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Real-World Experience of Treating Pediatric Chronic Myeloid Leukemia: Retrospective Study from a Cancer Center in Southern India

Sivasree Kesana[1] Venkatraman Radhakrishnan[1] Jayachandran Perumal Kalaiyarasi[1] Nikita Mehra[1] Gangothri Selvarajan[1] Parathan Karunakaran[1] Krishnarathinam Kannan[1] Manikandan Dhanushkodi[1] Shirley Sundersingh[2] Samson Mani[3] Trivadi S. Ganesan[1] Tenali Gnana Sagar[1]

[1] Department of Medical Oncology, Cancer Institute (WIA), Adyar, Chennai, Tamil Nadu, India
[2] Oncopathology, Cancer Institute (WIA), Adyar, Chennai, Tamil Nadu, India
[3] Molecular Oncology, Cancer Institute (WIA), Adyar, Chennai, Tamil Nadu, India

Address for correspondence Venkatraman Radhakrishnan, MD, DM, Professor, Medical and Pediatric Oncology, Cancer Institute (WIA), Adyar, Chennai, Tamil Nadu 600020, India (e-mail: venkymd@gmail.com).

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Abstract

Introduction Chronic myeloid leukemia (CML) is rare in children and constitutes 2% of all leukemia. We present our institute experience in treating pediatric CML for 20 years.

Objectives There is a paucity of data on pediatric CML from India, hence we would like to present treatment responses and survival rates in our pediatric population treated with tyrosine kinase inhibitors at our center.

Materials and Methods Patients aged less than 18 years, diagnosed with CML from 2000 to 2019, and treated with imatinib were analyzed retrospectively considering demographic features, treatment characteristics, and survival outcomes. Descriptive analysis was done for the baseline characteristics. Event-free survival (EFS) and overall survival (OS) were calculated using the Kaplan-Meier method and the factors were compared using the log-rank test.

Results During the study period, 95 patients were diagnosed with CML of which 54 (56.8%) were males. The most common stage at presentation was the chronic phase (CP) with 84 (88.4%) patients followed by accelerated phase (AP) and blast crisis (BC) with 6 (6.3%) and 5 (5.3%) patients respectively. The median duration of follow-up for all patients was 98 months. EFS and OS at 8 years for patients with CML-CP were 43.1% and 80.4% respectively. Complete hematological response, complete cytogenetic response, and major molecular response was documented in 91 (95.7%), 73 (76.8%), and 63 (66.3%) patients respectively.

Conclusion Outcomes in pediatric CML are comparable to that of adults. Imatinib is well tolerated in children.

Keywords
- pediatric
- chronic myeloid leukemia
- imatinib
- responses
- survival outcomes

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Introduction

Chronic myeloid leukemia (CML) is rare in children and constitutes 2% of all leukemia in pediatric age group younger than 15 years and 9% in adolescents aged between 15 and 19 years.[1–3] Management of CML in children is challenging due to the lifelong treatment with tyrosine kinase inhibitors (TKIs) like imatinib and long-term adverse effects of TKI.[2,4] These challenges are amplified in resource-challenged settings in low/middle-income countries due to delayed presentation, poor compliance to treatment, treatment abandonment, and access to drugs.

The use of hematopoietic stem cell transplantation (HSCT) to treat children in the chronic phase (CP) CML is no longer recommended with the advent of TKI.[2,5] Imatinib has been the backbone for treating CML in children and recent evidence suggests that second-generation TKIs like dasatinib and nilotinib are safe and efficacious in children with CML.[5,6]

Our study adds to the literature from India on pediatric CML by providing details on the clinical profile, management, and outcomes of pediatric CML treated at our center.

Materials and Methods

Inclusion Criteria

Retrospective data on 95 consecutive patients aged less than 18 years and diagnosed as Philadelphia (Ph) chromosome-positive CML at our hospital from January 2000 to December 2019 treated with TKI (imatinib) were analyzed.

Exclusion Criteria

CML patients aged more than 18 years and those who did not receive TKIs were excluded.

Baseline characteristics and other clinico-pathological features were extracted from the patient records. The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional) and with the Helsinki Declaration of 1964, as revised in 2013. This being a retrospective study, informed patient consent was waivered and approved by the hospital ethics committee (Institutional Ethics Committee, Cancer Institute (WIA), Adyar, Chennai; Accreditation number: EC-CT-2020–0141; Reference Number IEC/2020/Oct 01) on October 3, 2020.

