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Research Article

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Pediatric Chronic Myeloid Leukemia: A Decade of Clinical Experience at the NBK Children Specialty Hospital

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ABSTRACT

Background: Chronic myeloid leukemia (CML) is a rare disease in children, distinct from its adult counterpart in terms of presentation and management. This study aims to evaluate the clinical characteristics and treatment outcomes of pediatric CML patients treated at the National Bank of Kuwait (NBK) Children Specialty Hospital in Kuwait over a decade.

Methods: A retrospective review was conducted on the medical records of children diagnosed with CML between 2010 and 2020. Data on patient demographics, clinical presentation, treatment regimens, and outcomes were collected and analyzed.

Results: All patients presented with leukocytosis and most had splenomegaly. Imatinib, a first-line tyrosine kinase inhibitor (TKI), achieved a good response rate, with none of the patients requiring bone marrow transplantation. Despite some patients required dose adjustments or second-line TKIs due to complications or loss of response, the overall outcomes were positive, reinforcing the efficacy of TKIs in pediatric CML.

Conclusion: This study highlights the distinct clinical presentation and response to TKI therapy in children with CML, compared to adults. The rarity of pediatric CML presents challenges in understanding disease characteristics and optimizing treatment approaches. Further research is needed to determine optimal treatment duration for this population.

Keywords: Chronic Myeloid Leukemia (CML), Children, Tyrosine Kinase Inhibitors (TKIs), Imatinib, Treatment Outcomes, Retrospective Study

Table of Abbreviations

Abbreviation	Full Name
CML	Chronic Myeloid Leukemia
NBK	National Bank of Kuwait
TKI	Tyrosine Kinase Inhibitors
Ph	Philadelphia
CP	Chronic Phase
AP	Accelerated Phase
BP	Blast Phase
WBC	White Blood Cells
SCT	Stem Cell Transplantation
CBC	Complete Blood Count
GOSH	Great Ormond Street Hospital
ELN	European Leukemia Net
TLS	Tumor Lysis Syndrome
CHR	Complete Hematological Response

Introduction

CML is a rare malignancy in children, accounting for approximately 3% of all childhood leukemias [1, 2]. The incidence rate in Kuwait is approximately 6 cases per 100,000 individuals [3]. While the global annual incidence is 1-2 cases per million, its

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rarity in children presents a challenge in understanding disease characteristics and optimal treatment approaches [1]. CML is a malignant clonal hematological disease defined by the spread of myeloid neoplastic cells in the circulating blood and in the bone marrow. It is characterized by the presence of the Philadelphia (Ph) chromosome, which leads to the formation of the BCR-ABL fusion transcript [1]. The pathological activity of BCR-ABL leads to myeloid neoplasia as well as genomic instability [4]. CML progresses through three phases: chronic phase (CP), accelerated phase (AP), and blast phase (BP) [2]. There are clear differences between CML in children and adults in terms of disease presentation and progression, along with differences in the underlying CML biology and host factors, which should be considered when treating pediatric patients [5,6]. Chronic phase CML (CML-CP) in children, adolescents, and young adults often presents with more aggressive features, though the impact on prognosis remains debatable [6,7].

Among children, the median size of the spleen is 8 cm, which is below the costal margin (range, 0-25 cm). This number is not very different from that of adults; however, it is proportionally larger in children because the age-based normal size of the spleen in children is smaller than in adults [8]. The median baseline white blood cells (WBC) count in children with CML was approximately 250 × 109/L in an international registry, which is higher than the range of 80 × 109/L to 150 × 109/L in adults [9,10]. Additionally, the prognostic scoring systems used in adults to identify high-risk patients at diagnosis, like the Sokal and Hasford scores, are not yet established for children [11-14].

The goal of treatment in children with CML should be cure, rather than merely the suppression of disease symptoms [5]. Tyrosine kinase inhibitors (TKIs) like Imatinib have revolutionized CML treatment in adults, but the optimal treatment duration in children remains unclear [6,15]. This is due to the low incidence of CML in children, as only a few pediatric studies have evaluated the efficacy of treating this disease with TKI therapy in children [14]. The efficacy of TKI, whether as first or second-line treatment are heavily investigated in adults [16]. Limited data exist on the use of second-generation TKIs in children [14]. Historically, allogeneic stem cell transplantation (SCT) was the primary treatment for CML [17]. However, the introduction of TKIs revolutionized CML therapy, leading to a significant decline in SCT use [18]. While the introduction of TKIs has significantly improved outcomes in adult CML, data on pediatric CML management remains limited [1]. This study has three aims: to know the characteristics and trend of CML, to evaluate the treatment outcomes and survival rate in children, and to assess the applicability of diagnostic scales used for adults with CML to the pediatric population. The limited global data on pediatric CML and the importance of region-specific studies, emphasizes the importance of this study.

