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Intrathecal liposomal cytarabine: More friend than foe?

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Intrathecal chemotherapy is an integral component of treatment for acute leukemia and non-Hodgkin lymphoma, and together with intensive systemic chemotherapy, has largely replaced cranial irradiation as central-nervous-system (CNS)-directed therapy, even in patients with high-risk disease.¹ However, the optimal intrathecal treatment has yet to be established. Because cytotoxic concentrations of conventional intrathecal chemotherapy are maintained in the cerebrospinal fluid for only a short time and frequently repeated lumbar punctures may pose technical difficulties in some patients, a sustained-release formulation of cytarabine was developed.

By encapsulating in spherical multivesicular, biodegradable lipid-based particles known as DepoFoam, liposomal cytarabine is released gradually after administration, thereby prolonging exposure to the drug in cerebrospinal fluid. This liposomal formulation has a half-life of 100 to 263 hours after intrathecal or intraventricular administration at doses of 12.5 mg to 75 mg, as compared to only 3.4 hours after intrathecal administration of 30 mg of free cytarabine.²⁻⁴ Thus, while one dose of conventional cytarabine results in cytotoxic concentrations (≥ 0.1 $\mu\text{g/mL}$) in the cerebrospinal fluid for < 24 hours, one dose of liposomal cytarabine maintains concentrations for 8 days or more in children and for more than 14 days in most adults.^{2,4} Based on its significantly improved response rate as compared to standard formulation of cytarabine in a randomized trial,⁵ liposomal cytarabine was approved by the Food and Drug Administration for the treatment of patients with lymphomatous meningitis.

In Phase I/II studies in adults and children, liposomal cytarabine was very effective.^{2,4-6} Chemical arachnoiditis, characterized by headache, back pain, fever, nausea, and vomiting, was common but could be prevented by concomitant administration of systemic dexamethasone.^{2,4-6} The recommended dose of liposomal cytarabine is 50 mg for adults and 35 mg for children, administered with systemic dexamethasone for 5 days, every 2 weeks during induction and consolidation therapy, and every 4 weeks during continuation therapy.^{2,4-6}

In the early studies when liposomal cytarabine was given as a single agent or together with conventional doses of systemic chemotherapy, neurotoxicity other than arachnoiditis was uncommon. In a study at M.D. Anderson for adults with newly diagnosed acute lymphoblastic leukemia, patients were treated with their hyper-CVAD regimen which includes high-dose methotrexate and high-dose cytarabine, modified by substituting liposomal cytarabine for conventional intrathecal therapy for CNS prophylaxis.⁷ To minimize the potential overlapping toxicity of intrathecal and systemic cytarabine, the investigators separated liposomal cytarabine treatments by at least 12 days, and did not begin intrathecal treatment until at least 7 days after the last dose of systemic cytarabine. Despite this precaution and the concomitant use of dexamethasone orally or intravenously for 5 days, a high rate (16%) of significant neurotoxicity

that include encephalopathy, cauda equina syndrome, seizure and pseudotumor cerebri, was observed among 31 patients treated, prompting the termination of the study. The investigators suggested that intrathecal liposomal cytarabine given concomitantly with systemic chemotherapy that crosses the blood-brain barrier can result in significant neurotoxicity.

In a subsequent study using modified hyper-CVAD regimen in which liposomal cytarabine treatments were given further apart (every 3 weeks), 2 of 14 adults with leukemia or lymphoma still developed significant neurologic events (severe headache and somnolence plus hyponatremia, respectively).⁸ The findings of these two studies led to the suggestion that liposomal cytarabine should not be given prior to or during treatment with high-dose chemotherapy that penetrates the blood-brain barrier.⁹

