

## Profile of Pediatric Chronic Myeloid Leukemia in the Era of Imatinib: A Study from South India

### Abstract

**Introduction:** Chronic myeloid leukemia (CML), a chronic hematologic malignancy, is rare in pediatric patients. Studies of the tyrosine kinase inhibitor imatinib are required so that uniform guidelines may focus on disease therapy and follow-up for children. We analyzed the clinicohematologic features of the disease, treatment response to imatinib, follow-up measures, and the impact of the disease on the patients and their family. **Materials and Methods:** All pediatric patients diagnosed with CML and treated and followed-up were studied regarding demographics, clinical features at presentation, and diagnostic profile, including laboratory parameters, peripheral blood smear test, fluorescent *in situ* hybridization and karyotyping, and reverse-transcriptase polymerase chain reaction for the BCR-ABL fusion gene. Treatment modalities, adverse reactions, remedial measures, assessment at every follow-up visit, patient's education, parents' socioeconomic status, and economic and psychological stresses were also evaluated. **Results:** Six patients were administered upfront therapy with a standard dose of imatinib. Hematological and biochemical parameters were monitored after the drug administration. We assessed the treatment response using molecular detection of the BCR-ABL transcripts. All patients who complied with drug therapy showed a complete molecular response and minimal toxic symptoms. However, parents found it difficult to cope socially and economically. **Conclusion:** Imatinib mesylate is effective and has a good molecular response, minimal toxicity, and good patient compliance. However, due to its cost, families reacquire financial debt, and the disease creates uncertainty about the child's future, thereby necessitating psychosocioeconomic support for parents. Changes in the policies of cancer support groups are urgently needed to provide lifelong, lifesaving drugs free of cost.

**Keywords:** Chronic myeloid leukemia, imatinib, pediatric leukemia, socioeconomic impact

### Introduction

Chronic myeloid leukemia (CML) is a chronic hematologic malignancy involving the myeloid cells due to translocation t(9; 22) causing the formation of BCR-ABL fusion gene. This disease is rare in pediatric patients.<sup>[1]</sup> Allogeneic stem cell transplantation (SCT) is the only treatment modality for children, but it is beyond the reach of almost all people in developing countries.<sup>[2]</sup> With the advent and approval of the tyrosine kinase inhibitor imatinib, an oral drug, there is hope for children who are affected by this chronic malignant disease. Few clinical trial reports and single-center experiences are available because the disease is rare and the patient population is small, especially in developing countries and in children. Imatinib mesylate must be used during a patient's

lifetime. However, due to its associated costs and lack of financial support, it has increased abandonment rates. Long-term medications, drug toxicity and monitoring, long-term follow-up of outcomes, growth, education of children, family support, and the psycho-socioeconomic impact of the disease on the family must be analyzed and documented. More studies are required, especially in developing countries, so that a consensus can be reached regarding treatment and so that uniform guidelines may be created to address disease therapy and follow-up. We analyzed the clinico-hematologic features of and treatment response to imatinib, the follow-up measures, and the impact of the disease on patients and their families.

### Materials and Methods

This prospective, descriptive study was performed at the departments of pathology and paediatric hematologic oncology at our

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institution. The Institutional Ethics Committee approved the study and informed consent was obtained from the parents of the patients. All pediatric patients diagnosed with CML between 2011 and 2016 were included in the study. The patients' medical records were thoroughly read, and we interviewed the patients and parents when they attended a review clinic. The demographics and clinical features at presentation were recorded. The diagnostic profile, which included laboratory parameters, peripheral blood smear test results, fluorescent *in situ* hybridization (FISH), karyotyping, and reverse-transcriptase polymerase chain reaction (RT-PCR) for the BCR-ABL gene, were recorded.