Materials and Methods

This retrospective study reviewed data from the National Bank of Kuwait Children Specialty Hospital, the sole national referral center for childhood cancer in Kuwait. The study period spanned from January 2010 to January 2020. Ethical approval for the study was obtained from the Standing Committee for Coordination of Health and Medical Research and the Pediatric Departments' Council at Kuwait's Ministry of Health (Approval Number: P116-13MK-01). The research protocol was conducted in accordance with the principles of the Helsinki Declaration.

Data for children with CML over the last decade were highlighted from our local registry and reviewed. The data collected included age, sex, nationality, date of admission, clinical status at presentation, diagnostic tests at diagnosis, and at different points throughout the treatment journey. Other variables included lab results at diagnosis, treatment options, and PCR-ABL results at diagnosis, every three months during the first year, and then every six months as long as the child was under 16 years of age. Data from January 2010 to January 2020 was gathered from our in-house database and entered into the SPSS data program.

There were some missing data for certain patients. Generally, all children with leukemia in Kuwait are referred to the sole center for childhood cancer for further management and confirmation of diagnosis. All children with leukemia, including those with CML, are admitted to the hospital for induction chemotherapy treatment. Once their condition stabilizes, they are discharged to be seen in the outpatient department for continued treatment and monitoring, as well as in the emergency room in case of any emergencies thereafter.

Suspected leukemia cases underwent admission and the following investigations:

- Complete blood count (CBC) with differential
- Renal function tests
- Liver function tests
- Lactate dehydrogenase
- Serum uric acid
- Serum electrolytes
- Abdominal ultrasound (spleen size and other findings)
- Bone marrow aspiration and cytogenetics
- FISH and molecular PCR-ABL from bone marrow and peripheral blood
- Immunophenotyping

Following induction therapy, patients underwent regular monitoring to assess response and disease status. Tests would be repeated at designated intervals. A complete hemogram was repeated at least monthly or when needed. BCR-APL test was repeated every month for the first three months, every three months until the second year, and every six months thereafter.

Inclusion criteria

Children diagnosed with CML between 2010 and 2020 at NBK Children Specialty Hospital were included if they aged 0-16 years at diagnosis and diagnosed with Philadelphia chromosome-positive or BCR-ABL fusion gene-positive.

Exclusion criteria

Patients who did not meet the inclusion criteria, had missing data, or had additional cancers or immunodeficiency diseases were excluded.

Treatment

Our center adopted treatment recommendations established by Great Ormond Street Hospital (GOSH) due to the lack of pediatric-specific CML guidelines at the time [11]. Treatment followed a tiered approach:

The first step in the management, initiated upon admission, is to start the supportive treatment, together with hydroxyurea (25 to 50 mg/m^2/day). Once results of CML are confirmed, Imatinib would be introduced at a dose of (340mg/m^2), together with the continuation of hydroxyurea until WBC normalization. Leukapheresis is considered for children with severe hyperleukocytosis (WBC > 200 x 10^9/L) and leukostasis symptoms (pulmonary infiltrates, priapism, or severe retinopathy/papilledema).

Following WBC normalization and clinical improvement, patients are transitioned to outpatient care. Regular monitoring includes monthly CBC, repeated BCR-ABL at set points during the first year.

Response evaluation

The European Leukemia Net (ELN) guidelines were used to assess treatment response [12]. This included:

- Hematological response: Defined by specific criteria for WBC count less than 10 x 10^9/L, basophils less than 5%, platelet count less than 450 x 10^9/L, blood film showing no evidence of immature cells (blast, promyelocytes and myelocytes) and clinically non-palpable spleen.
- Cytogenetic response: categorized as minimal (66 - 95% Ph-positive), minor (36 - 65% Ph-positive), major (< 36% Ph-positive), complete cytogenetic response (0% Ph-positive), and partial cytogenetic response (1 - 35% Ph-positive).
- Molecular response: Defined as complete molecular response (undetectable transcript in two samples), major molecular response (BCR-ABL/ABL ratio < 0.1%) (International scale) [11]. Sokal and Hasford risk scores were calculated for each patient [13,19,20].

