EMERGENCY TREATMENT OF LIFE-THREATENING INTRATHECAL METHOTREXATE OVERDOSE BY CSF EXCHANGE

Y. Finkelstein[1], S. Zevin[2], J. Heyd[2], Y. Bentur[3], Y. Zigelman[4], M. Hersch[4]

[1] Dept. of Neurology; [2] Dept. of Internal Medicine, [4] Intensive Care Unit, Shaare Zedek Medical Center; [3] Israel Poison Information Center

Introduction

- Methotrexate (MTX) is an antimetabolite antineoplastic agent
- Mechanism of action: inhibition of folate – dependent biosynthesis
- High – dose MTX is used in ALL, osteosarcoma, breast carcinoma
- Intrathecal MTX is used for CNS prophylaxis in ALL and high – grade lymphomas
- CNS toxicity is dose and route dependent
- MTX crosses the BBB poorly, limited by low lipid solubility and slow passive diffusion
- MTX has little neurotoxicity when administered orally or in regular intravenous doses

MTX Pharmacokinetics

- Volume of distribution: 0.2-0.5 l/kg
- Predominantly renal clearance
- Two – compartment model
- Alpha $T_{1/2}$ is 3 hours, with significant amount eliminated during this phase
- Beta terminal $T_{1/2}$ is 10 hours; starts when levels are about 0.5 mcM
- Therapeutic plasma concentrations for leukemia: in the range of 10-16 mcM; and < 1 mcM 48 hours post start
- Toxic plasma concentrations: > 1 mcM 48 hours post start
- Toxic CSF concentrations: > 100 mcM

MTX – CNS toxicity

High – dose IV MTX (> 1 gr/ m2), or IT MTX (12 – 15 mg):

- Acute encephalopathy (within 24 – 48 hours): seizures as principal manifestation
- Subacute encephalopathy (within days to weeks): stroke – like episodes resulting in multifocal deficits
- Chronic delayed encephalopathy (3 months or more): leukoencephalopathy

Case Presentation

- 34 years old male with diffuse aggressive lymphoma with bone marrow involvement
- Treatment: CHOP with IT- MTX for CNS prophylaxis
- CHOP was administered 2 days before IT-MTX
- IT-MTX prescribed dose was 15 mg along with Hydrocortisone 100mg
- Shortly after IT injection: agitation and low back pain
- Two hours later: confusion followed by generalized seizures
- At this stage – it was realized that the dose contained **1200 mg** of MTX
- Later – ARDS and coma; the patient intubated and transferred to ICU
- Immediate treatment:
- IV Leucovorin 1200 mg and 15 mg q 6 hours thereafter for 72 hours
- CSF exchange with warm normal saline via IT catheter was initiated 6 hours after IT-MTX injection
- Initially, CSF exchange was very slow (60 ml only overnight);

  after IT dexamethasone administration (2 mg X 5) – further 150 ml were exchanged more rapidly during the next 36 hours
- IT Leucovorin 2 mg with final dose of Dexamethasone were given at the end of CSF exchange
- ICU course included agranulocytosis complicated by ongoing sepsis treated with multiple broad- spectrum antibiotics
- Two weeks later – recovery of WBC
- Three weeks later – tracheostomy and weaning from the ventilator
- Patient regained consciousness, but remained with cognitive and motor long - tract deficits
- Despite further chemotherapy, malignant lymphoma progressed relentlessly and the patient succumbed 70 days later

IT – MTX Meningeal Toxicity

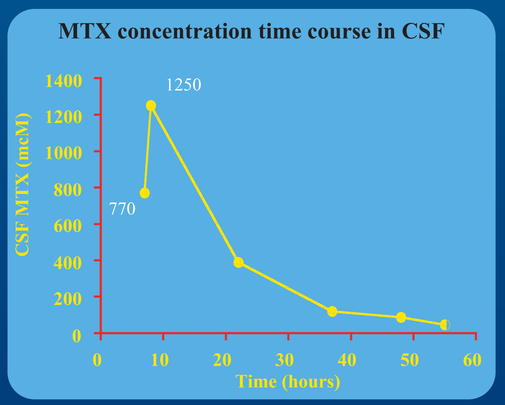
- Onset – within few hours of IT treatment
- Acute chemical meningitis
- CSF: pleocytosis, elevated protein

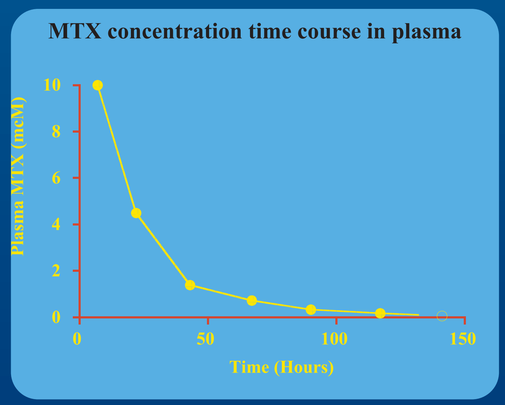
IT MTX Overdose

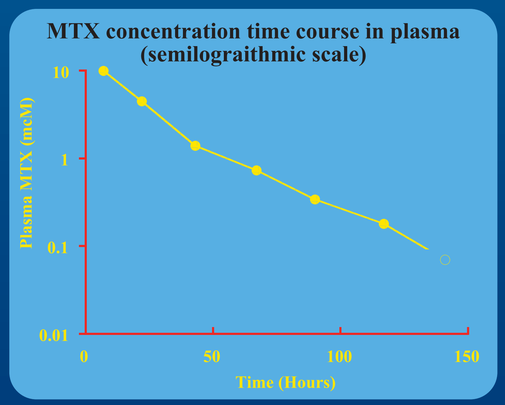
- Few reported cases
- The highest reported IT dose after which the patient survived – 625 mg
- Symptoms of acute encephalopathy of both white and gray matter
- No clear guidelines for treatment

MTX Plasma Levels

- Plasma levels of MTX declined in a log – linear fashion
- Beta phase was not reached during the time levels were measured
- However, alpha phase elimination half life time was longer than expected (19.8 hours vs 3 hours)
- CSF may constitute an endogenous reservoir which slowly releases MTX to plasma







Discussion

- This case is up to date the highest reported dose of IT – MTX (80 - fold the therapeutic dose)
- The major clinical manifestations were those of acute leukoencephalopathy and acute chemical arachnoiditis
- Chemical arachnoiditis probably caused the initial slow rate of CSF exchange
- IT Dexamethasone probably relieved arachnoiditis thus enabling more efficient CSF exchange
- CSF protein was normal and there were no cells
- In some other cases, CSF pleocytosis and elevated protein were reported
- Leucovorin (folinic acid) is a pharmacologically active form of folic acid
- Leucovorin (IV or orally) is used as rescue treatment after high – dose MTX treatments and for MTX overdoses
- Leukovorin is neurotoxic when given IT
- Fatality was reported after IT - Leucovorin given to a child following IT - MTX overdose
- This patient was given high dose IV Leucovorin (mg per mg) as soon as the mistake was realized, which was continued according to standard protocol
- In addition, 2 mg Leucovorin were given IT at the end of CSF exchange

Treatment options for IT – MTX overdose

- Ventricular – lumbar washout
- CSF exchange with normal saline
- Investigational agents carboxypeptidase G1 and G2 which rapidly hydrolyze MTX
- IV Leucovorin
- IT- Leucovorin and IT- Dexamethasone are debated

Summary

This case indicates that IV high dose Leucovorin, CSF exchange and IT-Dexamethasone may be an effective treatment for IT – MTX overdose

Low dose of IT-Leucovorin may be considered