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# Pharmacokinetics and Safety of Intrathecal Liposomal Cytarabine in Children Aged <3 Years

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## Abstract

**Background and objective:** Liposomal cytarabine (DepoCyte®) is a slow-release formulation for intrathecal application, ensuring prolonged drug exposure. Although there is an urgent need for new treatment options for infants with leptomeningeal dissemination of a malignant brain tumour, there are no clinical and pharmacokinetic data available on this drug for children aged <3 years. The objective of this pilot study was to determine the feasibility, safety and pharmacokinetics of cytarabine after intrathecal administration of liposomal cytarabine 25 mg in patients aged <3 years.

**Patients and methods:** Six male patients with a mean age of 21 months and CNS primitive neuroectodermal tumours (n = 3) or atypical teratoid/rhabdoid tumours (n = 3) were included. Liposomal cytarabine (25 mg) was administered intraventricularly. One patient also received the drug by lumbar puncture. Dexamethasone was used concomitantly for 3–5 days to prevent arachnoiditis. Cerebrospinal fluid (CSF) and plasma samples were collected before administration of liposomal cytarabine and 1 hour, 12 hours, 24 hours, 1 week and 2 weeks post-dosing. Noncompartmental pharmacokinetic analysis of CSF and plasma was performed.

**Results:** Liposomal cytarabine was generally well tolerated; only grade 2 headache occurred in one patient. After intraventricular administration of cytarabine 25 mg, free and encapsulated drug concentrations above the cytotoxic drug level of 0.1 μg/mL were detectable in the CSF for at least 7 days and up to 14 days post-dosing. The average elimination half-lives were 56.7 hours for encapsulated cytarabine and 59.3 hours for free cytarabine. After intralumbar administration, the elimination half-life of free cytarabine, measured in the ventricular CSF during two courses in one patient, was significantly shorter (32.7 hours).

**Conclusion:** Application of liposomal cytarabine with concomitant dexamethasone appears to be safe and well tolerated in children aged <3 years. Drug exposure in infants aged <3 years after an intraventricular dose of 25 mg is comparable to that after administration of 50 mg in adult patients and 35 mg in older children.

## Background

Although there is a clear demand for safe and tested treatment regimens for children with malignant diseases, most newly developed drugs are evaluated and approved only in adult patients. One reason for this is the fact that adults constitute the major oncology patient group, being economically more important. Another reason is that trials in children are particularly delicate, imposing additional regulatory requirements and therefore discouraging potential study sponsors. Hence, paediatricians are often obliged to seek compassionate use of many drugs to provide their patients with an efficient treatment.

Tumours of the CNS constitute the largest group of solid neoplasms in children and are second only to leukaemia in their overall frequency during childhood. Treatment of malignant childhood brain tumours is complicated by their tendency towards leptomeningeal dissemination. Intravenous chemotherapy may be augmented by intrathecal chemotherapy, particularly in very young children, in whom craniospinal irradiation is not an option. However, various chemotherapeutic drugs used for treating these tumours show only limited penetration into the cerebrospinal fluid (CSF).[1] To date, the standard agents available for intrathecal chemotherapy are methotrexate and cytarabine, which are not very effective in

treating solid tumours. Therefore, there is a compelling need to find additional drugs or formulations for intrathecal treatment of solid tumours.

Cytarabine is a pyrimidine nucleoside analogue of cytidine that is transported into the cell by facilitated diffusion. It is converted intracellularly to its active form, arabinosylcytosine triphosphate (Ara-CTP), which subsequently exerts its antineoplastic effect either as a competitive inhibitor of DNA polymerase or by incorporation into DNA. Systemically administered cytarabine is primarily deaminated to the inactive compound uracil arabinoside (Ara-U), which is eliminated renally.[2]

