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Response to: Comment on “Delayed methotrexate excretion in infants and young children with primary central nervous system tumors and postoperative fluid collections”

Letter of Response to Professor Cohen

We appreciate the letter by Professor Cohen and thank him for his complimentary comments regarding our recently published study of delayed methotrexate excretion in infants and young children with brain tumors and postoperative fluid collections. Generally, he agrees with our conclusions regarding administration of high dose methotrexate (HDMTX) in infants with intracranial fluid collections [1]. He notes that we do not discuss neurotoxicity as part of our toxicity pattern after HDMTX. Our study focused on the first course of HDMTX during which neurotoxicity was not observed in any patient regardless of fluid collection status. A detailed discussion of neurotoxicity would be more appropriate following completion of all courses of HDMTX; however, this is likely to be wrought with a number of confounding variables as patients are exposed to additional toxic chemotherapeutic agents, and in some cases, more surgery and/or subsequent irradiation.

Professor Cohen suggests that our cumulative leucovorin dosage of 75 mg/m² is less than what he has shown as optimal (i.e., 105 mg/m²) in children with acute lymphocytic leukemia from a retrospective review of the literature [2]. Several factors must be considered in this comparison. First, and perhaps the most obvious, is the patient population. Our patient population consisted of infants and young children less than three years of age with primary central nervous system tumors receiving HDMTX; whereas, he performed a literature search to identify studies that mentioned a connection between leucovorin dosage, schedule, cure rate or rate of neurotoxicity. None of the studies reviewed were in infants or young children with brain tumors. Second, Professor Cohen uses the term neurotoxicity very broadly and as noted by several investigators, HDMTX neurotoxicity can be subdivided into acute (within 24 hours), subacute (7 to 9 days), and chronic (weeks to years) phases. Each of these types of neurotoxicity has specific presenting symptoms that may vary across these categories. Acute symptoms, for example, include, but may not be limited to, nausea/vomiting, headaches, confusion, and somnolence; whereas, subacute symptoms include seizures, focal neurologic deficits, and mental disturbances. Chronic neurotoxicity focuses on impairment of higher cognitive functions. Professor Cohen does not specify what is meant by neurotoxicity in his patient population, but our patients were carefully monitored for both acute and subacute symptoms, neither of which occurred in our population. Additionally, it is impossible to make any conclusions regarding chronic neurotoxicity solely from HDMTX in this population at this time. Lastly, in our study the protocol defined leucovorin dosage was 75 mg/m². In the event a patient encountered delayed methotrexate excretion, renal dysfunction, or any methotrexate-related toxicity, the leucovorin dosage was individualized for that patient. To be clear, patients received at a minimum the leucovorin dosage of 75 mg/m²; some patients may have required additional leucovorin.

As Professor Cohen mentioned in his letter, we were unaware of the results of his study at the time of our trial. If the results of our ongoing clinical trial prove that our current approach to leucovorin rescue (dosage and timing) are not appropriate, we will re-evaluate it based upon our clinical data and revise the rescue regimen accordingly. The results from the cohort of patients we recently published, however, would suggest that we can safely administer HDMTX to infants and young children with intracranial fluid collections [1].

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