
NDC 67457-486-04
Methotrexate
Injection, USP
100 mg/4 mL
(25 mg/mL)
Sterile Isotonic Solution
Preservative free
May be diluted
CAUTION: CYTOTOXIC AGENT
For intramuscular, intravenous, intra-arterial or intrathecal use
Mylan
Rx only Single-Dose Vial
Methotrexate
Mylan

Mode of Action

- MTX is a folic acid anti-metabolite.
- MTX acts via inhibition of DHFR.
- The affinity of DHFR to methotrexate is far greater than its affinity to folic acid or dihydrofolic acid.

B-Methotrexate:

MOA:

An anticancer, acts by competitive inhibition of the enzyme dihydrofolate reductase and enzyme involved in protein synthesis as well as anti-inflammatory and cytokine-modulating effects.

It is well absorbed orally $t_{1/2}$ 5 hr. response occur sooner than other. Doses are less than that in cancer therapy(7.5 mg weekly).

Table 1 FDA-Approved Indications for Methotrexate

Neoplastic diseases

- Acute lymphocytic leukemia
- Breast cancer
- Chorioadenoma destruens
- Epidermoid cancers of the head and neck
- Gestational choriocarcinoma
- Hydatidiform mole
- Lung cancer (squamous and small-cell)
- Meningeal leukemia
- Mycosis fungoides (advanced; a type of cutaneous T-cell lymphoma)
- Non-Hodgkin's lymphoma (advanced stage)
- Osteosarcoma (non-metastatic; after surgical resection or amputation for the primary tumor)

Autoimmune diseases

- Polyarticular-course juvenile rheumatoid arthritis (active)
- Psoriasis (severe, recalcitrant, disabling)
- Rheumatoid arthritis (severe, active)

Data from methotrexate prescribing information.[15]

Box 1. Contraindications to Methotrexate Therapy

Absolute Contraindications

- Intrauterine pregnancy
- Evidence of immunodeficiency
- Moderate to severe anemia, leukopenia, or thrombocytopenia
- Sensitivity to methotrexate
- Active pulmonary disease
- Active peptic ulcer disease
- Clinically important hepatic dysfunction
- Clinically important renal dysfunction
- Breastfeeding
- Ruptured ectopic pregnancy
- Hemodynamically unstable patient
- Inability to participate in follow-up

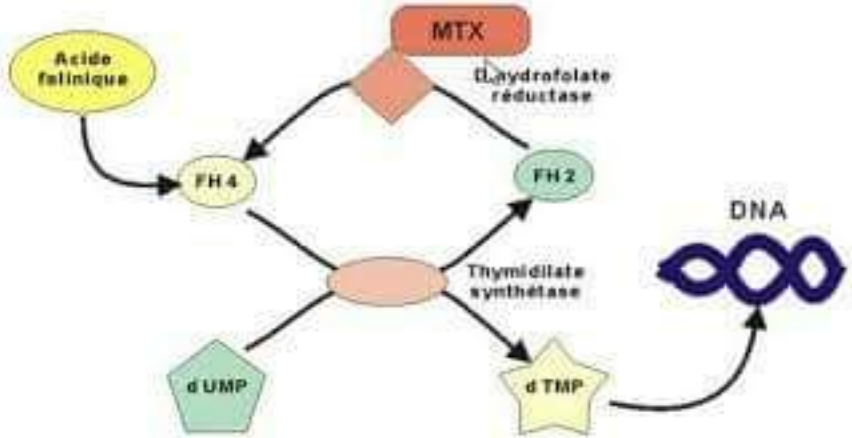
Relative Contraindications

- Embryonic cardiac activity detected by transvaginal ultrasonography
- High initial hCG concentration
- Ectopic pregnancy greater than 4 cm in size as imaged by transvaginal ultrasonography
- Refusal to accept blood transfusion

Modified from Medical treatment of ectopic pregnancy: a committee opinion. Practice Committee of American Society for Reproductive Medicine. Fertil Steril 2013;100:638–44.

