

Intrathecal liposomal cytarabine in combination with temozolomide in low-grade oligoastrocytoma with leptomeningeal dissemination

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Abstract Leptomeningeal dissemination of low-grade gliomas is an uncommon event. A 43-year old male presented with dizziness, gait ataxia, and diplopia. A nonenhancing lesion in the right cerebellar peduncle was identified, subtotally resected, and diagnosed as a grade II astrocytoma. After one year a nodular spread in the brain and

leptomeninges was diagnosed, so the patient started chemotherapy with temozolomide and liposomal cytarabine. Complete remission was achieved after 12 months of treatment and the patient is still free from the disease after a follow-up of 24 months. We suggest that this combination may be a valuable treatment option.

Keywords Leptomeningeal carcinomatosis · Low-grade astrocytoma · Liposomal cytarabine · Temozolomide

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Introduction

Low-grade gliomas (LGG) are a group of relatively uncommon primary brain tumors, including astrocytomas, oligodendrogliomas, and mixed gliomas, classified by the World Health Organization (WHO) grading system (2007) as grade 2 lesions. The natural history of LGG shows great variability, and optimum disease management remains a challenge for the treating physician [1]. Leptomeningeal dissemination (LMD; also referred to as neoplastic meningitis) is a rare and serious complication of LGG. Current treatment of LMD is designed to improve or stabilize neurologic symptoms and to prolong survival.

In this paper we report the case of a 43-year-old patient diagnosed with LMD from grade II oligoastrocytoma for whom complete remission was achieved after treatment with a sustained-release formulation of liposomal cytarabine combined with temozolomide. To the best of our knowledge, this is the first report describing long-lasting remission after treatment with this combination in an adult patient with LMD from low-grade oligoastrocytoma.

Case report

A 43-year-old male presented in July, 2005 with a five-month history of dizziness, gait ataxia, and intermittent diplopia. The patient had an unremarkable medical history and no relevant family history of disease. Magnetic resonance imaging (MRI) revealed a nonenhancing lesion in the right cerebellar peduncle (Fig. 1). The patient underwent surgery and partial resection of the tumor was performed. Histologic examination revealed a grade II astrocytoma (WHO) with an oligodendroglial component (Fig. 2a), and no 1p/19q co-deletion (Fig. 2b). After surgery, the symptoms improved, therefore we considered it safe to adopt a policy of surveillance following surgery. The patient was closely followed by MRI every three months.

In July, 2006 the patient was readmitted to the hospital with symptoms of dizziness, diplopia, and ataxia. MRI of the brain and spine showed nodular spread of the tumor in the brainstem, cerebellum, ventricles, and leptomeninges. The patient received whole brain radiotherapy (30 Gy for 10 days), but after two months an MRI showed further progression of the leptomeningeal and parenchymal dissemination with extensive enhancement in the cervical and thoracic regions of the spinal cord (Fig. 3a–d). Analysis of the CSF showed mild hyperproteinorrhachia (1.17 g/L), mild hypoglycorrachia, and the presence of malignant cells positive for glial fibrillary acid protein (GFAP).

Because of the young age of the patient, good performance status (Karnofsky performance status >70), and tumor histology, a combination of systemic and intrathecal

Fig. 1 **a** Axial T1-weight MRI with gadolinium showed a nonenhancing lesion in the right cerebellar peduncle. **b** Axial T2-weight MRI showed a high-signal-intensity lesion in the right cerebellar peduncle

