INTRODUCTION

Chronic myeloid leukaemia is a clonal disease that results from an acquired genetic change in a pluripotential hematopoietic stem cell. It is characterized by balanced reciprocal translocation involving chromosome 9 and 22, which creates the Philadelphia (Ph') chromosome. The generation of Philadelphia chromosome is associated with the formation of break point cluster region-abelson (BCR-ABL) chimeric gene associated with increased tyrosine kinase activity, which is now believed to play a central role in the pathogenesis of CML.1 The natural history of CML is a triphasic process. In the two years after initial diagnosis of CML, 5-15% of untreated patients will enter Blast Crisis (BC). In subsequent years, the annual rate of progression increases to 20-25% commonly occurring between 3 and 6 years after diagnosis.2

With the advent of imatinib, a selective tyrosine kinase inhibitor in 1998, this has since been shown to produce impressive results in the treatment of patients with CML in chronic phase.3,4 Molecular targeted BCR-ABL kinase inhibitors have changed the paradigm and are now considered first-line treatment for CML. Allogenic stem cell transplant is still the only proven curable treatment for CML. Next generation kinase inhibitors hold promise for patients having imatinib resistance.5,6 Current data on CML, at the time of presentation in the West, revealed that 96.8% reported in chronic phase, 2.2% in accelerated phase, while 0.9% found in blast crisis.7

CML accounts for 15% of all adult leukaemias in the West with slight male preponderance. The only known risk factor for the development of this disease is exposure to ionizing radiation in high doses. The most rewarding results in this disease are only achieved when treated in early chronic phase with any modality of its treatment.8-10

Local studies indicate that CML behaves quite differently in developing countries as compared to the Western population.10 CML has identical response to treatment in both the communities.11,12 This study was carried out to determine the behaviour of CML by evaluation of phase at presentation.

METHODOLOGY

This descriptive study was conducted in the Oncology Department, Combined Military Hospital (CMH), Rawalpindi, from June 2006 to December 2007. On their first presentation in outpatient department, all CML patients newly diagnosed on blood complete picture and bone marrow examination, aged 18 years or above, were included. Any case of CML received prior chemotherapy and patients not consenting to participate were excluded from the study. Informed written consent was obtained from every patient and permission to undertake the

ABSTRACT

Objective: To determine the frequency of three phases of chronic myeloid leukaemia at first presentation.

Study Design: Case series.

Place and Duration of Study: Department of Oncology, Combined Military Hospital (CMH), Rawalpindi, from June 2006 to December 2007.

Methodology: Forty-five patients of either gender with Chronic Myeloid Leukaemia (CML) at their first presentation in outpatient department were included in the study by consecutive sampling technique. All patients were diagnosed on blood complete picture and bone marrow examination including aspiration, trephine and cytogenetics at Armed Forces Institute of Pathology (AFIP). Each phase was defined on the basis of World Health Organization (WHO) criteria.

Results: Out of 45, there were 31 (68.9%) male and 14 (31.1%) female patients. The mean age of presentation was 37.9 years. The pattern of presentation revealed 35 (77.8%) in Chronic Phase (CP), 7 (15.5%) in Accelerated Phase (AP) and 3 (6.7%) in Blast Crisis (BC). Philadelphia chromosome was detected in 39 (86.7%) cases on culture method. Splenomegaly was observed in 37 (82.2%) patients. The mean total leukocyte count, platelet count, haemoglobin and marrow blast were 214.3x10^9/L, 551.4x10^9/L, 9.94 g/dl and 9.3% respectively.

Conclusion: CML presented at a younger age in the chronic phase.

Key words: Chronic myeloid leukaemia. Philadelphia chromosome. Chronic phase.
study was sought from the hospital ethical committee. A detailed history was taken followed by a thorough physical examination of each patient. Investigations including blood complete picture with differential counts, platelet count, bone marrow aspiration, trephine and cytogenetics were carried out by consultant haematologist in Haematology Department of AFIP, Rawalpindi. The cytogenetics were done with the help of Giemsa-trypsin banding culture method of blood or bone marrow. At least 20 metaphases in each were examined to identify standard translocation of chromosome 9 and 22 in the region of q34;q11. Due to cost factor, methods to detect BCR-ABL fusion gene were not used in Ph' negative patients. Data was entered in a specially-designed data card. After completion of investigations, each phase of CML was defined on the basis of WHO criteria. CP was defined as myeloid blasts less than 10% in peripheral blood or bone marrow, while AP and BP were defined with 10-19% and more than 20% blasts respectively.

The data were analyzed through SPSS for windows version 10. The numerical data such as age and laboratory variables like haemoglobin, total leucocytes count, platelets and blasts were reported as mean ± S.D. The categorical data like gender of the patient, cytogenetics and different phases of disease were calculated and expressed as frequencies (percentages).

