



The importance of adequate methotrexate and adequate folinic acid rescue doses in the treatment of primary brain lymphoma

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To the Editor,

Adhikari et al. [1] are to be congratulated on their clinical study published recently in the journal in which they present several important findings. The high dose Methotrexate (HDMTX) protocol given with appropriate dose folinic acid rescue (200 mg/m² after 3.5 g/m² MTX) was not associated with any systemic toxicity and resulted in no neurotoxicity on neuropsychological assessment. Reducing the dose of radiotherapy did not decrease the early neurotoxicity but on this MTX protocol, prognosis was compromised by a reduction in radiation dose in those patients who achieved a complete remission on HDMTX based chemotherapy. This suggests that the MTX dose was inadequate.

I would like to contribute to the authors' search for improved therapy by reminding them that the first report of successful treatment of primary brain lymphoma by high dose MTX, in 1986, (without radiotherapy) used 7.5–12 g/m² MTX with 400–760 mg/m² of folinic acid. These are appropriate doses for such MTX doses. This protocol was without any neurotoxicity and the then 3.5 year old patient, now married with two children, currently works as an inland revenue inspector of taxes [2]. The doses used were based on the requirement to achieve a minimum therapeutic concentration of 10⁻⁶ M in the CSF for a minimum of 24 h [2]. There is little published adult data but we have been able to show that in children with brain tumors, who have not been irradiated, doses of less than 10 g/m² methotrexate cannot be relied on, to achieve a guaranteed 24 h MTX CSF level of 10⁻⁶ M [3]. It is important to know that no evidence has been found for the existence of a fixed effective MTX/folinic acid

ratio but doubling the dose of MTX, in at least one mouse model, has been shown to require an increase of 3 or 4 times the folinic acid dose needed to prevent fatal side effects [3]. The CSF levels of methotrexate achieved after radiotherapy are much higher due to disruption of the blood brain barrier and consequently there is a greater danger of neurotoxicity because of inadequate folinic acid rescue. This explains the well known phenomena that MTX after radiotherapy is associated with neurotoxicity that does not occur when the methotrexate precedes radiation. Obviously there are major differences between children and the elderly but both inadequate doses of MTX and inadequate folinic acid rescue cause problems in both age groups in a similar manner.

The clinical significance of “over rescue” by too much folinic acid after HDMTX is neither evidence based nor has been found to be supported by the published claims of its existence [4]. Significantly no published series can be found that documents a reduced prognosis with increased folinic acid rescue.

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