

## High Dose Methotrexate in Oncological Practice: A Review and Update on Recent Trends in Administration and Management of Toxicity

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### Abstract

In cancer chemotherapy, therapeutic drug monitoring (TDM) has been practical only for methotrexate (MTX) with its main role in high doses (HDMTX) for adjuvant therapy of osteosarcoma, intracranial lymphomas, childhood leukemia and pediatric Non-Hodgkin lymphomas. HDMTX is defined as doses of 3-15 g/m<sup>2</sup> over a period of 6-24h. One has to be very careful while administering HDMTX as it can have renal, haematological, skin and mucosa associated toxicities. Patients with underlying renal diseases, old age and those on non-steroidal anti-inflammatory drugs are much more predisposed to methotrexate toxicity. TDM is an effective tool in managing the toxicity profile and guiding the dosage of leucovorin, which is the most effective way of preventing any toxicity of methotrexate. Leucovorin (5-formyl-tetrahydrofolic acid; LV) replenishes intracellular stores of reduced folate and attenuates the toxicity secondary to HDMTX. This leucovorin has greater uptake in normal cells and less in cancerous cells and thus are selectively protective to normal cells and destroys cancerous cells. There has been lot of studies regarding the dosing and various schedules followed in various protocols. This review article is an update on the latest trends followed with reference administration of HDMTX.

**Keywords:** Methotrexate; High Dose; Toxicity; Leucovorin; Glyceridase

### Introduction

Prior to 1950, the treatment of majority of cancers was limited to surgery or use of radiation therapy (RT). Anti-folate drugs were among the first antineoplastic agents. In 1948, aminopterin was used in childhood acute lymphocytic leukemia (ALL) and the related agent MTX is still an important component of modern treatment for ALL as well as a number of other hematologic malignancies [1]. The role of single agent Methotrexate in gestational choriocarcinoma (or GC) led to the development of many of today's common cancer treatments. Methotrexate has both anti-proliferation and anti-inflammatory activity. Among the anti-cancer activity, it is used in T-cell ALL, Acute promyelocytic Leukemia (APML), non-hodgkins lymphoma (NHL), breast cancer, gastric cancer, esophageal cancer and head and neck malignancies. Among anti-inflammatory activity its role is defined in rheumatological disorders,

dermatological disorders, gastrointestinal diseases and in graft versus host disorder.

### History

Folate is required for production and maintenance of new cells especially in rapidly dividing cell as in infants and during pregnancy. In 1949, Sidney Farber, a pathologist and clinician used this knowledge to use a drug that is a folate inhibitor, such as methotrexate, to suppress rapidly dividing cells in cancer. By giving methotrexate to children with acute lymphoblastic leukemia (ALL), a fast-growing type of blood cancer, Farber saw an improvement in the children's symptoms. However, methotrexate achieved only short-term ALL remission, until combination chemotherapy was attempted in 1970. Roy Hertz [2] at the National Institutes of Health (NIH) studied the effect of folic acid on the female urogenital tract, the or-

gan system of the reproductive organs and the urinary system. He studied the effect of anti-folate treatments, such as methotrexate, on rapidly dividing cells of the reproductive tract specifically the placenta [2]. In 1972 Hertz and Li were awarded the prestigious Lasker Award, often considered to be the "American Nobel prize" for their ground-breaking work.

### Definition of HDMTX

Depends upon the protocols used:

1. HDMTX: dose of  $\geq 500$  mg/m<sup>2</sup>, as are used for central nervous system (CNS) prophylaxis in patients with leukemia and high-risk lymphoma, and for the treatment of leptomeningeal metastases, primary CNS lymphoma, and osteosarcoma.
2. Intermediate dose: Doses between 50 and 500 mg/m<sup>2</sup>, as used for malignant gestational trophoblastic disease (GTD), are considered intermediate-dose MTX. In general, these patients do not require aggressive hydration or urinary alkalinisation. Leucovorin rescue is rarely needed with doses  $\leq 250$  mg/m<sup>2</sup> unless unexpected toxicity is encountered.
3. Low-dose MTX: dose  $< 50$  mg/m<sup>2</sup> is used intravenously for the treatment of bladder and breast cancer and desmoid tumors, and orally for patients with T-cell large granular lymphocyte (LGL) leukemia, ALL, acute promyelocytic leukemia, mycosis fungoides, and various non-malignant immune-mediated disorders.

