Response to trabectedin treatment in a highly pretreated patient with an advanced meningeal hemangiopericytoma

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Meningeal hemangiopericytoma is an uncommon and aggressive malignancy that, in contrast to meningiomas, shows a high propensity for local recurrence and the development of late extraneural metastases. The results of chemotherapy in advanced hemangiopericytoma have been disappointing, and they have been particularly poor in cases located in the meninges. We report a case of a heavily pretreated metastatic meningeal hemangiopericytoma in which fourth-line chemotherapy with trabectedin, a marine-derived antineoplastic agent effective in treating advanced soft tissue sarcomas, resulted in clinical benefit. *Anti-Cancer Drugs* **21:795–798**

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Introduction

Meningeal hemangiopericytoma (HPC) is an uncommon and aggressive malignancy that accounts for less than 1% of all central nervous system tumors [1]. In contrast to meningiomas, meningeal HPC shows a high propensity for local recurrence and the development of late extraneural metastases [1–4]. The mainstay of the treatment of HPCs, including meningeal HPC, is complete surgical resection [5,6], which has been identified as the most important factor for reducing recurrence [7]. Although not completely elucidated, it seems that adjuvant radiotherapy [1,3,4,8] may also have a favorable effect on prognosis. The results of chemotherapy in advanced HPC have been disappointing [6], and they have been particularly poor in cases located in the meninges [5]. More recently, antiangiogenic therapies using agents such as interferon-α [9–11], combination therapy with temozolomide and bevacizumab [12], sorafenib [13,14], and sunitinib [14,15] have shown promising results. However, there is still a need for new and more effective chemotherapeutic agents [5,6].

We report a case of a heavily pretreated metastatic meningeal HPC in which fourth-line chemotherapy with trabectedin, a marine-derived antineoplastic agent effective in treating advanced soft tissue sarcomas, resulted in clinical benefit.

Case report

In January 2002, a 32-year-old man was evaluated at another institution because of his complaints of a persistent and progressive occipital headache, with signs and symptoms of intracranial hypertension. He had a history of appendectomy 10 years ago and had no relevant family history. Computed tomography (CT) and MRI showed an expansive mass in the right cerebellar hemisphere (measuring 5–6 cm) involving the transverse sinus, tentorium, and occipital region (Fig. 1). The patient underwent complete tumor resection in February 2002, and histologic evaluation of the tumor showed a malignant HPC with small foci of necrosis, severe nuclear atypia, and five mitoses per 10 high-power fields (i.e. WHO grade III tumor) (Fig. 2). After surgery, the patient received radiation with 50 Gy in the tumor bed and the whole brain.

The patient was referred to our hospital in May 2002 for further follow-up and management. During a regular follow-up in June 2006, a thoracoabdominal CT scan showed multiple pulmonary nodules bilaterally and a hypodense nodule adjacent to the principal left pulmonary artery measuring 27.5 mm, all of which were suggestive of metastases. The MRI did not show local tumor recurrence. On account of the multiple and bilateral nature of the lesions, surgery was turned down, and the patient immediately underwent chemotherapy with ifosfamide at a dose of 2 g/m^2/day and adriamycin 20 g/m^2/day on days 1–3 every 3 weeks. After six cycles, a CT scan performed in October 2006 showed stable pulmonary lesions. However, in February 2007, a new CT scan showed further progression in the preexisting pulmonary lesions, a metastatic lesion on the right hepatic lobe, and another one in the left iliac fossa. Therefore, the patient initiated second-line chemotherapy with gemcitabine 1800 mg/m^2 infused over 3 h, followed by dacarbazine 500 mg/m^2 every 2 weeks, all as part of a clinical trial from the Spanish Group for Research on Sarcomas (GEIS) group [16]. In the first CT scan control (April 2007) after three cycles, the disease was stable, but in June 2007, after seven

