Treatment of Advanced Malignant Uterine Perivascular Epithelioid Cell Tumor with mTOR Inhibitors: Single-institution Experience and Review of the Literature

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Abstract. Uterine perivascular epithelioid cell tumors (PEComas) are rare mesenchymal tumors. Many have malignant behavior, and no successful treatment strategy has been established. Identification of mutations in the tuberous sclerosis 1 (TSC1) and TSC2 genes producing constitutive activation of the mammalian target of rapamycin (mTOR) pathway presents an opportunity for targeted therapy. Patients with advanced malignant uterine PEComa treated with mTOR inhibitors were identified and records were retrospectively reviewed for treatment response based on radiographic assessment. Three patients with advanced uterine PEComas underwent debulking surgery followed by mTOR inhibitor therapy; two had a complete response to therapy and disease in one patient progressed. Conclusion: Given the absence of effective therapies for malignant uterine PEComas, targeting the mTOR pathway is a logical strategy to pursue given the known pathobiology involving the Tuberous Sclerosis complex. Treatment of malignant uterine PEComas with mTOR inhibitors was effective in two out of three patients after surgical resection, with durable response.

Perivascular epithelioid cell tumors (PEComas) are a relatively recently described medical entity, first recognized as a distinct group of tumors with specific morphologic and immunohistochemical characteristics by the World Health Organization in 2002 (1). They have myomelanocytic differentiation, epithelioid morphology, and a propensity for perivascular distribution. PEComas demonstrate smooth muscle markers (smooth muscle actin), melanocytic markers (human melanoma black 45 (HMB45), melan-A), and cathepsin K (2). These tumors lack expression of protein S-100, cytokeratin and desmin, which differentiates them from melanomas, clear-cell sarcomas and smooth-muscle tumors (1-6). PEComas are mesenchymal neoplasms belonging to a group of rare tumors including angiomyolipoma (AML), clear-cell sugar tumor, and lymphangioleiomyomatosis (LAM). The uterus is the most commonly reported site of PEComa-Not Otherwise Specified, comprising 38/100 reported cases in this group (4).

The clinical behavior of uterine PEComas in the literature is varied and ranges from benign, through uncertain malignant potential, to aggressive malignant behavior with a propensity for metastasis. Pathological features associated with aggressive, malignant behavior include tumor size >5 cm, coagulative necrosis, high mitotic activity (>1/10 high-power fields), cytologic atypia, lymphovascular invasion, and infiltrativeness (7). Tumors in the PEComa group are rare and usually sporadic. However, they can be associated with tuberous-sclerosis complex (TSC), and both sporadic and TSC-related cases demonstrate similar genetic alterations of the TSC1 or TSC2 locus (8, 9). The TSC1 and TSC2 gene products form a complex which negatively regulates mammalian target of rapamycin complex 1 (mTORC1) and therefore PEComas as well as LAM and AML, have constitutive activation of the mTOR pathway. Given the poor prognosis of malignant PEComas and the lack of effective therapies, there is increasing research into targeting molecular pathways as treatment alternatives. Recently, a number of reports have described the use of sirolimus, a drug targeting the mTOR pathway, to treat several tumor types.
including AML, LAM and PEComas (9-11). The response in these patients is encouraging and warrants further investigation into the use of mTOR inhibitors in TSC-associated tumors. Here we report our institution’s experience with advanced uterine PEComas treated with mTOR inhibitors.

Patients diagnosed with advanced malignant uterine PEComas treated with mTOR inhibitors were retrospectively identified and records reviewed on an active protocol (IRB 7419). Three patients with advanced uterine PEComas underwent debulking surgery followed by mTOR inhibitor therapy and met the inclusion criteria (pathological diagnosis of malignant uterine PEComa; advanced disease at time of presentation; treatment with an mTOR inhibitor); two had a complete response to therapy and disease in one patient progressed. These cases are described below.

Case Reports

Patient 1 is a 30-year-old individual with a past medical history of tuberous sclerosis who presented to a Cleveland Clinic satellite hospital in October 2012 with worsening abdominal pain. She was found to have an acute abdomen with profound anemia (hemoglobin 4.4 mg/dl) and a 26.85×15.9×29.2 cm complex pelvic mass on computed tomographic (CT) scan. The patient was given fluid resuscitation, transfused multiple units of packed red blood cells and underwent emergency exploratory laparotomy, total abdominal hysterectomy, L salpingo-oophorectomy, omentectomy, and mesenteric resection by a staff Gynecologic Oncologist. Findings at the time of surgery included a large mass originating from the left side of the uterus and a 4000 cc hemoperitoneum. Pathology revealed the mass to be consistent with a malignant PEComa. Post-operatively she was transferred to the Intensive Care Unit for stabilization and was discharged on postoperative day 5.

The patient was started on gemcitabine (900 mg/m² day 1 and 8 every 3 weeks) and docetaxel (100 mg/m² on day 8 every 3 weeks) for three cycles; however, her disease progressed with suspected bone metastases and therapy was changed to temsirolimus 25 mg weekly. She responded well initially; however, after five cycles she developed a large pelvic hematoma. Imaging revealed a pelvic mass separate from the hematoma, therefore Medical Oncology recommended changing therapy to the closely related mTOR inhibitor sirolimus. She was treated with a 6 mg loading dose followed by 3 mg daily. The pelvic mass decreased on imaging and as of October 2015, there had been no signs of progression or metastatic disease, 36 months from her original presentation.

