

High-dose Methotrexate

Abstract

High-dose methotrexate (HDMTX) is defined as methotrexate dose of ≥ 500 mg/m². It is used in the treatment of acute lymphoblastic leukemia, osteosarcoma, and primary central nervous system lymphoma. Administration mandates adequate hydration; urine alkalinization; leucovorin rescue, monitoring of urine output, serum creatinine, and methotrexate levels. Delayed methotrexate clearance is managed by increasing hydration and leucovorin dose. Glucarpidase is the antidote for patients with renal toxicity. Studies from India have shown that HDMTX can be administered without monitoring of methotrexate levels with strict monitoring of urine pH, urine output, and serum creatinine and extended hydration and leucovorin doses.

Keywords: High-dose methotrexate, methotrexate levels, toxicity

Introduction

Methotrexate is a folate antagonist having anticancer, anti-inflammatory, and immunomodulatory properties. It is used in a wide range of malignancies as well as in psoriasis and rheumatoid arthritis. It can be delivered via oral, intramuscular, intravenous, and intrathecal route.

Mechanism of Action

Methotrexate enters the cells through a reduced folate carrier (RFC) and is polyglutamated. This competitively and reversibly inhibits dihydrofolate reductase, the enzyme that converts dihydrofolate to tetrahydrofolate. The lack of tetrahydrofolate inhibits DNA, RNA, and protein synthesis.^[1] Methotrexate is most active against rapidly dividing cells during the S phase of a cell cycle.

Leucovorin (5-formyl-tetrahydrofolic acid) enters cells through the RFC and replenishes intracellular stores of tetrahydrofolate and attenuates the toxicity of high-dose methotrexate (HDMTX).^[2]

Discovery

In 1947, Sydney Farber showed that aminopterin (folic acid analog) developed by Yellapragada Subbarao (Indian) induced remission in acute lymphoblastic leukemia (ALL). In 1956, animal studies

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showed that the therapeutic index for methotrexate was better than aminopterin.

Approval

Methotrexate is Food and Drug Administration approved for the treatment of malignancies including ALL, breast cancer, gestational trophoblastic disease, lung cancer, osteosarcoma, mycosis fungoides, and non-Hodgkin's lymphoma.

HDMTX definition

It is defined as a dose of >500 mg/m² delivered over 4–36 h duration and supplemented with leucovorin rescue to terminate the side effects of methotrexate. The maximum dose that has been tried is 33 g/m² in ALL to avoid cranial irradiation.^[3]

Uses

HDMTX is used in the treatment of ALL, osteosarcoma, and primary central nervous system lymphoma [Table 1].

Administration

- Ensure baseline complete blood count and liver function is normal and creatinine clearance >60 ml/min. Any third-space fluid collection (ascites, pleural effusion) should be drained before starting HDMTX
- As HDMTX is a low emetogenic drug, 5-HT₃ antagonist alone is used to prevent nausea and vomiting

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Manikandan Dhanushkodi

Department of Medical Oncology, Cancer Institute (WIA), Chennai, Tamil Nadu, India

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Address for correspondence:

Dr. Manikandan Dhanushkodi, Cancer Institute (WIA), 38, Sardar Patel Road, Chennai - 600 036, Tamil Nadu, India.

E-mail: dmani1982@gmail.com

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Table 1: Clinical trials with high-dose methotrexate

Tumor	Study	HDMTX dose	Duration of HDMTX	Leucovorin dose	Time from methotrexate to leucovorin
All	Hill <i>et al.</i> MRC UKALL XI ^[4]	Age ≤4 years→6 g/m ² Age >4 years→8 g/m ²	10% bolus, reminder over 23 h	15 mg/m ² every 3 h, then every 6 h until methotrexate levels <0.2 micromolar	36 h
Osteosarcoma	Souhami <i>et al.</i> European Osteosarcoma Intergroup ^[5]	Age ≤12 years→8 g/m ² Age >12 years→12 g/m ²	-	15 mg/m ² every 6 h orally for 10 doses	24 h
Primary CNS lymphoma	Batchelor <i>et al.</i> NABTT study ^[6]	8 g/m ²	4 h	Pharmacokinetically guided until methotrexate levels <0.1 micromolar	24 h

HDMTX – High-dose methotrexate; CNS – Central nervous system; ALL – Acute lymphoblastic leukemia