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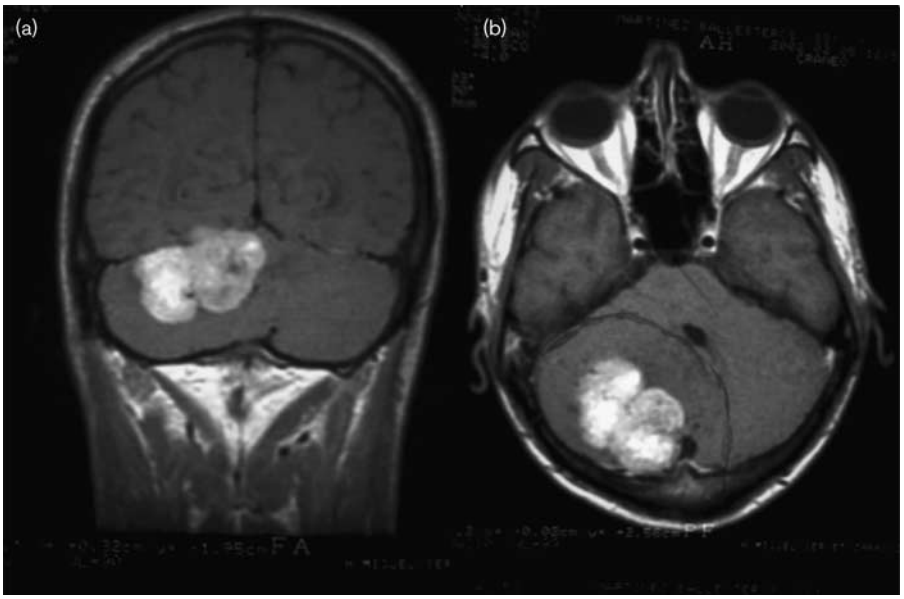
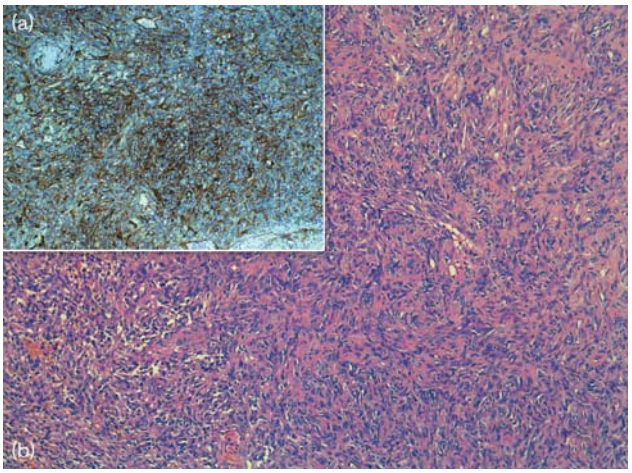
Fig. 1



Preoperative MRI scan (a: coronal; b: axial) showing an expansive mass in the right cerebellar hemisphere involving the transverse sinus, tentorium, and occipital region.

Fig. 2



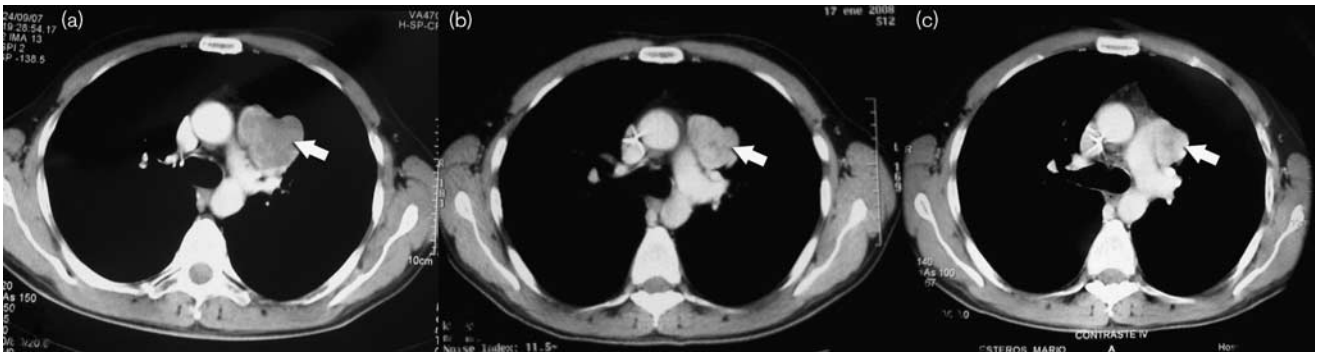
(a) Tumor specimen with elongated cells, with poorly defined cytoplasmic limits, densely packed and with an irregular orientation (hematoxylin-eosine $\times 10$); (b) immunohistochemistry: CD-34 positive cells.

