Original Article

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Pathology Section

Clinico-haematological Profile of Chronic Myeloid Leukaemia: An Institutional Based Study from Bihar

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ABSTRACT

Introduction: Chronic Myeloid Leukaemia (CML) is a myeloproliferative disorder characterized by translocation between chromosome 9 and 22 resulting in Philadelphia (Ph) chromosome and BCR-ABL fusion gene. The final diagnosis of CML depends on demonstration of Ph chromosome or BCR-ABL fusion by cytogenetic or molecular studies which also contributes towards understanding the disease biology and has important implications in treatment and management of CML patients.

Aim: This study evaluates the clinico-haematological profile of patients based on age, sex, haematological parameters, clinical presentations and frequencies of three phases of CML. Sokal and European Treatment and Outcome Study (EUTOS) scoring were performed.

Materials and Methods: This was a retrospective observational study conducted over a period of 30 months that included 64 diagnosed patients of CML based on clinical examination, peripheral blood and bone marrow analysis and demonstration of BCR-ABL by Fluorescent In Situ Hybridization (FISH).

Results: Of the 64 patients included in the study, the mean age of the subjects was 33 years with male preponderence (59.3%). The most common presenting symptom was low grade fever (89.0%). The frequency of patients in the Chronic Phase (CML-CP), Accelerated Phase (CML-AP) and Blast Crisis (CML-BC) were 41 (64.0%), 18 (28.1%) and 5 (7.8%) respectively. The most frequent age group to be involved was 20-35 years for CP, 41-50 years for AP and BC. All 64 cases showed BCR-ABL fusion and are doing well on follow-up except one patient which turned resistant to first generation Tyrosine Kinase Inhibitors (TKIs). Majority of the patients were in the low sokal scores (48.4%).

Conclusion: In our study most CML patients were from younger age group, mean age being 33 years as compared to 45-55 years in western world. In contrast to other Indian studies majority of our patients belonged to low Sokal score and low EUTOS score. Males were more commonly affected than the females. As compared to western literature incidence of microcytic hypochromic anaemia is more in CML patients in this part of the world.

Keywords: European treatment and outcome study score, Philadelphia chromosome, Sokal score

INTRODUCTION

Chronic Myeloid Leukaemia (CML) is a haematological disorder caused by clonal proliferation of haematopoietic progenitor stem cell in the bone marrow leading to marked increase in granulocyte series of cells in the peripheral blood and bone marrow. The characteristic molecular abnormality in more than 90% of cases is the Philadelphia (Ph) chromosome which results from translocation between chromosome 9 and 22 {(9;22) (q34;q11)}. This translocation leads to the formation of Break-point Cluster Region and Abelson's (BCR-ABL), a new hybrid fusion gene that encodes for an oncoprotein (p210) located in the cytoplasm that has a strong capacity to activate tyrosine kinase resulting in the activation of several downstream signals that transform haematopoietic stem cells into leukaemic cells. Thus, currently tyrosine kinase activity is thought to play the central role in the pathogenesis of CML [1].

Clinically, nearly 50% of patients remain asymptomatic. The rest present with fever anaemia, splenomegaly, hepatomegaly, lymphadenopathy, bleeding manifestations and complications such as renal failure, hearing loss and priapism [2,3].

The bone marrow morphology in CML patients reveals hypercellularity due to excessive proliferation of granulocytes with myelocyte bulge and presence of blasts. World Health Organization (WHO-2017) criteria based on the blasts from <10% to >20% in the bone marrow or peripheral blood divide CML into chronic and accelerated phases and blast crisis [4].

There are many predictive and prognostic scores to risk stratify CML-CP at baseline with respect to response to first line of treatment to Tyrosine Kinase Inhibitor (TKI). In Indian population Sokal and EUTOS score have predictive value but EUTOS score has better prognostic efficacy [4].

This study was undertaken to evaluate the clinico-haematological profile of patients based on age, sex, haematological parameters, clinical presentations and frequencies of three phases of CML as there is a paucity of published data from the state of Bihar.