Cytidine deaminase, the enzyme that catalyses the metabolism of cytarabine to Ara-U, is present only at low levels in the CSF. The clearance rate of cytarabine from the CSF is similar to the rate of CSF bulk flow, suggesting that the elimination of cytarabine from the CSF occurs by bulk flow.[3,4] For cell-cycle-specific, antineoplastic drugs such as cytarabine, the duration of exposure of neoplastic cells to cytotoxic drug concentrations is a critical factor influencing therapeutic efficacy. Because free cytarabine has a short elimination half-life of only 3.4 hours after intrathecal injection, cytotoxic concentrations in human lymphoblasts are maintained for only about 24 hours.[3]

Depending on the target cell threshold concentration and proliferation rate, a widely used treatment schedule for intrathecal free cytarabine in haematological malignancies consists of lumbar injections twice weekly. Solid tumours have a lower proliferation rate and are thought to have a higher cytotoxic threshold requiring constant infusion or even more frequent injections to maintain cytotoxic concentrations in the CSF, particularly when using a cell-cycle-specific drug such as cytarabine. However, frequent intrathecal injections are impractical, uncomfortable for patients and increase the risk of infectious meningitis.

Liposomal cytarabine is a slow-release formulation in which cytarabine is encapsulated in microscopic particles that average 19 μm in diameter, containing numerous nonconcentric chambers bound by a single bilayer lipid membrane.[5] Cytarabine is gradually released from these particles into the CSF, thereby prolonging exposure to the drug and intensifying the effect.

The recommended dose of liposomal cytarabine for adults is a single injection of 50 mg every 2 weeks, leading to a mean elimination half-life of free cytarabine in the CSF of 80 hours versus 3.4 hours for native cytarabine.[6] Patients between the ages of 3 and 21 years showed more rapid elimination of liposomal cytarabine from the CSF than adults treated at similar dose levels. Children tolerated an overall lower dose than adults, leading to a recommended phase II dose of 35 mg.[7] In spite of the urgent need for intrathecal antineoplastic treatment in children aged <3 years, there are no safety and pharmacokinetic data available on liposomal cytarabine for this patient group.

The aim of the present pilot study was to test the pharmacokinetics and safety of intrathecally administered liposomal cytarabine for the first time in children aged <3 years. Hence, an adequate dosage of intrathecal liposomal cytarabine had to be defined in this patient group. For this purpose, the appropriate CNS volume was estimated. In contrast to the body surface area, which continues to increase throughout childhood and adolescence, the CSF volume, like the head circumference, increases rapidly during the first years of life, with achievement of adult volume at the age of 3–4 years.[8] It has been confirmed that the percentage of the CSF that occupies the intracranial space remains nearly constant at 7–9% from early childhood to early adolescence.[9] Considering these facts, we decided to use half of the adult intrathecal dose, i.e. 25 mg of liposomal cytarabine, for children aged <3 years to determine the feasibility, safety and pharmacokinetics of liposomal cytarabine.

## Patients and Methods

### Eligibility Criteria

Patients aged <3 years with a histologically proven diagnosis of a malignant brain tumour and leptomeningeal dissemination or the risk of such, for whom no routine protocol was available, were included in the present study. Patients received intrathecal liposomal cytarabine on a compassionate use basis. Other eligibility criteria were (i) a life expectancy of at least 8 weeks; (ii) written informed consent from the parents; (iii) serum creatinine <1.5 mg/dL; (iv) total serum bilirubin <2.0 mg/dL and ALT <5 times the upper limit of normal; and (v) a platelet count >40 000/mm$^3$ within 48 hours before the first treatment. The exclusion criteria were (i) severe uncontrolled infection; and (ii) evidence of obstructive hydrocephalus or compartmentalization of CSF flow. Patients were still eligible if they received local radiotherapy to their primary tumour and other therapy targeted at their leptomeningeal disease and/or concomitant systemic chemotherapy. The study protocol was approved by the ethics committee of the Medical University of Vienna (Vienna, Austria). The patient history, physical examination and laboratory tests (complete blood count, electrolytes, blood urea nitrogen, creatinine, liver function, calcium and phosphorus) were obtained before treatment. A baseline head and spine magnetic resonance imaging (MRI), with and without contrast, was obtained before liposomal cytarabine treatment to exclude obstructive hydrocephalus or compartmentalization of CSF flow. Routine safety measures

included monitoring of the cell count, microbiology, cytology, protein and glucose in the CSF.

