RESEARCH ARTICLE

Treatment and Survival in Patients with Chronic Myeloid Leukemia in a Chronic Phase in the West of Iran

Mehrdad Payandeh1&, Masoud Sadeghi2*, Edris Sadeghi2

Abstract

**Background:** CML includes 30% of all leukemias, and occurs from childhood to old age. The present study was a retrospective analysis of chronic phase CML patients registered to a Hematology Clinic in Kermanshah, Iran, with checking of treatment options. **Materials and Methods:** Between 2002 and 2014, 85 CML patients referred to our hematologic clinic were enrolled in our study. We surveyed age, sex, B-symptoms, splenomegaly, Sokal score, Hasford score, treatment and survival in all patients. Philadelphia chromosome analysis was conducted for each patient by conventional cytogenetics. We compared treatment in the patients with three drugs, imatinib, hydroxyurea (HU) and interferon alpha (IFN-α). **Results:** The mean age of the patients at diagnosis was 47.5±14.5 years (range, 23-82 years), with 43 (50.6%) being male. Some 13 (15.3%) were referred to our clinic for the first time with B-symptoms and 44 patients (51.8%) had splenomegaly. The Sokal score for 77 (90.6%) was low, 4 (4.7%) was intermediate and 4(4.7%) was high, but Hasford (Euro) scores for all patients were low. The 5-year survival rate for treated patients with imatinib, imatinib plus HU and imatinib plus HU plus IFN-α was 90.5%, 81.1% and 55.6%, respectively. **Conclusions:** The results show that imatinib therapy alone provides better survival in CML patients compared to HU or IFN-α. Combinations of IFN-α and/or HU with imatinib probably reduce survival.

**Keywords:** Chronic myeloid leukemia - imatinib - interferon alpha - survival

Asian Pac J Cancer Prev, 16 (17), 7555-7559

Introduction

Chronic myelogenous/myeloid leukemia (CML) the most common myeloproliferative disorder, has a characteristic t (9:22) cytogenetic abnormality that involves fusion of the BCR gene on chromosome 22 with the ABL gene on chromosome 9. The BCR/ABL fusion results in constitutive activation of tyrosine kinase, which leads to uncontrolled proliferation of myeloid cells. (Payandeh et al., 2014) CML affects approximately 3000-5000 Americans each year, with the American Cancer Society expecting 4600 new cases in 2004 (Menzin et al., 2004). CML includes 30% of all leukemias, (Chavan et al., 2006) and occurs from childhood to old age (Oguz et al., 2003). Based on clinical and hematological parameters, two prognostic scoring systems, i.e., Hasford and Sokal index scoring systems are available to predict survival duration of CML patients on Imatinib therapy (Sinha et al., 2013).

Treatment for CML has changed substantially over the first few years of the 21st century. Until 2001, the standard treatment for CML was hematopoietic stem cell transplant, if possible, and Interferon alpha (IFN-α) with hydroxyurea (HU) and other chemotherapeutic agents used in cases of poor response or intolerance to IFN-α or lack of donor or inability to tolerate transplant. In May, 2001, Imatinib, the first tyrosine kinase inhibitor (TKI) specifically developed to block the activity of the Bcr-abl protein, was approved for use in CML in the United States. (European Medicines Agency, 2009) Although use of Imatinib in older patients has been shown to be safe and effective in clinical trials, its use in older patients in the general population has lagged (Pulte et al., 2013). IFN-α has been able to achieve hematologic and cytogenic remissions in a significant number of patients, and recent studies show a survival advantage for patients treated with IFN-α compared with those treated with conventional chemotherapy (Cortes et al., 1996). The 5-year relative survival for patients with CML is high, especially for younger patients, in both the US and Germany, although survival is higher in the US for some age groups. Survival is improving in both countries, with greater improvement seen among middle-aged patients (age 60-69) in the US, perhaps suggesting improved uptake of TKIs among these patients (Pulte et al., 2013).

