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ORIGINAL ARTICLE

Comparative Study of Clinico-hematological Features, Molecular Spectrum and Response to Imatinib in Chronic Myelogenous Leukemia Patients: Pediatric and Adolescent Versus Adults

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Abstract Chronic myelogenous leukemia (CML) is a rare disease in children, accounting for approximately 3% of leukemias in children and adolescents, with an annual incidence of 1 case per million children in western countries. This study was conducted, at PGIMER, Chandigarh. Ninety eight patients, 48 in children and adolescents group, and 50 in adult group were included in the study. Their hematological profiles along with the bone marrow findings were analyzed. The diagnosis of CML was confirmed by cytogenetics and/or molecular analysis. The complete hematological response (CHR) was analyzed at 3 months and cytogentic response (CgR) at 12 months after starting imatinib therapy. Compared to adults, pediatric and adolescent patients were more symptomatic at presentation (93.5 vs. 75%). Among symptomatic patients, massive splenomegaly (>10 cm), higher total leucocyte and platelet counts were seen more frequently in pediatric patients. The most common transcript in both groups was e14a2. The distribution of pediatric and adolescent cases in Sokal, Hasford and EUTOS score, showed only statistically significant difference for low risk Sokal group, which had more patients in pediatric group. Compared to adults, pediatric and adolescent patients had similar CHR rate (91.3 vs. 92%), but showed lesser major CgR rate (90.9 vs. 95.5%) however, this was not statistically significant.

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Introduction

Chronic myeloid leukemia (CML) shows certain features which differ amongst the pediatric and adult groups [1, 2]. However, variable age ranges have been used by different authors. Recently, another age group of 15–29 years, termed as the adolescent and young adult population (AYA), is increasingly been recognized [3].

The Surveillance, Epidemiology and End Result (SEER) programme of the National Cancer Institute (NCI), United States of America, has analyzed the age specific rates for CML by subdividing the patients into small subgroups. The SEER programme has analyzed patients up to the age of 19 years in one subgroup (pediatric and adolescent) and ≥20 years in another (adult group) [4, 5]. Based on SEER results, in our study, we divided patients into 2 groups: ≤19 and >19 years, and compared the disease characteristics and outcome with imatinib therapy. Only few reports are published on pediatric CML patients [1–5], therefore this study was undertaken to analyze differences in clinico-hematological features of pediatric versus adult CML patients.

Materials and Methods

For the pediatric and adolescent group, consecutive 48 patients were enrolled who fulfilled the 2008 World Health Organization (WHO) CML diagnostic criteria [6] and had a follow up data available at 3 and 12 months after imatinib therapy. In the adult group, 50 consecutive CML patients,

on imatinib therapy with a follow up at 3 and 12 months, were included.

Genetic Studies

For *Cytogenetic analysis for Philadelphia (Ph) chromosome* a minimum of 20 metaphases were analyzed and percentage positivity noted.

Molecular analysis for BCR-ABL1 fusion gene was done by reverse transcriptase polymerase chain reaction (RT-PCR) using primers specific for p210 (e13a2 and e14a2) and p190 (e1a2) [7].

This work was done as a part of DM Hematopathology thesis, wherein only RT-PCR data was included; RQ-PCR data of CML patients is being reported separately.

Prognostic scoring systems, Sokal, Hasford, and European treatment and outcome study (EUTOS) were applied at diagnosis for risk stratification [8–10].

The hematological response was evaluated at 3 months and the cytogenetic responses (CgR) were evaluated at 12 months as per National Comprehensive Cancer Network (NCCN) guidelines [11].

Results

Of 48 pediatric and adolescent patients studied, 46 were in chronic phase (CP) at presentation and only 1 (2.1%) each was in accelerated (AP) and blast crisis phase (BP). Of the 50 adult CML patients, 44 were in CP and 3 (6%) each in AP and BP. Since the number of patients was less in AP and BP, the comparison of clinical, hematological features and outcome, between the two groups, could be done in CP patients only.

