Chronic Phase Chronic Myeloid Leukemia: Response of Imatinib Mesylate and Significance of Sokal Score, Age and Disease Duration in Predicting the Hematological and Cytogenetic Response

M Usman*, NN Syed**, GN Kakepoto***, SN Adil*, M Khurshid+

Abstract

Objective: To evaluate the response of imatinib mesylate in chronic phase of chronic myeloid leukemia and to observe the significance of Sokal score and various factors which predict the response.

Methods: This was a descriptive, prospective study conducted from May 2001 to September 2006. One hundred and thirty six patients with diagnosis of chronic myeloid leukemia in chronic phase were analyzed. Hematologic and cytogenetic responses were assessed according to defined criteria.

Results: The median age at time of diagnosis was 33 years (range, 12-65 years). Among them 86 were males, 50 were females. At the end of study response was analyzed overall and according to Sokal score. At median follow-up of 18 months, 122 patients were evaluable for cytogenetic response. Complete hematologic response was seen 86% while complete and major cytogenetic response was observed in 34.4% and 49.2% cases respectively.

Analysis of variables like younger age, disease duration at time of starting imatinib failed to show any significant influence on response to imatinib mesylate, however, response was found to be higher in patients who had low Sokal score at the time of presentation.

Conclusion: Imatinib mesylate has substantial activity in chronic phase of CML. Low Sokal score at time of presentation predict the higher hematologic as well as cytogenetic response in patients with chronic phase.

INTRODUCTION

Chronic myeloid leukemia (CML) is a clonal haemopoietic disorder which is characterized by a specific translocation t(9;22)(q34;q11), the Philadelphia chromosome which is a dysregulated tyrosine kinase, which is sufficient for leukaemogenesis.

Imatinib mesylate (Glivec, Gleevec), the most successful new generation of specific inhibitor of signal transduction, inhibits the BCR/ABL tyrosine kinase activity by competing with ATP at the ATP binding site of BCR/ABL, leading to decreased phosphorylation on the tyrosine.

Among the other available options allogenic bone marrow transplantation is curable but less than 30% patients have an HLA matched sibling donor. Interferon-α produces complete cytogenetic response in variable number of cases and Hydroxyurea cannot induce cytogenetic response. Clinical trials of imatinib mesylate have shown promising results in chronic phase of CML.

Based on laboratory and clinical parameters at time of presentation, there are uncertainties regarding traditional prognostic indicators, such as Sokal and Hasford scores. Whether these scores predict response to imatinib mesylate in CML is still not clear.

Here in, we analyzed the response rate of imatinib mesylate in chronic phase of chronic myeloid leukemia and the significance of Sokal score and other prognostic factors to predict the response.

MATERIAL AND METHODS

This was a descriptive, prospective analysis conducted over a period extending from May 2001 to September...
Patients with Ph and/or BCR/ABL positive CML (chronic phase according to WHO criteria), in all age groups and both sex treated with imatinib mesylate at Aga Khan University Hospital with support of Max foundation sponsored multinational study were recruited after obtaining informed consent.

The diagnosis of CML was based on characteristic peripheral blood smear and bone marrow examination findings and was confirmed by presence of Philadelphia chromosome on bone marrow cytogenetic studies or detection of BCR/ABL translocation by polymerase chain reaction (PCR).

**Chronic phase:**

Chronic phase was defined by leucocytosis with peripheral blast cells counts less than 5% and bone marrow hypercellularity with presence of blast cells less than 10% of bone marrow nucleated cells.

**Treatment protocol:**

All patients underwent a complete physical examination and the baseline spleen size was recorded. Treatment was started at dose of 400mg/day. Before starting imatinib mesylate, complete blood count, serum creatinine and electrolytes were checked.

While on therapy complete blood counts were monitored weekly for the first month and then fortnightly thereafter till patient achieved hematological response and then monthly. Treatment was held if absolute neutrophils count dropped below 500/cumm and platelets less than 50,000/cumm. On recovery, therapy was resumed at the full initial dose.

Hematological response was evaluated after four weeks of commencement of therapy.

**Response criteria:**

- **Complete hematological response (CHR):** was defined as normalization of the bone marrow (blast cells less than or equal to 5%) for at least four weeks and the peripheral leucocyte count <10 x 10^9/L and platelets <450 x 10^9/L, without peripheral blasts, promyelocytes and myelocytes), in addition to the disappearance of all signs and symptoms of CML.

