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Evaluation and Characterization of Indian Chronic Myeloid Leukemia Patients on Imatinib

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Abstract

Background: Chronic myeloid leukemia (CML) is a clonal malignant disorder of hematopoietic stem cell characterized by the classical chromosomal translocation, Philadelphia (Ph) chromosome in more than 90% of the patients. CML is associated with significantly high granulocyte numbers in the bone marrow and peripheral blood.

Materials and Methods: This is a retrospective study conducted at the All India Institute of Medical Sciences, New Delhi, India aimed to evaluate the incidence and characteristics of CML patients. We have evaluated the demographic, clinical, and hematological data of 158 consecutive patients who visited the hospital from 2012 to 2014.

Results: The diagnosis and stage of CML were determined based on the World Health Organization criteria, followed by the polymerase chain reaction. 158 patients evaluated in this study, consist of males (n = 98, 62%) which was higher than females (n = 60, 38%)(M:F::1.6:1). The mean + SD of male and female was 35.6 + 12.7, mean + SD of males was (35.7+ 13.6) and mean + SD of females was (35.4+11.3). While 17 (10.7%) patients were below 20 years of age, 94 (59.4%) were between 21–40 years, 40 (25.3%) were between 41–60 years, and 7 (4.4%) were more than 60 years of age. The predominance of younger patients (59.4.%) were belong to the age group of 21-40 years. While the most predominant symptom was fatigue and bone pain, the most common clinical sign was hepato-splenomegaly, followed by remarkable weight loss, and epistaxis.

Conclusion: A patient with an increased WBC count, weakness, bone pain, low LAP score and hepatosplenomegaly should clearly be evaluated for CML.

Keywords: Chronic Myeloid Leukeima; Imatinib; Major Molecular Response (MMR).

Introductions

Chronic Myeloid Leukemia (CML) is one of the most common adult leukemias and its annual incidence is—1–2 per 100,000 in west.[1,2] CML is a clonal malignant disorder of pluripotent hematopoietic stem cell characterized by insidious onset of symptoms, progressive splenomegaly, marrow hypercellularity, anemia and leukocytosis with myeloid series of cells in all stages of maturation.[2,3,4] CML develops in three phases, the first phase, a chronic phase (CP) accounting 85–90% of subjects during the stage of diagnosis, second stage which is an accelerated phase(AP) and third stage which is either myeloid or lymphoid blast crisis.[2,3,5] If untreated, this disease follows a typical course, from chronic phase (CP) toward to an ill defined accelerated phase (AP) and then to the final stage of blast crisis (BC) which might results with a deadly outcome with in a period of 5 years.[6] After the introduction of BCR-ABL tyrosine-

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kinase inhibitors (TKIs), which is considered to be the first-line therapy for patients with CML[7,8] the survival of overall patients with CML in the CP stage was significantly improved.[9] For first line treatment, the gold standard is imatinib mesylate (IM) and it is available as a common drug in most of the countries.[3,5,9,10] Though the imatinib was used as the first line therapy, it is expected that around 20% of patients mainly treated with this drug, may become primary or secondary resistance to this drug.[11] Those patients in the chronic phase (CP), whose treatment with imatinib was failure due to the intolerance or resistance were regularly offered with the second generation of TKI treatment, dasatinib, nilotinib, ponatinib or Bousitib.[5,12] The epidemiological data shows that the CML patient's age differs at the time of analysis depicts the median age ranges among 52–64 years.[13] The TKI therapy is considered to be the life long suggestion for CML, however the TKI withdrawal is safe for those who withstand the enduring treatment free remission (TFR).[14] The other front line therapy consist of imatinib higher doses or merging TKI with added agent like IFN-a[15] The choice of TKI therapy must be focused on the factors like toxicity, age, risk score and patients capacity to bear the therapy.[16] The occurrence of CML is 0.6–2.0 cases per 100,000 populations and the frequency of CML increases with age. It appears in higher occurrence in male while compared to female with a ratio of male to female ranges between 1.3 and 1.8[17] Those adult patients maintain major molecular reponse(MMR) can expect a normal life expectancy as long they obtain lifelong treatment.[18] This study was conducted to investigate the demographic, clinical, and hematological characteristics of Indian CML patients on imatinib.

Materials and Methods

Patients and data collection

We retrospectively collected the demographic, clinical, and hematological data of 158 CML patients who had been referred to the Hematology department of AIIMS, New Delhi, from January 2012 to January 2014. The demographic data included age, gender, clinical symptoms and signs, such as splenomegaly, hepatomegaly, and lymphadenopathy. The hematological data included total leukocyte and platelet counts, and levels of hemoglobin.

