Intracavitary chemotherapy (Gliadel®) and oral low-dose etoposide for recurrent anaplastic ependymoma

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Abstract. Anaplastic ependymoma is associated with a higher incidence of tumor recurrence and its prognosis still remains unsatisfactory. Consolidated therapy for ependymoma includes surgery followed by focal radiotherapy when resection is incomplete. In the case of relapse treatment, options are limited especially for patients who have already received radiotherapy. We sought to establish the feasibility of administering low-dose oral etoposide (50 mg/m^2/day for 21 days) in combination with the implantation of intracavitary carmustine (BCNU) wafers (Gliadel®) at the gross total resection for achieving synergistic treatment in three children affected by recurrent anaplastic ependymoma. All patients had Karnofsky performance scale (KPS) scores >80%. The therapy was tolerated safely and well in all patients without any post-surgery complications. After BCNU wafer implantation, all patients achieved radiological and clinical stabilization for an average period of 3 months. Two patients relapsed after 4 months as shown in brain MRIs. The other patient went to progression two months after the Gliadel implantation. This multimodal approach was not effective for the treatment of refractory anaplastic ependymoma and further studies are required in order to define the role of the combination of multidrug systemic chemotherapy with BCNU wafer implantation in children with high-risk brain tumors.

Introduction

The past decades have seen an increase in the survival rates of certain pediatric brain tumors, thus, efforts have been focused on obtaining better results in the treatment of high-risk tumors, such as anaplastic ependymoma. A characteristic of anaplastic ependymoma is recurrence at the primary site and only a small number of patients present evidence of dissemination. The consolidated treatment for intracranial ependymomas includes gross total resection (GTR) followed by post-operative focal radiotherapy and/or systemic chemotherapy when resection is incomplete (1-4). Radiation therapy has been shown to delay the time of local failure whereas the role played by chemotherapy for recurrent anaplastic ependymomas still remains unclear (5,6). Beyond surgery, novel approaches that aim at improving the outcome and quality of life are now available due to new breakthroughs in the molecular biology of ependymoma. Intracavitary chemotherapy has considerable clinical implications for the treatment of malignant brain tumors (7-9). This approach allows for the by-passing of the blood-brain barrier (BBB) and obtaining a high concentration of BCNU in the tumor bed which protects the drug from early degradation and minimizes systemic side effects and toxicity.

Beyond the resistance of anaplastic ependymoma, it is possible that a high concentration of carmustine in the tumor bed in combination with a low dose of systemic chemotherapy could be effective in prolonging survival. We report on three pediatric patients with recurrent anaplastic brain ependymoma who were first treated with surgery, then followed by carmustine wafer (Gliadel®) implantation and continuous low doses of etoposide.

Case reports

Case 1. In April 2001, a 9-year-old boy was referred to our hospital with a history of right brachio-crural deficit. A Gd-enhanced magnetic resonance (MR) scan was performed and revealed the presence of a left fronto-parietal tumor. The patient underwent a GTR, with good motor function recovery. The histopathological diagnosis was anaplastic ependymoma (WHO III). The patient was free of disease for the next 18 months, until a brain MR showed local recurrence. He then began a radiotherapy program. In August 2002, following two seizures, he was subjected to another MR scan that showed local recurrence with central necrosis. He then underwent another round of radical surgery. After that, he began a chemotherapy program that included daily low doses of etoposide, according to the Sandri *et al* (10) study. Two