The diagnosis of CML was established by clinical examination supported by hemogram, peripheral smear, bone marrow aspiration, and demonstration of the Ph chromosome either by conventional cytogenetics or fluorescent in situ hybridization (FISH).[7] Confirmation of the presence of breakpoint cluster region-Abelson (BCR-ABL) fusion gene transcript was done by the reverse transcriptase polymerase chain reaction (RT-PCR) method.[8]

Accelerated phase (AP) was defined by any of the following features: basophils $\geq$ 20%; blasts 10 to 19% in peripheral blood or bone marrow; persistent thrombocytopenia ($<100 \times 10^9$/L) unrelated to therapy or persistent thrombocytosis ($>1{,}000 \times 10^9$/L) unresponsive to therapy; increasing total white blood cell (WBC) count and increasing spleen size unresponsive to therapy; megakaryocytic proliferation in sizable sheets and clusters associated with marked reticulin or collagen fibrosis and/or severe granulocytic dysplasia; and cytogenetic evolution.[9] Blast crisis (BC) was defined as blasts $\geq$ 20% in blood or bone marrow, large foci or clusters of blasts in bone marrow biopsy, or extra-medullary blast proliferation. All other patients who did not meet the criteria for AP or BC and blasts $<$ 10% in peripheral blood or bone marrow were considered as CP.[9]

In children weighing $<$ 40 kg, imatinib was started at 260 to 300 mg/m^2.[10] Children weighing $\geq$ 40 kg were started on imatinib 400 mg daily.[11] Dose escalation of imatinib was done if there was nonattainment or loss of response. Toxicity details were captured from the case files and were graded according to the Common Terminology Criteria for Adverse Events, version 4.03. Treatment was started after obtaining written informed consent for TKI from the parent/guardian.

Regular follow-ups included clinical examination and complete blood count. A complete hematologic response (CHR) was defined as WBC $< 10 \times 10^9$/L, a platelet count $< 450 \times 10^9$/L, no palpable spleen, no immature cells, and basophils $<$ 5% in peripheral blood smear.[12,13] Cytogenetic response assessments have been replaced by real-time quantitative RT-PCR assessment at our center since 2013. A complete cytogenetic response (CCyR) was defined as the absence of the Ph chromosome in all analyzable metaphases on karyotyping. A BCR-ABL1/ABL1 transcript ratio $\leq$ 1% on the international scale by quantitative RT-PCR was considered equivalent to CCyR.[12–15] A major molecular response (MMR) was defined as a BCR-ABL1/ABL1 transcript ratio $\leq$ 0.1% on the international scale by real-time quantitative RT-PCR, whereas a complete molecular response (CMR) was defined as an undetectable BCR-ABL1 transcript by two consecutive RT-PCRs with assay sensitivity of 10^{-4}.[13,16–18] Management of CML has evolved over the 20-year period, and this has reflected on patient care. Cytogenetic and molecular responses were assessed using FISH or quantitative PCR for BCR-ABL transcript levels from peripheral blood. Response assessment was not performed according to the guidelines due to financial constraints.

Imatinib was withheld for grade 3 or 4 toxicity and restarted at a lower dose and escalated based on tolerance. In patients who had progression of disease to AP or BC, the dose of imatinib was increased or palliative treatment with hydroxyurea initiated. More recently, with availability of second-generation TKIs these have been administered if there is no response to imatinib. Imatinib resistance mutational analysis (IRMA) was performed where feasible.

Statistical Analysis

Descriptive analysis was done for the baseline characteristics. An event in the study was defined as any loss of CHR or nonattainment at 3 months, CCyR at 6 months, and MMR at 12 months or progression to AP or BC or death due to any cause. Event-free survival (EFS) was calculated from the date of the start of therapy until the date of the first event. Overall survival (OS) was calculated from the date of the start of

Table 1 Baseline clinical and laboratory parameters

Characteristics	Number of patients (%): total number = 95
Hemoglobin	
> 10 gm/dL	34 (35.8)
< 10 gm/dL	61 (64.2)
Total leucocyte count (x10^9/L)	
< 50	11 (11.6)
50–100	13 (13.7)
100–200	42 (44.2)
> 200	29 (30.5)
Platelet count (x10^9/L)	
< 300	22 (23)
> 300	73 (77)
Spleen (below costal margin)	
< 10 cm	45 (47.5)
> 10 cm	45 (47.5)
Missing data	5 (5)
Sokal score	
Low risk	33 (35)
Intermediate risk	41 (43)
High risk	14 (15)
Missing data	7 (7)

