Treatment for recurrent medulloblastoma with intrathecal liposomal cytarabine and systemic metronomic combination therapy

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The prognosis of recurrent medulloblastoma is dismal, with a median survival of less than 1 year. Our patient was initially diagnosed with high-risk medulloblastoma when he was 14 years old. He had a recurrence 18 months after the end of therapy. Recurrence treatment consisted of 13 intrathecal applications of liposomal cytarabine over an 18-month period, and oral metronomic antiangiogenic therapy with thalidomide, celecoxib, and etoposide. Side effects from the intrathecal treatment were most likely related to arachnoiditis despite prolonged prophylaxis with steroids. He also developed partial hearing loss. Neutropenia was the main side effect of the metronomic therapy. He remains alive, with a good quality of life and without evidence of disease 34 months from the start of recurrence therapy. This combination of local antineoplastic and systemic antiangiogenic therapy seems to be promising for recurrent medulloblastoma. However, more patients and standardized protocols are needed to verify the benefit of this combination therapy and to define the correct duration of treatment. ***Anti-Cancer Drugs*** **23:342–346 © 2012 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

Medulloblastoma is the most common malignant brain tumor in children [1,2]. It is located in the cerebellum and accounts for approximately 20% of pediatric brain tumors. About 30% of pediatric patients with medulloblastoma have a progression or recurrence, which carries a dismal prognosis. We report a patient with recurrent medulloblastoma with a remarkable response to a combination of local and metronomic therapy. As local therapy, we used intrathecal liposomal cytarabine. Systemic metronomic combination therapy consisted of thalidomide, celecoxib, and etoposide.

Case report

This boy was diagnosed with medulloblastoma of classical histology when he was 14 years old. He was treated in St Olav University Hospital, Trondheim, Norway. In addition to the primary tumor in the cerebellum (largest diameter 4.7 cm), he had a supratentorial lesion (largest diameter 2.1 cm) in the anterior part of the third ventricle (Fig. 1). No intraspinal metastases were seen on MRI, but cytology of the cerebrospinal fluid revealed malignant cells 2 weeks postoperatively.

Our patient was treated for 15 months according to the Swedish VCTB-95 high-risk primitive neuroectodermal tumor protocol. A macroscopic total resection of the cerebellar tumor was performed, followed by a partial resection of the metastasis. He received three courses of chemotherapy (etoposide/carboplatin and vincristine/cisplatin × 2) before irradiation (35 Gy to the craniospinal axis and 20 Gy tumor boosts to the posterior fossa and the cerebral tumor) with concomitant weekly vincristine. Maintenance chemotherapy consisted of six courses of cyclophosphamide and lomustine (vincristine was omitted because of neurotoxicity), followed by three cycles of temozolomide.

The patient was in clinical and radiological remission at the end of therapy. Routine MRI controls (every 4 months) were negative. He had late effects from the disease and its treatment: ataxia, dysartria, hypothyroidism, visual, cognitive, and coordination problems. However, his speech and vision gradually improved, and after intensive physical training, he was able to walk with support.

On routine MRI control of the spine, 33 months after the initial diagnosis and 18 months after the end of primary therapy, no intracranial tumors were found. However, he had multiple nodular intraspinal metastases from C5 to S1 (Fig. 2). Cytology of the cerebrospinal fluid was negative. In retrospect, the boy was admitted because of increasing pain localized to the buttocks throughout the previous 3 months, attributed to immobilization in a wheelchair.

