Chronic myeloid leukemia in children and adolescents: A single center experience from Eastern India

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Abstract

Context: Chronic Myeloid Leukemia (CML) constitutes around 3% of leukemia in the children and adolescent age group. **Aims:** The aim of the study was to evaluate the characteristics at presentation and the treatment outcome of CML in the children and adolescent age group. **Settings and Design:** Retrospective analysis was carried out at a single center in India. **Materials and Methods:** Thirteen patients (≤17 years) attending CML outdoor from April 2008 to August 2012 were included in the analysis. **Statistical Analysis Used:** The mean and median of various parameters were calculated using a Microsoft excel sheet. SPSS 16.0 version software was used to calculate OS and PFS. **Results:** CML-CP was the most common phase at presentation. Maximum patients belonged to the 14 - 17 year old age group. Disease was common in the male sex. Splenic discomfort and asthenia were the most common symptoms and splenomegaly was the most common sign. **Conclusions:** The treatment with Imatinib was effective and well-tolerated.

Key words: Children and adolescents, chronic myeloid leukemia, imatinib

Introduction

Chronic Myeloid Leukemia (CML) constitutes around 3% of leukemia in the children and adolescent age group, with an annual incidence of one in 1,000,000. It constitutes around 10% of the CML cases. The median age at presentation was reported as 11 - 12 years.[1] In India, the age-specific incident rate of 0.04 per 100,000 was reported during 2001 - 2005.[2] CML results from reciprocal translocation of genes on chromosome 9 and 22. This results in juxtaposition of the breakpoint cluster region (BCR) gene on chromosome 22 with the Abelson leukemia virus (ABL) gene. The fused BCR-ABL protein has constitutive tyrosine kinase activity. It activates a number of intracellular signal transduction pathways like STAT, RAS, JUN, MYC, and phosphatidylinositol-3 kinase. This plays an important role in increasing myeloid proliferation and differentiation and suppressing apoptosis. This manifests clinically as CML.[3] The three phases of CML are chronic phase (CP), accelerated phase (AP), and the blast phase (BP). In this article, we share our experience in managing CML in this age group. The aim of the study was to evaluate the characteristics at presentation and the treatment outcome of CML in the children and adolescent age group. Not many studies have been published from India addressing this issue.

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Materials and Methods

This retrospective analysis was carried out at a single center in India. The study was approved by the Institutional Ethics Committee and it conforms to the provisions of the Declaration of Helsinki (as revised in Edinburgh 2000). At our institute a separate outdoor is run every Saturday for the management of CML patients. This was started from April 2008, with the purpose of dedicated care for the CML patients. Hence, records were analyzed from April 2008 to August 2012. A total of 995 CML patients were enrolled in the outdoor during this period. There were 13 patients ≤17 years in these 995 patients. These patients were included in the analysis. Their symptoms, signs, and laboratory parameters at presentation were recorded. The diagnosis was confirmed with conventional cytogenetic studies in 10 patients, by fluorescence *in situ* hybridization (FISH) for *BCR-ABL* in one patient, and by reverse transcriptase polymerase chain reaction (RT-PCR) in two patients. The samples for these tests were sent outside, as our institute lacks the infrastructure required to carry out these tests. The patients were treated with hydroxyurea till the diagnosis was confirmed. Thereafter, the patients were treated with Imatinib (260 mg/m^2). Hydroxyurea was continued in patients who could not take Imatinib due to financial constraints. The patients' follow-up and response assessments were done as per the European Leukemia Net guidelines for monitoring CML in adults.[4] Toxicity grading and evaluations were done according to the American National Cancer Institute Common Toxicity Criteria Manual Version 1. Not a single patient underwent stem cell transplant due to financial issues.

Statistics

Patients aged 18 years or more from the CML outdoor were taken as controls for comparing the clinical features at presentation. Microsoft excel was used for analysis.

