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Clinico-pathologic features of chronic myeloid leukemia and risk stratification according to sokal score

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ORIGINAL ARTICLE

CLINICO-PATHOLOGIC FEATURES OF CHRONIC MYELOID LEUKEMIA AND RISK STRATIFICATION ACCORDING TO SOKAL SCORE

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ABSTRACT

Objective: To compile the clinical and haematological parameters of chronic myeloid leukemia (CML) and risk stratification according to Sokal score in our population.

Design: A descriptive analysis.

Place and Duration of Study: The Aga Khan University Hospital, during the period from August 1997 to August 2005.

Subjects and Methods: All patients with diagnosis of chronic myeloid leukemia treated as outpatient in haematology clinic, or admitted in haem-oncology wards in The Aga Khan University Hospital were included. Records were retrospectively analyzed for clinicopathologic features. Risk groups were assigned as per Sokal scoring.

Results: During the 8 years study period, 245 patients with chronic myeloid leukemia were analyzed, the median age of presentation was 35 years (range 11-73); with male to female ratio 1.69:1. At the time of diagnosis, 178 patients (72.6%), 48 (19.7%) and 17 (7.8%) of patients were in chronic, accelerated and blast phase of the disease respectively. Abdominal fullness was the frequent clinical presentation followed by fever. Laboratory parameters revealed mean hemoglobin 10.0 g/dl (range 4.6-15), mean total leukocyte count 168x10^9/L (35-959) and mean platelets 408x10^9/L (range 30-2335). The mean size of spleen at the time of presentation was 9.2 cm below the left subcostal margin. A large number of patients (46.2%) were in high risk group according to Sokal score i.e. >1.2.

Conclusion: CML occured more commonly at younger age in this series. Most of these patients were in high risk group according to Sokal score.

KEY WORDS: *Chronic myeloid leukemia. Sokal score. Philadelphia chromosome.*

INTRODUCTION

Chronic myeloid leukemia (CML), a clonal disorder, results from the neoplastic transformation of primitive hemopoietic stem cell[1,2], in which cells of myeloid lineage undergo massive clonal expansion.[3] The hallmark of CML is the formation of a BCR-ABL fusion gene[4], results from reciprocal translocation of chromosomal material between long arm of chromosome 22 and 9, an event referred as t(9;22) (q34;q11), Philadelphia chromosome (ph).[5,6]

CML is a rare disease[7]; however, incidence appears to be constant worldwide. It occurs in about 1.0-1.5 per 100,000 of the population per annum in all countries where statistics are adequate.[7,8]

Most of the cases identified in 5th and 6th decades of life[7]; with the median age at diagnosis of CML is 50-60 years. Less than 10% of cases occur under 20 years of age.[2,8,9] Recently there has been a decrease in proportion of patient aged above 60 years.[10] The disease occurs slightly more often in men than women but have similar clinical manifestation and course.[9]

There is no familial predisposition and no definite association with HLA genotype has been recognized.[7,8] No contributory infectious agent has been incriminated.[8]

Despite the presence of a uniform molecular abnormality, CML demonstrates a paradoxical clinical heterogeneity.[10,11] Clinically, CML is characterized by biphasic or triphasic course, usually diagnosed in chronic phase in over 80% of cases.[2,5] Approximately two-third of patients go through an intermediate phase known as acceterated phase before progression to blast phase.[11]

The presenting features of chronic myeloid leukemia are variable.[2] ranging from silent disease to nonspecific symptoms and signs including fatigue, weight loss, night sweats, hyperleucocytosis and splenomegaly mostly.

Various clinical and laboratory parameters have been identified to have prognostic significance; based on these several prognostic models have been developed to classify patients in to risk groups with different prognoses.[12,13] Among them most widely used is one proposed in 1984 by Sokal and colleagues[14]; which helps to determine the aggressiveness of the disease and median survival.

The objective of this study was to compile the clinical and haematological parameters of CML and risk stratification according to Sokal score in our population.

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Subjects and Methods

This was a descriptive study conducted during the period from August 1997 to August 2005. The files of all patients with a diagnosis of chronic myeloid leukemia treated as out-patient in hematology clinic, or admitted in haem-oncology wards in The Aga Khan University Hospital during the study period were retrieved from medical record section, which use international classification of disease (ICD 9.0 version) database.