### Drug Administration and Toxicity Assessment

Liposomal cytarabine (DepoCyte®, Mundipharma GesmbH, Vienna, Austria) was supplied by the hospital pharmacy in 2 mL syringes containing 25 mg. The drug was administered intrathecally through an intraventricular (IVT) reservoir or via a lumbar puncture. Reservoirs were flushed with approximately 2 mL of artificial CSF after drug administration. Patients who received intralumbar drug were kept in a recumbent position for 1 hour following drug administration to increase drug distribution throughout the neuroaxis. All patients received concomitant dexamethasone (0.15 mg/kg/dose intravenously or orally) for a total of 5 days to prevent arachnoiditis. In two patients, the duration of dexamethasone treatment was reduced to 3 days, when evidence emerged from experience in adult patients that 3 days of concomitant dexamethasone might be sufficient to prevent arachnoiditis. A proton pump inhibitor was given to prevent gastric complications of dexamethasone therapy. Treatment cycles were separated by a wash-out period of at least 2 weeks.

Toxicity was assessed on an ongoing basis according to the WHO grading system.[10] Patients were considered assessable for toxicity if they received at least one dose of liposomal cytarabine.

### Pharmacokinetic Studies

Pharmacokinetic samples for assessment of cytarabine concentrations were obtained prospectively from a subset of patients enrolled in the study. Ventricular CSF (1 mL) and blood (1.2 mL) samples from all evaluable patients (including the one with intralumbar application) were obtained before liposomal cytarabine administration and at 1, 12 and 24 hours, 1 week and 2 weeks after dosing.

Following collection, CSF samples were immediately transferred to polypropylene tubes containing 40 μmol/L tetrahydrouridine to prevent *in vitro* catabolism of cytarabine to Ara-U. CSF samples were centrifuged at 600 *g* for 5 minutes to separate liposomal particles (pellets) from the free cytarabine fraction (supernatant), 200 μL of methanol was added to the pellets and the volume was adjusted with distilled water to a final volume of 1 mL. The free cytarabine fractions were analysed without further processing. All samples were snap frozen and stored at −80°C until analysis.

Blood samples were collected directly into heparinized tubes, and tetrahydrouridine was immediately added to reach a concentration of 40 μmol/L. Samples were then centrifuged at +4°C and 3500 rpm for 10 minutes. Plasma was transferred to a polypropylene tube and stored at −80°C until analysis.

Cytarabine concentrations were analysed using a validated high-performance liquid chromatography method with UV detection. Plasma and CSF samples were deproteinized by addition of 50% trichloroacetic acid and centrifugation. The supernatants were adjusted to pH 3.0 with 2.5 N sodium hydroxide solution. The methanolic extracts of precipitated liposomal cytarabine particles were acidified with 50 mmol/L citric acid and co-extracted with acetonitrile and dichloromethane. Separation of cytarabine was performed on a reverse-phase column (Symmetry C18, 150 × 2.1 mm, 5 μm particle diameter; Waters Corporation, Milford, MA, USA). The mobile phase consisted of 50 mmol/L sodium citrate buffer (pH 3.0), 5 mmol/L 1-octanesulfonic acid and 5% methanol, and was pumped with a flow rate of 0.5 mL/min. The detection wavelength was set at 270 nm. Elution of cytarabine was followed by a column washing step with 70% methanol. The coefficients of variation of inaccuracy and imprecision of this method were ≤7.3% and ≤3.5%, respectively, in plasma and ≤5.6 and ≤2.2%, respectively, in CSF and methanolic cytarabine extracts. The (lower) threshold for cytarabine quantification was 0.05 mg/L.

