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Original Research Article

Clinico Hematological Profile and Phase Distribution of Chronic Myeloid Leukemia

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Abstract

Chronic myeloid leukemia is a clonal hematopoietic stem cell disorder. CML is caused by the BCR-ABL1 chimeric gene product, which results from a reciprocal balanced translocation between the long arms of chromosomes 9 and 22, t (9; 22) (q34.1; q11.2), known as the Philadelphia chromosome (Ph) and its codes for a constitutively active tyrosine kinase. CML is a common hematological malignancy in adults and accounts for 15% of all hematological malignancies. Worldwide incidence of CML is 1-2 cases per 1 lakh population per year.

Material and Methods: This was a cross sectional, observational and Descriptive study conducted in tertiary care centre & teaching institute during the period from November 2018 to December 2020. Total 100 patients of Chronic Myeloid Leukemia irrespective of etiology were included in this study.

Results: In our study most of the patients were aged between 31-40 years. Majority of the patients were males (62%) and male to female ratio was1.6:1. Generalized weakness was the most common symptom (52%) followed by fatigue (35%), pain in abdomen (22%), Anemia (46%) and splenomegaly (58%) & 16% of the patients were Asymptomatic. Among 100 CML cases, Chronic phase (CP) cases were 95%, Accelerated phase (AP) cases were 3%, Blast crisis (BC) cases were 2%. But majority of patients were in chronic phase (95%) which is a good sign as the disease is completely treatable in the modern era.

Conclusion: CML accounts for one of the most common leukemia which is treatable with oral medications when presented at an early stage. TKIs have revolutionized the treatment of CML.

Keyword: CML, BCR ABL, Clinical Profile, CP, AP, BC, TKIs.

Introduction

Chronic myeloid leukemia (CML) is a clonal hematopoietic stem cell disorder. CML is caused by the BCR-ABL1 chimeric gene product, which results from a reciprocal

balanced translocation between the long arms of chromosomes 9 and 22, t (9; 22) (q34.1; q11.2), known as the Philadelphia chromosome (Ph) and it codes for a constitutively active tyrosine kinase [1]. Among the leukemias CML accounts for ~15% of all [2]. CML Being more common in male with a male: female ratio is 1.4:1. It is uncommon in children [3]. The median age reported for CML patients is late 40's to early 50's [4]. CML is a common hematological malignancy in adults with a worldwide incidence of 1-2 cases per 1 lakh population per year [5]. But no familial association is seen in CML. Etiologic agents are not incriminated, and no associations have been found to exist with exposures to benzene or other toxins, fertilizers, insecticides, or viruses. There is increased risk with exposure to ionizing radiation (e.g., nuclear accidents, radiation treatment for ankylosing spondylitis or cervical cancer), which peaks at 5-10 years after exposure and is dose-related. The t (9; 22) (q34.1; q11.2) is present in >90% of classical CML cases [6]. Mostly patients with CML (90%) present in the indolent or chronic phase [7]. Anemia and splenomegaly are the most common symptoms, when present [8]. The most common physical finding is splenomegaly, occurring in 20–70% of patients. Other less common findings include hepatomegaly (5–10%), lymphadenopathy (5-10%), and extramedullary disease (skin or subcutaneous lesions) [9]. Mean haemoglobin level ranged from 9-11 gm/dL, Median total leucocyte count ranged from 46000/cumm to 1.86 lac/cumm [10]. The diagnosis of CML depends on documenting the t (9;22), (q34.1;q11.2), which was done by FISH (BCR-ABL) studies. This is known as the Philadelphia chromosome (initially identified in Philadelphia as a minute chromosome), later identified to be chromosome 22 [11].

Therapy of chronic myeloid leukemia was historically divided into pre-TKI era and TKI era. The annual mortality in CML was 10% in the first 2 years and 15–20% thereafter and this picture was seen before the imatinib era [12]. But after the initiation of imatinib therapy, the annual mortality in CML decreased to 2% in the first 16 years of observation. Further the use of second-generation TKIs (nilotinib, dasatinib) as frontline therapy have reduced the incidence of transformation in the first 2–3 years from 6–8% with imatinib to 2–5% with nilotinib or dasatinib [13].

