7

The Use of Immunotherapy for Treatment of Gynecologic Malignancies

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Cite this chapter as: Agyemang AF, Lele S. The Use of Immunotherapy for Treatment of Gynecologic Malignancies. In: Lele S. editor. *Ovarian Cancer*. Brisbane (AU): Exon Publications. Online first 29 Jul 2022.

Doi: https://doi.org/10.36255/exon-publications-ovarian-cancer-immunotherapy

Abstract: Gynecological malignancies continue to present significant morbidity and mortality in women notwithstanding current traditional and new targeted treatments. The advent of immunotherapy and its successes in hematologic malignancies, melanoma and lung cancer led to immense interest in exploring its effects in chemoresistant, advanced stage and recurrent gynecologic cancers. The tumor microenviroment is characteristically immunosuppressive to infiltrating cytotoxic T cells. Thus, the goal of immune based therapies is two-fold: overcome this immunosuppression and enhance tumor destruction. In this chapter, we discuss some of the preclinical studies and clinical trials investigating vaccines and other immunotherapies in gynecologic cancer patients. We present key

In: Lele S (Editor). *Ovarian Cancer*. Department of Gynecologic Oncology, Roswell Park Comprehensive Cancer Center, Buffalo, New York, USA. ISBN: 978-0-6453320-8-7. Doi: https://doi.org/10.36255/exon-publications-ovarian-cancer

advances in the development of cancer vaccines, adjuvants, immune modulators, adoptive cell therapies for the generation of optimal immunogenicity, and immuno-persistence and the ultimate eradication of resistant, advanced, and recurrent gynecologic cancers.

Keywords: cervical cancer vaccines; endometrial cancer antigens and vaccines; immunotherapy for gynecologic malignancies; ovarian tumor antigens and vaccines; treatment of gynecologic malignancies

INTRODUCTION

In recent decades, immunotherapy has emerged as a promising therapeutic option for gynecologic cancers. The immune system ensures protection against the development of primary tumors, regulation of tumor immunogenicity through cancer immunosurveillance, and immunoediting (1, 2). A major advantage of immunotherapy is the potential to treat solid cancers despite the state of drug resistance. Thus, the current focus of active research involves harnessing the host immune system for the efficient destruction of tumor cells. Optimization of anti-tumor immunity involves multi-step processes to ensure (i) a high concentration of tumor specific effector T cell populations, (ii) effective trafficking of tumor infiltrating T cells that can defeat the immunosuppressive tumor microenvironment (TME), target tumor antigens and differentiate into antigen-specific effector cells (iii) and persistence of anti-tumor T cells (1, 2). Tumor infiltrating lymphocytes (TIL), when present in ovarian tumors, correlate with improved survival (3–5). When TIL arrive in the TME, their functions can be severely limited by immunosuppression leading to ineffective tumor destruction.

The TME is composed of suppressor immune cells regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSC), tumor-associated macrophages (TAM), intratumoral neutrophils (6), inhibitory cytokines (TGF-β, IL-10), PD-1/PD-L1 interactions, anomalous vessel formation in a network of cancer cells, stromal cells and inhibitory molecules expressed by the extracellular matrix (3, 6). Hypoxia, oxidative stress, mitochondrial DNA, aberrant metabolism such as indoleamine-2,3-dioxygenase (IDO) mediated tryptophan catabolism leading to nutrient depletion are prevalent within this hostile TME (7, 8). Moreover, tumor cells plasticity leads to antigen loss variants, heterogeneous expression of tumor antigens and very few unique tumor antigens. To overcome tumor progression, T cells must navigate the intricacy of TME suppression. The complexities of TME suppression suggest that a combined targeting approach is critical for effective immunotherapies.

Currently, immune strategies for the treatment of gynecologic cancers include checkpoint inhibition, cancer vaccines, oncolytic virotherapy and adoptive cell therapy. This chapter discusses the molecular and immune-based strategies currently being investigated for targeting and eradicating gynecologic cancers.

