SAS Journal of Medicine
Abbreviated Key Title: SAS J Med
ISSN 2454-5112
Journal homepage: https://saspublishers.com

OPEN ACCESS

Hematology & Oncology

Care of Children with Chronic Myeloid Leukemia in the Pediatric Hematology and Oncology Department

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DOI: https://doi.org/10.36347/sasjm.2025.v11i05.010 | **Received:** 02.04.2025 | **Accepted:** 07.05.2025 | **Published:** 10.05.2025

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Abstract **Original Research Article**

Introduction: Chronic myeloid leukemia (CML) is a rare pediatric pathology characterized by the presence of the Philadelphia chromosome and requiring specific management. ***Goals:*** Report the epidemiological, clinical and evolutionary and prognostic chronic myeloid leukemia in children. ***Materials and Methods***: This retrospective study, conducted over 10 years, describes the epidemiological, clinical and therapeutic profile of CML in children. Imatinib remains the standard treatment, but long-term monitoring is essential to optimize management and limit complications. This study aims to analyze the epidemiological, clinical, biological and evolutionary characteristics of chronic myeloid leukemia (CML) in children, while comparing the results obtained with data from the literature. ***Discussion-Conclusion***: Pediatric chronic myeloid leukemia (CML) is a rare blood disease with specific features compared to the adult form, including male predominance, early onset, and often marked splenomegaly. Biologically, hyperleukocytosis is common, associated with significant myelemia and the systematic presence of the Philadelphia chromosome and the BCR-ABL1 transcript. The standard treatment remains imatinib, with a good initial clinical response, although the molecular response may be slower than in adults. In case of resistance or intolerance, second-generation TKIs may be indicated. Long-term follow-up is essential, due to potential side effects such as slowed growth and endocrine disorders. Finally, although therapeutic discontinuation strategies are being explored in adults, they require great caution in children.

Keywords: Chronic Myeloid Leukemia – Childhood – Philadelphia Chromosome – Tyrosine Kinase Inhibitors.

INTRODUCTION

Chronic myeloid leukemia (CML) is a rare childhood hematological malignancy, accounting for approximately 2–3% of all pediatric leukemias [1]. It is characterized by the t(9;22) translocation that results in the formation of the Philadelphia chromosome and the expression of the BCR-ABL1 fusion gene, responsible for constitutive tyrosine kinase activation and uncontrolled myeloid proliferation [2]. Although CML is primarily an adult disease, its diagnosis in pediatrics presents biological and clinical particularities that influence patient management and prognosis [3].

The advent of tyrosine kinase inhibitors (TKIs), notably imatinib, has revolutionized the treatment of CML, achieving a sustained hematological and molecular response in the majority of patients [4]. However, the management of pediatric CML poses several challenges, including monitoring long-term side effects, such as impact on growth and pubertal development, as well as long-term treatment adherence [5].

Goals: Report the epidemiological, clinical and evolutionary and prognostic chronic myeloid leukemia in children.

MATERIALS AND METHODS

Retrospective descriptive study of 10 cases over a period of 10 years (January 2014 to December 2024) in the pediatric hematology and oncology department (SHOP) of the Mohammed VI University Hospital in Marrakech.

RESULTS

Boys were the most affected 7 cases (70%). The average age was 8 years, with extremes ranging from 1 year to 14 years. Low socioeconomic status affected 55% of patients. The time between the onset of symptoms and the first consultation was an average of 5 months (1