Intrathecal therapy for recurrence was started with 50 mg of liposomal cytarabine (DepoCyte; Mundipharma AB,

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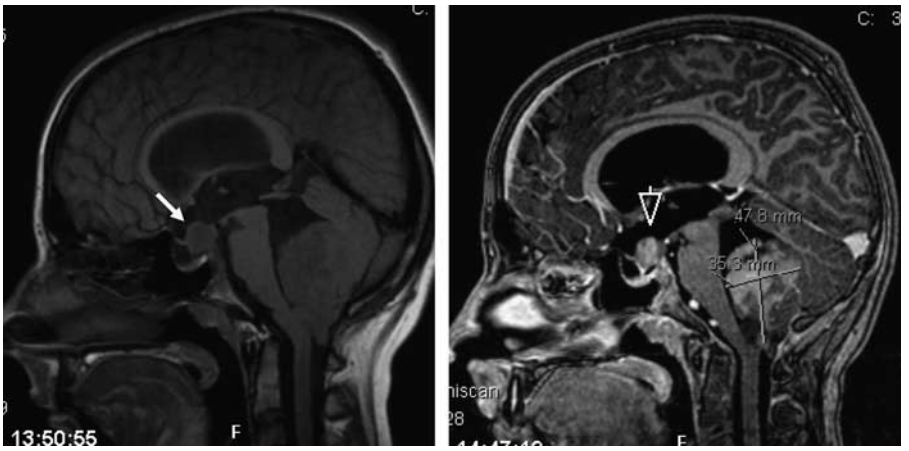
Fig. 1



Primary cerebellar tumor and metastasis in the third ventricle. T1 MRI images before and after gadolinium. Relatively homogenous, partly enhanced tumor. Arrows point to metastasis in the third ventricle.

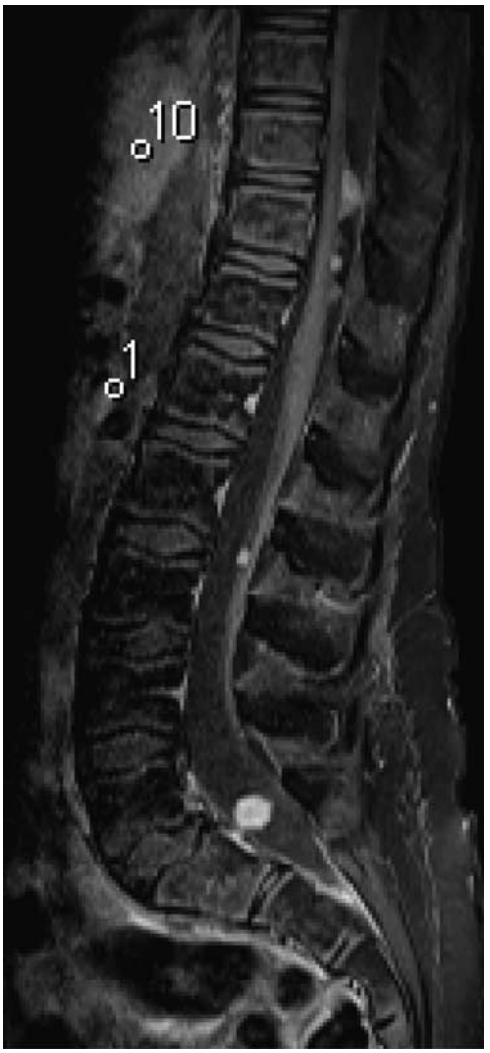
Göteborg, Sweden) with concomitant prednisolone succinate (20 mg). Adult dose was found to be appropriate, as his body weight was 75 kg and height was 173 cm. The intrathecal medication was administered by lumbar puncture every other week, three times, until an Ommaya reservoir was established for intraventricular application. Intervals were then gradually increased to every other month. From the second course onwards, oral dexamethasone was added to prevent arachnoiditis, 4 mg × 2 for 6 days. The seventh course was followed by a 3-month break, and prophylactic steroid treatment was prolonged for 2 weeks, tapering off the dose during the second week. All lesions had disappeared on MRI after nine applications. Intrathecal therapy was stopped after altogether 13 doses of liposomal cytarabine (cumulative dose 650 mg) 18 months after the start of recurrence therapy.