Clinical Features

Compared to adults, a significantly higher incidence of symptomatic presentation was seen in pediatric and adolescent patients, 93.5 versus 75% (p value 0.01). The most common presentation was with abdominal discomfort in both groups of patients. On examination, incidence of palpable splenomegaly was almost similar for both, however, massive splenomegaly was more frequently seen in adults.

Hematological Features

The difference between the hemoglobin (Hb) values in the two groups was statistically significant (p value 0.02). The patients in the pediatric and adolescent group were more anemic than the adult group.

Adult patients had higher total leucocyte and platelet counts at presentation, however, this was not statistically significant.

In adult group, significant inverse correlation was seen for liver size with Hb value, and Hb with TLC, and a direct significant correlation was seen between spleen size with TLC. There was no significant correlation between spleen size and platelet counts.

Bone marrow showed increased megakaryopoiesis more frequently in adults (47.7 vs. 32.6%). On differential count, mature neutrophils were significantly more in pediatric and adolescent group compared to adult group.

Genetic Studies

The cytogenetic analysis for Ph chromosome was available for all enrolled patients, however, RT-PCR for *BCR-ABL1* fusion gene was available for 27 pediatric and adolescent patients only, as 16 patients in this group were diagnosed before 2006 and this facility was not available at that time in the department and diagnosis was confirmed by cytogenetics alone in these patients. The most common transcript in both groups was e14a2; e1a2 transcript was not seen in any patient.

Details of clinical and hematological features are outlined in Table 1.

Prognostic Scoring

In both pediatric and adolescent group and adult group, majority of patients were assigned to intermediate risk group by Sokal and Hasford scoring, and low risk group by EUTOS scoring. The difference in the two groups was statistically significant for the low risk Sokal score only. The distribution of cases is shown in Table 2.

Response to Imatinib

Complete Hematological Response (CHR) at 3 Months

In both the groups, majority of patients achieved CHR at 3 months, 42 (91.3%) in pediatric and adolescent group and 41 (92%) in adult group.

Cytogenetic Response at 12 Months

Of the 46 pediatric and adolescent patients, one patient progressed to BP and one to AP during the follow up period. Of the remaining 44 patients, 40 (90.9%) achieved major cytogenetic response (MCgR) and 4 (9.1%) achieved minor cytogenetic response (mCgR).

Table 1 Details of clinical and hematological features in CML-CP patients

Parameters	Pediatric and adolescent patients (≤19 years) N = 46	Adult patients (>19 years) N = 44	*p* value
Age range (median)	5–19 (12.5)	22–70 (43)	–
Male:female	2:1	1.8:1	0.301
Incidental diagnosis/asymptomatic at presentation	03 (6.5%)	11 (25%)	**0.01**
Symptoms	43 (93.5%)	33 (75%)	
Abdominal discomfort	33 (71.7%)	18 (40.9%)	–
Weakness	22 (47.8%)	11 (25%)	
Fever	21 (45.7%)	11 (25%)	
Loss of weight	16 (34.5%)	22 (50%)	
Loss of appetite	15 (32.6%)	22 (50%)	
Splenomegaly			**0.04**
Not palpable	02 (4.5%)	01 (2.3%)	
<5 cm	04 (8.7)	11 (25%)	
5–10 cm	13 (28.3%)	17 (38.6%)	
>10 cm	27 (58.7%)	15 (34.1%)	
Hepatomegaly	35 (76%)	28 (63.6%)	0.20
Hemoglobin			
<8.0 gm/dL	11 (23.9%)	3 (6.8%)	**0.023**
8–10 gm/dL	32 (69.6%)	32 (72.7%)	
>10 gm/dL	3 (6.5%)	9 (20.5%)	
Total leucocyte count			
$<100 \times 10^9$/L	10 (21.7%)	17 (38.6%)	0.194
$100–300 \times 10^9$/L	29 (63%)	23 (52.3%)	
$>300 \times 10^9$/L	7 (15.2%)	4 (9.1%)	
Platelet count			
$<450 \times 10^9$/L	29(63%)	30 (68.2%)	0.645
$450–1000 \times 10^9$/L	16 (34.8%)	12 (27.3%)	
$>1000 \times 10^9$/L	1 (2.2%)	02 (4.5%)	
BCR-ABL1 transcripts			
p210-e13a2	10 (37.1%)	12 (35.3%)	0.166
p210-e14a2	17 (62.9%)	22 (64.7%)	
p190-e1a2	0	0	