month to 1 year). None of the patients had any particular pathological history. The predominant clinical pattern was abdominal distension in 90% of cases, followed by deterioration of the general condition in 10%. Bone marrow failure syndrome was complete in 30% of patients, with mucocutaneous pallor, fever and hemorrhagic syndrome (epistaxis and ecchymosis). Splenomegaly was present in all patients, with splenic stents ranging from 11 cm to 19 cm. Hepatomegaly was found in 50% of patients with an average hepatic stent of 14 cm. Cervical and inguinal lymphadenopathy were systematic. As revealing complications, leukostasis syndrome was observed in all patients and lysis syndrome in only one patient. The blood count showed major hyperleukocytosis with normochromic normocytic anemia in 100% of patients, and a blood smear revealed myelemia up to 70%. The myelogram confirmed the diagnosis in all patients. 90% were in the chronic phase and 10% in the accelerated phase. Karyotype confirmed the presence of the Philadelphia chromosome (t(9;22)) in all patients. Molecular biology was performed in 90% of patients, confirming the presence of the BCR-ABL1 transcript. Radiologically, chest X-ray showed mediastinal widening in 20% of patients, the rest being normal. Abdominal ultrasound revealed organomegaly in 100% of patients, 25% had iliac lymphadenopathy and 10% had peritoneal effusion. Regarding management, alkaline hyperhydration of 3 L/m2 was performed urgently in all patients due to major hyperleukocytosis, until normalization of white blood cells, associated with hydroxycarbamide (Hydréa) at 10 mg/m2/day for 5 days. Specific treatment with imatinib (BCR-ABL protein tyrosine kinase inhibitor) at a dose of 400 mg/m2/day was administered as soon as the diagnosis was confirmed then dose reduction to 268mg/m2/day. The one-month evolution was marked by regression of splenomegaly and normalization of white blood cells in 100% of patients. Quarterly monitoring was carried out in all patients, with a good response, first by karyotype then after normalization by PCR. Only one patient was unable to complete treatment and was subsequently lost to follow-up after one year of treatment. No deaths were recorded, but side effects were observed, including growth retardation in 20% of patients after 10 years of follow-up. No relapse was observed in our patients and in particular no switch to second-line treatment.

Table 1: summarizing the clinical and paraclinical signs and evolution

Category	**Parameter**	**Results**
Sex	Boy	7 cases
	Girl	3 cases
Demographic Data	Mean age	8 years (1 to 14 years)
	Low socio-economic status	5 cases
	Delay before consultation	5 months (1 month to 1 year)
Medical History	Past medical history	None
Clinical Presentation	Abdominal distension	9 cases
	Bone marrow failure syndrome	3 cases
	General condition deterioration	1 case
	Splenomegaly	10 cases
	Hepatomegaly	5 cases
	Lymphadenopathy	10 cases
Revealing Complications	Leukostasis syndrome	10 cases
	Tumor lysis syndrome	1 case
Biological Tests	Major hyperleukocytosis	10 cases
	Normochromic normocytic anemia	10 cases
Myelogram (disease phase)	Chronic phase	9 cases
	Acceleration phase	1 case
	Acute phase	0 cases
Cytogenetic and Molecular Tests	Karyotype (Philadelphia chromosome)	10 cases
	Molecular biology BCR-ABL1	9 cases
Chest X-ray	Normal	8 cases
	Mediastinal widening	2 cases
Abdominal Ultrasound	Organomegaly	10 cases
	Iliac lymphadenopathy	3 cases
	Peritoneal effusion	1 case
Treatment	Initial treatment	10 cases
	Specific treatment (Imatinib)	10 cases
Outcome	Response at 1 month	10 cases
Follow-up	Compliance	1 patient lost to follow-up
	Death	None
Side Effects	Growth delay (height and weight)	2 cases

DISCUSSION

Pediatric CML remains a rare disease requiring specific management. Compared to adult CML, the pediatric form presents biological and clinical particularities that influence diagnosis, treatment and disease progression. Studies show a higher prevalence of additional mutations in children, which could influence the response to treatment [1]. Epidemiological differences are also marked. While adult CML occurs mainly in elderly patients, the pediatric form mainly affects boys and can be diagnosed in early childhood [3]. In our study, the dominant clinical signs were splenomegaly (100%), hepatomegaly (50%), abdominal distension (90%) and general deterioration (10%), these results are consistent with those of previous studies, which show that splenomegaly is often more marked in children than in adults, with splenic arrows up to 20 cm below the costal margin [6]. Leukostasis is a common complication due to high levels of circulating leukocytes, and may require urgent measures such as that hyperdiuretics and administration of hydroxycarbamide, as observed in our series [7]. Biologically, hyperleukocytosis was systematic, with significant myelemia and a rate of moderate to severe anemia. The presence of the Philadelphia chromosome (t(9;22)) and the BCR-ABL1 transcript was confirmed in 100% of the patients tested, which is expected in pediatric CML and corresponds to the results of other studies published on the subject [8].

