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CASE REPORT

Old drugs still work! Oral etoposide in a relapsed medulloblastoma

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Abstract

Medulloblastoma is the most common malignant brain tumor in children. Approximately 30% of children with medulloblastoma will progress or relapse despite being treated. New therapies have been proposed in recent years, including high-dose chemotherapy, immunotherapy, and targeted therapy. However, the best treatment for these patients remains unclear, and in this situation prognosis is poor. Oral etoposide has been used as a single agent or in combination for treating relapsed brain tumors since the 1990s. We report an 8-year-old patient with recurrent metastatic medulloblastoma who had an excellent response after treatment with oral etoposide, maintaining a great quality of life. As clinicians, we must always try to include our patients in clinical trials; however, when this is not possible, we should not forget that "old drugs" such as oral etoposide may work in some patients, with a good response of the tumor, and what is most important, providing the patient with a good quality of life.

Keywords Oral etoposide · Relapsed medulloblastoma · Chemotherapy · Children

Abbreviations

MRI	Magnetic resonance imaging
VP	Ventriculo-peritoneal
VP-16	Etoposide
PR	Partial response
CR	Complete response
SD	Stable disease
PD	Progressive disease

Introduction

Medulloblastoma is the most common malignant brain tumor in children [1]. Despite conventional treatment with surgery, radiation, and chemotherapy (high-dose chemotherapy in infants), 30% of the cases will relapse. The chance of relapse is correlated with risk at diagnosis (high-risk EFS at 5 years, 42%) and molecular subgrouping (WNT 5 years PFS 85–90%; SHH 60%; group 3, 42%; group 4, 62%) [2]. Prognosis in this situation is discouraging [3–5] and the best treatment for these patients remains unclear. Etoposide (VP-16) was first used in 1940 [6]. It inhibits the nuclear enzyme DNA-topoisomerase II and is widely used for treating many childhood cancers, including brain tumors in first line [4, 7–10]. New chemotherapy compounds, targeted therapies, immunotherapy, etc. [11] have emerged in recent years, and we sometimes "forget" the "old drugs" when a patient relapses. We report a patient with recurrent medulloblastoma with an excellent response to oral etoposide.

Case report

An 8-year-old male was diagnosed with metastatic medulloblastoma M3 in October 2012. A gross total resection of the primary tumor was performed, followed by a VP shunt. He received four courses of chemotherapy, which included cyclophosphamide (65 mg/kg), etoposide (4 mg/kg), cisplatin (3.5 mg/kg), vincristine (0.05 mg/kg), and methotrexate (400 mg/kg) [12]. After chemotherapy, craniospinal irradiation was given (31.2 Gy in the craniospinal axis and 54.6-Gy tumor boost to the posterior fossa) as consolidation. The patient was in complete remission at the end of therapy in March 2013. Post-therapy complications included peripheral

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facial palsy, mild right hemiparesia, and mild neurocognitive impairment. On a routine MRI follow-up more than 3 years after the end of therapy (October 2016), with the patient being asymptomatic, leptomeningeal progression was reported in the posterior fossa (Fig. 1a). A month later, the patient suffered status epilepticus, which was completely resolved with levetiracetam. A new MRI showed progression of the lesions (Fig. 1b). Spinal MRI and CSF were negative. Because of the parents' denial for a biopsy, and the good clinical condition of the patient, a new MRI was performed 2 months later, where further progression was observed (Fig. 1c). Oral etoposide was then started at an initial dose of 35 mg/m^2/day for 21 days every 28 days in February 2017. Etoposide was well tolerated without remarkable side effects. After 2 cycles, the MRI showed a partial response (Fig. 1d), including decreased size of leptomeningeal contrast enhancement and

