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Investigating the role of pharmacogenomics in personalizing medication therapy for children: a pilot study

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ABSTRACT

An antimetabolite that is frequently given for the treatment of both adult and pediatric malignancies is methotrexate (MTX). Because of MTX-related toxicity and pharmacokinetic unpredictability, HDMTX treatment is challenging. Methotrexate disrupts the metabolism of folate by blocking the methylenetetrahydrofolate enzyme (MTHFR). MTHFR polymorphism may affect how well a patient tolerates MTX. Therefore, the study intends to connect the clinical outcome of pediatric ALL patients receiving HDMTX infusions with the serum methotrexate level and MTHFR polymorphism. Between February 2023 and May 2024, a prospective study was conducted at CMC Hospital in Vellore. Acute Lymphoblastic Leukemia (ALL) relapses in children who were younger than 18 years old at enrollment and who are on high doses. Serum methotrexate levels 48 hours following the initiation of HDMTX infusion may be associated with severe methotrexate toxicity. While most patients with the A1298 C homozygous mutant (CC) exhibited increased liver enzymes, we observed that patients with the C667 T variation (CT) had delayed methotrexate elimination. MTHFR genotyping and serum methotrexate drug level prediction are crucial for preventing toxicities in individuals receiving high doses of methotrexate infusion.

Keywords: *High dose Methotrexate, serum methotrexate level, Acute Lymphoblastic Leukaemia.*

1. INTRODUCTION

Adolescent and pediatric cancer is uncommon, and the biology of childhood cancer is distinct from that of adult cancer. Low- and middle-income nations account for more than 80% of all pediatric cancer cases. According to estimates from 2008, approximately 148,000 childhood cancer cases were documented in children aged 0–14. Tumors in patients aged 5 to 14 years are the eighth leading cause of death in India [1]. Leukemia and lymphoma are often the most prevalent children cancers among the various cancer forms. 8.Leukemia is the most common disease in children, accounting for one out of every three pediatric cancer cases, according to the American Cancer Society. Leukemia is frequently reported in both developed and poor nations. Children are most commonly affected with Acute Lymphoblastic Leukemia (ALL) out of all the leukemia kinds. Every year, 10,000 instances of childhood ALL are reported in India. Chemotherapy advancements have improved treatment outcomes and raised the survival rate in ALL. Childhood ALL is a complicated condition that takes time to cure. Ten distinct chemotherapeutic drugs are administered as combination therapy through various methods of administration over a period of two to three years [9]. Induction, consolidation, and a long-term maintenance phase with CNS prophylaxis are the stages of chemotherapy. Broad-spectrum cytotoxic medicines are the chemotherapeutic medications used to treat cancer. Despite the fact that chemotherapeutic regimens enhance the results of treatment, ALL therapy is linked to a number of adverse effects and may impair the function of numerous organ systems. [2]. Because chemotherapy medications destroy both malignant and healthy cells, their limited specificity is frequently linked to their negative side effects. Chemotherapeutic chemicals are currently delivered in set doses with an emphasis on body surface area. Therefore, the pharmacokinetic dosage factors were not taken into account. Drug absorption, distribution, metabolism, and clearance may vary with age in comparison to adults. When the same medicine is administered to various people, these pharmacokinetics factors cause significant variance in plasma concentrations. Furthermore, a patient's capacity to metabolize or eliminate a medication may also contribute to pharmacokinetic variability. Therefore, therapeutic drug monitoring enhances the effectiveness of chemotherapeutic drugs and reduces toxicity [3].

