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Gynecologic Cancers (LA Cantrell, Section Editor)

Anti-programmed Death-1 Immunotherapy for Endometrial Cancer with Microsatellite Instability–High Tumors

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Opinion statement

Among gynecologic malignancies, mismatch repair–deficient endometrial cancers show the greatest response to anti-programmed cell death-1 (PD-1) antibodies, such as pembrolizumab. Routine immunohistochemical (IHC) and molecular testing should be performed on all endometrial cancers at the time of diagnosis in order to identify endometrial cancers with mismatch repair deficiency that may show improved response to anti-PD-1 therapy in the progressive or metastatic setting. Institutional effort to enroll patients in clinical trials investigating the use of immune checkpoint inhibitors in endometrial cancer should be prioritized.

Introduction

A growing body of evidence over the past several years demonstrates the important role the immune system plays in carcinogenesis and cancer metastases. Consequently, several cancer therapeutics targeting aspects of the immune pathway have been developed. These include immune checkpoint

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inhibitors, vaccine therapies, genetically altered T cell therapy, and immunomodulators. Medications targeting immune checkpoint inhibitor programmed cell death ligand (PD-L1), such as pembrolizumab, have shown activity against gynecologic malignancies including ovarian, cervical, and endometrial cancer [1]. In 2018, the FDA expanded approval for pembrolizumab to include tumors with microsatellite instability or mismatch repair deficiency that have not responded to prior therapy [2••]. This was the first disease-site agnostic FDA approval for a cancer therapeutic, ushering in a new era of therapy focused on tumor features rather than organ of origin. Studies demonstrate mismatch repair–deficient/microsatellite instability—high endometrial cancer shows the greatest response to PD-L1 inhibition among gynecologic malignancies. This has led to increased attention to consideration of treatment of progressive or recurrent endometrial cancer with pembrolizumab.

Programmed cell death-1 inhibition

Activated immune cells, such as cytotoxic T cells (CTLs), are present in the tumor microenvironment but are often not active enough to completely eliminate a tumor. Additionally, cytotoxic T cells have their activity attenuated by tumor-activated immunosuppression [3]. One immunotherapeutic strategy employs antibodies targeted to specific molecules on T cells, enhancing their activity against tumor cells. This class of immunotherapy is referred to as immune checkpoint inhibition (ICI) and includes anti-programmed cell death-1 (anti-PD-1) antibodies [4]. Treatment with ICI encompasses a variety of responses including baseline tumor regression, stability followed by a slow decline in tumor burden, initial increase in tumor burden followed by a delayed response, or response after the appearance of new tumor [5].

Programmed death-1 (PD-1) is a receptor found on immune cells, including CTLs. Tumor cells, as part of their immune escape mechanism, express programmed death ligand-1 (PD-L1) or programmed death ligand-2 (PD-L2). When PD-L1 on tumor cells binds to PD-1 on CTLs, the anti-tumor response of CTLs is suppressed [6]. Pembrolizumab (Keytruda©) is an anti-PD-1 antibody that blocks the interaction between the PD-1 receptor on T cells and programmed cell death ligand-1 (PD-L1) on tumor cells, enhancing T cell activity against the tumor and leading to the activation of CTLs.

Pembrolizumab was first studied as a monotherapy in non-small cell lung cancer (NSCLC) and melanoma. It demonstrated acceptable tolerability with response rates of 20–30% [7, 8]. Following its demonstrated activity in these tumor types, immune checkpoint inhibition was studied in other cancer types and has demonstrated activity in renal, urothelial, breast, and gynecologic malignancies [9–13]. The use of immune checkpoint inhibition in gynecologic malignancy is less common, in part due to a lack of reliable biomarkers, including PD-L1 expression, associated with response to treatment with PD-1 inhibitors [14]. The recent discovery of mismatch repair deficiency (dMMR) and microsatellite instability (MSI) prediction of PD-1 blockade response offers the most promising evidence of PD-1 inhibition activity in gynecologic malignancy, particularly given the relatively high percentage of mismatch repair deficiency present in endometrial cancers.

