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# Hematologic and Cytogenetic findings in eleven Chronic Myelogenous Leukemia Patients treated with Imatinib Mesylate at a Tertiary Care Hospital

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## Abstract

**Objective:** To evaluate the response of Imatinib mesylate in patients with myeloid leukemia in chronic , accelerated and blast phase.

**Patients and Methods:** Eleven patients with established diagnosis of chronic myeloid leukemia were treated with Imatinib mesylate. Adverse events were documented with regular follow ups. Hematological and cytogenetic responses were assessed according to established criteria. Patients with zero percent Philadelphia positive metaphases were labeled as complete cytogenetic response while patients with 1% to 35% Philadelphia positive metaphases were termed as partial responders.

**Results:** Of 11 cases there were 7 males and 4 females with a mean age of 39.5 years and median age 51 years (range 21-69). Male to female ratio was 7:4. Median follow-up was 34 weeks (range 8-78). Four patients were in blast crisis, 1 in accelerated phase and remaining six patients were in chronic phase. All patients achieved hematological response. Cytogenetic response was present in six patients, 3 were responders and the remaining were non responders. Two patients achieved complete cytogenetic response and one patient had partial cytogenetic response. Both patients with complete cytogenetic response relapsed in twelve weeks time.

**Conclusion:** Imatinib mesylate is a drug with curative potential and can be used as a first line drug in the management of CML, however at present the cure rate is unknown (JPMA 54:17;2004).

## Introduction

Chronic myeloid leukemia is a hemopoietic stem cell clonal disorder characterized by granulocytic leucocytosis, basophilia, anemia, thrombocytosis and splenomegaly. Chronic myeloid leukemia is characteristically a tri-phasic disease in which the chronic phase usually lasts for three to six years followed by transformation to accelerated phase and blast crisis.[1]

The hallmark of this malignancy is the Philadelphia chromosome positivity, a reciprocal translocation between the long arms of chromosomes 9 and 22. bcr from chromosome 22 binds to abl of chromosome 9 which results in a fusion gene, the bcr-abl gene that directs the synthesis of a novel 210 KD oncoprotein, the bcr-abl protein. It constitutes an active protein tyrosine kinase with an important role in the cell growth.[2,3]

Among the available treatment options, the allogenic bone marrow transplantation is potentially curable but less than 30% of patients have an HLA matched sibling donor. Interferon can induce a complete cytogenetic response in 5 to 20 percent of patients, however with substantial serious side effects. Hydroxyurea and other cytotoxics can produce remarkable hematological responses but cytogenetic response is rare.[4] Recently Imatinib mesylate has been introduced which is a potent Inhibitor of the bcr-abl tyrosine kinase protein. Imatinib mesylate has already showed remarkable hematological and cytogenetic responses in patients with all phases of chronic myeloid leukemia in phase trials.[5] In this study, we share our experience of Imatinib mesylate in eleven patients.

## Patients and Methods

The study was conducted at the Aga Khan University Hospital on patients with a diagnosis of chronic myeloid leukemia treated with Imatinib mesylate from May 2001 to October 2002. Inclusion criteria were: age more than eighteen years. Chronic myeloid leukemia was diagnosed on chromosomal studies revealing Philadelphia chromosome on bone marrow or bcr-abl translocation by polymerase chain reaction (PCR) analysis. Chronic phase was defined as peripheral blast count of less than 5% and the presence of less than 10% blast cells or less than 20% blasts plus promyelocytes in the marrow. Accelerated phase was defined as peripheral blasts more than 5% and the presence of 10% blast cells or 20% blasts plus promyelocytes in the marrow. Blast phase was defined as blast cells more than 30% in the bone marrow. Chronic phase interferon resistant was defined as who failed to achieve any cytogenetic response on bone marrow in six months time.

Before the start of Imatinib mesylate, complete blood count, liver function tests, serum creatinine and electrolytes were done. While on Imatinib mesylate complete blood counts were done once a week, while the other investigations were performed in four weeks time. Treatment was held if absolute neutrophil count dropped below 500/cumm and platelet count less than 10,000/cumm in patients with blast crisis and accelerated phase. In patients with chronic phase disease, the dose of the drug

was titrated with absolute neutrophil count of 1000/cumm and platelet count of 50,000/cumm.