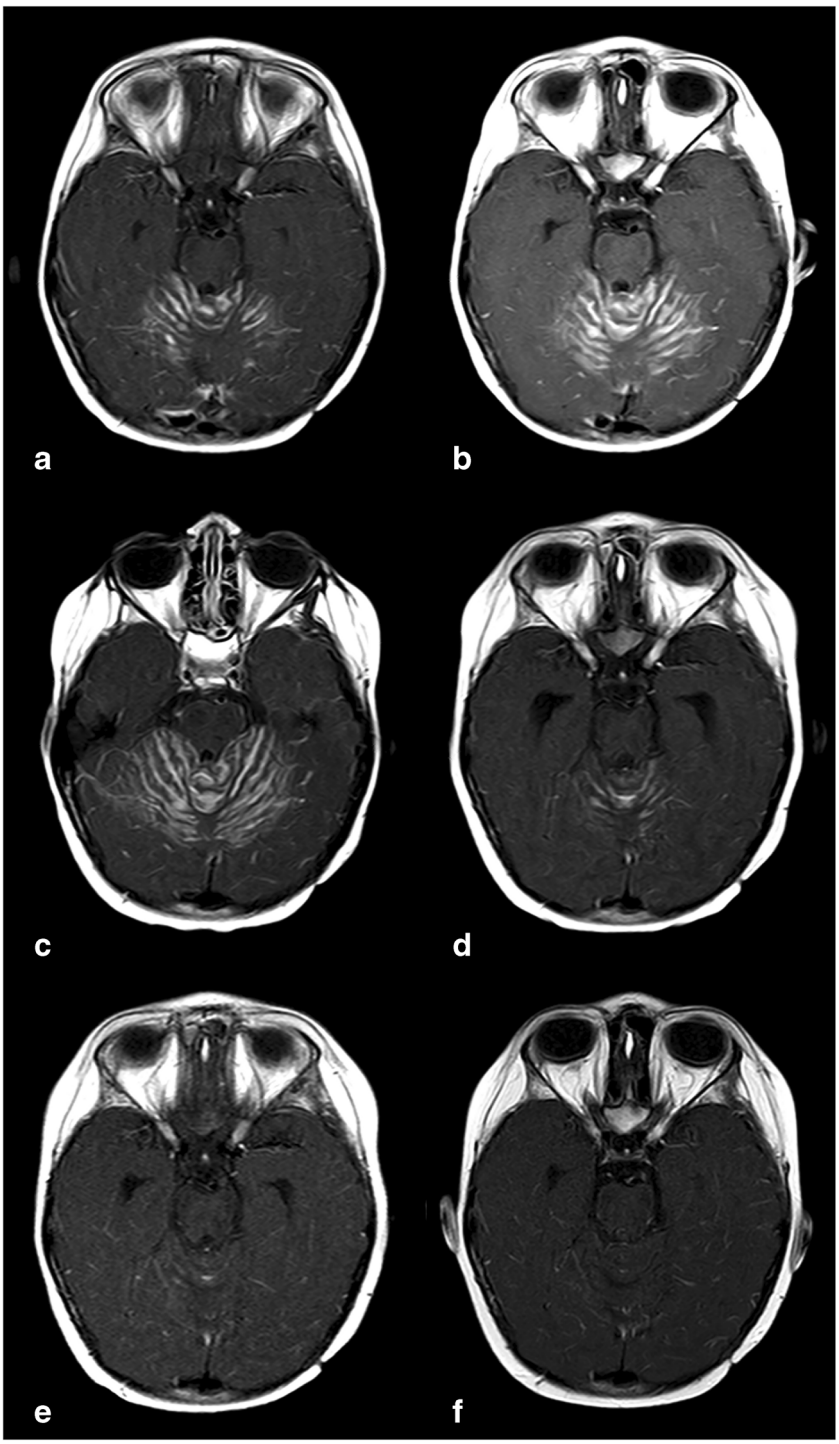

Fig. 1 Axial T1-weighted, contrast-enhanced magnetic resonance images (MRI). **a**–**c** Linear enhancement of cerebellar folia due to cerebellar leptomeningeal dissemination. Note that leptomeningeal contrast enhancement progressed in the consecutive studies. **d**, **e** Leptomeningeal dissemination on MRI decreased following therapy. **f** No anomalous contrast enhancement as a result of complete response

improved FLAIR/T2W lesions. After 4 cycles using the same dose, there was an excellent response of the tumor, with complete resolution of all lesions (disappearance of all enhancing disease; Fig. 1e). After the fifth cycle of etoposide, and due to the great response observed, other metronomic drugs were added [13]: fenofibrate, thalidomide, and celecoxib. Despite the great response to chemotherapy, the parents refused high-dose chemotherapy. Thalidomide was discontinued after 15 days due to severe somnolence. After 8 cycles (Fig. 1f), etoposide was discontinued and replaced by oral cyclophosphamide (2.5 mg/kg for 21 days every 28 days) due to the risk of developing secondary leukemia. The patient suffered another episode of status epilepticus, which resolved completely. An MRI again showed progression of the leptomeningeal disease 18 months after diagnosis of relapse. Etoposide was restarted with bevacizumab (10 mg/kg every 2 weeks). The MRI after 2 cycles of etoposide again showed response in contrast enhancement and in FLAIR/T2W. To date, the patient continues treatment with fenofibrate, celecoxib, bevacizumab, cyclophosphamide, and etoposide and has received 12 cycles of etoposide (cumulative dose 7.5 g/m^2) and 8 cycles of cyclophosphamide. Metronomic chemotherapy has been well tolerated. The patient remains at home, and 25 months after the diagnosis of relapse, he continues to attend school, maintains daily activities, and has the same good quality of life that he had before the relapse. We have retrospectively classified the patient's tumor to the molecular entity group 4 using DNA methylation–based classifiers [14]. No evidence of MYCn or MYC amplification was identified.

