Abstract. Anaplastic ependymoma is a rare brain tumor, induced both in the brain and the spine. The treatment relies on surgery and radiotherapy. Upon failure of these treatments, chemotherapy has modest effects. Here, we report two cases of anaplastic ependymoma with prolonged radiological and clinical responses to a metronomic cyclophosphamide, cisplatin and bevacizumab regimen. Two patients with anaplastic ependymoma, refractory to surgery and radiotherapy were proposed for a chemotherapeutic treatment. These patients had both spina and brain nodules. Neurological symptoms included arm deficiencies and paraparesia. Results: Six cycles of the metronomic cyclophosphamide (50 mg per day, daily), cisplatin (100 mg/m\(^2\) every four weeks) and bevacizumab (10 mg/kg every two weeks), as a chemotherapeutic regimen, induced both radiological response on magnetic resonance imaging and clinical response with neurological deficiency regression. At one year, the patients were still under maintenance therapy with metronomic cyclophosphamide and cisplatin. This treatment still continues to control tumor progression and symptoms. Conclusion: This is the first report showing an impressive efficacy of metronomic the cyclophosphamide, cisplatin and bevacizumab chemotherapeutic regimen for the treatment of refractory anaplastic ependymoma.

Ependymoma is a rare type of glioma, representing 5% of all central nervous system malignancies in adults (1, 2). This tumor arises from the ependymal cells of the cerebral ventricles, the central canal of the spinal cord, and cortical rests (3, 4). The tumor can occur at any age. Most ependymomas are infratentorial in young children (at a mean age of 6 years) and are supratentorial and spinal in adults (at a mean age of 20 years) (1). The World Health Organization (WHO) tumor classification separates ependymomas into sub-ependymomas (WHO grade 1), myxopapillary ependymomas (WHO grade 1), ependymomas (WHO grade 2) and anaplastic ependymomas (WHO grade 3) (2-4). Optimal management of grade 2 and 3 ependymomas first includes evaluation of the extension in the central nervous system, both in the brain and the spine using contrast-enhanced magnetic resonance imaging (MRI). Surgery is a first treatment option. Recurrent ependymomas are managed by re-operation of tumors that are surgically accessible, by radiotherapy and by salvage chemotherapy (5-8). Because of the low incidence of this disease, no large prospective clinical trials have been performed and consequently, there is no standard chemotherapy regimen. Modest benefit was observed with the used of alkylating agents (9, 10). Platinum derivates are also frequently used (11). Angiogenesis and VEGF seem to have an important role in the biology of ependymoma and encouraging results were observed in a series of eight patients treated with bevacizumab, a recombinant humanized monoclonal antibody against VEGF (12). Here we present two cases of recurrent anaplastic ependymoma refractory to surgery and radiotherapy that exhibited prolonged radiological and clinical responses to metronomic cyclophosphamide, cisplatin and bevacizumab therapy.

Case Reports

Case 1. A 39-year-old man presented lower limb neurological deficiency and dorsal pain. MRI of the thoraco-lumbar spine revealed a diffuse lesion from the tenth thoracic to the second lumbar vertebra. There was patchy contrast enhancement of the lesion. Partial surgery was performed in July 2010. Histopathological examination revealed a hypercellular tumor with predominantly rounded tumor cells. The cells’
cytoplasmic processes formed perivascular pseudorosettes. Upon immunohistology, tumor cells were labeled by antibodies against glial fibrillary acidic protein (GFAP) and S100 protein. There were large areas of necrosis. A diagnosis of anaplastic ependymoma (WHO grade III) was performed. The MRI confirmed residual tumor masses of the conus medullaris. The patient still experienced lower limb motor deficiency and sphincter problems. The cerebrospinal fluid cytology and cerebral MRI were normal. Rapidly, local recurrence occurred one month after surgery. Intensity-modulated radiation therapy with 44 Gy in 22 fractions over 33 days was delivered to the conus medullaris. This treatment induced clinical and radiological stable disease for eight months. In May 2011, a recurrence was detected in the left frontal lobe. The management included surgical resection and whole-brain radiotherapy at a dosage of 30 Gy with a boost at 44 Gy to the tumor bed in the left frontal lobe. In July 2011, MRI showed progression in the spine in the conus medullaris and new lesions occurred in the region of the third and fourth lumbar vertebra and in the right frontal lobe of the brain. The patient suffered from lower-limb motor deficiency and back pain. After consultation with a multidisciplinary neurooncology team, chemotherapy was recommended. The patient was treated with cisplatin at 100 mg/m² every four weeks and bevacizumab at 10 mg/m² every two weeks; cyclophosphamide was added at 50 mg orally every day. Toxicity was minimal with only grade 2 asthenia. In December 2011, MRI showed partial response of the tumor of the left brain with a marked decrease in contrast enhancement on T1-weighted sequence and a near-complete response of the right frontal tumor (Figure 1A). The tumor of the medullaris conus showed stability but the central part of the tumor showed mark necrosis (Figure 1B). The patient demonstrated clinical benefit with impressive diminution of the lower-limb deficiency and reduction of back pain. The patient is still under maintenance therapy with metronomic cyclophosphamide (50 mg per day) and bevacizumab (10 mg/kg every two weeks). From the last MRI in July 2012, the patient is still in partial remission.

