Teaching Case

Molecularly Targeted Radiation Therapy Using mTOR Inhibition for the Management of Malignant Perivascular Epithelioid Cell Tumor (PEComa): A Case Report and Review

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Introduction

Malignant perivascular epithelioid cell tumor (PEComa) is a rare and aggressive mesenchymal tumor that most frequently develops within the gastrointestinal tract or pelvis and less commonly in the lung.1 Activation of the mammalian target of rapamycin (mTOR) signaling pathway, typically as a result of mutations or deletions in the tuberous sclerosis genes TSC1 or TSC2, has been implicated as a key molecular driver of PEComa.2 Limited retrospective studies examining the mTOR inhibitor sirolimus have found that it is generally well tolerated and usually associated with radiographic responses.3 Although there is some data on the efficacy and safety of co-administering radiation therapy with mTOR inhibitors across some cancer types,4,5 there is no existing literature on concurrent administration for the management of PEComa. This report describes the clinical course of a patient with PEComa of the lung who received palliative radiation therapy for bulky intrathoracic disease while concurrently receiving sirolimus.

Case Presentation

The patient is a 67-year-old gentleman with a past medical history otherwise remarkable for nonalcoholic steatohepatitis complicated by hepatocellular carcinoma status post autologous liver transplantation. The patient was in his usual state of health until he developed a progressive cough and dyspnea on exertion. The patient received a plain film chest radiograph demonstrating a left upper lobe mass along the lateral left midlung measuring 5.8 × 5.0 cm; this mass was newly developed since chest imaging obtained 1 year earlier. Follow-up imaging with computed tomography (CT) of the chest with contrast was obtained. This scan redemonstrated the left upper lobe mass with additional identification of satellite nodules in the left upper lobe, mediastinal and hilar lymphadenopathy, a right chest wall nodule, a right adrenal nodule, and a trace left pleural effusion. A whole body positron emission tomography-CT study was performed and showed associated hypermetabolic activity at the left upper lobe mass, mediastinal nodes, and right adrenal nodule. Also noted were fluorodeoxyglucose avid soft tissue nodules in the right lateral abdominal wall and left gluteal area, both suspicious for additional sites of disease.

Further workup included endobronchial ultrasound-guided biopsy with pathology demonstrating a high-grade malignancy with abundant necrosis, with insufﬁcient viable tissue for performance of molecular genetics analysis. The patient subsequently received left video-assisted
Thoracoscopic surgery. Pathology again demonstrated malignancy with abundant necrosis, with immunostaining demonstrating expression of TFE3, Melan A, and vimentin. Epithelial markers, neuroendocrine, melanoma, and neuroectodermal markers were negative. Cytogenetic study demonstrated that 44% of tumor cells gained 1 copy of TFE3, but no TFE3 rearrangement was detected. Molecular genetics analysis was performed and showed a nonsense mutation and loss of heterozygosity in TSC2, a missense mutation in TP53, and a TERT promoter mutation. On the basis of the immunostaining and next-generation sequencing findings (loss of TSC2), the patient was diagnosed with malignant PEComa of the left lung. By American Joint Committee on Cancer eighth edition lung cancer staging, the clinical stage was T4N2M1c; group IVB. A medical oncologist evaluated the patient and initiated sirolimus at 2 mg daily.

The patient was referred to the radiation oncology clinic for further evaluation and consideration of palliative radiation therapy in alleviating his progressive dyspnea and cough. He was initially planned to receive 36 Gy in 12 fractions to his left upper lobe mass and hilar/mediastinal disease burden using a 3-field beam arrangement (anteroposterior, postero-anterior, and left lateral fields) with 10 MV photons (Fig 1). He received daily cone beam CT throughout treatment for daily image guidance and received 8 treatment fractions (total dose of 24 Gy). A significant reduction in tumor volume was noted on cone beam CT review. The patient received repeat CT simulation with replanning to account for this reduction in tumor volume for delivery of the final 4 fractions of treatment (Fig 1). The patient’s initially contoured gross tumor volume was measured to be 470.5 cm³, and his gross tumor volume during replanning had decreased by 43% to 268.6 cm³.

The patient tolerated his course of radiation therapy well with grade 1 in-field dermatitis managed with a topical moisturizing and anti-inflammatory skin care regimen and grade 2 esophagitis noted at his final treatment fraction managed with a 1:1:1 solution of Benadryl, Maalox, and xylocaine (Magic Mouthwash) and a proton pump inhibitor. At 1-month posttreatment follow-up, he was found to be doing well overall, with complete resolution of all symptoms noted during his treatment course. He was re-evaluated again at 4 months posttreatment and noted an intermittent cough without evidence of low-grade fever or dyspnea. The patient’s imaging demonstrated excellent radiographic response to treatment with

**Figure 1** Initial treatment plan (1) for palliative radiation therapy of left lung tumor burden using a 3-field technique compared with replan for final 4 fractions of treatment (2) after tumor response during treatment, shown in the axial (a) and coronal (b) views.
significant reduction in the size of the intrathoracic disease at his initial posttreatment follow-up, with further resolution of intrathoracic disease noted on imaging obtained 4 months after treatment (Fig 2). Additionally, there was no radiographic evidence of pneumonitis noted at 4 months (Fig 2). After radiation therapy, the patient continued on sirolimus; although his intrathoracic disease responded dramatically to the combination of radiation therapy with sirolimus, the patient was noted to have a mixed response elsewhere (Fig 2), with resolution of his right adrenal metastasis and left gluteal metastasis noted at 1-month postradiation but development of a new splenic lesion and new right gluteal metastasis noted at 4 months postradiation.