MATERIALS AND METHODS

This retrospective observational hospital based study was conducted in the Haematopathology section of Department of Pathology at All India Institute of Medical Sciences, Patna , Bihar, India, from January 2015 to August 2017(30 months). Institutional ethical clearance was obtained, its number being AIIMS/ Pat/ IEC/2018/295.

Total 64 cases of CML were studied and all the relevant data pertaining to clinical history and physical examination were retrieved. The peripheral blood samples, bone marrow aspirate and bone marrow biopsy samples were studied for the analysis of complete blood count and bone marrow examination for the diagnosis of three phases of CML and correlated with BCR-ABL fusion studies performed for confirming the diagnosis. BCR-ABL study was done by FISH. Patients peripheral blood samples were collected in EDTA vacutainer for BCR-ABL study, bone marrow samples were collected in Heparin vacutainers.

Inclusion Criteria: All Ph chromosome positive CML patients were included in this study.

Exclusion Criteria: 1) Ph chromosome negative CML patients were not included; 2) Patients did not receive any other concurrent

chemotherapy or radiation therapy during the study; 3) Previously diagnosed and treated CML patients were excluded from the study.

CML-CP is defined when blasts comprises less than 10% in the peripheral blood or bone marrow. CML-AP is labelled when blasts % range from 10%-19% of white blood cells in peripheral and/or bone marrow cells, persistent thrombocytosis (>1000x10^9/L) unresponsive to therapy or persistent thrombocytopenia (<100x10^9/L) unrelated to therapy, increasing white blood cells and splenic size unresponsive to therapy and or cytogenetic evidence of clonal evolution. CML-BC is defined as percentage of blasts ≥20% in peripheral blood or bone marrow aspirates, extramedullary blast proliferation (excluding liver and spleen) and large foci of clusters of blasts on bone marrow biopsy [4].

Sokal and EUTOS scores were calculated with the data at presentation.

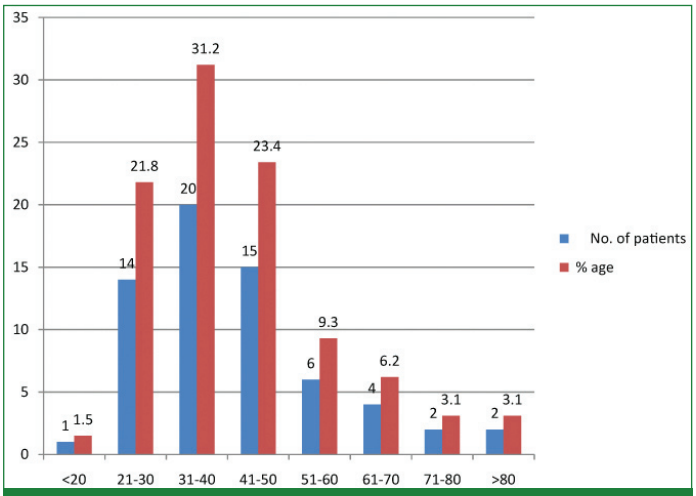
All the patients received imatinib (400 mg daily) as the first line TKI. Patients were monitored for haematological response every month. Complete Haematological Response (CHR) was defined as white blood cell <10 x 10^9/L, basophils <5%, platelet count <450 x 10^9/L, no immature cells in differential count (myelocytes, promyelocytes or blasts) and nonpalpable spleen.

STATISTICAL ANALYSIS

Continuous variables were expressed in mean±standard deviation. Categorical variables were expressed in terms of frequency and percentage. Microsoft excel software was used for this study.

RESULTS

A total of 64 diagnosed patients of CML were identified. All were Ph chromosomes positive (100%). Median age of the patients was 33 years (range being 18-85 years) with male to female ratio being 1.4:1 [Table/Fig-1].



[Table/Fig-1]: Incidence of CML in different age groups.
X axis denotes: age range; Y axis denotes: percentage of patients

The major clinical features at presentation are shown in [Table/Fig-2]. Most common symptom was low grade fever (89%) followed by abdominal fullness (85.9%). Splenomegaly was encountered in 85.9% of cases. Splenic size ranged from 7-15 cm.

