CLINICO-PATHOLOGICAL PROFILE OF CHRONIC MYELOID LEUKEMIA

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ABSTRACT

Objective: *This study was aimed to find out the clinico-pathological profile of chronic myeloid leukemia (CML) in patients presenting to a tertiary care setting of NWFP.*

Material and Methods: *We retrospectively analyzed the data of patients presented with CML to Oncology unit, Lady Reading Hospital unit from April 1997 to March 1999. Diagnosis was based both on clinical and hematological parameters. Data for age, sex and diagnosis (including laboratory data) was analyzed.*

Results: *Out of 59 patients, 34 (58%) patients were male while 25 (42%) were female. Age ranged from 20 months to 70 years (median 36.6 years). Two (3%) patients had juvenile CML. Chief complaints at presentation were fever (65%), mass/pain left hypochondrium (63%), weakness (37%) and aches and pain (36%). Clinical signs at presentation included splenomegaly in 98% patients, hepatomegaly in 57% patients and anemia in 47% patients. Pathological/hematological values at presentation were: hemoglobin < 10 gm/dl in 59%, total leucocyte count (TLC) > 200000/cumm in 41%, platelet count < 150000/cumm in 15% and >500000/cumm in 10%, bone marrow blasts <5% in 68% patients and >10% blasts in 12% patients. Philadelphia chromosome (tested in limited cases) was positive in 11/12 (92%) cases.*

Conclusion: *In our study, CML tended to appear at a relatively younger age (mid-thirties) with a slight male preponderance. Fever and mass left hypochondrium were the commonest presentations and hepatosplenomegaly and anemia were the common signs. The incidence of thrombocythemia was lower in our population.*

Key Words: *Chronic Myeloid Leukemia, Anemia, Splenomegaly, Hepatomegaly,*

INTRODUCTION

Chronic myeloid leukemia (CML) is a disease derived from clonal proliferation of hematopoeitic proginator stem cell in the bone marrow and is characterized by vast increase in circulating granulocytes in the blood.[1,2] Characteristic molecular abnormality in this disease is the Philadelphia chromosome which results from a translocation or chromosome breaks between chromosome 9 and chromosome 22 [t(9:22); (q34:q11)][3-6] This translocation transposes c-abl proto-oncogene from chromosome 9 to the breakpoint cluster region (bcr) on chromosome 22. This new hybrid bcr-abl oncogene is responsible for changing the normal hematopoeitic cell into a CML cell.[7] Relationship between these molecular events resulting in the development of CML has been shown in mouse models.[8,9] Over 90% patients with CML show positivity for the Philadelphia chromosome.[10,11]

Incidence of CML is extremely varied in different geographic areas of the world. In Western literature, CML comprises 15-25% of adult leukemias with an incidence of 1-1.5/100000 population and a median age of 50 at diagnosis.[12-14] Survival after diagnosis is highly variable but the disease has three distinct phases: chronic phase lasting from 3-5 years; accelerated phase lasting up to one year and a terminal blast crisis phase lasting 3-6 months.[11,15-17] Survival ranges from 5-9 years in the western countries depending on stage of presentation and treatment received.

Some studies in Asia have shown differences in presentation of CML and survival of

CLINICAL PRESENTATION

Parameter	No. of patients n=59	% age
Fever	38	64.4%
Pain/mass left hypochondrium	37	62.7%
Weakness/fatigue	22	37.3%
Aches and pains	21	35.6%
Splenomegaly	58	98.3%
Hepatomegaly	34	57.6%
Clinical anemia	28	47.5%

Table 1

these patients the East compared to Western countries.[18-20] We performed this retrospective analysis of our patients suffering from CML to confirm the findings of these studies and present our data here.

MATERIAL AND METHODS

This retrospective, descriptive study included all patients diagnosed as CML and having full data available presenting to Oncology OPD at Post-Graduate Medical Institute, Lady Reading Hospital, Peshawar, during the 24 month study period (from April 1997 to March 1999). No exclusion criterion was used and all patients with CML were included in the study. The diagnosis was based on characteristic laboratory and clinical criteria using the established criteria for diagnosis of CML[11] that includes:

High total leucocyte count (TLC) (bimodal peak) with increase in myeloid cells in different stages of maturation with accompanying basophilia and eosinophilia

Low or undetectable leucocyte alkaline phosphatase (LAP) score

Gross myeloid hyperplasia (with increased myeloid to erythroid ratio) with left shift on examination of the bone marrow

Presence of Philadelphia chromosome in bone marrow cell cultures

Splenomegaly

Patients of all age groups diagnosed with CML were included in the study in order to look for the percentage of juvenile CML (< 15 years) in our population. Patients presenting in all three phases of the disease at the time of initial diagnosis were included in the study. Clinico-pathological parameters including full history, physical findings (anemia, splenomegaly, hepatomegaly etc), laboratory findings including peripheral blood picture, bone marrow examination, LAP score etc were noted for these patients.

