Treatment with the mTOR inhibitor temsirolimus in patients with malignant PEComa

Perivascular epithelioid cell tumors (PEComas) are rare mesenchymal tumors recently recognized as a distinct entity by the World Health Organization [1]. The natural history of these tumors is highly variable ranging from indolent benign lesions to lesions with an aggressive clinical course including distant metastases. No effective medical treatment has been reported for patients with advanced disease. We report here two cases of malignant PEComa successfully treated with the mammalian target of rapamycin (mTOR) inhibitor temsirolimus.

the cases

case 1

Patient 1 is a previously healthy 69-year-old woman who underwent resection of a uterine malignant PEComa in June 2008. A metastatic work-up including a thoracic, abdominal and pelvic computed tomography (CT) and a 2-[fluorine-18]fluoro-2-deoxy-D-glucose–positron emission tomography (FDG–PET) scan revealed a solitary hypermetabolic pulmonary nodule of 17 mm in the right upper lobe (Figure 1A). A biopsy of this nodule was done and confirmed its metastatic nature.

Figure 1. Objective metabolic response to temsirolimus of a malignant metastatic uterine PEComa (case 1). (A) Initial staging with a 2-[fluorine-18]fluoro-2-deoxy-D-glucose–positron emission tomography (FDG–PET)/computed tomography (CT) showing an hypermetabolic solitary pulmonary nodule of 17 mm in the right upper lobe (standardized uptake value (SUV) max of 3.5, mediastinal background (MB) 1.3 SUV). (B) Tumor response assessment by PET/CT after 1 month of treatment with temsirolimus. The large diameter of the lesion was reduced by 35% (11 mm) and the metabolic activity by 50% (SUV max 1.8, MB 1.1 SUV). (C) Tumor response assessment by PET/CT after 2 months of treatment with temsirolimus. Objective partial response was confirmed and no significant FDG uptake was found anymore in the residual lesion (activity inferior to the MB, SUV max of 1.3, MB 1.4 SUV).
Additional immunohistochemical revealed a strong expression of the phospho-ribosomal protein S6 (clone 91B2; Cell Signaling, Danvers, MA), both in the primary and the metastatic tumors (Figure 2). The patient began treatment with the mTOR inhibitor temsirolimus according to a planned schedule of 25 mg i.v. given on a weekly basis. A first tumor evaluation carried out at 1 month revealed a reduction by 35% of the large diameter of the lesion and by 50% of the metabolic activity (standardized uptake value max 1.8). At 2 months, a second PET/CT was carried out, and no significant uptake was found anymore in the residual lesion (Figure 1B and C). Temsirolimus was discontinued 1 month prior a right upper lobectomy which was carried out with the aim to obtain a complete remission. Histopathological examination of the surgical specimen revealed residual viable tumor cells with a mitotic activity reduced by 40% in comparison with the primary uterine tumor. Nine months after the diagnosis of the metastatic disease, the patient is well and free of disease. She is still receiving temsirolimus as a ‘maintenance’ treatment.

case 2
The second case is a 55-year-old woman who underwent resection of a uterine malignant PEComa in 1992. Cardiac and thoracic metastases were noted in March 2007 and all sites of disease were completely resected. The patient remained disease free until January 2008 when a follow-up CT scan revealed new liver lesions. She received first-line adriamycin–ifosfamide combined chemotherapy with stable disease being the best response noted. Subsequently, the patient received liver external beam radiotherapy combined with concomitant etoposide. A few months later, the patient experienced disease progression with detection of a new thoracic lesion. Additional immunohistochemical analysis revealed a strong expression of the phospho-ribosomal protein S6 both in the primary and the metastatic tumors. The patient began treatment with the mTOR inhibitor temsirolimus according to a planned schedule of 25 mg i.v. given on a weekly basis. The first tumor evaluation carried out after 8 weeks of treatment showed partial response (Figure 3), which was confirmed by a second tumor assessment. Unfortunately, temsirolimus had to be discontinued 22 weeks after its initiation because of disease progression. The patient is currently alive and treated with gemcitabine.

discussion
The World Health Organization defines PEComa as ‘a mesenchymal tumor composed of histologically and immunohistochemically distinctive perivascular epithelioid cells’ [1]. In 1996, the term PEComa was used for the first time to designate mesenchymal neoplasms containing epithelioid cells with a close association to vessel walls and immunophenotypic features of smooth muscle and melanocytic differentiation. In 2009, PEComas represent a group of ubiquitous visceral, soft tissue and bone neoplasms sharing morphological and immunohistochemical distinctive features including, at least conceptually, angiomyolipomas (AML), clear-cell ‘sugar’ tumor of the lung, lymphangioleiomyomatosis (LAM), clear-cell myomelanocytic tumor of the falciform ligament/ligamentum teres and unusual extrapolmonary clear-cell tumors. Some of these conditions such as angiomylipoma and LAM represent a subset of PEComas that are strongly associated with tuberous sclerosis complex (TSC) [2, 3].
The uterus is the most frequent site of origin for PEComas occurring outside the context of tuberous sclerosis [4]. Uterine PEComa can have a malignant behavior leading to distant metastases and death as expected with a high-grade sarcoma. Although definitive criteria for malignancy of PEComas are not yet established, tumor size >5 cm, infiltrative growth pattern, high nuclear grade, necrosis and mitotic activity >1/50 high

Figure 2. Activation of the mammalian target of rapamycin (mTOR) pathway in a malignant uterine perivascular epithelioid cell tumors (case 1). Immunohistochemistry analysis shows a strong cytoplasmic reactivity for the phospho-ribosomal protein S6, a crucial marker for the activity of the mTOR pathway.

Figure 3. Objective response to temsirolimus of a malignant metastatic uterine perivascular epithelioid cell tumor (case 2). (A) Initial staging with a thoracic computed tomography scan showing a right parietal metastasis. (B) Partial response observed after 8 weeks of treatment with temsirolimus.
power field have been associated with aggressive clinical behavior [5]. Tumors occurring in patients with TSC are caused by mutations in the TSC1 or TSC2 tumor suppressor genes [6, 7]. Normally, the cytoplasmic TSC1 and TSC2 proteins interact and inhibit mTOR activity. In the absence of a normally functioning TSC1–TSC2 complex, mTOR activity increases, leading to the development of tumors in various organ systems including the kidney, lung, brain and skin. TSC1/2 inactivation and m-TOR hyperactivation have also been demonstrated in non-TSC PEComas using immunohistochemical detection of the phospho-ribosomal protein S6, which is a crucial marker for the activity of the mTOR pathway [2, 3]. Altogether, these findings support inhibition of mTOR as a rational therapeutic target in tumors occurring in patients with TSC as well as in non-TSC PEComas. Recently, Bissler et al. [8] have reported promising results from the use of the mTOR inhibitor sirolimus on renal AML and on LAM associated with the TSC. To our knowledge, the two patients described in our report represent the first description of an mTOR inhibitor activity in malignant PEComa. The significant response observed in these patients indicates that the activity of temsirolimus and other mTOR inhibitors in patients with PEComas related or not with TSC warrants further study.

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