Safety and toxicity of intrathecal liposomal cytarabine (Depocyte) in children and adolescents with recurrent or refractory brain tumors: a multi-institutional retrospective study

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This retrospective study aimed to evaluate the safety and toxicity of intrathecal liposomal cytarabine (Depocyte) in children and adolescents with refractory or recurrent brain tumors. Nineteen heavily pretreated patients (males, *n*=14; females, *n*=5; median age at diagnosis 8.5 years; range, 1.4–22 years) were given intrathecal liposomal cytarabine on a compassionate use basis for recurrent refractory medulloblastoma (*n*=12), mixed germ cell tumor (*n*=2), central nervous system primitive neuroectodermal tumors of the pons (*n*=1), anaplastic ependymoma (*n*=1), anaplastic oligodendroglioma (*n*=1), atypical teratoid rhabdoid tumor (*n*=1), or rhabdoid papillary meningioma (*n*=1). Eighteen patients received concomitant systemic radiochemotherapy. A total of 88 intrathecal injections of liposomal cytarabine (dose range, 20–50 mg) were administered with concomitant dexamethasone prophylaxis. The median number of doses per patient was four (range, 1–10). Duration of treatment ranged from $^1/_2$ to 10 months. Eleven patients (57.9%) did not show any side effects, whereas eight patients (42.1%) developed side effects related to either chemical arachnoiditis (*n*=4) or neurological progression (*n*=2). Less typical treatment-related symptoms (e.g. lethargy, ataxia, and slurred speech) were observed in two patients. Treatment with intrathecal liposomal cytarabine was discontinued twice because of side effects. In conclusion, although intrathecal liposomal cytarabine was generally well tolerated, it should be used cautiously and only with dexamethasone prophylaxis in extensively pretreated patients with recurrent brain tumors. Proof of efficacy requires a prospective single-agent phase II study. *Anti-Cancer Drugs* 20:794–799 © 2009 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

The outcome of patients with recurrent or refractory malignant brain tumors is still poor [1–6]. In addition to local, whole brain or neuroaxis irradiation, which has been shown to improve prognosis in several childhood brain tumors [7–10], intrathecal (IT) chemotherapy is meanwhile increasingly used in children with brain tumors to avoid radiotherapy [11] or treat leptomeningeal spread. Among the limited number of antineoplastic compounds available for IT administration [12], methotrexate (MTX) is the most commonly used. Extensive experience with IT MTX has been obtained primarily from children with acute leukemia who have now received IT MTX both for treatment and prophylaxis of leukemic meningitis for almost 50 years [13,14]. Rutkowski *et al.* [11] recently showed that intravenous chemotherapy with concomitant IT MTX can produce excellent survival rates in young children with medulloblastoma without exposing them to irradiation. Other drugs suitable for IT application include thiotepa, etoposide, mafosfamide, busulfan, and topotecan [12,15–20]. As the management of children with unfavorable brain tumors is still a major therapeutic challenge, physicians have to weigh carefully the benefits and side effects of their therapeutic options, taking quality of life into account.

IT liposomal cytarabine is a sustained release formulation of cytarabine that allows maintenance of therapeutically effective concentrations of free cytarabine for a prolonged period of time after the injection into the cerebrospinal

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fluid (CSF) [21]. The half-life of free cytarabine in pediatric patients ranges from 50 to 57 h and 32 to 44 h after intraventricular and intralumbar administration, respectively [22]. Patients treated with IT liposomal cytarabine might benefit from less frequent administration than with standard IT chemotherapy. In this retrospective study, we evaluated the safety profile of IT liposomal cytarabine in a cohort of 19 children and adolescents with refractory or relapsed brain tumors.