**RESULTS**

During the 18 months, 45 cases of chronic myeloid leukaemia were enrolled and analyzed. There were 31 (68.9%) male and 14 (31.1%) female patients with male to female ratio of 2.2:1. The mean age of presentation was 37.87 ± 12.1 years (ranging from 18 to 65 years). Seventeen patients (37.8%) were in their fourth decade of life, while 9 (20%) were in third decade, 7 (15.5%) each in fifth and sixth decade, 4 (8.9%) in second and 1 (2.2%) in seventh decade of life. At the time of diagnosis, 35 (77.8%) were in chronic phase, 7 (15.5%) in accelerated phase and 3 (6.7%) were in blast crisis. The highest number of patients, 15 (33.3%), were in the fourth decade, 4 (8.8%) in second and 1 (2.2%) in seventh decade of life. Philadelphia chromosome was detected in 39 (86.7%) cases, whereas 6 (13.3%) cases had normal karyotype. Maximum number of Philadelphia positive cases, 14 (31.1%), were in the fourth decade. Twenty-eight (62.2%) were male, while 11 (24.4%) were female patients. Splenomegaly was found in 37 (82.2%) and hepatomegaly in 7 (15.5%) cases. The maximum spleen size observed was 25 cm below left costal margin, while maximum recorded hepatomegaly was 8 cm. Mean haemoglobin was 9.94 g/dl (± SD 1.8 – range 6.3-14.4). Mild anaemia (Hb 9-12 g/dl) was observed in 21 (46.7%), moderate anaemia (Hb 6-9 g/dl) in another 15 (33.3%) while remaining 9 (20%) had haemoglobin within normal range. The mean TLC, platelets, blood and marrow blasts were 214.3x10^9/L, 551.4x10^9/L, 3.4% and 9.3% respectively. The various laboratory findings in different phases of CML are shown in Table II.

**DISCUSSION**

The natural history of chronic myeloid leukaemia has changed in recent years, partly as a result of earlier diagnosis but mostly due to availability of effective therapies. CML is extensively studied in the West but there is paucity of data available in the country. The disease characterization originates from the West like...
many other diseases described in the literature. Whether such characterization holds true when applied to patients in the developing countries is uncertain. In this study, the mean age of presentation in CML was 37.87 years (range 18-65 years), which is significantly younger age than reported in European7 (median age 55 years) and American literature15 (median age 66 years). Local series results are in conformity with the present observation, where the mean age of presentation is 34-37 years.11,16-18 while in a regional Indian study, the mean age was 42.76 years.20 There was no identifiable contributing factor that would explain the occurrence of CML at young age in this population. This study also provides the basis for future research, exploring the risk factors leading to early onset of CML. CML should be included in the differential diagnosis of patients presenting with leucocytosis and splenomegaly even at younger age.17 Fortunately, the impact of new therapies on CML has significantly increased long-term survival in young patients; 10-year relative survival increased from 16-72% in age group 15-44 years in a large German study,19 hence, providing a better future hope for the affected population. The male to female ratio in this study was 2.2:1. In other local studies, this ratio was 2:112 and 1.5:1,17 while in a regional Indian study, it was 1.9:1.20 High male to female ratio in this case was probably due to restricted entitlement factor in armed forces. The frequency of all three phases of CML at their presentation in this study was 77.8%, 15.5%, and 6.7% in CP, AP and BC respectively. A locally conducted study, which included 275 cases of CML, revealed the frequency of CP, AP and BC as 87.3%, 8.1% and 4.7% respectively.12 In a large multi-centered French study, at the time of diagnosis, the frequency of CP, AP and BC were 96.8%, 2.2% and 0.9% respectively.7 Comparing own data with this study, the frequency of CP was lower in this case series, while AP and BC were higher. The possible explanation can be either reporting late by patients in our community or the natural behaviour of disease is different. In another local series, the frequency of CP, AP and BC were 72.6%, 19.7% and 7.8% respectively.16 The clinico-epidemiological features of this study also correlate with other local investigators with small variations.16-18 The data of this study further elaborated that male gender dominated in all phases of CML. Female patients presented relatively at higher age brackets in all phases than men. However, the number of female patients is low to represent the true picture. It was also observed that female were more anaemic, possibly due to their menstrual loss in pre-menopausal cases. The age of presentation in blast crisis was quite early (mean age: 30 years) associated with moderate to severe anaemia. This was probably due to the aggressive behaviour of the disease right from the outset. Spleen was palpable in all patients of AP and BC, while three-fourth patients had splenomegaly in CP, which is higher than what is described in the Western literature,21,22 however, it is similar to the local series.16 Total leucocyte and platelet counts were higher in CP than AP and BC. The Philadelphia chromosome positivity was observed more consistently in BC than AC and CP. Due to cost factor, we could not carry out methods to detect BCR-ABL in this study, therefore, the percentage of Philadelphia chromosome was marginally low (86.7%). Moreover, these observations were comparable with regional Indian study, where successful culture-based Philadelphia detection was 86.5%.20 The clinical and laboratory findings like splenomegaly, hepatomegaly and blood counts were in conformity with those of other investigators.16,17 There was little correlation observed between TLC and spleen size. There were some limitations in the study. The study population did not represent the whole picture due to restricted entitlement in armed forces. We did not segregate the ethnic groups, socioeconomic background and educational status of the patients. However, this will be one step forward for future research addressing all these issues.

CONCLUSION
CML affects people at a young age in our population. High proportion of patients present in aggressive phase of the disease.

REFERENCES