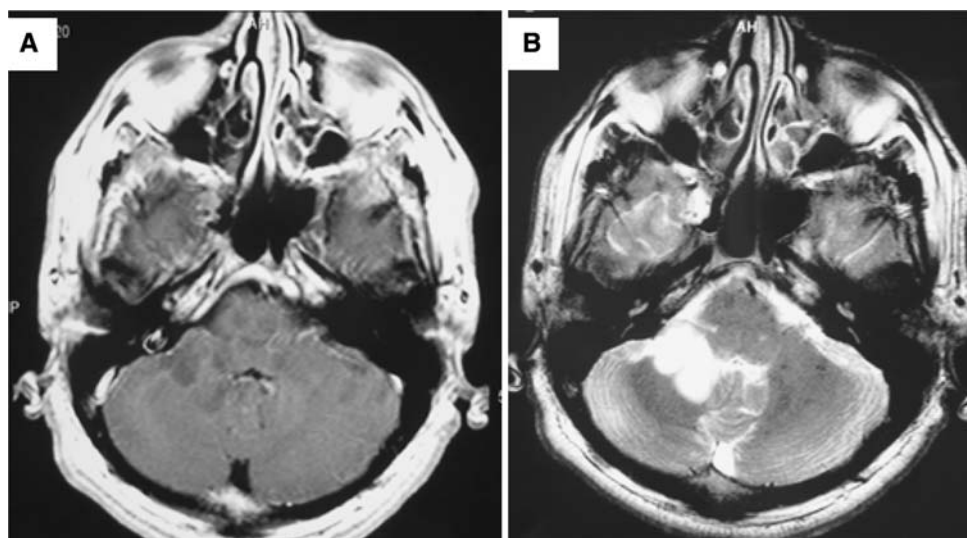


Fig. 2 **a** H&E staining shows an intermingled grade II oligoastrocytoma (400×). **b** Fluorescence in-situ hybridization to assess 19q status: a probe for 19q13.4 (red in the online version of the figure) is paired with 10p13 (green in the online version of the figure); 19q is intact (fluorescent probe-stained cells, original magnification 1000×)

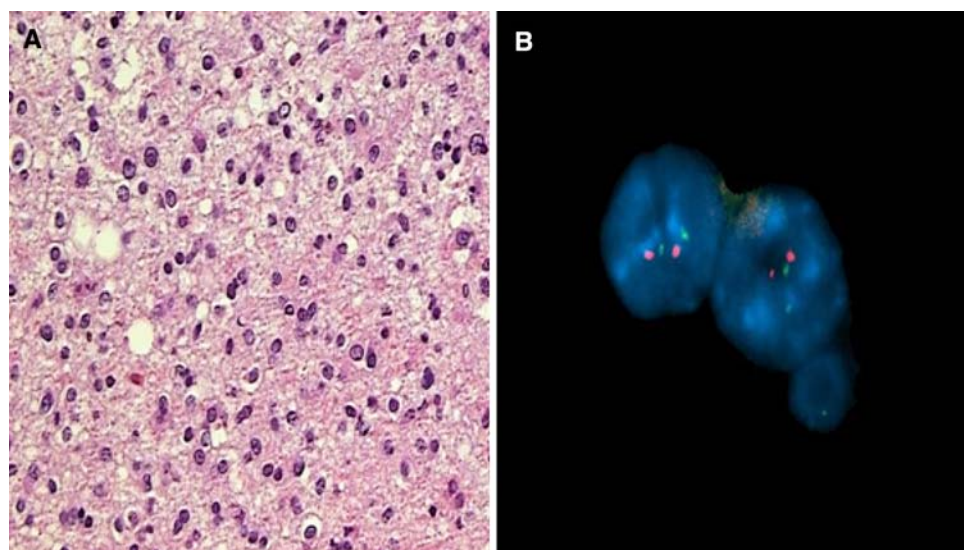


Fig. 3 a–d MRI showed progression of the leptomeningeal and parenchymal dissemination with extensive enhancement of cervical regions C4–C5 and C6–C7 and thoracic region D2



chemotherapy was started. In November, 2006 the patient received temozolomide at the standard dose of 200 mg/m² for five days every 28 days in combination with intralumbar liposomal cytarabine. During the induction phase, the patient received two doses of liposomal cytarabine 50 mg every two weeks. The consolidation phase consisted of four doses of liposomal cytarabine 50 mg administered every two weeks, followed by two doses every four weeks. Maintenance therapy was administered once every four weeks for a total of six doses. Concomitant intravenous dexamethasone (0.15 mg/kg) was given every 12 h from the day before liposomal cytarabine was infused until the fourth day after cytarabine treatment. The patient also received systemic chemotherapy with temozolomide for up to 12 cycles. During treatment, neuroimaging studies for evaluation of disease status were performed every three months and as clinically indicated. In addition, a CSF examination was performed before each dose of liposomal cytarabine.

MRI examination after three cycles of temozolomide and the consolidation phase of liposomal cytarabine revealed a reduction in subependymal enhancing lesions, but an increase in lesions in the cerebellar peduncles (Fig. 4a–d). The patient had complete clearing of malignant cells from