Patients and methods

Nineteen patients (males, $n = 14$; females, $n = 5$; median age at diagnosis 8.5 years; range, 1.4–22 years) who received IT liposomal cytarabine between January 2005 and June 2008 at six pediatric oncological centers were included. Initial diagnostic and follow-up examinations including preoperative and postoperative contrast-enhanced magnetic resonance imaging scans of the brain were performed according to center and/or protocol guidelines. Cytological examination of CSF and additional spinal magnetic resonance imaging were ordered for patients with medulloblastoma, ependymoma, and germ cell tumors (GCT). Thirteen (68.4%) patients underwent central neuropathologic review. After informed consent was obtained, 14 patients received highly standardized first-line treatment according to the HIT 2000 prospective multicenter trial, which is the currently active protocol of the German Society of Pediatric Oncology and Hematology for children and adolescents with medulloblastoma, central nervous system (CNS) primitive neuroectodermal tumors (CNS-PNET) and ependymoma. Briefly, the protocol is based on the previous HIT 88/89, HIT 91, HIT SKK 87, and HIT SKK 92 trials [1,23–25], and stratifies patients according to diagnosis, age, and disease stage. The two patients with intracranial GCT were treated according to the prospective multicenter trial for secreting GCT of the CNS (CNS sGCT) [26]. The chemotherapy of two patients (patients 9, 14; atypical teratoid rhabdoid tumor and rhabdoid papillary meningioma) was individualized owing to the rarity of these tumors and consisted of elements from the HIT 2000 study alone or in combination with other protocols. The patient with anaplastic oligodendroglioma (patient 8) was primarily treated by surgical resection alone.

All patients developed disease recurrence or were refractory to first or second line treatment including intensive chemotherapy and/or local or neuroaxis irradiation. Compassionate use of IT liposomal cytarabine (Depocyte; Mundipharma, Cambridge, UK) was therefore given in these cases either by lumbar puncture or through ventricular access devices as part of an individualized multimodal salvage therapy (Tables 1 and 2). Although the treating physicians were familiar with the recommendations of the only phase I study of IT liposomal cytarabine in children and adolescents reported to date [22], the drug dosage, intervals of administration, and total duration of the treatment were determined individually for each patient, because all but one of the study patients were receiving concomitant systemic chemotherapy (and other treatment modalities) in addition to IT liposomal cytarabine. Patients and/or their legal representatives were informed of the potential benefits and side effects of this experimental approach and gave their consent before the first administration of IT liposomal cytarabine. During therapy, patients were closely monitored for toxicity with special emphasis on neurological side effects. Patients were given prophylactic dexamethasone as recommended to prevent chemical arachnoiditis [22]. Response to the multimodal salvage treatment was assessed clinically and radiographically at regular intervals. The aim of this retrospective study was, however, to determine the safety and toxicity of IT liposomal cytarabine and not the efficacy of the drug. One of our patients (patient 4) has been reported previously [27].

Results

Histopathological diagnoses and salvage treatment modalities are summarized in Table 1. The disease was initially localized in 10 patients (medulloblastoma, $n = 6$; mixed GCT, $n = 2$; anaplastic ependymoma, $n = 1$; anaplastic oligodendroglioma, $n = 1$), whereas nine patients had already developed metastases at the time of diagnosis (medulloblastoma/CNS-PNET of the pons, $n = 7$; atypical teratoid rhabdoid tumor, $n = 1$; rhabdoid papillary meningioma, $n = 1$). The highest Chang stages at diagnosis were M3 in five patients, M2 in two patients and M1 in two patients. Seventeen patients underwent resection of the tumor, which was total in seven, near total in three, subtotal in five and partial in two patients; in the remaining two patients, only a biopsy was taken. First-line treatment included radiotherapy (craniospinal, $n = 11$; local or posterior fossa, $n = 4$) in 15 patients and chemotherapy in 17 patients.