Table 2 Results of imatinib treatment

Parameter	Number (%)
Duration to attain CHR	91 (95.7)
<3 months	57 (60)
>3 months	34 (35.7)
Nonattainment of CHR	4 (4.4)
Duration to attain CCyR	73 (76.8)
<12 months	33 (34.7)
>12 months	40 (42.1)
Nonattainment of CCyR	22 (23.1)
Duration to attain MMR	63 (66.3)
<18 months	26 (27.3)
>18 months	37 (38.9)
Nonattainment of MMR	32 (33.6)
Modification of imatinib dose	
Escalated	38 (40)
De-escalated	4 (4.2)
Progressed on imatinib	25 (26.2)
Lost to follow-up	14 (14.7)
IRMA	
Tested	12 (12.6)
Positive	5 (5.2)
T315I mutation	3 (3.1)
E355G/E459L	1 (1.0)
T277I	1 (1.0)

Abbreviations: CCyR, complete cytogenetic response; CHR, complete hematological response; IRMA, imatinib resistance mutational analysis; MMR, major molecular response.

therapy to the date of death or last follow-up. EFS and OS were analyzed using the Kaplan-Meier method and the factors were compared using the log-rank test. Statistical analysis was done using SPSS version 17.0 (SPSS Inc, IBM, Chicago, United States).

Results

During the study period, 95 patients were diagnosed with CML, of which 54 (56.8%) were males and 41 (43.2%) were females. The median age at presentation was 13 years. The most common stage at presentation was CP with 84 (88.4%) patients followed by AP and BC with 6 (6.3%) and 5 (5.3%) respectively. Low- and intermediate-risk Sokal score (SS) was observed in 74 (78%) patients. Four patients initially received hydroxyurea for 1 to 3 years followed by imatinib after the drug was made available in India from 2002 through an initiative called the Glivec International Patient Assistance Program.[19] Baseline clinical and laboratory parameters are listed in ►**Table 1**.

Response

CHR, CCyR, and MMR were documented in 91 (95.7%), 73 (76.8%), and 63 (66.3%) patients respectively. Primary imatinib resistance was seen in three (3%) patients. Results with imatinib treatment including attainment of CHR, CCyR, and MMR are provided in ►**Tables 2** and **3** (according to timelines). Response assessment was not performed as per the guidelines due to logistic or noncompliance issues in 18 patients.

Toxicity

Most common imatinib-related side effects were polyarthralgia observed in 17 (17.8%) patients, hypopigmentation of skin in 11 (11.5%), hematological toxicity in 9 (9.4%), facial puffiness/peripheral edema in 7 (7.3%), nausea/vomiting/diarrhea in 6 (6.3%), and skin rash in 5 (5.2%) patients. Grade 3–4 toxicity (myelosuppression) was seen in four (4.2%) patients. Imatinib was stopped in three patients due to toxicities, one of whom progressed to BC; one patient was rechallenged with imatinib successfully and the other patient received nilotinib, due to imatinib intolerance.

Second-Line TKI and Transplantation

Nilotinib was administered to three patients, due to primary TKI resistance in two and imatinib intolerance (myelosuppression and rash) in one. Indications for dasatinib (two patients) were deranged liver enzymes while on nilotinib in one patient and loss of CCyR in the other. Twelve patients

Table 3 Responses with imatinib treatment as per timelines

Time since diagnosis	CHR (%)	CCyR (%)	MMR (%)
At 3 months	57 (60%)		
At 6 months	+19 (80%)	14 (14.7%)	5 (5.2%)
At 12 months	+6 (86%)	19 (34.7%)	+13 (18.8%)
At 18 months[a]	+2 (88.4%)	+8 (43.1%)	+08 (27.3%)

Abbreviations: CCyR, complete cytogenetic response; CHR, complete hematological response; MMR, major molecular response.
[a]Seven patients did not achieve CHR at 18 months (attained later).

were tested for IRMA, and three had T315I mutation. One patient with T315I mutation underwent allogeneic HSCT with a matched sibling donor (MSD) and the remaining patients died due to progressive CML.

Four patients underwent allogenic HSCT, indications being T315I mutation in one patient and CML-BC at diagnosis in three other patients. Two patients received HSCT from MSD and one each received a haploidentical transplant from father and matched unrelated donor. Of the four, two patients are alive and in CMR. One patient (BC at diagnosis) succumbed to progressive disease and the other (T315I mutation) due to chronic graft versus host disease after 2 years. Both these patients had received HSCT from MSD.