Microsatellite instability as a biomarker for response to PD-1 inhibition

Non-gynecologic cancers

Microsatellite instability (MSI) arises from germline mutations in mismatch repair (MMR) proteins (MSH6, MSH2, MLH1, PMS2) or somatic hypermethylation of the MLH1 promoter. Microsatellites, stretches of DNA with repetitive sequences of nucleotides, are particularly susceptible to errors when MMR gene function is deficient or compromised. Cancer cells with dMMR exhibit increased number of microsatellite nucleotide repeats, or MSI [15]. Tumors are classified as MSI-high (MSI-H) if two or more of the five markers of the panel show instability or more than 30% of markers show instability in other panels. Tumors are classified as MSI-low (MSI-L) if one of the five markers of the panel shows instability or fewer than 30% of markers show instability in other panels. Tumors are MSI-stable if no markers show instability [16, 17]

The genomes of dMMR tumors include numerous somatic mutations regardless of organ or tumor type. Studies have demonstrated a correlation between mutation burden and response to PD-1 blockade, specifically among dMMR colorectal cancers [18, 19]. In a phase II trial published in 2015, Le et al. investigated the response rate and progression-free survival of patients with MMR-deficient colorectal cancer, MMR-proficient colorectal cancer, and MMR-deficient non-colorectal cancer. The MMR-deficient non-colorectal cancer group included two MMR-deficient endometrial cancer patients. They found the immune-related objective response rate and progression-free survival were higher in patients with MMR-deficient colorectal cancer compared with those with MMR-proficient colorectal cancer (40% vs. 0%, 78% vs. 11%, respectively). Patients with MMR-deficient non-colorectal cancer, including the two endometrial cancer patients, had similar responses to those with MMR-deficient colorectal cancer. A majority of those with response to pembrolizumab experienced a progression-free survival of greater than 6 months (more than 78% of responders). They also demonstrated somatic mutation load was associated with longer progression-free survival among the same cohort. In 2017, Overman et al. reported more than 30% of patients with metastatic or recurrent dMMR/microsatellite instability–high (MSI-H) colorectal cancer achieved response when treated with nivolumab, a PD-1 immune checkpoint inhibitor.

Endometrial cancer

Mismatch repair deficiency (dMMR) is common in endometrial cancers. It is estimated approximately 30–40% of endometrioid endometrial cancers have microsatellite instability (MSI) [20]. Routine immunohistochemical (IHC) testing for MMR has been widely adopted into routine practice for endometrial cancer to improve screening for Lynch syndrome and can also be used to identify MSI [21, 22]. The integrated genomic characterization of endometrial carcinoma identified four genomic classifications for endometrial cancers: (1) microsatellite instability hypermutated, (2) copy number low, (3) copy number high, (4) polymerase e (POLE) ultramutated [20]. Microsatellite instability hypermutated, also known as MSI-high (MSI-H), endometrial carcinomas are

highly associated with Lynch syndrome and may also be more susceptible to PD-1 blockade [23].

Based on the response seen in dMMR colorectal cancers, the study of the efficacy of PD-1 blockade was further expanded to other dMMR tumor types, including endometrial cancer [2••]. Le et al. prospectively enrolled 86 patients with 12 different types of tumors with dMMR to receive PD-1 blockade with pembrolizumab [2••]. They reported 53% of patients had a response to therapy, including complete response in 21% of patients. They also reported endometrial cancer had the highest proportion of mismatch repair–deficient tumors among all tumor subtypes tested. Endometrial cancer patients made up approximately 20% of patients included in the study and were found to have the highest percentage of tumors with dMMR (17%).

Yamashita et al. investigated the relationship between MSI and PD-1/PD-L1 expression among 149 patients with endometrial cancer. They reported approximately 28% of tumors showed loss of MMR and there was no association between loss of MMR and age, cancer stage, pelvic node metastases, or depth of myometrial invasion. Those with loss of MMR had significantly higher amounts of cytotoxic T cells (CD8+) and PD-1/PD-L1 expression in their tumors compared with those without loss of MMR. These results further support the use of dMMR/MSI as a predictor for response to PD-1 blockade in endometrial cancer [24].