Nine patients were treated with IT liposomal cytarabine for the 1st relapse, five patients for the 2nd relapse, and one patient for the 1st and 2nd relapses (Table 2). The remaining four patients never achieved complete remission after first-line therapy and received IT liposomal cytarabine for persistent or progressive residual tumors and/or metastatic lesions. Six patients had undergone cytological examination of CSF before the initiation of IT liposomal cytarabine (positive, $n = 5$; negative, $n = 1$), but unfortunately, this was not repeated at the end of the therapy. The median time from diagnosis of relapse or progression to initiation of the treatment with IT liposomal cytarabine was 1.5 months (range, 0–14), indicating that in some of the patients IT liposomal cytarabine was not given immediately after the diagnosis of relapse/progression, but later during the course of the

Table 1 Treatment of relapse, dose and number of administrations of IT liposomal cytarabine

Patient (Sex/diagnosis)	Indication to start IT liposomal cytarabine	Treatment of relapse/progression	Dose of IT liposomal cytarabine	Number of IT liposomal cytarabine administrations
1 (M/MB)	1st relapse (distant)	CSI (24 Gy; sparing PF), CARBO/VP16 (4 courses), TMZ, autologous PBSCT, IT MTX	20	7
2 (M/MB)	2nd relapse (distant)	TMZ, IT mafosfamide, HIT SKK[a] (3 courses), IT MTX	35 (2x), 25 (2x)	4
3 (F/CNS-PNET)	Persistent contrast enhancing spinal metastasis	IT mafosfamide (alternating with IT liposomal cytarabine)	35	3
4 (M/MB)	1st relapse (distant)	TMZ, CSI	35	8
5 (M/ependymoma III)	Progressive residual tumor	VP16, tamoxifen, TMZ, IT mafosfamide, tumor boost (6 Gy)	35	4
6 (M/mixed GCT)	1st relapse (diffuse subependymal)	BEP (1 course), CARBO/VP16 (1 course), autologous PBSCT	35	4
7 (M/mixed GCT)	1st relapse (distant)	CARBO-PEI (1 course), double autologous PBSCT, RT	50	3
8 (F/oligodendroglioma III)	2nd relapse (local)	Surgery, local RT (54 Gy), TMZ, autologous PBSCT	50	1
9 (M/ATRT)	1st relapse (local, distant)	Topotecan, imatinib, TMZ	35	6
10 (M/MB)	1st relapse (local, distant)	HIT-REZ 2005 (phase II study)[b]	40	2
11 (M/MB)	1st relapse (distant)	TMZ	40	7
	2nd relapse (local)	TMZ	40	3
12 (F/MB)	2nd relapse (local)	TMZ	50	4
13 (M/MB)	1st relapse (distant)	HIT-REZ 2005 (phase II study)[b]	35	4
14 (F/meningioma)	1st relapse (local)	HIT-REZ 2005 (1 course)[c] + IVC etoposide	50	1
15 (M/MB)	1st relapse (local, distant)	HIT-REZ 2005 (phase II study)[b]	35	2
16 (M/MB)	PD after 2nd relapse (distant)	VP16, IT cytarabine, CYC, TMZ, VP16, trofosfamide	25	1
17 (F/MB)	1st relapse (distant)	Focal RT, TMZ, radioimmunotherapy	25 (1x), 30 (5x)	6
18 (M/MB)	Persistent vital primary tumor	Chemotherapy [DOXO, ACT, VCR (3 courses), TMZ]	25 (1x), 30 (7x)	8
19 (M/MB)	Persistent contrast enhancing primary tumor	TMZ	30 (1x), 35 (9x)	10

ACT, actinomycin D; ATRT, atypical teratoid rhabdoid tumor; BEP, bleomycin, etoposide, cisplatin; CARBO, carboplatin; CNS-PNET, central nervous system primitive neuroectodermal tumor; CSI, craniospinal irradiation; CYC, cyclophosphamide; DOXO, doxorubicin; F, female; GCT, germ cell tumor; IT, intrathecal; IVC, intraventricular; M, male; MB, medulloblastoma; MTX, methotrexate; PBSCT, peripheral blood stem cell transplantation; PD, progressive disease; PEI, cisplatin, etoposide, ifosfamide; PF, posterior fossa; RT, radiotherapy; TMZ, temozolomide; VCR, vincristine; VP16, etoposide.
[a]HIT SKK courses consisted of CYC/VCR (termed EII), MTX/VCR (2x; termed EIIIS), CARBO/VP16 (termed EIV) ± IT MTX.
[b]HIT-REZ 2005 (phase II study) consisted of IVC etoposide (3x; 1 mg on days 1–5).
[c]HIT-REZ 2005 chemotherapy courses consisted of intravenous CARBO/VP16 [± IT etoposide (4x)].