OVARIAN CANCER

Ovarian cancer is the most lethal gynecologic malignancy with a mortality rate of 6.8 per 100,000 women (9). Primary treatment involves surgical tumor debulking and combined platinum and taxane chemotherapy with treatment response rates as high as 80% in advanced epithelial ovarian cancer patients (10, 11). Despite chemotherapy and targeted therapies, exceptionally high recurrence rates due to chemoresistance account for 90% of deaths. Immunotherapy is a promising treatment option for ovarian cancer regardless of drug resistance. TIL correlate with improved survival in ovarian cancer patients (3–5). TIL function is severely limited by TME immunosuppression leading to ineffective tumor eradication. The complexities of TME suppression suggest that a combined targeting approach is critical for effective immunotherapies. Major strategies to increase TIL frequency and function in ovarian tumors include (i) developing cancer vaccines to elicit tumor antigen-specific T cell populations *in vivo*, (ii) enriching antigen specific T cells *ex-vivo* for adoptive cell therapy, (iii) immune checkpoint inhibitors (ICI) and (iv) IDO inhibitors.

Ovarian tumor antigens and vaccines

Two spontaneously immunogenic cancer testis antigens (CTA), NY esophageal squamous cell carcinoma 1 (NY-ESO-1) and melanoma associated antigen 1 (MAGE-A), are highly prioritized for ovarian cancer vaccines (12–15). Abnormal NY-ESO-1 expression can be found in approximately 40–43% ovarian tumors (16, 17). Clinical trials with NY-ESO-1 based vaccines have shown a potential survival benefit (18–21). A retrospective analysis of 11 clinical trials showed a 2-year OS advantage in ovarian cancer patients with NY-ESO-1 expressing tumors who received a NY-ESO-1 based vaccine compared to those who received no vaccine (17). Study limitations include small patient numbers in individual trials, variation in treatments, and selection bias with cancer centers versus community hospitals. Notwithstanding, this is promising for NY-ESO-1 as an immunotherapy target and suggests a need for randomized controlled trials.

In platinum resistant ovarian cancer, the NYESO-1 vaccine combined with liposomal doxorubicin and decitabine showed enhanced cytotoxic T cell responses in 50% and antigen specific humoral responses in 67% of patients (21). Also, 50% of patients achieved SD with a median duration of 6.3 months (range 3.9 to 7.8 months) and 10% of patients had partial response/disease remission. The median duration of the partial response was 5.8 months. Approximately 78–95% ovarian cancer patients express at least 1 MAGE antigen (13, 22, 23). Clinical prognosis may depend on MAGE antigens; MAGE-A1 and -A10 were associated with poor outcomes whereas MAGE-C1/CT7 correlated with improved outcomes. MAGE-A4, a highly expressed CTA, regulates other MAGE antigen co-expression (13). MAGE-A4 vaccines elicit humoral and T cell responses resulting in decreased tumor burden and improved survival (24–26). However, a phase II trial of combination MAGE-A1 vaccine and chemotherapy in ovarian cancer patients was terminated due to low enrollment. Additional studies are needed to explore this promising immunotherapeutic target.

Oncolytic virotherapy

Oncolytic viruses may work synergistically with immunotherapies in solid tumors (27). Significant successes using oncolytic virotherapy in metastatic melanoma patients led to FDA approval (28). On-going therapeutic strategies for platinum resistant ovarian cancer patients include trials investigating T-VEC (NCT03663712), a GM-CSF encoding adenovirus ONCOS-102 (NCT02963831), an adenovirus based enadenotucirev (29) and measles virus expressing human sodium iodide symporter MV-NIS (NCT02364713).

