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ORIGINAL ARTICLE

Liposomal cytarabine in neoplastic meningitis from primary brain tumors: a single institutional experience

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Abstract Neoplastic meningitis (NM) is diagnosed in 1–2 % of patients with primary brain tumors. Standard treatment of NM includes single-agent or combination chemotherapy, with compounds such as methotrexate, thiotepa, and cytarabine (Ara-C) or its injectable, sustained-release formulation Depocyte®. In this Report, we reported the data of efficacy and tolerability of an intrathecal Depocyte® regimen for patients presenting with NM from primary brain tumors. We described 12 patients with NM confirmed at magnetic resonance imaging (MRI) and with a positive cerebrospinal fluid (CSF) cytology. Patients were treated with repeated courses of intrathecal Depocyte® (once every 2 weeks for 1 month of induction therapy and as consolidation therapy on a monthly base in responding patients). Twelve patients (10 males and 2 females) were treated by our Institution. The diagnosis of primitive brain tumor was medulloblastoma in six patients, germinoma in two patients, pylocitic astrocytomas with spongioblastic aspects, teratocarcinoma, meningeal melanoma, and ependimoma in the other four patients. The total number of Depocyte® cycles ranged from one to nine. In 7/12 patients, there was clinical and/or radiological response after Depocyte®, and the toxicity was moderate and transient, mainly due to the lumbar puncture procedure. In the two patients with germinoma, we observed a normalization of MRI Imaging and negativization of CSF with disappearance of the tumor cells. OS was 180 days (range 20–300, CI 95 %).

Keywords Neoplastic meningitis · Primitive brain tumors · Liposomal cytarabine

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Introduction

Neoplastic meningitis (NM) is diagnosed in 1–2 % of patients with primary brain tumors [1]. An increased incidence of NM was recently observed because of the development of new, effective antineoplastic treatments for primary tumors and improvements in imaging diagnosis [2]. Tumors arising within the brain, such as gliomas, ependymomas, medulloblastomas, and germinomas could display an intra-cerebrospinal fluid (CSF) dissemination of neoplastic cells [3].

Despite aggressive treatment including intra-CSF chemotherapy or systemic chemotherapy and focal radiation to bulky or symptomatic sites, the prognosis of these patients remains extremely poor [4]. Chemotherapeutic agents

administered intravenously are frequently ineffective because of difficulty in crossing the blood–brain barrier (BBB). Up to date, intrathecal chemotherapy is the mainstay of NM treatment. Standard chemotherapy treatment includes methotrexate, thiotepa, and cytarabine (Ara-C) as single agent or in combination, administered through a ventricular reservoir or by lumbar puncture. No substantial difference in response has been seen when comparing single-agent methotrexate with thiotepa or when using multiple agent versus single-agent methotrexate treatment [1].

Depocyte® is an injectable, sustained-release formulation of the chemotherapeutic agent, cytarabine. The major advantage of this formulation is that it gradually releases the drug into the CSF and extends the dosing interval to once every 2 weeks as compared to the standard intrathecal chemotherapy [5]. Moreover, Depocyte® produces a response rate comparable to that of methotrexate and significantly increases the time to neurological progression [6].

In this report, we describe data on efficacy and tolerability of an intrathecal Depocyte® regimen for patients presenting with NM from primary brain tumors.

Patients and methods

We retrospectively evaluated all consecutive patients with primary brain tumors that developed NM during their disease course, treated in our Institution from 2006 to 2011. Only patients treated for NM with courses of intrathecal Depocyte® by lumbar puncture were analyzed in this study. The decision of treating patients with intrathecal Depocyte® was based on patient's symptoms, adeguate patient's performance status [Karnofsky performance status (KPS) > 60], and absence of contraindications of lumbar puncture procedure. Demographic data, primary brain tumor histology, clinical, radiological and CSF findings of NM, and treatment were evaluated. With respect to treatment, previously administered chemotherapy regimens and time from the primary tumor diagnosis to the onset of NM were reported.