Cytogenetic analysis of bone marrow metaphases was performed every 3-6 monthly. Cytogenetic response was based on the proportion of the Ph-positive metaphases among at least 20 metaphases, and was defined as complete cytogenetic response; CCR (0% Ph-positive metaphases), partial cytogenetic response; PCR (Ph-positive 1-35%), and rest of the other responses were merged in a single category; no cytogenetic response (>35% Ph positive metaphases)

Major cytogenetic response was characterized as combination of both complete and partial cytogenetic responses.

Clonal cytogenetic evolution (CE) was defined as the appearance of additional chromosomal aberration in at least two metaphases.

Cytogenetic response was not assessed in patients with overt hematologic progression.

We applied Sokal score in our patients for risk stratification at the time of presentation by using four clinical variables: age; size of spleen; percentage of blast cells and platelet count. The hazard ratio (Sokal score) was calculated by entering data in the following equation:

\[
\text{Exp} [0.116 \times \text{(age- 43.4)}] +0.0345 \times \text{(spleen size-7.51)} +0.188 [(\text{platelets/700})-0.563] +0.0887 \times \text{(blast %-2.10)}.
\]

This classification divides patients into three groups: low risk group (sokal score <0.8), intermediate risk (sokal 0.8-1.2) and high risk group in which sokal score was >1.2.

**Statistical Methods:**

All statistical analysis was computed with SPSS statistical software (version 13.0.1). Data was presented as mean or median values; and percentages.

Response rate was reported as intension to treat analysis; patients who withdrew from treatment before a confirmed response were counted as non-responder. Response rate was checked overall and according to Sokal scoring system and by using various other prognostic factors in all patients.

**RESULTS**

A total of one hundred and thirty six patients were registered over a period of five years. The median age at time of presentation was 33 years (range, 12-65 years) among these 86 were males and 50 were females (M:F 1.7:1). Only two patients were younger than 15 years at time of starting treatment with imatinib mesylate.

The laboratory and clinical parameters that were observed at first time of presentation are shown in Table 1.

In majority of cases medical opinion was sought because of abdominal fullness or distension and

<table>
<thead>
<tr>
<th>Table 1 : Patient characteristics at the time of diagnosis (n=136)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age at time of diagnosis</strong></td>
</tr>
<tr>
<td><strong>Range</strong></td>
</tr>
<tr>
<td><strong>Median age at start of Imatinib</strong></td>
</tr>
<tr>
<td><strong>Range</strong></td>
</tr>
<tr>
<td><strong>M:F</strong></td>
</tr>
<tr>
<td><strong>Prior Interferon therapy</strong></td>
</tr>
<tr>
<td><strong>Median time from diagnosis to start of Imatinib</strong></td>
</tr>
<tr>
<td><strong>Range</strong></td>
</tr>
<tr>
<td><strong>Median follow-up (months)</strong></td>
</tr>
<tr>
<td><strong>Range</strong></td>
</tr>
<tr>
<td><strong>Sokal score</strong></td>
</tr>
<tr>
<td><strong>Low risk n, (%)</strong></td>
</tr>
<tr>
<td><strong>Intermediate n, (%)</strong></td>
</tr>
</tbody>
</table>
fever. At the time of presentation; 89 patients (65.4%) had enlarged spleen; complete blood counts revealed hyperleucocytosis (WBC >100 x 10⁹/l) in 105 (77.2%), anemia (hemoglobin <10g/dl) in 50 (36.7%) and thrombocytosis (platelet >600 x 10⁹/l) in 16 (11.7%) cases.

Patients were also classified into prognostic groups using the Sokal formula at time of initial presentation. 93 (68.3%) of patients had Sokal score <0.8 which means they were in low risk group, intermediate risk group comprised of 37 (27.3%) (Sokal score 0.8-1.2) and 6 (4.4%) were high risk (Sokal score >1.2).

One hundred and thirty six patients in chronic phase were started on imatinib mesylate at standard dose of 400 mg per day; eighty patients received the drug within one year of the diagnosis. However, two patients did not tolerate full dose of therapy and received drug at lower than recommended dose.

