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TDM monograph Methotrexate (MTX)

Synonyms: MTX, Amethopterine, Emthexate, Ledertrexate

Summary

Indication:	Patients treated with high-dose (≥ 500mg/m^2) methotrexate (HDMTX).
Sample material:	Serum, Na-Heparin, Lithium-Heparin or EDTA-plasma [1].
Time of sampling:	24 h, 48 h and 72 h after the start of HDMTX infusion (and longer if necessary).
Storage conditions:	Up to two weeks at 2 to 8°C. If testing will be delayed, specimens may be stored frozen (≤ -10°C) [1]. Samples stored frozen must be centrifuged first because of hemolysis that interferes with immunoassays.
Interpretation:	If MTX concentration <0.1–0.2 µmol/L, folinic acid rescue therapy can be stopped.
Evidence level:	2

Contents

Introduction

Methotrexate (MTX) doses ≥ 500 mg/m^2 are called high-dose MTX (HDMTX). HDMTX is mainly used in the treatment of various types of leukemia, as prophylaxis in patients with high-risk lymphoma, central nervous system lymphoma, the treatment of leptomeningeal metastases, high-risk trophoblastic tumor and osteosarcoma.

TDM of MTX is not used to optimize effectiveness. Instead, TDM is used to reduce MTX induced toxicity by serving as guidance for adequate folinic acid dosing. Treatment with folinic acid is called rescue therapy.

Folinic acid treatment initiation is recommended 12 – 24 hours after the start of a 1 – 6 hour MTX infusion and 36 – 48 hours after the start of a 24-hour MTX infusion [2, 3]. Folinic acid is generally initiated at a dose of 15 mg/m^2 (or 30 mg for adults), every 6 hours (q6h) intravenously until the MTX blood concentration is measured. Based on the measured MTX blood concentrations, the folinic acid dose may be adjusted. See further under *sampling conditions* and *interpretation of results*.

Dosing guidelines

Dosing and frequency of MTX are highly variable amongst different oncological indications and are subject to frequent changes. Specific treatment protocols are best consulted. For hematological malignancies and osteosarcoma, dosages commonly range from 1 – 8 g/m^2 and 8 – 12 g/m^2, respectively. In pediatric patients, the dose of HDMTX depends on age and indication with a maximum dose of 12 g/m^2 [2, 4].

The low dose indications (e.g. rheumatoid arthritis, psoriasis, Crohn's disease) generally have doses between 5 mg to 25 mg once weekly.

Dosing guidelines in patients with altered pharmacokinetics

MTX is mainly excreted renally via glomerular filtration and active tubular secretion. Therefore, MTX should be used with caution and in reduced dose in patients with impaired renal function. Although there is no consensus on the degree of dose adjustment in renal impairment, the following estimated Glomerular Filtration Rate (eGFR) may serve as guidance;

- eGFR<50 ml/minute: dose reduction of 50% or more is advised

- eGFR 50-80 ml/minute: dose reduction of 20 – 35% can be considered [2, 5-7].

Patients with a body surface area (BSA) exceeding 2 m^2 are at an elevated risk of developing acute kidney injury (AKI). Moreover, overweight patients, characterized by a body mass index (BMI) over 25 kg/m^2, compound this risk [8].

For considerations regarding patients with third-space compartments, please refer to the distribution section within the pharmacokinetics chapter.

Indications/Criteria for TDM

- HDMTX (≥500 mg/m^2)

- No TDM is required for the (relatively) low-doses of 5 – 25 mg weekly used for rheumatoid arthritis, psoriasis and Crohn's disease. When used for these indications, folic acid (instead of folinic acid) should be taken weekly (at least 24 hours after MTX intake).
    - When large quantities of oral MTX are taken at once (e.g. auto intoxication), determining MTX concentrations can be of added value. Although the chance of toxicity in such cases seems small given the saturability of the absorption process, determining MTX concentrations may be used to confirm this. However, in case of incorrectly administering the weekly MTX dose daily, blood MTX levels may be undetectable, but can lead to serious toxicities and death. Furthermore, due to reduced elimination, patients with renal impairment are at risk to develop toxicity upon a single overdose. In appropriate cases, treatment with folinic acid should be explicitly considered [9-12].
    - Although rarely used in practice, there is increasing evidence that TDM can be useful in rheumatoid arthritis and Crohn's disease. Higher methotrexate-polyglutamate concentrations in erythrocytes are associated with DAS28-CRP scores in rheumatoid arthritis and increased MTX drug-survival in Crohn's disease [13-15].