### Pharmacokinetic Data Analysis

Each of the two study periods of a single subject included in the pharmacokinetic subgroup was handled as a separate dataset.

Pharmacokinetic parameters of cytarabine in the CSF were calculated by standard noncompartmental analysis using Kinetica 3.0 software (Innaphase Sarl, Philadelphia, PA, USA). The value of the area under the concentration-time curve from time zero to infinity ($AUC_\infty$) was calculated from non-fitted data using the linear trapezoidal rule. The residual area from the last observed concentration ($C_{last}$) to infinity was calculated using the approximation $AUC_{t\text{-}\infty} = C_{last}/k_{el}$, where $k_{el}$ represents the individual elimination rate constant. The apparent terminal elimination half-life of the terminal slope was defined as $t_{1/2} = \ln 2/k_{el}$. Values are presented as means ± standard deviations.

## Results

### Demographics

Six male patients aged <3 years with childhood brain tumours were treated with intrathecal liposomal cytarabine on a compassionate use basis. Their ages at first administration

ranged from 11 months to 35 months (mean 20.8 months). Three patients had atypical teratoid/rhabdoid tumours (ATRT) and three had a CNS primitive neuroectodermal tumour (PNET). Three patients had experienced recurrences and three were treated with liposomal cytarabine at primary diagnosis. Liposomal cytarabine was administered over a period of 4–20 months (mean 8.1 months) with a total of 39 applications (3–10 per patient, mean 6.5 applications). Details of the clinical characteristics of the six patients are given in table I. All patients had surgery on their primary tumours, were treated with systemic chemotherapy concomitant to intrathecal therapy, and had received additional intrathecal chemotherapy consisting of methotrexate and etoposide prior to inclusion in the present study. None of the patients received systemic cytarabine therapy. Two patients were switched to intrathecal liposomal cytarabine because of methotrexate-induced leukoencephalopathy.

Two patients were treated with liposomal cytarabine on a compassionate use basis prior to the start of the pharmacokinetic study. These patients were treated in the same manner with concomitant dexamethasone for 5 days and assessed only for toxicity data. Pharmacokinetic data were available from a subset of four patients (13, 16, 24 and 26 months of age), providing a total of seven IVT and two intralumbar treatment periods. Two patients had pharmacokinetic samples from two periods of IVT treatment and one patient had pharmacokinetic samples from one IVT period only. In one patient, pharmacokinetic sampling was performed during two IVT cycles and during two additional cycles with lumbar dosing. This patient received intralumbar liposomal cytarabine during local radiotherapy for his CNS PNET to prevent spinal leptomeningeal seeding.

### Safety

Intrathecal liposomal cytarabine was generally well tolerated with routine administration of concomitant dexamethasone. One patient with a relapse of a CNS PNET experienced grade 2 headache, which resolved after treatment with paracetamol (acetaminophen). No immediate toxicities such as infectious complications, pleocytosis, aseptic meningitis or arachnoiditis occurred in any of the six patients. None of the patients experienced a seizure or hyponatraemia resulting from inappropriate secretion of antidiuretic hormone.

Four of the six patients enrolled in the study had white matter changes noted at baseline. One of the patients showed slight progression of the leukoencephalopathy during the whole course of his antitumour therapy, including local radiotherapy to his CNS PNET. This patient also had persisting connatal toxoplasmosis. None of the patients required discontinuation of treatment due to toxicity.

### Clinical Response

Since all patients received concurrent systemic chemotherapy, the efficacy of liposomal cytarabine could not be assessed independently. However, five of six patients were still alive as of 16 March 2009 (four in complete remission and one in partial remission) with a mean follow-up of 32 months (range 20–47 months) after initiation of intrathecal liposomal cytarabine treatment. None of the patients has progressive leptomeningeal disease as evidenced by CSF cytology and/or MRI. One patient died of tumour progression at the local site.