The combination of adoptive T-cell therapy and oncolytic viral delivery may have a beneficial synergistic effect (30, 31). Antigen-nonspecific T cells loaded with oncolytic vesicular stomatitis virus (VSV) efficiently delivered the virus to metastatic lymph nodes leading to antitumor immune priming and tumor clearance (32). The resulting pro-inflammatory TME enhanced antigen-specific T-cell proliferation and survival (33). Moreover, Her-2 specific CAR T cells efficiently delivered VSV to the ovarian TME and enhanced tumor killing (34). ACT and oncolytic virotherapy is expanding to include irradiated autologous tumor cells as conduits for virus into the TME (35–37). IL-12 encoding Maraba virotherapy recruited IFN-g producing NK cells for tumor lysis and improved survival (37). Interestingly, first in human studies are testing Maraba virus encoding MAGE-A3 vaccine in solid tumors expressing this CTA (NCT02285816, NCT02879760). Phase I/II studies are exploring the use of irradiated autologous or allogeneic tumor cell vaccines (NCT00722228) to stimulate anti-tumor immune responses. The trial results will inform and enhance research efforts to reprogram the TME into an immunogenic niche, enhance humoral and cytotoxic immune responses for the ultimate benefit of ovarian cancer patients.

ACT in ovarian cancer

Several ongoing or completed studies are testing CD8 TCR redirected T cells in ovarian cancer patients. These studies are targeting the family of CTAs including NY-ESO-1 (NCT03017131, NCT02650986, NCT03691376, NCT01567891) and MAGE-A4 (NCT02096614). Although spectacular responses have been observed in a small fraction of patients, most clinical responses are short-lived with ultimate disease recurrence. A major explanation for this sub-optimal outcome is the relatively limited long-term survival and effector function due to suppression or exhaustion of the infused engineered T cells. Previous ACT trials focused on the use of CD8 TCR but not on CD4 TCR. Since $CD4^+$ T cells maintain $CD8^+$ T-cell responses (38, 39) and rescue exhausted T cells (40), long-lasting anti-tumor responses are expected from the synergy of CD8 TCR- and CD4 TCR-engineered T cells. Two types of tumor antigen (NY-ESO-1)-specific $CD4^+$ T cells, tumor recognizing and non-tumor recognizing, play distinct roles at the local tumor site (41). Whereas both $CD4^+$ T cell types recognize exogenous NY-ESO-1 protein that is processed and presented by APCs, only tumor recognizing CD4 lymphocytes directly recognize cancer cells in MHC class II-restricted and antigen-specific manner (41, 42). T cells that are expanded *ex vivo* to maintain more stem like T cell populations known as T stem cell memory (Tscm) cells, are capable of a more sustained response by replenishing effector T lymphocytes (43). A benefit of transferring less mature, more stem-like cells is increased persistence

and replenishing capability of these cells *in vivo*. Conceptually, the regenerative nature of hHSCs may provide a long-lasting, potentially life-long supply of effector T cells with TCRs engineered against TAAs. This is being tested in a phase 1 trial with platinum resistant ovarian cancer patients (NCT03691376).

Engineered CARs have specificity for non-MHC restricted tumor antigen presentation (44). Adoptive therapy with CAR T cells showed CR in 70–90% of patients with chemoresistant hematological cancers leading to FDA approval for CD19-targeted CAR T cells for treatment of B cell lymphoma (45, 46). In the last decade, studies have expanded this success to solid tumor treatment with CAR T cells specific for disialoganglioside GD2 in pediatric neuroblastoma (47), HER2 positive sarcoma (48) and IL-13Rα2 in disseminated glioblastoma (49). CAR T cells specific for ovarian tumor antigens, MUC16 or mesothelin, are being tested in ongoing or completed clinical trials (50), NCT03814447, NCT03907852 and NCT03054298.

CAR T cells modified to co-express chemokine receptors improved T cell migration and function (51–53). Preclinical studies showed improvement in lymphocyte trafficking and effector function when CXCR4/CXCL12 interactions were blocked within the ovarian tumor microenvironment (54, 55). Targeted intratumoral delivery of the CXCR4 antagonist using an oncolytic virus was shown to be efficacious and resulted in direct tumor lysis as well as enhanced effector T cell function (55). These approaches are limited by the diversity of tumor chemokines/receptors expression, lack of unique tumor chemokine secretion and the potential for aberrant accumulation of CAR cells at non-target sites.

