Compassionate use of intrathecal depot liposomal cytarabine as treatment of central nervous system involvement in acute leukemia: report of 6 cases

The depot formulation of liposomal cytarabine (DepoCyte®) has proven to be useful as intrathecal (IT) treatment of neoplastic and lymphomatous meningitis. We report the results of compassionate use of DepoCyte® in 6 patients diagnosed with acute leukemia (AL) and CNS involvement. Two patients had CNS involvement at diagnosis and the remaining 4 had CNS relapse. Three patients received DepoCyte® as adjuvant therapy and achieved complete response whereas 2 out of the remaining 3 cases treated with DepoCyte® as the only drug showed sustained response. The side effects were mild and manageable in all patients. These findings justify the development of clinical trials to evaluate the efficacy and safety of IT depot cytarabine in meningeal involvement of AL.

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Meningeal involvement in solid tumors and hematological malignancies is associated with a poor prognosis. Central nervous system (CNS)-directed therapy is based on the administration of high dose systemic chemotherapy with drugs able to pass through the blood-brain barrier, such as methotrexate (MTX) and cytarabine, cranial or craniospinal irradiation, and intrathecal (IT) administration of MTX and/or cytarabine. However, these approaches only have modest efficacy and are associated with side effects for the patients.[1,2] A depot formulation of liposomal cytarabine (DepoCyte®) which can be administered at doses of 50 mg to adult patients every two weeks, has proven to be useful in clinical trials as a treatment of neoplastic meningitis and lymphomatous meningitis.[3-6] However, its value for the prophylaxis or treatment of CNS involvement in acute leukemias (AL) has only been demonstrated in individual cases[7,8] and few series have been reported.[9] In this article we performed a retrospective review of all cases in which IT depot cytarabine was employed as compassionate therapy for CNS involvement of AL in Spain.

From March 2004 to January 2005 six cases (5 females) were recorded (Table): 3 patients with acute lymphoblastic leukemia (ALL), 2 acute myeloid leukemia (AML), and 1 lymphoid blast crisis of chronic myeloid leukemia (CML). The median (range) age of the patients was 25 (5-50) years. Two patients (ALL and AML_{5b}) had CNS involvement at diagnosis. In one (AML_{5b}), IT depot liposomal cytarabine was administered after failure of triple intrathecal therapy (TIT) (MTX, cytarabine and dexamethasone), whereas the other (ALL) patient received IT depot liposomal cytarabine as adjuvant therapy after TIT and cranial radiotherapy. The remaining 4 patients (2 ALL, 1 blast crisis of CML and 1 acute promyelocytic leukemia [APL]) had CNS relapse. The two cases of ALL received CNS prophylaxis with TIT and TIT plus radiotherapy, respectively, whereas the patients with blast crisis of CML and APL did not receive any prophylaxis. Intrathecal depot liposomal cytarabine was administered as treatment of a second CNS relapse in the two ALL patients, and as adjuvant to TIT plus cranial radiotherapy in the patient with blast crisis of CML and to TIT plus all-trans retinoic acid (ATRA) plus arsenic trioxide (As_2O_3) in the patient with APL. ATRA does not cross the blood-brain barrier, whereas there is some evidence that As_2O_3 penetrates the blood-brain barrier. Out of the 3 evaluable cases (AML5b and 2 cases with ALL in second CNS relapse) treated with IT depot liposomal cytarabine as the only drug, clearance of blasts in cerebrospinal fluid (CSF) was observed with sustained response in two (9 and 11 months). The remaining patient presented neurologic progression at 3 months and died. The dose of DepoCyte® was 50 mg every 2 weeks, except in the pediatric patient, who received 35 mg. Concurrent dexamethasone therapy (4 mg twice per day for 5 days) was administered with each dose of IT depot liposomal cytarabine. The median number of IT depot cytarabine administrations was 4^{1-10} and the total number of doses administered was 29. Side effects included headache (4 patients), dizziness (2), vomiting (1), nausea (1) and fever (1).

To our knowledge, this is one of the few series published on the efficacy of the sustained-release formulation of liposomal cytarabine in the treatment of CNS involvement in AL. The standard therapy for meningeal involvement in patients with solid tumors, lymphomas and leukemias is based on CNS-directed treatment, including frequent IT administrations of drugs by lumbar punctures or through an Ommaya reservoir. This causes a decrease in the quality of life due to both CNS involvement itself and to the side effects of the repeated IT therapies. DepoCyte® is a sustained-release formulation of liposomal cytarabine that remains at therapeutic concentration in CSF for more than 14 days when used by IT or the intraventricular route at doses established in previous trials.[10,11] Although several studies have demonstrated the efficacy of this formulation of cytarabine in the treatment of neoplastic meningitis from solid tumors[3,5,6] and lymphomas,[4] few experiences have been published on the efficacy of DepoCyte® in the treatment of CNS involvement in patients with AL. Bomgaars *et al.*,[9] included 18 children with neoplastic meningitis in a phase I trial of IT depot liposomal cytarabine: 10 with AL (one AML and 9 ALL) and 8 with CNS tumors. Regarding the AL patients, the authors observed an objective response in all the 7 evaluable cases, being complete (defined by complete clearing of malignant cells from CSF) in 4: 3 patients achieved clearance of blasts from CSF with only one IT administration and the remaining required 3 doses of DepoCyte.® The other 3 patients showed partial response (PR) and were removed from the study due to toxicity or to drug supply issues, but 2 had complete clearing of malignant cells. Successful results of depot liposomal cytarabine in AL have also been communicated in isolated reports.[7,8] In our series, 2 out of the 3 evaluable patients in which DepoCyte® was the only drug administered as treatment achieved CR with sustained response. In the remaining 3 patients in whom DepoCyte® was administered as adjuvant therapy, sustained response was also obtained.