Treatment modalities, adverse reactions, and remedial measures performed were recorded on data sheets. Patients were assessed at every follow-up visit and the treatment response was recorded. Treatment responses were assessed as the complete hematologic response (CHR) (white blood cell count [WBC]  $<10 \times 10^3/\mu\text{l}$ , platelet count  $<450 \times 10^3/\mu\text{l}$ , myelocytes and metamyelocytes  $<5\%$  in the peripheral blood, no blasts, promyelocytes in the peripheral blood, and basophils  $<20\%$  with no extramedullary involvement), major cytogenetic response including both the complete response (CCyR) and partial response (PCyR) (CCyR: 0% Ph + metaphases; PCyR: 1%–35% Ph + metaphases), major molecular response (MMR), and complete molecular response (CMR) (MMR:  $<0.1\%$  or 3-log reduction of BCR-ABL transcripts; CMR: Transcripts were undetectable or  $>3$ -log reduction in transcripts).<sup>[3,4]</sup> The response criterion for imatinib according to the timeline was defined as an optimal or suboptimal response, and failure was defined according to the European LeukemiaNet panel.<sup>[3,4]</sup>

Patients were interviewed regarding their education. The socioeconomic status of the parents was assessed using the modified Kuppuswamy's socioeconomic status scale.<sup>[5]</sup> A questionnaire was developed after extensive research of the literature, and it was validated by experienced pediatric hemato-oncologists from three other institutions. It consisted of 15 questions and was composed of variables such as economic and psychological stresses due to chronicity of the disease and frequent hospital visits, social stigma, and funding sources. The questionnaire was prepared according to the situations that typically occur in developing countries and was validated.<sup>[6]</sup> Parents were asked to complete the questionnaire at a semi-structured, scheduled interview. The data were tabulated and a descriptive analysis was performed.

## Results

Between 2011 and 2016, seven patients were diagnosed with CML. At our center, 3.6% of pediatric patients had leukemia and 9% had CML. Among these seven patients, one patient opted out of treatment. The six remaining patients were followed up.

Among these six patients, four were male and two were female. Three (50%) of these patients were between 15

and 19 years old, 2 (33.3%) were between 10 and 14 years old, and 1 (16.7%) was between 5 and 9 years old. Four patients were classified as lower-middle class, one was classified as upper-middle class, and one was classified as upper class.

The hematological findings at presentation are shown in Table 1. Three patients (50%) had hyperleukocytosis with more than  $100 \times 10^3/\mu\text{l}$  WBC in the peripheral blood.<sup>[7]</sup> Among these patients, 2 (33.3%) had a low red blood cell count and hemoglobin. Only one patient had thrombocytopenia. Splenomegaly was not noted in two patients (33.3%). Hepatomegaly was not observed.

All patients were started on upfront therapy with a standard dose of imatinib mesylate in tablet form. Initially, all patients received hyperhydration and allopurinol. Imatinib was started at  $100 \text{ mg/m}^2$ , which was escalated slowly to  $340 \text{ mg/m}^2$  as tolerated. We monitored the clinical, hematological, and biochemical parameters of all patients.<sup>[8-10]</sup>

Toxic symptoms (as per the common toxicity criteria) are shown in Table 2.<sup>[11,12]</sup> One patient required hospitalization for toxic gastrointestinal symptoms. The dose of imatinib was reduced and then gradually escalated. Five patients were compliant with the drug consumption protocol and follow-up.

**Table 1: Hematological findings**

Parameter	n (%)
WBC ( $\times 10^3/\mu\text{l}$ )	
40-60	2 (33.3)
60-80	2 (33.3)
$>200$ - $>300$	1 (16.6)
$>400$ - $<500$	1 (16.6)
Hemoglobin (g/dl)	
$<8$	1 (16.6)
8.12	4 (66.6)
$>12$	1 (16.6)
RBC ( $\times 10^3/\mu\text{l}$ )	
$<3$	1 (16.6)
$>3$ -4	5 (83.3)
Genetics	
FISH t(9;22)	6 (100)
Karyotyping	6 (100)
RT-PCR (BCR-ABL)	6 (100)
Platelet ( $10^3/\mu\text{l}$ )	
150-450	4 (66.6)
450-600	1 (16.6)
$>600$	1 (16.6)
Diagnostic phase	
Chronic phase CML	6 (100)

FISH – Fluorescent *in situ* hybridization;

RT-PCR – Reverse-transcriptase polymerase chain reaction;

CML – Chronic myeloid leukemia; WBC – White blood cell;

RBC – Red blood cell

The treatment response and follow-up are shown in Table 3. One patient did not have an MMR, even at 3 years, due to lack of compliance and irregular follow-up. If the patient experienced failure or had a suboptimal response that could not be defined as cytogenetic, then the workup was not performed.