Discussion

Metronomic chemotherapy is defined as low-dose, continuous, and long-lasting oral chemotherapy [3, 10]. It modulates anti-tumoral immunity, which induces tumor control [9]. The continuous administration of oral etoposide may allow the inhibition of topoisomerase II function during an extended period of time [7, 8]. Chamberlain et al. used 50 mg/m^2/day of oral etoposide in 8 patients with local recurrent medulloblastoma during the 1990s. Five of them showed stable disease (SD) or partial response (PR) [7]. Davidson et al. reported 3/14 PR when the same dose was used in relapsed medulloblastoma/PNET [15]. Subsequently, Ashley et al. reported 7 patients who received oral etoposide at 50 mg/m^2/day with 21-day repeated courses. Their results showed 6/7 PR after the second course of VP-16 evaluation [8]. Needle et al. reported a phase II study of daily oral etoposide in patients diagnosed with brain tumors, in which 3/4 patients with medulloblastoma partially responded to daily oral etoposide (50 mg/m^2/day). They also concluded that having previously received IV etoposide does not exclude a possible response to later treatment [4, 6]. Oral VP-16 has been used alone [8] or in combination with other chemotherapies in metronomic chemotherapy regimens [13]. It was later suggested that the addition of bevacizumab and intrathecal therapy improves progression-free survival for refractory or recurrent embryonal CNS tumors. In seven recurrent medulloblastomas, 3 complete responses (CR) and 2 PR were achieved. Two patients died from disease progression [9]. Korones et al. and Ruggiero et al. described the use of VP-16 in addition to temozolomide for patients diagnosed with malignant gliomas

Table 1 Relapsed medulloblastomas treated with oral etoposide previously reported

Reference	*n*	Tumor	Treatment	CR	PR	SD	PD
Chamberlain et al. [7]	8	Medulloblastoma	Oral etoposide 50 mg/m^2/day 21 days	0	2	3	3
Ashley et al. [8]	7	Medulloblastoma	Oral etoposide 50 mg/m^2/day 21 days	0	6	1	0
Peryl et al. [9]	5	Medulloblastoma	Thalidomide 1.5–8 mg/kg, celecoxib 50–400 mg, fenofibrate 90 mg/m^2, alternating oral etoposide (35–50 mg/m^2) and cyclophosphamide 0.5–2.5 mg/kg, and bevacizumab 10 mg/kg every 2 weeks	3	2	–	–
Robison et al. [10]	6	Medulloblastoma	Thalidomide 1.5–8 mg/kg, celecoxib 50–400 mg, fenofibrate 90 mg/m^2, alternating oral etoposide (35–50 mg/m^2/day) and cyclophosphamide 0.5–2.5 mg/kg	1	0	2	3
Ruggiero et al. [4]	12	Medulloblastoma	Temozolomide 150 mg/m^2/day and etoposide 50 mg/m^2/day	1	1	7	3
Needle et al. [6]	4	PNET/medulloblastoma	Oral etoposide 50 mg/m^2/day 21 days	0	3	0	1
Nyaard et al. [3]	1	Medulloblastoma	Intrathecal therapy with liposomal cytarabine and thalidomide of 200 mg (3 mg/kg), etoposide of 100 mg (50 mg/m^2), and celecoxib of 400 mg	1	0	0	0
Davidson et al. [15]	14	PNET/medulloblastoma	Oral etoposide 50 mg/m^2/day 21 days	0	3	6	5

and recurrent medulloblastoma, respectively, both reporting a good response [4, 16]. Korones and colleagues also found good results with oral etoposide alone [16]. Oral etoposide has also been reported as part of the first-line therapy, being given during radiation in newly diagnosed high-risk medulloblastomas showing minimal toxicity, which suggests that this formulation could also be considered as front-line therapy [17] (Table 1).

Treatment with 50 mg/m^2/day of oral etoposide for 21 days every 4 weeks has minimal toxicity. This dose can be reduced depending on the patient's condition. Our heavily previously treated patient started with 35 mg/m^2/day. Myelosuppression and infections are the main toxicities reported using oral etoposide. The association between etoposide and the development of secondary leukemias has been previously reported [10, 18–20]. There is a high risk to develop secondary leukemia when treatment with continuous etoposide is prolonged more than 6 months, and when the cumulative dose is greater than 6 g/m^2 [18, 21]. In our patient, the cumulative dose of etoposide has exceeded this limit. As our patient has shown an excellent response to this drug, it is difficult to determine when it should be stopped. Frequent blood analyses are performed to rule out any sign of secondary leukemia. The patient has not developed any significant toxicity during treatment.

Molecular subgrouping is changing the landscape of medulloblastoma [22]. Group 4 is correlated with good prognosis and with late relapses. These relapses have been identified with overall long-term survival. This is in accordance with our case, in which retrospective molecular subgrouping revealed a group 4 [23].

This case shows that oral etoposide could be a good treatment for children with recurrent medulloblastoma. However, more patients and standardized protocols are needed to assess the benefits and the best schedule of administration. In recent years, a large number of studies have evaluated new strategies for children diagnosed with recurrent medulloblastoma such as targeted therapies and high-dose chemotherapy followed by stem cell rescue and conventional chemotherapeutics with limited impact in their outcome and compromising the patients' quality of life [11]. As clinicians, we always must try to include our patients in clinical trials; however, when this is not possible, we should not forget that "old drugs" such as oral etoposide may work in some patients, and what is most important, providing a good quality of life.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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