Clinical trials using autologous activated TILs expressing endogenous TCRs in ovarian cancer patients are ongoing or recently completed. A phase I trial showed the clinical efficacy of autologous TILs in metastatic ovarian cancer patients (56). Another phase I trial is investigating the effect of "re-stimulated" TILs and low-dose IL-2 in platinum resistant ovarian cancer patients (NCT01883297). A few phase II trials are studying the efficacy of TIL treatment in patients with recurrent or refractory ovarian cancer, pancreatic cancer and osteosarcoma (NCT03610490, NCT03449108). Future TCR or CAR T cell technology present unique opportunities to incorporate multiple immunotherapy targets into one vehicle. CARs or TCR transgenic cells could be engineered with (i) co-expression of dominant-negative receptors to bock inhibitory signals to T cells, (ii) local delivery of stimulatory cytokines such as IL-12 and IL-18, (iii) suicide genes (57–59) to facilitate depletion of CAR-T cells and mitigate toxicity, (iv) NKG2D receptor (60, 61), (v) ligands for Erb B receptors and many more. Using allogeneic CAR-T derived from healthy donors has been suggested as a practical means for generating T cells without prolonged exposure to tumor cells and lacking TCR and HLA molecules to minimize graft-versus-host disease (62, 63). Moreover, this approach may have significant financial benefits and a shorter period for manufacturing. Current research efforts continue to be focused on finding solutions to the challenges involved in CAR and TIL therapies for ovarian cancer patients.

Ovarian TME

Strategies for targeting immune checkpoint interactions have used blocking antibodies against either the receptors or their ligand(s). A phase 1 trial using inhibitors of PD-1 (Nivolumab) or its ligand, PD-L1 (BMS93655) showed CR or PR in

6% of advanced stage ovarian cancer patients (64). Subsequently, a phase I trial using Nivolumab demonstrated ORR as high as 15% and 45% with SD in patients with platinum resistant ovarian cancer (65). Blocking immune checkpoint targets in ovarian cancer patients has yet to produce dramatic anti-tumor responses. The challenges faced by checkpoint inhibitor monotherapy may be attributed to variable expression of intrinsic tumor antigens; expression of alternate immune checkpoints following monotherapy and TIL expression of multiple co-inhibitory receptors (66, 67). *Ex vivo* studies in which PD-1 and LAG-3 were blocked or downregulated revealed very robust T cell responses (66). Monotherapy using α-PD-L1 antibody, Avelumab (68) or α-PD-1 antibody, Pembrolizumab (69) showed CR in a few or no patients but PR and SD in most patients.

The potential for ICI to control disease progression has led to significant interest in combination therapy with traditional chemotherapy and/or maintenance regimens. Pembrolizumab, Cisplatin and Gemcitabine in treating recurrent platinum resistant ovarian cancer patients showed no clinical benefit beyond chemotherapy alone (70). Many trials have investigated the role for PARPi therapies in combination with ICI. The TOPACIO/KEYNOTE-162 trial is a phase I/II study of patients with platinum resistant ovarian cancer or triple negative breast cancer treated with the PARPi, niraparib and Pembrolizumab (71). Of the pooled 62 ovarian cancer patients, 48% had platinum resistant status, 35% were homologous recombination deficient and 79% had $BRCA^{wt}$ tumors. Median follow-up of 12.4 months with 47% SD, 13% PR, 5% CR and 33% disease progression. The median PFS was 3.4 months (71). The recently completed MENDIOLA trial, is a phase 1/2, multicenter, open label, basket trial of Durvalumab and Olaparib in solid tumors including germline *BRCA*-mutated, metastatic ovarian cancer patients (NCT02734004). An ongoing phase I/II trial involves Durvalumab, Olaparib and/or Cediranib in advanced or recurrent solid tumors including ovarian cancer (NCT02484404). Additional studies include a phase Ib/II trial of Avelumab in combination with the PARPi, Talazoparib (NCT03330405) and the Javelin Medley trial with Avelumab and immune modulators, 4-1BB and OX40 (NCT02554812). Phase III trials are investigating a combination of Atezolizumab, platinum chemotherapy plus Bevacizumab as second/third line and/or maintenance therapy in platinum sensitive recurrent ovarian cancer patients (NCT02891824, NCT03598270). Ongoing and recently completed trials propose to investigate the efficacy of ICI combined with TIL therapy (NCT03287674), intraperitoneal chemotherapy (NCT03734692) and autologous engineered tumor cells expressing immune stimulatory, GM-CSF and shRNA for downregulation of furin, a critical enzyme in TGF-β production (NCT03073525). In addition, a phase II study of Pembrolizumab and p53 expressing modified vaccinia virus ankara vaccine (P53MVA) is ongoing in recurrent or platinum resistant ovarian cancer (NCT03113487).

