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Acute Kidney Injury in Methotrexate treated Leukemia

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Abstract

Background: The study was performed to know the incidence of acute kidney injury within 48 hours following high dose methotrexate administration in children with high-risk B cell Acute Lymphoblastic Leukemia along with its risk factors and toxicities. Most studies have been conducted in adults and have included non-Hodgkin lymphoma along with leukemia. There is a paucity of data regarding the burden of Acute kidney injury with Methotrexate use in the pediatric age group with B cell Acute Lymphoblastic Leukemia.

Methods: It was a prospective observational study conducted at the pediatric ward of All India Institute of Medical Sciences, New Delhi between September 2019 to June 2021. Children between 1 to 18 years with high-risk B lineage Acute Lymphoblastic Leukemia planned for high-dose methotrexate at 3gm/m^2 were enrolled. The measurement of serum creatinine was done at baseline, 24 and 42 hours while serum methotrexate at 24 and 42 hours, adverse reactions were assessed till 14th day of methotrexate administration.

Results: The incidence of Acute kidney injury and severe Acute kidney injury (stages 2 and 3) at 42 hours of high dose methotrexate infusion was 24.3% and 12.8% respectively. Low serum albumin was associated with an increased risk of Acute kidney injury ($p = 0.004$). Transaminitis and thrombocytopenia were common toxicities.

Conclusions: Acute kidney injury is common following high dose methotrexate administration in B cell Acute Lymphoblastic Leukemia. Low serum albumin level increases renal toxicity following methotrexate infusion. The measures to prevent renal toxicity should be instituted promptly in high risk groups.

Keywords: Acute kidney injury; Acute lymphoblastic leukemia; Methotrexate

Declarations

Ethics approval and consent to participate: This study was approved by the Institute Ethics Committee of All India Institute of Medical Sciences, New Delhi, India (IECPG-401/27.06.2019, RT-20/29.08.2019) and informed consent was obtained from participants before the enrollment.

Consent for publication: Informed consent was obtained from the patient for the publication of identifying features along with the manuscript.

Availability of data and materials: The full data set supporting this research is available upon request by the readers.

Competing interest: None

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Authors' contributions: BKS: study design, literature search, data acquisition, data analysis, statistical analysis, manuscript drafting, critical review of the manuscript for intellectual contribution. RS: critical review of the manuscript. AS, AG, JPM: data analysis and critical review of the manuscript. All authors have read and approved the final manuscript.

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BACKGROUND

Acute Lymphoblastic Leukemia (ALL) is the most common childhood malignancy accounting for 20% of all cancers before 20 years of age. Standard risk patients who constitute > 50% of patients with childhood Acute Lymphoblastic Leukemia have a better prognosis as compared to high risk. The five year overall survival is 90% in high income countries whereas nationwide data in relation to mortality is lacking. Long-term survivors of childhood Acute Lymphoblastic Leukemia are at increased risk for late morbidity and mortality due to cancer treatment [1]. Indian data suggests the overall survival in Acute Lymphoblastic Leukemia is from 45% to 80% [2]. The lower socioeconomic status is associated with poor outcomes in Acute Lymphoblastic Leukemia [3].

Methotrexate has been used in various dose ranges in childhood Acute Lymphoblastic Leukemia, non-Hodgkin lymphoma, and osteosarcoma [4]. The dose ≥ 500 mg/m² is considered to be a high dose Methotrexate (HDMTX). Acute kidney injury (AKI) is common in Acute Lymphoblastic Leukemia patients receiving high-dose Methotrexate despite ensuring standard of care. The incidence and risk factors of severe Acute kidney injury associated with high-dose Methotrexate have not been adequately studied in children with high-risk B cell Acute Lymphoblastic Leukemia. The causes of renal impairment in high-dose methotrexate have not been clearly understood. Methotrexate and its metabolites have a direct effect on renal tubules. It also causes changes in pre-glomerular resistance and has a direct effect on the glomerulus.

