

Diagnosis and Treatment of Methotrexate (MTX) Neurotoxicity in Oncology Patients

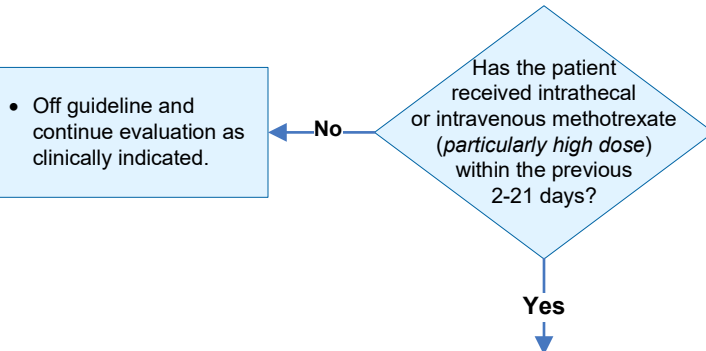


Inclusion Criteria: Oncology patients receiving methotrexate (intrathecal or intravenous) who present with new neurologic symptoms concerning for methotrexate neurotoxicity.

Exclusion Criteria: Patients not receiving methotrexate; diagnosis of ischemic stroke, PRES, CNS infection, metabolic derangement, or leukemic CNS involvement.

Recommendations/ Considerations

- Methotrexate neurotoxicity is a syndrome-based clinical diagnosis supported by timing, clinical presentation, neuroimaging, and exclusion of alternative etiologies.
- Oncology team must be notified and involved in the work up and care.
- MRI findings may be normal; diagnosis should not rely solely on imaging findings.



Assessment

Clinical Presentation – symptoms may include; but not limited to the following:

- Altered mental status
- Aphasia
- Ataxia
- Dysarthria/slurred speech
- Facial asymmetry
- Headache
- Hemiparesis
- Hemisensory deficits
- Seizures
- Visual disturbance

Note: Symptoms may fluctuate / wax and wane

Neuroimaging (for pre-existing)

- Magnetic Resonance Imaging (MRI) brain with diffusion-weighted imaging (DWI) may demonstrate restricted diffusion in a non-vascular distribution.

Exclusion of alternative diagnoses – Evaluate for:

- Acute ischemic stroke
- Posterior reversible encephalopathy syndrome (PRES)
- Central nervous system (CNS) infection
- Metabolic derangements
- Leukemic CNS involvement

If acute stroke is suspected, follow the **Acute Stroke – Oncology Code Stroke Protocol** immediately.

Interventions

Diagnostic Evaluation

- Complete Blood Count (CBC)
- Comprehensive Metabolic Panel (CMP)
- Vitamin B12 level
- Methotrexate level
- Additional studies as clinically indicated to evaluate for infection or metabolic abnormalities

Neuroimaging

- Obtain non-contrast Computed Tomography (CT) head to rule out acute hemorrhage or other intracranial pathology, STAT.
- If symptoms persist or methotrexate neurotoxicity remains suspected, obtain:
 - MRI brain with and without contrast with DWI
 - Consider Magnetic Resonance Angiography/Magnetic Resonance Venography (MRA/MRV) when clinically indicated to exclude alternative diagnoses.

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If clinical presentation and workup are consistent with MTX neurotoxicity and alternative diagnosis is excluded, proceed with treatment:

Pharmacologic Management

Dextromethorphan

- 2 mg/kg/day orally divided twice daily (max 120 mg/day)
- Continue for up to 7 days
- Discontinue sooner if symptoms resolve

and/or

Aminophylline

- 2.5 mg/kg IV (max 100 mg; *use ideal body weight*)
- Infuse over 1 hour every 24 hours until symptom resolution
- Obtain aminophylline level before the third dose
- Goal serum concentration: < 15 mcg/ml

and/or

Vitamin B12

- Begin Vitamin B12 100 mcg daily
- Continue pending Vitamin B12 level
 - If Vitamin B12 < 200 pg/mL, continue supplementation
 - If Vitamin B12 level is normal, discontinue supplementation

Medication Considerations

- Aminophylline is a major substrate of CYP1A2.
- The following drugs are in Category D or above and should be avoided as they increase theophylline level and have the potential to cause theophylline toxicity:
 - Belumosudil
 - Carbamazepine
 - Systemic erythromycin
 - Moderate or strong CYP1A2 inhibitors

Additional Recommendations / Considerations

- Leucovorin is *not recommended* for treatment of methotrexate neurotoxicity unless otherwise clinically indicated.
- Vitamin B6 and folic acid are *not routinely recommended* because evidence supporting their use is limited.
- Consult Neurology and the primary Oncology service for ongoing management.
- Consider repeat MRI if neurologic symptoms persist despite an initially unrevealing study and clinical suspicion remains high.

Discharge Criteria

- Neurological symptoms have resolved or significantly improved.
- No alternative neurologic emergency requiring inpatient management is identified.
- Patient is clinically stable.
- Appropriate Oncology follow-up has been arranged.
- Caregivers understand return precautions.

Patient / Family Education

- Methotrexate neurotoxicity is an uncommon but recognized complication of methotrexate therapy.
- Symptoms are often temporary and generally improve with supportive care, with complete resolution in most cases.
- Return immediately for:
 - New weakness
 - Difficulty speaking
 - Vision changes
 - Seizure
 - Altered mental status
 - Worsening neurologic symptoms
- It is important to have close follow-up with the Oncology team.

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