treatment cycles, the CT scan showed disease progression in all the preexisting lesions. On the basis of earlier reported results [9,10], the patient then began receiving compassionate treatment with interferon-α at a dose of 10 000 IU given subcutaneously three times weekly. In September 2007, a follow-up CT scan showed further disease progression, finding an increase in the size of the mediastinal and liver masses and the development of a pelvic intraperitoneal metastasis (10.7 cm); the remaining metastatic lesions were stable.

On account of disease progression and a lack of other chemotherapeutic alternatives, in September 2007, we initiated a fourth-line treatment with trabectedin at a dose of 1.5 mg/m^2 every 21 days administered through outpatient 24-h infusion with a central venous access device. After the patient had completed three cycles, in January 2008, a CT scan showed a decrease in the size of the mediastinal mass enough for a partial response (Fig. 3) and disease stabilization of the other four metastatic sites; no new sites of the disease had developed. In April 2008, a CT scan repeated after another three cycles of trabectedin showed no changes. The patient received a total of eight cycles of trabectedin with side effects including grade 1 asthenia, grade 2 anemia, grade 3 thrombocytopenia, and grade 4 neutropenia. Hematological toxicities caused delays in five cycles and led to the use of the granulocyte colony-stimulating factor and erythropoietin after the third cycle. Although the patient did not require hospital admission for treatment of the toxicities and the disease was stable, the treatment with trabectedin was discontinued in July 2008 because of the lack of hematological recovery.

From July to September 2008, the patient received sunitinib at a dose of 50 mg/day for 4 weeks, followed by 2 weeks off. However, during this time he again showed disease progression. In October 2008, we initiated

Fig. 3



Computed tomography scan evaluation during trabectedin treatment on the mediastinal mass at (a), baseline; (b), after three cycles; and (c), after six cycles.

treatment with temozolomide 150 mg/m^2 orally on days 1–7 and bevacizumab 5 mg/kg on day 8, repeated at 14-day intervals. The patients showed a stable disease until a CT scan in October 2009 showed an increase in the size and number of the lung and liver metastases. Positron emission tomography imaging confirmed these findings. Treatment with trabectedin was restarted in November 2009 at a dose of 1.35 mg/m^2 every 21 days. However, the dose had to be reduced because of the lack of hematological recovery. In January 2010, a CT scan showed disease progression in the preexisting lesions and the development of two new renal lesions. Currently, the patient exhibits good general health, with an Eastern Cooperative Oncology Group performance status of 0–1, and is receiving bevacizumab combined with weekly paclitaxel.