High dose methotrexate forms a major therapy in treating and preventing leukemia involving the central nervous system [5]. The adverse effects include bone marrow suppression, hepatotoxicity, nausea and vomiting, mucositis manifesting as diarrhea, abdominal pain, and oral ulcerations, pulmonary toxicity leading to hypersensitivity pneumonitis, neurologic toxicity leading to acute or subacute encephalopathy [6, 7].

One of the major issues with the treatment of High dose methotrexate is Acute kidney injury. The rise in serum creatinine in relation to the High dose methotrexate infusion has been associatedwith decreased methotrexate clearance in children with Acute Lymphoblastic Leukemia [8]. The identification and incidence of High dose methotrexate-induced renal damage becomes valuable to prevent its toxicity. There are various factors including the age of the patient, the dosage of the drug, and serum albumin which predict the toxicity of methotrexate. The objectives of the study are to measure the incidence of Acute kidney injury in children receiving High dose methotrexate, risk factors associated with severe Acute kidney injury, and the spectrum of adverse effects in B cell Acute Lymphoblastic Leukemia children.

METHODS

The Prospective observational study was conducted from September 1, 2019, to June 30, 2021, in pediatric inpatients with B cell Acute Lymphoblastic Leukemia in the Pediatric Oncology unit of All India Institute of Medical Sciences, New Delhi, India. Patients with B Acute Lymphoblastic Leukemia planned for High dose methotrexate (total 4 cycles) were included. The following were the inclusion criteria: (a) age 1 to 18 years, (b) newly diagnosed Acute Lymphoblastic Leukemia with high-risk B- lineage, (c) planned for therapy with methotrexate at 3 g/m^2 infusion over 24 hours, (c) absolute neutrophil count > 750/mm^3 and platelet count > 100,000/mm^3. These were the exclusion criteria: (a) Evidence of pleural effusion/ascites, (b) Clinical evidence of infection, diarrhea, mucositis, (c) Therapy with drugs known to interfere with Methotrexate clearance, (d) Relapsed Acute Lymphoblastic Leukemia, (e) Estimated GFR (Glomerular filtration rate) < 90 ml/min/1.73 m^2, (f) Total serum bilirubin > 2 mg/dl and serum alanine or aspartate aminotransferase > 10 times upper limit of normal.

The study was approved by the Institute Ethics Committee of All India Institute of Medical Sciences, New Delhi, India (IECPG-401/27.06.2019, RT-20/29.08.2019). Non-probability consecutive sampling technique was used. Previous studies showed incidence of Acute kidney injury between 9% - 26.2%. Vaishnavi et al, 2015 [9] found Acute kidney injury in 23% cycles. Assuming that Acute kidney injury will occur in about 20% of episodes with B Acute Lymphoblastic Leukemia receiving high-dose methotrexate, with an absolute deviation of ± 10%, the sample size was calculated to be 64 episodes. Each patient had to receive 4 doses/cycles of High dose methotrexate according to the ICiCLe (Indian Collaborative Childhood Leukemia Study Group) protocol [5]. Hence, a single patient was enrolled multiple times and each enrollment was termed an episode. The variables age, gender, underweight, socio-economic status, and serum vitamin D were expressed in terms of the number of patients while serum albumin, calcium, phosphate, and cycle of Methotrexate infusion were expressed in terms of the number of episodes. A total of 43 patients with 80 episodes were enrolled. A patient information sheet was provided and written consent was obtained from parents. Serum methotrexate and creatinine were collected at 24 hours and 42 hours following High dose methotrexate infusion and were estimated by Microparticle Enzyme Immunoassay [10] and modified Jaffe's method (kinetic method) [11] respectively. Acute kidney injury was defined using the Kidney Disease Improving Global Outcomes (KDIGO) criteria as stage 1 if the rise in serum creatinine was 1.5-1.9 times baseline, stage 2 if 2 - 2.9 times the baseline, and

stage 3 if ≥ 3 times the baseline [12].