**Table I.** Clinical characteristics of patients enrolled in the study

| Patient no. | Age at first application of liposomal cytarabine (mo) | Diagnosis | Metastases | | Treatment route | Overall no. of applications of liposomal cytarabine | No. of treatment periods with pharmacokinetic data |
|---|---|---|---|---|---|---|---|
| | | | CSF | MRI | | | |
| 1 | 35 | CNS PNET | – | – | IVT | 8 | ND |
| 2 | 11 | ATRT (recurrence) | + | + | IVT | 9 | ND |
| 3 | 13 | CNS PNET | – | – | IVT | 3 | 1 |
| 4 | 26 | CNS PNET (recurrence) | – | + | IVT, LP | 8 | 2 (IVT), 2 (LP) |
| 5 | 24 | ATRT | + | – | IVT | 4 | 2 |
| 6 | 16 | ATRT (recurrence) | – | – | IVT | 5 | 2 |

**ATRT** = atypical teratoid/rhabdoid tumour; **IVT** = intraventricular; **LP** = lumbar puncture; **ND** = no pharmacokinetic data; **PNET** = primitive neuroectodermal tumour; + indicates present; – indicates absent.

**Table II.** Pharmacokinetic parameters after intraventricular (IVT) or lumbar injection of liposomal cytarabine 25 mg in cerebrospinal fluid[a]

| Parameter | IVT (n = 7) | | Lumbar (n = 2) | |
|---|---|---|---|---|
| | encapsulated cytarabine | free cytarabine | encapsulated cytarabine | free cytarabine |
| $C_{max}$ (mg/L) | 222.7 ± 79.5 | 21.3 ± 21.9 | 6.5 ± 5.5 | 5.4 ± 0.4 |
| $AUC_{\infty}$ (mg • h/L) | 1215.5 ± 228.9 | 363.7 ± 231.6 | 103.2 ± 99.7 | 134.0 ± 112.0 |
| $t_{1/2}$ (h) | 56.7 ± 34 | 59.3 ± 23 | 55.7[b] | 32.7[b] |

a Values are expressed as mean ± SD.

b n = 1, because the terminal slope could not be determined for one dataset.

**$AUC_{\infty}$** = area under the concentration-time curve from time zero to infinity; **$C_{max}$** = maximum concentration; **$t_{1/2}$** = elimination half-life.

### Pharmacokinetics

Overall, seven pharmacokinetic profiles in CSF and in plasma after IVT application of liposomal cytarabine were available from four patients, and two pharmacokinetic profiles were available from one patient after lumbar applications. The results are summarized in tables II and III and figures 1 and 2.

These nine pharmacokinetic datasets included a total of 48 plasma samples (36 after IVT and 12 after lumbar dosing). Free cytarabine was undetectable after ventricular or lumbar dosing in the majority of plasma samples (n = 44). Cytarabine concentrations ranging from 0.052 to 0.075 μg/dL, i.e. just above the detection limit, were found in four samples from one patient.

## Discussion

This study was the first to determine the feasibility, safety and pharmacokinetics of liposomal cytarabine administered intrathecally in children aged <3 years.

In adult patients with lymphomatous and solid tumour neoplastic meningitis, liposomal cytarabine produced a higher response rate and a better quality of life, and significantly increased the time to neurological progression compared with free cytarabine and methotrexate.[11,12] The efficacy of liposomal cytarabine could not be assessed independently in the present study because the patients received concurrent therapies.