Material and Methods

This was a cross sectional, observational and Descriptive study conducted in tertiary care centre & teaching institute during the period from November 2018 to December 2020. This study was started after getting valid written permission from institutional ethical committee, total 100 patients of Chronic Myeloid Leukemia irrespective of etiology were included in this study. Inclusion criteria were Patients aged 18 years or older ,who gave valid written informed consent with confirmed diagnosis of CML on PS, Bone marrow aspiration, flow cytometry and FISH (BCR-ABL) and Exclusion criteria were Patients who refused to give consent, those who were Ph positive ALL.

Detail Procedure of study

100 patients of Chronic Myeloid Leukemia from general medicine wards, ICU or OPD irrespective of etiology were included in this study. After enrollment detailed clinical history was obtained from each case, which included the age and sex of the patients, relevant history, presenting symptoms and Thorough clinical examination was done, Routine Blood Investigations, Peripheral smear, Bone marrow examination, liver function tests, kidney function tests and Routine blood counts were performed. The peripheral blood smears were studied in

detail. Biochemical, Cytochemical staining and flow cytometric, FISH study were performed in all patients for BCR-ABL Mutation. A person is considered to have chronic myeloid leukemia on the basis of clinical findings, peripheral smear and bone marrow reports and FISH as per Guidelines. Flow cytometry was done in suspected PH+ ALL cases or those with blast crisis. Patients on treatment were followed up for changes in pre decided parameters and treatment response was decided.

Results

Majority of the patients (23%) belong to 31-40 years age group followed by 20% of the patients were in 51-60 years age group, 20% of the patients were more than 60 years, 19% of the patients were in 41-50 years age group, 12% of the patients were in 21-30 years age group and only 6% of the patients were less than <20 years of age. Among all cases 62% of the patients were males and 38% of the patients were females. In symptoms Majority (52%) of the patients had generalized weakness, 35% of the patients had fatigue, 22% of the patients had pain in abdomen, 16% of the patients were Asymptomatic, 14% of the patients had fever, 14% of the patients had loss of appetite, 9% of the patients had mass per abdomen and 6% of the patients had Distension of abdomen. In signs 46% of the patients had pallor, 58% of the patients had splenomegaly, 14% of the patients had hepatomegaly and only 1% of the patients had edema.

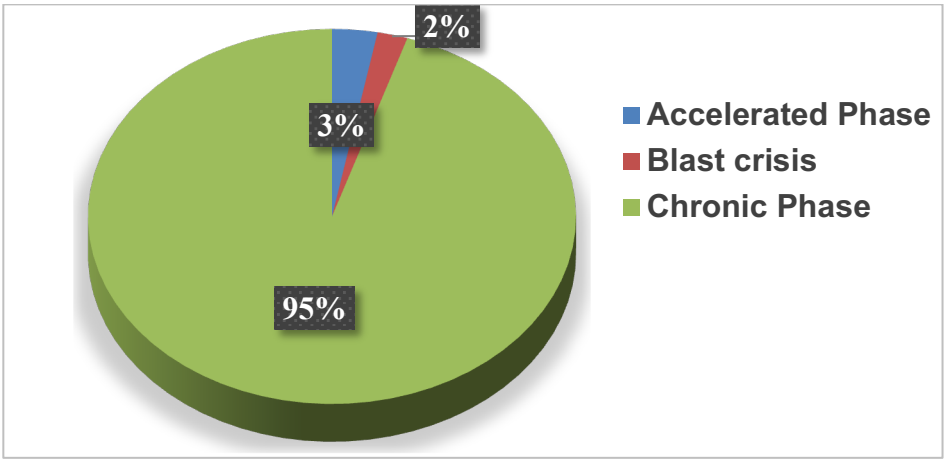
Among 100 cases 32% of the patients had moderate splenomegaly, 16% of the patients had severe splenomegaly, 10% of the patients had mild splenomegaly and 42% of the patients had no splenomegaly.

Hemoglobin range was from 6.2 to 14 gm/dl and mean Hemoglobin was 9.41± 1.44. Total leucocyte count range was from 3300/cumm to 6.85 lac/cumm and mean TLC was 2.04 lakh/cumm. Platelet range was from 65000/cumm to 9.3 lakh/cumm with mean of 3.15 lakh/cumm.

Table 1: Distribution of patients according to stage of CML

CML Phase	Frequency (N)	Percentage (%)
Accelerated Phase	3	3.0%
Blast crisis	2	2.0%
Chronic Phase	95	95.0%

95% of the patients were in chronic phase, 3% of the patients were in Accelerated phase and 2% of the patients were in Blast crisis.