Since facilities for detection of Philadelphia chromosome were not available in NWFP at the time of study, therefore not all the patients were required to have this test done. Since majority of patients in our part of the world do not come for follow-up regularly therefore this study does not include the long term follow-up data of these patients.

RESULTS

A total of 850 patients were seen in our OPD during the study period. Out of these 59 (6.9%) had CML. Of the 59 patients included in the study 34/59 (58%) were male while 25/59 (42%) were female. Male to female ratio was 1.36:1. Age ranged from 20 months to 70 years (median 36.6 years). Only 02/59 (03%) patients had juvenile CML. Of the twelve patients tested for Philadelphia chromosome, 11/12 (92%) patients had Philadelphia chromosome positive CML. Chief complaints at the time of initial presentation included fever, pain/mass in the left hypochondrium, weakness/fatigue and generalized aches and pains (Table I). Combination of these complaints was present in more than 90% of patients at presentation. Clinical features at the

HEMATOLOGICAL/PATHOLOGICAL VALUES AT PRESENTATION IN THE STUDY GROUP

Parameter		Frequency n=59	% age
Hemoglobin	< 10 gm/dl	35	59.3%
	> 12 gm/dl	06	10.2%
Total Leucocyte Count	< 100000/ mm^3	10	16.9%
	> 200000/mm^3	24	40.7%
Platelet Count	< 150000/mm^3	9	15.3%
	> 500000/mm^3	06	10.2%
Bone marrow blasts	< 05%	40	67.8%
	05-10%	12	20.3%
	> 10%	07	11.9%

Table 2

time of diagnosis included splenomegaly, hepatomegaly and anemia (Table I). Hematological values at the time of diagnosis are summarized in Table 2. Eighty eight percent of these patients presented in chronic phase of the disease while twelve percent presented in accelerated or blast crisis phase of CML.

Mean LAP score was <10 while mean M:E (myeloid to erythroid) ratio was 25:1. All of these patients were treated with Hydroxyurea 50 mg/kg at presentation and then dose of Hydroxyurea was reduced to 25-30 mg/kg for maintenance (for a TLC range of 5000-15000/cumm). Since majority of these patients were lost to follow-up therefore no data is presented on outcome in detail. Briefly, for those patients who did come regularly for follow-up and treatment, median duration of chronic phase was 36 months, 10 months for accelerated phase and approximately 3 months of blast crisis.

DISCUSSION

CML is a common hematological malignancy in adults with a worldwide incidence of 1-2 cases per 100000 population per year and an incidence of 15-25% of all adult hematological malignancies. Some studies have suggested variations in the presentation of the disease in various geographical areas.[18-20] In Western literature, the median age reported for CML patients is late forties to early fifties.[17,21,22] Incidence of anemia (Hb < 10 gm/dl) is 10%, thrombocythemia (platelet counts over 500000/cumm) is 20-40% (16, 21) and bone marrow blasts > 5% is 11% in the Western literature.[22]

In our study, the median age at presentation was found to be 36 years which is a decade lower than in patients in Western countries. Male to female ratio was 1.36: as compared to 2:1 in West. Incidence of anemia (Hb < 10 gm/dl) was high at almost 60% in our patient population while thrombocythemia incidence was low at 10%. Bone marrow blasts > 5% were present in almost 20% patients in our population compared to 11% in the West. Incidence of splenomegaly was also higher than in the West. These differences were reported in a preliminary report at the Proceedings of American Society of Clinical Oncology meeting at Los Angeles, USA in 1998 as an abstract.[23] Since then our preliminary and now the final findings presented in this paper have been confirmed by many publications from Pakistan as well as India which show similar results as our study.[18-20,24] A large study of 461 patients from all over Pakistan carried out at Shaukat Khanum Memorial Cancer Hospital and Research Center (SKMH) in Lahore confirms our report as well.[24]

Although follow-up of patients in our part of the world is dismal, but from the few patients who adhered to long term follow up and were treated with single agent follow-up, it was noticed that the chronic phase tends to be shorter by 12-18 months in our patients. Details of outcome were not presented due to extremely high number of lost to follow-up cases. This was also confirmed by the SKHM study that also faced the same problem of more than half the patients lost to follow-up and those who did come for long term follow-up showed the same shorter chronic phase period. A Japanese study has suggested Interferon as first line agent rather than Hydroxyurea in Asian patients if HLA matched sibling donor is not available for bone marrow transplant.[25] It is very difficult to explain these differences in presentation of the disease compared to West but it is postulated that genetic or environmental/ biological differences may be involved. A Scottish and Turkish study has shown an influence of several HLA genotypes on the age of onset of CML.[26] Differences in these genotypes in various regions of the world may play a part in these differences. Such studies, along with genetic analysis of our CML patients, need to be done in our population also to explain the differences in presentation of the disease in our patients.

In summary, differences occur in the presentation of CML between European/American (Western) patients and our patients. CML tends to appear at a younger age in our patients (mid thirties) compared to Europe and USA (late forties), incidence of thrombocythemia is lower compared to West and the disease appears to be more aggressive with shorter chronic phase in our patients.

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