The present study was a retrospective analysis of chronic phase CML patients registered to Hematology Clinic in Kermanshah, Iran, with checking of treatment...
Materials and Methods

Patients and Scores

In a retrospective analysis between of 2002 to 2014, 85 CML patients referred to Hematology Clinic that selected them for our study. We surveyed age, sex, B-symptoms, Splenomegaly, sokal score, hasford score, treatment and survival in all patients. Philadelphia (Ph) chromosome analysis was done for each patient by conventional cytogenetics. We compared treatment in the patients with three drugs. Dose of Imatinib, HU and IFN-α were 400mg/d, 1500 to 3000mg/d and 1000000 to 3000000U/w.

Statistic analysis


Hasford risk score in patients with CML

Total score calculation:
1. Age × 0.6666 if age > or = 50 else 0
2. 0.042 × spleen size
3. 1.0956 if platelet count > or = 1500 × 10 3 /μl else 0
4. 0.0584 × myoblast percentage
5. 0.0413 × eosinophil percentage
6. Basophil percentage × 0.2039 if basophils >3%

Total (summation of above scores)
Relative risk = Total × 1000.

As per Hasford score, a CML patient is categorized as low risk if he/she has a relative risk <780, intermediate risk if relative risk 781-1479, high risk if relative risk > or = 1480.


Sokal index in patients with CML

\[ \text{exp}[0.116 \times \text{age}-43.4] + 0.0345 \times \text{spleen size}-7.51 + 0.188 \times \text{platelets}/700 - 0.563 + 0.0887 \times \text{% blasts} - 2.1. \]

As per Sokal score, a patient is categorized as low risk if Sokal index <0.8, intermediate risk if Sokal index is 0.8-1.2 and high risk if Sokal index >1.2.

We analyzed the mean age and other variables in the patients by IBM SPSS statistics V.19. Also, the 3-year and 5-year OS were plotted by GraphPad Prism 5 software with Log-rank test and Kaplan-Meier test for comparing two or three groups.

Results

The mean age of the patients at diagnosis was 47.5±14.5 years (range, 23-82 years), with 43 patients (50.6%) male (Table 1). We divided the patients to 5 groups based on age that with increasing of age, number of patients reduce. 13 patients (15.3%) referred to clinic for the first time with B-symptoms (e.g., fever, night sweats, and weight loss) and 44 patients (51.8%) had splenomegaly. Sokal Score for 77 patients (90.6%) was low, 4 (4.7%) was intermediate and 4 (4.7%) was high, but Hasford (Euro) Score for all patients was low.

<p>| Table 1. Baseline Variables at the First Diagnosis in Patients with Chronic Myelogenous Leukemia (N=85) |</p>
<table>
<thead>
<tr>
<th>Age(year)</th>
<th>N(%)</th>
<th>Mean±SD</th>
<th>Median±SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>23-39</td>
<td>26</td>
<td>30.6</td>
<td>25.6</td>
<td>23-39</td>
</tr>
<tr>
<td>40-49</td>
<td>25</td>
<td>29.4</td>
<td>28.5</td>
<td>23-39</td>
</tr>
<tr>
<td>50-59</td>
<td>15</td>
<td>17.6</td>
<td>16.5</td>
<td>23-39</td>
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<tr>
<td>60-69</td>
<td>10</td>
<td>11.8</td>
<td>11.1</td>
<td>23-39</td>
</tr>
<tr>
<td>≥70</td>
<td>9</td>
<td>10.6</td>
<td>9.0</td>
<td>23-39</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sex</th>
<th>N(%)</th>
<th>Mean±SD</th>
<th>Median±SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>43</td>
<td>50.6</td>
<td>48.9</td>
<td>23-39</td>
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<tr>
<td>Female</td>
<td>42</td>
<td>49.4</td>
<td>48.9</td>
<td>23-39</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>B-symptoms</th>
<th>N(%)</th>
<th>Mean±SD</th>
<th>Median±SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>13</td>
<td>15.3</td>
<td>15.3</td>
<td>44(51.8)</td>
</tr>
<tr>
<td>No</td>
<td>72</td>
<td>84.7</td>
<td>84.7</td>
<td>23-39</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sokal Score</th>
<th>N(%)</th>
<th>Mean±SD</th>
<th>Median±SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>77</td>
<td>90.6</td>
<td>90.6</td>
<td>23-39</td>
</tr>
<tr>
<td>Intermediate</td>
<td>4</td>
<td>4.7</td>
<td>4.7</td>
<td>23-39</td>
</tr>
<tr>
<td>High</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>23-39</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hasford (Euro) Score</th>
<th>N(%)</th>
<th>Mean±SD</th>
<th>Median±SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>85</td>
<td>100</td>
<td>100</td>
<td>23-39</td>
</tr>
<tr>
<td>Intermediate</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>23-39</td>
</tr>
<tr>
<td>High</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>23-39</td>
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</table>

