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Original Article

Biochemical Abnormalities Associated with High Dose Methotrexate (HDMTX) Toxicities in Children with ALL and NHL

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ABSTRACT

Introduction: *Childhood leukemia and lymphoma are two common malignancies that cause morbidity and mortality. Acute lymphoblastic leukemia (ALL) is the most prevalent type, while non-Hodgkin lymphoma (NHL) is the third most common. Treatment for these malignancies often includes high-dose methotrexate (HD-MTX), which can cause significant toxicity. MTHFR gene polymorphisms have been linked to increased toxicity. This study aims to document the biochemical abnormalities associated with HDMTX toxicity in children.* ***Methods & Materials:*** *This study was conducted prospectively in the Department of Pediatric Hematology & Oncology at BSMMU in Dhaka between July 2015 and December 2015. The study population included children under the age of 15 who were diagnosed with Acute Lymphoblastic Leukemia (ALL) or Non-Hodgkin Lymphoma (NHL) and were receiving high-dose methotrexate (HDMTX) as part of their treatment.* ***Results:*** *The study population consisted of 30 patients with childhood malignancy, with Acute Lymphoblastic Leukemia (ALL), being the most common malignancy 76.7% followed by non-Hodgkin lymphoma 23.3%. Biochemical toxicities such as elevated transaminases and raised creatinine were observed in 6.7% and 3.3% of patients, respectively, but no neurotoxicity was reported. Hematological toxicities such as neutropenia*

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and thrombocytopenia were observed in 26.7% and 3.3% of patients, respectively, with a higher occurrence in cycles 2 and 3 compared to cycle 1.Hematological recovery occurred by day 12 in most cases. ***Conclusion:*** *This study found that elevated transaminases and raised creatinine were the major biochemical toxicities associated with HDMTX infusion, while neutropenia and thrombocytopenia were the major hematological toxicities observed.*

Keywords: *HDMTX, ALL, NHL, Abnormalities*

INTRODUCTION

Acute lymphoblastic leukemia (ALL) and Non-Hodgkin Lymphoma (NHL) are two of the most common types of childhood malignancies, which are responsible for significant morbidity and mortality [1]. Leukemia is a clonal disease that results from genetic mutations and the transformation of a single early progenitor myeloid or lymphoid cell. Although much research has been conducted, the exact causes of acute leukemia in children remain largely unknown [2]. Among childhood leukemia cases, the majority are classified as acute lymphoblastic leukemia (ALL) [3]. On the other hand, lymphomas are the third most common group of cancers in children, with non-Hodgkin's lymphomas (NHLs) accounting for approximately 40-50% of these diagnoses [4]. Non-Hodgkin's lymphomas are a heterogeneous group of lymphoid neoplasms, with lymphoblastic lymphoma of the precursor B- or T-cell types (LBL) being one of the three major subgroups of childhood NHL according to the World Health Organization Classification. Children with LBL are typically treated according to childhood acute lymphoblastic leukemia (ALL) protocols, which include the administration of high-dose methotrexate (HD-MTX) [5]. While HD-MTX treatment is effective, it often causes significant toxicities, leading to post-HDMTX toxicity. This toxicity is associated with an increased risk of infections and interruption of maintenance treatment, which has been linked to a reduced cure rate. The enzyme methylene tetrahydrofolate reductase (MTHFR) is responsible for the irreversible conversion of 5,10-methylene tetrahydrofolate to 5 methyl tetrahydrofolates, which play a crucial role in DNA synthesis and methylation [6]. However, genetic polymorphisms of the MTHFR gene have been linked to altered enzyme activity, leading to increased HDMTX toxicity. The manifestations of HDMTX toxicity are diverse and may include bone marrow depression, mucositis, diarrhea, liver and kidney dysfunction, dermatitis, and neurological disturbances. While these toxicities are well known, severe and even fatal reactions have also been reported following the administration of HDMTX, highlighting the need for careful monitoring and management of these patients [7]. Given the prevalence of ALL and NHL in children in Bangladesh, it is crucial to study the biochemical abnormalities associated with HDMTX toxicities in this population. This study aimed to observe and document the various biochemical abnormalities that arise as a result of HDMTX toxicity in children with ALL and NHL at a tertiary care center in Bangladesh, namely the Bangabandhu Sheikh Mujib Medical University. This study will help to identify

the factors contributing to HDMTX toxicity in this population and ultimately aid in the development of better management strategies for these patients.