Additional data regarding the use of pembrolizumab in endometrial cancer was published in a subset report of the KEYNOTE-028 study, a multi-cohort phase Ib study evaluating the safety and efficacy of pembrolizumab in patients with PD-L1-positive advanced solid tumors [25•]. Endometrial cancer patients (n=24) made up a small subset of patients in the KEYNOTE-028 study. Pembrolizumab was administered at 10 mg/kg every 2 weeks until disease progression, unacceptable toxicity, or a maximum of 24 months. Pembrolizumab showed activity in previously treated endometrial cancer patients with advanced PD-L1-positive endometrial cancers. Three patients had responses to pembrolizumab with response duration as long as 65 weeks (data collection ongoing). Three additional patients had stable disease. Among patients with tumor samples evaluable for MSI status (19/24), one patient had MSI-H status and 18 patients had non-MSI-high status. The one patient with MSI-H status had the best response of progressive disease. Treatment-related adverse events occurred in 13 out of 24 patients (54.2%). Fatigue, pruritus, and pyrexia were the most common symptoms described. No patients experienced a grade 4 or 5 adverse event.

Preliminary data from an open-label, phase 2, two-cohort, two-stage trial of the use of avelumab, a PD-L1 inhibitor, in endometrial cancer was published as an abstract this year. The two cohorts included a MSI/POLE cohort which included endometrial cancers with complete loss of at least one MMR protein and/or a mutation in POLE and a microsatellite stable (MSS) cohort which included endometrial cancers with normal expression of MMR. The MSS cohort was closed due to futility of treatment as only 1/16 patients exhibited a response (overall response rate (ORR) 6.25%). In the MSI/POLE cohort, 4/15 patients showed an overall response (1 complete and 3 partial responses; ORR, 26.7%). Six patients exhibited progression-free survival at 6 months, including the 4 patients with overall response. At the time of abstract publication, 4 of these patients had ongoing response and 2 had response approaching 2 years [26, 27].

FDA approval of pembrolizumab for mismatch repair–deficient tumors

In May 2017, the FDA expanded the approval of Keytruda© (pembrolizumab) for the treatment of unresectable or metastatic adult and pediatric solid tumors with microsatellite instability high (MSI-H) or mismatch repair deficiency (dMMR) that have not responded to prior therapy. This approval was based on data from five clinical trials including 15 cancer types among 149 patients showing an overall response rate of 39.6% with more than 78% of patients experiencing a progression-free interval of six months or more. The most common cancer types included in these trials included colorectal, endometrial, and other gastrointestinal tumors [28]. This is the first FDA approval based on the presence of a specific abnormality in the tumor itself rather than a specific histologic organ type.

Among gynecologic cancers, pembrolizumab shows the most promise in dMMR/MSI-H endometrial cancers with response rates similar to slightly better than standard chemotherapy in the recurrent or progressive setting. The National Comprehensive Cancer Network now recommends MSI-H or dMMR testing for recurrent endometrial cancer and includes pembrolizumab as a treatment option for recurrent MSI-H or dMMR endometrial cancer that has progressed after standard cytotoxic chemotherapy [29].

Clinical use

Tumor testing

In our practice, all patients diagnosed with an endometrial carcinoma undergo IHC evaluation for dMMR and MSI at the time of diagnosis. Tumors of patients diagnosed with advanced endometrial cancers (stage III or stage IV) also undergo molecular testing (genomic analysis) by referral to the Strata Trial (NCT03061305) in the primary setting. Patients who present with recurrent endometrial carcinoma are referred secondarily to the Strata Trial™ for the identification of actionable mutations, including PD-L1 biomarkers, and dMMR/MSI-H evaluation is confirmed. We believe that obtaining the IHC analysis at the time of diagnosis is (1) cost effective (IHC is less expensive than genomic analysis) and (2) helpful for the triage of patients at high risk for germline mutations (such as Lynch syndrome) to a genetic counselor. Identifying Lynch carriers can be particularly impactful for colon cancer screening and identification of at-risk relatives.