Patient 2 is a 43-year-old individual who presented to a hospital in Saudi Arabia in June 2012 with severe abdominal pain and syncope. She had an acute abdomen so an emergency exploratory laparotomy was performed with resection of extensive tumor. The patient required urgent blood transfusion for significant hemoperitoneum, requiring 8 units packed red blood cells and 8 units fresh frozen plasma. She remained in the Intensive Care Unit for 3 days with progressive improvement and was discharged in a stable condition. Histopathology showed a high-grade endometrial stromal sarcoma. Chemotherapy was initiated with carboplatin and paclitaxel for three cycles in Saudi Arabia, and subsequently the patient sought a second opinion at our Institution which led to transfer of care after the third cycle. Imaging in January 2013 demonstrated a mass superior and left of the vaginal cuff extending into the left pelvis. This mass appeared unchanged compared to the prior imaging the patient had brought with her and was thought to represent postoperative changes. Chest imaging revealed no evidence of metastasis. The patient was continued on her fourth of an intended six cycles of carboplatin and paclitaxel. Pathology review at our institution demonstrated an extensively infiltrating malignant PEComa of the endometrium and myometrium involving the omentum, transverse colon, and segmental excisions. Her therapy was therefore switched to temsirolimus at 25 mg weekly. In June 2013, after 4 months of treatment, CT imaging of the chest, abdomen, and pelvis revealed no evidence of disease. There was no sign of recurrence at 12 months from completion of treatment, and the patient subsequently returned to Saudi Arabia.

Patient 3 is a 64-year-old female who underwent a laparoscopic hysterectomy and bilateral salpingo-oophorectomy with morcellation in October 2013. Pathology demonstrated a uterine leiomyosarcoma, and she was treated with three cycles of gemcitabine (900 mg/m² day 1 and 8 every 3 weeks) and docetaxel (100 mg/m² day 8 every 3 weeks). At that time positron-emission tomography CT was negative and therapy was discontinued. The patient experienced recurrence in August 2014 with multiple abdominal nodules. Pathology review of the original specimen at our hospital demonstrated architecture and immunophenotype consistent with a malignant uterine PEComa. In September 2014, she underwent exploratory laparotomy with tumor cytoreduction to microscopic residual disease, including ileal and rectosigmoid resections. Pathology was consistent with recurrent malignant PEComa. The patient was started on 25 mg of temsirolimus weekly from 14th October 2014 until 13th January 2015, and imaging after 3 months of treatment revealed interval progression of disease with enlarging pelvic masses, an enlarged para-aortic lymph node, and several indeterminant lung nodules suspicious for metastases. Temsirolimus was therefore discontinued. In February 2015, the patient developed a malignant bowel obstruction that failed conservative management, and she subsequently died in March 2015.
Discussion

Most patients with aggressive PEComas and extensive dissemination have a uniformly poor prognosis. Current chemotherapy strategies have not been successful in advanced disease, and recent focus has been drawn to targeting the mTOR pathway, which is up-regulated in PEComas. There are several reports in the medical literature describing a total of seven patients with uterine or 'gynecologic' PEComas who received treatment with mTOR inhibitors, with varying degrees of success [50%-100% response rates (8-12)]. Given this robust response and the plausible theoretical basis behind it, we proceeded to manage three cases of advanced PEComas with mTOR inhibitors. Two out of three patients had a significant and prolonged response to treatment with mTOR inhibitors. All patients had advanced disease at the time of presentation to our service, two of which led to acute, life-threatening illness. All three patients underwent extensive debulking surgery and all were treated with mTOR inhibitors; this treatment strategy was both well tolerated and to date has been successful in two out of the three patients with no sign of recurrence or progression. Patient 3, whose disease progressed, had a tumor lacking smooth muscle actin or desmin positivity, which has been noted in previous studies in PEComas with a transcription factor binding to IGH enhancer 3 (TFE3) fusion gene product instead of mTOR pathway alterations (13), and this may explain the lack of response to temsirolimus. Additionally, approximately 75% of sporadic PEComas have alterations in TORC2, which in renal cell carcinomas is relatively more resistant to mTOR inhibitors (14, 15). Testing for the TFE3 fusion gene product (Xp11) should be considered in patients with malignant uterine PEComas, as combination treatment with vascular endomethial growth factor- or phosphatidylinositol-3-kinase-directed biological therapies may be more effective in this group.

Notably, patient 1 was treated with temsirolimus and responded, and when her disease progressed, therapy was switched to sirolimus, with a complete response and the patient remains disease-free. As far as we are aware, this is the first report of a patient with progression of PEComa on therapy with mTOR inhibitor which was successfully rescued with another mTOR inhibitor. To date in literature, treatments of cases with mTOR inhibitors which subsequently progressed were changed to another class of chemotherapy or treatment was stopped altogether. Although it is possible that PEComas develop dependence on alternative pathways for tumorigenesis, the fact that they often demonstrate mutations in the mTOR pathway make it worth considering a trial of an alternative mTOR inhibitor. Currently, post-operative treatment of PEComas with mTOR inhibitors is still preliminary and is limited to a few reports. We suggest that prospective cooperative trials, as well as further molecular profiling, including of TFE3 fusion and mTOR pathway genes, are needed to more fully investigate the clinical benefit of this strategy in patients with malignant uterine PEComas, which has the potential to significantly impact the prognosis of such patients.

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References

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