Oral antiangiogenic therapy was initiated 2 weeks after the start of intrathecal therapy. It consisted of thalidomide, celecoxib, and etoposide according to the Nordic Angiocomb protocol [3]. At the most, he was on daily doses of thalidomide of 200 mg (3 mg/kg), etoposide of 100 mg (50 mg/m^2), and celecoxib of 400 mg × 2 (430 mg/m^2), which was a higher maximum dose than the original protocol (celecoxib 230 mg/m^2). Dose reductions were necessary mostly due to neutropenia, followed by mucositis, sinusitis, and fatigue. On two occasions, following episodes with neutropenia and fever, etoposide was removed completely for a few weeks. During the last 8 months, he received 25 mg every other day. After a cumulative dose of 11.5 g/m^2, given over a 31-month period, etoposide was completely discontinued. Three months later, the remaining metronomic therapy with 50 mg thalidomide and 100 mg celecoxib daily is still ongoing.

Response to the recurrence therapy has been remarkable. Clinically, he experienced relief from back pain already 1 day after the first cytarabine application. Correspondingly, the MRI scans showed decreasing tumor size, loss of enhancement, and finally, 10 months after the start of recurrence therapy, no visible metastasis at all. He remains in clinical and radiological remission 34 months after relapse and 67 months after the initial diagnosis (Fig. 3).

The side effects caused by the intrathecal therapy were assumed to be related mainly to chemical arachnoiditis. A few days after the first treatment course, our patient had headache [Common Toxicity Criteria (CTC) grade II], chest pain, ataxia, and numbness in the arms and legs. These problems subsided during later courses after systemic oral steroids for 6 days were started from the day before the procedure. However, 1 week after the seventh injection, the same symptoms reoccurred, and he also lost his hearing and developed slurred speech and severe chest pain. He had fallen on a hard tile floor and was found deeply somnolent (CTC grade III), remaining so for about 36 h. When hospitalized, he was found to be febrile, neutropenic, and with elevated C-reactive protein. Blood cultures were negative, but he received antibiotic treatment and etoposide was temporarily discontinued. Dexamethasone was administered for two more weeks. He recovered, except for remaining hearing deficit of high frequencies (right ear 110 dB and left ear 65 dB at 6–8000 Hz), having had normal hearing until this episode. At this point, one of the spinal lesions was still visible on MRI. After an interval of 3 months, the intrathecal therapy with liposomal cytarabine was therefore resumed, along with prolonged oral dexamethasone. It was well tolerated thereafter, except for two minor episodes of headache, anxiety, confusion, paresthesias, and slurred speech occurring after steroids were discontinued. In both cases, the symptoms subsided after one extra dose of dexamethasone.

Fig. 2



Spinal metastasis at recurrence.

Intrathecal therapy was stopped after 13 injections (cumulative dose 650 mg), but much later, he had two separate episodes with similar, although not so grave symptoms as those after his seventh course of liposomal cytarabine. These incidents, occurring, respectively, 10 weeks and then again 9 months after the last dose, were characterized by headache, anxiety, paresthesias, and slurred speech, followed by deep somnolence. In both cases, he was hospitalized and found to be neutropenic and febrile. As previously, EEG did not show epileptic activity and blood cultures were negative. The symptoms disappeared after a day. Antiepileptic medication was given only for a short period, but as he did not have any further attacks, it was discontinued. However, he still has hearing loss (CTC grade 3), requiring a hearing aid.

The antiangiogenic triple medication caused hematological toxicity, mainly neutropenia (CTC grade IV), requiring dose reduction. For several months, he also had a persistent purulent sinusitis accompanied by listlessness and loss of appetite. After the dose reductions during the last 8 months, he has had no serious adverse effects due to the systemic treatment. He has had a good quality of life, copes well with his disabilities, and goes to regular school with extra assistance.