1.1 The Issues with Drug Safety Monitoring

In a clinical setting, therapeutic drug monitoring, or TDM, is crucial for delivering tailored medication therapy based on the needs of each patient. As a result, TDM has gained widespread acceptance among clinicians in recent decades for use in clinical practice. To increase therapeutic effects, reduce toxicities, or both, TDM entails estimating and comprehending drug concentrations in biological fluids and customizing dosages or regimens. Because of their narrow therapeutic index and unpredictable toxicities, cytotoxic medicines are perfect for the development of therapeutic drug monitoring (TDM) [4]. With the exception of methotrexate (MTX), therapeutic drug monitoring is not now frequently utilized for chemotherapeutic drugs. The issue is that the majority of antitumor medicines lack clearly characterized pharmacodynamics, or concentration-effect connections, which severely restricts the use of TDM. Well-defined pharmacodynamic connections in MTX, teniposide, etoposide, carboplatin, and mercaptopurine have not been demonstrated in many representative clinical investigations. The use of TDM, a method to tailor chemotherapy medications for their effectiveness and prevent toxicity, is a result of the beneficial effects of correlations found in multiple studies for anticancer medications. Twelve In a sense, adopting a target value is the focus of tailoring the chemotherapy dosage throughout treatment depending on the observed drug concentrations. Because therapeutic techniques can be applied in a clinical setting, TDM may be able to enhance cancer chemotherapy by improving patient outcomes and survival. Even while TDM for anticancer drugs has numerous obstacles, if it is used properly in oncology clinics, it has the potential to significantly improve cancer treatment. Chemotherapeutic medications must have narrow therapeutic indices and significantly variable pharmacokinetics in order to meet TDM requirements. Given the wide-ranging effects chemotherapy has on cancer patients, maximizing its effectiveness in treating various cancers is crucial. Underdosing cancer patients may jeopardize their chances of recovery from cancers that can be cured with chemotherapy, which is unacceptable. Similarly, some cytotoxic side effects, such myelosuppression, can be lethal at normal dosages. Therefore, a treatment range that describes the amounts causing both desired side effects and efficacy has significant clinical value [5]. Additional possible advantages of TDM include improving medication compliance and dose adjustment in patients with hepatic and renal failure, reducing pharmacokinetic variability among patients, and identifying any drug interactions. Clinical study reviews have documented the toxic effects of anticancer medications, which are very helpful in determining the level of treatment when combination chemotherapy is recommended. TDM improves the effectiveness of cancer chemotherapy, however the highest treatment intensity may have the tendency to create undesirable anticancer effects. Therefore, more research is needed to determine concentration-effect connections in a wide range of anticancer medications. The use of TDM techniques in cancer patients' treatment regimens may improve results and reduce toxicity associated with chemotherapy in pediatric cancer. Although the requirements for drug monitoring in children and adults are comparable, there are still a lot of elements to take into account because of the physiologic and biochemical changes that occur with age. Because there is a dearth of published pharmacokinetic (PK) data on chemotherapeutic drugs in children, pediatric dosages are extrapolated from adult dosages.[17] Drug toxicity and substantial inter-patient variability in pediatric patients receiving the same treatment regimen are the results of this. In the pediatric population, more precise and customized dose for chemotherapeutic medications is required. One significant medication for CNS prophylaxis in pediatric acute lymphoblastic leukemia is high-dose methotrexate (HDMTX). Because of its limited therapeutic window and notable pharmacokinetic variability, HDMTX is linked to a number of toxicities. Even with the same treatment regimen, HDMTX-associated toxicity differ from patient to patient [15]. Oral mucositis, myelosuppression, and acute liver damage with temporarily raised serum levels of alanine aminotransferase (ALT) and aspartate aminotransferase (ASAT) are among the side effects of MTX that have been documented. A longer hospital stay, treatment suspension, and a postponement of the planned chemotherapy are all possible outcomes of these adverse effects.[11][14] Treatment results for ALL may be negatively impacted by treatment delays and interruptions.[13]. However, the clinical observation data only suggested toxicity because of the restricted Indian study and previous literature.[10][12] Therefore, an examination of the relationship between the MTHFR polymorphism and serum methotrexate levels, as well as any impact on MTX delay elimination and toxicities, may be helpful.[6].

1.2 Hypothesis

We postulated that genetic diversity in folate-metabolizing enzymes would affect MTX dose acceptability; this could potentially affect serum MTX levels and MTX-induced toxicities in pediatric patients undergoing HDMTX infusion. Estimating the blood MTX level, correlating it with MTX-induced toxicity, and examining the impact of MTHFR polymorphism on serum MTX levels in pediatric ALL patients undergoing HDMTX infusion are the goals of the study [7].

to establish a correlation between the level of methotrexate (MTX) in the blood, the genetic polymorphism of Methylenetetrahydrofolate Reductase (MTHFR), and the incidence of MTX-induced toxicity in children with acute lymphoblastic leukemia (ALL) who are receiving high doses of HDMTX infusion.