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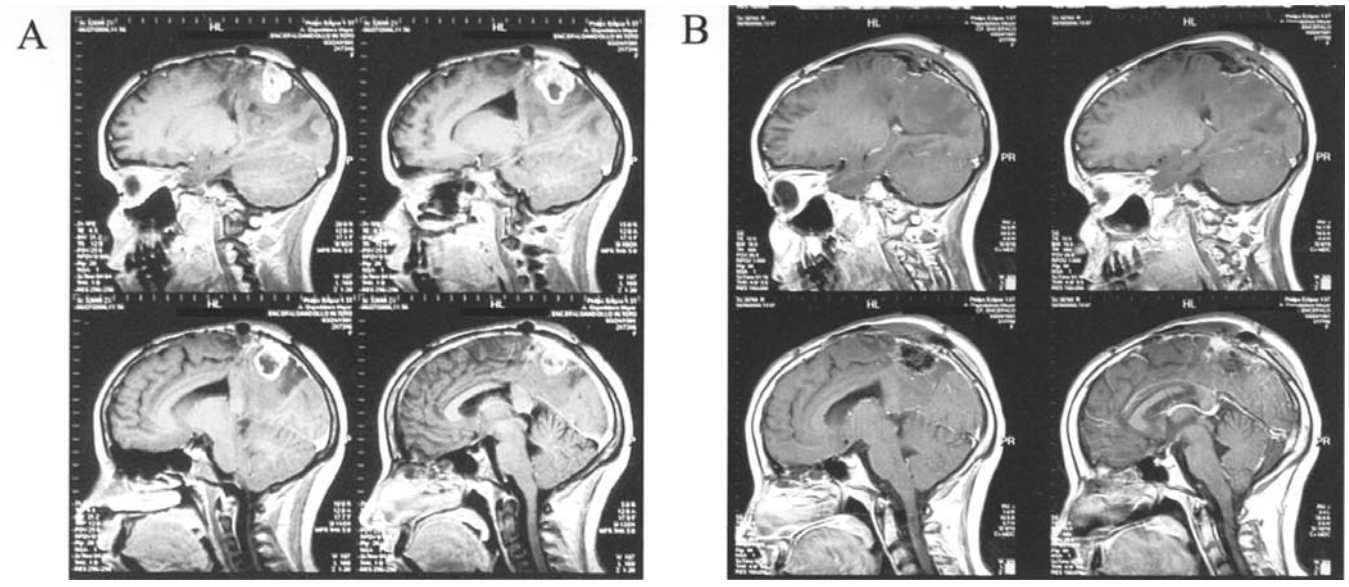

Figure 1. (A) Preoperative sagittal Gd-enhanced T1-weighted MR images demonstrating the tumor on the right prerolandic area. (B) Postoperative sagittal Gd-enhanced T1-weighted MR scans showing the GTR with intracavity BCNU wafer implantation.

years later, an MRI scan showed the third recurrence and he underwent GTR surgery. A temozolomide (TMZ) chemotherapy program ensued with 180 mg/m^2/day doses for 5 days out of every 28 (11). After ~11 months of oral TMZ administration, an MRI scan revealed further tumor growth at the same site, leading to the decision to stop chemotherapy and perform another surgical resection. After his fifth recurrence, three months later, the patient underwent a new GTR with the placement of Gliadel wafers into the excised tumor bed. The postoperative period was uneventful with a good motor function recovery. A histopathological examination confirmed that the original tumor type was an anaplastic ependymoma. After three days, he began systemic chemotherapy with a 50 mg/m^2/day dose of etoposide to be administered 21 days per month for six cycles (10). Three months after surgery, the patient developed hypotonia and paraesthesia. An MR scan revealed a small lesion localized in front of the previous tumor site. Subsequently, brachytherapy was initiated (a total dose of 1400 cGy). As of the last follow-up in December 2006, the patient was doing well with a KPS score of 90%.

Case 2. In April 2004, a 10 year-old boy was referred to another Hospital with a history of seizures, headaches, nausea and vomiting. The physical examination was negative, except for a venous congestion in his left eye, horizontal bilateral nystagmus and diplopia. An MR scan was performed and revealed the presence of a tumor in the fronto-temporo-parietal lobes. The patient underwent partial surgery for resection of the mass. The histopathological diagnosis was anaplastic ependymoma. Two months later, an MR showed a local progression of tumor size and GTR surgery was performed. He thus enrolled in a radiotherapy program that was followed by chemotherapy with four courses of vincristine, etoposide and cyclophosphamide (VEC) according to a program proposed by Massimino *et al* (4). Ten months later, an MR scan showed a recurrence with progression of the disease. We decided on a further surgical procedure. Twelve months after the second GTR, another surgical procedure was undertaken to treat the relapse of the tumor. An MR scan of the brain, three months later showed a new, widespread local relapse. Since the tumor was particularly aggressive, the neurooncology team decided to proceed with a craniotomy and placement of Gliadel wafers. The surgical exploration revealed a more substantial extension of the tumor in respect to the preoperative neuroradiological findings. We still placed eight BCNU wafers on the tumor bed. Five days later, he began chemotherapy with oral etoposide. Two months later, he was admitted to the emergency room with a severe headache, vomiting and a worsening of neurological conditions. The CT scan of the brain showed that the disease had progressed at the residual lesion where the BCNU wafers were not implanted. The boy died a few days later, just six months after the Gliadel wafers were implanted.

