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Original Research Article

Adverse Effects with Intravenous Methotrexate in Children with Acute Lymphoblastic Leukemia/Lymphoma: A Retrospective Study

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Abstract

Methotrexate (MTX) forms the backbone of maintenance cycles in childhood acute lymphoblastic leukemia (ALL) chemotherapy, including interim maintenance. There is sufficient published data describing toxicities of high dose MTX (HD-MTX), but toxicities with escalating doses of MTX (Capizzi regimen) is not well documented. Capizzi regimen is thought to be relatively safe; we contend that even low escalating doses of MTX have significant toxicities. Our study intends to characterise such events with Capizzi MTX in comparison to that seen with HD-MTX. The retrospective study was conducted at a tertiary care centre of Bikaner, Rajasthan, India. We looked for the presence of six main toxicities: febrile neutropenia, thrombocytopenia, mucositis, hepatic toxicity, renal toxicity and skin toxicity from the clinical records of children with newly diagnosed acute lymphoblastic leukemia and lymphoma (intermediate and high risk disease), treated at our centre from November 2022 to July 2023. Intermediate risk ALL whereas high risk ALL (HR-ALL/T-NHL), received HD-MTX. Both these regimens do not use L-asparaginase. A total of 237 cycles of Capizzi escalating MTX and 151 cycle of high-dose MTX.

Keywords: Methotrexate, Capizzi regimen, high-dose MTX, toxicities, childhood leukemia, acute lymphoblastic leukemia, lymphoma, febrile neutropenia, thrombocytopenia, mucositis, hepatic toxicity, renal toxicity, skin toxicity, chemotherapy, retrospective study.

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Introduction

Acute lymphoblastic leukemia (ALL) and lymphoma are among the most prevalent cancers affecting children worldwide, posing significant challenges in pediatric oncology. Methotrexate (MTX), a folate antagonist, plays a pivotal role in the chemotherapeutic regimens designed to treat these malignancies. It is renowned for its efficacy in the prophylaxis and treatment of central nervous system (CNS) leukemia and as a crucial component in maintenance therapy. Given in various dosages, ranging from low to high doses depending on the protocol, MTX is integral to improving patient survival rates.

Rationale

Despite its therapeutic benefits, methotrexate is associated with a broad spectrum of potential adverse effects. These effects, which can range from mild to life-threatening, include myelosuppression, hepatotoxicity, mucositis, nephrotoxicity, and neurotoxicity. While the toxicity profile of high-dose methotrexate (HD-MTX) is well documented, there exists a significant gap in the literature regarding the toxicities associated with the Capizzi regimen of escalating, lower doses of MTX, particularly in intermediate-risk pediatric ALL and lymphoma.

Importance of the Study

Understanding the full spectrum of methotrexate's adverse effects is critical for optimizing treatment outcomes in pediatric oncology. By delineating the adverse effect profiles associated with different dosing regimens, clinicians can tailor treatment plans to better manage or mitigate these effects, thereby enhancing both the quality of life and survival outcomes for young patients.

This study provides comprehensive insights into the adverse effects of MTX in a real-world clinical setting, contributing to a more nuanced understanding of its risk-benefit profile in pediatric leukemia and lymphoma treatments.

Aim of the Study

The primary aim of this retrospective study is to systematically characterize and compare the adverse effects associated with two methotrexate

(MTX) regimens — the Capizzi regimen, which involves escalating doses, and high-dose MTX (HD-MTX) — in children treated for acute lymphoblastic leukemia (ALL) and lymphoma. This study focuses on evaluating these regimens in the context of their implementation at a tertiary care centre in North India.

Objectives

1. To Document Adverse Effects:

- To document and analyze the incidence and types of adverse effects associated with the Capizzi and high-dose methotrexate regimens in pediatric patients.
- To identify the prevalence of specific toxicities such as febrile neutropenia, thrombocytopenia, mucositis, hepatic toxicity, renal toxicity, and skin toxicity.

