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SHORT COMMUNICATION

Cerebrospinal Fluid Drug Concentrations and Clinical Outcome of Patients with Neoplastic Meningitis Treated with Liposomal Cytarabine

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Abstract

Background and Objective Liposomal cytarabine is a slow-release formulation for intrathecal application in patients with neoplastic meningitis. Although standard dosing intervals range from 2 to 4 weeks, it is unclear whether sustained cytotoxic cerebrospinal fluid (CSF) concentrations can be achieved beyond 14 days from drug injection. The objective of this study was to assess CSF and plasma concentrations of liposomal cytarabine more than 2 weeks after lumbar drug administration and to correlate those findings with clinical outcome.

Methods 66 matched CSF and plasma drug concentrations were analyzed by a validated liquid chromatography–tandem mass spectrometry method starting at day 13 from lumbar drug injection in 19 patients with neoplastic meningitis treated with liposomal cytarabine. CSF drug concentrations were correlated with clinical outcome.

Results Overall response rate was 63.2% (12/19). 100% (9/9) of patients with positive CSF cytology at diagnosis achieved cytological complete remission, and none of the patients (0/19) experienced on-drug disease progression. In responding patients with controlled systemic disease, CNS-specific progression-free survival was 14 months ($n=4$; range 5–25 months). The median CSF concentration of free cytarabine was 156 ng/ml (range 5–4581 ng/ml) and 146 ng/ml (range 5–353 ng/ml) in samples withdrawn at days 13–16 and at days 25–29 after intrathecal drug injection, respectively. Free cytarabine concentrations > 100 ng/ml were detected in 58.8% (20/34) and 53.3% (7/13) of the CSF samples obtained at days 13–16 and days 25–29, respectively. CSF drug concentrations did not differ significantly between responding and nonresponding patients.

Conclusion Liposomal cytarabine permits prolonged CSF drug exposure, with cytotoxic cytarabine concentrations that are detectable for 4 weeks in the majority of patients. The preserved clinical activity seen in patients with inferior CSF drug concentrations (< 100 ng/ml) suggests that maintaining lower cytarabine concentrations for a longer period of time may be similarly effective as using short peak concentrations.

1 Introduction

Neoplastic meningitis is a devastating complication in cancer patients that occurs in approximately 5% of cases [1]. Besides systemic agents, standard local treatment comprises intrathecal chemotherapy and/or radiation. With currently available drugs for intrathecal application such as cytarabine and methotrexate, however, survival is still very limited [2]. Both agents act cell cycle specifically and have short half-lives in the cerebrospinal fluid (CSF), which very likely contributes to poor outcomes as it can result in insufficient exposure of tumor cells to cytotoxic CSF drug concentrations [3]. More frequent dosing may help to maintain therapeutic CSF drug concentrations for an extended period of time [4]. However, to achieve an adequate drug distribution throughout the complete neuraxis, surgical placement of an Ommaya reservoir for intraventricular drug administration is obligatory [5].

Liposomal cytarabine is a sustained-release formulation of cytarabine in which the drug is encapsulated in lipids (DepoFoam), resulting in a 40-fold prolongation of its

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Key Points

Effective treatment of neoplastic meningitis necessitates intrathecal chemotherapy at cytotoxic concentrations and, when using cell-cycle-specific agents such as cytarabine, for a prolonged period of time.

Liposomal cytarabine is a sustained-release formulation of cytarabine resulting in a 40-fold prolongation of its terminal half-life.

Liposomal cytarabine achieves sustained cerebrospinal fluid (CSF) drug concentrations that were demonstrated to be cytotoxic in vitro (> 100 ng/ml) until 4 weeks after lumbar drug injection.

Preserved clinical activity seen in patients with inferior CSF drug concentrations (< 100 ng/ml) suggests that maintaining lower cytarabine concentrations for a longer period of time may be similarly effective as using short peak concentrations.

terminal half-life [6]. Using liposomal cytarabine, cytotoxic CSF drug concentrations were found to be detectable for up to 14 days regardless of whether the agent was administered via the ventricular or the lumbar route. A biweekly induction dosing schedule was subsequently proposed and proved to be noninferior to intrathecal methotrexate in a phase III study in patients with neoplastic meningitis [7]. Pharmacokinetic CSF analysis of individual study patients further confirmed that prolonged CSF drug exposure is achieved with liposomal cytarabine as compared with standard cytarabine [8].

