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Original research article

Clinico - Hematological Profile and Bone Marrow Correlation of Chronic Myeloid Leukemia: A Multiparameter Study in a Tertiary Care Hospital

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Abstract

Background: Chronic myelogenous leukaemia is one of the common leukaemia seen with a proper understanding of the leukemogenic pathway which led to best treatment options as compared to other leukaemia's. Many aspects of the neoplasm are yet to be discovered in the light of current development in the investigation particularly molecular testing. The present study was under taken to find out the actual burden of the disease along with the estimating the prevalence of chronic myeloid leukemia in patients coming to IGIMS Patna as most of the patients usually present in the late stage of disease.

Material and Method: The study was carried out over a period of 2 year and 6 months, from June 2019 to Nov 2021. Total 58 patient who came to Hematology department with relevant clinical features and hematological findings suggestive of chronic myeloid leukemia were included in the study. Based on clinical findings, complete blood count and peripheral blood smear examination, bone marrow aspiration and biopsy were carried out. All the aspirate smear were stain with Leishman stain and trephine biopsies were stained with haematoxylin and eosin.

Result: In total, 58 patients were enrolled in the study. The median age of presentation of CML was 35 years and the mean age was 38.27 years. M: F ratio of 1.52:1. Of the total number of cases,48 patients (82.76%) were in CML-chronic phase (CP), 04 patients (6.89%) in CML-accelerated phase (AP) phase, and 6 patients (10.34%) were found in CML-blast crisis (BC) phase. The most common symptoms of the patients were abdominal discomfort (70.1%) were as the most common presenting sign was splenomegaly (87.93%). Among these 58 cases, Philadelphia chromosome was present in 54 (93.10%) cases.

Conclusion: Most CML patients in Bihar are relatively young (31–50 years) with a male predominance. Bone marrow aspiration and trephine biopsy along with physical examination and other haematological investigation plays a key role in early diagnosis but molecular testing is essential for confirmation along with follow up during treatment of the cases. Although the most common treatment method is chemotherapy at present day scenario, bone marrow transplants and radiation are also available options.

Keywords: CP, CML, AP, BP.

Introduction

Leukemia is a group of hematological malignancy in which there is an uncontrolled, unregulated and rapid proliferation of leukemic cells resulting in replacement of normal

hematopoietic cells by abnormal proliferating cells in bone marrow and spilling over peripheral blood as well.[1] These occurs in a number of forms which differ in their clinical, pathological and haematological features. The two main criteria used in the classification are the clinical course of the disease, and the type and degree of differentiation of the predominant leukemic cell population as revealed by the morphological examination of the blood and the bone marrow. Leukaemia is therefore classified as acute and chronic according to the clinical course, and as myeloid and lymphoid, according to the cell line predominantly involved in the leukemic process. Modern classification systems for acute and chronic leukaemia's are based on cytomorphology, cytochemistry, immunophenotyping, immunogenetics and molecular cytogenetics. [2] Chronic leukaemia's are also divided basically into lymphoid and myeloid categories, and tend to be more indolent in behaviour. Disorders that do not fulfil the criteria for either acute or chronic leukaemia are common and are seen in middle aged and elderly patients. They are called as indolent acute or smouldering leukaemia's. [3]

Chronic Myeloid Leukaemia (CML) is a haematological disorder caused by an abnormal proliferation of pluripotent bone marrow stem cell leading to marked increase in granulocyte series of cells in the peripheral blood and bone marrow and is characterized by the fusion of the ABL from chromosome 9q34 with the BCR on chromosome 22q11.2 manifested as a translocation t (9; 22) (q34; q11.2) known as the Philadelphia chromosome (Ph).This new hybrid fusion gene 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 leukemic cells. Thus, currently tyrosine kinase activity is thought to play the central role in the pathogenesis of CML [4]. Clinically in 50% of cases patients with CML are asymptomatic and remaining were present with anaemia, splenomegaly, fever, bleeding tendency, hepatomegaly, lymphadenopathy and complications such as renal failure, hearing loss and priapism, and laboratory findings include complete blood count, peripheral blood and bone marrow examinations showing low haemoglobin, total WBC count between 287×10^9 /L and 535.7×10^9 /L, thrombocytopenia or normal platelet count or thrombocytosis and peripheral blood smear showing increase number of mature and immature granulocytes including predominantly [5,6]. 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 20% in the bone marrow or peripheral blood divide CML into chronic and accelerated phases and blast crisis [7]. There is decreased or normal or increased megakaryopoesis as well as moderate to marked reticulin fibrosis with presence of small megakaryocyte containing hypolobulated nuclei, sea-blue histiocytes and gaucher cell and these changes are return to the normal state after treatment and the Immuno histo-chemistry is used for differentiating the myeloblastic and lymphoblastic crisis of CML [8,9]