Patients with stages 2 and 3 Acute kidney injury were considered to have severe Acute kidney injury. Patients were monitored in daycare follow-up for adverse effects till day 14 from the start of methotrexate infusion.

The risk factors for Acute kidney injury assessed were serum levels of albumin, calcium, phosphate, and vitamin D, along with anthropometric variables and socio-economic status. The serum albumin < 4 g/dl was considered to be hypoalbuminemia, hypocalcemia was considered when serum calcium level was < 9 mg/dl, similarly < 3.5 mg/dl for hypophosphatemia and serum vitamin D < 20 ng/ml was defined for insufficient levels. The socioeconomic status was assessed using a modified Kupuswammy scale.

The demographic and clinical parameters were recorded as per the proforma. The data was entered in Microsoft Excel 2016. Stata software version 64 was utilized for the analysis and calculating a 95% confidence interval. Descriptive statistics like mean with standard deviation, median was used and for inferential statistics, chi-square was used to compare proportion while t-test for comparing the mean between the groups. Statistical significance was set at $p < 0.05$.

Table 1: Baseline patient characteristics

Variables	Results
Age, Years (n = 43 patients)	
Mean ± SD	5.4 ± 2.6
Range	1.8 - 12
Gender, Number (%) (n = 43 patients)	
Male	33 (76.8)
Female	10 (23.2)
Underweight, Number (%) (n = 43 patients)	
No	35 (81.4)
Yes	8 (18.6)
Socioeconomic-status, Number (%) (n = 43 patients)	
Upper	0 (0.0)
Upper Middle	8 (18.6)
Lower Middle	21 (48.9)
Upper Lower	13 (30.2)
Lower	1 (2.3)
Serum Vitamin D, ng/ml (n = 22 patients)	
Mean ± SD	8.4 ± 3.6
Range	4.6 - 18.1
Serum albumin, g/dl (n = 80 episodes)	
Mean ± SD	4.3 ± 0.4
Range	2.7 - 5.2
Serum Calcium, mg/dl (n = 78 episodes)	
Mean ± SD	9.2 ± 0.4
Range	7.9 - 10.3
Serum phosphate, mg/dl (n = 75 episodes)	
Mean ± SD	5 ± 0.7
Range	3.0 - 6.4
Cycle/Dose of Methotrexate (n=80 episodes)	
First	23 (28.75)
Second	22 (27.50)
Third	18 (22.50)
Fourth	17 (21.25)

RESULTS

Among 43 patients with 80 episodes **(Table 1),** the mean age of children was 5.4 years, with male to female ratio of 3.3:1. The majority of children were underweight (81.4%) and around half (48.9%) belonged to the lower middle class. The mean serum vitamin D level was 8.4 ng/ml. Similarly, mean serum albumin, calcium & phosphorous levels were 4.3 g/dl, 9.2 mg/dl, and 5 mg/dl respectively. The frequency of episodes/admissions receiving first, second, third, and fourth cycle/doses of High dose methotrexate were 28.7%, 27.5%, 22.5% and 21.25% respectively.

The incidence of Acute kidney injury and severe Acute kidney injury within 48 hours of administration of High dose methotrexate was 24.3% (95% CI: 15.3 - 35.3) and 12.8% (95% CI: 6.3 - 22.3) respectively **(Table 2).**

Table 2: Incidence of severe AKI within 48 hours of HDMTX administration (N=78 episodes)

Variables interval	Number, Percentage	95% Confidence
The proportion of episodes with severe (stage 2 and 3) AKI within 48 hours of Methotrexate	10 (12.8%)	6.3 - 22.3
The proportion of episodes with AKI within 48 hours of Methotrexate	19 (24.3%)	15.3 - 35.3