Nevertheless, 14 days after liposomal cytarabine administration, CSF drug concentrations were frequently observed to be far below [8] the in vitro validated lower limit of cytotoxicity (> 100 ng/ml) as determined for various cancer cell lines upon 24 h of exposure [9–12]. Given the demonstrated clinical efficacy in the patients the CSF samples were taken from, it was suggested that the cell-cycle-specific mode of action of cytarabine may facilitate a similar cytotoxicity in vivo even when lower concentrations (> 20 ng/ml) of the drug are maintained over a longer period of time (> 24 h) [8]. However, these results are yet to be confirmed in a larger cohort, and they still do not explain the ongoing clinical response to liposomal cytarabine often seen in patients receiving the drug only monthly during the maintenance phase of treatment.

Thus, in the work reported here, we aimed to measure the CSF concentrations of liposomal cytarabine starting at day 13 post drug injection in 19 patients with neoplastic meningitis who were treated in Innsbruck, Austria, and to correlate those findings with clinical outcome.

2 Patients and Methods

Patients with neoplastic meningitis from various tumors treated with liposomal cytarabine at a tertiary university center (Innsbruck, Austria) between 2010 and 2015 were identified from the clinical database. Patients were treated at biweekly intervals during induction (5 injections at weeks 1, 3, 5, 7, and 9) and monthly intervals during the maintenance phase (5 injections at weeks 13, 17, 21, 25, and 29). Liposomal cytarabine was injected via the lumbar route at a dose of 50 mg per injection. All patients received dexamethasone (4 mg orally twice daily for 4 days after drug administration) for arachnoiditis prophylaxis. Treatment was continued until disease progression or up to a maximum of ten doses. A cytological complete response was defined as two consecutive negative CSF cytology examinations at least 1 week apart; all other constellations were considered nonresponsive. Patients with negative CSF cytology but signs of CNS involvement based on magnetic resonance imaging (MRI) at diagnosis were regarded as responsive when there was clinical improvement in neurologic signs or symptoms. As part of CNS-directed cancer therapy, all patients received concomitant irradiation of the brain and involved parts of the spinal column on MRI at a median dosage of 40 Gy (range 38.4–40.8 Gy). All except one patient received intravenous chemo(immuno)therapy in parallel with control systemic disease manifestation(s).

Paired CSF (1 ml) and blood (8 ml) samples were withdrawn at a single point of time after each lumbar drug injection during the course of treatment in all patients. Plasma was obtained after blood centrifugation at 4500 rpm for 5 min. Paired CSF and plasma samples were immediately frozen upon withdrawal and stored at the local CNS fluid biobank. Storage and analysis were performed with the approval of the local ethics committee.

Cytarabine was quantified in CSF and plasma with validated workflows employing liquid chromatography–tandem mass spectrometry (LC–MS/MS) with high-resolution multiple reaction monitoring (HR-MRM). For the quantification of cytarabine, ^{13}C3-cytarabine was used as internal standard (IS). For use as calibrators, stock solutions of 1.0 mg/ml cytarabine and 1.0 mg/ml ^{13}C3-cytarabine were prepared in methanol and stored at − 20 °C until use. Working standards of cytarabine were prepared by dilution of the stock solution with 0.1% heptafluorobutyric acid (HFBA) in water (v/v) to obtain concentrations ranging between 50 ng/ml and 5 µg/ml. The working solution of the IS was prepared by diluting the stock solution with 0.1% HFBA in water (v/v) to obtain a concentration of 500 ng/ml. Calibration samples were prepared by spiking 50 µl of blank CSF and blank plasma with 5 µl of IS working solution and aliquots of the cytarabine working solution to obtain nine different concentrations in

50 µl CSF (1, 2.5, 5, 10, 25, 50, 100, 500, and 1000 ng/ml) and seven different concentrations in 50 µl plasma (1, 2.5, 5, 10, 25, 50, and 100 ng/ml).