The clinical and laboratory parameters at presentation were compared with those of the adult cohorts (N = 187) from the same center. These 187 patients were on hydroxyurea. The data on these 187 patients was presented at the Fifty-first National Conference of the Indian Society of Hematology and Transfusion Medicine 2010, 18 - 21 November, 2010, Kolkata, India. Overall survival (OS) was defined as the time from initiation of treatment to death or date of last follow-up. Progression was defined as loss of the maximum response achieved. Nine patients on Imatinib were included to estimate the Progression-free survival (PFS). The analysis of OS and PFS using the Kaplan-Meier method was performed using the SPSS 16.0 version software.

Results

The patients' characteristics at presentation are shown in Table 1. The median age at presentation was 16 years. Male sex predilection was seen. The chronic phase was the most common phase of CML seen in 92% of the patients at presentation. The predominant symptoms at presentation were asthenia and splenic discomfort. The other symptoms are mentioned in Table 1. The most predominant clinical sign was splenomegaly (100% cases). The laboratory parameters at presentation are shown in Table 2. The median WBC count at presentation was 65 × 10^9/L. This appeared less frequently, as many patients received hydroxyurea before they were referred to our institute. In a majority (69%) of the patients the WBC count was between 20 × 10^9/L to 99 × 10^9/L.

The comparison between the clinical and laboratory findings of adult, pediatric, and adolescent CMLs is shown in Table 3.

The sex-wise distribution was the same. Splenic discomfort and asthenia were the most common presentations in both children and adolescents, and also adults. However 76% of the adults reported low-grade fever, which was not noticed in children/adolescents. Bleeding was rare in both the groups. Hepatosplenomegaly was the predominant finding in both the groups. Chronic phase CML was the most common phase in both the groups. Accelerated phase CML was not found in the pediatric group. The two groups did not differ in terms of clinical signs, median hemoglobin, median WBC, and the median platelet count at presentation. However, these findings must be taken with a word of caution, as the number of patients in the pediatric and adolescent age group were very less.

Response

Out of 13 patients two expired and two were lost to follow-up. One patient expired of tuberculous meningitis with obstructive hydrocephalous after three months of treatment with Imatinib. Complete hematological response (CHR) was documented in this patient at six weeks. The other patient was diagnosed to have blast crisis. Hydroxyurea was administered as part of palliation. He died of sepsis after three months of diagnosis. There was no documentation of any response in this patient. Two patients were lost to follow up, one after two weeks of diagnosis and one after five months of treatment with hydroxyurea alone. The responses of other nine patients are summarized in Table 4.

Table 1: Clinical features at diagnosis

Clinical features	*n*	%
Age in years		
0-4	2	15.3
5-9	1	07.6
10-14	2	15.3
15-17	8	61.5
Sex		
Male	9	69.2
Female	4	30.7
Symptoms		
Splenic discomfort	8	61.5
Asthenia	9	69.2
Bleeding	1	07.6
Fever	2	15.3
Bone pain	1	07.6
Priapism	1 (out of 9 males)	11.1
Signs		
Palpable spleen	13	100
Palpable liver	12	92.3
Lymphadenopathy	2	15.3
Purpura	1	07.6
Disease phase		
Chronic	12	92.3
Accelerated	0	0
Blastic	1	07.6

Table 2: Hematological findings at diagnosis

Laboratory measurement	Median	Range
WBC (x$10^{[9]}$/L) (*n*=13)	65	43.9-274
Hemoglobin, g/dL (*n*=13)	9.5	7-11.2
Platelets (x$10^{[9]}$/L) (*n*=13)	462	58-600
	n	**Percentage**
WBC (x$10^{[9]}$/L)		
10-19	0	0
20-99	9	69.3
100-400	4	30.7
>400	0	0
Hemoglobin, g/dL		
<8	1	07.6
8-12	12	92.3
>12	0	0
Platelets (x$10^{[9]}$/L)		
50-149	1	07.6
150-449	3	23.0
450-1000	9	69.2
>1000	0	0
Cytogenetics		
Karyotypic diagnosis, *t* (9;22)	10	76.9
FISH diagnosis, *t* (9;22)	1	07.6
RT-PCR for BCR-ABL	2	15.3