1.3 The specific objectives are

- To confirm the accuracy of the analytical technique described for determining the serum methotrexate levels in pediatric ALL patients undergoing large doses of methotrexate.
- To examine children with ALL undergoing HDMTX infusions for their serum methotrexate levels.

- To assess the relationship between MTX-induced toxicity and blood methotrexate levels in pediatric ALL patients undergoing HDMTX infusion.
- To establish a correlation between the Methylene Tetrahydrofolate Reductase (MTHFR) genotype and metabolic variance and poisoning susceptibility.

2. METHODOLOGY

Even when patients follow the same treatment regimen, there is significant inter-individual variation in the incidence of HDMTX-related toxicity. Monitoring serum MTX levels only aids in preventing MTX-induced toxicities; it is unable to account for the inter-individual variation in toxicities. Therefore, genetic determinants of MTX toxicities must be taken into account. According to this clinician, it can predict therapy response and helps us provide information on inherited genetic variability [8].

Table 1: Serum methotrexate level of ALL patients receiving HDMTX infusion at different time points

Details of patients	Dose of HDMTX infusion	Blood withdrawal time points	Serum MTX level
Patient 1	3 g/m^2 over 24 hours of infusion (first cycle)	At the end of the infusion 48 hours after start of the infusion	99.36 micromil/L 1.32 micromol/L
Patient 2	3 g/m^2 over 24 hours of infusion (first cycle)	6 hours after the start of infusion 48 hours after the start of the infusion	27.72 micromol/L 0.92 micromol/L
	3 g/m^2 over 24 hours of infusion (second cycle)	18 hours of the infusion 48 hours after the start of the infusion	48.80 micromol/L 0.31 micromol/L
	3 g/m^2 over 24 hours of infusion (third cycle)	At the end of the infusion 48 hours after the start of the infusion	92.14 micromol/L 0.55 micromol/L
Patient 3	3 g/m^2 over 24 hours of infusion (first cycle)	24 hours after the of the infusion	70.6 micromol/L

2.1 Study Population

During the study period, 44 HDMTX courses were administered at a dose of 1 g/m2 over 36 hours, and nine ALL patients experienced relapses. The BFM-based strategy, which included six rounds of HDMTX infusion at a dose of 1 g/m2 for 36 hours, was used to treat relapse patients. HDMTX was infused into seven patients over the course of six treatments. Due to HDMTX-induced fulminant hepatic failure, two patients only had one cycle and passed away following it. 36 hours after the HDMTX infusion began, 3 mL of blood samples were drawn in a plain tube, and the ARCHITECT Methotrexate test kit was used to quantify the serum MTX level. The Common Terminology Criteria for Adverse Events v.5.0 (CTCAE) score system was used to grade toxicity. The mean age of the nine patients was 11.87± 5.58 years, with boys making up the majority (66.67%). The CNS was the site of relapse in the majority of ALL patients (88.88%). Table No. 2 provides a summary of the traits of ALL relapse patients.

Table 2: Characteristics of ALL relapse patients receiving HDMTX infusion

Characteristics	Number of patients (%)N=9
Gender	
Boys	06 (66.67)
Girls	03 (33.33)
Age at the time of diagnosis(years)	
1-6	2 (22.22)
13-18	7 (77.77)
Mean age :	11.87 ± 5.58years
BSA (m^2)	
Range	0.5 – 1.8
Median	0.76
Immophenotype	
T cell	1(11.1 %)
B cell	8 (88.8%)
Total number of HDMTX cycle	44 cycles
Site of relapse	
CNS	08 (88.88)
Testes	01 (11.11)

2.2 Data Analysis

The average number of drugs prescribed is a key prescription analysis metric. The mean number of medications per prescription should be kept as low as feasible because bigger numbers always lead to a higher risk of drug interactions and higher hospital charges (Gupta N, 1997). Only two drugs, Ibuprofen (55.86%) and Voveran (29.29%), had a 90% drug consumption rate among the orthopaedic population in the tertiary health care facility, per the current study. Both medications are classified as "high-risk" NSAIDs in the current study.