Bold numbers indicate significant *p* value (< 0.05)

Table 2 Distribution of risk according to the prognostic scores

Scoring system	Risk	Pediatric and adolescent patients (≤19 years) N = 46	Adults (>19 years) N = 44	*p* value
Sokal	Low	18 (39.1%)	5 (11.4%)	**0.002**
	Intermediate	19 (41.3%)	23 (52.3%)	0.296
	High	9 (19.6%)	16 (36.4%)	0.075
Hasford	Low	16 (34.8%)	14 (31.8%)	0.09
	Intermediate	25 (54.3%)	22 (50%)	0.17
	High	5 (10.9%)	8 (18.2%)	0.97
EUTOS	Low	26 (56.5%)	27 (61.4%)	0.22
	High	20 (43.5%)	17 (38.6%)	0.22

Bold number indicates significant *p* value (< 0.05)

In adult group, cytogenetic responses were evaluated in all the patients. MCgR was seen in 42 (95.5%) and mCgR in 2 (4.5%).

CHR and Cytogenetic Response

Of the 42 pediatric and adolescent patients who achieved CHR, 40 were evaluated for cytogenetic response, and of these 36 (90%) achieved MCgR and 4 (10%) mCgR. In the adult group, of 41 patients with CHR, 39 (95.1%) achieved MCgR and 2 (4.9%) mCgR. No statistically significant difference was observed between pediatric and adolescent versus adults group and on attainment of CHR with MCgR.

Impact of Prognostic Scores in Predicting CHR and Cytogenetic Response

On evaluating the CHR and cytogenetic responses with Sokal, Hasford and EUTOS scoring systems no significant correlation was observed, and these scores were not able to predict CHR, cytogenetic response rates for CML patients on imatinib in our study groups (Table 3).

Discussion

CML accounts for 3% of newly diagnosed leukemia cases with an annual incidence of approximately 1 per million in children and adolescents <20 years. The reported median age at diagnosis is 12 years with approximately 10% presenting in advanced phases [12]. The median age in our study was similar, being 12.5 years, however, only 4% patients were in either BP or AP at presentation.

Approximately 20–40% CML patients are incidentally detected at the time of routine medical examination. In the present study, 25% adults were asymptomatic at presentation, whereas only 6.5% pediatric and adolescent patients were asymptomatic. Thus, compared to adult patients, lesser number of pediatric and adolescent patients were asymptomatic at presentation.

Palpable splenomegaly was seen in most pediatric and adolescent and adult patients (95.5 and 97.7% respectively), however, massive splenomegaly was more frequent in pediatric and adolescent compared to adult patients (58.7 vs. 34.1%), difference being statistically significant.

Association between splenomegaly with higher TLC and lower platelet count has been reported [13]. We also found a direct significant correlation between spleen size with TLC, however, there was no significant correlation between spleen size and platelet counts.

Most patients in both groups had anemia, however, severe anemia was more frequent in pediatric and adolescent group (23.9 vs. 6.8%), difference being statistically significant. Overall, incidence of anemia was higher than that reported in previous studies [1, 2]. This could be due to associated nutritional deficiency anemia prevalent in our group of patients.