Among the parents, 66.6% belonged to the lower-middle income class; the rest belonged to the upper and upper-middle income classes. Among the patients, 66.6% missed more than 6 months of, while schooling. The others coped with their disease without missing any of their education. The psychosocial impact of chronic disease on families is summarized in Table 4.

## Discussion

CML is rare in children. Our rate of leukemia in pediatric patients (3.6%) was similar to the rates in a few reports from Western countries. At our center, 9% of all leukemia patients had CML; this rate is higher than that in those in reports from Eastern India, but the percentage is approximately the same as those in reports from the Western world.<sup>[13,14]</sup> All our patients were older than 5 years at the time of diagnosis and boys were predominantly affected (2:1). The same observations were noted at many other centers.<sup>[15]</sup> The predominant clinical symptoms were fever, abdominal pain, and weight loss. One patient was diagnosed incidentally when he presented with a sore throat. The most common clinical sign was splenomegaly. Symptoms and signs of the pediatric age group did not differ from those of

adults with CML and coincided with those of similar studies of CML.<sup>[16]</sup>

Hyperleukocytosis was present in 50% of cases. The other 50% presented with a total WBC count  $<100 \times 10^3/\mu\text{l}$ . However, all patients were diagnosed using a peripheral blood smear examination. All patients had chronic-phase CML at the time of diagnosis. FISH detected t(9; 22) (q34; q11) in all patients, although the percentage of cells varied (range, 50% and 100%). The findings suggested that leukemogenesis biology is shared by both pediatric and adult patients. Karyotyping confirmed the FISH findings. RT-PCR showed the upper detection level in all patients.

Initially, allogeneic SCT was the standard care offered to children who were diagnosed with CML, although this was accessible to only a few due to the high cost, donor availability, and scarcity of centers where the procedure is performed.<sup>[2]</sup> The 3-year overall survival rates were 75% and 65% for sibling-donor SCT and unrelated-donor SCT, respectively.<sup>[17]</sup> The 5-year event-free survival rates of patients who underwent SCT in the CML-PEAD1 trial were 87% and 52% at various centers.<sup>[18]</sup> Comparative studies showed that patients who were treated with imatinib had better survival rates than those who were treated with SCT.<sup>[19]</sup> The tyrosine kinase inhibitor imatinib, which binds to the inactive conformation of the BCR-ABL gene, has given hope to adult patients with CML since 2001. This drug was approved for use by pediatric patients in 2003.<sup>[9]</sup> All patients in our study were administered imatinib mesylate using the standard pediatric protocol.

At 3 months after drug administration, CCyR was noted in two (33.3%) patients, whereas others had CHR. Four patients had CMR at 12–18 months, whereas another two had MMR. A few trials have reported MMR at 18 months, and this result was similar to ours.<sup>[17]</sup> Among the patients in our study group, one who had CHR at 3 months was not compliant with drug therapy and follow-up and could not achieve MMR at 2 years; however, she achieved CHR. MMR was achieved at 1 year in approximately 31% of patients in a French national phase 4 trial.<sup>[20]</sup> Five children in a study by Kolb *et al.* achieved CMR within 1 year.<sup>[10]</sup> Although

**Table 2: Imatinib toxicity**

Toxicity	n (%)
GI intolerance	4 (66.6)
Skin rash	2 (33.3)
Hypopigmentation	2 (33.3)
Bone pain	2 (33.3)
Myalgia	1 (16.6)
Cramps	1 (16.6)
Necessity to reduce dose	1 (16.6)