Presenting clinical sign and symptom	No.of patients (n=64)	Percentage
Fever	57	89.0%
Pain/mass left hypochondrium	55	85.9%
Splenomegaly	55	85.9%
Weakness	51	79.6%
Hepatomegaly	47	73.4%
Pallor	44	68.7%

[Table/Fig-2]: Clinical presentations in patients with CML.

Baseline characteristics of patients were shown in [Table/Fig-3]. Mean haemoglobin,total leucocyte count, platelet count, eosinophil % and basophil % was 8.5 g/dL, 1.4 lac/cumm, 2.4 lac/cumm, 4%, and 5% respectively.

Baseline characteristics	Value
Age, years;median (range)	33 (18-85)
Gender, male:female ratio	1.4:1
Haemoglobin, gm/dL; median (range)	8.5 (5.5-13)
Total leucocyte counts, lacs/cumm; median (range)	1.4 (1-9)
Platelet count, lacs/cumm; median(range)	2.4 (1.8-6.5)
Esoinophil ,%;median (range)	4 (0-8)
Basophil %;median (range)	5 (0-20)
Spleen,cm;median (range)	10 (6-14)

[Table/Fig-3]: Baseline characteristics of CML patients.

The haematological parameters at time of presentation are shown in [Table/Fig-4]. Peripheral blood smear examination in majority ofthese patients showed normocytic normochromic blood picture (33 cases; 51.5%), rest showed microcytic hypochromic (27 cases; 42.1%) and dimorphic blood picture in only 4 cases (6.2%).

Haematological parameter	Level	Frequency	Percentage
Haemoglobin	<10 gm/dL >12 gm/dL	56 8	87.5 % 12.5 %
Total Leucocyte count (TLC)	<2 lacs/cumm >2 lacs/cumm	26 38	40.6 % 59.3 %
Platelet count	<1.5 lacs/cumm >1.5 lacs/cumm	13 51	20.3 % 79.6 %
Type of anaemia on peripheral blood smear	Normocytic normochromic Microcytic hypochromic Dimorphic	33 27 4	51.5 % 42.1 % 6.2 %
Bone marrow blasts	<10 % 10%-19 % >20%	41 18 5	64.0% 28.1% 7.8%

[Table/Fig-4]: Haematological parameters of CML patients.

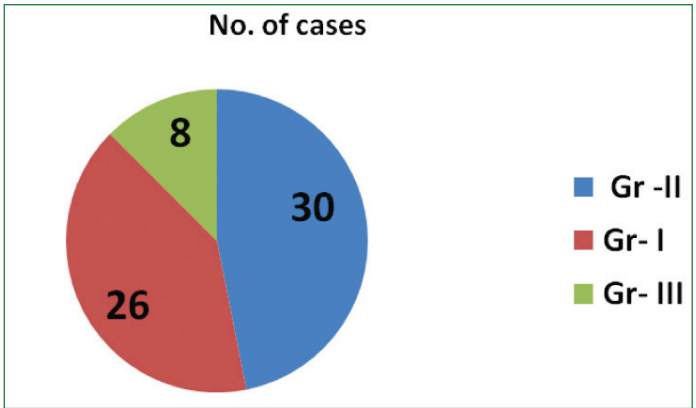
Phases of CML	Chronic phase	Accelerated phase	Blast crisis
Frequency	41 (64%)	18 (28.1%)	5 (7.8%)
Age	28±7	43±6	44±8
Sex	Male: 25 Female: 16 (1.5:1)	Male: 10 Female: 8 (1.2:1)	Male: 3 Female: 2 (1.5:1)
Splenic size	<10 cm	10-15 cm	>15 cm
Number of blasts in peripheral blood and bone marrow smears	5±2	15±2	24±5

[Table/Fig-5]: Frequency of three phases of CML based on age, sex, splenic size and number of blasts in peripheral and bone marrow smears.

