RESEARCH COMMUNICATION

Clinico-pathological Features and Outcomes in Chronic Phase Chronic Myeloid Leukemia Patients Treated with Hydroxyurea

Syed Muhammad Irfan¹, Yasmin Bhurgri¹,² *

Abstract

Objective: To study the clinico-pathological features and major outcomes in patients with chronic myeloid leukemia, chronic phase, treated with hydroxyurea. Methods: This is a single centre study extending from January 1997 to June 2003. Data were retrieved from the patients’ records on predetermined performa and analyzed. Patients were primarily diagnosed on the basis of clinical findings, complete blood counts and leukocyte alkaline phosphate (LAP) scores. Bone marrow/trephine and genetic studies were conducted where appropriate. Patients were primarily treated with capsule hydroxyurea 30-50/ kg/day. Results: One hundred and seventy six patients, 104 (59%) male and 72 (41%) females were included in the study. The median age at diagnosis was 39 years (range 11 to 66 years). The median delay in diagnosis was 156 days (range 30 to 360 days). Eighty four patients (47.7 %) presented with pain/discomfort in the left hypochondrium. The mean hemoglobin, white blood cell count and platelet counts were 10.3 g/dl, 141,000/UL and 341,000/UL respectively associated with a low LAP score. Hyper-leucocytosis was observed in 19 (10.7 %) cases. LDH values above 1000 ug/l were observed in 38 (21.5 %) cases and creatinin above 1.5 ug/l in 21 (12 %) cases. All patients tested, were positive for Philadelphia chromosome and bcr-abl transcripts. At the close of the study, disease advancement was observed in 76 (43.2 %) cases, of which 35 (20%) transformed to acute leukemia. One hundred and forty three patients (81%) were alive at the close of the study. One hundred and two (58.4%) patients were in chronic phase, 22 (12.5 %) in accelerated phase and 19 (10.7 %) in blast crisis. Disease progression remained the major cause of death and was seen in 29 (16.4 %) patients. Conclusion: In the study population, CML was observed in a younger age group with significant delay in definitive diagnosis. Clinico-pathological features and major outcomes, however, appear comparable to published data.

Key Words: Chronic myeloid leukemia - chronic phase - hydroxyurea - outcome - Karachi, Pakistan

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Introduction

Chronic Myeloid Leukemia (CML) is an acquired stem cell disorder characterized by uncontrolled proliferation of myeloid cells. The incidence of CML increases with age, the median age at diagnosis is 67 years with a slight male predominance (Lee, 2000). The hallmark of CML is an elevated white blood count (WBC) count, a median WBC count at diagnosis of 150,000/UL and a low leukocyte alkaline phosphate (LAP) score (Lee, 2000). Conclusive evidence of CML relies on cytogenetic and molecular studies to detect chromosomal abnormalities viz. Philadelphia chromosome (Ph) or ther presence of bcr-abl transcripts (Gale et al., 1993; Melo, 1996; Fröhling and Döhner, 2008).

Approximately 90% of CML patients are in chronic phase at diagnosis. Patients with chronic phase CML have effective immune systems and generally feel well for prolonged periods. The first 2 years after diagnosis hold the lowest risk for transformation with only 5-10% of patients developing blast crises. After 2 years, the annual progression rate increases to 20-25 % (Gratwoh et al., 1998; McGlave et al., 2000).

Currently accepted therapies for chronic phase CML, range from relatively non-toxic oral medications like hydroxyurea to allogenic stem cell transplantation (Sokal et al., 1984; Goldman et al., 1993; Campbell and Green, 2006). In the past median survival for CML was 3-4 years. With interferon based therapies, this increased to 5-6 years (Mahon et al., 1998). It is reported that the treatment of CML has changed with the introduction of imatinib mesylate (Mahon et al., 1998; Schiffer 2007). It is predicted that imatinib will lead to marked improvement in survival rates, but this remains to be proven (Drukar et al., 1998; Schiffer, 2007).

The present study was a retrospective analysis of chronic phase CML patients registered at a tertiary care public health centre in Karachi, with the primary aims of determining the biological behavior and outcomes of the disease.

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Materials and Methods

This study included 176 patients of chronic phase CML registered at a tertiary care hospital in Karachi, during 1st January 1997 to 30th June 2003.

Patients were diagnosed according to standard criteria (Hoffbrand AV et al., 1999). The patients’ data were collected on predetermined performa. All patients had basic work up done including complete blood count (CBC), renal and liver profiles, serum creatinin, lactate dehydrogenase (LDH), serum uric acid, ultrasound abdomen, X-ray chest and urine detailed report (DR). LAP score was done in 59 patients. Bone marrow/trephine biopsy was performed in patients with advancing disease. Cytogenetics and molecular genetics were done in cases with uncertain diagnosis or those who could afford it.

Exclusion criteria included patients with unstable/advanced disease at diagnosis or with a history of chemotherapy or with associated unclassified/other myeloproliferative disorders or solid malignancies and pregnant patients.

The treatment modalities used were: hydroxyurea in patients with chronic phase CML; hydroxyurea and/or busulphan in patients transformed to AML and prednisolone and/or vincristine weekly (4-6 weeks) to cases transformed to ALL. Imatinib mesylate (Glivec) was used in two cases in accelerated phase. Interferon or leukapheresis were not used in any patient. In almost 100% of the cases drugs were given to the patients through individual donors.

Results

One hundred and seventy six patients, 104 (59%) male and 72 (41%) females were included in the study. The median age at diagnosis was 39 years (range 11 to 66 years). Thirteen (7.3%) patients were below 18 years of age.