Results

Twelve children with CML were identified. The median age at presentation was 8.4 years (range, 4.3-13.3 years) with equal distribution among genders (Table 1).

Table 1: Patients characteristics and demographics

Age (n=12)	
Mean	8.4083 Years
Range	4.30 - 13.30 Years
Sex (n=12)	
Male	6
Female	6
Nationality (n=12)	
Kuwaiti	7
Non-Kuwaiti	5

All patients presented with leukocytosis, and most had splenomegaly. The mean size of the spleen at presentation was 10.6 cm below the costal margin (range, 2-16 cm). Most of the patients' WBC were more than 50 X 10^9 (11/12). The median value for the hemoglobin (Hb) was 87 g/l, and for platelets were 575× 10^9/L. The mean value for the WBC at presentation was 358 x 10^9 (Table 2). The Sokal and Hasford scores for the patients are shown at table 3 below.

Table 2: Clinical and hematological features of children with CML at presentation

Features	Total Population (n = 12)
Hemoglobin level (g/L)	
Median	87
Mean	90
Range	68-119
Leukocyte count (X 10^9 /L)	
Median	315
Mean	345
Range	8.8-800
Platelet count (X 10^9/L)	
Median	575
Mean	585
Range	198-1105
Spleen size (in cm below costal margin)	
Median	12
Mean	10.6
Range	2-16

During the first few days, four out of twelve patients (25%) required leukapheresis, a procedure that removes excess white blood cells from the circulation. This intervention aimed to rapidly reduce the white blood cell count to prevent a potential complication known as acute tumor lysis syndrome (TLS). Additionally, hydroxyurea, a medication that helps lower white blood cell production, was administered to nine patients (75%). These findings emphasize the importance of promptly addressing leukocytosis in children with CML to prevent TLS. All patients were initially eligible for first-line treatment with Imatinib at a dose of 375 mg/m^2 and responded well. Within two weeks of medication, WBC and platelet levels in ten patients showed near normalization (mean WBC: 10.9 x 10^9/L). (Tables 4, 5)

Table 3: Prognostic risk scores for the population*

Risk	SOKAL	SOKAL 2	Hasford	EUTOS
Low	5	6	6	6
Intermediate	2	1	1	0
High	2	2	2	3
Total (n=9)	9	9	9	9

*The numbers denote the number of children for each category

Table 4: Levels of WBC at different intervals after treatment

Time Intervals	N	Minimum	Maximum	Mean	Std. Deviation
WBC at Presentation	12	35.9	722.0	385.542	201.4224
WBC at 2weeks	10	4.6	38.4	10.940	10.0070
WBC at 2months	10	3.7	12.6	7.860	2.7969

WBC at 6months	10	2.9	10.5	7.420	2.6050
Valid N (listwise)	10				

Table 5: Levels WBC and platelets at presentation and at one-year post-treatment

	platelets at presentation (X 10^9)	platelets at one year ($X10^9$)	WBC at presentation ($X10^9$)	WBC at one year ($X10^9$)
n	12	12	12	12
Mean	601.17	283.833	358.542	7.933
Median	575.00	263.500	365.000	8.350
Minimum	321	189.0	35.9	3.4
Maximum	1105	590.0	722.0	12.7

Similarly, PCR-ABL levels, a marker of treatment efficacy, showed a significant decrease at three months, where the mean PCR-ABL1 value was 5, with a range of 0.0004 to 20. (Table 6)

Table 6: Results for PCR-ABL for the patients at diagnosis and different intervals

PCR-ABL (Time Intervals)	N	Minimum	Maximum
PCR-ABL at Presentation	11	12.0	86.0
PCR-ABL at 3 months	5	0.0004	20.0000
PCR-ABL at 6 months	5	0.0033	1.1000
PCR-ABL at one year	7	0.0002	0.0900
PCR-ABL at 2 years	9	0.0004	49.0000
PCR-ABL at 3 years	6	0.0001	0.0500
PCR-ABL at 4 years	5	0.0003	0.2100
PCR-ABL at 5 years	5	0.0002	0.0220