In this issue of *Leukemia & Lymphoma*, Parasole *et al*¹⁰ reported the efficacy and safety of intrathecal liposomal cytarabine in 6 heavily pretreated children with acute lymphoblastic leukemia (4 T-cell and 2 B-cell precursor) and CNS relapse, representing the first relapse in 2 patients, second relapse in 3, and third relapse in 1. The patient with third relapse had been previously treated with cranial irradiation and total body irradiation for transplantation. All patients including one with Down syndrome tolerated liposomal cytarabine relatively well with sustained clearance of blasts in cerebrospinal fluid. Only one child developed grade 2 headache, and none experienced significant neurotoxicity. Importantly, 5 of the 6 patients received concurrent systemic high-dose cytarabine (2 gm/m²/dose). There are several plausible explanations for the apparently contrasting experience between adult and childhood cases. First, children may tolerate the liposomal cytarabine better than adults. However, in a prior study of 5 children with neoplastic meningitis,¹¹ one heavily pretreated patient developed transient encephalopathy 4 days after receiving high-dose methotrexate and a single dose of liposomal cytarabine. Secondly, Parasole *et al*¹⁰ judiciously used age-adjusted doses of liposomal cytarabine as is standard with other intrathecal agents in pediatrics. Thirdly and perhaps of interest, they instilled intrathecal methylprednisolone concurrently with liposomal cytarabine in two of their patients. In this regard, intrathecal prednisone may be more effective than systemic dexamethasone in preventing local inflammatory effects of liposomal cytarabine. However, many more patients need to be treated to confirm the potential protective effect of intrathecal prednisone. Having no neurotoxicities in six patients does not establish improved safety with this approach, because statistically the true rate of events can still be as high as 39%. Nonetheless, if the finding of Parasole and colleagues is confirmed by additional studies, it most certainly will generate greater enthusiasm to use this effective treatment.

The potential neurotoxicity of liposomal cytarabine has been a major concern of leukemia therapists in using this treatment modality despite its great effectiveness. Preventive measures may reduce, but are not likely to totally eliminate the risk of neurotoxicity. Liposomal cytarabine is beneficial, especially in refractory patients and its use in a broader clinical practice requires careful assessment of both risks and benefits. We have summarized published studies in Table 1. Several large phase II adult studies are ongoing in the United States and Europe to further test the safety and efficacy of intrathecal liposomal cytarabine alone and in combination with chemotherapeutic drugs as well as monoclonal antibodies. As more data becomes available, we will learn optimal use of this highly effective drug.

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Table 1
Summary of neurotoxic events in studies using intrathecal liposomal cytarabine[#]

Study	No. of patients (age)	Type of study	Indication	Dose and frequency of liposomal cytarabine	Total no. of doses	Route of administration	Measures taken to prevent neurotoxicity	Concurrent cranial RT or high dose chemotherapy	Neurotoxicity (≥ Grade III)	Proportion of patients with ≥ grade III neurotoxicity (95% CI)	Cytologic response (No. of patients)
Kim et al ⁴ (1993) ⁴	12 (6–73 yrs)	Phase I	Neoplastic meningitis (4 hematologic malignancies, 8 solid tumors)	12.5–125 mg; Q 2–3 weeks	47	IVT: 11 LP: 1 Both: 3	NR	Cranial irradiation: 2	Encephalopathy: 3 Headache: 2	5 of 47 cycles 10.6% (1.8% to 19.5%)	7 of 9 evaluable patients
Chamberlain et al ³ (1995) ³	9 (23–67 yrs)	Phase I	Neoplastic meningitis (4 NHL, 1 AML, 3 solid tumors)	75 mg; Q 2 weeks	18	LP	Dexamethasone PO in 15 cycles	NR	None	0 of 9 0% (0% to 28%)	6 of 8 evaluable patients
Glantz et al ⁶ (1999) ⁵	14 (35–86 yrs)	Randomized phase II	Lymphomatous meningitis	50 mg; Q 2 weeks X 2 months, Q 4 weeks X 8 months	74	IVT: 13 LP: 1	Dexamethasone PO/IV	None	Headache: 4 Meningismus: 2 Confusion: 2 Somnolence: 2	10 of 74 cycles 13.5% (5.7% to 21.3%)	10 of 14
Glantz et al (1999) ⁶	31 (19–74 yrs)	Randomized phase II	Neoplastic meningitis (solid tumors)	50 mg; Q 2 weeks X 2 months, Q 4 weeks X 8 months	102	IVT: 29 LP: 2	Dexamethasone PO/IV	Cranial or spinal irradiation: 4	Headache: 4 Altered mental status: 5 Seizures: 1 Sensory/Motor: 1 Drug related meningitis: 3 CNS infection: 3	17 of 31 54.8% (37.3% to 72.3%)	8 of 31
Jaekle et al ¹² (2001) ¹²	53 (28–74 yrs)	4 studies (1 randomized, included 11 patients from Glantz et al ⁶ , 3 non randomized)	Neoplastic meningitis (breast cancer)	50 mg; Q 2 weeks X 2 months, Q 4 weeks X 2 months	177	IVT: 42 LP: 8 Both: 3	Dexamethasone PO/IV	Cranial irradiation: 13	Headache: 2 Arachnoiditis: 4	6 of 177 cycles 3.4% (0.7% to 6%)	12 of 43 evaluable patients
Bomgaars et al (2004) ²	18 (4–19 yrs)	Phase I	Neoplastic meningitis (9 ALL, 1 AML, 8 brain tumors)	25–50 mg; Q 2 weeks X 1 month, Q 4 weeks X 2 months, Q 8 weeks X 12 months	78	IVT: 3 LP: 12 Both: 3	Dexamethasone PO/IV	None	Headache: 3	3 of 18 16.6% (0% to 33.9%)	8 of 14 evaluable patients