### Mechanism of action

1. Interference with folate metabolism: The anti-proliferative activity of antifolates such as MTX results from interference with folate metabolism. A normal dividing cell uses large amounts of reduced folates to maintain ongoing purine and thymidine synthesis demand is even greater for rapidly dividing malignant cells. Dihydrofolate reductase (DHFR), converts dihydrofolate to tetrahydrofolate, which is required for continuous replenishment of cell's supply of reduced folates. Competitive inhibition of DHFR represents the main mechanism of action of methotrexate [3].
2. Role in thymidine synthetic pathway: The enzyme thymidylate synthetase (TS) uses a methyl group from the reduced folate, 5-methylenetetrahydrofolate, to synthesize deoxy thymidylate monophosphate (dTMP) from deoxy uridylate monophosphate (dUMP).
3. Role in purine synthetic pathway: Within the purine synthetic pathway, the enzymes glycinamide ribonucleotide transformylase (GARFT) and aminoimidazole carboxamide transformylase (AICARFT) both use the formyl

groups of the reduced folate N (10)-formyltetrahydrofolate to initiate synthesis of adenosine and guanosine.

4. MTX inhibits DHFR which leads to cessation of thymidine synthesis, DNA synthesis, and eventually cell death. Since most of the rapidly dividing cells are in S-phase, the maximum requirements of nucleotides are in this phase and it is here that the role of methotrexate is maximum.

### Polyglutamation

Polyglutamation is caused by addition of various carboxyfolates by the enzyme folyl polyglutamate synthetase (FPGS), it increases the intracellular pool of folates, as polyglutamated folates are not easily transported out of the cell because of their size and charge [4]. For polyglutamation to occur cells require to be exposed to minimum concentration of 2 micro mols/litre for a minimum of 6 hours [5] Polyglutamated Methotrexate (PGMTX) amplifies and increases the anti-proliferative effects of MTX by prolonging the inhibition of DHFR. PGMTX bind to other enzymes involved in DNA synthesis such as thymidilate synthase, AICARFT, and GARFT; further depleting intracellular thymidine and inhibits purine synthesis. Polyglutamation is the main cause for toxicity and hence any delay in administration of leucovorin beyond 36 hours increases polyglutamation and hence its toxicity [3].

Prevention and management of HDMTX toxicity: The guiding principles for prevention of HDMTX toxicity, namely maintaining urine output, urinary alkalinization, monitoring serum creatinine, electrolytes, and plasma MTX concentrations, and pharmacokinetically-guided leucovorin rescue, are also the cornerstones of management for patients who develop early signs of renal dysfunction and delayed MTX elimination.

### Major side effects of HDMTX

Side effects of HDMTX are related to both drug dose and duration of drug exposure; some are idiosyncratic. The major side effects of HDMTX are

1. Hepatotoxicity: acute elevation in serum Transaminase up to 20 times in spite of leucovorin rescue is noted. In case alanine aminotransferase (ALT) has not returned to less than 180 IU/L or serum bilirubin is higher than 3 mg/dl the dosage for next cycle should be reduced.
2. Nausea, vomiting, and stomatitis: MTX doses above 250 mg/m<sup>2</sup> are considered moderately emetogenic; American Society of Clinical Oncology (ASCO), patients receiving MTX  $\geq 250$  mg/m<sup>2</sup> should be pre-treated with a serotonin receptor antagonist and dexamethasone, with or without preparent [6].

3. Mucositis is typically rare in patients who undergo leucovorin rescue.
4. Renal toxicity: HDMTX can affect kidney in two ways [7].
  - a. Precipitation of MTX in tubules causing direct tubular injury. This is aggravated in acidic urine and with volume depletion;
  - b. Afferent arteriolar constriction or mesangial cell constriction.
5. Hematologic toxicity: seen more commonly in low dose methotrexate administration, seen rarely with HDMTX.
6. Pulmonary toxicity: mostly seen as hypersensitive pneumonitis presenting with dyspnoea, non-productive cough and peripheral eosinophilia.
7. Neurologic toxicity: acute or sub-acute encephalopathy is the most important neurotoxicity of HDMTX. This complication is characterized by somnolence, confusion, and seizures within 24 hours of treatment. Symptoms usually resolve spontaneously without sequelae, and retreatment is often possible.
8. Dermatologic toxicity: a variety of dermatologic side effects from nonspecific morbilliform drug rash, which is usually erythematous, macular, pruritic, and often confined to the neck and trunk [8].