Recently, an open label, single arm cohort trial tested Pembrolizumab combined with Bevacizumab and Cyclosphosphamide in 40 patients with recurrent platinum sensitive, resistant, or refractory disease. 95% of patients showed clinical benefit and the duration of responses >12 months in 25% of patients. The median PFS was 10 months (90% CI, 6.5 to 17.2) with an ORR of 47.5% including CR in 7%, PR in 40% and SD in 47.5% of patients (72).

Preclinical research is focused on investigating the possible roles for alternative TME immune cells including myeloid and NK cells expressing CAR

receptors (73, 74). Ongoing trials are testing NK cells as ACT for ovarian cancer patients. These studies are exploring the potential clinical benefits of monotherapy with NK CARs (NCT03692637, NCT03213964, NCT03634501) and combinations with (i) NK like cytotoxic lymphocytes and dendritic cell (DC) vaccines (NCT03735589) and (ii) NK cells and chemotherapy (NCT02118285, NCT03539406).

Inhibition of indole-amine 2,3 dioxygenase

TME tryptophan catabolism by IDO in the kynurenine pathway is emerging as an attractive immunotherapy target in ovarian cancer (7). IDO enzymatic breakdown of tryptophan leads to its depletion and accumulation of kynurenines which have deleterious effects on T differentiation, proliferation, effector function and longevity. IDO facilitates the differentiation of naïve $CD4^+$ T cells into a Treg phenotype (75). However, trials in which platinum resistant ovarian cancer patients received monotherapy with IDO inhibitors yielded little clinical benefit (SEASCAPE, NCT02575807). An ongoing study is exploring combinations with IDO, traditional chemotherapy, and T cell activation via PDX-Survivac (NCT02785250). One multimodal strategy involves vaccine-induced tumor specific T cells within a TME deficient in IDO activity. A completed phase I/IIb trial investigated the effect of an IDO inhibitor, Epacadostat combined with a DEC205mAb/NY-ESO-1 fusion protein and poly ICLC adjuvant therapy in ovarian cancer patients in remission (NCT02166905). If these strategies are successful, they will highlight valuable tools for preventing recurrence and prolonging remission in ovarian cancer.

ENDOMETRIAL CANCER

Carcinoma of the uterine corpus is the most common gynecologic malignancy in US women with an estimated 65,620 new cases and 12,590 deaths in 2022 (76). Standard treatment involves surgical staging surgery with adjuvant chemotherapy or radiation. Early stage disease is diagnosed in approximately 66.7% of women with 5-year survival of 95% (77). Unfortunately, endometrial patients with metastatic disease have a poor prognosis with a 5-year survival of 16.8% (77). For recurrent endometrial cancer, traditional treatment includes systemic chemotherapy with or without radiotherapy. However, treatment responses are dismally low leading to a critical need of effective therapeutic options for advanced, metastatic, relapsed, or refractory endometrial cancer.