Table 2: Leucovorin rescue schedule

Clinical situation	Laboratory findings	Leucovorin dose and duration
Normal methotrexate elimination	Serum methotrexate level <10 micromolar at 24 h, <1 micromolar at 48 h and <0.2 micromolar at 72 h	15 mg IV q 6 hourly for 60 h (10 doses starting at 24 h after start of methotrexate infusion)
Delayed late methotrexate elimination	Serum methotrexate level >0.2 micromolar at 72 h, >0.05 micromolar at 96 h	Continue 15 mg IV q 6 hourly, until methotrexate level <0.05 micromolar
Delayed early methotrexate elimination/acute renal injury	Serum methotrexate level >50 micromolar at 24 h, >5 micromolar at 48 h >100% increase in serum creatinine level from baseline at 24 h	150 mg IV q 3 h, until methotrexate level <1 micromolar; then 15 mg IV q 3 h until methotrexate level <0.05 micromolar

IV – Intravenous

- Serum creatinine, methotrexate levels, and urine output should be monitored to assess methotrexate clearance
- Intravenous hydration (3 L/m²/day) should be started 6 h before starting methotrexate and continued until clearance of methotrexate levels
- Strict monitoring of input/output chart is mandatory. Urine output should be at least 150 ml/m²/h before starting methotrexate
- Methotrexate and its metabolites precipitate when urine pH is <5.7. Urine alkalinization increases methotrexate solubility and excretion. Hence, urine pH should be kept >7.0 by urine alkalinization until methotrexate levels fall <0.1 micromolar.^[7] Sodium bicarbonate (40 mEq/L) should be supplemented with intravenous fluids
- After methotrexate administration, plasma methotrexate levels should be measured at 24, 48, and 72 h after starting methotrexate and should be repeated until methotrexate levels fall <0.2 micromolar
- Leucovorin (15 mg/m² Q 6 hourly) should be started within 24 h of starting methotrexate until methotrexate levels are <0.2 micromolar. Starting leucovorin early can reduce methotrexate efficacy [Table 2].

Toxicity

Acute renal toxicity can happen in 2%–12% of patients receiving HDMTX.^[8] Nephrotoxicity is due to crystallization of methotrexate in the renal tubular epithelium. The risk factors include baseline renal dysfunction, volume depletion, acidic urine, use of

nonsteroidal anti-inflammatory drugs (NSAIDs), and drug interaction. Furthermore, advanced age, low serum protein, higher dose, and 1st HDMTX have been associated with increased toxicity.^[9] Genetic polymorphism that alters the metabolism of methotrexate can lead to toxicity.^[10] Renal toxicity delays methotrexate clearance and causes myelosuppression, mucositis, skin toxicity, and hepatotoxicity. A study from Cancer Institute, Chennai, showed that 42 h methotrexate levels predicted delayed clearance and toxicity.^[11] Change in the creatinine from the baseline after HDMTX predicts hematologic toxicity.^[12] HDMTX up to 5 g/m² can be safely administered without monitoring of methotrexate levels by extended hydration, additional leucovorin, and monitoring of serum creatinine and urine pH.^[13]

When there is delayed clearance of methotrexate, hydration and leucovorin should be increased to prevent toxicity. In case of toxicity, glucarpidase (50 U/kg over 5 min) should be given along with leucovorin. This eliminates extracellular methotrexate by converting into nontoxic 4-deoxy-4-amino-N-10-methylpteroic acid. Glucarpidase is currently unavailable in India and needs to be imported. High-flux dialysis is an option if all the above measures fail.^[14]

Hepatotoxicity is more common with oral methotrexate than with HDMTX. Risk factors are long-term methotrexate, consumption of alcohol, and hepatitis B and C infection. The other rare side effects include cortical blindness, hemiparesis, seizure, and pulmonary toxicity.

Practical Tips

1. Third-space fluid collections such as ascites or pleural effusion should be drained before initiation of methotrexate^[7]
2. Drugs such as aspirin, cotrimoxazole, aminoglycosides, amphotericin, penicillin, NSAIDs, and proton pump inhibitors should be avoided while on HDMTX^[1]
3. Adequate hydration, urine alkalinization, leucovorin rescue, and monitoring of methotrexate levels help to prevent toxicity^[7]
4. If methotrexate levels are unavailable, monitoring of urine output, pH, and creatinine and twice-daily examination of mucous membrane can allow usage of HDMTX^[15]
5. Leucovorin should not be administered 2 h before or after administration of glucarpidase
6. Within 48 h of administration of glucarpidase, only high-performance liquid chromatography method should be used to detect methotrexate levels.

Conclusion

HDMTX administration is feasible with adequate hydration; urine alkalinization; leucovorin rescue; and monitoring of urine output, serum creatinine, and methotrexate levels.

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Conflicts of interest

There are no conflicts of interest.

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