Discussion

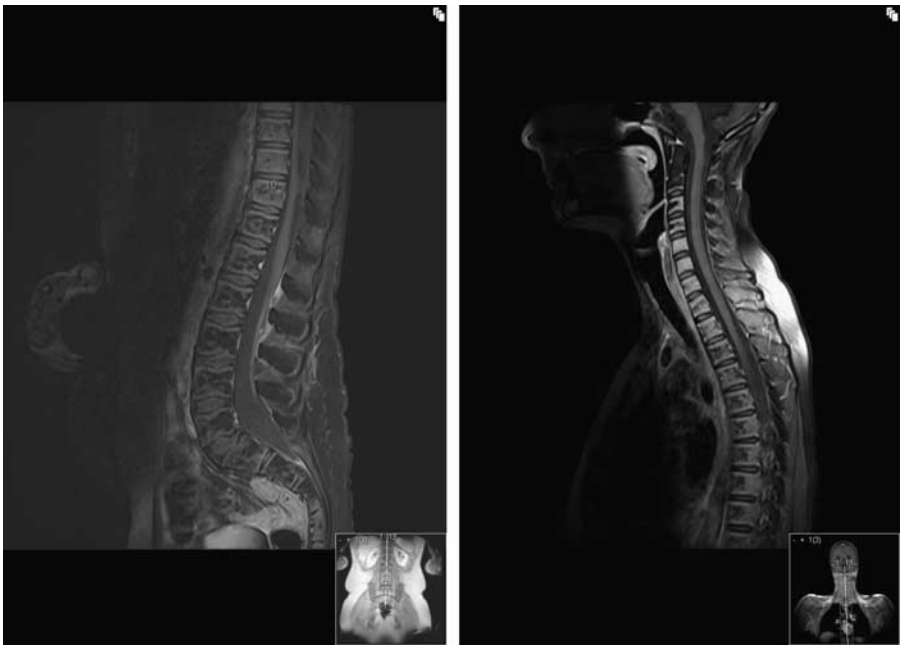
The prognosis of recurrent medulloblastoma remains dismal, with a median survival of less than 1 year despite reports of slight improvements [4–6]. Standardized relapse protocols are few. Many treatment modalities, even high-dose chemotherapy with stem cell rescue, have been used, without any prognostic breakthrough [6–8].

Our patient had a high-risk medulloblastoma with leptomeningeal dissemination at initial diagnosis. Analyses of biological markers were not carried out at that time. He was heavily pretreated with chemotherapy and radiation to the total neuroaxis already before the recurrence. The metastases were diagnosed 33 months after the primary diagnosis and 18 months after the end of primary therapy. With informed consent, the combination of intrathecal cytarabine and oral antiangiogenic therapy was started on a compassionate basis, aimed at alleviation of back pain and prolongation of life. Considering long-term survival to be unrealistic, the risk of treatment-related late effects was accepted. But so far he has been disease-free and has a good quality of life nearly 3 years after recurrence. It needs to be emphasized that it is difficult to evaluate the respective roles of intrathecal and systemic therapy in the context of such a combined approach. But the convincing and rapid clinical response can most likely be attributed to the intrathecal cytarabine, whereas the metronomic, antiangiogenic oral therapy may have contributed as maintenance therapy.

Liposomal cytarabine is a slow-release preparation for intrathecal use. It has been studied both as an alternative and an addition to radiotherapy [9,10]. Pharmacokinetic studies have shown cytotoxic drug levels in the cerebrospinal fluid for 1–2 weeks in children as well as in adults [11–13]. The most common side effect is arachnoiditis with symptoms like headache, nausea, vomiting, and fever [14]. Chemical arachnoiditis is usually alleviated by corticosteroids. Unconsciousness, paraparesis, and cauda equina syndrome have also been reported. Local intrathecal chemotherapy has been studied for pediatric patients with different brain tumors, including medulloblastoma [13–17] (Table 1), showing responses and good tolerability.

The main side effects from liposomal cytarabine in our patient were thought to be related to arachnoiditis, possibly also to neurotoxicity. It is noteworthy that they reappeared after discontinuation of oral steroids, requiring increasingly longer prophylaxis than usually recommended.

Fig. 3



Spinal MRI after 15 months of therapy for the recurrence.