Majority of pediatric and adolescent patients had TLC between 100 and 300 $\times$ 10^9/L and platelets <450 $\times$ 10^9/L and this trend was similar to that in adult patients. Overall, no significant difference was seen for TLC and platelet count for pediatric and adult patients. Previous studies in children have also reported a higher TLC and also a higher platelet count [1, 2].

Most commonly detected transcript types in CML are e13a2 and e14a2 [7]. In our study also, most common transcript type in both groups, was e14a2, seen in 62.9 and 64.7% respectively. Variable frequencies of *BCR-ABL* fusion transcripts have been reported in different studies, some mention e13a2 to be more common [13] whereas other study found e14a2 to be more common [14].

Similarly, association of e13a2 and e14a2 with age has been variably reported. Suryanarayan et al. [15] reported predominance of e13a2 in children and Mondal et al. [16] of e14a2. In our study most common transcript was e14a2 in both groups of patients.

Table 3 Analysis of prognostic scores versus CHR versus cytogenetic response

Scoring system	Risk	Pediatric and adolescent patients		Adult patients		Pediatric and adolescent patients		Adult patients	
		CHR	No CHR	CHR	No CHR	MCgR	mCgR	MCgR	mCgR
Sokal	Low	17 (94.4%)	01 (5.6%)	05 (100%)	–	15 (88.2%)	02 (11.7%)	05 (100%)	–
	Intermediate	17 (89.5%)	02 (10.5%)	21 (91.3%)	02 (8.7%)	17 (94.4%)	01 (5.5%)	22 (95.6%)	01 (4.4%)
	High	08 (88.9%)	01 (11.1%)	15 (93.8%)	01 (6.3%)	08 (88.8%)	01 (11.1%)	15 (93.7%)	01 (6.3%)
Hasford	Low	14 (87.5%)	02 (12.5%)	14 (100%)	–	13 (86.6%)	02 (13.4%)	13 (92.8%)	01 (7.2%)
	Intermediate	23 (92%)	02 (8%)	19 (86.4%)	03 (13.6%)	22 (91.6%)	02 (8.4%)	21 (95.4%)	01 (4.6%)
	High	05 (100%)	–	8 (100%)	–	05 (100%)	–	08 (100%)	–
EUTOS	Low	24 (92.3%)	02 (7.7%)	26 (96.3%)	01 (3.7%)	22 (88%)	03 (12%)	26 (96.2%)	01 (3.8%)
	High	18 (90%)	02 (10%)	15 (88.2%)	02 (11.8%)	18 (94.7%)	01 (5.3%)	16 (94.1%)	01 (5.9%)

Various risk scoring systems are used for CML—Sokal, Hasford and EUTOS. The Sokal and Hasford scores were derived before the advent of *BCR-ABL*—targeting tyrosine kinase inhibitors (TKI), and the EUTOS score was specifically formulated and tested in patients on imatinib therapy. However, all 3 scoring systems have been variably used in patients on TKI.

As a separate pediatric CML scoring system has not yet been established, same scoring systems are used for children also. In our study, all 3 scoring systems were used to risk stratify patients. With Sokal and Hasford score, majority of the pediatric and adolescent patients were in the intermediate risk group (41.3 and 54.3% respectively), and with EUTOS in low risk group. Compared to adults, no significant difference was seen in risk group stratification for children, except for the Sokal low risk, which had higher number of pediatric and adolescent patients.

The first-generation TKI—imatinib received accelerated approval for adult CML patients in 2001 and in pediatric patients in 2003. It is recommended that frontline therapy for pediatric CML in CP to be TKI therapy without transplantation. Patients in AP or BP or who fail to reach landmarks on TKI should undergo SCT [17]. There are limited studies on the use of TKI in pediatric CML. Data in children with CML-CP treated with first-line imatinib have shown that 96% achieve a CHR and 69% CCgR after 1 year [18]. A recent study from India on 43 children and adolescent CML patients showed that 100% achieved CHR and 58.1% CCgR [19].