Overall, IT depot liposomal cytarabine was well tolerated, with headache being the most prevalent side effect in the patients of this series, similar to what has been observed in other studies.[3,4,9] The absence of arachnoiditis is of note, probably due to concomitant dexamethasone therapy.

Despite its retrospective nature, the present study shows that the depot formulation of cytarabine is a safe and effective therapy for meningeal involvement in AL. This justifies the development of clinical trials to evaluate the efficacy and safety of IT depot cytarabine in meningeal involvement of AL.

Table 1. Patients with AL and CNS involvement treated with DepoCyte® as compassionate therapy.

Variable	*Patient 1*	*Patient 2*	*Patient 3*	*Patient 4*	Patient 5	Patient 6
Diagnosis	ALL (pre-B ALL)	ALL (common)	ALL (common)	AML (5b)	CML (lymphoid blast crisis)	APL
Age (yr) /Sex	24 / Female	5 / Female	39 / Female	18 / Female	50 / Male	26 / Female
Date of diagnosis	November 1999	April 2004	October 1998	May 2004	January 2001	October 2001
CNS prophylaxis	TIT* + cranial radiotherapy (18 Gy)	No (CNS involvement at diagnosis)	TIT	No (CNS involvement at diagnosis)	No	No
Date of 1st CNS relapse	August 2001	April 2004**	June 2003	May 2004**	January 2004	April 2004
Type of relapse	Isolated	Combined	Combined	Combined	Combined	Combined
Treatment of 1st CNS relapse or CNS involvement	TIT + cranial radiotherapy (22 Gy)	TIT + cranial radiotherapy + DepoCyte®***	TIT	TIT (one dose with failure) + DepoCyte®	TIT + craniospinal radiotherapy + DepoCyte®***	TIT
Systemic therapy	VCR + DNR + PDN Allogeneic SCT	VCR + DNR + PDN	VCR + MTZ + DXM Maintenance chemotherapy	DA (12 mg/m^2/d for 3 days) + ARA-C (200 mg/m^2/d for 7 days) Allogeneic SCT	Imatinib	ATRA + IDA SCT
Date of 2nd CNS relapse	July 2004	-	April 2004	-	-	January 2005
Treatment of 2nd CNS relapse	DepoCyte®	-	DepoCyte®	-	-	TIT + ATRA + As_2O_3 + DepoCyte®***
Number of injections of DepoCyte®	9	1	3	10	4	2
Clinical symptoms therapy	IV cranial pair paralysis, before DepoCyte® dysesthesia	Headache, upper extremities	Headache	Chin dysesthesias	Headache, Weakness in both legs	Headache, numbness of left arm
Blast cells in CSF before DepoCyte® therapy	492	5	5	6	6	217
Response (clearance of CNS blasts)	PR	CR	CR	CR	CR	CR
Subsequent evolution/ Length of response (months)	Neurologic progression at 90 days and death / 3	Continuous clinical a nd cytological CR / 16	Continuous clinical / 9 and cytological CR	Continuous clinical and cytological CR /11	Continuous clinical and cytological CR / 18	Continuous clinical and cytological CR / 7
Side effects of DepoCyte® (grade)****	Headache (2), vomiting (2)	None	Dizziness (1)	Headache (2)	Headache (2), dizziness (2)	Headache (1), fever, nausea (1)

*AL: acute leukemia; ALL: acute lymphoblastic leukemia; AML. acute myeloid leukemia; APL: acute promyelocytic leukemia; CML: chronic myeloid leukemia; CNS: central nervous system; TIT: triple intrathecal therapy; SCT: stem cell transplantaion; VCR: vincristine; DNR: daunorubicin; PDN: prednisone; DXM; dexamethasone; MTZ: mitoxantrone; IDA: idarubicin; ARA-C: citarabine; CSF: cerebrospinal fluid; PR: partial response; CR: complete response. *TIT included methotrexate (12 mg), cytarabine (30 mg) and hydrocortisone (20 mg). **CNS involvement at diagnosis of AL. ***DepoCyte® was administered as adjuvant therapy. ****WHO/CTC scale.*

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