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 Concerning, 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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Conflict-of-interest disclosure: The authors declare no competing financial interests.

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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
was interrupted for hydrocephalus and hearing loss in 1 patient each, although toxicities were not directly attributed to the agent. In their letter, Chamberlain and Glantz comment on the neurologic syndromes we reported and question attribution to liposomal cytarabine. Our attributions were based on 15-year experience in nearly 500 adults with acute lymphoblastic leukemia without central nervous system (CNS) disease, treated with hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone) and standard CNS prophylaxis (methotrexate 12 mg day 2; cytarabine 100 mg day 7 for 3-8 cycles). In this setting, seizures are extremely uncommon (3 of 482 patients [0.006%]). The long half-life of liposomal cytarabine made attribution plausible in patient 1, given absence of discernable metabolic or other etiology. We have not observed hydrocephalus with standard CNS prophylaxis. Obesity and corticosteroids contribute to pseudotumor cerebri. Patient 2 was not obese, and dexamethasone dosing was only slightly increased. Investigators in our Department of Neuro-Oncology have also attributed anecdotal hydrocephalus cases to liposomal cytarabine (Morris D. Groves, M. D. Anderson Cancer Center, written personal communication, March 22, 2007). These data, taken in aggregate with the case in the lymphoma trial, raise the question whether association of hydrocephalus with liposomal cytarabine has been unrecognized or underreported.

Findings for patient 3 are better described as partial cauda equina syndrome or sacral radiculopathy. Although Chamberlain and Glantz suggest any chemotherapy given via lumbar puncture (LP) could cause such neurologic sequelae, we have not observed this after standard CNS prophylaxis given almost exclusively via LP. Decreased perineal sensation and lower-extremity paresthesias in patient 4 were also consistent with sacral radiculopathy. Standard intrathecal chemotherapy was delayed until 4 months later. The morbidity of urinary and/or fecal incontinence associated with these syndromes in 2 of 31 patients was considered unacceptable.

Encephalopathy is more appropriate terminology for patient 5; encephalitis implies an inflammatory process. Encephalopathy related to high-dose systemic methotrexate-cytarabine usually manifests during administration or immediately thereafter, not on day 15, in this case approximately 36 hours after liposomal cytarabine. An exhaustive evaluation was unable to discern any other etiology for the neurotoxicity, which led to the patient’s demise. To what degree each agent contributed is an unanswerable question but does not preclude an association.

The character, constellation, and severity of neurotoxicity was concerning in potentially curable patients. We felt it prudent to alert other investigators of the need for monitoring and reporting of neurotoxicity if this agent was used in a similar manner. The absence of similar neurotoxicity in the 56 patients treated with standard CNS prophylaxis since terminating the liposomal cytarabine trial further supports our conclusions.

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Research grant support and drug were provided by Enzon Pharmaceuticals and Skye Pharma.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

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References

To the editor:

Therapeutic drug monitoring in CML patients on imatinib

Imatinib dosing in patients with chronic myeloid leukemia (CML) is flat, as pharmacokinetic (PK) studies showed that plasma trough concentrations are correlated with dose, whereas body weight or body surface area are of minor importance. However, there is considerable interindividual variability. In a recent study, Picart et al reported that the median imatinib plasma concentration at steady-state is higher in patients with a major molecular response (MMR) than in patients without MMR, suggesting that therapeutic drug monitoring may be useful for optimizing therapy.

We have measured imatinib plasma concentrations in selected patients in specific clinical situations (Table 1). In patients nos. 1 to 3, unusually severe toxicity raised the question of higher than expected imatinib plasma concentrations. All 3 patients were treated with a starting dose of 300 mg imatinib twice a day because of high Sokal risk or an initial delay in commencing therapy. Dominant side effects were grade 3 myalgia in patient no. 1, transfusion-dependent erythropoietin-refractory anemia (associated with bone marrow hypoplasia) in patient no. 2, and diffuse pulmonary infiltrates in patient no. 3. Plasma trough concentrations on the initial dose of imatinib (patient nos. 1 and 2) or on 400 mg imatinib daily after transient escalation to 400 mg twice a day were considerably higher than expected from the phase 1 data (Table 1).

After dose reduction, myalgia improved in patient no. 1 and patient no. 2 became transfusion independent. Repeat PK studies showed plasma concentrations that were similar to or slightly above the concentrations observed in the phase 1 study, providing reassurance that after dose reduction drug concentrations were still in a therapeutic range. In patient no. 3, imatinib was permanently discontinued, as the risk of further aggravating her side effects was felt to be unacceptable.

In 2 patients, PK studies were done because of concerns about inadequate imatinib plasma concentrations. Patient no. 4, a 9-year-old girl, achieved a complete cytogenetic response but not MMR after 11 months on 300 mg of imatinib. Dose escalation to 400 mg/day failed to improve on the molecular response, which raised the issue of inadequate drug concentrations. However, the plasma imatinib concentration was higher than expected at 2341 ng/mL. Based on this, the dose was not escalated because of concerns about side effects. Patient no. 5 failed to attain a complete hematologic response (CHR) on 400 mg imatinib daily. Replacement of carbamazepine with valproic acid for suspected drug interaction and dose escalation to 600 mg/day led to CHR but without any cytogenetic response. Sequencing of BCR-ABL did not reveal a kinase domain mutation. Given multiple comediations, low plasma imatinib concentrations were suspected.
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