Regarding therapeutic management, imatinib, a first-generation tyrosine kinase inhibitor (TKI), is currently the first-line treatment of choice for pediatric CML [9]. All our patients received this treatment at the standard dose of 400 mg/day, and the clinical response was favorable with regression of splenomegaly and normalization of hyperleukocytosis within one month. Other studies show that imatinib achieves a complete hematological response in 90 to 95% of pediatric patients, with a 5-year overall survival greater than 90% [10].

However, the molecular response is slower in children compared to adults, which may be explained by pharmacokinetic and biological differences [11]. In some cases, switching to a second-generation TKI, such as dasatinib or nilotinib, is necessary due to resistance or intolerance to imatinib, which remains limited by age. Approximately 15 to 20% of pediatric patients require such a change of treatment [12]. One of the major challenges of TKI treatment in pediatrics is the monitoring of long-term side effects. Several studies have documented slowed growth in children receiving imatinib, with a more pronounced impact in prepubertal patients [13]. This effect appears to be related to interference with the GH-IGF-1 axis, although the exact mechanisms remain to be elucidated [14]. In addition, endocrine disturbances, including abnormal thyroid function and pubertal delays, have been reported in some pediatric cohorts under prolonged treatment [15]. The long-term outcome of pediatric CML is generally favorable under TKI treatment. However, the question of therapeutic discontinuation in case of a deep molecular response is still debated. In adults, several studies have shown that some patients can maintain a prolonged remission after discontinuation of TKIs, but pediatric data remain limited [16]. Careful monitoring is therefore necessary before considering such a strategy in children. Before the advent of TKIs, allogeneic hematopoietic stem cell transplantation (HSCT) represented the only therapeutic option for patients with CML. In children, this approach probably retains a more important place than in adults, with TKIs still constituting a lifelong treatment to this day [17]. A study by Suttorp *et al.*,, in 2009 showed that the overall survival of pediatric patients in the chronic phase after allogeneic HSCT was close to 90% [18]. Although overall survival after allogeneic HSCT is generally satisfactory, this approach remains associated with significant sequelae. This is why first-line treatment in patients in the chronic phase is based on TKIs. In the event of failure of a well-conducted second line, recourse to allogeneic HSCT becomes a reasonable option [17]. In a 2003 study in France, 66 children were studied after allogeneic HSCT [19]. Overall survival in patients with chronic disease is 73% compared to 27% in patients with advanced disease. The leading cause of transplant-related death is graft-versus-host disease (GVHD).

The NCCN Committee (The National Comprehensive Cancer Network) recommends performing an allogeneic hematopoietic stem cell transplant within three to six months after diagnosis of the blast phase [20]. A recent study showed a negative effect of the use of three different lines of TKIs on the post- transplant mortality rate not related to relapse compared to patients who received one to two lines of TKIs [21]. It therefore seems justified to seek a donor after the failure of two lines of treatment with tyrosine kinase inhibitors, in order to limit the toxicity linked to their continuation if an allogeneic transplant becomes necessary.

CONCLUSION

Our study confirms the clinical and biological specificities of pediatric CML and highlights the challenges associated with its management, particularly in terms of therapeutic response and long-term follow-up. Imatinib remains the standard treatment, but rigorous monitoring is essential to detect possible late complications. The search for new therapeutic strategies adapted to pediatric specificities, including second-generation TKIs and therapeutic discontinuation approaches, is essential to improve the management of these young patients.

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