Graph 1: Graph showing Distribution of patients according to stage of CML

Among patients with Accelerated Phase 66.7% were males and 33.3% were females. Among patients with Chronic Phase 61.1% were males and 38.9% were females. Among patients with Blast crisis all were males. P value was 0.525, so there was no statistically significant difference found between sex and CML stage. Mean age among patients with Accelerated Phase was 49.67±9.23 years, Mean age among patients with Blast crisis was 54±15.5 years and Mean age among patients with Chronic Phase was 45.18±15.36 years. P value was 0.643, so there was no statistically significant difference found between age and CML stage. Mean number of blast cells in patients who had Blast crisis was 32±6. Mean number of blast cells in patients who had Accelerated Phase was 15± 3. Mean number of blast cells in patients who had Chronic Phase was 3± 3.

Discussion

CML is a common hematological malignancy in adults with a worldwide incidence of 1-2 cases per 1 lakh population per year [5]. It comprises 15-25% of all haematological malignancies [2]. In Indian population it accounts for 30-60% of all adult leukaemias [2]. The median age reported for CML patients is late 40's to early 50's [4]. In study done by Bhutani M. *et al* [2] , 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. In a study done by Ruchi Sinha *et al* [3] the median age at presentation was found to be 33 years. In our study Majority of the patients (23%) were belong to 31-40 years age group followed by 20% of the patients were in 51-60 years age group, 20% of the patients were of more than 60 years, 19% of the patients were in 41-50 years age group, 12% of the patients were in 21-30 years age group and only 6% of the patients were less than <20 years. In a study done by Ruchi Sinha et. al [3] male to female ratio was 1.4:1. In our study male to female ratio was 1.6:1

Asymptomatic presentation is quiet common (40%) [14], 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.[10] Majority of Indian patients are symptomatic and mostly present with dull aching pain in left hypochondrium.[15,16] In our study Majority (52%) of the patients had generalized weakness, 35% of the patients had fatigue, 22% of the patients had pain abdomen, 16% of the patients were Asymptomatic, 14% of the patients had fever, 14% of the patients had loss of appetite, 9% of the patients had mass per abdomen and 6% of the patients had Distension of abdomen. In a study done by Yaghmaie M. *et al* [17] Weakness, Pain in abdomen Were the main presenting complaints.

In our study 95% of the patients were in chronic phase (CP), 3% of the patients were in Accelerated phase (AP) and 2% of the patients were in Blast crisis (BC). In a study done by Ruchi Sinha *et al* [3] 64 CML patients, were categorized into CP 41 (64.0%), 18 (28.1%) in AP, 5 (7.8%) in BC in their study. In a study done by Ahmed R et. al [7] reported that frequency of CP, AP and BC were 77.8%, 15.5% and 6.7% respectively among the 45 patients suffering from CML.

Table 2: Comparison of various studies with present Study

Name of Study	No. of patients	Mean age	M: F ratio	Chief complaints	Phase distribution
Ahmed R *et al*., [7]	83	37.9	2.2:1	Anaemia, massive splenomegaly	AP-62, CP-17, BC-03

Yaghmaie M *et al*., [17]	63	37.4	2:1	Weakness, Pain abdomen	CP-39, AP-7, BC-2
Bhatti F *et al*., [9]	335	35.5	2:1	Anaemia, massive splenomegaly	AP-241, CP-31, BC-15
Malhotra H *et al*., [8]	213	39	1.95:1	Anaemia, massive organomegaly	NA
Ruchi Sinha *et al*; [3]	64	33	1.4:1	Fever, pain abdomen, splenomegaly	AP-41 CP-18 BC-05
Present study	100	45.5	1.6:1	generalized weakness fatigue pain abdomen	AP-03, CP-95, BC-02

Note : **AP-** Accelerated Phase, **CP-** Chronic Phase- **BC-** Blast crisis phase

According to various Indian studies like Prasad R.R.et.al [10] mean haemoglobin range was from 9-11 gm/dL, Median Total Leucocyte count range was from 46000/ cumm to 1.86 lac/cumm. In our study Hemoglobin range was from 6.2 to 14 gm/dl and mean Hemoglobin level was 9.41± 1.44. In our study Total leucocyte count range was from 3300/cumm to 6.85 lac/cumm and mean TLC was 2.04lakh/cumm.

In our study among patients with Accelerated Phase 66.7% were males and 33.3% were females. Among patients with Chronic Phase 61.1% were males and 38.9% were females. Among patients with Blast crisis all were males. P value was 0.525, so there was no statistically significant difference found between sex and CML stage.