Case 3. At 4 years of age, this 15-year-old girl experienced left lower-extremity hypotonia and paretic march. An MR evaluation of the brain revealed a right fronto-parietal tumor. She underwent surgical GTR, without complications and had good improvement of the neurological condition. Afterwards, she enrolled in a VEC chemotherapy program attended by radiotherapy. Three years later, during follow-up, she had a relapse of the tumor and needed two consecutive GTR procedures followed by interstitial brachytherapy. After one and two years, new recurrences were respectively treated with surgery. After two years, neuroradiological control showed a new local relapse. She then began an 18-session chemotherapy program with TMZ (11). An MR scan of the brain showed evidence of disease progression and in December 2005 she underwent GTR surgery for the fifth recurrence. In June 2006 (during the follow-up for tumor re-growth), a further GTR was required after the sixth relapse. This time, Gliadel wafers were placed in the resection bed (Figs. 1 and 2). Three days later, she began on daily oral etoposide. Her postoperative course passed without complication and she was discharged

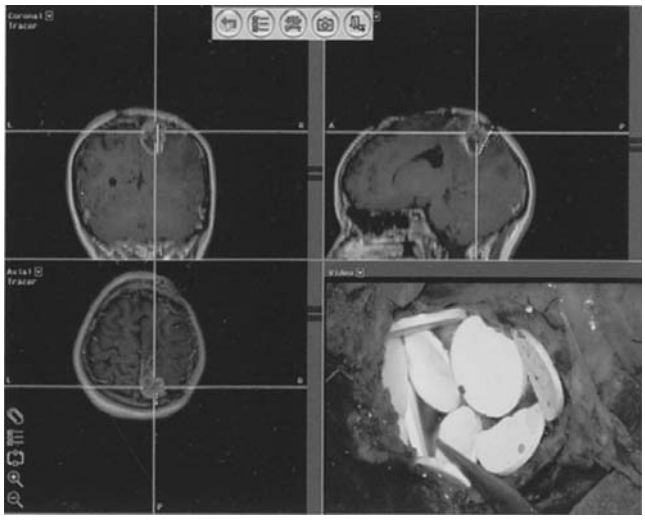

Figure 2. Intraoperative picture showing an implant of carmustine wafers assisted by a neuronavigator to assess the limits of the tumor resection.

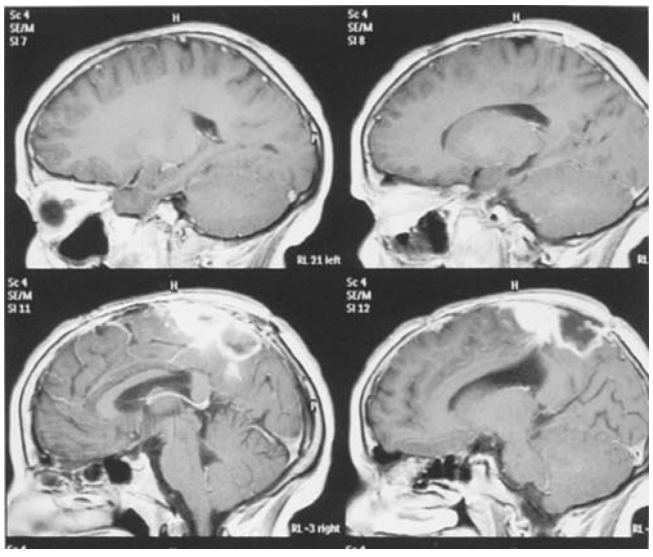

Figure 3. Four-month follow-up of sagittal Gd-enhanced T1-weighted MR scans clearly showing the recurrence by the side of the previous tumor bed resection and Gliadel® implant.

with hemisyndrome and a KPS score of >80%. A histopathological diagnosis of all recurrence lesions showed the tumor was an anaplastic ependymoma. The last follow-up at four months showed a recurrence outside the area affected by intracavitary wafer implantation (Fig. 3).

