High Dose Methotrexate in Children with Cancer Without Drug Level Monitoring – 133 Cycles Experience

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Abstract

Two years data from children receiving HDM were collected (Jun 2019 – June 2021). Diagnosis, baseline blood parameters were recorded. Alkaline hyperhydration was done overnight; subsequently intrathecal methotrexate followed by intravenous (IV) methotrexate (2–5 g/m2) was given over 24 h. Post chemotherapy alkaline hyperhydration was continued. Urine output and serum creatinine level were monitored. Serum MTX level was not monitored. Leucovorin (15 mg/m2) was given intravenously for six doses (start at 42 h from initiation of HDM). There were 133 cycles administered in 35 children (age range 1–14 years and M:F = 17:18). Underlying diagnosis include B-ALL (28), T-ALL (4), Lymphoblastic lymphoma (2) and medulloblastoma (1). All cycles were administered using peripheral IV cannula. With overnight hydration, target urine pH ≥ 7 was reached in 95/133 (71%). Rapid correction of IV NaHCO3 was given in rest. Median dose of IV methotrexate was 4 g/m2. Children were discharged within four days in 90% of cycles. Notable adverse events were seen in 45/133 (34%) cycles. These include excess vomiting (19), fever (15), gastroenteritis (8), oral mucositis (6), transient SGPT elevation > 5 times normal (3), head ache (3), delayed transient asymptomatic elevation in serum creatinine (3), culture positive sepsis (2), allergic rash over eyelids and scalp (1), acute kidney injury - AKI (1). AKI (oliguric) occurred in a three years old girl who had high-grade fever and diarrhea on third day of HDM, which completely resolved with prolonged hydration and high doses of IV leucovorin along with parenteral antibiotics for sepsis. High dose methotrexate (2–5 g/m2 IV over 24 h) can be administered safely in children with cancer in stable condition without monitoring drug level. Extended alkaline hyperhydration, prompt leucovorin rescue, urine output and serum creatinine monitoring should be followed strictly.

Keywords: Childhood leukemia, High dose methotrexate, leucovorin

Introduction

High dose methotrexate (HDM) is a commonly used therapeutic regimen in children with acute lymphoblastic leukemias, lymphomas and few other tumours. Majority of treatment centers in the low and middle-income countries have no or limited access to perform serum methotrexate (MTX) levels monitoring [1]. The standard recommendations mandates serial monitoring of serum MTX levels while administering HDM. The other precautions to prevent toxicity include hyperhydration, alkalinisation of urine, monitoring urine output and serum creatinine levels, avoiding drugs that interact with methotrexate and administering leucovorin as a rescue starting 42–48 h after starting intravenous MTX [1]. Based on serial drug level monitoring, the treatment protocols recommend modifications in the dose and duration of leucovorin; and duration of hyperhydration. Even if the other measures can be strictly followed in remote centers, availability of serum MTX level in time is a challenge in delivering HDM. Scant literature is available in administering HDM without MTX level monitoring and using other alternative measures to ensure safety and efficacy [1]. In this study, we share our experience in administering HDM in children with cancer without monitoring MTX level; while adhering to other precautions.

Methods

Data was collected from children with cancer (age 0–17 years) who were admitted for high dose methotrexate (2–5 g/m2) in Pediatric Hematology–Oncology Unit in Kauvery Hospital, Trichy over a two years study period (Jun 2019–June 2021). The demographic details, underlying diagnosis, anthropometry, baseline blood investigations, dose of IV MTX given and the details of subsequent monitoring as per protocol (discussed below) were recorded. Any side effect during or after high dose methotrexate was also recorded. Details of multiple cycles administered in same patient were recorded separately.

High dose methotrexate protocol

Prior to admission for chemotherapy, history and examination of the child were done in outpatient department to rule out active infections or other co-morbidities. Children with extravascular fluid collections like ascites and pleural effusion were deferred for HDM (as it may cause delayed MTX excretion). Baseline evaluation of complete blood count, serum creatinine and SGPT levels were checked. If the findings are satisfactory, child will be admitted on the evening of day 1 for prehydration.

Extended hydration with alkalinisation

On day 1 evening (around 6 PM), IV alkaline hyperhydration (125 ml/m2/h) with a solution of 0.45% sodium chloride, 5% dextrose with sodium bicarbonate (40 mmol/L) was started and was given overnight. Next day morning 6 AM, urine pH was checked (target pH ⩾ 7). If urine pH < 7, IV rapid correction of NaHCO3 was given over 1 h and urine pH was rechecked. IV alkaline hyperhydration was continued along with MTX infusion and for at least 72 h from the start of IV MTX. Inj. Furosemide 0.5 mg/kg IV was given once daily in the morning. Intake and urine output was strictly monitored and charted every 6 h throughout admission

MTX infusion

On day 2 at 9 AM, lumbar puncture was done and intrathecal methotrexate was given (dose as per age) under IV sedation (midazolam and ketamine). Immediately after lumbar puncture, IV high dose MTX was started using peripheral venous access. A 10% of total MTX dose was infused over 30 min, and the remaining 90% over 23.5 h.