The frequency of patients in the CML-CP,CML-AP and CML-BC were 41 (64.0%), 18 (28.1%) and 5 (7.8%) respectively. The most frequent age group to be involved was 20-35 years for CP, 41-50 years for AP and BC [Table/Fig-5]. BCR-ABL study was performed in all the cases by FISH and only Ph positive cases were included in the study.

Marrow fibrosis of grade II was present in 46.8% of cases followed by grade I (40.62%) and grade III (12.5%) fibrosis of cases. All five patients who were in blast crisis and three patients who were in accelerated phase had grade III fibrosis [Table/Fig-6].

Sokal scoring was performed [Table/Fig-7]. Highest and lowest Sokal scores were 1.34 and 0.62 respectively. Highest Sokal score was seen in 41-50 years age group and lowest in 21-30 years of age group. Sokal score range was higher in males as compared to females [Table/Fig-8,9]. Similarly EUTOS scoring was also performed as shown in [Table/Fig-10,11].



[Table/Fig-6]: Piechart showing grading of bone marrow fibrosis.

Sokal score	No.of cases	Percentage
Low	31	48.4
Intermediate	24	37.5
High	09	14.0

[Table/Fig-7]: Sokal scoring.

Age (years)	No. of patients	Sokal score
<20	01	1.03
21-30	14	0.62-1.20
31-40	20	0.80- 1.26
41-50	15	0.72-1.34
51-60	06	0.78-1.30
61-70	04	0.78- 1.32
71-80	02	0.64-1.10
>80	02	0.68-1.28

[Table/Fig-8]: Age wise break up of sokal score.

Gender	Sokal score
Male (n=38)	0.78-1.34
Female (n=26)	0.62-1.30

[Table/Fig-9]: Gender wise break up of sokal score.

EUTOS score	No of cases (%)
Low risk	38 (59.37)
High risk	26 (40.62)

[Table/Fig-10]: EUTOS score.

Gender	Low	High
Male	24	14
Female	14	12

[Table/Fig-11]: Gender wise break up of EUTOS score.

At end of three months Complete Haematological Response (CHR) was achieved in 97.1% cases. Cytogenetic and molecular responses could not be followed up due to various reasons including financial constraints and inavailability of tests.

One 65 year male CML-CP patient on imatinib for two years showed disease progression despite escalating the drug dosage. Imatinib Resistance Mutational Analysis (IRMA) by nested RT-PCR technique was performed but it revealed no mutations.

A 32-year-old female patient who was on Imatinib conceived twice during treatment and gave birth to healthy babies both the times without discontinuation of TKI. On follow-up both the mother and children are fine.

DISCUSSION

CML is a common haematological malignancy in adults with a worldwide incidence of 1-2 cases per 1 lac population per year [4]. It comprises 15-25% of all haematological malignancies [5]. In Indian population it accounts for 30-60% of all adult leukaemias [5]. The incidence in Bihar has been reported as 70% [6]. The reason for this variation in the incidence of the disease could be due to geographical differences [7].

As per western studies like Baccarani M et al., the median age reported for CML patients is late 40's to early 50's [7]. Asymptomatic presentation is quiet common (40%) [8,9]. Incidence of anaemia (haemoglobin <10 gm/dL) is 10%, thrombocytopenia (platelet counts less than 1.5 lacs/cumm) is 20-40% and bone marrow blasts more than 10% is 11% in the Western literature [6,10].

Bhutani M et al., showed median age at presentation was younger compared with age presented in European (median age 55 years) as well as in American (median age 66 years) literature. Majority of Indian patients are symptomatic and mostly present with dull aching pain in left hypochondrium [5,11].

According to various Indian studies mean haemoglobin ranged from 9-11 gm/dL, median total leucocyte count ranged from 46000/cumm to 1.86 lac/cumm. Median percentage of patients presenting in chronic phase in Indian scenario is 89.5% [6,12].