In our study, CHR was achieved in 91.3% patients and CCgR in 60.9% pediatric and adolescent patients. The CHR was comparable to that seen in adults (92%), however, CCgR was lower than adults (75%).

Achievement of CCgR is an important short-term goal of CML therapy, and predicts improved survival. Studies have shown that patients with low Sokal score achieve superior CgR [2]. Similar findings were appreciated in our study in the adult group where all the patients in the low Sokal score achieved CCgR. However, CCgR was achieved in only 88% pediatric and adolescent group patients with low Sokal score.

Kantarjian et al. [20] reported that survival by Sokal risk groups was significantly different before 2001 ($p < 0.001$), but not since 2001 ($p = 0.4$). Overall, in our study, low scores by all three scoring systems did not translate into better CCgR rates.

A recent pilot study analyzed pediatric CML patients, applying the established prognostic scores for adults to see which scoring system most specifically classifies the prognosis of pediatric CML with regard to early molecular response on imatinib. The authors found that for pediatric cohort, the Sokal and Hasford scores did not predict a poor imatinib treatment response at month 3 while the EUTOS score achieved borderline significance and suggested that there is a need for development of a more specific pediatric risk score system [21].

Although the biology of CML has been known for long and behavior of pediatric CML patients is quite similar to adults, still many aspects need to be studied further.

1. Studies are needed to determine if imatinib can be stopped in children who are responding to it, considering that in this age, the adverse effects of prolonged therapy on the growth development are also important. Growth retardation has been reported from our institute, as a significant adverse effect in children with CML [22]. Imatinib stoppage appears feasible in children also, considering the results of a recent pilot study on adult patients where imatinib was discontinued after having achieved a complete molecular response lasting more than 2 years. It was found that a proportion of patients with CML-CP who have perfectly responded to TKI treatment, could safely stop treatment for an as-yet-unknown period [23].
2. Recently, adolescents and young adults (15–29 years) with CML are being considered as a separate group, as studies in this set of patients have shown that they have unfavorable outcome compared to other age group patients [3].

Additional research in this population is required, so as to better define outcomes, understand the cause of clinic-hematological differences, and to help make better treatment recommendations for different age group patients.

Compliance with Ethical Standards

Conflict of interest There are no conflict of interest to declare.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

References

1. Millot F, Traore P, Guilhot J, Nelken B, Leblanc T, Leverger G et al (2005) Clinical and biological features at diagnosis in 40 children with chronic myeloid leukemia. Pediatrics 116:140–143
2. Hasan SK, Sazawal S, Kumar B, Chaubey R, Mishra P, Mir R et al (2006) Childhood CML in India: b2a2 transcript is more common than b3a2. Cancer Genet Cytogenet 169:76–77
3. Pemmaraju N, Kantarjian H, Shan J, Jabbour E, Quintas-Cardama A, Verstovsek S et al (2012) Analysis of outcomes in adolescents and young adults with chronic myelogenous leukemia treated with upfront tyrosine kinase inhibitor therapy. Haematologica 97:1029–1035
4. Altekruse SF, Kosary CL, Krapcho M, Neyman N, Aminou R, Waldron W et al (eds) SEER cancer statistics review, 1975–2007,