GI – Gastrointestinal

**Table 3: Treatment response**

Patient number	3 months	6 months	12±1 months	18±1 months	Within 3 months of last follow-up	Duration of follow-up	Treatment response
1	CCyR	MMR	MMR	CMR	CMR	6 years 5 months	Optimal
2	CHR	CCyR	MMR	CMR	CMR	2 year 6 months	Optimal
3	CHR	CHR	CHR	-	< MMR	3 years 4 months	Suboptimal/failure (due to lack of compliance and irregular follow-up)
4	CHR	CCyR	MMR	CMR	CMR	5 years 4 months	Optimal
5	CCyR	CCyR	MMR	MMR	CMR	3 years 2 months	Optimal
6	CHR	CCyR	CMR	CMR	CMR	5 years 6 months	Optimal

CCyR – Complete cytogenetic response; MMR – Major molecular response; CHR – Complete hematological response; CMR – Complete molecular response

**Table 4: Impact of the disease on the psycho-socioeconomic aspect of the parents**

Variable	Percentage
Guilt	33
Depression	50
Worried about the future	50
Difficulty in coping with the chronic disease	50
Burdened	50
Stigmatized	17
Neglected	17
Worried about the worsening economic status	33

5 (83.3%) patients in our study experienced an optimal response to imatinib, 1 (16.6%) patient had a suboptimal response due to lack of compliance and default follow-up. None of our patients died due to the disease, although death was reported by other centers.<sup>[10,21]</sup> There was no need to switch to second-line drugs, although this occurred at another center in India within 3 years of follow-up.<sup>[22]</sup> For our patients, the duration of follow-up ranged between 2 years and 6 months and 6 years and 5 months. The most common side effect among our patients who were administered imatinib mesylate was gastrointestinal intolerance, followed by skin rash, hypopigmentation, myalgia, and cramps; these were similar to the side effects reported in other studies.<sup>[11,23]</sup> None of our patients had hematologic toxicity or growth restriction, as noted by authors from India and abroad.<sup>[22-24]</sup> Only one patient was hospitalized for toxic gastrointestinal symptoms of mucositis and required a reduction in the dose, with later escalation. Although a few studies have been performed in India with a greater number of patients, the patients' molecular responses were not assessed consistently.<sup>[25]</sup>

Four patients were absent from school for more than 6 months and missed 1 year of schooling, whereas older children could cope with their schooling despite frequent absences. However, all our patients were eager to study, with the primary aim of supporting their families in the future.

Only one of the families had personal insurance. The others were dependent on state government insurance, which paid for only half of the drug expenses. The expenses for follow-up investigations and the remaining drug costs were paid for by donations from charitable trusts and money borrowed from friends, relatives, and colleagues. Most of these families had to sell their assets or were in debt because none of the various cancer support groups and nongovernment organizations provided free lifetime drugs. The cost of imatinib mesylate for 1 month, at an average dose of 400 mg/day, is \$156.90. The cost of an RT-PCR quantitative analysis for the BCR-ABL gene is \$97.13.

When we analyzed the questionnaire, feelings of guilt were noted in 33% of the parents. Some felt self-guilt. Others thought their interpersonal relationships affected their

children. This feeling of guilt has been noted in parents of children with acute leukemia in developing countries such as India.<sup>[26]</sup> Of the parents in our study, 50% had depression and easily became upset and worried about the future of their child. They felt burdened, and their daily activities were affected by their feelings. Depression was observed in most of the patients with acute leukemia as well as in children with other types of cancer in studies by Bayat *et al.*<sup>[27]</sup> and Rao *et al.*<sup>[26]</sup> One-third of the parents felt stigmatized or neglected and did not want to socialize. This might have been due to the constant care they needed to offer their child and because they wished to avoid being interrogated regarding their child's disease. This psychosocial behavior was also mentioned by Kohlsdorf *et al.* in a literature review.<sup>[28]</sup> None of the parents turned to drugs, alcohol, or smoking to cope with their feelings. In fact, two parents stopped smoking and drinking.

