Methotrexate toxicity

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- Vitamin A and Oral Ulceration: while the package insert for MTX states "…certain side effects such as mouth sores may be reduced by folate supplementation", my experience suggests this is rarely so and the Cochrane review supports this non-association. Dr. Kamen taught me that when rats are given oral MTX, a severe enterocolitis ensues. However when these same rats are pre-treated with vitamin A – no such GI toxicity was observed. This led to our clinic study that showed Vitamin A given as 8,000 IU day was effective in nearly two-thirds of patients in reducing oral ulcerations and post-MTX nausea. It was less effective, but worthwhile, in reducing the diarrhea sometimes seen.
- Dextromethorphan and the "Blahs": Neurotoxicity is quite common with high-dose MTX chemotherapy (10% seizures) and more frequent than most realize with low-dose weekly MTX. A survey of clinic patients showed that nearly 50% of MTX patients admitted to some neurologic manifestations – usually manifest as post-MTX somnolence/fatigue or "the Blahs", but may also include headache, cognitive dysfunction, impotence, blindness or numbness. Usually such symptoms last for 24-36 hours. Again, it was Dr. Kamen who taught me that the metabolism of MTX leads to excess homocysteine and that homocysteine leads to a number of excitogenic amines that includes homocyteic acid, amongst others. Interestingly these amines will noncompetitively bind NMDA receptors in the brain and presumeably mediate the neurotoxicities seen. NDMA binding can be noncompetitively inhibited by dextromethorphan. Dr. Kamen often related stories of children with leukemia who were receiving intrathecal MTX and would go into a coma. He would then perform his magic by taking a bottle of Robitussin DM and pouring down the NG tube so that his residents and fellows could watch the child awaken from the drug induced coma. This led to our study in 1999 that was published as an ACR abstract wherein we treated our MTX patients who had the "blahs" and showed again that two-thirds promptly responded and had less or no CNS symptoms. Hence we now recommend the use of dextromethorphan (20-50 mg) be given weekly with the MTX dose and again 8-12 hours later. We usually prescribe this as a tablet (Mucinex DM).