AKI: Acute Kidney Injury HDMTX: High dose methotrexate

There were no episodes of oliguria and requirement for hemodialysis. Among those with severe Acute kidney injury, there were six children (all males) and 10 episodes; three episodes each in the first and second cycle while two episodes each in the third and fourth cycles of methotrexate. The mean age was 4.2 years, most (four children) belonged to the middle class and two children were underweight. The mean serum albumin, vitamin D, calcium, and phosphorous levels were 3.9 g/dl, 9.5 ng/ml, 9 mg/dl, and 4.9 mg/dl respectively in the severe Acute kidney injury group **(Table 3).**

There was no statistically significant difference in age ($p = 0.110$), gender ($p = 0.300$), socioeconomic status ($p = 0.268$), nutritional status (underweight) ($p = 0.268$), the cycle of high-dose methotrexate ($p = 0.999$), serum vitamin D ($p = 0.857$), serum calcium ($p = 0.062$), serum phosphorous ($p = 0.590$) between groups with and without severe Acute kidney injury. However, there was a statistically significant difference in serum albumin levels ($p = 0.004$) between those with and without severe Acute kidney injury **(Table 3).**

Transaminitis and thrombocytopenia were common side effects of High dose methotrexate in 40% and 17.5% of episodes respectively **(Table 4).**

Table 3: Risk factors associated with severe AKI

Variables	Severe AKI (Mean/Median)	No Severe AKI (Mean/Median)	p - value
Socio-demographic parameters			
Age (n = 43 patients)	4.2 ± 1.7	5.7 ± 2.7	0.11
Gender (n = 41 patients)(%)			
Female (n = 9)	0 (0.0)	9 (100.0)	0.3
Male (n = 32)	6 (18.7)	26 (81.3)	
Socioeconomic status (n = 41 patients)(%)			
Upper	0 (0.0)	0 (0.0)	0.268
Upper Middle	2 (25.0)	6 (75.0)	
Lower Middle	2 (10.0)	18 (90.0)	
Upper Lower	2 (16.7)	10 (83.3)	
Lower	0 (0.0)	1 (100.0)	
Underweight (n = 41 patients) (%)			
Yes	2 (28.6)	5 (71.4)	0.268
No	4 (11.8)	30 (88.2)	
Biochemical parameters			
Serum albumin (n = 78 episodes)	3.9 ± 0.6	4.3 ± 0.3	**0.004**
Serum Vitamin D (n = 21 patients)	9.5 (4.6 - 14.5)	7.1 (4.6 - 18.1)	0.857
Serum Calcium (n = 76 episodes)	9.0 ± 0.4	9.2 ± 0.4	0.062
Serum Phosphorous (n = 73 episodes)	4.9 ± 1.0	5.0 ± 0.6	0.590
Cycles of High dose Methotrexate (n=78 episodes) (%)			
First	3 (13.0)	20 (87.0)	0.999
Second	3 (14.3)	18 (85.7)	
Third	2 (11.2)	16 (88.8)	
Fourth	2 (12.5)	14 (87.5)	

AKI: Acute Kidney Injury HDMTX: High dose methotrexate

Table 4: Adverse effects associated with high dose Methotrexate

Toxicity profile	Number (%)
(N= 80 episodes)	
Transaminitis	32 (40.0)
Thrombocytopenia	14 (17.5)
Mucositis	3 (3.75)
Rashes	2 (2.5)
Febrile Neutropenia	1 (1.25)
Seizures	1 (1.25)
Anemia	0 (0.0)
Enterocolitis	0 (0.0)