In all cases, the diagnosis of NM was based on clinical signs and symptoms, CSF, and magnetic resonance imaging (MRI) of the brain and spine. Compatible symptoms and signs consisted in supratentorial symptoms such as cognitive impairment, seizures, motor and sensory involvement, infratentorial symptoms such as cranial nerves, radicular or spinal involvement, and symptoms due to intracranial hypertension or encephalopathy. KPS was evaluated in all patients at the time of diagnosis and after three cycles of treatment and at progression. All patients underwent brain and spinal cord contrast MRI at the time of diagnosis and every three Depocyte® cycles. Brain MR images were obtained in axial, sagittal, and coronal planes including aT2-weighted, pre-contrast fluid-attenuation inversion-recovery, non-contrast enhanced, and contrast-enhanced T1-weighted sequences.

In all cases, a CSF analysis with pressure, biochemical evaluation of glucose and proteins, and cytologic examination was performed at diagnosis of NM and every Depocyte® administration.

All the patients were treated with repeated courses of intrathecal Depocyte® by lumbar puncture, with concomitant dexamethasone and antibiotic prophylaxis. Depocyte® 50 mg was injected once every 2 weeks for 1 month of induction therapy. Responding patients were treated with an additional 3 months consolidation therapy.

The primary endpoint of this study was response, defined as clinical and radiological response (stable disease or partial/complete response), conversion of the CSF cytology from positive to negative, and the absence of neurologic progression at the time the cytologic conversion was documented. Secondary end points were toxicity and time to progression (TTP) and overall survival (OS) from the time of NM diagnosis.

Results

Twelve patients who had a diagnosis of NM from a primary brain tumor and were treated at the onset of NM with intrathecal Depocyte® in the Neuro-Oncology Unit of our Institute from 2006 to 2011 were described in this study (Table 1). They were 10 males and 2 females, with a median age at the time of primary brain tumor diagnosis of 25, 2 years (range 18–37 years) and a median age at the time of NM diagnosis of 27 years (range 20–45 years). The diagnosis of primitive brain tumor was medulloblastoma in six patients, germinoma in two patients, pylocitic astrocytoma with spongioblastic aspects, teratocarcinoma, meningeal melanoma, and ependimoma in the other four patients.

In all patients, neurosurgery and radiotherapy was performed at the time of primitive brain tumor diagnosis, followed by platinum and etoposide-based chemotherapy in 8/12 patients. In four patients (the one with teratocarcinoma, the one with ependimoma, the one with meningeal melanoma and the one with pylocitic astrocytoma), no chemotherapy was performed at the initial diagnosis.

The median interval time from the primitive brain tumor diagnosis and the NM detection was 2 years (range 0–9 years). At the time of NM diagnosis two patients developed only a cerebral symptoms and signs of NM, six patients had cerebral and spine symptoms and signs, and in four cases the NM was limited at spine, without brain

Table 1 Patients characteristics at NM diagnosis

PZ	Sex	Age	Hystology of primary brain tumor	Site of primary brain tumor	Previous treatment	Time interval from diagnosistonm	KPS	Symptoms	MRI dissemination	CSF
1	M	27	Medulloblastoma	Posterior fossa	Surgery, RT CDDP + VP16	18 months	70	Headache, vomit	Brain (linear), hydrocefalus	Glu 35 mg/dl, prot 100 mg/dl, 35 nc
2	M	34	Medulloblastoma	Cerebellar	Surgery, RT CDDP + VP16	10 months	80	Headache + back pain	Brain and spine (linear and nodular)	Glu 31, prot 130 mg/dl 50 nc
3	M	22	Medulloblastoma	Cerebellar	Surgery, RT CDDP + VP16	5 months	80	Back pain	Spine (nodular)	Glu 38, prot 112 mg/dl, 65 nc
4	M	45	Medulloblastoma	Cerebellar	Surgery, RT CDDP + VP16	2 years	90	Ataxia	Brain and spine (linear)	Glu 50 mg/dl, prot 68 mg/dl 20 nc
5	M	23	Medulloblastoma	Posterior fossa	Surgery, RT CDDP + VP16	20 months	70	Headache, vomit	Brain linear hydrocefalus	Glu 46 mg/dl, prot 58 mg/dl 14 nc after 2 LP
6	M	36	Medulloblastoma	Cerebellar	Surgery, RT CDDP + VP16	9 years	80	Ataxia and back pain	Brain and spine (linear and nodular)	Glu 60 mg/dl, prot 71 mg/dl 12 nc after 2 LP
7	M	20	Germinoma	Pineal region	Surgery, RT CDDP + VP16	5 years	90	Back pain	Spine (linear and nodular)	Glu 32 mg/dl prot 90 mg/dl 12 nc
8	M	21	Germinoma	Pineal region	Surgery, RT CDDP + VP16	3 years	90	Back pain	Spine (linear)	Glu 28 mg/dl prot 108 mg/dl 45 nc
9	F	45	Ependymoma	Cerebellar	Surgery, RT	4 years	100	Back pain	Spine (nodular)	Glu 63 mg/dl prot 60 mg/dl 5 nc after 2 LP
10	M	28	Teratocarcinoma	Temporal lobe	Surgery, RT	2 years	80	Back pain + IV cranial nerve palsy	Brain and spine (nodular)	Glu 27 mg/dl prot 76 mg/dl 10 nc
11	M	20	Meningeal melanoma	Frontal lobe	Surgery, RT	4 months	70	III, IV e VI cranial nerve palsy	Brain and spine, (linear)	Glu 71 mg/dl prot 53 mg/dl 22 nc after 2 LP
12	F	28	Pylocitic astrocytoma with spongioblastic aspects	Brainstem	Surgery, RT	4 years	80	Ataxia + back pain	Brain and spine (linear)	Glu 30 mg/dl prot 64 mg/dl 22 nc