In paediatric patients aged between 3 and 21 years, mild headache and back or neck pain were the most common adverse effects.[7] Similar toxicities have been observed in adult patients.[6,11-13] In the present study, liposomal cytarabine was generally well tolerated in children aged <3 years. Immediate toxicity (mild headache) occurred in only one patient, and five patients did not experience any immediate toxicity at all. Arachnoiditis, as previously observed in two older paediatric patients,[7] was successfully prevented by a short course of concomitant dexamethasone. In contrast to the present experience in children aged <3 years, a previous trial in adults reported severe neurotoxicity, including seizures, papilloedema, encephalitis and cauda equina syndrome, when liposomal cytarabine was administered concomitantly with systemic chemotherapy for acute lymphocytic leukaemia.[14] No long-term sequelae, as evidenced by MRI and neurological evaluation, have been observed in our patients after a mean period of 26 months after treatment. No neurotoxicity was observed in our patients who received concurrent radiotherapy and/or chemotherapy (temozolomide, cisplatin, carboplatin, ifosfamide, etoposide).

**Table III.** Concentrations of encapsulated and free cytarabine after intraventricular (IVT) administration (n = 7), and ratio of encapsulated : free cytarabine in cerebrospinal fluid over time

| Time after injection | Encapsulated cytarabine (mg/L) | | Free cytarabine (mg/L) | | Ratio |
|---|---|---|---|---|---|
| | mean ± SD | median (range) | mean ± SD | median (range) | |
| 1 h | 222.70 ± 79.53 | 196.3 (142.1–367.6) | 21.34 ± 21.85 | 13.5 (5.4–71.8) | 16.5 ± 10.4 |
| 12 h | 14.33 ± 6.11 | 12.0 (7.3–25.3) | 3.84 ± 1.56 | 3.3 (1.3–7.0) | 4.1 ± 1.6 |
| 24 h | 4.64 ± 2.71 | 2.8 (1.3–9.4) | 2.87 ± 1.61 | 2.7 (0.9–5.4) | 1.7 ± 0.8 |
| 1 wk | 0.22 ± 0.23 | 0.2 (0.0–0.7) | 0.19 ± 0.10 | 0.1 (0.1–0.4) | 1.3 ± 1.7 |
| 2 wk | 0.10 ± 0.10 | 0.1 (0.0–0.4) | 0.10 ± 0.19 | 0.0 (0.0–0.6) | 0.8 ± 0.8 |

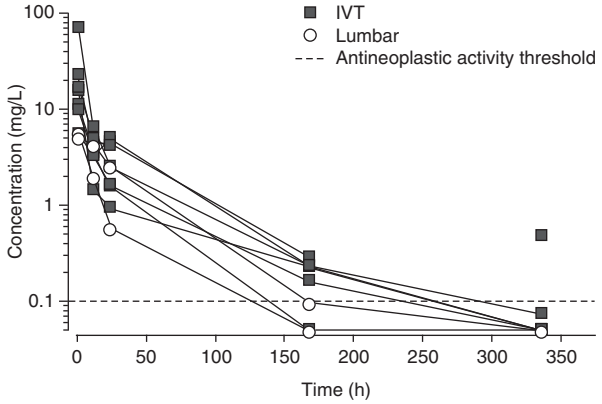


**Fig. 1.** Individual concentration-time profiles of free (unbound) cytarabine in ventricular cerebrospinal fluid after intrathecal application of liposomal cytarbine 25 mg through an intraventricular (IVT) reservoir or via a lumbar puncture.

As expected, free and encapsulated cytarabine concentrations showed a peak 1 hour after IVT injection and declined rapidly within the first day after injection, as distribution occurred throughout the neuroaxis. After 24 hours, the mean concentration of free cytarabine decreased to 2.87 ± 1.61 mg/L from 21.34 ± 21.85 mg/L at 1 hour. Overall, intra- and inter-individual variability of drug concentrations in the CSF was moderate (see standard deviations in table II) and in accordance with previous studies in other age groups.[7,15]

*In vitro* studies demonstrated that the continuous presence of 2.4 mg/L cytarabine in culture medium kills both glial and neuronal cells after about 6 days of exposure.[16] In the present study, about 1–2 days after administration of liposomal cytarabine, the concentrations of free cytarabine approached or fell below this neurotoxic threshold (see figure 1). This suggests that the risk of neurotoxicity may be acceptable at the doses of 25 mg used in the present study.