Survival Analysis

The median duration of follow-up for all patients was 98 months (range: 1–243 months). EFS and OS at 8 years for patients with CML-CP were 43.1% and 80.4% respectively (►**Supplementary Figs. S1** and **S2**). On univariate analysis, attainment of CHR at 3 and 6 months, CCyR at 12 months, and CP was significantly associated with better OS (►**Table 4**). Attainment of CCyR at 6 and 12 months and MMR at 12 months was associated with significant EFS on univariate analysis (►**Table 4**). On multivariate analysis, CP was associated with better OS ($p < 0.001$) and CCyR at 12 months was associated with better EFS ($p = 0.04$).

Poor compliance with treatment was observed in 19 (20%) patients. To date, 64 of 95 patients are alive, 12 patients are lost to follow-up (all poorly compliant), and 19 patients have expired due to progressive CML.

Discussion

CML in children is rare. The majority of children with CML present with CP as was observed in our study where 88.4% of patients had CP at diagnosis. However, AP and BC accounted for 6.3 and 5.3% of cases respectively at diagnosis. In a report from Delhi, 3% and 17% of patients had a diagnosis of AP and BC respectively.[20] Reports from developed countries indicate that 2–6% of children present in AP and 2–4% BC.[6,21] CML in children is different compared with adults (~2% AP and 1% BC), as a higher proportion present in AP and BC.[22]

Our findings were consistent with other studies in India, which report that CML is predominantly a disease of adolescents (►**Table 5**). Most studies report a median age of 13 years similar to our findings.[5,23–28] We observed a male to female ratio of 1.3:1—this is similar to reports from southern India and considerably lesser than a higher male to female ratio reported by studies from northern and western India.[20,23–28] The higher male to female ratio in CML observed in northwestern India could be due to social bias where females are not provided similar access to healthcare as males.

Response to treatment in our study is comparable to reports from other centers in India and developed countries. The 8-year EFS and OS for patients with CML-CP in our study were 43.1% and 80.4% respectively. This is the longest duration of follow-up and survival reported by any study in India. There is a 35% gap between EFS and OS in our study, which is comparable to the observation of a 28% gap in another report (5-year EFS and OS: 64% and 92% respectively).[20] This gap highlights the fact that many patients with suboptimal responses to imatinib continue to respond for a prolonged time and the lower EFS is mostly due to noncompliance to treatment in our study. More recently, the availability of second-generation TKIs like nilotinib and dasatinib can be prescribed to those who fail imatinib.

Adult prognostic scoring systems like the Sokal, European Treatment and Outcome Study, and Hasford were not useful to predict outcome in pediatric patients with CML.[2,29] This was also observed in our study where the SS was not prognostic of the outcome. Attaining CCyR at 12 months is an important landmark predicting superior outcomes in adult patients.[14] Similarly, we also observed that the attainment of CCyR at 12 months was associated significantly with better EFS (8-year EFS: 69.1% vs 31.6%; $p = 0.002$) and better OS (8-year OS: 96.8% vs 72.8%; $p = 0.02$). Formal compliance was not assessed in our study as it was retrospective. However, it was documented in the case records that 20% of patients were noncompliant to treatment and 12% were lost to follow-up (includes patients who were noncompliant).

Animal studies, clinical cases, and prospective studies had shown deleterious effects of imatinib on growth kinetics and bone metabolism.[30,31] Growth failure or retardation is an important and unique toxicity to be considered when using TKIs in the pediatric population.[32] We do not have the data on serial growth monitoring as this study was retrospective.

Long-term follow-up of the stop imatinib study confirms that imatinib discontinuation is safe in adults.[33] Pediatric studies on stopping imatinib in patients who are in CMR are ongoing.[34] Future research in pediatric CML includes the safety, toxicity profile, long-term effects of second- and

Table 4 Univariate analysis of factors predicting the survival in the study population

Parameter (N)	8-year EFS (%)	*p*-Value	8-year OS (%)	*p*-Value
Age		0.17		
≤10 years (22)	59.9		90	0.2
>10 years (73)	37.5		96	
Sex		0.93		
Male (54)	43.7		80.3	0.95
Female (41)	41.5		77.2	
Stage		0.29		0.000
Chronic phase (84)	43.1		80.4	
Accelerated phase (6)	33.3		66.7	
Blast crisis (5)	00		00	
Splenomegaly		0.99		0.77
>10 cm (45)	41.0		81	
<10 cm (45) Missing data (5)	43.6		77	
Hemoglobin (g/dL)		0.37		0.79
>10 gm/dL (34)	57.2		79.8	
<10 gm/dL (61)	38.2		78.3	
Total leucocyte count at presentation (x10^3cells/μL)		0.60		0.68
< 200 (66)	42.2		84	
>200 (29)	42.9		73.4	
Platelet count (x10^3cells/uL)		0.56		0.97
<300 (22)	32		79.7	
>300 (73)	44.7		77.6	
Sokal score		0.36		0.68
Low risk (33)	45.1		86.3	
Intermediate risk (41)	45.5		72.3	
High risk (14)	24.5		77.9	
CHR at 3 months		0.49		0.009
Yes (57)	47.3		90.6	
No (38)	37.2		69.5	
CHR at 6 months		0.08		0.000
Yes (76)	49.8		90.3	
No (19)	21.1		44.9	
CCyR at 6 months		0.03		0.19
Yes (14)	79.5		100	
No (81)	38.5		77.4	
CCyR at 12 months		0.002		0.02
Yes (33)	69.1		96.8	
No (62)	31.6		72.8	
MMR at 12 months		0.02		0.07
Yes (13)	75.4		100	
No (82)	36.6		75.8	