Because CML is a chronic disease, apart from medical expenses, it involves invisible financial costs, including transportation for regular follow-up appointments, long-term hospital stays, food, absence from jobs, and loss of pay. Of the parents who were evaluated in this study, 33% were worried about paying the financial costs associated with treatment and had to work excessively; 17% had to sell assets. The Glivec International Patient Assistance Program (GIPAP), which was initiated in 2002 by the Max Foundation, provides imatinib mesylate free of cost to eligible patients in developing countries who do not have the resources to buy drugs for life-threatening malignancies. Although the GIPAP has extended its support throughout South Asia, only a few centers are eligible to apply for funding. Although our hospital is not recognized by the Max Foundation as eligible for imatinib mesylate funding, our patients were reluctant to continue treatment at other medical centers that are recognized as eligible for funding due to various reasons such as a need to travel a longer distance and hesitancy to continue treatment in a new hospital setting.

The health-related quality of life of parents with children with CML was low in our study; this result was similar to that reported in Western studies.<sup>[28,29]</sup> Despite the psycho-socioeconomic impact of disease, parents were worried about the outcomes of disease and the future of their children. All parents were eager to know the duration of drug intake and were anxious about whether their child would be able to stop using the drugs in the future.

CML, a rare chronic hematologic malignancy in children, is diagnosed using basic hematologic investigations. However, cytogenetic and molecular studies are needed for initiating and maintaining therapy and follow-up. With minimal toxicity and good compliance, imatinib mesylate is effective because it has a good molecular response within 9 months to 1 year. Regular patient follow-up is essential because there is high risk of noncompliance due to the long-term need to use the drug for an unknown period. However, the

cost of the drug and the lifelong need to continue the drug caused substantial financial debt and created uncertainty in their minds about the future of their children, thereby necessitating psycho-socioeconomic support.

## Conclusion

Although the sample size was very small, this was the first study to assess the treatment response at the molecular level and the psycho-socioeconomic issues of families with children with CML who were administered imatinib with a continuous follow-up period of more than 6 years, as well as the supportive measures that are needed in developing countries. Because most cancer support groups do not financially support the lifelong use of drugs, there is an urgent need to change policies to provide these lifesaving drugs free of cost.

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## Conflicts of interest

There are no conflicts of interest.