In a study done by Ruchi Sinha *et al* [3] among 18 patients with Accelerated Phase 10 were males and 8 were females. Among 41 patients with Chronic Phase 25 were males and 16 were females. Among 5 patients with Blast crisis 3 were males and 2 were females. In study done by Chang F et. al [15] among 17 patients with Accelerated Phase 11 were males and 6 were females. Among 62 patients with Chronic Phase 42 were males and 20 were females. Among 3 patients with Blast crisis 2 were males and 1 was female.

In our study Mean age among patients with Accelerated Phase was 49.67±9.23 years, Mean age among patients with Blast crisis was 54±15.5 years and Mean age among patients with Chronic Phase was 45.18±15.36 years. P value was 0.643, there was no statistically significant difference found between age and CML stage.

In a study done by Ruchi Sinha et.al [3] Mean age among patients with Accelerated Phase was 43±6 years, Mean age among patients with Blast crisis was 44±8 years and Mean age among patients with Chronic Phase was 28±7 years

In study done by Chang F. *et al* [15] Mean age among patients with Accelerated Phase was 45±6 years, Mean age among patients with Blast crisis was 45.5±9.5 years and Mean age among patients with Chronic Phase was 30±7 years. In our study Mean number of blast cells in patients who had Blast crisis was 32 ± 6. Mean number of blast cells in patients who had Accelerated Phase was 15± 3. Mean number of blast cells in patients who had Chronic Phase was 3 ± 3. In a study done by Ruchi Sinha et.al [3] Mean number of blast cells in patients who had Blast crisis was 24± 5. Mean number of blast cells in patients who had Accelerated Phase was 15± 2. Mean number of blast cells in patients who had Chronic Phase was 5± 2. In study done by chang F et.al [15] Mean number of blast cells in patients who had Blast crisis was 26± 5 Mean number of blast cells in patients who had Accelerated Phase was 16±4. Mean

number of blast cells in patients who had Chronic Phase was 6±2.

Summary

Chronic Myeloid Leukemia is one of the common leukemia which is treatable. This study was undertaken to look for the clinico-hematological profile of patients presenting with CML. In our study most of the patients were aged between 31-40 years and mainly presented with generalized weakness, fatigue, pain abdomen, anemia and splenomegaly. The age group of presentation was similar to other Indian studies. Most of the patients were symptomatic which suggests delayed presentation when compared with Western studies. But majority of patients were in Chronic phase (95%) which is a good sign as the disease is completely treatable in the modern era.

Conclusion

CML accounts for one of the most common leukemia which is treatable with oral medications when presented at an early stage. TKIs have revolutionized the treatment of CML. But this disease needs much awareness in the public. Majority of the patients presenting in our study were symptomatic which suggests that there is delayed presentation and no screening modality available for this disease. A routine blood investigation would be enough to screen the disease. Majority of Indian population resides in rural areas and illiteracy being a major concern. Hence it is important to educate the public and create awareness regarding the disease and prevent fatal complications in near future.

Limitations

The study population was small, no **conventional** cytogenetic or molecular study and follow ups were not done due to unavailability and non- affordability of patients, however FISH BCR ABL was done in all cases.

List of Abbreviations

CML: Chronic Myeloid Leukemia
Ph: Philadelphia chromosome
BCR: Break point Cluster Region
DNA: Deoxyribose Nucleic Acid
ABL: Abelson murine lymphosarcoma virus; ABL1 gene is named so because it was first encountered in this virus
TKI: Tyrosine Kinase Inhibitor
ACS: American Cancer Society
LAP: Leukocyte Alkaline Phosphatase
CP- CML: Chronic Phase- Chronic Myeloid Leukemia
BP- CML: Blastic Phase- Chronic Myeloid Leukemia
AP- CML: Accelerated Phase- Chronic Myeloid Leukemia
PCR: Polymerase Chain Reaction
CVAD: Cyclophosphamide, vincristine, doxorubicin, and dexamethasone
SCT: Stem Cell Transplantation
ELTS: The European Treatment and Outcome Study Long term Survival
OS: Overall survival
EUTOS: European Treatment and Outcome Study
ACA: Additional Chromosome Abnormalities
CBA: Chromosome Banding Analysis
MMR: Major Molecular Remission
ELN: European Leukemia Net
WHO: World Health Organization
CCA: Clonal chromosome abnormalities
WBC: Whole Blood Count
FDA: Food and Drug Administration
PS: Peripheral smear
FISH: Fluorescent in situ hybridization

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