METHODS & MATERIALS

This study was conducted prospectively in the Department of Pediatric Hematology & Oncology at BSMMU in Dhaka between July 2015 and December 2015. The study population included children under the age of 15 who were diagnosed with Acute Lymphoblastic Leukemia (ALL) or Non-Hodgkin Lymphoma (NHL) and were receiving high-dose methotrexate (HDMTX) as part of their treatment. The sample size was 150. Data were collected from patients and their parents through detailed history-taking, clinical examination, and hospital documents, and included details on drug dose, duration, laboratory values, and possible toxicities. The data were recorded and analyzed using the statistical package for social science (SPSS) software, Version 23.0, and statistical tests such as unpaired t-test and chi-square test were performed to verify the results. The ethical implications of the study were addressed by obtaining informed consent from study subjects/attendants in compliance with the Helsinki Declaration for Medical Research Involving Human Subjects 1964. A p-value of less than 0.05 was considered statistically significant.

Inclusion criteria

- Children aged 1 to 15 years suffering from ALL or NHL who are on high-dose methotrexate (3-5 grams/m^2)

Exclusion criteria

- Children with ALL or NHL who are not receiving HDMTX

RESULTS

Table I shows a common pattern of childhood malignancy such as ALL, Non-Hodgkin lymphoma, which was 23(76.7%) and 07(23.3%) respectively.

Table I: Pattern of childhood malignancy of the study population (N=30).

	Number	Percentage
ALL	23	76.7
Non-Hodgkin lymphoma	07	23.3

Table II shows the mean age was 6.11(±3.31) years, the minimum age was 1 year and the maximum age was 12 years.

Table II: Distribution of age according to study population (N=30).

Age group	Frequency	Percent
1-3 years	7	23.33
3-6 years	8	26.67
6-9 years	9	30
9-12 years	6	20
Total	30	100
Mean SD	6.11(±3.31)	Range 1-12

Figure 1 shows majority 60% were male and 40% were female, and the male-female ratios were 1.55:1.

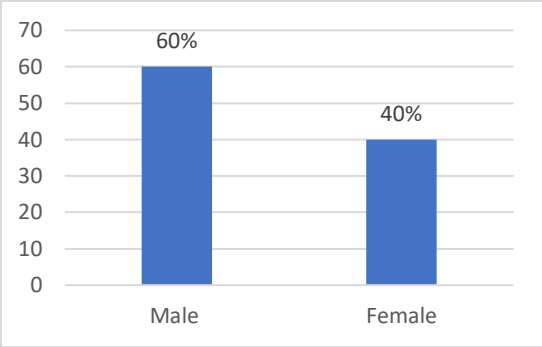

Figure 1: Sex distribution of the study population (N=30)

Transient elevation of serum alanine transaminase levels up to 5 times the upper limits of normal occurred in 6.67% of cases. Nephrotoxicity (raised serum Creatinine level) occurred in 3.3% of patients which became normal in subsequent follow-up but neurotoxicity (seizures) was not observed in any patient (**Table III)**.

Table III: Observed Biochemical Toxicities with HDMTX Infusion (N=30).

Patient no, 30	**Cycle 1, no. (%)**	**Cycle 2, no. (%)**	**Cycle 3, no. (%)**	**Total, no. (%)**
Elevated transaminases	1(6.25)	00	1(16.67)	02(6.7)
Raised Creatinine	01(6.25)	00	00	1(3.3)

Hematological toxicity in the four's neutropenia (ANC <1 x109/L) was observed in 9.9% of patients whereas thrombocytopenia (platelet count <50.0 x 109/L) was associated with 3.3% of patients only. This change starts to occur from day 4 onwards and hematological recovery usually occurred by day 12 as evidenced by the day 12 median ANC and median platelet count. Neutropenia was more in cycles 2&3 than 1(2=3>1) and thrombocytopenia was more in stage 3 than 1&2 (3>2>1) but the p value was not significant in these cases (**Table IV)**.