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Sancho et al (2006) ¹³	6 (5–50 yrs)	Retrospective series	CNS involvement in leukemia	50 mg; Q 2 weeks (25 mg in 5 yr old)	29	LP	Dexamethasone PO/IV	NR	None	0 of 6 (0% to 39%)	2 of 3 evaluable patients
Jabbour et al (2007) ⁷	31 (>18 yrs)	Phase II	Newly diagnosed adult ALL	50 mg Day 2 and 15 of HyperCVAD cycle, Day 10 of MA cycle	NR	LP	Dexamethasone PO/IV Liposomal cytarabine >7 days after HD cytarabine	High dose methotrexate and cytarabine: 31	Papilledema and blindness: 1 Increased intracranial pressure: 2 Cauda equina syndrome: 2	5 of 31 (16.1% (3.2% to 29.1%))	Prophylactic use 1 combined marrow and CNS relapse
Bensch et al (2007) ¹¹	5 (5–18 yrs)	Retrospective series	Neoplastic meningitis (4 leukemia, 1 medulloblastoma)	15–50 mg; Q 2–4 weeks (Single dose in 1 patient)	33	LP	Dexamethasone PO/IV	High dose methotrexate (8 gm/m ²): 1 TBI: 1	Encephalopathy: 1 Seizures*: 1	2 of 5 (40% (0% to 82.9%))	3 of 5
Sancho et al (2007) ¹⁴	10 (18–57 yrs)	Retrospective series	AML CNS involvement: 6 CNS relapse: 4	50 mg; Q 2 or 4 weeks (35 mg in 18 yr old)	39	LP	Dexamethasone PO/IV	High dose cytarabine: 6	Headache*: 3	3 of 10 (30% (1.6% to 58.4%))	9 of 9 evaluable patients
McClune et al (2007) ⁸	14 (23–72 yrs)	Retrospective series	Newly diagnosed ALL and aggressive lymphomas	50 mg (25 mg if intraventricular); Q 3 weeks	40	IVT: 2 LP: 12	Dexamethasone PO/IV Liposomal cytarabine Q3 weeks	High dose methotrexate and cytarabine: 14	Hyponatremia and somnolence*: 1 Headache*: 1	2 of 14 (14.3% (0% to 32.6%))	Prophylactic use No CNS relapses
Parasole et al (2008) ¹⁰	6 (2–26 yrs)	Retrospective series	ALL with CNS relapse	Q 2 weeks (Q 1 week X 4 in 1 patient)	33	LP	Dexamethasone PO/IV Methylprednisone IT (2 patients) Age adjusted dose	High dose cytarabine (2 gm/m ²): 5	None	0/6 (0% to 39%)	6 of 6

IVT: Intraventricular

LP: Lumbar puncture

NR: Not reported

ALL: acute lymphoblastic leukemia

AML: Acute myeloid leukemia

CNS: Central nervous system

RT: Radiation therapy

Includes studies ≥ 5 patients, published in English

* Grade of toxicity not reported

^ Neurotoxic events reported per cycle of intrathecal liposomal cytarabine (not per patient)