Low-dose methotrexate toxicity

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1 Methotrexate is used at low doses for the treatment of autoimmune and inflammatory disorders

Low-dose methotrexate is an effective first-line treatment for early rheumatoid arthritis and other inflammatory arthropathies,[1] and as a maintenance therapy in Crohn disease, vasculitis and refractory atopic dermatitis. The usual dose is 5 to 25 mg once weekly. Patients should take folic acid (1 mg) on days they are not taking methotrexate to prevent folate depletion.

2 Complete blood count, liver and renal function should be monitored during treatment

Before starting treatment, liver and kidney disease should be excluded, and screening done for alcohol use. Pretreatment investigations should include baseline complete blood count, assessment of liver and renal function, chest radiograph and pregnancy test (in women of childbearing age).[2] Complete blood count, creatinine and liver function test should be assessed every 2–4 weeks for the first 3 months, then 8–12 weeks for the following 3–6 months, and every 12 weeks thereafter.[1]

3 Toxicity can cause bone marrow, hepatic and pulmonary disorders

Pancytopenia occurs in less than 1% of patients and typically resolves after stopping treatment.[3] Hepatotoxicity ranges from mild steatosis to severe fibrosis and cirrhosis, and is associated with long-term use, obesity, diabetes and alcohol use.[3] Pulmonary toxicity occurs in less than 8% of patients, usually within the first year of treatment.[3] Painful stomatitis and gastrointestinal upset are the most common minor adverse effects.[3] See Appendix 1 (available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.181054/-/DC1) for reasons to re-evaluate therapy.

4 Decreased clearance, drug–drug interactions and dosing errors are risk factors for toxicity

Additionally, hypoalbuminemia and renal failure increase the risk of toxicity.[3] Toxicity can occur with the combination of trimethoprim-sulfamethoxazole and methotrexate because both inhibit folate metabolism; prophylactic doses of trimethoprim-sulfamethoxazole are considered safe.[3] Patients may mistakenly take doses daily instead of weekly, and because folate and methotrexate tablets look similar, one tablet may be mistaken for the other (Appendix 2, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.181054/-/DC1).

5 Folic acid or folinic acid (leucovorin) is used to prevent and treat toxicity

Folic acid decreases the risk of gastrointestinal adverse effects by 9%, elevated liver function tests by 16%, and rates of drug discontinuation by 15%.[4] With gastrointestinal upset, the dose can be increased to 5 mg. Leucovorin (2.5 mg to 5 mg once weekly) can be given to mitigate adverse effects, including stomatitis, when higher doses of folic acid have failed. It treats toxicity by bypassing methotrexate inhibition of dihydrofolate reductase, the enzyme required to reduce folate to tetrahydrofolate.[4]

References

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