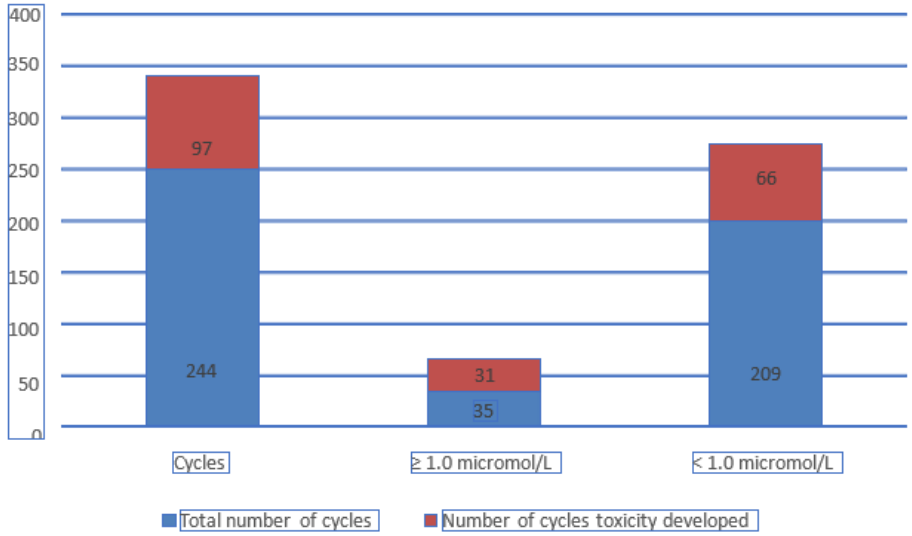

Figure 1: Distribution of ALL patient's serum methotrexate level (micromol/L) and toxicities in different cycles

Gastrointestinal toxicities were the most common (96.9%). Oral mucositis in 22 infusions (22.7%) and vomiting in 48 cycles (49.5%) were the most common GIT toxicity symptoms. In seven cycles, there was an increase in alanine aminotransferase (SGPT) of 7.2%. One (0.01%) infusion showed signs of acute renal damage brought on by HDMTX treatment. Additional hazards linked to HDMTX included eye diseases (2.1%), CNS (4.1%), and skin rashes (8.2%). Of the different toxicities linked to HDMTX, oral mucositis (p 0.0001), liver enzyme elevation (p 0.0100), febrile neutropenia (<0.0001), and dermatological toxicities (p = 0.0118) were found to be statistically significant when the serum methotrexate concentration was greater than or equal to 1.0 micromol/L (Table 7.11).

