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Original Article

The Biology of Chronic Myelogenous Leukemia in Childhood and Young Adolescents: An Indian Perspective

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Abstract

Objective: The purpose of this study was to determine the clinical, biological, and molecular characteristics at diagnosis in children and adolescents with chronic myelogenous leukemia (CML) in the Indian scenario at our tertiary patient care center. **Subjects and Methods:** We evaluated 51 children and adolescents with CML registered at our clinic, from January 2007 to December 2015. The mean and median of various parameters were calculated using a Microsoft excel sheet and SPSS software version 16. **Results:** The median age of presentation in children was 16 years; 92.2% of them were older than 10 years, with a higher prevalence in boys than girls (gender ratio 2.6:1). The symptoms at presentation were fatigue, fever, awareness of mass due to splenomegaly, and bleeding manifestations. One patient presented with Bell's palsy. Markedly raised leukocyte counts were present in 29.4% patients (median white blood cell count >400 × 10^9/L). Most of the patients presented in the chronic phase of the disease, four each were in accelerated phase and blast crisis, respectively. Majority of patients were categorized as intermediate risk as per Sokal and Hansford score. About 60.7% of these pediatric patients fell in low-risk category as per European Treatment and Outcome Study score at baseline. A predominance of transcript P210-b3a2 (68%) was observed in the children who were studied for the type of chimeric BCR-ABL mRNA. **Conclusions:** This is one of the most recent reported series of CML in children and adolescents from India highlighting the difference in presentation from adults; mainly hepatomegaly, bleeding manifestations, and higher leukocyte count. Presence of b3a3 transcript of p210 breakpoint of BCR-ABL was more common in children (68%) than b2a2 transcript (32%) when compared to adults as recently described in a study from India, which may explain the differences at presentation.

Keywords: *BCR-ABL transcripts, chronic myelogenous leukemia, clinical presentation, pediatric*

Introduction

Chronic myelogenous leukemia (CML) is primarily an adult disease and its incidence is rare in children and adolescents, accounting for only 2% to 3% of all leukemias in this age group with an annual incidence of 1 case per million children in Western countries (Surveillance, Epidemiology, and End Results [SEER]).[1] Although the age-adjusted rates for CML in pediatric and young adults are slightly higher in India than in SEER registries,[2] the characteristic features of this myeloproliferative disease in the younger population are based on studies of a limited number of patients. The aim of this study was to determine the main presenting features of CML in children and adolescents in the Indian population as well as to characterize the molecular subtype of the BCR-ABL transcript, as the studies pertaining to this entity are sparse.

Subjects and Methods

We reviewed the records of 51 children and adolescents who were treated for CML at this center over a period of 9 years, between January 2007 to December 2015. The diagnosis of CML was confirmed by the presence of the BCR-ABL translocation by reverse transcription polymerase chain reaction (RT-PCR). The symptoms, physical signs, peripheral blood, and bone marrow analysis at initial diagnosis were recorded. Stage of the disease (chronic phase, accelerated phase, or blast crisis) was classified according to the WHO 2008 criteria.[3] Anemia was diagnosed when the hemoglobin level was <110 g/L in children who were between 0 and 6 years of age, <130 g/L in boys who were >6 years of age, and <120 g/L in girls who were >6 years of age. Thrombocytosis was diagnosed when the platelet count was >450 × 10^9/L, and thrombocytopenia was diagnosed when the

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platelet count was <150 × 10^9/L. The BCR-ABL fusion gene was analyzed in all patients and the type of fusion transcript was determined in 25 patients. The Sokal, European Treatment and Outcome Study (EUTOS) scores were evaluated for patients.

Statistical analysis

The mean and median of various parameters were calculated using a Microsoft excel sheet and IBM SPSS statistic software version 16, Armonk, New York, United States.

Results

Patient characteristics of the children and adolescents are reported in Table 1. There was a male preponderance with male to female ratio of 2.6:1. The median age at diagnosis was 16 years (range: 7–17 years). Most of the patients were >10 years of age (92.2%) and were diagnosed in the chronic phase (84.4%). The median duration of symptoms before the diagnosis of CML was 2 months (range: 10 days to 48 months). The main presenting symptoms are reported in Table 1. Generalized weakness was the most common symptom followed by fever and abdominal discomfort or awareness of mass. Bleeding such as menorrhagia or epistaxis was seen in 8 patients, of whom 7 had normal platelet count and one had thrombocytosis. The nature of the symptoms and their duration before the diagnosis of CML did not differ between boys and girls. One of the patients with Bell's palsy was detected to have blast crisis.