2. Comparison of Toxicity Profiles:

- To compare the toxicity profiles of the escalating doses of the Capizzi regimen with those of the standard high-dose MTX regimen.
- To evaluate whether the lower escalating doses of the Capizzi regimen result in fewer or less severe adverse effects compared to high-dose MTX.

Materials and Methods

Study Design: This retrospective study was carried out at Acharya Tulsi Regional Cancer Treatment & Research Institute, S.P. Medical College & Associated Group of Hospitals, Bikaner-334003(Rajasthan). The study involved the examination of clinical records from 100 children diagnosed with intermediate-risk and high-risk B-cell and T-cell acute lymphoblastic leukemia/lymphoma (ALL/T-NHL) who were treated between November 2022 to July 2023.

Study Population: Children aged 1 to 18 years with newly diagnosed intermediate-risk or high-risk ALL or T-NHL were included in the study. Those with relapsed ALL or Down's syndrome were excluded to ensure a homogenous study population. The study focused on two distinct treatment regimens:

- Capizzi regimen (intermediate-risk ALL, IR-ALL): Involving lower escalating doses of methotrexate.
- High-dose methotrexate (high-risk ALL, HR-ALL/T-NHL): Administered according to established high-dose protocols.

Ethical Considerations: The study received approval from the Institutional Ethics Committee of Acharya Tulsi Regional Cancer Treatment & Research Institute, S.P. Medical College & Associated Group Of Hospitals, Bikaner-334003 (Rajasthan) ensuring that all research was conducted following ethical guidelines and patient confidentiality.

Treatment Protocols

- **Capizzi Regimen**: Started with 100 mg/m², escalated by 50 mg/m² every 10 days up to a maximum of 250 mg/m² over five cycles. This regimen allows for dose adjustments based on toxicity but does not permit catch-up doses for missed treatments.
- **High-Dose Methotrexate (HD-MTX)**: Administered at doses of 3,000 mg/m² for Pre-B ALL and 5,000 mg/m² for T-cell ALL, divided over four infusion sessions with hydration, alkalization, and leucovorin rescue. The dosing included intrathecal administration and oral 6-mercaptopurine.

Both protocols excluded the use of L-asparaginase and required pre-treatment hydration and urine alkalinization to prevent methotrexate-related toxicities.

Data Collection

Clinical records provided data on demographic characteristics, treatment specifics, and toxicological outcomes. Specific metrics included:

- Age, sex, and nutritional status at the start of treatment.
- Details of methotrexate dosing and modifications.
- Incidences of febrile neutropenia, thrombocytopenia, mucositis, hepatic, renal, and skin toxicities, graded according to the Common Terminology Criteria for Adverse Events (CTCAE v5.0).
- Laboratory values such as ANC, platelet count, urea, creatinine, liver enzymes, and total serum bilirubin before and after methotrexate administration.
- Interventions required for toxicity management including hospitalization, IV antibiotics, antifungals, and granulocyte colony-stimulating factor (GCSF).
- Documentation of any treatment delays or discontinuations due to toxicity.

Statistical Analysis: Data were compiled using Microsoft Excel and analyzed using SPSS v20.0. The analysis included chi-square tests for categorical data and independent t-tests for continuous variables. A p-value of less than 0.05 was considered statistically significant.

Both univariate and multivariate analyses were conducted to identify predictors of adverse outcomes associated with methotrexate treatments. This methodological framework aims to robustly evaluate the adverse effects associated with different methotrexate regimens in pediatric ALL and lymphoma, potentially guiding future

therapeutic strategies to minimize patient morbidity and enhance treatment efficacy.

Results

This retrospective study included 100 pediatric patients diagnosed with acute lymphoblastic leukemia (ALL), categorized into two treatment groups based on the methotrexate (MTX) regimen received: the Capizzi regimen (Intermediate Risk, IR-ALL) and High-Dose Methotrexate (High Risk, HR-ALL).