Abbreviations: CCyR, complete cytogenetic response; CHR, complete hematological response; EFS, event-free survival; MMR, major molecular response; OS, overall survival.

Table 5 Published studies of pediatric CML from India

Study	Number	Duration	CP/AP/BC	Male (M): Female (F)	CHR	CCyR	MMR	Median follow-up	Outcome
Ganguly et al[20]	124[a]	13 years	CP-99 (80%) AP-4 (3%) BC-21 (17%)	3.1:1	79.7% at 3 months	54% at 12 months	50.9% at 12 months	67.4 months	5-year OS: 92% ± 3% 5-year EFS: 64% ± 6%
Ganta et al[23]	48	4 years	CP	1.18:1	100% at 3 months	79% at 6 months	NA	NA	NA
Chandra et al[27]	51	9 years	CP-43 (84.4%) AP-4 (7.8%) BC-4 (7.8%)	2.6:1	NA	NA	NA	NA	NA
Ganta et al[24]	106	5 years	CP	1.14:1	94% at 3 months	75% at 12 months	NA	NA	4-year EFS: 81%
Madabhavi et al[26]	65	17 years	CP-60 (92.3%) AP-3 (4.6%) BC-2 (3.07%)	3.3:1	77.7% at 3 months	48% at 12 months	40.7% at 18 months	36 months	3-year OS: 96.2% 3-year PFS: 66.6%
Linga et al[25]	64[b]	10 years	CP	1.9:1	NA	NA	NA	36 months	3-year OS: 94.5% 3-year PFS: 56.8%
Parikh et al[28]	30	NA	CP	M > F	90%	83.3%	NA	NA	3-year OS: 100% 3-year PFS: 81.5%
Present study	95	20 years	CP-84 (88.4%) AP-6 (6.3%) BC-5 (5.3%)	1.3:1	80% at 6 months	35% at 12 months and 43% at 18 months	19% at 12 months and 27% at 18 months	98 months	8-year OS: 80.4% 8-year EFS: 43.1%

Abbreviations: CCyR, complete cytogenetic response; CHR, complete hematological response; MMR, major molecular response; CP, chronic phase; BC, blast crisis; AP, accelerated phase; OS, overall survival; PFS, progression-free survival; EFS, event-free survival; NA, not available.
[a]Only 81 patients out of 124 were analyzed for treatment response.
[b]Only 37 patients out of 64 were analyzed for treatment response.

third-generation TKIs, and discontinuation of TKIs. Successful discontinuation of the therapy in children with CML will reduce the long-term side effects associated with TKIs.

The role of HSCT in pediatric CML has reduced since the advent of TKIs. HSCT is currently performed in patients with CML BC or T315I mutation.[34] Only 4 out of 95 patients in our cohort underwent HSCT.

Limitations of our study include the retrospective nature, availability of quantitative BCR-ABL PCR for response monitoring only from 2013, monitoring of BCR-ABL levels in patients on treatment being variable due to financial constraints, and nonavailability of data on growth kinetics.

Conclusion

Data on pediatric CML at our center are comparable to that of other Indian studies and western literature. Outcomes in pediatric CML are comparable to that of adults. Imatinib is well tolerated in children. The necessity of HSCT has drastically decreased after the introduction of TKIs.

Availability of Data and Material

The data regarding the findings of this study are available on request from the corresponding author.

Author Contributions

All coauthors have reviewed and contributed substantively and intellectually to the work described.

Note

Abstract on "A Retrospective Study of Pediatric Chronic Myeloid Leukemia" from 2000 to 2016 was presented in HAEMATOCON and PHOCON conferences in 2018, ICKSH-2019.

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Conflict of Interest

No conflicts of interest or competing interest.

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