Diagnosis

Patients were examined for the presence of a palpable spleen, liver, and lymphadenopathy. The routine blood tests included total and differential complete blood count (CBC), blast cell count, LAP score and the blood film test. For RT-PCR, mRNA was extracted from CML patients and converted to cDNA using reverse transcriptase. The stage of CML was assigned as per WHO assessment.

Statistical Methods

The Stata 11 Statistical package was used to analyze the data's. The frequency of standard descriptive statistics such as mean and standard deviation were used to summarize patient characteristics. A p-value less than ≤0.05 is considered as statistically significant.

Results

Patient characteristics

Table 1 summarizes the characteristics of the 158 patients evaluated in this study with mean age 35 years.

Table 1: The Demographical Characteristics of CML patients.

	Age Distribution	Number	%	Mean+SD
	<20	17	10.7	16.7+1.9
	21-40	94	59.4	31.2+5.9
	41-60	40	25.3	48.6+3.3
Age	>60	7	4.4	65.7+3.3
	All patients	158		35.6+12.7
Sex	Male	98	62	35.7+13.6
	Female	60	38	35.4+11.3

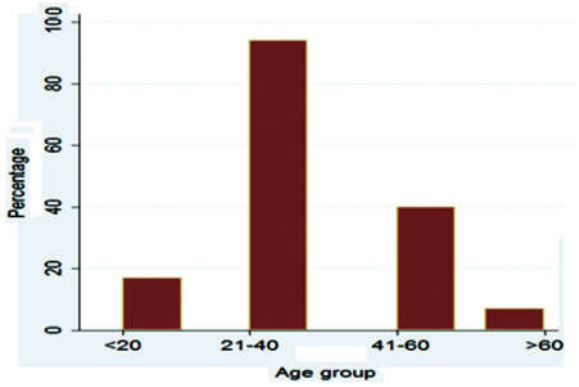

Fig.1: The age group wise percentage of CML patients.

The participants consist of males (n = 98, 62%) which is higher than females (n = 60, 38%M:F::1.6:1). p = 0.558 (Fig.1 and 2). All these patients were considered for our study and were treated with 400mg-600mg imatinib per day. The mean + SD of male and female was 35.6 + 12.7 and mean + SD of

males is (35.7+ 13.6) and for females is (35.4+11.3). While 17 (10.7%) patients were below 20 years of age, 94 (59.4%) were between 21–40 years, 40 (25.3%) were between 41–60 years, and 7 (4.4%) were more than 60 years of age (Table 1). Most of the patients 59.4.%, were belong to the age group of 21-40 years with median age 35 years (Fig.1).

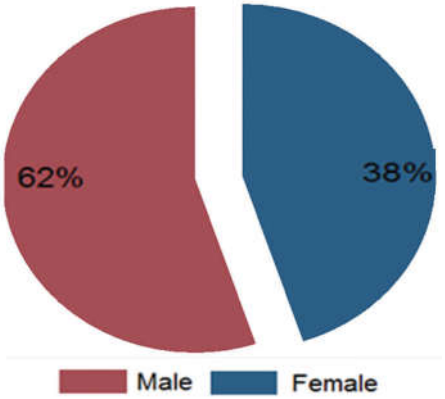

Fig. 2: Gender distribution of CML patients.

Associations between patient characteristics and the obtained therapeutic responses

Overall, there is no differences in therapeutic responses were seen based on sex, age, or social status.

Presenting features

Table 2 summarizes the clinical features of CML patients. low sokal risk was reported in 73(46%), Intermediate risk in 57 (36%) and high risk was reported in 28 (17%).

Table 2: The Clinical features of CML patients.

Baseline Characteristics (n=158)	No. of Patients (n)	(%)
Sokal score		
Low risk	73	(46)
Intermediate risk	57	(36)
High risk	28	(17)
Presenting symptoms		
Weakness and bone pain	77	(44.8)
Eosinophil	74	(46.8)
Basophils	109	(68.9)
Splenomegaly	113	(71.5)
Hepatomegaly	62	(39.2)
Total number of patients having low lap score (LAP)	116	(73)
Phase of disease		
Chronic Phase (CP)	124	78.4
Accelerated Phase (AP)	20	12.6
Blast crisis (BC)	14	8.8
Outcome after 3 years		
EFS (Event Free Survival)	111	71
Morality	18	11.3

While 77(44.8%) patients presented with extreme weakness and bone pain affecting their work and sleep, 74 (46.8%) of them had high eosinophils, and 109 (68.9%) had high basophils . While 9 (5.7%) patients were accidentally found to have a high WBC count during routine investigations, 113 (71.5%) and 62 (39.2%) of them had enlarged spleen and liver, respectively. The 124 (78.4%) patients were in chronic phase of the disease, 20 (12.6%) patient were in the accelerated phase, and 14 (8.8%) of them were in blast crisis (BC). The hematological data for all the patients have been summarized in Table 3.