ABL=Abelson leukemia virus, BCR=Breakpoint cluster region, RT-PCR=Reverse transcriptase polymerase chain reaction, FISH=Fluorescence in situ hybridization

Table 3: Clinical and laboratory parameters at presentation of CML in adult (Arm 1) and pediatric and adolescent age groups (Arm 2)

Clinical features	Arm 1 (*n*)	Arm 1 (%)	Arm 2 (*n*)	Arm 2 (%)
Sex				
Male	130	69.5	9	69.2
Female	57	30.4	4	30.7
Symptoms				
Splenic discomfort	86	45.8	8	61.5
Asthenia	100	53.4	9	69.2
Bleeding	1	00.5	1	07.6
Fever	143	76.4	2	15.3
Bone pain	5	02.6	1	07.6
Priapism	0	00.0	1 (out of nine males)	11.1
Signs				
Palpable spleen	170	90.9	13	100
Palpable liver	132	70.5	12	92.3
Lymphadenopathy	3	01.6	2	15.3
Purpura	0	00.0	1	07.6
Disease phase				
Chronic	181	96.7	12	92.3
Accelerated	5	02.6	0	0
Blastic	1	00.5	1	07.6
Laboratory measurement	**Median**	**Range**	**Median**	**Range**
WBC (x10[9]/L)	68.9	4-390.67	65	43.9-274
Hemoglobin, g/dL	9.2	5.6-14	9.5	7-11.2
Platelets (x10[9]/L)	419	48-5676	462	58-600

Arm 1=Adult (18 years or more) *N*=187, Arm 2=Children and adolescent age group (less than 18 years) *N*=13, CML=Chronic myeloid leukemia

Complete hematological response was documented in 11 out of 12 (91%) evaluable responses. Karyotyping from bone marrow was not available in all patients because of financial constraints. Hence, cytogenetic responses could be evaluated in four patients. A complete cytogenetic response was seen in three out of four patients (75%). The molecular response was assessed in five patients. At 18 months of treatment, a major molecular response (MMR) was achieved in three out of five evaluable patients. In one of the remaining two patients MMR was documented at 24 months, while in the other patient less MMR was documented at 12 months, as the evaluation at 18 months was not done till 21 months of follow-up, due to financial constraints. At the end of the study period, a major molecular response was observed in four out of five patients (80%). The estimated OS was 84% and the PFS on Imatinib was 100% after a median follow-up of 21 months.

Toxicity

Eleven patients received Imatinib. It was tolerated very well. Grade 3 thrombocytopenia and neutropenia was seen in one patient, who required temporary discontinuation of the drug. Leg cramps was the most common non-hematological toxicity. Findings are summarized in Table 4.

Discussion

The data on the clinical and laboratory parameters of CML in the children and adolescent age group are scanty, due to the rarity of the disease in this age group. A phase-one study from the children's oncology group included 31 patients from 23 centers, signifying the rarity of CML in this age group.[5] A comparison between Imatinib and

Table 4: Response to treatment

Patient	Three months	Six months	12 months	18 months	Till last follow-up	Duration of follow-up
1	CHR	PCgR	-	-	PCgR at six months of treatment with Imatinib	Eight months
2	CHR	NA	NA	NA	CHR documented at six weeks of treatment. Patient expired of TBM after three months of Imatinib	Three months
3	CHR	Lost to follow-up after five months	NA	NA	Received hydroxyurea only	Five months
4	CHR	-	bcr-abl/abl <0.1%	bcr-abl/abl <0.1%	MMR till last follow-up	42 months
5	CHR	-	bcr-abl/abl <0.1%	bcr-abl/abl <0.1%	MMR till last follow-up	42 months
6	CHR	PCgR	CCgR	-	MMR 24 months	34 months
7*	No response documented	NA	NA	NA	Expired of BC in three months of palliation with hydroxyurea	Three months
8	CHR	-	bcr-abl/abl 0.9%		Received hydroxyrea for six weeks followed by Imatinib	21 months
9	No response documented	NA	NA	NA	Lost to follow up after two weeks of diagnosis	Two weeks
10	CHR	CCgR	-	-	CCgR	11 months
11	CHR	-	CCgR		CCgR till last follow-up	Eight months
12	CHR	-	-	-	-	Five months
13	CHR	-	-	bcr-abl/abl <0.1%	MMR till last follow-up	28 months

