To the editor:

Neurologic complications associated with intrathecal liposomal cytarabine given prophylactically in combination with high-dose methotrexate and cytarabine to patients with acute lymphocytic leukemia

Elias Jabbour and colleagues reported on the novel use of intralumbar liposomal extended-release ara-C (DepoCyt; SkyePharma, San Diego, CA) administered in lieu of standard central nervous system (CNS) prophylaxis for adult patients with acute lymphocytic leukemia (ALL).1 Concerningly, 5 of the 31 patients receiving DepoCyt (16%) developed neurologic complications attributed by the investigators to intralumbar DepoCyt. We would like to comment on the neurologic syndromes observed in this patient cohort and attributed to DepoCyt.

In one instance, an unprovoked, uncomplicated seizure was reported. Seizures occasionally occur (more than 1%) with intracerebrospinal fluid (intra-CSF) chemotherapy and in particular following intraventricular drug instillation. However, in the authors’ experience, seizures occur in relation to acute drug administration (ie, either at time of drug injection or as a complication of drug-induced chemical meningitis).2 A seizure occurring 10 days after intralumbar therapy seems unlikely to be related to intra-CSF chemotherapy and more likely metabolic in etiology or cryptogenic and occurring in a genetically predisposed patient.

Patient 2 developed “pseudotumor cerebri” characterized by progressive visual loss and increased opening pressure on lumbar puncture.3 Treatment with ventriculoperitoneal (VP) shunting resulted in partial visual restoration. Intra-CSF chemotherapy often produces transient chemical meningitis, which, rarely, gives rise to an adhesive arachnoiditis and, as a result, CSF flow disturbances. This sequence of events, culminating in communicating hydrocephalus, has only previously been described following intraventricular drug administration. The risk factors for this poorly understood disorder likely include female sex and corticosteroid administration.

The third patient was described as having a cauda equina syndrome with isolated incontinence and saddle anesthesia. Cauda equina syndromes are characterized by lower motor neuron asymmetric paraparesis and dermatomal lower-extremity sensory loss with the late appearance of incontinence. The symptoms in this patient suggest instead a conus medullaris syndrome typified by early incontinence and sacral sensory disturbance. Unfortunately, this is a rare complication of intralumbar chemotherapy regardless of drug administered.

The fourth patient was also described as having a cauda equina syndrome though the clinical findings were incontinence only. Incontinence as the sole manifestation of spinal cord dysfunction is rarely seen. The fact that this symptom did not progress (or new symptoms develop) despite continued intralumbar DepoCyt seems unusual and unlikely to represent spinal cord injury.

The final patient developed what was characterized as encephalitis; however, encephalopathy seems more precise. Again, a relation between the encephalopathy and DepoCyt administration seems unlikely. The radiographic findings are more suggestive of multifocal white matter injury such as a small vessel vasculopathy (reported with both high-dose intravenous methotrexate). Because intra-CSF administered chemotherapy penetrates only 1-3 mm into brain, it is difficult to reconcile chemotherapy administered by the lumbar route with deep brain parenchymal injury. A toxic encephalopathy related to high-dose methotrexate or cytarabine seems more plausible.

The paper by Jabbour illustrates the challenges in treating adult patients with ALL and the not infrequent neurologic complications that may result from leukemia-directed therapy. We should, however, be careful not to discard effective therapy for the wrong reasons. We are concerned that the complications attributed to intralumbar DepoCyt, particularly in patients 1, 2, and 5, may in fact have other, more plausible explanations.

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References


Response:

Neurologic toxicity of intrathecal liposomal cytarabine when used for CNS prophylaxis in conjunction with the hyper-CVAD regimen

In randomized trials using liposomal cytarabine for carcinomatous meningitis, toxicity profile was similar to standard intrathecal chemotherapy (free cytarabine for lymphomas; methotrexate for solid tumors).1,2 A higher frequency of headaches and chemical arachnoiditis occurred with the liposomal preparation. Glantz et al2 commented that attributing neurotoxicity to either tumor or side effects of intrathecal chemotherapy was often difficult. Notably, systemic chemotherapy was permitted for disease outside the meninges (not high-dose methotrexate [> 500 mg/m²/d] or cytarabine [> 2 mg/m²/d] for lymphomas). Neurotoxicity was not delineated by systemic therapy (43% of lymphoma; 20% of solid tumor participants). In the lymphoma trial, liposomal cytarabine
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