Sokal and EUTOS scoring system is primarily used for predictive value and prognostic significance in Indian population so as to risk stratify CMLCP patients at baseline with respect to response to first line of treatment to Tyrosine Kinase Inhibitor (TKI) [4].

Epidemiological data regarding the incidence rates for CML cases are scarce for population of Bihar as most of the patients usually present in the late stage of disease [18]. Although most of the patients are receiving Imatinib[19] as first-line therapy, but there is limited availability of diagnostic facilities for molecular monitoring. In order to assess the burden of these illness for public health planning, it is important to know their frequency.

Materials and methods:

Study design: A retrospective 2.5 years observational study conducted at a tertiary care center in Bihar.

Duration of study: June 2019 to Nov 2021 (2.5 years).

Study Population: All patients who came to Hematology department with relevant clinical features and hematological findings suggestive of chronic myeloid leukemia. Sample size would be approximately 50 cases. It may increase or decrease depending on the availability of cases.

Place of study: Department of Hematology, IGIMS Patna.

Inclusion criteria:
1. All patients presenting with relevant clinical features and hematological findings suggestive of chronic myeloid leukemia
2. Patients with bone marrow examination findings suggestive of CML.
3. Ph chromosome positive CML patients
4. Patients in blast crisis of CML presenting as acute leukemia.

Exclusion criteria:
1. Patients on prior chemotherapy or radiotherapy.
2. Ph chromosome negative CML patients
3.Previously diagnosed and treated CML patients.
4.All covid positive and viral cases.

Sample collection and parameters estimation:
The required quantity of venous blood was collected in EDTA vials. The collected blood was analysed by using fully automated analyser, SIEMENS ADVIA 2120i having 6-part from which cases with marked leukocytosis was noted and subsequently peripheral blood smears prepared in such cases on glass slides and stained with Leishman's stain. Special stains like MPO and PAS was done in those CML cases which were in blast crisis phase. Bone marrow examination was done for the diagnosis of three phases of CML and correlation with BCR-ABL fusion studies (FISH) was performed for confirming the diagnosis. Patients peripheral blood samples was collected in EDTA vacutainer for BCR-ABL study and bone marrow samples collected in Heparin vacutainers.

Statistical analysis:
Percentage will be calculated from categorical variables. Mean and standard deviation (SD) will be calculated from numerical values. Software used for data analysis will be SPSS version 22.

Result
During the period of study, a total of 58 cases of CML were identified with a Mean age of the patients [Table 1] was 38.27 years (range being 10-80 years) with male to female ratio [Table 3] being 1.52:1
The major clinical features at presentation are shown in [Table 2] with the most common symptom was abdominal discomfort (70.1%) followed by loss of weight (51.72%). Anemia was the most common sign seen in 57 cases (98.27%). Mean haemoglobin, total leucocyte count, platelet count, and basophil % was 6.5 g/dL, 1.6 lac/cumm, 1.4 lac/cumm, and 5% respectively [Table 4,5 6]. Normocytic normochromic blood picture (35 cases; 60.34%) was

the most common peripheral blood picture followed by microcytic hypochromic (20 cases; 34.4%) and dimorphic blood picture in only 3 cases (5.17%).
The frequency of patients in the CML-CP, CML-AP and CML-BC were 48 (82.76%), 04 (6.89%) and 6 (10.34%) respectively [Table 7]. The most frequent age group to be involved was 31-50 years for CP, 25-55 years for AP and BC. BCR-ABL study was performed in all the cases by FISH and only Ph positive cases were included in the study.
At end of three months Complete Haematological Response (CHR) was achieved in 95.1% cases. Cytogenetic and molecular responses could not be followed up due to various reasons including financial constraints and unavailability of tests.