M male, *F* female, *RT* radiotherapy *LP* lumbar puncture, *glu* glucose, *prot* proteins, *nc* neoplastic cells

symptoms. In 4/12 patients, there was primary brain tumor recurrence in concomitance with the NM diagnosis.

Symptoms at the NM diagnosis were due to infratentorial involvement in 5/12 patients, such as cranial nerves palsies, ataxia and gait instability, in two cases symptoms due to intracranial hypertension with headache, nausea, and vomiting were signaled and in 9/12 patients diffuse radicular signs or spinal involvement with back pain were described.

Brain and spine contrast MRI showed leptomeningeal involvement in all patients, presented as linear enhancement, or nodular meningeal tumor.

Cerebrospinal fluid analysis at the time of NM diagnosis revealed reduction in CSF glucose levels in 7/12 patients and in all cases the presence of elevated proteins. Cytological examination of CSF revealed the presence of neoplastic cells at first lumbar puncture in 8/12 patients (Fig. 1) and in all cases after two consecutive examinations.

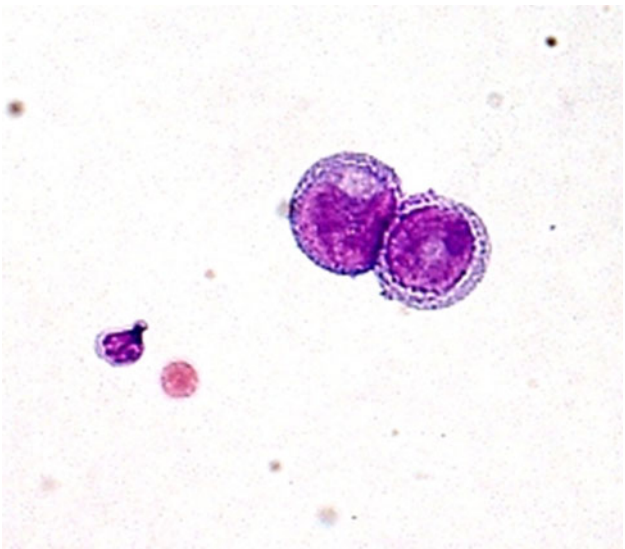

Fig. 1 Two large germinoma cells, with round nuclei and prominent nucleoli. On the *left*, one small lymphocyte and one *red* cell

As treatment is concerned, three patients with nodular meningeal involvement (two with a brain involvement and one with a dorsal spine involvement) underwent also radiosurgery at the time of NM diagnosis. In all cases, intrathecal Depocyte® by lumbar puncture was administered (in 4/12 patients this treatment was concomitant to a systemic chemotherapy, consistent in a rechallenge with etoposide-based chemotherapy).

In Table 2, treatment response is reported. The total number of Depocyte® cycles ranged from one to nine (with a median of four). Unfortunately, in three patients (two with medulloblastoma and one with teratocarcinoma), only one cycle of Depocyte® was administrated due to a rapid disease progression.