*In vitro*, the minimum concentration of cytarabine able to exert antineoplastic activity was found to be 0.1 mg/L, as determined by incubation of several cancer cell lines with cytarabine for 24 hours.[17,18] In the present study, the free drug concentrations of cytarabine after IVT dosing were above this threshold of antineoplastic activity for >1 week in most (n = 6 of 7) measured profiles (figure 1). The mean free cytarabine concentration approached the minimal cytotoxic level of 0.1 mg/L 14 days after the initial injection (figure 2). This prolonged intrathecal exposure to cytotoxic drug concentrations suggests good local antineoplastic activity and was achieved with almost no drug exposure in the systemic circulation.

In children aged <3 years, we found a terminal elimination half-life of 59.3 hours for free cytarabine and a terminal elimination half-life of 56.7 hours for encapsulated cytarabine. These values are similar to the previously published elimination half-life of 50–57 hours for free cytarabine in older children.[7] In contrast, the ventricular concentrations of free cytarabine in adults showed a longer terminal elimination half-life of 80 hours after injection of liposomal cytarabine 50 mg into the CSF.[6]

In the present study, the free cytarabine concentrations after 12 and 24 hours in ventricular CSF following lumbar application were comparable to those after IVT dosing. In agreement with previous studies,[15] this demonstrates that cytarabine can spread throughout the neuroaxis even after intralumbar injection of liposomal cytarabine in children aged <3 years.

On the other hand, the IVT concentrations of encapsulated cytarabine were lower after lumbar injection than after IVT dosing. One and 2 weeks after lumbar injection, the IVT concentrations of liposomal cytarabine were near to or below the detection limit, indicating more rapid elimination of liposomal cytarabine after lumbar administration. This appears to be in accordance with data published in adult patients and children aged >3 years.[6,7] Hence, it may be speculated that IVT application is more effective than lumbar injection of liposomal cytarabine and that IVT application should be preferred or alternated with lumbar application whenever possible.

Liposomal cytarabine substantially reduces the number of intrathecal drug administrations, thereby decreasing anxiety associated with injections and hospital visits in this young age-group of patients. Furthermore, the risk of bacterial infections due to frequent intrathecal applications might be reduced as well.

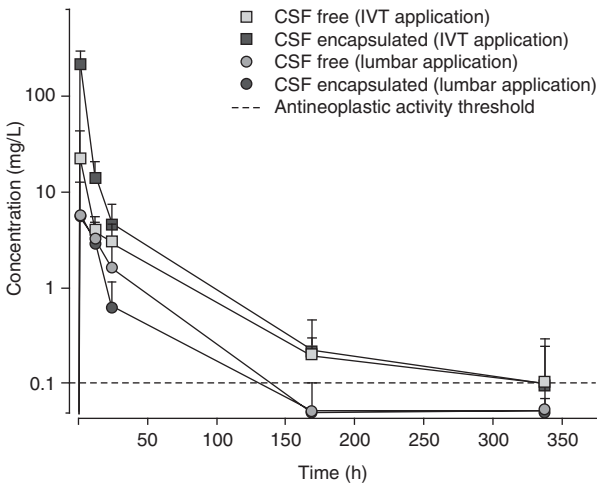


**Fig. 2.** Mean (+SD) drug concentrations of cytarabine in cerebrospinal fluid (CSF) over time after intrathecal application of liposomal cytarabine 25 mg through an intraventricular (IVT) reservoir (n = 7) or lumbar puncture (n = 2).

## Conclusion

The results of this study show that administration of liposomal cytarabine 25 mg in children aged <3 years appears to be safe and well tolerated if combined with concomitant dexamethasone. With this dose, the drug exposure in the CSF in children aged <3 years is comparable to that achieved after administration of 50 mg in adult patients and 35 mg in older children.

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