Table 1: Age wise distribution of the patients with leukaemia.

AGE (YEARS)	NO OF CASES WITH CML
10-20	5
20-30	10
30-40	14
40-50	13
50-60	12
60-70	1
>70	3
TOTAL	58

Table 2: Clinical presentation in CML patients

CLINICAL PRESENTATION	NO. OF CASES WITH CML	% (PERCENTAGE)
ABD DISCOMFORT	41	70.10
FEVER	25	43.20
LOSS OF WEIGHT	30	51.72
LOSS OF APPETITE	28	48.27
SPLENOMEGALY	51	87.93
HEPATOMEGALY	22	37.93

Table 3: Sex wise distribution of cases.

SEX	TOTAL
MALE	35
FEMALE	23
TOTAL	58

Table 4: Distribution of study subjects as per Haemoglobin%

HEMOGLOBIN % IN GM/DL	NO OF CASES WITH CML	% (PERCENTAGE)
<5	38	65.51
5-8.9	15	25.86
9-11.9	4	6.89

>12.0	1	1.72
TOTAL	58	100

Table 5: Distribution of study subjects as per Total leucocytes.

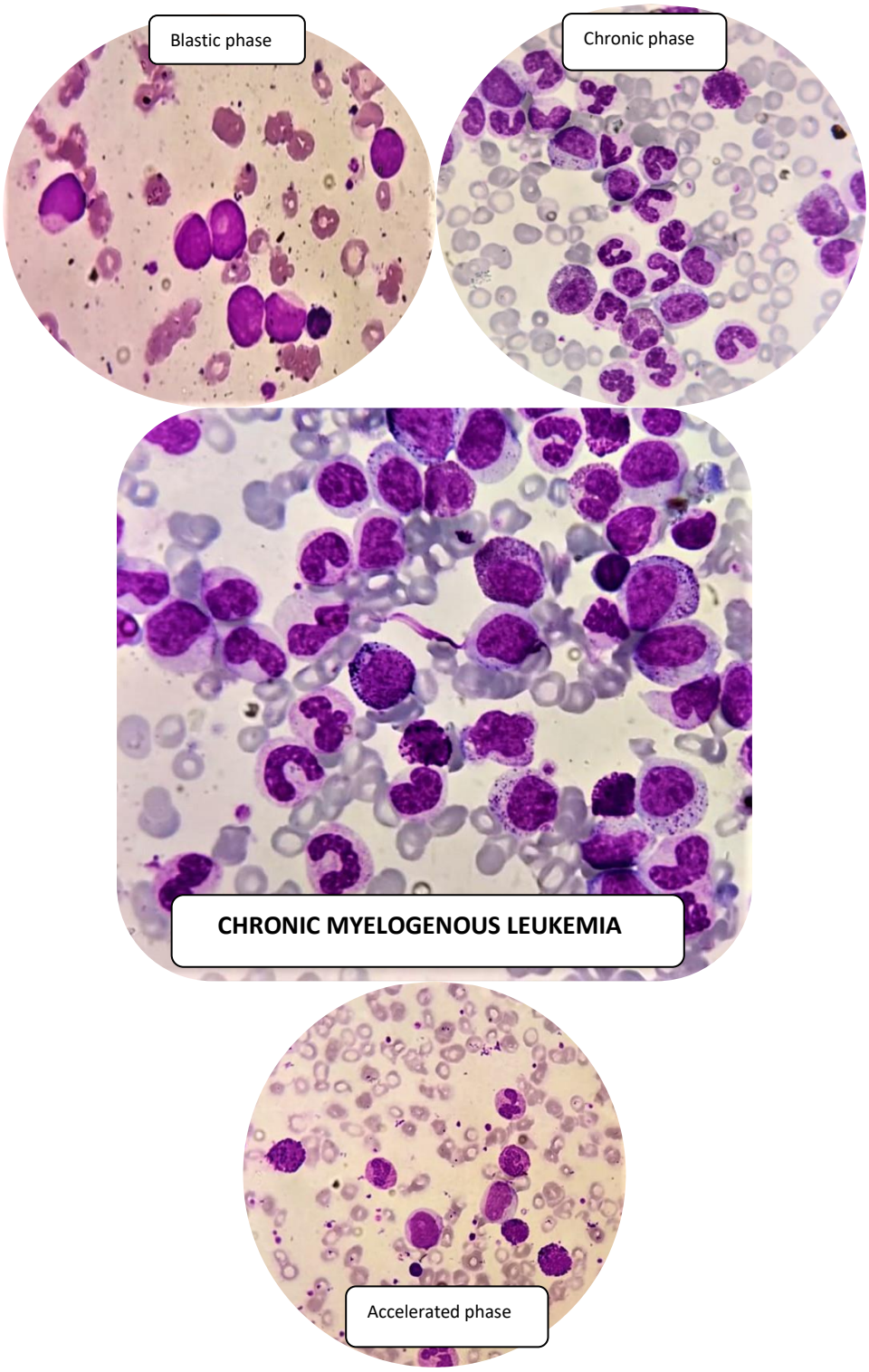
TOTAL LEUKOCYTES	NO OF CASES WITH CML	% (PERCENTAGE)
>50,000	6	10.34
50,000-1.0 LAKHS	4	6.89
1.0-2.0 LAKHS	10	17.24
2.0-4.0 LAKHS	36	62.06
>4.0 LAKHS	2	3.44
TOTAL	58	100