National Cancer Institute. Bethesda, MD. http://www.seer.cancer.gov/csr/1975-2007
5. Horner MJ, Ries LAG (2007) Leukemia. In: Ries LAG, Young JL, Keel GE, Eisner MP, Lin YD, Horner M-J (eds) SEER survival monograph: cancer survival among adults: U.S. SEER program, 1988–2001, patient and tumor characteristics. National Cancer Institute, SEER program, NIH, 07-6215
6. Vardiman JW, Melo JV, Baccarani M, Thiele J (2008) Chronic myelogeneous leukemia, BCR-ABL1 positive. In: Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H et al (eds) World Health Organization classification of tumours of haemopoietic and lymphoid tissues. IARC Press, Lyon, pp 32–37
7. Anand MS, Varma N, Varma S, Rana KS, Malhotra P (2012) Cytogenetic & molecular analyses in adult chronic myelogenous leukaemia patients in north India. Indian J Med Res 135:42–48
8. Sokal JE (1987) Prognosis in chronic myeloid leukaemia: biology of the disease versus treatment. Baillieres Clin Haematol 1:907–929
9. Hasford J, Pfirrmann M, Hehlmann R, Allan NC, Baccarani M, Kluin-Nelemans JC et al (1998) A new prognostic score for the survival of patients with chronic myeloid leukemia treated with interferon alfa. J Natl Cancer Inst 90:850–858
10. Hasford J, Baccarani M, Hoffman V, Guilhot J, Saussele S, Rosti G et al (2011) Predicting complete cytogenetic response and subsequent progression-free survival in 2060 patients with CML on imatinib treatment: the EUTOS score. Blood 118:686–692
11. National Comprehensive Cancer Network (2012). NCCN clinical practice guidelines in oncology: chronic myelogenous leukemia. Version 3. 2013. http://www.nccn.org
12. Hehlman R, Hochhaus S, Baccarani M (2007) European Leukemia Net. Chronic myeloid leukemia. Lancet 370:342–350
13. Paz-J-Miño C, Burgos R, Morillo SA, Santos JC, Fiallo BF, Leone PE (2002) BCR-ABL rearrangement frequencies in chronic myeloid leukemia and acute lymphoblastic leukemia in Ecuador, South America. Cancer Genet Cytogenet 132:65–67
14. de Lemos JA, de Oliveira CM, Scerni AC, Bentes AQ, Beltrão AC, Bentes IR et al (2005) Differential molecular response of the transcripts B2A2 and B3A2 to imatinib mesylate in chronic myeloid leukemia. Genet Mol Res 4:803–811
15. Suryanarayan K, Hunger SP, Kohler S et al (1991) Consistent involvement of bcr gene by 9;22 breakpoints in pediatric acute leukemias. Blood 77:324–330
16. Mondal BC, Bandyopadhyay A, Majumdar S, Mukhopadhyay A, Chandra S, Chaudhuri U et al (2006) Molecular profiling of chronic myeloid leukemia in eastern India. Am J Hematol 81:845–849
17. Andolina JR, Neudorf SM, Corey SJ (2012) How I treat childhood CML. Blood 119:1821–1830
18. Suttorp M, Millot F (2010) Treatment of pediatric chronic myeloid leukemia in the year 2010: use of tyrosine kinase inhibitors and stem-cell transplantation. Hematol Am Soc Hematol Educ Program 2010:368–376
19. Lakshmaiah KC, Bhise R, Purohit S, Abraham LJ, Lokanatha D, Suresh TM et al (2012) Chronic myeloid leukemia in children and adolescents: results of treatment with imatinib mesylate. Leuk Lymphoma 53:2430–2433
20. Kantarjian H, O'Brien S, Jabbour E (2012) Improved survival in chronic myeloid leukemia since the introduction of imatinib therapy: a single institution historical experience. Blood 119:1981–1987
21. Suttorp M, Glauche I, Salas DG, Tauer JT, Nowasz C, Thiede C (2013) Scoring systems for predicting outcome of chronic myeloid leukemia in adults are poorly informative in pediatric patients treated with imatinib. 55th ASH, New Orleans, Dec 7–10, 2013: abstract no. 2725
22. Bansal D, Shava U, Varma N, Trehan A, Marwaha RK (2012) Imatinib has adverse effect on growth in children with chronic myeloid leukemia. Pediatr Blood Cancer 59:481–484
23. Mahon FX, Rea D, Guilhot F et al (2009) Discontinuation of imatinib therapy after achieving a molecular response in chronic myeloid leukemia patients. Blood 114:859 **(ASH Annual Meeting Abstract)**