonpalpable spleen.<sup>3</sup>

#### Statistical analyses

We performed analysis of event-free survival and overall survival using Kaplan Mayer method according to all available data. We used the life table method to determine yearly event probabilities. To study the association of complete hematologic response duration with overall survival, a cutoff point of four weeks was set. We stratified the patients into two groups of “rapid responder” defined as patients with complete hematologic response of duration shorter than or equal to four weeks, and “slow responder” who were patients with a complete hematologic response that occurred after four weeks. Differences between subgroups of patients in groups of rapid responders and slow responders as well as patients with positive and negative BCR-ABL (after treatment) were calculated by the log rank test.

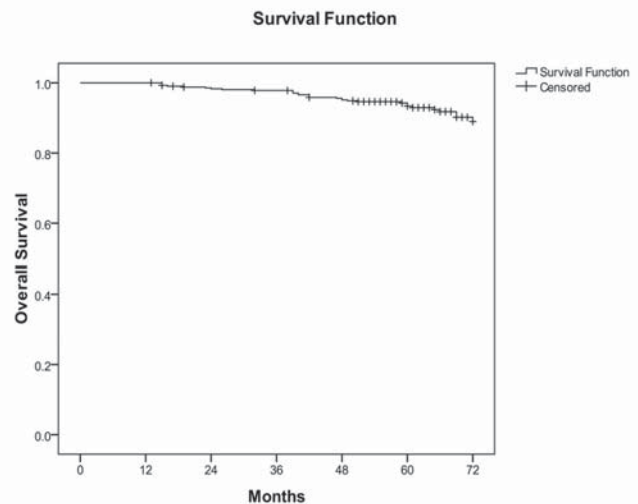
## Results

The mean age of patients was  $40.9 \pm 14.5$ . There were 220 (52%) men. At the time of diagnosis, the white blood cell count mean was  $95.5 \times 10^3 \pm 73.3 \times 10^3/\mu L$ , hemoglobin mean was  $10.32 \pm 1.5$  mg/dL, and platelets mean were  $23.6 \times 10^4 \pm 12.4 \times 10^4/\mu L$ . Spleen size in 89 (21.3%) cases was less than 2 cm, in 250 (59.9%) it ranged between 2 – 8 cm and in 78 (18.8%) spleen size was greater than 8 cm. There were 223 out of 417 cases that completed five years or more of study treatment. Censored observations were non-informative and carried no prognostic information about subsequent survival. Discontinuation was usually due to adverse events, withdrawal of consent, insufficient efficacy, and lost to follow up. None of the patients underwent bone marrow transplantation. Complete hematologic response at three months was seen in 99% of patients and 221 (53%) cases had complete hematologic response prior to four weeks.

A total of 17 (4.1%) of our patients had adverse events, which occurred in the first or second year of the study. The adverse events, in order, were thrombocytopenia in 6 (1.4%), leukopenia in 5 (1.2%), edema (including peripheral and peri-orbital edema) in 4 (1%), and diarrhea in 2 (0.5%). Newly occurring or worsening grade 3 or 4 hematologic or biochemical adverse events were infrequent after two and four years of therapy.

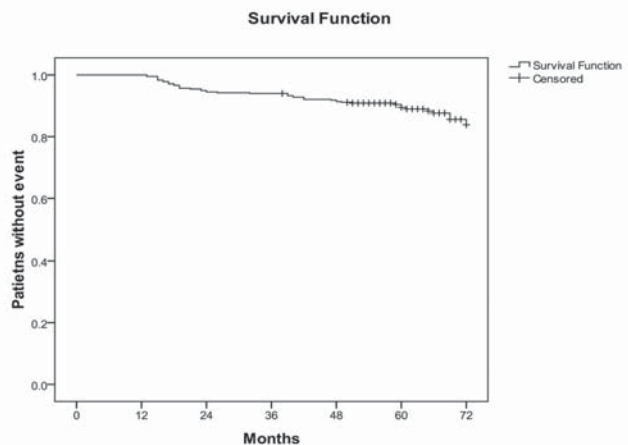
The median time for achieving a complete hematologic response was four weeks, which 99.3% occurred before three months of the study. Among the entire studied population, three patients developed myelofibrosis, of which all were BCR-ABL positive. Six progressed into AML after two months of therapy. At 72 months, the estimated rate of event free survival was 83%.

After a median follow up of 60 months, hematologic relapse occurred in 46 (11%), and death occurred in 31 (7.4%) patients. Among those who died, 26 (83.8%) had relapse, and 5 (16.3%) died due to myocardial infarction and car accident. At 72 months, the estimated rate of overall survival was 89% (Figure 1).



**Figure 1.** Kaplan Meyer estimate of overall survival of patients receiving imatinib at 72 months study duration.

Patients with positive BCR-ABL had a lower overall survival compared to those with negative BCR-ABL (0.81% vs. 0.96%,  $P < 0.001$ ). There were 30 patients who had positive BCR-ABL at 72 months study duration who did not progress to the accelerated phase. Furthermore, we did not increase the imatinib dose to 600 mg in any of them due to financial limitations. There was no significant difference in overall survival rate between groups stratified according to the duration of complete hematologic response using the log rank test ( $P = 0.24$ ). All patients in the rapid responders group received hydroxyurea, whereas none of the patients in the slow responders group received hydroxyurea (Figure 2).



**Figure 2.** Kaplan Meyer estimate of event free survival of patients receiving imatinib at 72 months study duration.

## Discussion

We showed an overall survival rate of 89% at six-years follow up whereas in an international randomized study of interferon and STI (IRIS), it was reported to be 97.2% at 18 months,<sup>5</sup> 89% at 5 years, 88% at 6 years,<sup>6</sup> and 86% at 7 years.<sup>7</sup> The safety profile of imatinib was also significantly higher in our studied patients compared to

other reports. In the IRIS study, 30% of the patients had grades 3/4 adverse events that included fatigue, depression, myalgia, arthralgia, neutropenia, and thrombocytopenia, whereas none of our studied population had adverse events from imatinib therapy higher than grades 1/2. There were no reports of nausea, muscle cramps, joint pain, and skin hypopigmentation in our studied patients, as usually reported in Caucasians.<sup>5</sup>

On the other hand, it should be taken into account that most of our patients were unable to buy imatinib regularly, as cancer treatment is not fully covered by insurance companies in Iran. The mean age of patients in other studies was about 20 years older than our study. It has been recently shown that older patients experience more adverse events and have a lower response rate to imatinib therapy compared to younger patients.<sup>8</sup>

As with previous studies, we showed better survival in patients with negative BCR-ABL compared to patients with positive BCR-ABL (after treatment). However, there were 30 patients who remained BCR-ABL positive at six years who were in complete remission. These patients were on the 400 mg dose of imatinib and did not adhere to their treatment regimen. Many studies have suggested a higher than average dose of imatinib in patients who show lower responses to the standard doses of imatinib.<sup>9</sup>

Similarly, discontinuation of imatinib, even in patients with undetectable levels of BCR-ABL, results in relapse.<sup>10</sup> We could not find any explanation for this observation. Furthermore three of our studied population were affected with myelofibrosis which is not consistent with a report by Kantarjian et al. which showed a higher rate of myelofibrosis in response to imatinib therapy in chronic-phase CML.<sup>10</sup>

In conclusion, we showed a higher efficacy and safety of imatinib therapy among Iranian patients with CML. Whether these findings are due to the genetic background of our patients or their younger ages, which was unexplainable, it should be studied in the future.

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