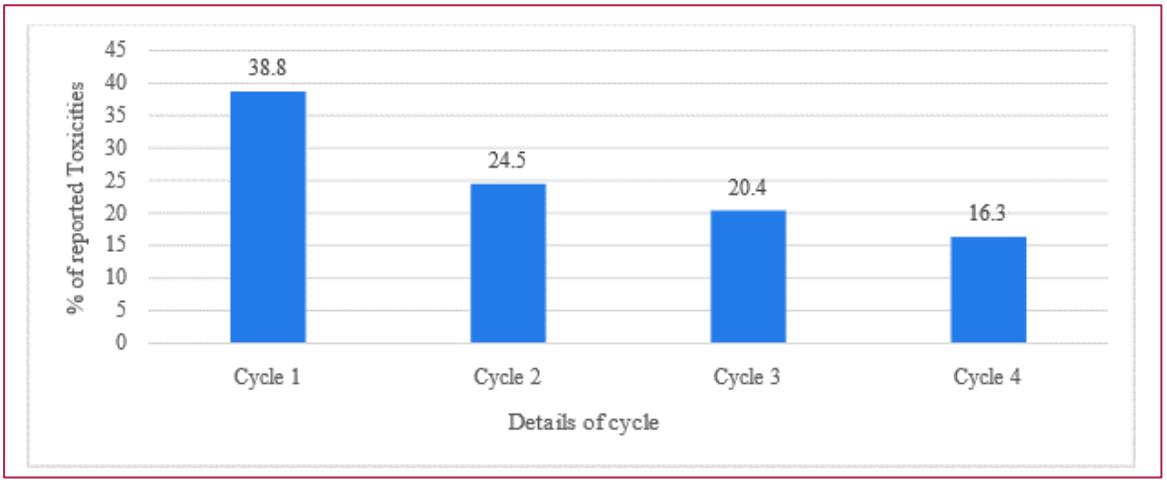

Figure 2: Details of toxicities reported in each cycle in ALL patients

Despite the fact that the patients' medicine expenses were not found to be very high, this charge could not be disregarded. Other costs, such as travel charges and the time and money required to find alternative providers, added to the overall burden. Both direct and indirect costs are mostly to blame for the increasing financial burden on caretakers. Patients with orthopaedic IPD need long-term care, which drives up treatment expenses. In addition to the NSAIDs, the calcium supplement was given for a longer duration.

Table 3: Characteristics of ALL relapse patients receiving HDMTX infusion

Reported toxicities	Serum methotrexate level at 48 hrs after start of HDMTX infusion (micromol/L)		Chi- Square Distribution P value	Total Number of patients	Total Number of cycles
	More than or equal to 1.0 micromol/L	Less than or equal to 1.0 micromol/L			
	Number of cycles				
i) Gastrointestinal disorders					
Vomiting Grade 1 & 2	09	39	<0.0001	28	48
Nausea grade 1 & 2	02	08	*0.0323	8	10
Abdominal pain Grade 1 & 2	01	10	*0.0006	4	11
Diarrhoea Grade 1 & 3	00	02 (100)	-	2	
Oral Mucositis (Grade 1-4)	20	02	*< 0.0001	21	22
Gastric haemorrhage	01	00	-	1	01
ii) Immune system disorders					
Anaphylaxis	01		-	01	01
iii) Renal and urinary disorders					
Acute kidney injury	01	00	-	01	01
Reported toxicities	**Serum methotrexate level at 48 hrs after the start of HDMTX infusion (micromol/L)**		**Chi- Square Distributi -on P value**	**Total Number of patients**	**Total Number of cycles**
iv) Blood and lymphatic system disorders					
Febrile Neutropenia Grade (1-4)	6	4	-	06	10
Anaemia (grade 2)	18	00	-	18	24
v) Nervous system					
Seizure grade1	01 (100)	00	-	01	01
Headache	01 (33.33)	02 (66.67)	0.9999	03	0.3
vi) Dermatological					
Rash maculo- papular	07 (87.5)	01 (12.05)	***0.0118**	08	08
vii) Eye disorders					
Watering eyes (grade 1)	00	01	-	01	01
Eye pain (grade 1)	00	01	-	01	01
viii) Investigations					
Alanine aminotransferase increased	06 (85.7)	01 (14.3)	***0.0100**	07	07
Platelet count decreased (grade1- 3)	08 (100)	**00**	-	05	08
White blood cell decreased	21	07	***0.0002**	14	28
Neutrophil count decreased	21	07	***0.0002**	14	28
*Statistically significant					

3. DISCUSSION

According to the results of our investigation, the ARCHITECT methotrexate assay kit provides a quick and accurate analytical technique for tracking serum methotrexate in a clinical context. Monitoring serum MTX 48 hours after the infusion begins aids in detecting delayed MTX elimination. Serum MTX levels greater than or equal to 1 micromol/L 48 hours following the start of HDMTX infusion were the highest toxicities recorded in pediatric ALL patients. However, regardless

of the serum MTX level, gastrointestinal toxicity, including nausea and vomiting, was experienced by all ALL participants.