Table 6: Distribution of study subjects as per Platelet count.

PLATELET COUNT	NO OF CASES WITH CML	% (PERCENTAGE)
>50,000	10	17.24
50,000-1.0 LAKHS	16	27.58
1.0-1.5 LAHS	29	50.00
>1.5 LAKHS	3	5.17
TOTAL	58	100

Table 7: Distribution of study subjects as per Bone marrow blasts

% BONE MARROW BLASTS	NO OF CASES WITH CML	% (PERCENTAGE)
>10	48	82.76
10.0-20.0	4	6.89
>20.0	6	10.34



DIFFERENT PHASES OF CML

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 leukaemia's [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% 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 214.3x109 /L, platelet count 551.4×109 /L, and marrow blasts were 9.3 % respectively [14,15]. A comparative search of various studies done in past on clinicohaematological profile of CML patients is shown in [Table/Fig-12] [13-16]. 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].

Table 8: ETIOLOGY OF PANCYTOPENIA IN VARIOUS STUDIES

STUDY	YEAR OF STUDY	NO OF CASES	MEAN AGE	COMMON SIGN & SYMPTOMS	DISTRIBUTION OF CASES ACCORDING TO PHASE
Kalpana N et al	2020	50			
Sandip K et al	2019	90	38.6	Abdominal fullness Anemia	CP- AP- BC-
Farzana Chang et al	2015	83	39.5	Abdominal fullness Splenomegaly	CP-62 AP-17 BC-03
Ahmed R et al	2014	83	37.9	Anemia, Massive Splenomegaly	CP-62 AP-17 BC-03
Malhotra H et al	2013	213	39	Anemia, Massive Splenomegaly	NA
Bhatti F et al	2012	335	35.5	Anemia, Massive Splenomegaly	CP-241 AP-31 BC-15
Yaghmaie M et al	2010	63	37.4	Weakness, Pain Abdomen	CP-39 AP-7 BC-2
Present Study	2019	58	38.27	Abdominal Discomfort, Anemia	CP-48 AP-4 BC-6

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

The main aim of this study was to estimate the prevalence of chronic myeloid leukemia in patients coming to IGIMS Patna as there is paucity of data on CML from the state of Bihar. The major observation seen in our study was occurrence of CML at relatively younger age group (30-50 years) which was in concordance to different studies on CML done in other Indian studies. Majority of our patients presented with symptom of Abdominal discomfort (70.1%) whereas most common sign was splenomegaly which was present in 87.93% of cases. The incidence of normocytic normochromic anaemia was higher, incidence of thrombocytopenia is lower and the frequency of CML patients in blast crisis phase was more as compared to Western literature. Complete Haematological Response was achieved in all cases but cytogenetic and molecular monitoring was an issue due to financial constraint and also due to unavailability of the tests in our institute. Early diagnosis and compliance are vital for prognostication and choosing treatment modalities**.**

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