Imatinib treatment yielded positive results within three months. Eleven patients (91.6%) achieved complete hematological response (CHR), defined by specific criteria for white blood cell count, blood cell types, and spleen size. By the six-month mark, all patients were in complete hematological remission. At twelve months, all patients achieved major molecular response indicating a significant reduction in BCR-ABL1 levels. However, three patients eventually lost molecular response and required second-line TKIs (Dasatinib). One child progressed to accelerated phase and received Dasatinib. Another patient switched to Dasatinib due to TKI-related complications, despite achieving molecular remission. None of the patients required bone marrow transplantation. Three patients transitioned to adult care, and two reportedly remained in remission off-treatment.

Discussion

Kuwait's centralized referral system for childhood leukemia ensures all CML patients receive diagnosis and treatment at a single center with expertise in managing this rare disease. This likely contributes to the consistency in treatment approaches observed in our study population. CML is a rare disease in children with a very low incidence worldwide [14]. Our study reflects this rarity, with only 13 patients diagnosed over a decade, representing 2% of childhood leukemia cases (0-16 years). The mean age at diagnosis (eight years) and equal gender distribution aligns with established findings.

All patients presented with leukocytosis, often with very high white blood cell counts. Splenomegaly and peripheral blood blasts were common, while hemoglobin levels were typically low. This aggressive presentation necessitated immediate management with leukapheresis and/or hydroxyurea in many cases.

Similar to other studies, our patient population exhibited a larger spleen size, higher baseline white blood cell counts, and higher platelet counts compared to adults [7]. Despite these aggressive features, children responded well to supportive care and TKI therapy, achieving excellent outcomes.

The introduction of TKIs has significantly improved CML outcomes worldwide [18].

Consistent with this, nearly all our patients responded well to imatinib treatment and tolerated it with minimal complications. Long-term follow-up revealed a lack of response in some patients, prompting a switch to second-line TKIs like Dasatinib. Gastrointestinal toxicities, the most frequent side effects of TKIs, were the primary reason for Imatinib discontinuation in some cases [12]. These patients tolerated Dasatinib well and maintained molecular remission. Notably, only one child progressed to acute blastosis, a known complication reported in the literature [21].

Treatment adherence was high, with most patients continuing medication throughout their follow-up at our center. However, the lack of consensus on treatment cessation for children with CML, similar to adults, presents a challenge [16]. Two patients who transitioned to adult care reportedly discontinued treatment while remaining in remission. Our study is limited by missing data due to reliance on paper records, which are susceptible to loss over time. Additionally, the lack of a standardized follow-up protocol hindered patient tracking and proactive investigation planning. Implementing electronic medical records and a dedicated CML follow-up flowsheet could significantly improve data collection and patient management.

Conclusion

CML is a rare disease in children with distinct presentation, response, and outcome compared to adults. This study highlights the effectiveness of TKI therapy in achieving good outcomes in children with CML. While all patients initially responded well, some required a switch to second-line therapy due to lost molecular response. Our findings support the distinct presentation of childhood CML compared to adults, often characterized by more aggressive features. However, scarce evidence exists regarding the optimal treatment duration for this

vulnerable population. Further research efforts are necessary in our region to address this gap and explore other crucial areas such as minimizing TKI side effects and developing better risk stratification models for children with CML.

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Ethical Approval

Ethical approval for the study was obtained from the Standing Committee for Coordination of Health and Medical Research and the Pediatric Departments' Council at Kuwait's Ministry of Health (Approval Number: P116-13MK-01).

Human and animal Guidelines

The research protocol was conducted in accordance with the principles of the Helsinki Declaration.

Informed Consent (Not Applicable)

Author Contributions

- Dr Maha: Data acquisition, research design and drafting of manuscript
- Dr Mohammad: Data acquisition
- Dr Nashwa: Data acquisition
- Dr Mariam: Statistical analysis and drafting of manuscript
- Dr Mona: Data acquisition, research design and drafting of manuscript
- Dr Sundos: Analysis, critical revision of manuscript and approval of final version
- Dr Eman: Data acquisition and analysis

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Disclosure

The author(s) report no conflicts of interest in this work.

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