Original Study

# Outcome of Chronic Myeloid Leukemia-Chronic Phase Patients Treated With Imatinib: A Local Experience

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## Abstract

**Imatinib (Gleevec) was the first drug to target the breakpoint cluster region (BCR)-Abelson (ABL) tyrosine kinase and hence became the first line of therapy for patients with chronic myeloid leukemia. It provides a high rate of remission and survival benefits with minimal side effects.**

**Background:** Imatinib was the first tyrosine kinase inhibitor that has revolutionized the therapy of chronic myeloid leukemia. It binds breakpoint cluster region−Abelson kinase domain inducing apoptosis of the leukemic cells. In this study, we assessed the efficacy and toxicity of imatinib therapy in patients with chronic myeloid leukemia in chronic phase (CML-CP) in our hospital. **Patients and Methods:** We retrospectively analyzed the outcome of 17 patients with CML-CP treated with imatinib. **Results:** The median age at the time of presentation was 35 years with male preponderance. The most common presenting clinical features were fatigue, abdominal distention, and discomfort. Forty-seven percent of patients had fever at presentation whereas 35.29% were referred to our hospital because of incidental findings of high blood cell counts. With a median follow-up of 8 years (range, 2-16 years) the overall survival is 100% and progression-free survival 85%. Two patients had acceptable adverse effects. **Conclusion:** After a median follow-up of 8 years, imatinib was found to induce long survival with manageable side effect in adult Saudi patients with CML-CP.

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## Introduction

Chronic myeloid leukemia (CML) is a clonal hematopoietic stem cell disease characterized by proliferation of the granulocytic cell line without the loss of their capacity to differentiate and accounts for 20% of all leukemia in adults.[1] CML consists of a chronic, accelerated, and blast phase and all phases of CML harbor the Philadelphia chromosome. The breakpoint cluster region (BCR)-Abelson (ABL) oncoprotein is the hallmark of CML and responsible for myeloid proliferation and progression. The clonal expansion of CML results from a reciprocal translocation, which involves the ABL proto-oncogene on chromosome 9 and BCR on chromosome 22, t (9; 22) (q34; q11), known as the Philadelphia chromosome.[2,3]

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In Saudi Arabia, in 2009, leukemia accounted for 6.3% of all newly diagnosed cancers and it was the third most common form of cancer among men and fifth among women; the male: female ratio was 1.24:1. Of these, CML accounted for approximately 15% of all leukemia cases.[4,5]

In general, first-line therapies for all patients newly diagnosed with CML in the chronic phase (CML-CP) are the tyrosine kinase inhibitors (TKIs), including imatinib, dasatinib, and nilotinib. CML was a lethal disease until the introduction of these medications. Imatinib was the first TKI approved by the US Food and Drug Administration (FDA) for CML in 2001.[6,7] Nowadays, treatment plans for CML-CP have intent to diminish leukemic cell numbers and block malignant cell growth by inhibiting BCR-ABL kinase activity.[8]

A diagnosis of CML mandates therapeutic intervention even in asymptomatic patients. In chronic phase CML, BCR-ABL inhibitor therapy produced an unprecedented response rate. All patients diagnosed with Philadelphia chromosome-positive CML-CP have achieved complete hematological remission and approximately 85% of the patients have achieved cytogenetic remission. Approximately 67% of patients remained in a remission state even after 5 years with a low risk of progression to advanced-phase disease.[9-12]

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In this study, we present response to imatinib therapy and its adverse effects in adult patients with CML-CP, local experience.

## Patients and Methods

This was a retrospective study of adult Saudi patients with CML-CP treated with imatinib between June 2002 and June 2015 at King Fahd Hospital of the university, Eastern province Saudi Arabia. The diagnosis of CML-CP was according to findings of total white blood cell counts > 20,000 cells per deciliter with increased basophil or eosinophil. The bone marrow biopsies showed hypercellular marrow with expansion of the myeloid cell line and findings consistent with CML-CP. BCR/ABL mutation was analyzed using fully automated real-time reverse transcription polymerase chain reaction for quantifying the amount of BCR-ABL mRNA transcript using the Xpert BCR-ABL monitor assay (GeneXpert; Cepheid, Sunnyvale, CA).

Peripheral blood blasts < 10% in the peripheral blood and bone marrow were used to assign chronic phase as defined by the World Health Organization.[13] Patients were treated with imatinib at an oral daily dose of 400 mg with food.

Dose escalation to 800 mg daily was used to achieve a major molecular response (MMR) in 3 patients. Patients with progression and MMR > 0.1% were shifted to nilotinib treatment.