Reference values

Upon reaching MTX concentrations <0.1–0.2 µmol/L, the folinic acid rescue therapy can be stopped. For patients with delayed MTX elimination or evidence of AKI, MTX concentrations of <0.05 µmol/L can be considered. See also *interpretation of results* [2].

Toxicity

Nephrotoxicity
AKI develops in 0% – 12% of patients with an overall incidence rate of 1,8%. The subsequent delayed excretion leads to MTX accumulation, causing systemic toxicity. The renal injury is in general reversible [16].

Hepatotoxicity
MTX is known to cause elevations in serum alanine aminotransferase (ALT). Long-term therapy has been associated with the development of fatty liver, fibrosis and even cirrhosis. With HDMTX, serum ALT levels may rise to 10 – 20 times the upper limit of normal within 12 to 48 hours. Subsequently however, levels rapidly decline to normal with only rare cases of jaundice or symptoms of liver damage. In patients with long-term treatment with low to moderate doses of MTX, elevations in serum ALT or aspartate aminotransferase (AST) occur in 15% to 50% of patients. Usually these elevations are mild and self-limiting. If the serum ALT concentration is <180 IU/L, there is no reason to postpone a follow-up dose [17-19].

Hematologic toxicity
Neutropenia is encountered most frequently, but anemia and thrombocytopenia also develop in patients. Hematologic toxicity may also occur with HDMTX. This happens mostly in the presence of kidney dysfunction or by the use of specific concurrent medications delaying MTX clearance [4].

Pulmonary toxicity
MTX-induced pulmonary toxicity, including acute, subacute, and chronic interstitial pneumonitis has been

reported with low-dose methotrexate treatment. Pulmonary toxicity, such as pneumonitis, is rarely observed with HDMTX; however, cases have been published [4].

Neurotoxicity
Acute, subacute and chronic neurotoxicity are observed after HDMTX. Acute toxicity is generally transient with no permanent damage. In contrast, subacute and chronic toxicity is associated with changes in the central nervous system (CNS). This can be progressive. In severe cases, it leads to coma or death. It is believed that MTX directly exerts toxic effects on the CNS through neuronal tissue damage. Dextromethorphan and methylxanthines might be useful in the treatment of methotrexate-induced neurotoxicity [20, 21].

Mucositis
Oral mucositis has the potential to become a dose-limiting toxicity, necessitates opioid usage, heightens the risk of infection, and results in delays in chemotherapy treatment. Mucositis following HDMTX treatment arises from cellular damage affecting rapidly dividing epithelial cells throughout the gastrointestinal tract. Inadequate or delayed folinic acid rescue may impede the growth and regeneration of epithelial cells [5].

Dermatologic toxicity
Severe dermatologic reactions have been reported in patients using MTX, including erythema multiforme, erythroderma, Stevens-Johnson syndrome, and toxic epidermal necrolysis [4].

Sampling conditions

Based on the measured MTX blood concentrations, the folinic acid dose may be adjusted. Table 2 gives common high-dose MTX regimens including infusion duration, folinic acid start time and MTX monitoring times.

Folinic acid is generally initiated at a dose of 15 mg/m^2 (or 30 mg for adults), every 6 hours (q6h) intravenously until the MTX blood concentration is measured.

For 24-hour MTX infusions, table 3 gives a possible dosing strategy for intravenous folinic acid, based on the MTX concentration measured 36, 48, 72 and (more than) 96 hours after infusion initiation of MTX based on the HOVON 100 protocol [22].

For 1 – 6-hour MTX infusions, the first MTX concentration is best measured 24 hours after the start of the infusion. Adjustment of the folinic acid dosage can then be determined on the basis of the EURAMOS-1 protocol, see table 4 [23].

In general, oral folinic acid is not recommended given the potential chemotherapy-induced gastrointestinal disturbance and absorption saturability at doses above 40 mg, however, may be considered for patients with adequate MTX clearance and MTX blood concentration below 1 µmol/L [3, 24]. However, the HOVON 100 protocol is more lenient with regard to oral dosing.

An increase of creatinine ≥50% from the baseline at the end of infusion is predictive for delayed MTX elimination [3].

Indication	ALL	Osteosarcoma	Lymphoma
HDMTX dose	1–5 g/m^2	8–12 g/m^2	1–8 g/m^2
Infusion duration	24–36 h	4 h	2–6 h
Leucovorin start time	42 h	24 h	18–24 h
MTX monitoring times[a]	24 h, (36 h), 42 h, 48 h	24 h, 48 h, 72 h	24 h, 48 h, 72 h

Table 2. Common high-dose MTX regimens [3].