**Case 2.** The second patient is a 48-year-old man who presented lower-limb neurological deficiencies and dorsal pain in July 2009. A mass was discovered in the region of the 11th dorsal vertebra. An R1 surgical resection was performed. The diagnosis of anaplastic ependymoma was made. In September 2009 intensity-modulated radiotherapy was performed for residual disease, at a dosage of 45 Gy. In January 2010, two metastases of the left frontal brain were discovered. These lesions were responsible for a right arm deficiency. These brain metastases were treated by stereotactic radiotherapy. In March 2010, temozolomide treatment was begun because of rapid tumor progression. Upon progression of the brain metastases, from June 2010 to September 2010, the patient received bevacizumab therapy with no radiological or clinical efficacy. In January 2011, new lesions occurred in the conus medullaris and in the region of the third and fourth lumbar vertebra, associated with paraparesia. R2 resection was performed to liberate the spinal nerves. In May 2011, recurrence occurred both in the spine and in the brain with the appearance of a third lesion. The patient suffered from right arm deficiency and paraparesis and required a wheelchair. After consultation with a multidisciplinary neurooncology team, chemotherapy was recommended. The patient was treated with cisplatin at 100 mg/m² every four weeks, bevacizumab at 10 mg/m² every two weeks and daily metronomic cyclophosphamide (50 mg per day). Toxicity was moderate with grade 2 anemia and asthenia. In October 2011, MRI showed a marked decrease in contrast enhancement of the T1-weighted sequence both of the brain tumors and of the spinal nodules. Complete regression of right arm deficiency occurred. Paresis symptoms regressed and the patient became able to walk with two crutches. A maintenance therapy with metronomic cyclophosphamide (50 mg per day) and bevacizumab (10 mg/kg every two weeks) started. From the last MRI in July 2012, the patient is still in partial remission and paresis symptoms continue to regress. At this time, the patient became able to walk with one crutch.

**Discussion**

Anaplastic ependymoma is a rare brain tumor. Surgery is the main treatment and the extent of resection is the dominant prognostic factor for all subtypes and sites of ependymoma. However, because of anatomical constraints, gross total resection is rarely achieved. Five-year overall survival for patients with intracranial ependymoma and complete surgical resection ranges from 60% to 80% (13, 14). Conversely, patients with gross residual disease have a 5-year survival of 20% (15). Immediate second-look surgery should be considered in patients with gross residual disease on postoperative imaging. In a series of 40 patients with ependymoma, where 12 patients underwent second-look surgery, gross total resection was achieved in 10 out of 12 patients, with only one of the patients experiencing significant morbidity (16). Radiation therapy is considered as a standard adjuvant therapy after resection of intracranial ependymoma. While no randomized data are available due to the rarity of the tumor, multiple retrospective series have demonstrated that adjuvant radiotherapy improves local control of tumor, as well as overall survival of patients with ependymoma (17). Standard radiotherapy doses for patients without residual disease are 54-59.4 Gy in 1.8-Gy fractions. Chemotherapy has a limited role in the treatment of ependymoma. A pooled analysis of phase II studies of chemotherapy has suggested platinum agents to have the highest activity against ependymoma, but prolonged responses...
are rare (18). Combination therapy has been found to have higher response rates than single-agents, with single-agent response rates being as low as 11% (18). Treatment seems more effective in pediatric cases (19). In pediatric cases, alkylating agents demonstrated efficacy. Objective responses were found in more than 25% of patients receiving oral etoposide, temozolomide, or vincristine/etoposide/cyclophosphamide regimens (20).

Figure 1. Effect of the treatment in patient 1. T1-weighted magnetic resonance imaging sequence with gadolinium of brain metastases (A) and the lesion of the conus medullaris (B) before and after 5 months of therapy.
Anaplastic ependymoma is a tumor characterized by VEGF production by tumor cells and vascular proliferation (21). As a consequence, Green et al. (12) reported a median time-to-progression of more than four months when ependymoma was treated with bevacizumab as second-line therapy. We hypothesized that we could obtain synergy between chemotherapy and antiangiogenic agents in order to treat anaplastic ependymoma. Metronomic cyclophosphamide and bevacizumab are well-known antiangiogenic agents (22, 23). Here we proposed to combine metronomic cyclophosphamide and bevacizumab as antiangiogenic agents, with the most effective chemotherapeutic agent (cisplatin). In these two patients we observed surprisingly prolonged radiological and clinical responses with moderate toxicities. This finding warrants further clinical trial to validate the efficacy of this combination.

Conflicts of Interest

The Authors declare no financial disclosure or conflicts of interest.

References


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