disease to consolidate the remission status achieved by other treatment modalities. In all, 88 injections of IT liposomal cytarabine with doses ranging from 20 to 50 mg were given (Table 2). The median number of doses per patient was four (range, 1–10). The total duration of the treatment ranged from $^1/_2$ to 10 months.

IT liposomal cytarabine was usually well tolerated. Eleven patients did not show any clinical side effects at all. Neurological symptoms were observed in the remaining eight patients; in two of them (patients 15 and 16) these symptoms were primarily attributed to disease progression. Four patients (patients 1, 7, 8, 13) developed symptoms of chemical arachnoiditis (vomiting, headache, fever) leading to cessation of treatment in two of them (patients 1 and 8). One of these two patients (patient 1) experienced seizures 16 days after the 7th administration of 20 mg of IT liposomal cytarabine. Routine blood chemistry was normal. Analysis of CSF, however, showed mild pleocytosis (34/μl) and an elevated CSF protein level (150 mg/dl). The boy was put on phenobarbital and had no further seizures. Two patients had less typical symptoms after IT liposomal cytarabine therapy (patient 9: ataxia, slurred speech; patient 17: memory problems, lethargy).

The median time interval between the last dose of IT liposomal cytarabine and last follow-up was 0.76 years (range, 0.03–3.17). At present, 13 patients are alive; three of them are in complete remission. Six patients have died of their underlying disease.

Discussion

The exceptionally rare data on the use of IT liposomal cytarabine in childhood brain tumors are summarized in Table 3 [22,27–31]. All but one study has been presented in abstract form only. The study by Bomgaars *et al.* [22] is the only pediatric phase I trial presented to date and included eight patients with brain tumors and refractory neoplastic meningitis. This interpatient dose escalation study used a starting dose of 25 mg and recommended 35 mg of IT liposomal cytarabine for further clinical evaluation in patients between 3 and 21 years of age. To the best of our knowledge, our study, although

Table 2 Additional treatment characteristics during administration of IT liposomal cytarabine

Patient	Duration of IT liposomal cytarabine therapy (months)	Concurrent therapy	Side effects	Current disease status
1	5	CSI (24 Gy; sparing PF), CARBO/VP16 (4 courses), TMZ, autologous PBSCT, IT MTX	Headache, seizure (after 7th administration)	AWD
2	3	IT MTX (alternating with IT liposomal cytarabine)	None	AWD
3	2	IT mafosfamide (alternating with IT liposomal cytarabine)	None	AWD
4	6	TMZ, CSI	None	DOD
5	3	Bevacizumab	None	DOD
6	3	BEP, CARBO/VP16	None	NED
7	1 1/2	RT, CARBO-PEI	Vomiting, headache	NED
8	1/2	TMZ	Vomiting, headache	AWD
9	3	Topotecan, imatinib	Headache, focal cerebellar pathology (ataxia, slurred speech (DD:PD)	DOD
10	1	IVC VP16	None	AWD
11	1st relapse: 2 2nd relapse: 4	TMZ TMZ	None None	NED NED
12	2nd relapse: 5	TMZ	None	DOD
13	2	None	Headache, fever	AWD
14	1/2	CYC/VP16, PEI	None	AWD
15	1	Sandostatin	Clinically neurological progression	AWD
16	1/2	None	Clinically neurological progression	DOD
17	7	TMZ	Memory problems, lethargy (after 1st administration, memory problems present also during first-line therapy)	DOD
18	9	DOXO, ACT, VCR (3 courses)	None	AWD
19	10	TMZ	None	AWD