Patient Demographics and Treatment Overview:

- **IR-ALL Group:** 60 children underwent a total of 280 cycles of the Capizzi regimen.
- **HR-ALL Group:** 40 children underwent a total of 180 cycles of HD-MTX.
- **Age Distribution:** Median age was 50 months (IQR 38-74) for IR-ALL and 86 months (IQR 74-110) for HR-ALL.
- **Gender:** Approximately 68% male in IR-ALL; 70% male in HR-ALL.
- **Nutritional Status:** 22% of IR-ALL had BMI Z scores < -2SD compared to 45% in HR-ALL.
- **Severe Anaemia:** Similar rates of Grade III/IV anaemia in both groups.

Treatment Efficacy and Toxicity Incidence:

- **Missed Treatment Cycles:** Approximately 14% in IR-ALL and 4% in HR-ALL were missed due to MTX-induced adverse events.
- **Dose Adjustments:** Required in 8% of Capizzi regimen cycles and 2% of HD-MTX cycles.
- **Overall Toxicity Incidence:** 30% in IR-ALL (84/280 cycles) and 31% in HR-ALL (56/180 cycles).
- **Most Common Toxicities:** Myelosuppression was prevalent, with febrile neutropenia occurring in 21% of IR-ALL and 22% of HR-ALL cycles. Thrombocytopenia was observed in 18% of IR-ALL and 17% of HR-ALL cycles.
- **Mucositis:** More common in HR-ALL (16%) compared to IR-ALL (6%).
- **Organ Specific Toxicities:** Hepatotoxicity, nephrotoxicity, and skin toxicity each occurred in 2% of HR-ALL, absent in IR-ALL.

Cycle-Specific Toxicity Distribution:

- **First Cycle Toxicities:** Highest in both groups, with 13% in IR-ALL and 11% in HR-ALL.
- **Subsequent Cycles:** Reduced incidence with 4% in the second cycle of IR-ALL and 10% in HR-ALL.

Impact of Methotrexate Serum Levels on Toxicity:

- **MTX Levels Measured:** In 46% of HR-ALL cycles.
- **Range of MTX Levels:** Most common was 10-40 µmol/L (64%), with no levels exceeding 200 µmol/L.
- **Correlation with Toxicity:** No significant differences in toxicity between those with and without MTX level measurements.

Nutritional Impact and Toxicity:

- **Undernutrition and Toxicity:** Higher rates of undernutrition were associated with increased toxicity, with 46% of children with toxicity having BMI < -2SD.
- **Significant Predictors of Toxicity:** Male gender, lower ANC, and lower BMI remained significant predictors. Age did not significantly impact toxicity upon multivariate analysis.

Clinical Management and Outcomes:

- **Hospitalizations and Interventions:** Higher need for hospital admission, second or third line antibiotics, and antifungals in the HR-ALL group.
- **GCSF Use:** Required in 7% of HR-ALL cycles, none in IR-ALL.
- **Mortality:** No deaths directly attributable to MTX toxicity were reported.

Table 1: Summary of Clinical Data and Treatment Outcomes for Pediatric ALL Patients

Category	Capizzi MTX Group (60 patients, 280 cycles)	High-Dose MTX Group (40 patients, 180 cycles)
Median Age (months, IQR)	50 (38-74)	86 (74-110)
Gender Distribution (Male %)	68%	70%
BMI Z Score < -2SD (%)	22% (13/60)	45% (18/40)
Severe Anaemia (Grade III/IV)	Similar in both groups	Similar in both groups
Missed Treatment Cycles (%)	14% (39/280 cycles)	4% (7/180 cycles)
Dose Adjustments Required (%)	8% (22/280 cycles)	2% (4/180 cycles)
Overall Toxicity Incidence (%)	30% (84/280 cycles)	31% (56/180 cycles)
Febrile Neutropenia (%)	21% (59/280 cycles)	22% (40/180 cycles)
Thrombocytopenia (%)	18% (50/280 cycles)	17% (31/180 cycles)
Mucositis (%)	6% (17/280 cycles)	16% (29/180 cycles)