Paired CSF and plasma patient samples were quantitatively analyzed for free and encapsulated cytarabine in CSF and for free cytarabine in plasma. Sample preparation was performed in accordance with the method described by Kim and colleagues [6] who first introduced the concept of DepoFoam [13], and which has been adopted in all subsequent preclinical and clinical studies investigating the pharmacokinetics of liposomal cytarabine in humans with consistent results [8, 14, 15]. 50 µl CSF and 50 µl plasma were transferred to 0.6-ml Eppendorf tubes. CSF samples were centrifuged for 5 min at 4500 rpm and the CSF supernatant was transferred to another 0.6-ml Eppendorf tube. The residue (which contains the encapsulated cytarabine fraction) and the supernatant (which contains the free cytarabine fraction) of each CSF or plasma sample were each spiked with 5 µl of IS working solution. 300 µl acetonitrile were added to precipitate the protein in the CSF supernatant and plasma samples. The CSF residue was lysed with 300 µl isopropanol. All samples were vortexed for 30 s and centrifuged for 5 min at 4500 rpm. The solutions were transferred to 1.5-ml glass vials and evaporated to dryness at 60 °C under a gentle nitrogen steam. The dry residues were then reconstituted in 50 µl of 0.1% aqueous HFBA solution (v/v) for subsequent analysis.

The LC–MS/MS system consisted of a Waters ACQUITY UltraPerformance system (Waters Corporation, MA, USA) controlled by MassLynx V4.1 software and a TripleTOF 5600+ (ABSciex, MA, USA) controlled by Analyst TF 1.7 software. Chromatographic separation was accomplished with a Kinetex Polar C18 column (100 × 2.1 mm, 2.7 µm, 100A, Phenomenex, Aschaffenburg, Germany) protected with a SecurityGuard ULTRA cartridge (UHPLC Polar C18, 2.1 mm ID, Phenomenex). The column temperature was held at 50 °C. Mobile phase A was 0.5% aqueous acetic acid solution (v/v). Mobile phase B was a 0.5% aqueous acetic acid solution containing 25% methanol (v/v). Chromatographic separation was accomplished by isocratic elution with 1% B for 10 min at a flow rate of 200 µl/min. The injection volume was 7.5 µl. The column outlet was directly coupled with the electrospray ion source operating in positive ion mode. The IonSpray voltage was set at 5500 V. Gas flows of 50 arbitrary units for the nebulizer gas and 15 arbitrary units for the turbo gas were used. The temperature of the turbo gas was adjusted to 400 °C. The MS method consisted of a MS scan (accumulation time 50 ms, *m/z* range 50–700) and two product ion scans (244.1 at 70 eV, 247.1 at 60 eV, accumulation times of 50 ms, *m/z* range of 50–700). For quantification, selected ion chromatograms were built with MultiQuant 2.1 (244.1 > 95.025 for cytarabine and 247.1 > 98.035 for ^{13}C3-cytarabine). The ratio of the peak area of cytarabine to the peak area of the IS was plotted against the nominal concentration of cytarabine. The linear calibration curve was weighted with 1/*x*. The linear calibration range of cytarabine was 10–1000 ng/ml in CSF (limit of detection, LOD 2.5 ng/ml) and 10–100 ng/ml in plasma (limit of detection 1 ng/ml). Measured values above the upper limit of quantification were extrapolated. Measured values under the lower limit of quantification (LOQ) and above the LOD were set to LOQ × 0.5.

Categorical variables were summarized as frequencies and percentages, and continuous variables as median values and ranges. Comparisons between groups were performed using the Mann–Whitney test for continuous variables and Pearson's chi square for categorical data. A p value < 0.05 was considered statistically significant. Overall survival (OS) and progression-free survival (PFS) were calculated from the start of treatment with liposomal cytarabine to death/last follow-up and disease progression/last follow-up, respectively. All analyses were done using IBM SPSS Statistics 24 (New York, USA) and GraphPad Prism 8 (San Diego, USA).

3 Results

Nineteen patients with neoplastic meningitis treated with liposomal cytarabine were identified. Median age at diagnosis was 57 years (range 38–78 years), with a female to

Table 1 Baseline characteristics of the patients ($n = 19$)

Characteristic	Value
Sex	
Men	4 (21.1%)
Women	15 (79.9%)
Median age at diagnosis in years	57 (range 38–78)
Primary tumor	
Breast cancer	8 (42.1%)
NSCLC	4 (21.1%)
SCLC	2 (10.5%)
Ovarian cancer	2 (10.5%)
Rectal cancer	1 (5.3%)
Melanoma	1 (5.3%)
PCNSL	1 (5.3%)
Median number of prior systemic therapies	2 (range 0–4)
Concomitant radiotherapy	19 (100%)
Parallel systemic chemo(immuno)therapy	18 (94.7%)
Diagnosis of neoplastic meningitis based on	
MRI	10 (52.6%)
CSF cytology	8 (42.1%)
Both	1 (5.3%)
Positive CSF cytology for tumor cells	9 (47.4%)