Discussion

There is not much known about the efficacy and safety of mTOR inhibition with concurrent radiation therapy administration for target volumes situated within the lung, and there are currently no existing data to guide the utilization of radiation therapy for the management of PEComa. Sirolimus has increasingly been used as the drug of choice for this disease. A retrospective series of 10 patients published by the Royal Marsden Hospital found that 6 patients achieved response or stable disease by Response Evaluation Criteria in Solid Tumors. A recently opened prospective study assessing the safety and efficacy of albumin-bound sirolimus for malignant PEComa analyzed 34 patients and found a partial response rate of 42%, with 35% of patients demonstrating stable disease and 69% of partial responses achieved within the first 6 weeks following treatment. The most commonly identified treatment-related adverse effects of any grade were mucositis, fatigue, nausea, weight loss, diarrhea, and hematologic side effects of anemia and thrombocytopenia. The rate of grade 1 to 2 pneumonitis was 15% and no grade 4 events were observed.

As it relates to the safety and efficacy of the concurrent administration of radiation therapy to the lung with mTOR inhibitors, there is only limited retrospective data to currently guide management on. mTOR signaling has been implicated as a mechanism of radiation resistance in

Figure 2  Disease noted at the time of diagnosis (1a: intrathoracic, 2a: intra-abdominal [right adrenal metastasis], 3a: pelvic, left gluteal metastasis), at 1-month follow-up (1b: interval improvement of intrathoracic disease, 2b: resolution of right adrenal metastasis, 3b: resolution of left gluteal metastasis), and at 4-months follow-up (1c: complete resolution of irradiated mass, 2c: development of new splenic metastasis, 3c: development of new right gluteal metastasis) demonstrating durable in-field response to irradiation with sirolimus with mixed response systemically overall.
preclinical models. Therefore, the combined use of radiation and sirolimus in PEComa is predicted to improve treatment responses. In attempts to advance mTOR inhibitors towards efficacy testing, a phase I trial assessing sirolimus in combination with cisplatin and concurrent radiation therapy for management of non-small cell lung cancer evaluated 7 patients receiving 3-dimensional conformal radiation therapy with 60 Gy in 30 fractions administered concurrently with weekly intravenous cisplatin 25 mg/m² and escalating doses of oral sirolimus. None of the 4 patients treated with 2 mg daily sirolimus developed dose-limiting toxicities. Moreover, in preclinical, murine experiments the administration of concurrent sirolimus with radiation was not associated with an increased incidence of morbidity or mortality.

However, although these preliminary studies regarding the administration of radiation therapy concurrently with sirolimus provide some indications of tolerability, there remains concerns regarding the possible potentiation of adverse effects. For example, a case published by Manyam et al described the unfortunate situation of a 71-year-old gentleman receiving sirolimus concurrently with radiation therapy to the head and neck who experienced grade 4 esophagitis and mucositis after administration of 24 Gy in 12 fractions to the bilateral neck and facial lymph nodes. This report describes the administration of palliative radiation therapy of 36 Gy in 12 fractions for a patient receiving sirolimus 2 mg daily in the treatment of metastatic malignant PEComa of suspected pulmonary mesenchymal origin. To the authors’ knowledge, there is no existing literature on the utilization of concurrent radiation therapy with sirolimus for management of malignant PEComa, and there is minimal published experience limited to case reports on the utilization of radiation therapy alone. An excellent clinical and radiographic response was noted 1.5 weeks into treatment (Fig 1), 1 month after treatment (Fig 2), and 4 months after treatment (Fig 2), demonstrating radiotherapeutic efficacy with the concurrent delivery of sirolimus. Giving a significant palliative dose to the patient’s intrathoracic disease resulted in an excellent response, whereas systemic therapy yielded a mixed response in the patient’s distant sites of disease, with interval resolution of initially noted right adrenal and left gluteal lesions after 1 month of sirolimus and interval development of new splenic and right gluteal lesions after 4 months of sirolimus (Fig 2). The patient did not develop any symptoms of pneumonitis either during treatment or in the 5 months he was followed thereafter. Further study will be needed to determine the therapeutic efficacy of radiation therapy with sirolimus for malignant PEComa, and the potential interactive effects of this treatment strategy should be weighed against the potential for adverse events.

Conclusions

The present report describes the clinical scenario of a 67-year-old gentleman with history of metastatic malignant PEComa of the pulmonary mesenchyme with a confirmed TSC2 loss who received sirolimus 2 mg daily and palliative radiation therapy of 36 Gy in 12 fractions to the chest. The patient demonstrated a significant clinical and radiographic response early in his treatment course requiring replanning for the delivery of his final 4 fractions of treatment to minimize normal tissue toxicity. The patient’s treatment course was remarkable for grade 1 in-field dermatitis and grade 2 esophagitis, with resolution of all symptoms noted at his first posttreatment visit. Post-treatment imaging demonstrated excellent response to all sites of disease. Future studies will be needed to determine the role of mTOR inhibition in potentiating the effectiveness of radiation therapy while balancing concern for normal tissue toxicity in the setting of concurrent administration.

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