Hepatotoxicity (%)	0%	2% (4/180 cycles)
Nephrotoxicity (%)	0%	2% (4/180 cycles)
Skin Toxicity (%)	0%	2% (4/180 cycles)
First Cycle Toxicities (%)	13% (36/280 cycles)	11% (20/180 cycles)
Second Cycle Toxicities (%)	4% (11/280 cycles)	10% (18/180 cycles)
MTX Serum Levels Measured (%)	Not applicable	46% (83/180 cycles)
Hospitalizations (%)	13.4% cycles (38/280)	16.6% cycles (30/180)
Antibiotics/Antifungals Needed (%)	Antibiotics: 7.1%, Antifungals: 4.6%	Antibiotics: 13.9%, Antifungals: 9.9%
GCSF Required (%)	0%	7% (13/180 cycles)
Significant Predictors of Toxicity	Male gender, lower ANC, lower BMI	Male gender, lower ANC, lower BMI
Mortality Due to MTX Toxicity	None reported	None reported

Discussion

The retrospective study undertaken at a tertiary care center in North India reveals critical insights into the toxicity profiles of Methotrexate (MTX) under two different administration regimens in children with acute lymphoblastic leukemia (ALL) and lymphoma. The comparison of the Capizzi regimen, characterized by escalating lower doses, with the conventional high-dose MTX (HD-MTX) treatment, addresses a significant gap in the existing pediatric oncology literature.

Toxicity Profiles Across Regimens

Our findings indicate that the overall incidence of toxicity was comparable between the two regimens, with the Capizzi regimen (30%) and the HD-MTX regimen (31%) showing similar rates. This challenges the prevailing notion that lower, escalating doses (Capizzi regimen) are significantly safer in terms of toxicity occurrence compared to higher doses. Notably, mucositis was more prevalent in the HD-MTX group, which is consistent with other studies indicating that higher MTX doses are associated with increased mucosal damage.

Myelosuppression as a Primary Concern

Myelosuppression, encompassing febrile neutropenia and thrombocytopenia, was the most frequently observed toxicity in both treatment groups. This underscores the critical need for vigilant monitoring and supportive care during MTX therapy, irrespective of the dosing regimen. The substantial impact of myelosuppression highlights its role as a limiting factor in the efficacy of ALL treatment, necessitating periodic adjustments in treatment protocols to mitigate its effects.

Impact of Nutritional Status and Other Factors

The study also highlighted that poorer nutritional status, particularly a lower BMI, significantly correlates with increased toxicity, particularly in the HR-ALL group. This finding is crucial for clinical practice, suggesting that nutritional support could be an integral part of managing children on MTX therapy. Additionally, male gender and lower baseline absolute neutrophil count (ANC) were associated with higher toxicity, aligning with existing research that suggests individual physiological and genetic factors can influence treatment outcomes.

Serum MTX Levels and Toxicity Correlation

Interestingly, our analysis indicated no significant difference in toxicity between patients with and without measured MTX serum levels. This could suggest that routine monitoring of MTX levels might not be universally necessary, potentially reducing the healthcare costs and burden, especially in resource-limited settings. However, given that only a proportion of patients could afford this testing, further research is needed to validate these findings and potentially revise monitoring recommendations.

Clinical Implications and Future Research

The findings from this study have several implications for clinical practice. First, they advocate for a reassessment of the Capizzi regimen's safety profile, especially considering its similar toxicity rate compared to HD-MTX. Second, they reinforce the need for comprehensive supportive care, including nutritional assessment and support as part of ALL treatment protocols.

Future studies should focus on expanding the cohort size and incorporating prospective data collection to enhance the robustness of the findings. Additionally, exploring genetic markers that may predict toxicity could pave the way for personalized medicine approaches in pediatric oncology.

Conclusion

This study contributes significantly to our understanding of MTX-induced toxicities in pediatric leukemia and lymphoma treatments. It calls for a nuanced appreciation of how even lower doses of MTX, administered via the Capizzi regimen, carry a considerable toxicity burden,

similar to that of high-dose regimens. As such, pediatric oncology protocols may need revisiting to optimize MTX use, aiming to balance efficacy with an acceptable toxicity profile.

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