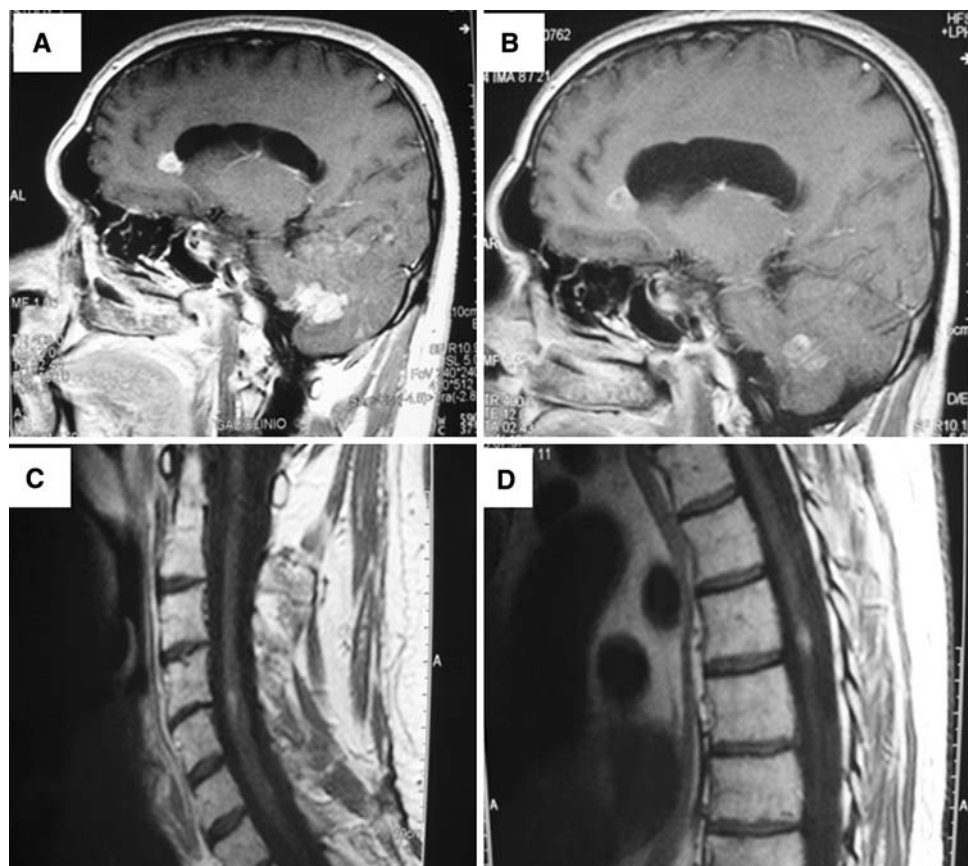
the CSF following two doses of liposomal cytarabine. At the end of the treatment (12 months from the start of treatment) the neurological status of the patient improved and he started to work. MRI showed the disappearance of lesions in both the brain and spinal cord (Fig. 5a–d); additionally, the CSF was negative for malignant cells. After a follow-up of 24 months, the patient remained clinically stable and free from relapse.

Treatment was well tolerated, with no observed grade III/IV hematologic or non-hematologic toxicity. During treatment the patient developed a deep vein thrombosis of the right leg, which was treated with low-weight heparin, and partial seizures, which were controlled with valproic acid and levetiracetam.

Discussion

Neoplastic meningitis is a serious and rare complication of LGG, with a median patient survival time ranging from a few weeks to a few months. In retrospective studies (some of which were published before the introduction of MRI), LMD was found in 5% of LGG patients at the time of

Fig. 4 a–d MRI after three months of therapy showed a reduction of the subependymal enhancing lesions, but an increase of the lesions in the cerebellar peduncles



diagnosis and in 7–10% of patients at the time of tumor progression [2, 3]. Recent studies that included patient autopsies, however, have suggested that the incidence of LMD may be higher than previously reported [4, 5].

Current treatment of LMD is designed to improve or stabilize neurological symptoms and to prolong survival. Available treatment options include focal radiation therapy for bulky disease, intrathecal therapy, and systemic chemotherapy [6]. The failure of conventional therapy to improve survival or prevent clinical progression might be related to the difficulty in maintaining cytotoxic levels of chemotherapeutic agents in the cerebrospinal fluid (CSF) when using standard dosing and schedules.