NSCLC non-small cell lung cancer, *SCLC* small cell lung cancer, *PCNSL* primary CNS lymphoma, *MRI* magnetic resonance imaging, *CSF* cerebrospinal fluid

male ratio of 15:4 (more detailed patient data are given in Table 1). In 52.6% of the cases, diagnosis was based on clinical presentation in combination with typical MRI findings in the absence of detectable tumor cells in CSF cytology. All other patients had positive CSF cytology. Liposomal cytarabine was administered intrathecally via the lumbar route at a dose of 50 mg per injection and a median frequency of 4 doses (range 2–10). Overall response rate was 63.2% (12/19). 100% (9/9) of patients with positive CSF cytology at diagnosis achieved cytological complete remission after a median of two doses (range 1–3 doses). In 30% (3/10) of patients with negative CSF cytology at diagnosis, an objective CNS response was observed based on clinical improvement in neurological function. On-treatment CNS disease progression was not observed. Systemic disease progression was the most common reason for treatment discontinuation in 31.6% (6/19) of patients after a median systemic PFS of 2 months (range 0–4 months). In responding patients with controlled systemic disease, CNS-guided therapy was stopped after a median of 5 doses ($n=4$; range 3–8), and a median CNS-specific PFS of 14 months ($n=4$; range 5–25 months) was achieved. Treatment outcomes are summarized in Table 2.

Table 2 Treatment outcome ($n=19$)

Outcome	Value
Overall response rate	63.2% (12/19)
Men	21.1% (4/19)
Women	79.9% (15/19)
Cytological complete response rate	100% (9/9)
Median no. of applications needed to achieve cytological complete response	2 (range 1–3)
Reasons for end of treatment with liposomal cytarabine	
Remission	21.1% (4/19)
Systemic disease progression	31.6% (6/19)
Systemic/CNS disease progression	5.3% (1/19)
Death	10.5% (2/19)
Others	15.8% (6/19)
Median CNS-specific PFS (months)	14 (range 5–25)
Median systemic PFS (months)	2 (range 0–4)
Median OS (months)	10 (range 0–21)

CNS central nervous system, *PFS* progression-free survival, *OS* overall survival

Except for one patient, treatment was well tolerated without any adverse events. This patient experienced anal incontinence after ten drug doses, making it difficult to distinguish between neurotoxicity and CNS disease progression, even though the tumor-cell-free CSF observed at that time suggested neurotoxicity.

Sixty-six frozen paired CSF and plasma samples from all patients starting at day 13 after lumbar drug injection were available for drug analysis. CSF drug concentrations are shown in detail in Fig. 1. For further analyses, CSF drug concentrations were grouped in a time-dependent manner (Fig. 2). Thirty-four matched samples were taken at days 13–16 after local drug injection, as the drug is administered biweekly during the induction phase. The median CSF concentration of free cytarabine at that point in time was 156 ng/ml (range 5–4581 ng/ml), and drug concentrations were > 100 ng/ml in 58.8% (20/34) of the samples analyzed. During the maintenance phase with monthly lumbar drug injections, 13 matched samples were available, which revealed a median CSF concentration of free cytarabine of 146 ng/ml (range 5–353 ng/ml) 25–29 days after the last drug injection. In 53.8% (7/13) of the CSF samples analyzed at that point in time, the free cytarabine CSF concentrations were > 100 ng/ml.

Matched CSF and plasma samples taken more than 28 days after drug injection were additionally available in 11 patients, and they were similarly analyzed for cytarabine concentrations. On days 34–38, 48, and 54–57 from the last lumbar dosing, median CSF concentrations of free cytarabine were 57 ng/ml (range 16–89 ng/ml; $n=4$), 110 ng/ml (range 104–116 ng/ml; $n=2$), and 20 ng/ml (range