In six patients, a clinical improvement of symptoms was described after two or three cycles of treatment, whereas in 5/12 patients, there was a stable disease after three cycles of treatment. Moreover, a partial response in 1/12 and MRI negativization in 2/12 patients were seen (Fig. 2).

As CSF is concerned, in 4/12 patients, a negativization of neoplastic cells detection was achieved after at least three cycles of treatment. In other 5/12 patients, a cells reduction was seen, as well as a protein reduction. In 3/12 patients (the same three who had only one cycle of treatment), a rapid clinical and radiological progression was seen and it was impossible to perform the second cycle of treatment. Three patients are alive at the moment (two of them are stable and one had a new recurrence). Four patients had a rapid progression (three after 1 month and one after 2 months) and died within 3 months from diagnosis. In the two patients with germinoma, we observed normalization of MRI Imaging and negativization of CSF with disappearance of the tumor cells after Depocyte® treatment (Fig. 3). OS was 180 days (range 20–300, CI 95 %).

Finally, toxicity was moderate and transient, mainly due to the lumbar puncture procedure. The major adverse events were headache and back pain. Headache occurred on 11 % of cycles; 90 % were grade 1 or 2. Back pain occurred on 19 % of cycles and both were responsive to steroid treatment. However, in one patient we observed a chemical aracnoiditis after four cycles of Depocyte®, that was characterized by fever, headache, and acute meningeal signs and that was resolved after high dose desametasone administration.

Table 2 CSF and radiological results after Depocyte

PZ	No. of depocyte cycles	KPS after 3 cycles	KPS after 6 cycles	CSF: nc after 3 cycles	CSF: nc after 6 cycles	MRI after 3 cycles	MRI after 6 cycles	Toxicity	TTP	OS from nm diagnosis
1	3	70	na	10	na	SD	na	Transient headache	48 days	93 days
2	6	90	70	7	14	SD	PD	Transient local back pain	186 days	260 days
3	4	80	na	26	na	SD	na	Aracnoiditis	74 days	180 days
4	6	100	70	3	11	SD	PD	No	190 days	300 days
5	1	50	na	na	na	na	na	Transient local back pain	15 days	20 days
6	1	60	na	na	na	na	na	No	30 days	50 days
7	6	90	60	No cells	5	CR	SD	No	210 days	239 days
8	5	100	na	No cells	na	CR	na	Transient headache	73 days	200 days
9	7	100	80	No cells	3	SD	SD	Transient headache	na	Alive
10	1	40	na	na	na	na	na	Transient local back pain	29 days	60 days
11	9	80	70	No cells	2	PR	SD	Transient local back pain	na	Alive
12	4	90	na	12	na	SD	na	Transient local back pain	60 days	192 days

glu glucose, *prot* proteins, *nc* neoplastic cells, *na* not applicable

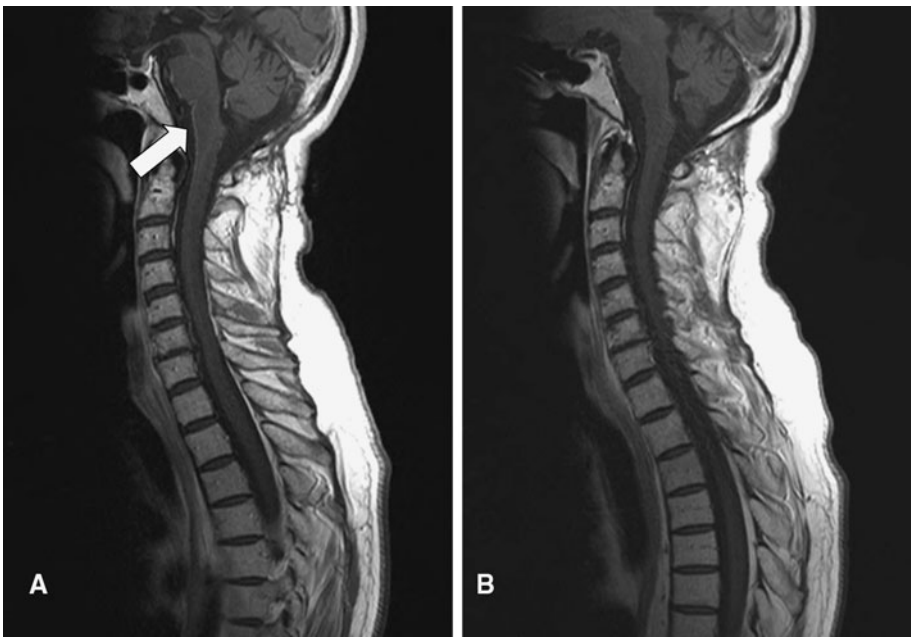

Fig. 2 Cervical contrast T1 MRI shows linear enhancement (**a**, *arrow*) in a patient with neoplastic meningitis from medulloblastoma, with a complete response and enhancement disappearance after four cycles of intratechal Depocyte® (**b**)