The diagnosis of these patients was made by complete blood count done on Coulter S+IV (Coulter Electronics, Florida, USA); bone marrow aspirate and trephine and bone marrow cytogenetics. Where necessary; BCR/ABL by polymerase chain reaction (PCR) was performed. The disease was classified into the chronic, accelerated or blast phases by using WHO criteria.[15] These cases were analyzed for their clinical manifestations and hemograms.

Sokal score was applied 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.[2,14]

Exp [0.116 (age- 43.4)] +0.0345 (spleen size-7.51) +0.188 [(platelets/700)^2-0.563] +0.0887 (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.[14]

Data was presented as mean and median values. All data was analyzed by using SPSS program (statistical package for social sciences) version 13.0.

Results

A total of 245 patients were diagnosed to have chronic myeloid leukemia, over a period of 8 years. The median age at the time of diagnosis was 35 years (range 11-73). Majority of patients, 154 (64%), were less than 40 years of age at the time of diagnosis. The peak incidence of CML (27%) was seen in 31-40 years age group (Figure 1).

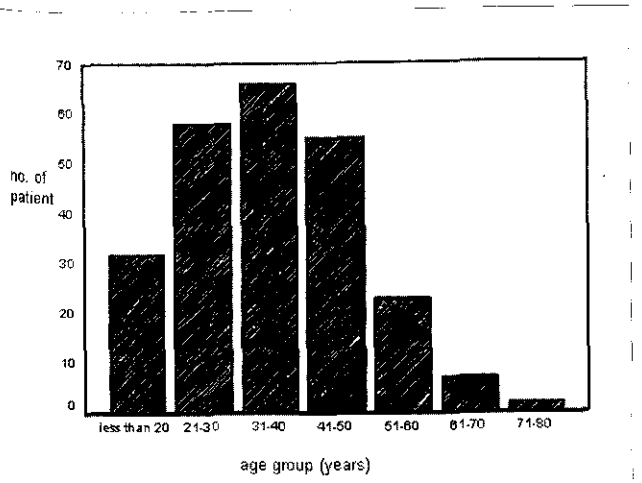

Figure 1: Age groups in chronic myeloid leukemia.

The series included 154 males (63%) and 91 females (37%). Male to female ratio was 1.69:1. At the time of diagnosis, chronic phase was seen in 178 patients (72.6%), 48 (19.7%) had accelerated phase of the disease and 19 (7.8%) were in blast transformation of chronic myeloid leukemia, according to WHO[15] criteria for phase of the disease.

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

Table I: Laboratory and clinical parameters at the time of presentation.

Presenting features	
Routine blood tests	101 (41.2%)
Abdominal fullness	97 (39.5%)
Fever	69 (28.1%)
Fatigue	40 (16.3%)
Weight loss	23 (9.3%)
Bleeding episodes	14 (5.7%)
Cytopenias	9 (3.6%)
Hemogram	
Mean hemoglobin (g/dl) range	10.0 4.6-15.2
Mean total leukocyte count (x10^9/l) range	168 35-959
Mean platelet counts (x10^9/l) range	408 30-2335
Mean size of spleen (cm)	9.2 cm

In most of the cases medical opinion was sought because the blood tests performed on a routine check-up, showed high white cell count. However, common presenting symptoms were abdominal fullness or distension, fever, fatigue and weight loss.

At the time of presentation, 220 patients (89%) had enlarged spleen; complete blood counts revealed hyperleucocytosis (WBC >100x10^9/l) in 121 (49%), anemia (hemoglobin <10g/dl) in 93 (37.9%) and marked thrombocytosis (platelet >600x10^9/l) in 30 (12.2%) cases.

At the time of presentation, patients were also classified into prognostic groups, using the Sokal formula. 44.9% of patients had Sokal score <0.8, which means they were in low risk group, intermediate risk group comprised of 8.2% (Sokal score 0.8-1.2) and 46.2% were high risk (Sokal score >1.2). Substantial number of patients who were in chronic phase of the disease fells into intermediate or high risk group.

Cytogenetic studies were performed in all patients. In 234 (95.5%) Philadelphia chromosome was detected, while 11 (4.5%) had normal karyotype. Subsequently PCR studies were performed in these patients for BCR/ABL translocation, which was found to be positive in all of them.

Discussion

Clinicopathologic aspects in chronic myeloid leukemia have not been studied in Pakistan. The aim of this study was to compile the local data in this regard.