Discussion

Meningeal HPCs have aggressive behavior [1] with higher local recurrence rates [17] and poorer responses to chemotherapy [5] as compared with HPCs from other locations. Once the tumor has recurred, the management of this malignancy constitutes a clinical challenge [6]. Although there are no clear clinical prognostic factors [6], the histopathology and tumor location of the patient we have described suggested a poor prognosis. The presence of cellular atypia, necrosis and a high number of mitoses tends to be associated with a higher incidence of local recurrence, distant metastases and decreased progression-free survival [6]. In addition, the tumor's location was infratentorial, and Guthrie *et al.* [1] have reported that regardless of the extent of the surgery, supratentorial tumors are associated with longer survival rates than tumors located on the posterior fossa or tentorium. The median survival rates after the recurrence of HPC in recent series have been found to be between 3.5 and 4.6 years [5,18]. However, the presence of extraneural metastases significantly reduces survival prospects [5]. The patient reported here, despite showing extraneural metastasis, is still alive 3.5 years after the first recurrence, suggesting that the new chemotherapies might help to prolong survival.

Although there is a lack of prospective data to guide evidence-based management of advanced meningeal HPC, the standard chemotherapy regimen, based on the findings of effectiveness in the limited body of published research on this topic, has been an anthracyclin-based regimen [19,20]. However, this regimen's results in terms of progression-free and overall survival are uncertain [6]. More recently, case series evaluating a sequential chemotherapeutic strategy that included interferon-α [11] and a retrospective comparison with the combined use of temozolomide and bevacizumab in a historical cohort [21] have reported that treatment with antiangiogenic agents seems to provide better results than the standard anthracyclin-based regimen of chemotherapy [11,21]. In this case, the best results, in terms of time to progression or to treatment failure, have been obtained with the fourth-line trabectedin and the sixth-line combination of temozolomide and bevacizumab.

We decided to use trabectedin after the failures of three chemotherapeutic regimens, including one using interferon-α, based on the efficacy showed by this drug in patients with heavily pretreated, advanced metastatic soft tissue sarcomas. Trabectedin (earlier known as ecteinascidin-743) is a marine-derived alkaloid that binds covalently to the DNA minor groove, interfering with transcriptional factors in a promoter-dependent way [22–24]. In addition, the lack of cumulative toxicity could make this drug adequate for prolonged treatment [25]. The 12 months that elapsed with stable disease and the partial response observed in one of the metastatic lesions suggest that trabectedin may be active in this type of tumor. It is true that the meaning of stable disease in tumors with slow growth rates, such as HPCs, is uncertain [26]. However, in our patient, progressive disease was clearly documented in the 3 months before initiating treatment with trabectedin, showing that this was not an

indolent outcome. Our claim about the activity of trabectedin in this case is reinforced by the presence of a partial response in one of the lesions with a fourth-line regimen and by the fact that the result obtained with trabectedin was better than the first-line combination of adriamycin and ifosfamide and two regimens subsequent to that. The fact that the RECIST response was detected in only one lesion is not surprising, because it is reported that a tumor's response to trabectedin does not always mean a volumetric decrease [27]. To our knowledge, this study is the first report on the activity of trabectedin in patients with HPC. We have conducted a literature search in PubMed for articles published up to April 2010 using 'hemangiopericytoma' or 'solitary fibrous tumor' as MeSH terms, in combination with 'trabectedin,' 'ET-743,' 'ecteinascidin,' or 'yondelis' as search terms in the article title or abstract. This literature search did not return any hits. However, in a very recent report on the use of antiangiogenic therapy in a patient with an advanced malignant HPC, an earlier treatment with second-line trabectedin chemotherapy is mentioned [14]. In that case, trabectedin was discontinued because of hepatic toxicity, but no other treatment details such as dosage or the number of cycles are provided [14]. In this case, we had to stop trabectedin because of the patient's lack of recovery from hematological toxicities (namely, grade 4 neutropenia and grade 3 thrombocytopenia). This finding is not unexpected, as the most common grade 3–4 hematological toxicities in phase II soft tissue sarcomas clinical trials were these side effects. However, these conditions were transient and resolved rapidly [28]. It seems that the severity of neutropenia depends on the trabectedin dose and the interdose interval [29].

The activity exhibited by trabectedin in this heavily pretreated patient with an advanced meningeal HPC is encouraging and supports the treatment's further use and study in this type of tumor.

Acknowledgement

There is no conflict of interest.

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