MTX level µmol/L	MTX level µg/L	H36	H48	H72	H96	>H96
>10	>4500	100 mg/m^2 i.v. × 4	100 mg/m^2 i.v. × 4^	200 mg/m^2 i.v. × 4^	200 mg/m^2 i.v. × 4^	200 mg/m^2 i.v. × 4^
>5	>2250	45 mg p.o. × 2	100 mg/m^2 i.v. × 4	100 mg/m^2 i.v. × 4	200 mg/m^2 i.v. × 4	200 mg/m^2 i.v. × 4
>1	>450	45 mg p.o. × 2	45 mg p.o. × 4	50 mg/m^2 i.v. × 4	100 mg/m^2 i.v. × 4	200 mg/m^2 i.v. × 4
>0.5	>225	45 mg p.o. × 2	45 mg p.o. × 4	45 mg p.o. × 4	50 mg/m^2 i.v. × 4	100 mg/m^2 i.v. × 4
>0.2	>90	45 mg p.o. × 2	45 mg p.o. × 4	45 mg p.o. × 4	45 mg p.o. × 4	50 mg/m^2 i.v. × 4
≤0.2	<90	No rescue	No rescue	No rescue	No rescue	No rescue

^Consider the application of glucarpidase.

Table 3. Folinic acid dosage regimen for a 24-hour MTX infusion, based on the HOVON 100 protocol [22].

MTX level µmol/L	MTX level µg/L	H24	H48	H72
>40	>18000	100 mg/m^2 i.v. x 4^	200 mg/m^2 i.v. x 8^	500 mg/m^2 i.v. x 8^*
>20	>9000	100 mg/m^2 i.v. x 4	200 mg/m^2 i.v. x 4	500 mg/m^2 i.v. x 8^*
>10	>4500	30 mg/m^2 i.v. x 4	100 mg/m^2 i.v. x 4	400 mg/m^2 i.v. x 8
>5	>2250	30 mg p.o. × 4	30 mg/m^2 i.v. x 4	200 mg/m^2 i.v. x 8
>1	>450	30 mg p.o. × 4	30 mg p.o. × 4	100 mg/m^2 i.v. x 4
>0.2	>90	15 mg p.o. × 4	15 mg p.o. × 4	15 mg p.o. × 4
≤0.1 – 0.2	<45-90	No rescue	No rescue	No rescue

**The maximum daily dose of folinic acid vary between clinics, ranging from around 1 gram to a maximum of 8 grams per 24 hours.*

^Consider the application of glucarpidase.

Table 4. Folinic acid dosage regimen for a 1 – 6-hour MTX infusions, based on the EURAMOS-1 protocol [23].

In cases where HDMTX infusions are closely spaced, a patient should be free of folinic acid for at least 1 day before starting a new session of HDMTX therapy, as folinic acid counteracts the effect of MTX [25].

The molar mass of MTX is 454.4 g/mol. To convert a methotrexate concentration in µmol/L to mg/L: divide by 2.2.

Background information

Pharmacodynamics

MTX is an antimetabolite and a structural analog of folic acid. It differs only in 4th position of the pteridine ring. MTX inhibits dihydrofolate reductase (DHFR) making DHFR unable to reduce folic acid to its biologically active forms. These active forms of folic acid are normally required for the synthesis of purine nucleotides and thymidylate. The net result is a blockade of DNA, RNA and protein synthesis. Folinic acid is a reduced, active form of folate. As such, it does not require DHFR for purine nucleotide and thymidylate formation. Contrarily, folic acid is unsuitable to counteract MTX toxicity because folic acid needs DHFR for purine nucleotide and thymidylate formation [24-26].

Pharmacokinetics

- ### Absorption
  After intravenous administration, peak serum concentrations of MTX are reached after approximately 0.5 – 1 hour. There is a strong inter-subject and intra-subject variation, especially with repeated administration. Saturation of oral absorption occurs at doses above 40 – 60 mg [3, 9, 24].

- ### Distribution
  About half of the absorbed MTX is reversibly bound to plasma proteins. MTX readily diffuses into cells, reaching the highest concentrations in the liver, spleen and kidneys in the form of polyglutamate, which can be incarcerated for several weeks or months. To a lesser extent, MTX also penetrates into the cerebrospinal fluid. Diffusion into breast milk is limited. However, as MTX has a long residence time, especially in neonates, use of low dose MTX is not recommended during breast-feeding. An abstinence period of at least 1 week after HDMTX has been suggested for breastfeeding women. Third space compartments have been considered as relative contraindication for HDMTX therapy. MTX slowly diffuses from third space accumulations, resulting in: prolonged terminal plasma half-life, delayed excretion and serious adverse effects. Possible third space compartments are pleural effusion, ascites and edema [2, 9, 27, 28].

