CLINICAL VIGNETTE

The Role of Immunotherapy in Metastatic Endometrial Cancer

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Case Report

A 56-year-old female with a history of stage Ib endometrial cancer status post total abdominal hysterectomy and bilateral salpingo oophorectomy followed by adjuvant radiation presented with new metastatic disease. Approximately six months after completing radiation the patient developed mild abdominal pain. Physical exam demonstrated hepatomegaly and mild tenderness to palpation over the right upper quadrant and right flank. Imaging revealed a soft tissue mass surrounding the right distal ureter with hydronephrosis, a 9.3 cm liver mass, and multiple serosal metastases in the abdomen and pelvis up to 5.3 cm in size. Biopsy of the liver lesion revealed an ER positive, high microsatellite instability (MSI), metastatic adenocarcinoma consistent with endometrial carcinoma. She underwent nephrostomy tube placement for right hydronephrosis. The patient declined chemotherapy and was treated with pembrolizumab 200 mg every 3 weeks, an anti-programmed cell death-1 (PD-1) humanized monoclonal antibody. She tolerated immunotherapy well with minimal side effects that included a grade 1 rash on bilateral hands and arms that completely resolved between treatments. Repeat imaging after 4 cycles of immunotherapy showed marked response with the liver lesion measuring 4.1 cm and the largest serosal lesion measuring 1.2 cm. Repeat imaging after cycle 8 revealed continued response with the liver lesion measuring 2.3 cm and resolution of the serosal implants. Finally, imaging after 10 months of treatment demonstrated only a 1.1 cm liver lesion and no other sites of disease. Treatment was changed to pembrolizumab 400 mg every 6 weeks given new FDA approval in the setting of COVID-19.

Discussion

Endometrial cancer is the fourth most common malignancy in women and the most common gynecologic cancer in developed countries with 65,620 estimated new cases in the United States in 2020.[1] The most common presenting symptom is abnormal uterine bleeding. As such, most women are diagnosed with early stage disease. However, a subset of women are diagnosed with advanced disease or develop distant recurrence after initial treatment which confers a poor prognosis. Thus, improved treatment options are needed.

As in other types of cancer, assessing for microsatellite instability (MSI) or mismatch repair deficiency (MMRd) has become increasingly important in the evaluation of endometrial cancer. Moreover, in 2017 the FDA granted approval for pembrolizumab 200 mg every 3 weeks to include tumors with MSI-high or MMRd that have not responded to prior therapy.[2] Importantly, MMRd is common in endometrial cancers. It is estimated that approximately 30% of endometrial cancers have microsatellite instability[3] making immunotherapies such as pembrolizumab an attractive treatment option.

Chemotherapy remains first line therapy for metastatic endometrial cancer and pembrolizumab is approved as second line therapy for patients with MSI-high or MMRd tumors. KEYNOTE-158, a phase II basket study, investigated the effect of pembrolizumab 200 mg every 3 weeks in multiple tumor types, including 49 patients with endometrial cancer who progressed on first line therapy. Results showed an overall response rate of 57.1% with 8 patients achieving complete response and 20 patients achieving partial response. Median PFS was 25.7 months and median overall survival was not reached.[4] The FDA granted accelerated approval of a new dosing regimen of pembrolizumab 400 mg every 6 weeks in 2020.[5] Overall, pembrolizumab is tolerated well, but is associated with diarrhea, rash, hyperthyroidism, pneumonitis, and other less common inflammatory events.

For patient without MSI-high or MMRd tumors, the FDA has approved pembrolizumab plus lenvatinib.[5] This was based on KEYNOTE-146, which included 94 patients with metastatic endometrial cancer that were not MSI-H or dMMR and progressed on prior therapy. ORR was 37.2%, with a complete response rate of 7.4% and a partial response rate of 29.8%.[6] Treatment-related adverse events are common with the combination of pembrolizumab plus lenvatinib. The most common treatment-related adverse events include hypertension, diarrhea, decreased appetite, fatigue, hypothyroidism, nausea, stomatitis, arthralgia, palmar-plantar erythrodysesthesia syndrome, proteinuria, and headache.

It is recommended that routine immunohistochemistry and molecular testing should be performed on all recurrent and metastatic endometrial cancers in order to identify microsatellite instability and mismatch repair deficiency that may indicate improved response to immunotherapy.

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