Our evolving understanding of the molecular phenotypes in endometrial cancers indicates a heterogenous group composed of four genetically distinct subsets including *POLE* ultra-mutated, MSI hypermutated, copy number low (endometrioid) and copy number high (serous-like). As a result of the high mutation rates in *POLE* ultramutated and MSI endometrial tumors, the endometrial TME contains increased expression of neoantigens, TILs and PD-1 (78). In addition, PD-L1 expression on tumor cells was similar in all molecular subtypes whereas a significant increased expression was noted in intraepithelial and peritumoral immune cells. This feature generates an attractive TME for immunotherapies, specifically ICIs. By contrast, recurrent endometrial cancer is comprised of copy number low

or copy number high tumors which are microsatellite stable (MSS) and associated with poor responses to current treatment. The role for vaccines, TILs and ICI in endometrial cancer treatment requires further investigation.

Endometrial cancer antigens and vaccines

Limited data exists for cancer vaccines in endometrial cancer treatment. Ongoing trials propose to explore a potential role for endometrial cancer vaccines. A pilot study is testing a personalized neoantigen peptide-based vaccine in combination with pembrolizumab in advanced solid tumors (PNeoVCA) including endometrial cancers (NCT05269381). Preclinical studies show that a humanized monoclonal antibody targeting Netrin-1 could restore apoptosis in cancer cells. A selective Netrin-1 inhibitor, NP137 in combination with chemotherapy and/or pembrolizumab is now being tested in a randomized, multicenter, open label phase I/II trial of endometrial and cervical cancer patients with recurrent locally advanced/metastatic disease (NCT04652076). The results of these trials are highly anticipated and may enhance the multi-strategy therapies for advanced or recurrent endometrial patients.

ACT in endometrial cancer

The increased presence of TILs in endometrial tumors is prognostic and associated with prolonged PFS and OS (79). In contrast to ovarian cancer, very few studies have been published on TIL treatment for advanced or recurrent endometrial cancer. An ongoing phase II trial of patients with metastatic cancers including endometrial cancer involves lymphodepletion, autologous TIL infusion and pembrolizumab (NCT01174121). An ongoing phase I/II trial involves autologous T cells engineered with neoantigen specific-TCR for treatment of refractory/recurrent solid tumors including endometrial cancer. A phase I/II trial is using an alkaline phosphatase, placental (ALPP) specific CAR T cells to treat patients with ALPP-positive metastatic ovarian and endometrial cancers (NCT04627740). Another phase I/II trial is testing NK cells (ACE1702) in patients with advanced Her2 expressing tumors (NCT04319757). An exploratory study was recently completed in 8 metastatic endometrial cancer patients treated with chemotherapy and DC loaded with tumor lysate, MUC1 and survivin Peptivators (NCT04212377). A first in human phase 1 study of adenovirally transduced autologous macrophages expressing α-HER2 CAR in treating patients with Her2 overexpressing solid tumors including endometrial cancer is recruiting (NCT04660929).

Endometrial TME

A number of trials have demonstrated a benefit for ICIs with or without targeted therapies in the treatment of microsatellite instability-high or mismatch repair-deficient (dMMR/MSI-H) tumors, such as endometrial carcinoma, leading to FDA approvals (80). A phase II trial of 12 distinct dMMR tumors showed an ORR of 53%. This trial included 15 endometrial cancer patients and showed the benefit of ICI in tumors with high mutation burden regardless of primary malignancy. In KEYNOTE 158, an open label, multi cohort, phase II trial of pembrolizumab in

patients with previously treated, advanced MSI-H/dMMR tumors, including endometrial cancer (81). The KEYNOTE-028 trial involved advanced, previously treated endometrial cancer patients with PD-L1 expressing tumors who were treated with Pembrolizumab and showed an approximate ORR of 13% (82). A Phase I trial of an ani-PD-1, Dostarlimab for treatment of advanced/recurrent dMMR endometrial cancer patients revealed an ORR of 42.3% with durable responses including CR in 12.7% and PR in 29.6%. The median follow up was 11.2 months and median duration of response (DOR) was not reached (83). In addition, Dostarlimab was investigated in an open label, single arm, phase I trial, GARNET, which involved endometrial cancer patients with dMMR/MSI-H or MSS tumors (84). The ORR was 43.5% in dMMR (11 CR and 36 PR) and 14.1% in MSS (3 CR and 19 PR) patients. In this study as well, the median DOR was not reached. As a result of the promising results from the phase I/II trials, a number of phase III trials were initiated to investigate the effect of ICI combined with chemotherapy in advanced or recurrent endometrial cancer. The RUBY trial (NCT03981796) involves Dosrtalimab or placebo combined with carboplatin and paclitaxel chemotherapy and GY018 (NCT02549209) involves pembrolizumab or placebo with carboplatin and paclitaxel in advanced/recurrent endometrial cancer patients.