Hematological response was evaluated every 2 to 3 months. MMR was evaluated every 4 to 6 months. However, cytogenetic response was not available. The response assessment was done according to an international recommendation; failure of imatinib therapy was defined as BCR-ABL/ABL ratio > 0.1% (Table 1).[10]

### *Statistical Analysis*

Survival analysis using all patients and statistical significance were determined using the log rank test as shown in Figure 1.

### *Ethical Approval*

Although this was a retrospective study and data were collected from charts of the patients, consents and permissions were taken from these patients during outpatient department follow-up. Ethical approval for the study was obtained from the Research Ethics Committee of our hospital and patients gave consent to participate in the study.

## Results

Seventeen patients with CML-CP were analyzed. The baseline characteristics of patients are shown in Table 2.

**Table 1** Definitions of Response to Imatinib Therapy in Chronic Myeloid Leukemia

| Response | Definition |
|---|---|
| **Clinical Response** | Disappearance of all symptoms and signs |
| **CHR** | WBC $<10 \times 10^3$ with normal differential, platelet count $<450 \times 10^3$, Hg > 10 g/dL |
| **Molecular Response** | |
| Complete (CMR) | BCR-ABL/ABL ratio not detectable or <0.001% |
| Major (MMR) | BCR-ABL/ABL ratio <0.1% or >3-log reduction from baseline |

Abbreviations: ABL = Abelson; BCR = breakpoint cluster region; CHR = complete hematological response; CMR = complete molecular response; Hg = hemoglobin; MMR = major molecular response; WBC = white blood cell counts.

Overall, the duration of response ranged from 2 years up to 16 years with a median of 8 years. At a median follow-up of 8 years, CML-CP patients are alive and with MMR as shown in Table 3. Among the 17 patients, 2 patients had progression after 6.5 years, as indicated by MMR, which was > 0.1% and these patients were shifted to nilotinib. These 2 patients responded to treatment with nilotinib. The overall survival and progression-free survival for all patients was 100% and 75%, respectively, as shown in Figure 1.

### *Toxicity*

Overall, imatinib was well tolerated. No severe toxicity or therapy-related death occurred. One patient developed moderate skin itching and rash requiring changing imatinib to nilotinib. One patient developed a right thigh lesion as shown in Figures 2 and 3. Biopsy of this lesion showed hemorrhagic necrosis and fibrosis. Findings of toxicity and progression are summarized in Table 4.

## Discussion

The clinical manifestations of CML-CP are insidious. The disease is often discovered incidentally either during a routine investigation of complete blood counts or when an enlarged spleen is found incidentally on clinical examination. In Western data, approximately 40% of patients with CML-CP are symptomatic and diagnosed on the basis of abnormal blood counts.[13,14] Similarly, 6 patients (35%) of our patients were diagnosed incidentally. The median age at presentation of our patients was almost similar to an Indian median age but a decade younger compared with Western countries.[15] This finding is similar to the findings reported from the Saudi national cancer registry as well.[5] Two-thirds of our patients has presented either complaining of nonspecific symptoms, fatigue, or abdominal distention secondary to splenomegaly. One patient presented with visual loss of the right eye secondary to retinal hemorrhage.

The first-line therapy for CML-CP is a TKI including imatinib, nilotinib, or dasatinib. Imatinib (Gleevec; Novartis, Basel, Switzerland) inhibits the abnormal BCR-ABL tyrosine kinase created by the Philadelphia chromosome translocation and induces apoptosis in cells positive for BCR/ABL. It was first used in 1998 to treat patients with CML-CP, FDA approval was in 2001,[6,7] and was first used in our hospital in 2002. Imatinib is a very useful and effective drug with mild to moderate side effects.

All of our patients (100%) achieved clinical, complete hematological response, and MMR initially. Only 2 patients progressed after 6.5 years of imatinib treatment. These 2 patients responded well to nilotinib and achieved MMR as well. The longest duration of follow-up was 16 years and the median duration of follow-up was 8 years. One study from Saudi Arabia was published in 2014 and reported the effectiveness of imatinib in adult Saudi patients with CML-CP and without major adverse effects.[16] The most sensitive and convenient method to follow response to therapy is the BCR-ABL monitor, which can identify 1 CML cell in approximately 100,000 cells. MMR has become a new target response to assess residual disease and accepted as a standard of care for long-term benefit in the treatment of CML-CP.[17-19]

Of all patients, 1 is in MMR 16 years, 3 are in MMR 13 years, 2 are in MMR 12 years, 2 are in MMR 10 years, 4 are in MMR 8 years, and 2 are in MMR for 6.5 years. Three patients were treated

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