Results and Discussion

We considered three consecutive multi-treated patients with recurrent anaplastic ependymoma. All cases received radiotherapy and chemotherapy treatments and received a second line chemotherapy with TMZ, which led to a short-term disease stabilization. Patients 1 and 3 received interstitial brachytherapy at the successive recurrence. In light of these therapeutical failures, our patients underwent Gliadel wafer implantation and systemic chemotherapy at the latest relapse with a low dose of etoposide administrated at 50 mg/m^2/day for 21 days per month for six cycles according to Sandri *et al* (10). The study was approved by the Ethics Board of 'A. Meyer' Children's Hospital and informed consent was obtained from all the parents of our patients. This combined approach of local chemotherapy with BCNU wafers and a systemic low-dose of oral VP-16 aimed at stopping the advance of the disease, avoiding side effects and possibly enhancing the post-operative radiotherapy effects by improving the EFS of anaplastic ependymoma.

All patients had a fast and good functional recovery without any post-surgery complications. After BCNU wafer implantation, all patients achieved radiological and clinical stabilization for an average mean period of 3.3 months. A brain MR scan showed that patients 1 and 3 relapsed after 4 months. Patient 2 went to progression two months after the Gliadel implantation.

Anaplastic ependymoma is an aggressive tumor with a dismal prognosis. Incomplete removal of the tumor, which is usually due to limitations imposed by the location of the lesion, is associated with a higher chance of tumor recurrence. However, based on our experience, to the forehead of a total tumor resection according to the opinion of a neurosurgeon and a neuroradiologist, a relapse has been observed at varying timetables. Surgery alone with strict follow-up surveillance is enough if the tumor is a low-grade ependymoma (WHO II) and has been completely resected without evidence of leptomeningeal dissemination. However, it is also possible to obtain improved survival with focal radiotherapy in these cases. Although the imperative role of radiotherapy, in terms of enhanced EFS for post-surgery treatment of anaplastic ependymoma, has been well documented, the prognosis of this tumor remains poor (2,6,12).

Currently, there is not enough evidence for consistent efficacy of adjuvant chemotherapy in the treatment of ependymoma. This tumor, especially in the anaplastic form, seems to be resistant to several drugs, including alkylant agents and platinum composts. Moreover, few studies have been carried out using carmustine in association with other agents (13-18). A prospective non-randomized study using post-operative radiotherapy and chemotherapy consisting of carboplatin, vincristine alternating with ifosfamide and etoposide for a total of 4 cycles in patients with partial resection showed a better survival rate in respect to historical series (19). In a clinical trial of the Children's Cancer Group (CCG), malignant ependymoma in infants was treated with a 1-day, eight-drug chemotherapeutic regimen, demonstrating that the overall survival (OS) remained unsatisfactory even if a subset of patients remained free from tumor recurrence (1). Some studies that investigated the role of high doses of chemotherapy with autologous stem rescue in patients with recurrent ependymoma showed that this treatment was ineffective and not without unanticipated and untoward side effects (5,20,21). Kalifa *et al* (22) demonstrated that even high-dose drug regimens did not offer substantial advantages in respect to conventional ones. Another study of CCG was conducted on patients more than 2 years old with newly diagnosed ependymomas, randomizing patients in two arms. They both received adjuvant chemotherapy with either

lomustine, vincristine and prednisone or the eight-drugs in a 1-day regimen following post-operative radiotherapy. The outcome of the results was fairly unsatisfactory, demonstrating no survival advantage for chemotherapy when compared to historical controls (23). Rojas-Marcos *et al* (24) obtained a complete response (CR) to treatment in an adult patient affected by recurrent and multifocal anaplastic ependymoma with tamoxifen and retinoids.