## References

- Raut LS. Chronic myeloid leukemia in children: A brief review. *Clin Cancer Investing J* 2014;6:467-71.
- Druker BJ, Sawyers CL, Capdeville R, Ford JM, Baccarani M, Goldman JM, *et al.* Chronic myelogenous leukemia. *Hematology Am Soc Hematol Educ Program* 2001;2001:87-112.
- Baccarani M, Saglio G, Goldman J, Hochhaus A, Simonsson B, Appelbaum F, *et al.* Evolving concepts in the management of chronic myeloid leukemia: Recommendations from an expert panel on behalf of the European leukemiaNet. *Blood* 2006;108:1809-20.
- Goldman JM. How I treat chronic myeloid leukemia in the imatinib era. *Blood* 2007;110:2828-37.
- Kumar N. Kuppuswamy's socioeconomic status scale-updating for 2007. *Indian J Pediatr* 2007;74:1131-2.
- Han HR, Cho EJ, Kim D, Kim J. The report of coping strategies and psychosocial adjustment in Korean mothers of children with cancer. *Psychooncology* 2009;18:956-64.
- Röllig C, Ehninger G. How I treat hyperleukocytosis in acute myeloid leukemia. *Blood* 2015;125:3246-52.
- Champagne MA, Capdeville R, Krailo M, Qu W, Peng B, Rosamilia M, *et al.* Imatinib mesylate (STI571) for treatment of children with Philadelphia chromosome-positive leukemia: Results from a children's oncology group phase I study. *Blood* 2004;104:2655-60.
- Millot F, Guilhot J, Nelken B, Leblanc T, De Bont ES, Békassy AN, *et al.* Imatinib mesylate is effective in children with chronic myelogenous leukemia in late chronic and advanced phase and in relapse after stem cell transplantation. *Leukemia* 2006;20:187-92.
- Kolb EA, Pan Q, Ladanyi M, Steinherz PG. Imatinib mesylate in Philadelphia chromosome-positive leukemia of childhood. *Cancer* 2003;98:2643-50.
- Andolina JR, Neudorf SM, Corey SJ. How I treat childhood CML. *Blood* 2012;119:1821-30.
- Bansal S, Prabhaskar K, Parikh P. Chronic myeloid leukemia data from India. *Indian J Med Paediatr Oncol* 2013;34:154-8.
- Suttorp M. Innovative approaches of targeted therapy for CML of childhood in combination with paediatric haematopoietic SCT. *Bone Marrow Transplant* 2008;42 Suppl 2:S40-6.
- Ray SS, Chakrabarti P, Nath U, Chaudhuri U. A single centre experience of treating CML in a tertiary care centre at Eastern India. 51<sup>st</sup> National Conference of Indian Society of Hematology and Transfusion Medicine 2010. 18<sup>th</sup>-21<sup>st</sup> November, 2010. Kolkata, India: Springer; 2010. p. 129-81.
- Burke MJ. Profile of imatinib in pediatric leukemia. *Pediatric Health Med Ther* 2014;5:1-7.
- Vardiman JW. Chronic myelogenous leukemia, BCR-ABL1+. *Am J Clin Pathol* 2009;132:250-60.
- Cwynarski K, Roberts IA, Iacobelli S, van Biezen A, Brand R, Devergie A, *et al.* Stem cell transplantation for chronic myeloid leukemia in children. *Blood* 2003;102:1224-31.
- Raut LS. Chronic myeloid leukemia in children. A brief review. *Clin Cancer Investig J* 2014;3:467-71.
- Muramatsu H, Kojima S, Yoshimi A, Atsuta Y, Kato K, Nagatoshi Y, *et al.* Outcome of 125 children with chronic myelogenous leukemia who received transplants from unrelated donors: The Japan Marrow Donor Program. *Biol Blood Marrow Transplant* 2010;16:231-8.
- Millot F, Baruchel A, Guilhot J, Petit A, Leblanc T, Bertrand Y, *et al.* Imatinib is effective in children with previously untreated chronic myelogenous leukemia in early chronic phase: Results of the French national phase IV trial. *J Clin Oncol* 2011;29:2827-32.
- Raut L, Bohara VV, Ray SS, Chakrabarti P, Chaudhuri U. Chronic myeloid leukemia in children and adolescents: A single center experience from Eastern India. *South Asian J Cancer* 2013;2:260-4.
- Linga VG, Ganta RR, Kalpathi KI, Gundeti S, Rajappa SJ, Digumarti R, *et al.* Response to imatinib mesylate in childhood chronic myeloid leukemia in chronic phase. *South Asian J Cancer* 2014;3:203-5.
- Ghadyalpatil N, Banawali S, Kurkure P, Arora B, Bansal S, Amare P. Efficacy and tolerability of imatinib mesylate in pediatric chronic myeloid leukemia in a large cohort: Results from a tertiary care referral centre in India. *J Clin Oncol* 2009;27:15s.
- Shima H, Tokuyama M, Tanizawa A, Tono C, Hamamoto K, Muramatsu H, *et al.* Distinct impact of imatinib on growth at prepubertal and pubertal ages of children with chronic myeloid leukemia. *J Pediatr* 2011;159:676-81.
- Ganesan P, Rajendranath R, Kandakumar V, Sagar TG. Treatment of chronic phase chronic myeloid leukemia with imatinib. *Indian J Pediatr* 2015;82:235-9.
- Rao GP, Malhotra S, Marwaha RK. Psychosocial study of leukemic children and their parents. *Indian Pediatr* 1992;29:985-90.
- Bayat M, Erdem E, Gül Kuzucu E. Depression, anxiety, hopelessness, and social support levels of the parents of children with cancer. *J Pediatr Oncol Nurs* 2008;25:247-53.
- Kohlsdorf M, Junior ALC. Psychosocial impact of pediatric cancer on parents: A literature review. *Paideia* 2012;22:119-29.
- Klassen AF, Klaassen R, Dix D, Pritchard S, Yanofsky R, O'Donnell M, *et al.* Impact of caring for a child with cancer on parents' health-related quality of life. *J Clin Oncol* 2008;26:5884-9.