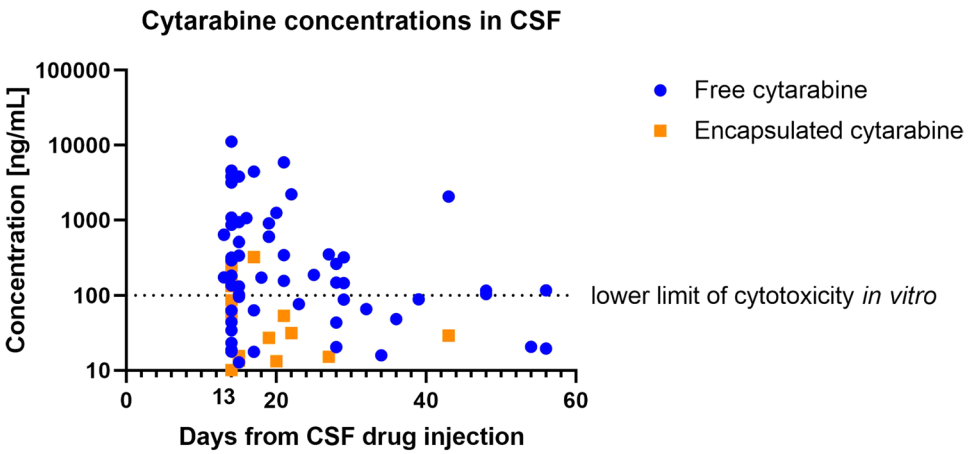

Fig. 1 Free and encapsulated cytarabine concentrations in cerebrospinal fluid (CSF)

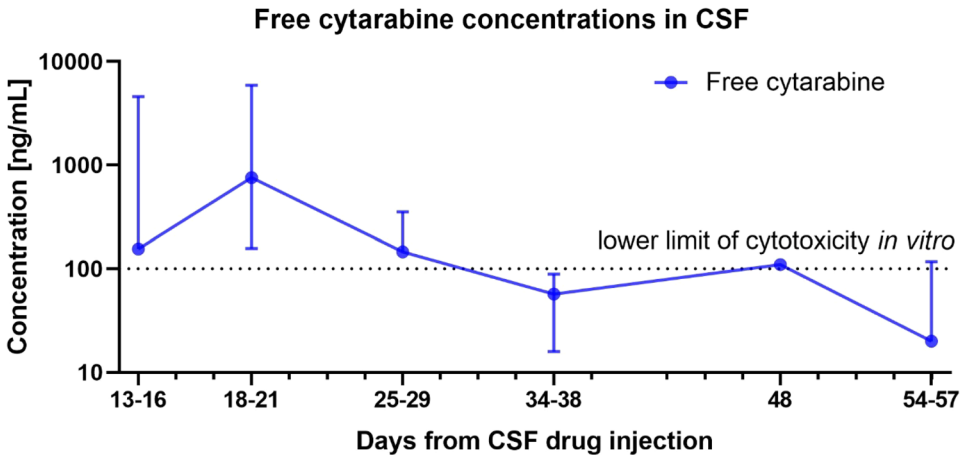

Fig. 2 Median grouped free cytarabine concentrations in cerebrospinal fluid (CSF)

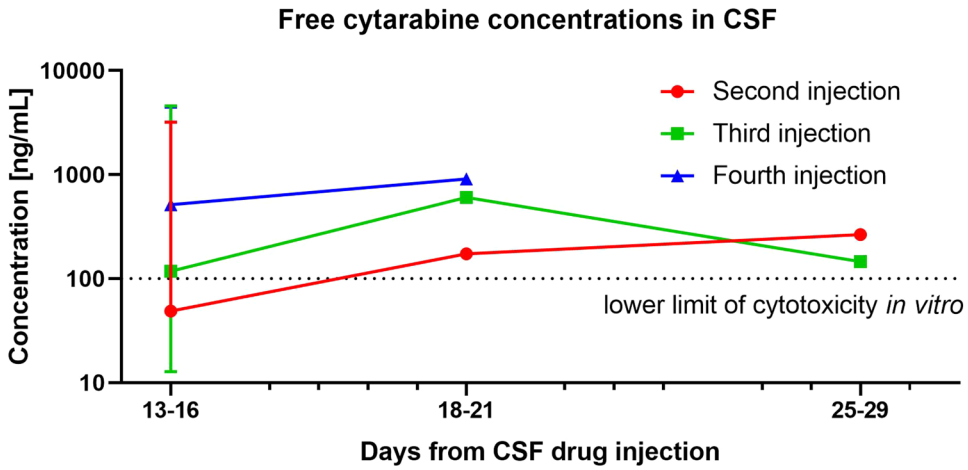

Fig. 3 Median free cytarabine concentrations in cerebrospinal fluid (CSF) with each course of treatment

5–117 ng/ml; $n=4$), respectively (Fig. 2). Overall, CSF drug concentrations were below LOQ and LOD in six and two CSF samples, respectively.