The POG 8633 infant and the SFPO studies detected the feasibility of post-surgery chemotherapy in delaying radiotherapy in children with ependymoma. The outcome of the results was nonetheless poor in terms of a partial response (PR) or CR in children with residual disease. However, a small percentage of patients were alive after 4 years without undergoing radiotherapy (25,26).

Notable results have been obtained in a small cohort of multi-treated ependymoma patients enrolled in a treatment with daily oral etoposide of 50 mg/m^2 (10).

It has been demonstrated that aggressive brain tumors show low response rates to conventional and intensified chemotherapy, so efforts have thus been focused on local tumor therapies to decrease side effects and preserve the therapeutic efficacy of chemotherapy agents on the neoplastic lesion.

Intracavitary chemotherapy with Gliadel wafers creates a high long-term, local concentration delivery of carmustine. This approach records lower toxicity than systemic BCNU therapy. The efficacy of carmustine wafer implantation has been demonstrated in adult patients with recurrent glioblastoma (7). Subsequent clinical trials tested the BCNU device at the first surgery for the therapy of high-grade glioma, concluding that this approach delayed both clinical and radiological progression and was able to increase the survival rate (9,27,28). Additionally, a small cohort of recurring pituitary adenomas and craniopharyngiomas were treated with Gliadel (29). Park *et al* (30) recently treated a recurrent esthesioneuroblastoma, a rare olfactory tumor of the nasal vault, with surgery and placement of BCNU wafers. In both studies, the therapy was well tolerated and the patient obtained a short-term disease stabilization. A recent meta-analysis conducted on a malignant glioma clinical trial demonstrated a survival advantage in the 2nd and 3rd-year follow-ups with patients who underwent wafer implantation during their first surgery in combination with radiotherapy when compared with a placebo (8).

Some studies established the feasibility of administrating systemic chemotherapy in combination with BCNU wafer implantations at the GTR for treatment of adults with high grade glioma. Limentani *et al* (31) showed that a pre-irradiation and immediate post-operative carboplatin administration following the intracavitary wafer implantation was well tolerated and registered a low-moderate toxicity in malignant gliomas enrolled in a phase I clinical trial. Previously, a protocol with carmustine device embedding and TMZ at the dose of 200 mg/m^2/day for 5 days monthly (with 10 recurrent, supratentorial high-grade gliomas enrolled) showed low toxicity at the maximum dosage level of TMZ (32). Recently, Weingart *et al* (33) reported the feasibility of intracavitary chemotherapy plus systemic administration of O6-benzylguanine, an inhibitor of DNA repair system without added toxicity for therapy of recurrent high-grade glioma.

Although these studies have been conducted on adult patients, they show that the Gliadel treatment is effective and well tolerated without the systemic complications usually associated with chemotherapy. Our study was undertaken for treating recurrent anaplastic ependymoma subjects who received multi-therapies and who presented an 80-90% KPS score. It has been well documented that the relapse could be treated without increasing the morbidity. Intracavitary chemotherapy with low doses of etoposide was not effective in controlling the aggressive behaviour of the anaplastic ependymoma. We showed that contrary to previous tumor resections, the relapse in all cases was distant from the BCNU wafer implantation, demonstrating effectiveness in stopping tumor cell proliferation in these areas. It seems possible to associate combining systemic chemotherapy with BCNU implantation for a better control of high-risk brain tumors.

As far as we have seen, although the disease comes back shortly after surgical resection, the recurrence was far from the tumor bed resection. Further investigations will be necessary in order to determine the potential role of BCNU wafer implantation in the tumor bed after the first tumor resection in addition to consolidated oncological therapies. Given the increased availability of new, biodegradable drug wafers and/or novel local administration strategies (alone or in conjunction with others), the challenge will consist of developing treatment strategies that will further enhance the survival and quality of life of anaplastic ependymoma patients.

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