Table 2. Experimental Variables at the First Diagnosis in Patients with Chronic Myelogenous Leukemia (N=85)

<table>
<thead>
<tr>
<th>Experimental Variables</th>
<th>Mean</th>
<th>Range</th>
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</thead>
<tbody>
<tr>
<td>Platelet(x10^3/μL)</td>
<td>393</td>
<td>13-1280</td>
</tr>
<tr>
<td>Hemoglobin(g/dL)</td>
<td>10.9</td>
<td>6-15.6</td>
</tr>
<tr>
<td>WBC(x10^3/μL)</td>
<td>82</td>
<td>10-630</td>
</tr>
</tbody>
</table>
Comparison of the 5-year survival based on type of treatment in patients with CML has been shown in Figure 3. Of 85 patients, 22 patients (25.9%) were treated with Imatinib, 41 (48.2%) with Imatinib plus HU and 9 (10.6) with Imatinib plus HU plus IFN-α (Table 1). The 5-year survival rate for treated patients with Imatinib, Imatinib plus HU and Imatinib plus HU plus IFN-α was 90.5%, 81.1% and 55.6%, respectively. Also, the mean survival was 38.4, 40.4 and 40.6, respectively.

Discussion

CML is a chronic disease that about 50% of patients are more than 60 years old, and about 50% of patients are asymptomatic (Payandeh et al., 2015). The known genetic abnormality associated with CML is the condition known as Philadelphia chromosome, which occurs as a result of reciprocal translocation between chromosome 9 and 22 leading to juxta-position of BCR-ABL gene (Bhat et al., 2012).

CML is more prevalent in males as compared to females (Redaelli et al., 2004). A number of studies reported that for CML, percentage of male is more than female (Bhat et al., 2012; Chavan et al., 2006; Irfan and Bhurgri, 2009; Usman et al., 2009) and also the mean age for the patients is around between 40 to 50 years (Chavan et al., 2006; Irfan and Bhurgri, 2009; Bhat et al., 2012) that our study confirmed these results, but in other study (Usman et al., 2007), the median age at time of diagnosis was 33 years. These results show that percentage of males is more than females for CML and also the mean age and median age at diagnosis for the patients in majority of studies is around 40-50 years.

Previous studies (Irfan and Bhurgri, 2009; Usmani et al., 2009) reported that Philadelphia chromosome (Ph chromosome) with standard translocation t (9;22) was seen in more than 90% patients with CML and also Ph chromosome was positive in more than 98% patients that also our study confirmed the results, but other study (Chavan et al., 2006) reported that out of the 175 cases, 96 cases (86.5%) showed the presence of Philadelphia (Ph') chromosome with standard translocation t (9;22). Therefore, we can say that Ph chromosome with standard translocation t (9;22) is positive more than 98% CML patients in majority of studies.

