Reply: Methotrexate neurotoxicity due to drug interactions: an inadequate folinic acid effect

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We thank Professor Cohen for his reply and his interesting points regarding the possible role of inadequate folinic acid rescue in contributing to neurotoxic side-effects of methotrexate. We can confirm that the patient reported in our article [1] had not received any previous exposure to any systemic methotrexate (oral or intravenous) even at low dose. In addition, the other published article on this possible interaction with nitrous oxide [2] reported a patient developing symptoms early during induction therapy on a protocol with a standard 3-drug induction (vincristine, asparaginase and corticosteroids). Therefore, concomitant systemic methotrexate appears not to be a contributing factor in either of these reported cases.

As pointed out by Prof Cohen the recent article by Krull et al [3] indicates, for the first time in acute lymphoblastic leukaemia (ALL), a direct association between methotrexate plasma levels (area under the curve) and adverse long-term neurocognitive outcomes. The role of folinic acid rescue in prevention of neurotoxic side effects remains speculative [4,5] and has never been tested in a randomised trial. In addition, the impact of over-rescue on leukaemic relapse is still uncertain [6,7] and differences in scheduling and concomitant chemotherapy as well as individual pharmacogenomics are all likely to play a part.

It is worth noting that nitrous oxide irreversibly inactivates vitamin B12 - a co-factor for methionine synthase- rather than directly interfering with Methotrexate induced inhibition of dihydrofolate reductase [8]. Since methionine synthase activity is required for homocysteine to methionine conversion, it may be that, in the presence of low/inactive B12, the efficacy of folinic acid rescue in reducing neurotoxic symptoms related to high homocysteine [9] and/or low methionine is more limited. In other words, even in the presence of adequate folinic acid rescue, the conversion of homocysteine to methionine may still be impaired due to low methionine synthase activity. However, to our knowledge this has never been tested experimentally.

In summary, further studies are clearly needed to investigate the optimal dosing of both methotrexate and folinic acid rescue in order to balance efficacy and toxicity. Yet, we still believe that the most effective way of reducing this potential drug interaction is to limit exposure to nitrous oxide, especially as a number of safe non-toxic alternative anaesthetic agents are in routine use.

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