Table IV: Observed Hematological Toxicities with HDMTX Infusion (N=30).

Patient no, 30	Cycle 1, no.	Cycle 2, no. (%)	Cycle 3, no. (%)	Total, no.(%)
Neutropenia	04(25.0)	2(25.0)	2(33.33)	08(26.7)
Thrombocytopenia	01(9.9)	00	00	01(3.3)

DISCUSSION

The study aimed to identify the biochemical and hematological toxicities associated with High Dose Methotrexate (HDMTX) infusion in children with Acute lymphoblastic Leukemia (ALL) and Non-Hodgkin's Lymphoma (NHL) at a tertiary care center in Bangladesh. The study found that elevated transaminases and raised

creatinine were the major biochemical toxicities associated with HDMTX infusion, while neutropenia and thrombocytopenia were the major hematological toxicities observed. The study population consisted of 30 children, of whom 23 had ALL (76.7%) and 7 had NHL (23.3%). The age of the patients ranged from 1 to 12 years, with a mean of 6.11 years (±3.31). The male-female ratio was 1.55:1, with 60% being male and 40% female. A study involving 50 children with ALL and NHL examined the effects of HDMTX (9 patients had ALL and 41 patients had NHL), with 87.7% of the patients being male and 12.3% being female [8]. Similar findings were also reported in other studies [9, 10]. The study found that transient elevation of serum alanine transaminase levels up to 5 times the upper limits of normal occurred in 6.67% of cases. Another study found that serum alanine transaminases (ALT) levels occurred in 12.5% of cases, ranging from 5 to 30 times higher than the normal limit [11]. More studies also reported similar findings [12, 13]. This finding is consistent with previous studies that have reported elevated transaminases as a common side effect of HDMTX infusion. The raised serum creatinine level was observed in 3.3% of patients, which became normal in subsequent follow-ups. Another study reported that serum creatinine levels were observed in 22.5% of patients [14]. More studies found similar findings [15,16] This finding is consistent with previous studies that have reported nephrotoxicity as a common side effect of HDMTX infusion. However, neurotoxicity (seizures) was not observed in any patient in this study. The study found that neutropenia (ANC <1 x109/L) was observed in 9.9% of patients, while thrombocytopenia (platelet count <50.0 x 109/L) was associated with 3.3% of patients only. Another study found neutropenia (24.8%) and thrombocytopenia (2%) [17]. This change starts to occur from day 4 onward, and hematological recovery usually occurs by day 12, as evident by the day 12 median ANC and median platelet count. Neutropenia was more in cycles 2&3 than 1(2=3>1) and thrombocytopenia was more common in stages 3 than 1 and 2 (3 > 2 > 1), but the p-value was not significant in these cases. In total, Hematological toxicity in the form of v3.0 neutropenia was observed in 26.7% which is the same as what other studies have reported at 25% [18, 19].

Limitations of the study

The small sample size and short study period may affect the generalizability of the findings to larger populations or over longer periods.

CONCLUSION

This study found that elevated transaminases and raised creatinine were the major biochemical toxicities associated with HDMTX infusion, while neutropenia and thrombocytopenia were the major hematological toxicities observed. The findings of this study are consistent with previous studies that have reported these toxicities. Further studies with larger sample sizes and control groups are needed to confirm these findings and to determine the optimal management of HDMTX toxicities in children with ALL and NHL.

RECOMMENDATIONS

In this study, children receiving high-dose methotrexate (HDMTX) for the treatment of ALL and NHL should be closely monitored for potential biochemical and hematological toxicities. Specifically, monitoring of liver function tests, serum

creatinine levels, and blood counts should be performed regularly to detect and manage any toxicities that may arise. Additionally, it may be beneficial to consider adjusting the dosing and schedule of HDMTX based on age and individual patient characteristics to minimize the risk of toxicities while still maintaining efficacy. Education and counseling of patients and families on the potential side effects of HDMTX treatment can also help to improve adherence to monitoring and reduce the severity of toxicities. Finally, further studies are needed to explore the impact of various treatment regimens on toxicities in this population and to identify additional strategies for optimizing treatment outcomes while minimizing toxicity.

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