In a study (Usmani et al., 2006) more than 95% patients had presented with fever, fatigue, left upper quadrant pain or a combination of the above to other hospitals where the diagnosis was suggested on CBC and splenomegaly was present in 90% of chronic phase, but in our study, 15.3% patients were presented with B-symptom and 51.8% with splenomegaly. The results show that quality of tests in our area is better and awareness of the patients about the dangers of this disease is higher and therefore the patients come to the clinic, before exacerbate symptoms.

In a study (Irfan and Bhurgri, 2009) was checked CBC in one hundred and seventy six patients that the mean hemoglobin, WBC and platelet counts are higher than other study that it need more studies about the means and relationship between them and CML. A study (Pulte et al., 2013) reported that the five-year relative survival for CML patients was 68.7% overall in Germany and 72.7% in the US. In this study (Iran), the 3-year and 5-year survival were 87.5% and 79.7%, respectively. Therefore, survival in our patients in Iran is better than Germany and the US.

In this study, the 5-year survival in CML women is better than men that this difference is statistically significant. A number of studies (Berger et al., 2005; Pulte et al., 2013) are agreement with our result.

The treatment options presently available for chronic phase CML include HU, IFN-α, IFN-α plus cytarabine, Imatinib, dasatinib, and allogeneic SCT (SCT) (Henkes et al., 2008).

In our study, combination of HU and IFN-α with Imatinib reduced survival in our patients from 90.5% for Imatinib alone to 81.1% and 55.6%, respectively. Clinical trials of CML patients in chronic phase treated with Imatinib showed 5-year survival rates of nearly 90% and up to 95%. (Druker et al., 2006; Hochhaus et al., 2009).

In a study (Jain et al., 2013) was checked hematological response survival analysis in CML patients and showed significantly better results in Imatinib group when compared to HU group. In other study, (Hehmann et al., 2015).
2003) the median survival was 64 months for IFN-α/HU and 53 months for HU-treated patients. Studies (Baccarani et al., 2002; Hehlmann et al., 2003) concluded that IFN-α in combination with HU achieves a significant long-term survival advantage over HU mono-therapy. Results from over 1500 randomized patients demonstrated that IFN-α significantly improved patient survival, with a 5-year survival rate of 50–59% compared with 29–44% for patients receiving HU (Allan et al., 1995; Ohnishi et al., 1995). Therefore, these results show that Imatinib therapy alone approves survival in CML patients compared to HU or IFN-α and also IFN-α has better survival compared to HU. Combination of IFN-α to HU is better than HU alone for treatment of patients, but combination of IFN-α and/or HU with Imatinib probably reduces survival.

Based on clinical and hematological parameters, two prognostic scoring systems, i.e., Hasford and Sokal index scoring systems are available to predict survival duration of CML patients on Imatinib therapy. Out of these 66 patients, the number of patients belonging to low, intermediate and high risk categories were 21, 33 and 12, respectively by Hasford score and 12, 32 and 22 respectively by Sokal index (Sinha et al., 2013). Of 85 patients in this study, the number of patients belonging to low, intermediate and high risk categories for Sokal score are 77, 4 and 4, respectively and all patients are low risk for Hasford score. Therefore, probably in our area (west Iran), Sokal score has better response (determination of high risk patients) compared to Hasford score and screening of patients is better that do in Iran by Sokal score for the future studies.

Number of studies reported that the incidence of CML increases with age (Menzin et al., 2004; Rohrbacher and Hasford, 2009) but this study don’t confirm it (Table 1).

In conclusion, the results show that percentage of males is more than females for CML and also the mean age and median age at diagnosis for the patients are around 40-50 years. Also, the results show that Imatinib therapy alone approves survival in CML patients compared to HU or IFN-α and also IFN-α has better survival compared to HU. Combination of IFN-α to HU is better than HU alone for treatment of patients, but combination of IFN-α and/or HU with Imatinib probably reduce survival that this last result need to more studies with emphasis on combination of IFN-α and HU with Imatinib.

References