Methotrexate Mechanism of Action

- MTX acts as a competitive analog of folate blocking dihydrofolate reductase preventing the formation of THF and blocking purine biosynthesis
- This drug much like AZA induces the apoptosis of activated lymphocytes



Folate antagonist: Methotrexate

Adverse effects:

- *MTX* causes stomatitis, myelosuppression, erythema, rash, urticaria, and alopecia.
- Most frequent toxicities: nausea, vomiting, and diarrhea.
- **Adverse effects can be prevented or reversed by administering *leucovorin*.**
- **Hepatic function:** Long-term use of *MTX* may lead to cirrhosis.
- **Renal function:** Variable
- **Neurologic toxicities:** subacute meningeal irritation, stiff neck, headache, and fever. Rarely, seizures, encephalopathy or paraplegia occur.
- **Contraindications:** Because *MTX* is teratogenic in experimental animals and is an abortifacient, it should be avoided in pregnancy.

Most common side effects	Treatment
Nausea (feeling sick) vomiting, loss of appetite & diarrhoea	• Folic acid (vitamin tablet / liquid) • Anti-emetics (anti-sickness medication) • May be reduced by giving methotrexate by injection
Skin rash / sun sensitivity	• Use high factor sun screen and hats
Mouth ulcers Sore gums Sore throat	• Folic acid (vitamin tablet)

Rare side effects	Treatment
May cause hair thinning Disturbance in the blood counts (change in blood tests results) Upset liver function	• Usually returns to normal if methotrexate dose reduced or stopped

Methotrexate Toxicity

- Usually presents with malaise, myalgias, fever, cough and dyspnea, skin rash in some cases
- Radiographs vary from normal to mild atelectasis to bilateral alveolar infiltrates: Gallium scans are positive
- Dramatic response to corticosteroids
- Seldom leads to fibrosis

Methotrexate (MTX)

- Toxicity
  - Bone marrow suppression: leukopenia
  - Nausea and vomiting
  - Sores in the mouth or the lips (ulcerative stomatitis)
  - Hair loss (from head and body).
  - Signs of infection/fever, chills, cough, sore throat
  - Bruising or bleeding, black, tar-like stools.
  - Red spots on skin, rash, itching
- Leucovorin (甲酰四氢叶酸)

HDMTX Toxicities

TOXICITY	INCIDENCE PER HDMTX COURSE	RISK FACTORS / COMMENTS
AKI	Uncommon	Volume depletion, acidic urine, inadequate leucovorin, drug-drug interactions
Mucositis	Common	Uncommon to reach grade 3
Emesis	Common	Can usually be prevented
Hepatic	Very common	Elevated transaminases occur after most HDMTX courses, but elevated bilirubin in only 25%
Myelosuppression	Very common	Growth factors are not required, absolute neutrophil count < 1,000 is very common
Rash	Uncommon	Up to 10% of courses; rarely severe
CNS	Uncommon	Motor dysfunction, seizure, etc.

Preventing HDMTX Toxicity

- Before administration of therapy
  - Careful patient selection and medication reconciliation[a,b]
  - Rigorous hydration[a]
  - Alkalinization of urine[c]
    - Bicarbonate
    - Acetazolamide
  - Drainage of third-space fluids[a]
- After administration of therapy[d]
  - Regular monitoring of MTX plasma levels
  - LV rescue
  - Regular assessment of kidney function/urine pH