Extended leucovorin rescue

IV leucovorin rescue (15 mg/m2/dose) was started at 42nd h of starting IV MTX and was continued every 6 h for a minimum of 6 doses, then stopped if clinical and laboratory parameters remain satisfactory.

Serum Creatinine level monitoring

Serum Creatinine level was monitored after completion of MTX infusion at two different time points (1st at 24–48 h; 2nd at 48–72 h). Based on clinical parameters and the individual's responses in previous HDM cycles, only a single time point creatinine level was checked in some cycles and repeated if necessary.

Avoidance of drugs interfering with MTX excretion

Drugs like NSAIDS, Cotrimoxazole, proton pump inhibitors, Amphotericin and Levetiracetam were avoided.
If clinical and laboratory parameters are satisfactory, child was discharged at 72 h of starting IV MTX. In case of any derangements, IV alkaline hyperhydration and leucovorin were continued till child improved.

Results

There were 133 cycles administered in 35 children during the study period. The demographic and clinical details are given in Table 1.

Table 1: Demographic and clinical data of 35 children

Age range	1–14 years (Median: 4 years)
Sex ratio	17 boys: 18 girls
Underlying Diagnosis	B-acute lymphoblastic leukemia – 28 T-acute lymphoblastic leukemia – 4 T-lymphoblastic lymphoma – 2 Medulloblastoma – 1
No. of HDM cycles per child	27 children received 4 cycles each 6 children received 3 cycles each 1 child received 6 cycles 1 child received 1 cycle only
Weight range	8.8–51.4 kg (Median – 15.1)
Height range	78–157 cm (Median – 105)
Body surface area (Median)	0.43–1.49 m2 (Median – 0.66)
Dose of IV methotrexate	Median dose: 4 g/m2 2–2.9 g/m2 in 12 cycles 3–3.9 g/m2 in 37 cycles 4–5 g/m2 in 84 cycles

The baseline laboratory parameters were summarized in **Table 2.**

Table 5: Descriptive analysis of folate deficiency and homocysteine elevation in the study population (N = 65).

Parameter	Range	Median
Hemoglobin (in g/dL)	7.1–14	10.5
White cell count (per mm3)	1600–9500	4600
Absolute neutrophil count (per mm3)	352–5632	1678
Platelet count (per mm3)	75000–15.6 lakhs	2.64 lakhs
SGPT (in U/L)	10–159	25
Serum creatinine (mg/dL)	0.06–0.45	0.29

First urine pH ≥ 7 was achieved in 95/133 (71%) cycles. In rest of cycles, the target was achieved with a single rapid correction. Serum creatinine level at 24–48 h was available in 83 cycles, while the level at 48–72 h was available in 117 cycles. The value at 24–48 h ranged from 0.11–0.5 mg/dL (median 0.32). The value at 48–72 h ranged from 0.17–0.57 mg/dL with median 0.32 (excluding one child which had a level 2.15 mg/dL along with high fever, diarrhea which is discussed separately below).

The duration of hospital stay ranged from 4–11 days (median 4). The hospital stay was for four days in 120/133 cycles (90%). One child had a prolonged stay for 11 days due to acute kidney injury with sepsis.

Side effects during or after MTX infusion were documented in 45/133 (34%) cycles that were mild to moderate in majority and are explained in Table 3. Mild nausea, vomiting and anorexia were seen in most of the cycles and were not included for analyzing side effects. There was no mortality related to HDM administration.

Table 5: Descriptive analysis of folate deficiency and homocysteine elevation in the study population (N = 65).

Side effect	No. of cycles
Excess vomiting	19
Fever	15
Gastroenteritis	8
Oral mucositis	6
SGPT elevation > 5 times upper normal	3
Headache	3
Delayed transient asymptomatic elevation in serum creatinine	3
Culture positive sepsis	2 (Acinetobacter 1; Pseudomonas 1)
Symptomatic acute renal failure	1
Edema over scalp & eyelids, itchy rash	1

Discussion

Methotrexate – a wonder drug discovered by an Indian

Methotrexate is an antimetabolite that interferes with the metabolism of folic acid. After entry into the cell, methotrexate is polyglutamated, binds dihydrofolate reductase (DHFR) with an affinity 1000-fold greater than that of folate, and competitively inhibits conversion of dihydrofolate to tetrahydrofolate. Tetrahydrofolate is essential for biosynthesis of thymidine and purines, which are needed for synthesis of DNA. Blockade of tetrahydrofolate leads to inability of cells to divide. Methotrexate is an essential component of therapy for Acute Lymphoblastic Leukemia (ALL) and is also active against many types of cancer. This wonder drug was first developed by Yellapragada Subbarao (an Indian Biochemist) while

working in Lederle laboratory and was first used in children with ALL by Sidney Farber in Harvard Medical School in 1947. This discovery was prompted by the observation that folic acid supplementation worsened leukemia in children leading to the hypothesis that anti-folate could kill leukemia cells. Dose of MTX > 500 mg/m2 has been considered as high dose MTX.