Encapsulated cytarabine CSF concentrations were detectable only sporadically and were frequently below LOQ (Fig. 1). No significant differences were seen when the CSF drug concentrations of free cytarabine were compared among treatment courses (Fig. 3) or between responding and nonresponding patients (Fig. 4). It should also be noted that CSF drug concentrations were not significantly higher in our patient with neurological deterioration (range 20.6–1250 ng/ml). Systemic cytarabine concentrations were not detectable in any of the matched plasma samples.

4 Discussion and Conclusion

In our series of 19 patients with neoplastic meningitis, liposomal cytarabine showed high efficacy. All patients with tumor cell positive CSF cytology at diagnosis achieved a cytological complete response and none experienced on-drug CNS disease progression. Treatment was well tolerated with standard dexamethasone prophylaxis, and only one of the patients experienced neurological deterioration. The variability of free cytarabine concentrations detected at days 13–16 after injection (5–4581 ng/ml; $n=34$) was similar to the variability described in previous pharmacokinetic analyses [6, 8, 14, 15], and 41.2% of the free cytarabine concentrations were below the lower limit of cytotoxicity derived in vitro (> 100 ng/ml).

We were able to demonstrate remarkably high concentrations of free cytarabine in the CSF samples acquired at days 25–29 after the last drug injection (5–353 ng/ml; $n=13$), with cytotoxically active drug concentrations (> 100 ng/ml) observed in 54% of cases. These results underline that usage of liposomal cytarabine leads to prolonged CSF drug exposure compared to the standard cytarabine formulation. Notably, our CSF drug analysis performed more than 14 days after drug injection suggests that cytotoxic CSF drug concentrations are preserved not only during induction but also during the maintenance phase of treatment in the majority of patients. No significant difference was seen when CSF drug concentrations were compared between responsive and nonresponding patients. Considering that the efficacy of cytarabine is a function of both concentration and duration of exposure, our data suggest

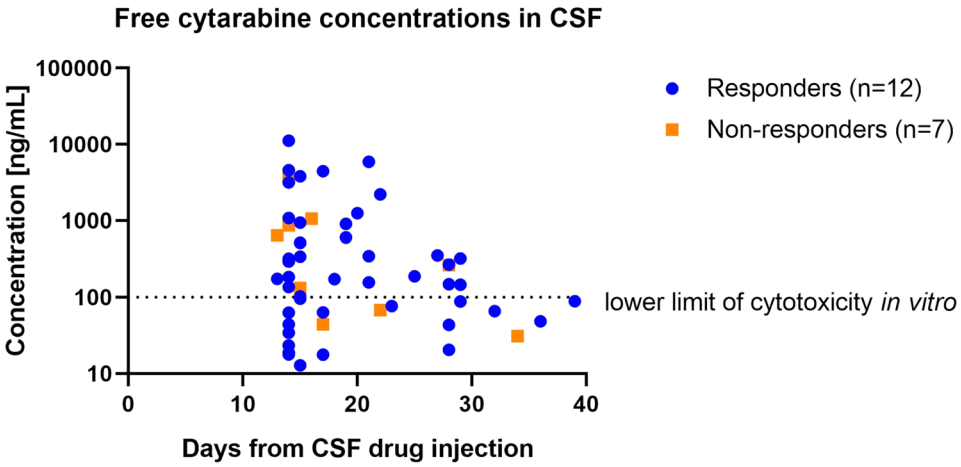

Fig. 4 Free cytarabine concentrations in cerebrospinal fluid (CSF) in responders and nonresponders

that maintaining lower cytarabine concentrations (< 100 ng/ml) for a longer period of time may be as effective as briefly exposing patients to higher cytarabine concentrations.

As drug penetration into the brain is a function of distance from the brain parenchyma, the detection of significant free cytarabine concentrations (> 20 ng/ml) in CSF for up to 56 days in our patients may in part also explain why intraparenchymal tumor lesions were associated with a favorable clinical outcome in a phase 3 study comparing liposomal cytarabine with methotrexate [7].