The physical signs at diagnosis are reported in Table 1. Splenomegaly was the predominant abnormality detected in 90.2% of patients with a median spleen size of 12 cm (range: 1–28 cm) below the costal margin, of these 67.4% of patients had massive splenomegaly (spleen size >8 cm below the costal margin). The presence of a splenomegaly was significantly more frequent in symptomatic (Fischer's exact test, $P < 0.05$) than in asymptomatic patients. Hepatomegaly was also present in 35.3% of the patients, while lymphadenopathy was unusual. The physical signs did not differ between boys and girls.

A white blood cell (WBC) count >10 × 10^9/L was observed in all of our patients [Table 2]. A higher presenting WBC count was associated with symptoms at diagnosis (Kruskal–Wallis test, $P < 0.01$) and splenomegaly at diagnosis ($P < 0.01$). About 92.1% of our patients presented with anemia. The level of hemoglobin was significantly lower in children with splenomegaly at diagnosis (Kruskal–Wallis test, $P = 0.01$). Nearly, 27.4% of our patients presented with thrombocytosis. There was no influence of age or gender on the WBC count, the hemoglobin level, or the platelet count.

About 27.5% and 25.5% of our patients were categorized as low risk as per Sokal and Hasford scoring system, respectively, and 60.7% fell in the low risk category as per EUTOS score at baseline [Table 3].

Table 1: Baseline clinical profile of children and adolescents (*n*=51) with chronic myelogenous leukemia

Clinical features	*n* (%)
Age (years)	
0-4	0
5-9	4 (7.8)
10-14	13 (25.5)
15-17	34 (66.7)
Sex	
Male	37 (72.5)
Female	14 (27.5)
Symptoms	
Weakness	43 (84.3)
Fever	40 (78.4)
Pain abdomen	19 (37.3)
Awareness of mass	37 (72.5)
Bone pain	3 (5.9)
Bleeding	8 (15.7)
Bell's palsy	1 (1.9)
Signs	
Splenomegaly	46 (90.2)
Hepatomegaly	18 (35.3)
Disease phase	
Chronic	43 (84.4)
Accelerated	4 (7.8)
Blastic	4 (7.8)

N – total number of patients included in the study; *n* – number of patients

Table 2: Baseline laboratory parameters of children and adolescents (*n*=51) with chronic myelogenous leukemia

Laboratory measurements	Median	Mean	Range
WBC (×10^9/L)	170	205.45	10.4-703.4
Hemoglobin (g/L)	78	80.8	34-117
Platelets (×10^9/L)	300	403.19	36-1200
Laboratory measurements		***n* (%)**	
WBC (×10^9/L)			
10-19		3 (6)	
20-99		11 (21.5)	
100-400		22 (43.1)	
>400		15 (29.4)	
Hemoglobin (g/L)			
<80		28 (54.9)	
80-120		23 (45.1)	
>120		0	
Platelets (×10^9/L)			
50-149		6 (11.7)	
150-449		31 (60.8)	
450-1000		12 (23.5)	
>1000		3 (6)	

WBC – White blood cell

Molecular analysis of BCR-ABL mutation was done using reverse transcription and the RT-PCR in our patients [Table 4]. Majority of the patients (50) were positive for p210 and 1 patient was positive for p230. None

Table 3: Prognostic scores of children and adolescents (*n*=51) with chronic myelogenous leukemia

Prognostic index	*n* (%)
Sokal	
Low score (<0.8)	14 (27.5)
Intermediate (0.8-1.2)	21 (41.1)
High risk (>1.2)	16 (32.4)
Hasford	
Low score (<780)	13 (25.5)
Intermediate (781-1480)	20 (39.2)
High risk (>1481)	18 (35.3)
EUTOS	
Low risk (<87)	31 (60.7)
High (>87)	20 (39.3)

EUTOS – European Treatment and Outcome Study

Table 4: Distribution of molecular subtype transcript of BCR-ABL p210

BCR-ABL p210 transcript *n*=25 patients	
	n (%)
P210-b3a2	17 (68)
P210-b2a2	8 (32)

of the patients were positive for p190. BCR-ABL p210 transcripts had been analyzed in 25 patients. These patients were studied for the type of chimeric BCR-ABL mRNA, of which b3a2 was positive in 17 and b2a2 was positive in 8 patients. The most common transcript was b3a2 in our patients.

Discussion

Till date, the major focus of studies on reported clinical and biological data has been in adults with CML with pediatric CML as an incidental part; similarly, at our center, adult CML data of 20 years was published in 2013.[4]

However, the numbers of children in most of these reports were small and were published between 1990–2010.[5-9] Earlier studies before 2002 may have included patients with juvenile myelomonocytic leukemia as there was a diagnostic dilemma between these two entities.[5,6,10] The earlier studies from AIIMS have presented data up to 2010 but without the molecular transcript data.[4] We, in our study, have retrieved data from the last 9 years and correlated it along with the molecular transcript data available.