One twenty two of 136 cases completed 6 months of treatment and are evaluable for cytogenetic response. One hundred and seventeen (86%) patients of 136 who were started on imatinib mesylate achieved complete hematologic response. Overall response rate of imatinib mesylate in chronic phase is described in Table 2.

Among 79 evaluable cases with low Sokal score, complete hematologic response was observed in 86% cases, 34 (43% of low risk group) patients had complete cytogenetic and 46 (58.2%) had major cytogenetic response (Table 3). Response among patients with low versus intermediate/high Sokal risk group was found to be statistically significant (P value = 0.03) and shown in Table 4. Analysis of age, disease duration on achievement of major cytogenetic response is described in Table 4.

Eight patients progressed to accelerated phase and eight had blast transformation. Twenty one patients showed clonal evolution and all failed to achieve cytogenetic remission with imatinib mesylate. At the end of study; nine patients expired and three were lost to follow-up.

DISCUSSION

Imatinib mesylate has changed the current approach to the management of chronic myeloid leukemia. With this therapy, the prognostic significance of some clinical variables is changing and few variables have been identified to have an impact on survival. We examined the response rate of imatinib mesylate in chronic phase of chronic myeloid leukemia and try to find out any correlation between the response and various factors.

Chronic myeloid leukemia is occurring in younger age group in our region however in western literature the median age at the time of presentation has been reported 53 years. This finding is comparable with reports from India where chronic myeloid leukemia was seen in third and fourth decades. The male to female ratio is 1.7:1 in our series which is comparable with studies from other parts of world.

Although no regional or international data was available for comparison of Sokal score at time of diagnosis. We found that substantial number of patients in our series were in intermediate or high risk group. This might be because of late presentation and delay in the diagnosis.

In our series, 86% patient achieved complete hematologic response. In contrast to this, considerable higher rate of complete hematologic response (91.8% and 99%) was observed by most. Cytogenetic response in our study is comparable with a regional report. Overall, among 122 cases complete cytogenetic response was observed in 34.4% and 49.2% had major cytogenetic response, our results are in concordance with phase II trial conducted earlier in chronic phase patients and a study by Deshmukh et al, although more encouraging results were found in studies from other part of world.

Although no regional or international data was available for comparison of Sokal score at time of diagnosis. We found that substantial number of patients in our series were in intermediate or high risk group. This might be because of late presentation and delay in the diagnosis.

In our series, 86% patient achieved complete hematologic response. In contrast to this, considerable higher rate of complete hematologic response (91.8% and 99%) was observed by most. Cytogenetic response in our study is comparable with a regional report.

Overall, among 122 cases complete cytogenetic response was observed in 34.4% and 49.2% had major cytogenetic response, our results are in concordance with phase II trial conducted earlier in chronic phase patients and a study by Deshmukh et al, although more encouraging results were found in studies from other part of world.

Table 2 : Response rate of imatinib mesylate in chronic phase of chronic myeloid leukemia

<table>
<thead>
<tr>
<th>Response</th>
<th>(n) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete hematologic response</td>
<td>117 (86%)</td>
</tr>
<tr>
<td>Cytogenetic response</td>
<td></td>
</tr>
<tr>
<td>Complete</td>
<td>42 (34.4%)</td>
</tr>
<tr>
<td>Partial</td>
<td>18 (14.7%)</td>
</tr>
<tr>
<td>Major (CR+PR)</td>
<td>60 (49.2%)</td>
</tr>
<tr>
<td>No</td>
<td>62 (50.8%)</td>
</tr>
<tr>
<td>Clonal evolution</td>
<td>21 (17.2%)</td>
</tr>
</tbody>
</table>

Table 3 : Response of imatinib mesylate according to sokal risk group

<table>
<thead>
<tr>
<th>Risk group</th>
<th>CHR</th>
<th>CCR</th>
<th>MCR</th>
<th>NCR</th>
<th>Not Evaluable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (93)</td>
<td>80</td>
<td>34</td>
<td>46</td>
<td>33</td>
<td>14</td>
</tr>
<tr>
<td>Intermediate (37)</td>
<td>32</td>
<td>7</td>
<td>13</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>High (6)</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

Table 4 : Analysis of Sokal score, age and disease duration for achievement of major cytogenetic response with imatinib mesylate