Table 3: The Hematological features of CML patients.

Parameters	Distribution	Number	%	Mean + SD
Hemoglobin (g/dL)	<8	58	36.7	34.79+13.8
	8-12	88	55.7	36.07+12.4
	>12	12	7.5	36.16+10.8
WBC (10^9/L)	<19	10	6.3	38.5+14.4
	20-99	34	21.5	35.7+11.10
	100-400	105	66.4	35.7+13.11
	>400	9	5.7	30.5+13.95
Platelet (10^9/L)	<100	24	15.1	35.54+11.21
	100-200	46	29.1	35.10+11.90
	200-400	43	27.2	35.79+13.51
	>400	45	28.4	36.0+14.10

Nearly 66.4% of the patients had a WBC count between 100–400, while some others had a count as high as >400 (n = 9, 5.7%). Higher number of patients had hemoglobin levels between 8−12 g/dL (n = 88, 55.7%) followed by <8g/dL (n=58, 36.7%). Platelets were the most compromised cells in CML patients. Platelet counts were below 100 in 15.1% of the patients and had episodes of epitasis.

Discussion

CML is a chronic myeloproliferative disorder that arrays clinically from a dormant to rapidly disastrous disease.[19] The present study analyzes the demographic, clinical, and hematological characteristics of 158 CML patients attending the Hematology Outpatient Department of the AIIMS, New Delhi. CML accounts for 20% of all leukemia's in adults. Currently, the only remedial management for CML is bone marrow transplantation.[20] In United States, the incidence rate of CML is approximately 1.6/100,000, and 5430 cases are forecasted for the year 2022. The race or ethnicity of the people has no association with incidence rate of CML.[21-22] CML incidence cases are increases with

age and it come out with all age groups. As stated in various cancer registries, CML is one of the most common adult leukemias in Indian population accounting for 30% - 60% of all adult leukemias.[23] The data presented in a CML meeting showed that the incidence of CML cases varied from 70% of all leukemia cases in Indira Gandhi Institute of Medical Sciences (IGIMS), Regional Cancer Centre (RCC), Patna, Bihar, to 16.6% Gujarat Cancer and Research Institute (GCRI), Gujarat, India.[24,25] This difference in the incidence of CML cases at two different centers is likely due to the fact that these are not population-based registries, and it is accountable to different cancer populations they cater to and referral bias.

Unlike, previous studies from other countries[26,27] In our study we found a lower median age (35.6+12.7 years) during diagnosis. Median age at presentation in India is a decade younger compared with the age presented in European (median age 55 years) as well as in American (median age 66 years) literature.[28,29] The median age of the Indian population varied from minimum 32 years to maximum 42 years.[30,31] This decade younger population was the most consistent fact presented in almost all studies in India. The reason for this early presentation remains elusive.

Like the worldwide trend, the males being more vulnerable to CML compared to females[32], we found no statistically significant difference in the incidence of CML between males (n = 98, 62%) which is higher than females (n = 60, 38%) (M:F::1.6:1. p = 0.558)The male to female sex ratio varied from 1:08 to 3:1 in India.[33,34]

The mean hemoglobin is ranged from 8 g/dl to 12 g/dl in India); the mean white blood cell count ranged from 0.46×10^9/cumm to 1.86×10^9/cumm in India.[24] The most common symptom was splenomegaly ranging followed by hepatomegaly, fatigue, weakness, dragging pain, pallor, or sometimes asymptomatic seen in 30% cases in Indian populations.[24,25] In comparison to Western data where approximately 40% of patients are asymptomatic and diagnosed on the basis of abnormal counts, majority of Indian patients are symptomatic.

We found the lower percentage of patients presenting in CP is 78.4%, which is slightly lower than other studies reported from India (85-97%) whereas in European data, the presentation of CML in CP has been reported to be as high as 96.8%[24, 28, 35]

The 5-year survival rate in patients with CML as per American Cancer Society has improved to 90%[36,37] Likewise, 3-year survival rate was 89% in the present study. Unfavorable hematological features such as leukocytosis and anemia were identified in a substantial proportion of the study population.

Therefore, a patient with an increased WBC count, weakness, bone pain, low LAP score and hepatosplenomegaly should clearly be evaluated for CML. The limitations of our study include (a) single-center (b) retrospective nature, (c) small sample size, and (d) short follow up. Multi-center studies with higher sample sizes and continued follow-up periods are therefore required to validate our findings in the Indian population. Exploration of CML in diverse populations can provide a deeper understanding of its molecular characteristics and thereby help in finding better treatment opportunities.

Conflict of interest: None

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