DISCUSSION

The study demonstrated Acute kidney injury in 24.3% (95% CI 15.3 - 35.3) and severe Acute kidney injury was observed in 12.8% (95% CI of 6.3 - 22.3) of episodes. The incidence of Acute kidney injury in the current study (24.36%) was similar to the study by Vaishnavi et al 2015 [9], where 100 episodes of high dose methotrexate were studied in children with Acute Lymphoblastic Leukemia and non-Hodgkin lymphoma. There was a rise in serum creatinine to greater than 1.25 times the baseline in 23% of cycles. The proportion of Acute kidney injury was higher in the current study in comparison to studies conducted by Cheng et al [13] and Amitai et al [14] as the former study included both intermediate and high risk populations with varying doses of methotrexate ranging from 2g/m² to 3g/m² and the later study was conducted at adult population with Non-Hodgkin Lymphoma and Acute Lymphoblastic Leukemia. Cheng et al [13] retrospectively studied 1329 courses of HD MTX in 336 Chinese children with Acute Lymphoblastic Leukemia and found Acute kidney injury in 8%. Amitai et al [14] retrospectively studied 160 adults with lymphoma and leukemia of which 9% had Acute kidney injury within 5 days of High dose methotrexate. However, there was no classification of Acute kidney injury into different stages in those studies. The variation in result from the above studies could be due to the heterogeneous population with ethnicity variation and in one study by Amitai et al 2018 [14] patients were followed up till day 5, so the creatinine values would have settled by then in contrast to our study where Acute kidney injury was studied at 48 hours.

The current study concluded a statistically significant difference (p = 0.004) in serum albumin levels between those with and without severe Acute kidney injury. The result was similar to a study by Cheng et al, 2018 [13] where Acute kidney injury was associated with lower serum protein at baseline (p = 0.021), age (p = 0.005), first

High dose methotrexate course (p = 0.013) and MTX dose (p = 0.015).

Rask et al, 1998 [15] found older age, prolonged exposure, and a higher number of cycles to be significant risk factors for MTX toxicity. In a study by Amitai et al, 2018 [14] serum albumin < 3.6 g/dl and serum creatinine above 0.9 mg/dl were predictors of Acute kidney injury. This could be due to the enrollment of newly diagnosed as well as relapsed cases in the other studies in contrast to our study which didn't include the relapsed cases and included only B Acute Lymphoblastic Leukemia while other leukemia and lymphomas were also enrolled in previous studies which may have a different impact on metabolic profile.

The incidence of adverse events like febrile neutropenia and mucositis in our study was lower as compared to the study conducted by Vaishnavi et al, 2015 [9] which could be explained by the fact that they used higher doses (5 grams/m^2 and 3 grams/m^2) as compared to a lower dose (3 gram/m^2) in our study.

It is important to note that there is limited data and a paucity of published studies in South Asian settings on the incidence of Acute kidney injury following High dose methotrexate use. The previous studies have been conducted on heterogeneous populations with variable doses of methotrexate. The current study could identify a group at risk for methotrexate induced acute kidney injury.

However, our study had certain limitations. This was a single center study and creatinine used as an assessment of kidney function varies among children according to muscle mass which may pose a problem in accurately identifying Acute kidney injury. There were a few samples which was sent to a different lab which might create variable creatinine values. There is a need for a multicenter study to validate the results.

CONCLUSION

Acute kidney injury is common following High dose methotrexate infusion in high risk B cell Acute Lymphoblastic Leukemia and there are significant differences in mean serum albumin between those with and without severe Acute kidney injury. Though the study highlighted the burden of Acute kidney injury in the high risk Acute Lymphoblastic Leukemia group, more studies are required with extensive follow-up to get conclusive findings.

Acute kidney injury can have an impact on long term complications such as progression to chronic kidney disease. Hence, its awareness among clinicians and the population is critical in early detection. Studies are lacking long term follow-up in children with recurrent episodes of Acute kidney injury.

There is scope for future research in the early detection of Acute kidney injury in high risk Acute Lymphoblastic Leukemia children using novel biomarkers namely plasma neutrophil gelatinase associated lipocalin (NGAL), tissue inhibitor metalloproteinase-2 (TIMP-2), insulin-like growth factor binding protein-7 (IGFBP-7), urine concentration of interleukin (IL-18) and liver-type fatty acid-binding protein (L-FABP).

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