- ### Metabolism and excretion
  The elimination from plasma is three-phase and MTX is largely excreted unchanged in the urine within 24 hours. The half-life of MTX ranges from about 3 to 10 hours during low-dose treatment and around 5 to 15 hours in HDMTX (with a terminal half-life of roughly 83 hours, primarily within the concentration range below 0.1 µmol/L). Approximately 95% percent of MTX is excreted in its original form in the urine. It is believed that HDMTX-induced renal dysfunction is mediated by the precipitation of MTX and its metabolite 7-OH-MTX in the kidney tubules or due to a direct toxic effect of MTX on the renal tubules. This precipitation results from the rapid renal excretion of MTX from HDMTX and leads to high urine concentrations. These high concentrations can then exceed the solubility limit of MTX and the metabolite 7-OH-MTX at pH<7. Alkalization of the urine with sodium bicarbonate and regular control that urine pH is >7 and forced diuresis are therefore recommended with HDMTX. Clearance itself is not affected by these methods, which is largely dependent on glomerular filtration in HDMTX. Neither standard hemodialysis nor peritoneal dialysis

increases the elimination of MTX. Acute intermittent hemodialysis using a highly permeable artificial kidney can be attempted in MTX intoxication [3, 9, 25, 29, 30, 32].

Glucarpidase

The antidote glucarpidase is indicated in the occurrence of HDMTX-induced AKI. Due to the high costs and possible poor availability, it is recommended to first evaluate the primary therapy of folinic acid, hyperhydration and alkalinization of the urine before applying glucarpidase. This antidote drug lowers the MTX level. Glucarpidase converts MTX into its inactive metabolites 2,4-diamino-N(10)-methylpteroic acid (DAMPA) and glutamate. Because both DAMPA and glutamate are metabolized by the liver, it provides patients with renal impairment an alternative pathway for MTX elimination. Glucarpidase should always be given with folinic acid to provide intracellular rescue as glucarpidase prevents only further accumulation of intracellular MTX by removing it from the extracellular compartment. However, folinic acid should not be given 2 hours before and 2 hours after the glucarpidase dose, as glucarpidase also has an affinity for folinic acid (although less than for MTX) which leads to a reduced effect on the degradation of MTX. After treatment with glucarpidase, the MTX immunoassay is no longer reliable due to overestimation of the MTX concentration [3, 25, 31, 32].

Pharmacogenetics

There is little conclusive evidence that genotyping of MTHFR C677T, A1298C, ABCB1 C3435T or SLC19A1 A80G is clinically relevant [2]. Therefore, it is not recommend for clinical practice currently.

Interactions

For drug-drug interactions with MTX, see the Lexicomp® Drug Interactions checker: https://www.uptodate.com/drug-interactions/

PK parameters

	F	Cl	Vd	$t_{1/2}$	Protein binding
Children	23-95% [4]	84 ml/min/m^2 (0-3 months) 89 ml/min/m^2 (0-6 months) 111 ml/min/m^2 (7-12 years) [33]		ALL: 0.7 – 5.8 h (dose range: 6.3 - 30 mg/m^2) pJIA: 0.9 – 2.3 h (dose range: 3.75 to 26.2 mg/m^2) [4]	
Adults	60% (<30 mg/m^2) [4]	11 l/h/1,73 m^2 [30]*	0.18 l/kg (initial) 0.4 - 0.8 l/kg (steady state) [4] 34 l/1,73m^2 [30]*	3 – 10 (low-dose) 8 – 15 (high-dose) [4] $t_{1/2}$-1 = 0.97 h $t_{1/2}$-2 = 5.58 h $t_{1/2}$-3 = 82.6 h [30]*	50% [4]

*The data originates from a pediatric population; however, the pharmacokinetic model in question fit adult data with an R^2 of 0.96.

Population models

A population model with its corresponding simulation tool at https://mtxpk.org/ can be used if sampling occurs outside of the given timeframes [30, 34].

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Colophon

This guideline has been constituted by drs. Roger de Rooij, hospital pharmacist in training Maastricht UMC+ and Zuyderland MC, dr. Judith de Ruijter – van Dalem, hospital pharmacist Maastricht UMC+, dr. Robin van Geel, hospital pharmacist-clinical pharmacologist Maastricht UMC+ and dr. Thijs Oude Munnink, hospital pharmacist UMC Groningen.

Under the auspices of TDM, Toxicology and Pharmacogenetics committee (TTF) of the Dutch Association of Hospital Pharmacists (NVZA) and the International Association of Therapeutic Drug Monitoring and Clinical Toxicology (IATDMCT)

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Appendices

Not applicable

Revision

Updated the information according to the most recent literature (published after October 2014) and the published first evidence-based guideline in 2021.[2]