The median delay in diagnosis (days between the initial symptoms and final diagnosis) was 156 days (range 30 to 360 days). The chief presenting complaints were pain and discomfort in the left hypochondrium (84 cases; 47.7%) and symptomatic anemia with fatigue (43 cases; 24.4%). Moderate to marked splenomegaly was seen in 69 cases (39%) and mild to moderate hepatomegaly in 22 (12.5%).

The mean lab values at diagnosis were: hemoglobin 10.3 g/dl, white blood count 141,000/ul, platelet count 3,341,000/ul and a low LAP score for 51 of 59 cases tested (86.4%). Hyperleucocytosis was observed in 19 (10.7%) cases. LDH values above 1000 ug/l were seen in 38 (21.5%) cases and creatinin values above 1.5 ug/l in 21 (12%) cases. Cytogenetics and molecular genetics were performed in 19 and 3 cases respectively and all turned out to be positive. At the close of the study, disease advancement was observed in 76 (43.2%) cases (Table 1). Transformation was recorded in 35 (19.9%) cases which entered blast crisis; 29 (16.5%) had acute myeloid leukemia (AML), 2 (1.1%) had acute lymphoblastic leukemia (ALL) and in 4 (2.2%) cases, the transformation was not classified.

Table 1: Disease Outcome in Chronic Myeloid Leukemia Patients in Karachi, Pakistan

<table>
<thead>
<tr>
<th>Disease advancement</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Within 2 years of diagnosis</td>
<td>9 (5.1%)</td>
</tr>
<tr>
<td>In the 3rd year</td>
<td>18 (10.2%)</td>
</tr>
<tr>
<td>In the 4th year</td>
<td>20 (11.3%)</td>
</tr>
<tr>
<td>In the 5th year</td>
<td>14 (8.0%)</td>
</tr>
<tr>
<td>In the 6th year</td>
<td>9 (5.1%)</td>
</tr>
<tr>
<td>In the 7th year (six months)</td>
<td>6 (3.4%)</td>
</tr>
<tr>
<td>Total</td>
<td>76 (43.0%)</td>
</tr>
</tbody>
</table>

One hundred and forty three (81%) patients were alive at the end of the study. Out of these 143 patients, 102 (71.3%) were in chronic phase, 22 (15.4%) in accelerated phase and 19 (13.3%) in blast phase. Thirty three patients (11%) died during the study. Disease progression was the primary cause of death which was seen in 29 patients (87.8%); others died of unrelated causes.

Discussion

CML is a clonal disorder affecting primitive stem cells and resulting in uncontrolled proliferation of myeloid cells. The disease follows an indolent course. It usually remains stable for years and subsequently transforms to a more overt malignant disease.

CML can manifest at any age but its frequency increases steadily with age, with median age at diagnosis of 67 years (Lee, 2000). In our series CML was observed in younger patients with a median age of 39 years at diagnosis. The factors which could be responsible for this younger age presentation are likely to be genetic and/or environmental with early risk exposure.

The disease is reported to be uncommon in the pediatric age, as also observed in our series, where only 7% of the patients were below 18 years of age (Gale et al., 1993). Chronic myeloid leukemia has been reported to be more common in males than in females with a male to female ratio of 1.4:1. The male/female ratio of 1.5:1 observed in our study also reflects a similar proportion as reported in earlier studies (Gale et al., 1993).

Philadelphia (Ph) chromosome is found to be an almost constant feature of the disease indicating that acquired chromosomal abnormality could be linked to a specific malignant process. Ph chromosome and bcr-abl translocation is seen in more than 90% patients with CML. In our study Ph chromosome was positive in all (19/19) patients and bcr/abl was positive in 3/3 patients. This finding which though pathognomonic of CML is not entirely restricted to CML, as the Ph chromosome is present in 25-50% of adult patients with acute lymphoblastic leukemia and 2% with acute myelogenous leukemia (Gale et al., 1993). Considering the small number of cases in our study, it would not be justified to deduce any result on cytogenetics and molecular findings.

The presenting features of CML in our study are more or less similar to reports from developed countries; however, there is significant delay in seeking diagnosis on the part of our patients compared to west (Lee, 2000, Gale et al., 1993). This probably reflects late referrals by family practitioners and also a tendency among the
community to seek late medical advice. The heavy treatment expenses and the deprivation due to a low socioeconomic status appear at the core.

Biological behavior of the disease on treatment with hydroxyurea appears as reported by other authors (Goldman, 1997). Earlier studies describe 100% transformation in chronic phase CML after approximately 3-8 years. After 2 years, the annual progression rate increases to 20-25%. Forty one (23%) of our patients had transformed to accelerated phase and another 35 (20%) to blast crisis in about 2-6 years of diagnosis. This behavior appears well in line with the western data (Lee, 2000).

Survival of our patients also appears comparable with the previously reported studies. Thirty three (18.7%) of our patients died within 2-6 years of diagnosis. In our observation 29 (16.4%) deaths were caused by progression of primary disease. This is in line with other studies, which report that more than 80% of CML patients treated with hydroxyurea or busulphan will eventually die of their disease despite the older age of the affected population (Cannelos et al., 1976; Coleman et al, 1980; Lee, 2000).

In conclusion, chronic myeloid leukemia in our population is observed in a relatively young age group with significant delay in definitive diagnosis. Clinico-pathological features and major outcomes, however, appear comparable to published data. The possibility of early exposure to environmental risk factors needs consideration and large scale epidemiological studies.

References