<table>
<thead>
<tr>
<th>Variable</th>
<th>Evaluatable patients, n</th>
<th>Major cytogenetic response, n (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 40 y</td>
<td>72</td>
<td>37 (51.3)</td>
<td>0.5</td>
</tr>
<tr>
<td>&gt;40 y</td>
<td>50</td>
<td>23 (46)</td>
<td></td>
</tr>
<tr>
<td>Sokal risk group</td>
<td></td>
<td></td>
<td>0.03</td>
</tr>
<tr>
<td>Low</td>
<td>79</td>
<td>46 (58.2)</td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>37</td>
<td>13 (35.1)</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>06</td>
<td>01 (16)</td>
<td></td>
</tr>
<tr>
<td>Time from diagnosis to Imatinib Mesylate, years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 1 year</td>
<td>69</td>
<td>35 (50.7)</td>
<td></td>
</tr>
<tr>
<td>&gt; 1 year</td>
<td>53</td>
<td>25 (47.1)</td>
<td></td>
</tr>
</tbody>
</table>
duration of follow-up or substantial number of patients was in intermediate or high risk category according to Sokal prognostic score. Comparing response of imatinib mesylate among Sokal risk categories, we found that our results are comparable with Rosti et al\textsuperscript{17}, reported 41%, 18% and 8% complete cytogenetic response in low, intermediate and high risk groups, respectively.

The prognostic factors which can predict response to imatinib mesylate have been of much interest.

In the present study, seventy nine patients received imatinib in an early chronic phase (within 12 months of diagnosis). Seventy two of which (91%) had complete hematologic response while in late chronic phase 45 (78.9%) out of 57 achieved complete hematologic response ($p$-value $=0.043$). Cytogenetic response was evaluable in 69 patients in early chronic phase. 35 (50.9%) achieved major cytogenetic response compared to 25 (47.1%) of 53 who were started on therapy after one year of diagnosis ($p$-value $=0.6$). Although significant difference was noted in the hematologic response among both groups but results are not comparable while cytogenetic response were evaluated. Similar to few\textsuperscript{14} the response of imatinib in early chronic phase has not really impressive or statistically significant in the present study. Although, encouraging results (major cytogenetic response-87.1%) reported in a largest study IRIS (International Randomized Study of Interferon and STI571), and established imatinib as the treatment of choice for newly diagnosed patients.

Similarly younger age group failed to show any significant correlation with major cytogenetic response with Imatinib Mesylate an observation concordance with Cervantes et al\textsuperscript{18}. In our study, lower response rate in early chronic phase and even younger age group is probably due to small sample size or substantial number of patients (43 cases) were in high or intermediate risk group according to sokal score.

However, low risk group according to Sokal scoring system at the time of diagnosis may predict higher response rate of imatinib mesylate ($p$-value$=0.03$), an observation concordance with previous studies.\textsuperscript{17-19}

Contrary to previous reports, we were not able to identify young age,\textsuperscript{15,18} time period from diagnosis to start of imatinib mesylate\textsuperscript{20} (within 12 months) as predictor of response to imatinib mesylate.

**CONCLUSION**

Imatinib mesylate is a safe and effective first line therapy for chronic phase of chronic myeloid leukemia. The introduction of imatinib in the treatment of CML has determined a high frequency of complete cytogenetic response. Although response rate in our series is less than most of the studies; however, in the current scenario of other available treatment modalities (interferon and bone marrow transplant) it seems to be the most effective treatment option. However, new tyrosine kinase inhibitors are the emerging modalities and should be utilized in the resistant cases.

This is the first large based local study from Pakistan compiling response of imatinib in CML and assessment of factors which can help to predict the response. Our results highlight only one predictive factor; however more local studies may be helpful in predicting the actual correlation in this regard.

**REFERENCES**


---

**Announcement**

**JAPI Judges for Best Paper Awards for JAPI (2006)**

We thank the judges Dr. Rajeev Gupta (Jaipur), Dr. Nandini Mukherjee (Kolkata), Dr. N.K. Hase (Mumbai), Dr. Rohini Handa (New Delhi) & Dr. N. R. Rao (Manipal) for the painstaking efforts put by them while evaluating all the articles published in JAPI for Selecting Dr. J.C. Patel and Dr. B.C. Mehta Best Paper Awards from 1st October 2005 through September 2006.

Shashank R. Joshi
Hon. Editor