High dose methotrexate

ALL in children is highly curable [2]. Central nervous system directed therapy is an integral part of childhood ALL therapy to prevent CNS relapse. High dose MTX along with intrathecal MTX has been found to be an effective CNS targeted therapy in various protocols, thereby avoiding cranial radiotherapy in majority of children. This helps in reducing the late adverse effects of cranial radiation. Using HDM is based on the principle of dose dependent increased formation of methotrexate polyglutamates, the potential to overcome mechanisms of methotrexate resistance related to impaired cellular drug uptake and the achievement of cytotoxic drug concentrations in the cerebrospinal fluid [2].

Acute kidney injury with high dose MTX

Even though HDM can safely be administered in a majority of children, acute kidney injury (AKI) attributable to crystallization of MTX in renal tubular lumen leading to tubular toxicity is a rare but dangerous complication [3]. When AKI occurs, increased hydration, high dose leucovorin and Glucarpidase (a drug causing enzymatic cleavage of MTX) helps in renal recovery without the need of dialysis. In our study, one child (three years old girl) developed high grade fever, diarrhea and subsequently developed AKI (oliguric) on third day of HDM, which was managed with increased hydration and high dose leucovorin along with parenteral antibiotics for sepsis. Glucarpidase was not used due to high cost and non-availability. With these supportive measures, the child's renal functions normalized. Further HDM doses were omitted. However, subsequent chemotherapy drugs were administered uneventfully and child is currently well in complete remission.

High dose methotrexate in a limited resource setting

Our study evaluated the safety of administering HDM using peripheral IV cannula without monitoring drug level in children with cancer. The standard protocols strongly recommends drug level monitoring to avoid renal toxicity that may be life threatening. However, non-availability of MTX levels that can be made available to make timely decisions precludes its use in many centers. Few studies are available to support the safe administration of HDM without drug level monitoring. Kapoor et al [2] from Delhi studied 149 cycles of HDM in children with ALL and documented toxicities including mucositis (39%), fever (28%), neutropenia (25%), transient elevation of transaminases (35%). The authors suggested that a single drug level at 42 h would be sufficient to identify those at high risk of toxicity. Vaishnavi et al. from PGIMER, Chandigarh studied 100 cycles of HDM without drug level monitoring given in children with hematological cancers with a mean age of 6.8 years [1]. Toxicities documented in their study include mucositis (32%), diarrhea (10%), febrile neutropenia (9%) and one mortality due to Dengue Shock Syndrome. The study conclude that it is safe to administer 3 or 5 g/m2 of MTX (24 h infusion) without measuring MTX levels, with extended hydration, additional doses of leucovorin, and monitoring of serum creatinine and urine pH [1].

Based on the available evidences, HDM was administered in our study population and similar adverse events and safety profile has been observed.

Conclusion

Based on our study, HDM without drug level monitoring can be safely administered in children with proper safety measures as given below:

- Satisfactory baseline parameters – CBC, SGPT, Creatinine
- Child should be free of any infection while giving HDM
- Sufficient alkaline hyperhydration (preferably for 12 h) prior to HDM and achieving urine pH ⩾ 7 prior to starting HDM.
- Strict vitals and I/O monitoring during and after chemotherapy
- Starting leucovorin sharply at 42 h of starting MTX and continuing for six doses
- Documenting change in serum creatinine level at 48 and 72 h before discontinuing precautionary measures.
- Early aggressive intervention and extended leucovorin rescue, if any changes in these parameters.

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Author contributions

All the authors were involved in the management of the child. Vinod Gunasekaran drafted the manuscript.

Competing interests

The authors have no competing interest to declare.

References

[1] Vaishnavi K, et al. Improving the safety of high-dose methotrex-ate for children with hematologic cancers in settings with- out access to MTX levels using extended hydration and additional leucovorin. Pediatr Blood Cancer. 2018;65:E27241.

[2] Kapoor G, et al. Experience with high dose methotrexate therapy in childhood acute lymphoblastic leukemia in a tertiary care cancer centre of a developing country. Pediatr Blood Cancer. 2012;59(3):448–53.

[3] Howard SC, et al. Preventing and managing toxicities of high-dose methotrexate. Oncologist. 2016;21(12):1471–82.