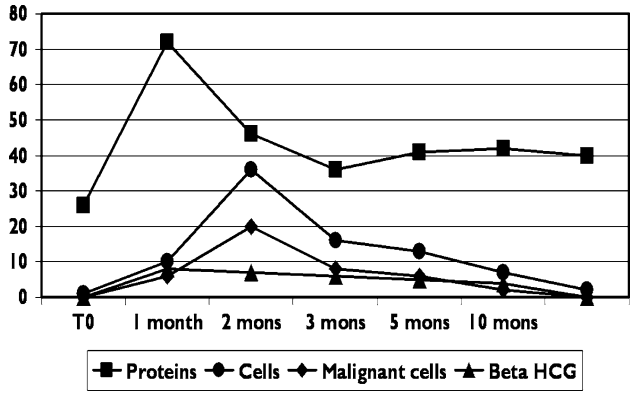

Fig. 3 CSF in one germinoma patient before and after Depocyte® treatment: disappearance of neoplastic cells and negativisation of intrathecal Beta-HCG synthesis

Discussion

Primary brain tumors may progress to NM, especially medulloblastoma (30 % of cases), ependymoma (10–20 % of cases) cerebellar astrocytomas, suprasellar germinoma (10–20 %), and choroid plexus carcinoma (70 % of cases) [7] Primary CNS lymphoma produces meningeal spread in up to 40 % of cases [8].

Diagnosis of NM is based on compatible symptoms and signs, contrast enhanced MRI studies and on the gold standard of detecting malignant cells in the CSF during cytological examination. Symptoms of NM may include either supratentorial symptoms such as psychiatric disturbances or cognitive impairment, seizures, motor, and sensory involvement, or infratentorial symptoms (ataxia or gait disturbances, cranial nerve palsies), diffuse radicular symptoms or spinal cord symptoms (such as back pain) [9] In the 12 patients, described symptoms at the NM diagnosis were due to infratentorial involvement in the majority of cases, even if diffuse radicular signs or spinal involvement with back pain was described in 9/12 patients.

Contrast MRI usually shows nodular or linear meningeal enhancement, or parenchimal nodular enhancement. Up to 7 % of these patients can present hydrocephalus at the time of diagnosis [10]. Moreover, the importance of MRI is supported by the fact that up to 10 % of patients with NM from primary brain tumor could be asymptomatic, functional signs may be misleading and the neurological examination may be normal [11].

Increased CSF opening pressure has been previously reported in 50–70 % of patients with NM, and elevated CSF protein and low glucose in approximately 75 and 40 % of cases, respectively. In all the patients. described CSF was positive for protein increase and neoplastic cells detected at cytological analysis [9].

Despite considerable research and numerous clinical trials, the prognosis of NM remains very poor, with <15 % 1 year survival [4] The median survival of untreated patients with NM is reported to be 4–6 weeks, and the treatment is often intended to improve or stabilize the neurologic status rather than prolong survival. Indeed the treatment evaluation is complicated by the lack of standard treatments. Up to date intrathecal chemotherapy is the mainstay of treatment for NM and literature suggests that the administration of chemotherapy into the CSF improves the outcome of this group of patients. Therapy is based on the administration of high dose systemic chemotherapy with drugs able to pass through the BBB, such as methotrexate (MTX) and cytarabine, cranial or craniospinal irradiation, and intrathecal administration of MTX and/or cytarabine. The role of systemic intravenous

chemotherapy is questionable since it is known that chemotherapeutic agents administered intravenously are not able to cross the BBB. Nowadays, however, some studies suggest that intravenous chemotherapy can improve both the response rate and survival in patients with solid tumors and NM [12]. For example, Boogerd et al. [13] comparing the efficacy of intrathecal treatment and systemic chemotherapy with systemic chemotherapy alone, found median survival longer in the no-intrathecal arm (30 vs. 18 weeks). A depot formulation of liposomal cytarabine (Depocyte®) has proven to be useful in clinical trials [5]. In lymphomatous meningitis, liposomal cytarabine offers superior response rates, improved patient quality of life, and a prolongation of the time to neurological progression as compared with MTX. When the cause of NM is a solid tumor, liposomal cytarabine prolongs the time to neurological progression and improves quality of life [14–16].