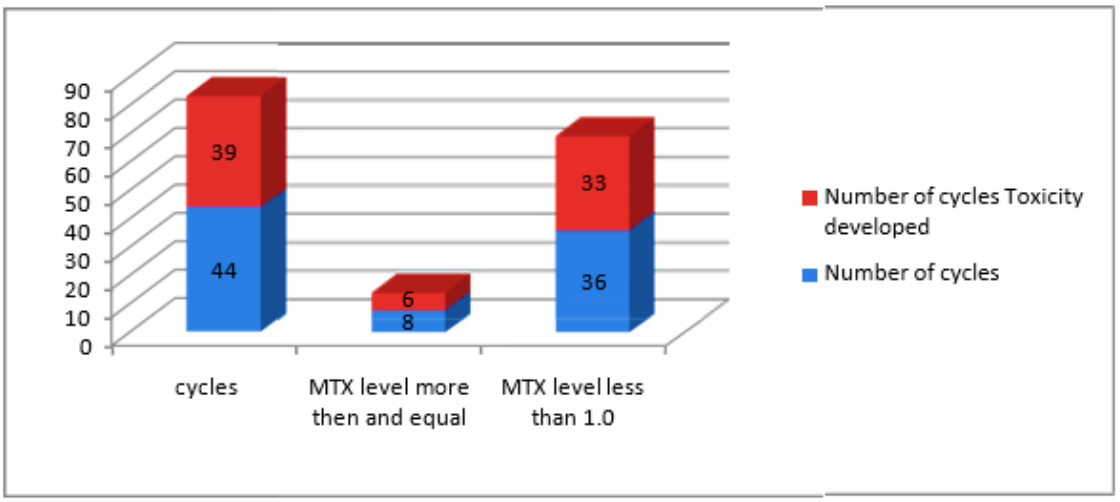

Figure 3: Details of toxicities reported in each cycle of ALL relapse patients

When serum methotrexate levels were greater than or equivalent to 1.0 micromol/L, ALL patients experienced treatment delays, dose reductions, and longer hospital stays. Prolonged neutropenia, myelosuppression, and grade 3 mucositis were the reasons for the dose reduction. Few patients experienced relapses during the research period, and the majority of ALL patients were receiving maintenance therapy. Most ALL patients experienced a recurrence in the central nervous system. Regardless of their serum MTX level, the majority of ALL-relapse patients exhibited toxicity, which may have been caused by an extended infusion period.

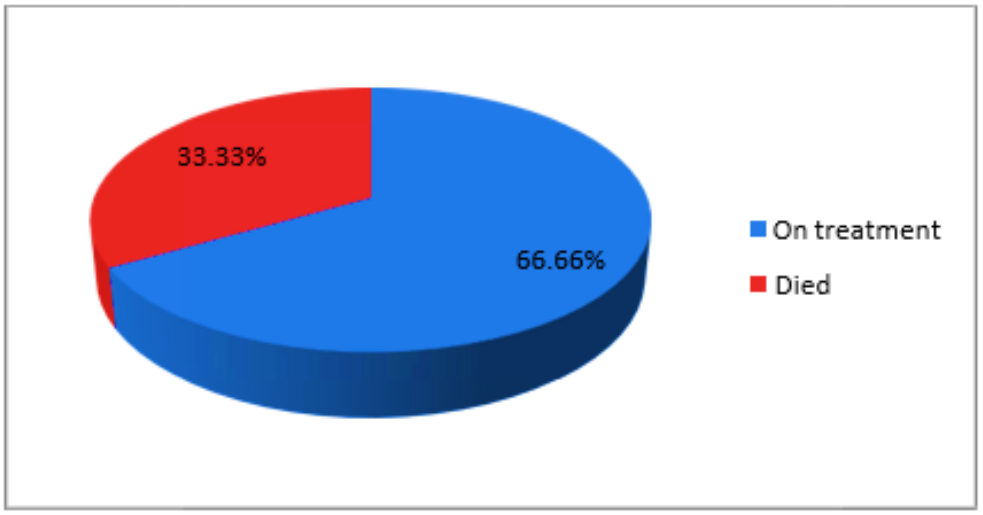

Figure 4: Outcome of ALL relapsed patients

Leucopoenia and anemia were the most common toxicities that arose in recurrence patients. Two deaths in patients with ALL relapse have been linked to HDMTX therapy.

4. CONCLUSION

However, parenteral methotrexate was chosen to be omitted, and desensitization was not taken into consideration for this patient. For the purpose of CNS prophylaxis, this youngster received cranio-cranial radiation. The ADR in this case report was found to be definitely/definitely caused by HDMTX, according to the causality assessment (using the WHO and Naranjo scale). The severity assessment (using Hartwig's scale) determined that the ADR required immediate discontinuation of the treatment (MTX) with an antidote/other treatment (pheniramine Maleate) and that there was no increase in the length of hospital stay.Finally, while prescribing MTX, especially for high dosage infusion in kids, oncologists should be aware of the potential for unanticipated hypersensitivity events and take these into account.

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