Our data show male preponderance; this has been reported both in pediatric cases by the French group and in our adult series.[8] CML remains extremely rare in very young children; more than 90% of children in our study were older than 10 years at diagnosis, as previously reported; this can be ascribed to the fact that the incidence of CML rises with increasing age. Similar trend of rising incidence with age in the pediatric patients has been seen in the SEER data and Asian studies including Indian and Japanese group.[1,2,11,12] The Japanese group found that CML represented 0.2% of leukemias between 1 and 4 years of age, 2.2% between 5 and 9 years, 3.7% between 10 and 14 years, and 8.3% between 15 and 19 years.[12] The Asian group diagnosed CML in 0.3% in age group 0–4 years, 1.2% in 5–9 years, 2.7% in 10–14 years, 5.1% in 15–19 years.[11] Only the French multicenter study has shown more patients in the younger age group which may be due to a separate adult CML clinic.[8] However, in the present study, the majority of our pediatric and adolescent population with CML were diagnosed in the age group >10 years. Out of these 43 were diagnosed in chronic phase and 4 in accelerated phase and 4 in blast crisis. The rate of detection of CML in aggressive phase is higher than reported by earlier studies, which may be ascribed to the delay in initiating therapy or confirming diagnosis.

Generalized weakness, fever, distress caused by splenomegaly, and bleeding were the most common presenting symptoms, which was different from previous pediatric studies by the French group and Raut *et al*., where bleeding manifestations were seen in rare cases.[8,9] Children with symptoms at diagnosis had higher leukocyte counts and lower hemoglobin levels than those without symptoms, as reported in adults in data published by our institution.[4]

Hepatomegaly was more common in our patients in comparison with a previous pediatric study by Raut (35% vs. 14%).[9] Hepatomegaly may be related to adverse prognosis as previously reported by some older studies, and these patients will require greater follow-up to monitor response to therapy before a definitive conclusion can be drawn. Mild hemorrhage was common in our patients, as in adult patients of our institution.[4] This was not associated with thrombocytopenia and may have been attributable to platelet dysfunction.[13]

The type of BCR-ABL transcript was investigated in 25 of the children in our study: two-thirds of these had b3a2 transcript of p210, as compared to adults where b2a2 transcripts are more common as reported in a recent study and data published from our center in the past.[14] This may explain the presence of higher leukocyte count at presentation in pediatric CML.[15,16]

The main difference in CML at presentation between the children in our study and adults with CML was the higher leukocyte count in the children (median: 170 × 10^9/L) than reported in several adult studies, which can be explained by two-thirds of patients having b3a2 transcripts[15,16] [Table 5]. Despite the high median leukocyte count in our study, leukostasis was evident in only a few of our patients which has also been seen in the French group study; this finding is in contrast to older reviews in which leukostasis was more common in children.[17] Bleeding manifestations were also more common in our study than previously published series. Hepatomegaly was also present in many of our patients which are in contrast to published data by the

Table 5: Comparison between adult[4] and pediatric chronic myelogenous leukemia patients

Variables	Adult CML (*n*=300)	Pediatric CML (*n*=51)
Median age	35	16
Male:female	1.6:1	2.6:1
Presenting symptoms (%)		
Asymptomatic	<5%	0
Fatigue	66.7	84.3
Abdominal fullness	43.5	72.4
Bleeding manifestations	12	15.7
Fever	60	78.4
Examination finding (%)		
Splenomegaly	94.3	90.2
Hepatomegaly	93	35.3
Good Sokal score	1	27.5
High-risk Sokal score	40	32.4
Variables	**Adult CML, median (range)**	**Pediatric CML, median (range)**
WBC ($\times 10^9$/L)	139 (112-245)	170 (10.4-703.4)
Hemoglobin (g/L)	110 (56-154)	78 (34-117)
Platelets ($\times 10^9$/L)	589 (125-1126)	300 (36-1200)

WBC – White blood cell

French group.[8] The most common BCR-ABL transcript was b3a2 in our study which is higher (41%) than as reported in a recent study in this part of the world.[15]

Conclusions

This retrospective study represents the largest series of children and adolescents in which the clinical signs and biology of CML have been reported from South Asian part of the subcontinent. The main differences that we have identified between the children and adolescents in this study are the higher leukocyte count at diagnosis, presence of hepatomegaly, bleeding manifestations at presentation, presence of b3a3 transcript of p210 breakpoint of BCR-ABL being more common in our patients. A prospective analysis of a larger cohort is needed to determine the clinical significance of these observations and also to identify if these factors affect response to tyrosine kinase inhibitor therapy or have any prognostic significance.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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