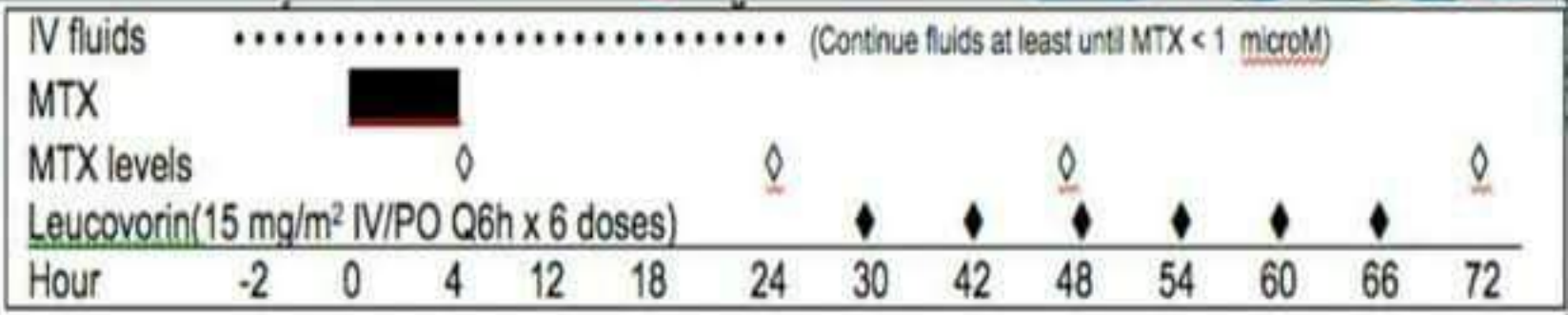
a. Treon SP, et al. *Clin Chem.* 1996;42:1322-1329[4]; b. Joint Commission website[16]; c. Shamash J, et al. *Cancer Chemother Pharmacol.* 1991;28:150-151[18]; d. Methotrexate injection PI 2011.[11]

HDMTX: Management of Toxicity

- Frequent monitoring of renal function[a,b]
- Aggressive hydration and urine alkalinization[a,c]
- Use of acetazolamide[d]
- Aggressive LV rescue[a,c,e]
- Administration of glucarpidase[f]
- May involve hemodialysis[g]

a. Methotrexate injection PI 2011[11]; b. Widemann BC, et al. *J Clin Oncol.* 2010;28:3979-3986[14]; c. Relling MV, et al. *J Clin Oncol.* 1994;12:1667-1672[5]; d. Shamash J, et al. *Cancer Chemother Pharmacol.* 1991;28:150-151[18]; e. Flombaum CD, et al. *J Clin Oncol.* 1999;17:1589-1594.[8]; f. Widemann BC, et al. *Pharmacotherapy.* 2013;[9] g. Rahiem Ahmed YAA, et al. *J Cancer Sci Ther.* 2013;5:106-112.[12]

Leucovorin Regimen



Clinical Situation	Laboratory Finding	Leucovorin Dosage and Duration
Normal Methotrexate Elimination	Serum Methotrexate level approximately 10×10^{-6} molar at 24 hours after administration 1×10^{-6} molar at 48 hours, and 0.1×10^{-6} at 72 hours	10 mg PO, IM or IV q 6 hours for 60 hours (10 doses starting at 24 hours after start of Methotrexate infusion)

Leucovorin Regimen

If the methotrexate concentration falls below $0.1x10^{-6}$ molar before the completion of the 72-hour rescue period.

If the methotrexate concentrations are still greater than $0.1x10^{-6}$ molar at 72-hr but less than $1x10^{-6}$ molar at 48 hour.

The rescue can be **discontinued.**

The rescue is **continued** At dose of 10 mg/m^2 every 6 hours until the MTX concentration falls below $0.1x10^{-6}$ molar.

Methotrexate plasma leval.			Leucovorin dose regimen.
At 24 hr	At 48 hr	At 72 hr	
$10x10^{-6}$ molar.	$1x10^{-6}$ molar.	$0.1x10^{-6}$ molar.	Normal leucovorin regimen of **10 mg\m²** q6hr (till 72 hr).
$10x10^{-6}$ molar.	$1x10^{-6}$ molar.	**More than** $0.1x10^{-6}$ molar.	Continue with **10 mg\m2** q6hr (Till methotrexate plasma level reach $0.1x10^{-6}$ molar).
More than $10x10^{-6}$ molar.	**More than** $1x10^{-6}$ molar.		increasing the leucovorin rescue dose **50 – 100 mg\m²** or more **(Toxic case).**