The Strata Trial™ (NCT03061305) aims to explore the proportion of patients available for precision medicine trials by expanding current access to next generation sequencing (NGS) to a broad range of patients at no cost. Our institution contracts with the Strata Trial™ to perform NGS without billing the patient our insurer using a waiver of consent protocol. Patients are eligible if they have advanced (defined as stage III or IV for gynecologic malignancies) or recurrent disease. After a physician requests next generation sequencing, our institutional Molecular Tumor Board office determines patient eligibility. The tumor block is requested and reviewed by our pathology office and sent to the Strata Trial™ for StrataNGS. The StrataNGS test identifies the coding sequence for the following tumor suppressor genes: ATM, BRCA1, BRCA2, CDKN2A, MSH2, MSH6, PTEN, RB1, TP53. Other specific regions are available by request. PD-L1 expression is reported as an RNA expression score (RES), ranging from 0

to 100, which indicates the percentage of maximum PD-L1 expression in the tumor sample. For samples with 50% or more tumor content, an RES threshold of >22 is used to determine PD-L1 RNA high status. The Strata Trial™ validated this threshold as 100% sensitive and 70% specific for predicting PD-L1 tumor proportion score of ≥50%. Sequencing is performed on tumor tissue only; therefore, germline mutations are not identified. Results are sent to the ordering physician as well as our institutional Molecular Tumor Board for review of eligibility criteria for clinical trials.

Indications in endometrial cancer

Pembrolizumab is indicated for the treatment of unresectable or metastatic solid tumors with microsatellite instability high (MSI-H) or mismatch repair deficiency (dMMR) that have not responded to prior therapy. In our practice, we consider the use of pembrolizumab in recurrent or advanced stage progressive endometrial cancer with dMMR or MSI-H tumors based on IHC testing or PD-L1 biomarkers as identified by the Strata Trial™. We also consider cytotoxic chemotherapy, hormonal therapy, or clinical trial participation, dependent on the patient's performance status, co-morbidities, and wishes.

Dosing and administration

Pembrolizumab for the treatment of unresectable or progressive dMMR/MSI-H and PD-L1 actionable endometrial carcinoma is given as an intravenous (IV) infusion of 200 mg every 3 weeks until progression or unacceptable toxicity [30]. Patients are typically pre-medicated with anti-emetics such as ondansetron 8 mg per mouth (PO) or IV prior to infusion. Immune-mediated toxicities are common, and assessment for end-organ damage related to immune activation is important. Baseline and repeated thyroid studies are drawn throughout treatment given the incidence of thyroid abnormalities with the use of immune checkpoint inhibitors. Cycles are held for the following parameters: absolute neutrophil count (ANC)≤1000/μL, platelets≤100 K/μL, creatinine>1.5 times upper limit of normal (ULN), AST>2.5 times ULN (or >5 times ULN if known liver metastases), ALT>2.5 times ULN (or >5 times ULN if known liver metastases), or total bilirubin >1.5 times ULN.

Toxicity

The most common immune-related adverse events (AEs) reported with the use of immune checkpoint inhibitors include diarrhea (26%), rash (>20%), hyperthyroidism (8.5%), pneumonitis (3.4%), type I diabetes (3.4%), and colitis (1.7%) [31]. In the KEYNOTE-028 trial subgroup of endometrial cancer patients, treatment-related AEs occurred in 13 of 24 patients (54.2%), including fatigue (20.8%), pruritus (16.7%), pyrexia (12.5%), and decreased appetite (12.5%) [25•]. There were no treatment-related discontinuations secondary to AEs among this cohort. Several organizations have published guidelines regarding the management of immunotherapy-related toxicities including the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN) [32, 33, 34••].

In our experience, lung toxicities, such as pneumonitis, can be the most challenging to diagnose given that pleural effusions are relatively common in advanced and recurrent gynecologic cancers and can mask the classic imaging

Table 1. FDA approved immune checkpoint inhibitor therapy in endometrial cancer

Drug combination	Indication
Pembrolizumab	Advanced or recurrent MSI-H/dMMR endometrial cancer that has progressed following ≥1 systematic therapy
Lavatinib/pembrolizumab	Advanced or metastatic non-MSI-H/pMMR endometrial carcinoma that has progressed following ≥1 systemic therapy

MSI-M, microsatellite instability–high; *dMMR*, mismatch repair deficiency; *pMMR*, proficient mismatch repair

findings of pneumonitis. Pneumonitis most commonly presents with dyspnea, cough, fever, and chest pain, but many times patients are asymptomatic. Fortunately, immune-related adverse events, if identified in a timely fashion, are readily treated with corticosteroids, although IV dosing is often required. Patients with moderate (grade 2) or severe (grade 3 to 4) immune checkpoint inhibitor–related pneumonitis should be treated with prednisone or methylprednisolone 1–2 mg/kg/day in addition to supportive respiratory care. Steroids should be continued at this dose until symptoms improve to grade 1, and then tapered over the following 4 to 6 weeks [34••].