**Managing HDMTX**

The guiding principles for prevention of HDMTX toxicity, namely maintaining urine output, urinary alkalisation, monitoring serum creatinine, electrolytes, and plasma MTX concentrations, and pharmacokinetically-guided leucovorin rescue, are also the cornerstones of management for patients who develop early signs of renal dysfunction and delayed MTX elimination.

1. Hydration remains to be mainstay of management of HD-MTX. 2.5 to 3.5 litres/m<sup>2</sup> of IV fluid per day starting 4 to 12 hours prior to initiation of the MTX infusion.
2. Alkalinisation of urine is required for solubility of MTX. At low pH, MTX gets deposited in the renal tubules.
 

A typical choice is IV 5% dextrose in water (D5W) with 100 to 150 mEq of sodium bicarbonate per litre, administered by continuous infusion at 125 to 150 mL/hour. Sodium bicarbonate can be given either by 50 mL of D5W containing sodium bicarbonate 1 mEq/kg can be infused IV over 30 minutes every 4- or 6-hours oral sodium bicarbonate can also be given starting with two x 650 mg tablets and increased up to five tablets every 2 to 4 hours.
3. Leucovorin rescue to be started within 24 to 36 hours after starting MTX infusion. 10 mg/m<sup>2</sup> IV or 15 mg/m<sup>2</sup> of leucovorin calcium orally (or 5 mg/m<sup>2</sup> of levoleucovorin IV) every 6 hours until plasma MTX levels are less than 0.05 to 0.1 micro mol [9]. Orally administered leucovorin can successfully reverse MTX toxicity [9].

**Monitoring during MTX administration**

Daily monitoring of plasma MTX levels (Table 1) is required along with serum electrolytes and creatinine [9].

Levels of MTX monitoring:

1. Avoiding drug interactions: Toxicity with MTX-HD may be increased when there is co-administration of drugs having the potential to displace MTX from serum proteins and/or to reduce MTX clearance. The most known are interaction with trimethoprim and sulfamethoxazole (TMP-SMX) and non-steroidal anti-inflammatory drugs (NSAID) [10]. Alteration of the elimination of MTX was also reported with pyrazoles, aminoglycosides, probenecid, some penicillins, macrolides and omeprazole.
2. Drainage of third space fluids: The presence of a third space fluid like pleural effusions or ascites is an important contraindication to the administration of HDMTX. Third space fluids lead to a prolonged MTX plasma half-life and subsequently to a prolonged exposure to MTX and to the risk of toxicity. Drainage of third space fluids before HDMT is recommended to prevent toxicity [11].

Monitoring period	Level of MTX (micro mol)
At 24 hours	5 to 10
At 48 hours	0.9 -1.0
At 72 hours	0.1

**Table 1**

**Glucarpidase**

Glucarpidase is the recombinant form of the Pseudomonas sp. (strain RS -16) enzyme carboxypeptidase G2 that is produced in Escherichia coli. In patients, glucarpidase inactivates methotrexate, and other antifolates, by hydrolysing glutamate on the carboxyl terminal of these compounds. Therefore, since methotrexate is eliminated enzymatically and not by the kidneys, glucarpidase is indicated in patients on methotrexate treatment who have kidney dysfunction and are experiencing an abnormally high plasma concentration of methotrexate (> 1 micromole per liter). Glucarpidase is marketed under the brand name Voraxaze.

**Indication for glucarpidase**

1. 24 - hour concentration is above 50 micro mol
2. 36 - hour concentration is above 30 micro mol
3. 42 - hour concentration is above 10 micro mol
4. 48 - hour concentration is above 5 micro mol
5. Serum creatinine is elevated relative to baseline measurement.

## Recommendations

Recommendations for glucarpidase usage are available from a year 2017 consensus guideline in patients with HDMTX-induced acute kidney injury and delayed MTX clearance [12].

1. For an HDMTX infusion  $\leq$  24 hours, if the 36-hour serum MTX concentration is above 30 micro mol, the 42 - hour concentration is above 10 micro mol, or the 48 - hour concentration is above 5 micro mol and the serum creatinine is significantly elevated relative to baseline measurement, glucarpidase may be indicated.
2. After an HDMTX infusion of 36 to 42 hours, glucarpidase may be indicated when the 48-hour MTX concentration is above 5 micro mol
3. Administration of glucarpidase should optimally occur within 48 to 60 hours from the start of the HDMTX infusion because life-threatening toxicities may not be preventable beyond this time point.

## Conclusion

Because MTX can cause many side effects and some of them are life threatening, it is important to recognize them as the drug must be discontinued immediately and rescue measures instituted. Many of these side effects can be avoided by a close monitoring and good prevention.

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