The incidence of CML is approximately 1 per 100,000 population per year. In 2002, it is estimated that there will be 4,400 new cases with 2,000 estimated deaths.[16] Local data reveals an incidence of CML in Karachi (1995-2002) is

1.2/100,000 in males and 0.8/100,000 in females[17]; the results are consistent with international studies.[7,8]

The median age at the time of presentation has been reported 53 years in Western literature[2], but all age groups, including children, are affected.[7,8] In this series, peak incidence of disease was seen in younger population. These results are comparable with reports from India where chronic myeloid leukemia was seen in third and fourth decades[18,19]; similar results were found in few local studies as well.[20,21] A study regarding breast cancer epidemiology from our country had shown that breast carcinoma occurs at a younger age group in (Karachi - Pakistan) than in western countries.[22] It remains unclear as to why there are such geographical differences in age frequency in chronic myeloid leukemia as well.

A regional study showed a higher male to female ratio; but in our series male to female ratio was 1.69, which is consistent with studies from other parts of world.[2,8,23]

At time of presentation most of the cases (80-90%)[2,5,19] are diagnosed in the chronic phase, however, in this series, 72.6% of patients were found in chronic phase of the disease at the time of diagnosis; contrary to the reported incidence worldwide. This could be explained by the delay in medical presentation or referral bias since this was a hospital-based study.

The clinical findings at presentation of chronic myeloid leukemia vary in our series; this compares quite favorably with the result in the literature.[23-25] The typical symptoms at presentation are abdominal fullness, fatigue, anorexia, and weight loss, but in about 20 to 50 percent of patients are asymptomatic, with the disease first being suspected from routine blood tests.[24,25] With progressive bone marrow involvement, these patients may develop cytopenias, various infections can occur as well as hemorrhage, anemia-related symptoms, and easy bruising with petechiae and purpura. In our group abdominal fullness was the commonest presenting complaint followed by fever, fatigue and weight loss. Small number of patients presented with bleeding from orifices or cytopenias during aggressive phase of the disease.

The most common abnormality on physical examination is splenomegaly, which is present in upto half of patients.[1,7] Hepatomegaly and lymphadenopathy may be present, and result in a sensation of abdominal fullness along with discomfort and early satiety.[25] Although lymphadenopathy is uncommon in chronic-phase CML, it may develop with more advanced stages of the disease.[7,8] Some patients with chronic leukemia may present with hyperleukocytosis that can result in marked splenomegaly. Marked thrombocytosis may present in some cases, which is consistent with the presence of a defect in a pluripotent hematopoietic stem cell.[7,8]

Faderl *et al.*[24] and Savage *et al.*[25], reported splenomegaly (48 and 76 percent), anemia (45 and 62 percent), white blood cell count above 100,000/cmm (52 and 72 percent), and platelet count above 600,000 to 700,000/cmm (15 and 34 percent) at time of diagnosis. Although, presence of enlarged spleen at the time of diagnosis was more prevalent in our population, but the frequency of hyperleucocytosis, anemia or thrombocytosis are almost comparable with the international studies.[7-8,24-25]

Presence of enlarged spleen is unexplainable in our population; it might be because of delay in presentation or might be due to high white blood cell count; however, it was associated with bad prognosis in one series.[21]

Patients with chronic-phase CML usually have a longer survival than those with the more advanced phases of the disease.[7] However, prognostic systems have been proposed to help better predict outcomes. Sokal *et al.*[14] found age, spleen size, platelet count, and the percentage of blasts to be independent prognostic factors.

Large number of patients in this series were in high risk group (Sokal score >1.2). This might be because of late presentation; prevalence of enlarged spleen in large number of patients, delay in the diagnosis and substantial number of patients were in aggressive or blast phase of the disease at the time of diagnosis. Sinclair *et al.*[4] reported poor prognosis in patients with high sokal score in chronic phase.[4]

There was characteristic balanced reciprocal translocation of chronic myeloid leukemia between the long arms of chromosomes 9 and 22 t(9;22) in 95.5% of cases which is similar to the reported incidence that is 90% to 95% of patients.[1-2,7]

There were several limitations of the study. The data was collected retrospectively, and was only of patients who presented to our center either for management or diagnostic workup, so the total number of patients diagnosed, age groups and prognostic scores might not be the exact representative of our population.

Conclusion

Chronic myeloid leukemia affects people at young age in this region, mostly in third decade with male predominance. Abdominal fullness/distension or fever was the commonest presenting complaints. Majority of patients were in chronic phase with high white cell counts and enlarged spleen. Substantial number of patients was in aggressive phase of disease according to Sokal score.

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