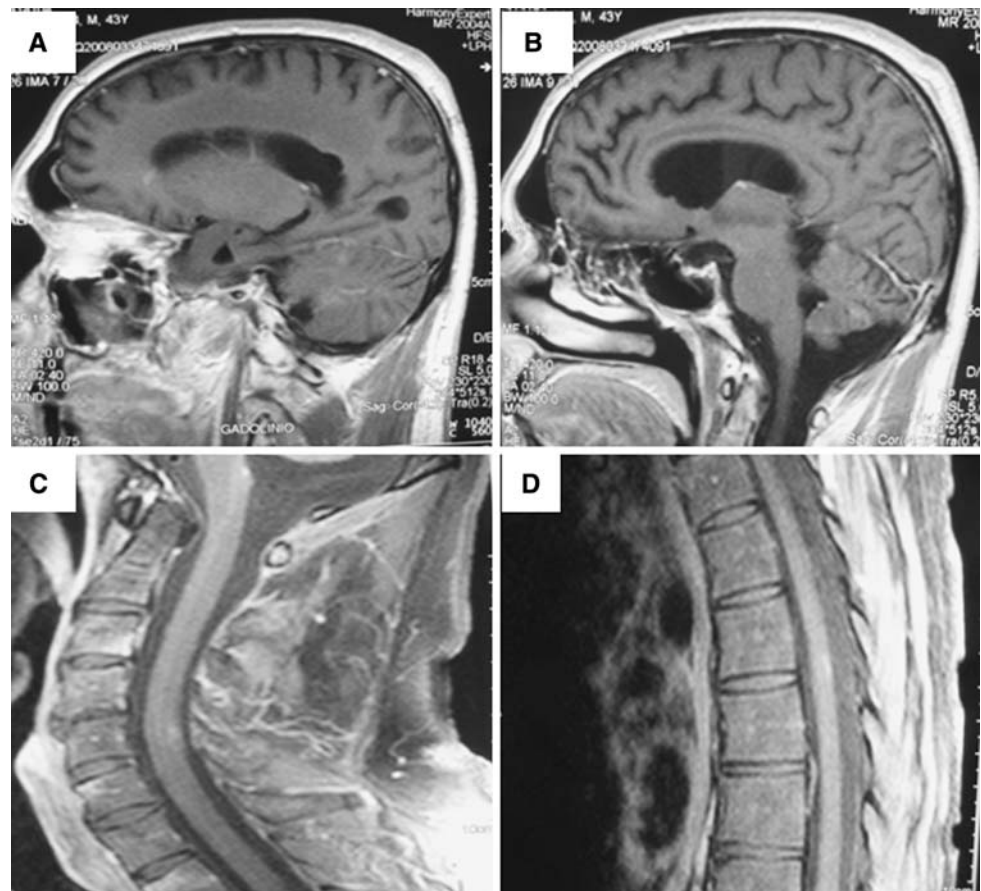
Recently, temozolomide, which is an oral alkylating agent with a favorable toxicity profile, has been shown to be active and particularly well tolerated when delivered as first-line therapy specifically to patients with low-grade gliomas [7–9]. Objective response rates reported in the literature range from 31 to 66% and the median time to maximum response range from five to twenty months.

Few data are available on the pharmacokinetics of temozolomide in cerebrospinal fluid (CSF). To the best of our knowledge Ostermann et al. analyzed the pharmacokinetics of temozolomide in the plasma and cerebrospinal fluid of 35

patients with newly diagnosed or recurrent malignant gliomas and found that the temozolomide CSF penetration corresponds only to 20% of systemic TMZ exposure [10].

Liposomal cytarabine is a slow-release formulation of cytarabine that is manufactured by encapsulating aqueous cytarabine in spherical multivesicular particles known as DepoFoam (DepoCyte; SkyePharma, San Diego, CA, USA) [11]. The pharmacokinetic advantage of this novel cytarabine formulation was demonstrated in adult phase I studies in which the terminal half-life of liposomal cytarabine was shown to be approximately 40 times longer than that of standard cytarabine [12]. This liposomal form yielded cytotoxic levels of cytarabine in the CSF for a period of 14 days [13]. Little has been published on the role of liposomal cytarabine in LMD from malignant glioma. Glantz et al. conducted a randomized, controlled trial of DepoCyte versus methotrexate (MTX) in 61 patients with neoplastic meningitis from histologically proven cancer and positive CSF cytologies. Responses occurred in 26% of DepoCyte-treated and 20% of MTX-treated patients and the DepoCyte group experienced a greater median time to neurological progression (58 versus 30 days), longer neoplastic meningitis-specific survival (343 versus 98 days), and better quality of life in patients [14]. These findings

Fig. 5 a–d MRI after one year of the treatment showed a disappearance of the lesions in both the brain and spinal cord



were confirmed also in the subgroup of patients ($N = 14$) with LMD from malignant glioma.

The patient described in our manuscript was young (43-year-old), had a good performance status (Karnofsky performance status >70), but was strongly symptomatic of the disease. On the basis of the previous prognostic factors we decided to offer to the patient an aggressive treatment to improve his neurological status and prolong survival while maintaining a good quality of life.

In our patient liposomal cytarabine combined with temozolomide was both safe and active.

In the literature Lassaletta et al. published a case report of a posterior fossa ependymoma with leptomeningeal dissemination in a two-year-old child, successfully treated with a combination of systemic chemotherapy and intrathecal liposomal cytarabine [15].

To the best of our knowledge, there are no previous reports of the use of temozolomide in combination with liposomal cytarabine for treatment of leptomeningeal spread from low-grade oligoastrocytomas.

Although it is impossible to draw any conclusion about the effectiveness of these drugs in the treatment of LGG, we suggest that this combination may be a valuable treatment option for patients with LMD from low-grade glioma.

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