Patients in chronic phase were treated with oral Imatinib mesylate at a dose of 400mg daily for a period of at least three months. Similarly patients of accelerated phase and blast crisis were started on Imatinib mesylate 600mg daily for three months. Treatment with Imatinib mesylate was held in those patients who achieved complete cytogenetic response on bone marrow and negative PCR examination for bcr-abl on blood. Complete blood counts and bcr-abl translocation in whole blood was performed monthly in patients who achieved complete cytogenetic response and treatment was restarted when the bcr-abl translocation reappeared in the blood.

Hematological response was evaluated after four weeks of Imatinib mesylate therapy.

Chronic phase patients: white blood cells less than 10,000/cumm, platelets less than 450,000/cumm, myelocytes plus metamyelocytes less than 5% in the blood, no blasts and promyelocytes in the blood and basophils less than 20%.

**Accelerated phase and blast crisis**

No evidence of blasts on peripheral film examination, absolute neutrophil count more than 1,000/cumm and platelet counts more than 20,000/cumm or return to chronic phase as described above.

Cytogenetic response was assessed at three months interval while evaluating cells for presence of Philadelphia chromosomes in bone marrow. At least fifteen cells were counted. A major response combines both complete and partial responses and that are defined as:

Complete: Zero percent Philadelphia positive metaphases in bone marrow.

Partial: 1% to 35% Philadelphia positive metaphases in bone marrow.

bcr-abl translocation in whole blood was examined who achieved complete cytogenetic response on bone marrow examination.

## Results

Eleven patients received Imatinib mesylate. At the start of the therapy, four patients were in blast crisis and one in accelerated phase. Among the remaining six patients, two were interferon resistant in chronic phase while the other four were in denovo chronic phase. Mean age of the patients was 39.5years, median age 51years (range 21-69). Male to female ratio was 7:4. Median follow up was 34-weeks (range 8-78 weeks). The other characteristics of patients are given in Tables 1 and 2.

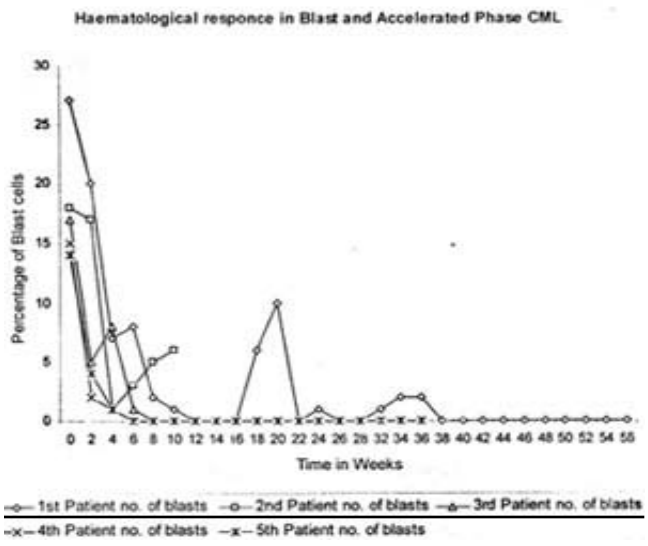
All patients achieved hematological responses

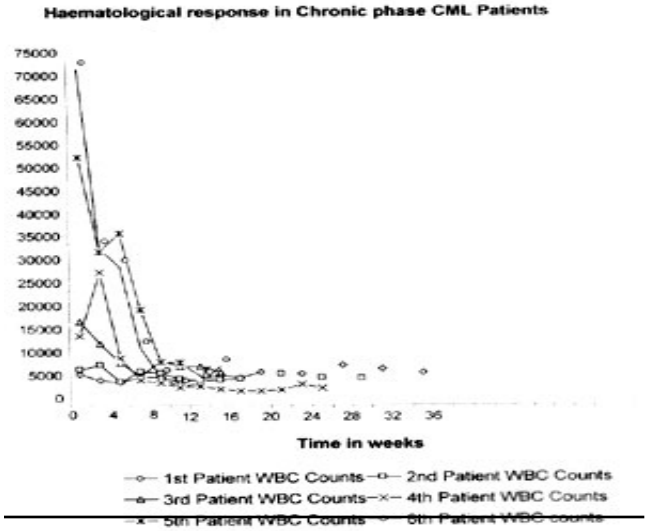
**Table 1. Characteristics of patients in blast and accelerated phase of CML.**

| No. | Age | Gender | Date of Diagnosis | Disease phase at start of Imatinib | Dosage of Imatinib | Weeks on Imatinib |
|---|---|---|---|---|---|---|
| 1 | 69 | F | June 1994 | Blast | 600 | 78 |
| 2 | 51 | M | September 1998 | Blast | 600 | 08 |
| 3 | 51 | F | June 1997 | Blast | 600 | 11 |
| 4 | 35 | M | November 2001 | Blast | 600 | 21 |
| 5 | 55 | M | May 2000 | Accelerated | 600 | 57 |