In our study, the median age at presentation was found to be 33 years which is consistent with Indian literature. Male:female ratio was 1.4:1 as compared to 2:1 in West. All our patients were symptomatic with splenomegaly being present in 85.9%. Incidence of anaemia (Hb <10 gm/dL) was high (87.5%) in our study while incidence of thrombocytopenia was low (20.3%). Bone marrow blasts >10% were present in 28.1% cases in our study population as compared to 11% in the West [8,13].

In the present study, 64 CML patients, were categorised into CP 41 (64.0%), 18 (28.1%) in AP, 5 (7.8%) in BC in our study. Ahmed R et al., reported that frequency of CP, AP and BC were 77.8%,15.5% and 6.7% respectively among the 45 patients suffering from CML with their mean age 37.9 years, and male: female ratio of 2.2:1 while clinico-haematological features were anaemia with haemoglobin of 9.94 g/dL and massive splenomegaly. The mean total leukocyte count 214.3x10^9/L, platelet count 551.4×10^9/L, and marrow blasts were 9.3 % respectively [14,15].

A comparative search of various studies done in past on clinico-haematological profile of CML patients is shown in [Table/Fig-12] [13-16].

Study	Year	No. of patients	Mean age	M:F ratio	Chief com-plaints	Phase dis-tribution
Yaghmaie M et al., [15]	2010	63	37.4	2:1	Weakness, Pain abdomen	CP-39 AP-7 BC-2
Bhatti F et al., [16]	2012	335	35.5	2:1	Anaemia, massive splenomegaly	AP-241 CP-31 BC-15
Malhotra H et al., [13]	2013	213	39	1.95:1	Anaemia, massive organomegaly	NA
Ahmed R et al., [14]	2014	83	37.9	2.2:1	Anaemia, massive splenomegaly	AP-62 CP-17 BC-03
Present study	2017	64	33	1.4:1	Fever, pain abdomen, splenomegaly	AP-41 CP-18 BC-05

[Table/Fig-12]: Comparison of previous studies with the present study.

It is very difficult to explain these differences in presentation of disease as compared to West but it is postulated that genetic or environmental differences may be involved. Differences in HLA genotypes in various regions of the world might play a part in explaining these variations. Such studies, along with genetic analysis of CML patients need to be done in our population so as to explain the differences in presentation of disease [16-18].

In some of the Indian studies done in the paston Sokal risk category, majority of the patients were in intermediate risk category (ranging from 27-47%) whereas in our study majority of the patients belonged to low sokal score. Sokal, Hasford, EUTOS and Euro scores have significant predictive efficacy in the Indian population. However, EUTOS score outperforms as a prognostic model in CML patients on Imatinib [10].

The treatment of pregnant women with CML is difficult because of few available therapeutic options and limited data regarding the potential harm to the fetus. Conception should be planned and TKI therapy should be discontinued during pregnancy. Individual risks should always be considered when unplanned pregnancy occurs [19].

In a cohort study done by Babu G et al., out of total 540 CML patients, 101 patients underwent IRMA of which 73% of them did not show any mutation, but rest of the patients had one mutation or the other, the most common mutation being T315I [20].

LIMITATION

There were small number of patients included, no cytogenetic or molecular study follow-ups due to unavailability and affordability of such tests in resource poor countries like ours.

CONCLUSION

This study was undertaken as there is lack of data on CML from the state of Bihar. CML tends to occur at a younger age in our patients (inmid-30's) which is consistent with other Indian studies. All our patients were symptomatic which might be due to delayed presentation. Splenomegaly was present in 85%. The incidence of microcytic hyochromic anaemia was higher, incidence of thrombocytopenia is lower and the frequency of CML patients with blast % greater than 10% is more as compared to Western literature.Most of the patients belonged to low Sokal score whereas other Indian studies have reported intermediate Sokal score and low EUTOS score. CHR was achieved in all cases but cytogenetic and molecular monitoring was an issue. The reason for this was that majority of our patients could not afford these tests and also the tests were unavailable in our institute. Timely diagnosis and compliance is associated with better outcome.

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