Given the very slow CSF-to-plasma cytarabine transfer rate via bulk flow of the entrained drug [3], cytarabine plasma concentrations were not detectable in any of our patients' samples, in accordance with previous pharmacokinetic studies [6].

However, there are several limitations of our study. First, our study design cannot exclude a certain level of information bias, as only patients with paired CSF and plasma samples available for drug analysis were included. Additionally, all of our drug analyses were performed in previously frozen biological fluid samples. Although recent pharmacokinetic data suggest that DepoFoam allows sustained controlled drug release upon freeze-thawing, as the large particles can split into smaller ones while retaining their nonconcentric and close-packed structure [16], we cannot exclude the possibility that cytarabine is released from the DepoFoam particles ex vivo, resulting in an artificial increase in the concentration of the free drug fraction. Furthermore, the nonsignificant difference in CSF drug concentrations between responders and nonresponders observed in this work may in part also reflect the large interindividual variability in the CSF drug concentrations analyzed. However, similarly wide ranges of analyzed CSF drug concentrations were found in all previous studies that investigated the pharmacokinetics of liposomal cytarabine in CSF [6, 8, 14, 15], and high concentration variability is commonly seen with other drugs administered intrathecally as well [17]. One major influence on lumbar CSF drug concentrations may be the position of the patient during sample withdrawal. Studies in nonhuman primates have consistently indicated that ventricular drug concentrations are higher in animals kept in a flat position than in those maintained in a upright position [18]. However, we could not determine each patient's position during CSF sample withdrawal in our study.

Moreover, all CSF samples were derived via the lumbar route. It is unclear whether adequate drug distribution throughout the ventricular compartment was achieved, although previous pharmacokinetic studies have demonstrated that drug distribution between the base-of-brain compartments and the ventricular system is rapid, suggesting a significant retrograde CSF flow [15].

Paradoxically, encapsulated cytarabine was detectable only sporadically in our patients. However, given the higher density of DepoFoam compared to free cytarabine, these particles have a tendency to settle at the bottom of an aqueous solution over time [19]. As such, free and encapsulated cytarabine may substantially differ in their CSF distribution patterns, resulting in discrepancies in concentration within any particular patient's derived CSF sample. Therefore, fractional drug concentrations analyzed in a single lumbar-derived CSF sample may not adequately reflect encapsulated and free cytarabine concentrations in CSF overall.

Nevertheless, to the best of our knowledge, this is the only study to investigate CSF drug concentrations of liposomal cytarabine administered at a standard dose of 50 mg per injection via the lumbar route in a larger cohort, and is the first study to demonstrate sustained CSF drug concentrations during the maintenance phase of treatment. Previous pharmacokinetic data were mainly derived at a dose of 70 mg [6, 15]; only three CSF drug analyses from patients receiving 50 mg liposomal cytarabine via the lumbar route have been reported so far [8]. Our CSF drug analyses and the clinical outcomes of our patients illustrate the feasibility and clinical efficacy of liposomal cytarabine given at a dose of 50 mg

in patients with neoplastic meningitis. The occurrence of sustained in vitro cytotoxic drug concentrations that were detectable for 4 weeks in the majority of patients suggests adequate tumor cell kill not only during induction but also during the maintenance phase of treatment.

Prospective clinical trials are warranted to further investigate the pharmacodynamics of liposomal cytarabine in CSF more than 14 days after lumbar drug injection and to help determine whether the current concept of treatment induction and maintenance phases is appropriate when liposomal cytarabine is used.

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Author contributions JB contributed to the study design and protocol, performed research, analyzed data, and wrote the paper; MS contributed to the study design and protocol, analyzed data, and wrote the paper; VR and HO performed research, analyzed data, and wrote the paper; GP and DW analyzed data and wrote the paper. All of the authors reviewed and interpreted the data and agreed on the content of the paper.

Compliance with Ethical Standards

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Conflict of interest Jan-Paul Bohn receives an unrestricted research grant from Mundipharma. Georg Pall, Günther Stockhammer, Michael Steurer, Herbert Oberacher, and Dominik Wolf declare that they have no potential conflict of interest.

Ethics approval The study was performed with the approval of the local ethics committee. The study was carried out under the Good Clinical Practice (GCP) guidelines of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH).

Informed consent All subjects provided written informed consent before being enrolled in the study.

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