**Table 2. Characteristics of patients in chronic phase of CML.**

| No. | Age | Gender | Date of Diagnosis | Disease phase | Dosage | Weeks on Glivec |
|---|---|---|---|---|---|---|
| 1 | 34 | M | September 1994 | IFN resistant Chronic | 400 | 68 |
| 2 | 43 | M | February 2000 | IFN resistant Chronic | 400 | 40 |
| 3 | 52 | M | December 2000 | Chronic phase | 400 | 32 |
| 4 | 37 | F | February 1999 | Chronic phase | 400 | 50 |
| 5 | 21 | F | May 2000 | Chronic phase | 400 | 10 |
| 6 | 37 | M | December 2001 | Chronic phase | 400 | 12 |




(Figures 1 and 2). Out of four patients of blast crisis, two went into chronic phase, the other two showed disappearance of blast cells, however, one of them expired after 8-weeks of therapy secondary to sepsis while the other patient revealed an initial response to drug but died of progressive disease after eleven weeks. Only one patient was in accelerated phase and he achieved complete hematological response in 8 weeks.

All six patients in chronic phase achieved complete hematological responses, but one of them developed blast crisis after 32-weeks of Imatinib therapy and died due to progressive disease.

Cytogenetic responses were evaluable in six patients (Table 3). Three were responders and the remaining three were non-responders. Out of three responders, two attained complete response and one showed partial response. All of them were in chronic phase. In the two patients who achieved complete cytogenetic response, bcr-abl translocation was not found in the blood.

**Table 3. Hematological and cytogenetic response.**

| | |
|---|---|
| **Hematological response** | |
| Response evaluable | 11 patients |
| Return to chronic phase and clearance of blasts | 5 patients (4 blast phase, 1 accelerated phase) |
| Normalization of counts | 6 patients (chronic phase) |
| **Cytogenetic response** | |
| Response evaluable | 6 patients |
| Responders | 3 patients |
| Non responders | 3 patients |
| Complete response ( 0 % Ph chromosome positive metaphases) | 2 patients |
| Partial response ( 1-35% Ph Chromosome positive metaphases) | 1 patient |

## Discussion

Chronic myeloid leukemia is invariably a fatal disease and only a small number of patients achieve cytogenetic response to interferon and few others are fortunate enough to receive HLA matched bone marrow transplant.[6] Imatinib mesylate which was marketed in year 2001 is probably the first drug which acts at the molecular level and is effective enough to produce remarkable results in an indolent malignancy. In phase III trials the most notable thing is the cytogenetic response of 49% in patients with chronic phase interferon resistant group.[5] Cytogenetic response is not only noted in chronic phase interferon resistant group but a substantial number of patients in accelerated phase and blast crisis attain cytogenetic remission which is not reported with any other form of therapy.

In a recently published study those patients who were in chronic phase interferon resistant group, the hematological and cytogenetic responses were 95% and 60% respectively after a follow-up of 18 months.[7] In another study the cytogenetic response was assessed after a follow-up of 14 months and approximately 1/3 of the patients were resistant, 1/3 were partial responders and 1/3 were complete responders.[8]

In this study six patients were in chronic phase, out of which two were interferon resistant, one expired because of blast transformation even though he was started on Imatinib mesylate soon after the diagnosis. In the remaining five patients, three showed cytogenetic response however one patient relapsed soon after cessation of therapy.

Four patients were in blast crisis, two patients returned to chronic phase with therapy while other two expired because of progressive disease and sepsis after an initial hematological response. Only one patient was in accelerated phase who achieved an excellent hematological response.

The drug was well tolerated and only minimal adverse reactions were noted including nausea, vomiting, periorbital edema and fluid retention.

In summary, our study is small but patients belonging to all phases of the disease were included. Hematological response was excellent. The most notable finding is the clearance of blasts and return to chronic phase in patients with blast crisis which is also noted in another study.[9] One of our patient is in chronic phase with a follow-up of more than one and a half year with continuing Imatinib therapy. However there was mixed cytogenetic response. The two patients who achieved complete cytogenetic response relapsed in twelve weeks time. This indicates that the therapy with Imatinib mesylate may need to be continued indefinitely for maintenance of hematological and cytogenetic responses. Despite the promising results, the resistance to Imatinib mesylate is a major concern.[10]

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