ACT, actinomycin D; AWD, alive with disease; BEP, bleomycin, etoposide, cisplatin; CARBO, carboplatin; CSI, craniospinal irradiation; CYC, cyclophosphamide; DD, differential diagnosis; DOD, dead of disease; DOXO, doxorubicin; IT, intrathecal; IVC, intraventricular; MTX, methotrexate; NED, no evidence of disease; PBSCT, peripheral blood stem cell transplantation; PD, progressive disease; PEI, cisplatin, etoposide, ifosfamide; PF, posterior fossa; RT, radiotherapy; TMZ, temozolomide; VCR, vincristine; VP16, etoposide.

Table 3 Studies and case series on the use of intrathecal liposomal cytarabine in children and adolescents with brain tumors

Reference	Type and year of presentation	Number of patients (total number of Depocyte doses)	Diagnoses	Side effects
[22][a]	Phase I study (2004)	8 (78)	Refractory MB ($n=7$), undifferentiated glial tumor ($n=1$)	Chemical arachnoiditis ($n=2$, at 25 mg DL, w/o DXM prophylaxis) headache grade II ($n=3$, at 25/35 mg DL), grade III ($n=3$, at 50 mg DL); fatigue II ($n=2$, at 35/50 mg DL); back/neck pain grade II ($n=4$, at 25–50 mg DL), grade III ($n=1$, at 25 mg DL)
[27]	Retrospective case series (2007)	1 (7)	Recurrent MB	–
[28]	Case report (2007)	1 (8)	Partially resected ependymoma	Mild headache
[29]	Abstract (2006)	10 (57)	Highly malignant tumors in the CNS	Headache grade II ($n=1$); transiently decreased vision, unsteady gait, decrease in bladder control ($n=1$)
[30][b]	Abstract (2007)	14 (80)	MB ($n=6$), ependymoma ($n=3$), PNET ($n=2$), others ($n=3$)	Chemical arachnoiditis ($n=4$), mild–moderate headache ($n=4$)
[31][b]	Retrospective case series (2009)	8 (40)	Ependymoma ($n=3$), PNET ($n=2$), MB ($n=1$), others ($n=2$)	Chemical arachnoiditis ($n=2$), irritability ($n=1$), headache/seizures ($n=1$), irreversible cauda equina syndrome ($n=1$)

CNS, central nervous system; DL, dose level; DXM, dexamethasone; MB, medulloblastoma; PNET, primitive neuroectodermal tumors; w/o, without.
[a]Side effects were reported for all study patients including patients with hematological malignancies.
[b]Overlapping study populations.

retrospective in nature, is presently the largest series on IT liposomal cytarabine in children and adolescents with brain tumors. As both the inclusion criteria (cytological or neuroradiographic evidence of leptomeningeal dissemination) and the histopathological diagnoses in this study were similar to those of other studies [17–20,22] reporting on IT chemotherapy in children with recurrent or refractory brain tumors, the use of this drug was considered justified in our study patients outside a formal clinical trial in an attempt to improve the outcome of this poor-prognosis population. IT chemotherapy in the studies cited above was not limited to patients with medulloblastoma/PNET, known for its propensity to spread throughout the leptomeninges, but was also given to patients with ependymoma, malignant glioma, choroid plexus carcinoma, pineoblastoma, gliomatosis, malignant glioma, or rhabdomyosarcoma [17–20,22]. The study by Rutkowski *et al.* [11] has yielded further encouraging

results, even in patients with medulloblastoma and macroscopic metastases. IT chemotherapy seems to be beneficial at least in (younger) patients with medulloblastoma who represent more than two-thirds of our study population. As all patients had undergone irradiation and had lesions not amenable to surgical resection, administration of IT or intraventricular chemotherapy was the remaining strategy of a 'local therapy', although we are aware that solid metastatic lesions (Chang stage > M1) are less susceptible to chemotherapy than microscopic metastases.