*CML blast crisis, NA=Not applicable, CHR=Complete hematological response, CCgR=Complete cytogenetic response, PCgR=Partial cytogenetic response, MMR=Major molecular response, CML=Chronic myeloid leukemia

stem cell transplant (SCT), as the therapy for childhood CML, included 30 patients in the Imatinib arm and 18 patients in the SCT arm.[6] In other studies, the patient number varied from four to thirty-nine.[7,8] Our study is one of the largest from a single center, catering to patients from the lower socioeconomic strata. Sixty-one percent of the patients in our study belonged to the age group of 15 - 17 years. In an analysis from the French group, the maximum (47%) number of patients belonged to the 10 - 14 year age group.[9] As found in the analysis from the French group, males predominated in numbers in our study.[9] This sex ratio may reflect a gender bias because of male preference for the access to treatment of this chronic disorder.

Asthenia and splenic discomfort were the predominant symptoms and splenomegaly was the predominant sign in our study. The majority of patients presented in the chronic phase. These findings are similar to studies in children and adults.[9,10]

The median hemoglobin, WBC counts, and platelet counts in our study are very similar to the analysis by Mohsen S. *et al.,* but lower than the French analysis.[6,9] The results are also similar to the findings in the adult cohort from our center [Table 5]. The number of patients and different patient population may have contributed to this variation.

The majority of patients seeking treatment at our center belong to the lower socioeconomic strata. The financial burden of treatment on these patients is managed with support from the government, in the form of aid for cancer treatment, involvement of non-government organizations (NGOs), support from pharmaceutical companies, who provide generic brands of Imatinib at a much cheaper rate, and last but not the least, the Max foundation's Glivec® International Patient Assistance Program (GIPAP). The patients are educated by counselors and compliance is ensured by the support staff in the CML outdoor.

The response rates in our study are similar to those in other studies.[11,12] The toxicity profile of Imatinib in our study was acceptable and similar to the toxicity profile demonstrated in other studies.[11,12] The effect of Imatinib on growth was not assessed in our retrospective study because of lack of data on the growth parameters.

Table 5: Imatinib toxicity (*N*=11)

Adverse events	All grades number (%)	Grade 3/4 numbers (%)
Hematological		
Thrombocytopenia	2	1
Neutropenia	1	1
Anemia	1	0
Non-hematological toxicity		
Muscle cramps	3	-
Skin hypopigmentation	1	-
Nausea	2	-
Diarrhea	1	-

The present study may not reflect the state-of-the-art treatment or management of CML but it shows the real picture of patient care at a tertiary care center run by the government in a developing country. Two out of 13 (15%) patients were lost to follow-up. These patients presenting as CML-BC could not afford further treatment. This reflects the poor financial status of the relatives. This issue has been addressed to some extent with the introduction of the GIPAP program. The outcome of patients from our center underlines the need of such help from the society.

Conclusion

To conclude, our study demonstrated that the presenting features of CML in the children and adolescent age group are similar to those shown in other studies. Comparison to the adult cohort was difficult due to the less number of patients. Imatinib was effective and well tolerated in this age group. However, being a single center data, the number of patients is small, emphasizing the need for collaborative efforts from different centers treating CML. Longer follow-up studies are needed to assess the long-term results and adverse events.

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