On this basis, we decided to include in this study patients with primary brain tumors who received this treatment. To the best of our knowledge, our study is presently the largest series on intrathecal liposomal cytarabine treatment in adult patients with NM from primary brain tumors. In particular, in literature, there are some studies about liposomal cytarabine treatment in NM from primary brain tumors mainly in children and young adults. For example, Partap et al. [17] reported the largest experience (17 patients with medulloblastoma, PNET, and atypical teratoid rhabdoid tumor) of liposomal cytarabine treatment in NM in children and young adults with very aggressive CNS embryonal tumors. The data showed that liposomal cytarabine is easily administered and well tolerated.

The majority of the patients described in the present report have a diagnosis of medulloblastoma, however, some peculiar cases are described as well, such as germinoma in two cases that responded particularly well to treatment, with CSF and MRI normalization. In our study, there is only a patient with glioma (pylocitic astrocytoma) treated with intratechal Depocyte®.

In the literature, neoplastic dissemination in glioma patient is largely studied. For malignant glioma dissemination varies from 25 % of supratentorial tumors to 60 % of infratentorial tumors; in particular cerebellar origin is significantly associated with LM dissemination [18]. NM rarely arises in patients with low-grade gliomas. In retrospective studies, this complication was found up to 5 % of patients with low grade glioma at the time of diagnosis and in 7–10 % of patients at the time of tumor progression. Moreover, a few cases of NM in spinal cord low-grade gliomas have been reported, mostly in children [19].

In our group of patients, a case of NM from pylocytic astrocytoma was described. These tumors rarely spread beyond the primary tumor site, and NM is uncommon. Previous studies show that NM in patients with pylocitic astrocytomas displays a better prognosis, compared to NM in other types of brain tumors, since median OS can reach 65 months [20]; Nonetheless in our case the survival from NM diagnosis was only 6 months, and only four cycles of chemotherapy with liposomal cytarabine were done before disease progression.

In general, in gliomatous NM, no established chemotherapy regimen exists, although general treatment guidelines include intrathecal chemotherapy with methotrexate, thiotepa and cytarabine. Moreover, the observation that systemic administration of temozolomide has produced significant responses in patients with high-grade intraparenchymal glial neoplasms provides the rationale for evaluating its activity as an intratechal chemotherapeutic agent in NM from glial tumors [21].

Few reports have been published on the role of liposomal cytarabine in NM from malignant glioma. Passarin et al. [22] described a case of low-grade oligoastrocytoma with leptomeningeal dissemination treated with Depocyte® in combination with temozolomide who showed complete remission after 12 months of treatment.

In conclusion, the prognosis of NM is very poor, especially in patients with a NM from systemic cancer. Long-term survival is occasionally observed in patients with NM from breast cancer, melanoma, and lymphoma, but in general the survival of most patients is short (only 3–4 months) [23]. The small number of patients and the presence of very heterogeneous tumor types in our study is insufficient to lead a conclusion about TTP or OS; in particular 2/12 patients are alive at the moment; in this report, it is not possible to conclude that the increase in OS is related to the treatment, however, our preliminary data indicate a median OS of 180 days (range 20–300 days). These data could indicate a better prognosis of NM in patients with a primitive brain tumor in comparison with patients with NM from systemic tumors.

As side effects are concerned, in our series of patients only one experienced a probable chemical arachnoiditis, that was, however, manageable with high dose corticosteroids. Chemical arachnoiditis (characterized by headache, fever, nausea, vomiting) was a common described side effect in patients receiving Depocyte®; in the majority of cases symptoms can resolve with oral dexamethasone [24–26] In the other patients described liposomal cytarabine was easily administered and well tolerated with only a moderate and transient toxicity, mainly due to the lumbar puncture procedure. These data are comparable to results reported in literature [24–26].

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