A number of phase I studies evaluating other drugs for IT use have been successfully completed [17–20], but some of the compounds tested (e.g. mafosfamide) are no longer available, most likely because of commercial considerations. None of these drugs, however, became standard treatment in children with neoplastic meningitis from solid/brain tumors or were further evaluated in prospective phase II/III studies. Apart from the well standardized IT chemotherapy in hematological malignancies [14] and the use of IT MTX in younger children with PNET/medulloblastoma [11], IT chemotherapy in children with recurrent or refractory brain tumors is insufficiently evaluated to date. Decisions concerning IT therapy in recurrent childhood brain tumors are primarily based on personal experience and low-level evidence. The pediatric oncology community is urgently awaiting prospective clinical trials not only on IT liposomal cytarabine, but also on other new drugs for children with cancer. As mentioned above, pharmaceutical companies are, however, very reluctant to initiate and perform prospective drug trials in children owing to the small number of patients, the commercial profit can be expected to be low compared with the adult population.

Chemical arachnoiditis, the most common side effect after IT administration of liposomal cytarabine [22], developed in four of our patients (patients 1, 7, 8, 13). Similar to one of our five patients reported in 2007 [27], a 2-year-old boy (patient 1) developed seizures after the 7th administration of the drug. He was not receiving any systemic chemotherapy at that time. In the study by Glantz *et al.* [32], two patients had experienced seizures [Cancer and Leukemia Group B (CALBG) toxicity grade 3 and 4] and five altered mental status (CALBG toxicity grade 3) after IT injections of liposomal cytarabine, a side effect that was also observed in one of our study patients (patient 17). Another patient (patient 9) developed ataxia and slurred speech, symptoms that have not yet been reported after the administration of IT liposomal cytarabine. We [27,33] and others [34,35] have observed (serious) neurotoxic side effects including encephalitis/encephalopathy, cauda equina syndrome, pseudotumor cerebri, and papilloedema in addition to the well-known chemical arachnoiditis after the administration of IT liposomal cytarabine in patients with hematological malignancies. Interestingly, we saw no such side effects, although our patients had previously received intensive CNS-directed therapies. Although current data suggest that particularly patients with hematological malignancies who receive IT liposomal cytarabine are at the risk of developing serious neurotoxicity, this drug should be used with great caution in patients with brain tumors who have to cope with CNS damage from previous radiochemotherapy or who have disturbances in CSF flow or CSF resorption. Although CSF flow studies are indicated in patients with metastatic brain tumors and clinically suspected CSF blocks, they were not done in our patients to definitely exclude interruption of CSF flow.

In conclusion, the toxic side effects after the administration of IT liposomal cytarabine can be grouped into three different categories. First, there are symptoms (fever, nausea, vomiting, back pain) that are caused by chemical arachnoiditis. These side effects are only transient and can be prevented or alleviated by appropriate dexamethasone prophylaxis [22]. Second, there are more serious neurotoxic effects such as cauda equina syndrome or papilloedema, some of which might involve severe and permanent neurological sequela [27,33–35]. These adverse effects were reported, in particular, after prior systemic administration of cytotoxic drugs penetrating the blood–brain barrier such as high-dose MTX or high-dose cytarabine. Third, there are fewer well-known toxic drug reactions including altered mental status or hematological toxicity that are reported in a minority of patients receiving IT liposomal cytarabine [32,36]. It should be noted that all side effects observed after IT liposomal cytarabine might result from a similar underlying pathogenesis (i.e. local inflammation owing to the long half-life of liposomal cytarabine) and might be related to each other. When discussing the side effects after the administration of IT liposomal cytarabine, one should consider other risk factors [e.g. the underyling disease, pretreatment (surgery, irradiation)] that might have contributed to these side effects. Although IT liposomal cytarabine was well tolerated in most of our patients, proof of efficacy requires a prospective single-agent phase II study.

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