Emerging therapies

Combination immune checkpoint blockade

The use of immune checkpoint inhibitor monotherapy in gynecologic cancer is limited mainly to endometrial cancers with dMMR or MSI-H mutations. Because of this modest response in gynecologic cancers, new combinations of targeted therapies are being investigated in gynecologic cancers in an effort to improve efficacy and overcome tumor resistance [35].

Table 2. Current trials of combination immune checkpoint inhibitor therapies for endometrial cancer

Trial number	Phase	Patient population	Study design	*Accrual status
NCT03884101	III	Stage III, IV, or recurrent endometrial carcinoma	Randomized, open-label study of first-line treatment with lenvatinib/pembrolizumab versus carboplatin/paclitaxel	Accruing
NCT03914612	III	Stage III, IV, or recurrent endometrial carcinoma	Randomized, placebo-controlled study of carboplatin/paclitaxel +/– pembrolizumab	Not yet accruing
NCT03015129	II	Persistent or recurrent endometrial carcinoma or endometrial carcinosarcoma	Randomized, open-label study of durvalumab +/– tremelimumab	Accruing
NCT02549209	II	Stage III, IV, or recurrent endometrial carcinoma with prior surgical management (hysterectomy and bilateral salpingo-oophorectomy)	Single-arm, open-label study of pembrolizumab in combination with carboplatin/paclitxel	Accruing

*As of June 30, 2019

An interim analysis from one of the first immunotherapy combinations used in endometrial cancer was published this year [36]. This phase 2, open-label trail investigated the use of a combination of lenvatinib, a VEGF inhibitor, and pembrolizumab in metastatic endometrial cancer regardless of MMR or PD-L1 status. They reported 21 of 53 patients (39.6%) showed an objective response to treatment by 24 weeks. Median study follow-up at the time of publication was 13.3 months. Among this cohort, 8% of patients had MSI-H status. Based on this data, the FDA approved lenvatinib and pembrolizumab for the treatment of advanced or metastatic non-MSI-H or mismatch repair–proficient (pMMR) endometrial carcinoma that has progressed following ≥1 systemic therapy (Table 1). A phase III randomized, open-label trial of the lenvatinib and pembrolizumab compared with standard chemotherapy for first-line treatment for advanced or recurrent endometrial cancer is currently ongoing (NCT03884101).

Several other clinical trials investigating new combinations including immune checkpoint inhibitors in endometrial cancer are actively accruing patients (Table 2). A phase III randomized, placebo-controlled trial investigating the addition of pembrolizumab to standard of care chemotherapy with carboplatin/paclitaxel in advanced or recurrent endometrial cancer is currently recruiting patients (NCT 03914612). A phase II trial of durvalumab (anti-PD-L1 antibody) with and without tremelimumab (anti-CTLA-4) in women with persistent or recurrent endometrial carcinoma or carcinosarcoma regardless of MMR status is currently enrolling patients (NCT03015129). Another phase II open-label trial currently enrolling patients includes the use of pembrolizumab in combination with carboplatin/paclitaxel in advanced or recurrent endometrial cancer (NCT02549209).

Conclusions

Among gynecologic malignancies, dMMR and MSI-H endometrial cancers show the greatest response to immune checkpoint inhibition therapy, though response in gynecologic malignancies remains modest compared with other solid tumors such as melanoma and non-small cell lung carcinoma. Routine MMR and PD-L1 biomarker testing should be undertaken in all patients with endometrial cancer in order to identify patients for which pembrolizumab could be considered. Institutional participation in large basket trials, such as the STRATA Trial™, should be considered. Enrollment of patients into clinical trials of combination immunotherapy regimens should be considered, as combinational therapies may offer the most promising outcomes, particularly for patients with advanced or recurrent endometrial cancer.

Compliance with Ethical Standards

Conflict of Interest

Janelle Sobecki-Rausch declares that there is no conflict of interest. Lisa Barroilhet declares that there is no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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