Table 1 Previous reports on the use of liposomal cytarabine in pediatric patients with embryonal central nervous system tumors

Author	Patients (*n*)	Age (years)	De-novo/ recurrent disease	Concomitant chemotherapy	Reference
Partap *et al.*	17	<30	Both	+	[17]
Benesch *et al.*	14	<23	Recurrent	–	[14]
Lassaletta *et al.*	4	<4	Both	–	[15]
Peyrl *et al.*	6	<3	Both	+	[13]

Other explanations for his untoward reactions were considered, especially when two episodes with similar symptoms occurred months after the last intrathecal injection. Infection was not confirmed. Epilepsy and migraine were also considered, the latter mainly because his sister is known to have migraine associated with neurological dysfunctions (including loss of speech). However, the intrathecal treatment remains the most likely cause.

Our patient also experienced a permanent hearing loss. This was most likely caused by the liposomal cytarabine, although it can be argued that previous treatment might have rendered him particularly vulnerable for potentially ototoxic treatment modalities at relapse. He had received two doses of cisplatin (80 mg/m^2) and one with carboplatin (700 mg/m^2) as well as radiotherapy during primary therapy. The hearing loss did not develop until 5 months after recurrence when he had received seven doses of liposomal cytarabine. However, given the poor prognosis of his illness, we chose to continue the intrathecal treatment with extra precautions until beyond the point when all metastases had disappeared on MRI. The patient continues with oral antiangiogenic medication, which may work as maintenance therapy for a longer period of time.

Angiocomb is established as an antiangiogenic protocol by the Nordic Society of Paediatric Haematology and Oncology, primarily for pediatric patients with diffuse brainstem and thalamic tumors [3]. There is theoretical background for antiangiogenic combination therapy of medulloblastoma [18,19]. This tumor has been shown to express vascular endothelial growth factor receptor 2 [20]. Celecoxib [21] and etoposide [22,23] are shown to have an effect on medulloblastoma *in vitro* and in mice. Thalidomide has not been used in murine medulloblastoma studies due to its different metabolism in mice. Clinically, antiangiogenic therapy, provided in a metronomic manner, has been studied earlier in a small number of patients with medulloblastoma [24–26]. Metronomic therapy is defined as low-dose, continuous, and long-lasting oral medication, the effect of which is directed against endothelial cells of the tumor [25]. Progression-free survival in these studies has been 8–33 months.

Treatment with etoposide is associated with a risk of secondary hematological malignancy. Le Deley *et al.* [27] reported 18 pediatric patients treated for recurrent tumors in a study where prolonged therapy with continuous

etoposide was associated with good responses. But five patients, all of whom had received cumulative doses of etoposide higher than 6 g/m^2, developed leukemia 10–25 months after initiation of the drug. As etoposide may have contributed to sustaining remission in our patient, stopping the drug to avoid a potential new malignancy was weighed against the risk of progressive disease. He had received altogether 11.5 g/m^2 when etoposide was discontinued after 31 months. For the last 3 months, his metronomic therapy has only consisted of thalidomide and celecoxib.

Our patient did not receive traditional maximal tolerated dose chemotherapy for his recurrence at all. It is remarkable that his rather severe disease responded well to the combination of local chemotherapy and oral metronomic treatment. Disease-free survival from the recurrence is now 34 months. This remarkable response raises several issues. Perhaps local intraventricular therapy should be considered already in the primary treatment for patients with leptomeningeal disease. It could also be combined with radiotherapy. Further studies may reveal whether certain biological features can define the tumors most likely to benefit from this kind of therapy. Our experience indicates that longer systemic steroid treatment, as prophylaxis for toxic arachnoiditis, may be required than that recommended so far and that ototoxicity could be a possible side effect of intrathecal liposomal cytarabine. More patients and standardized protocols are needed to verify the benefit of this combination therapy and to define the correct duration of treatment.

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Conflicts of interest

There are no conflicts of interest.

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