Therapeutic options are limited for patients with metastatic and recurrent endometrial MSS expressing tumors. However, combination of ICI with targeted therapies have shown promising results. KEYNOTE 775 was a phase III trial of Pembrolizumab and Lenvatinib, a kinase inhibitor (TKI), for advanced endometrial cancer patients with progression on prior therapy who did not have MSI-H/dMMR expressing tumors. The control arm received chemotherapy of the investigator's choice. The ORR was 30% in patients receiving pembrolizumab/lenvatinib versus 15% in control patients ($p<0.0001$). The mean DOR was 9.2 and 5.7 months and median PFS was 6.6 versus 3.8 months in patients receiving Pembrolizumab/Lenvatinib compared to controls. The mean overall survival was 17.4 compared to 12 months with a Hazard Ratio of 0.68 (95%CI 0.56–0.84, $p=0.0001$). Recently, a prospective, open label, single arm, phase II trial investigated the combination of an α-PD-1 inhibitor, Sintilimab, with an oral TKI, Anlotinib in recurrent endometrial cancer patients. The objective response rate was 77.3% with a median time to first response as early as 1.5 months (range 0.7–12.8). Disease control was observed in 92% of patients. However, the median progression-free survival was not reached. Further studies are needed to explore the potential benefit of this combination therapy in improving prognosis for recurrent endometrial cancer patients.

Ongoing studies are investigating a role for α-PD-L1 inhibitors in endometrial cancer patients. Patients with advanced stage endometrial cancer were divided according to *POLE*, MSI or dMMR status and the efficacy of Avelumab or Durvalumab was determined. For Avelumab, the ORR was 26.7% in dMMR compared to 6.25% in MSSwhereas the ORR was 43% in dMMR and 3% in MSS patients in the Durvalumab cohort. Current trials are exploring the role for Nivolumab in patients with MSI/dMMR endometrial tumors (NCT03241745). The molecular mechanism underlying treatment responses and resistance to ICI inhibitors is not well understood. In a recent single arm, open label phase II trial, pembrolizumab was assessed in 25 recurrent endometrial cancer patients with sporadic, somatic compared to germline MSI tumors (85). Germline MMR

mutations were not found in any patients, 6 patients had somatic mutations and 19 patients had sporadic mutations. ORR was 100% in the somatic versus 44% in sporadic MMR mutated patients (p=0.24). The median follow-up was 25.8 months with an overall ORR of 58%. 3-year PFS was 100% in somatic mutated versus 30% in sporadic mutated patients. Similarly, 3-year OS was 100% compared to 43% in somatic versus sporadic mutated patients. Interestingly, initial resistance to treatment was observed in 4 patients and secondary resistance was noted in 7 patients. 2 patients underwent surgical resection of solitary persistent lesions followed by off-protocol pembrolizumab treatment. Both patients experienced PFS at 41 and 42 months. The robust responses in endometrial cancer patients with somatic MMR mutations correlated positively with higher mean frequencies of $CD68^+$ macrophages. However, TILs and $CD20^+$ B lymphocytes exhibited similar frequencies.

CERVICAL CANCER

Cervical cancer is the 4th most common gynecological cancer globally. The annual US incidence of cervical cancer is 7.5 per 100,000 and mortality is 2.2 per 100,000 women. Human papillomavirus (HPV) infection is associated with 95% of all cervical cancers (86, 87). Early disease stage typically has a good response to treatment with surgery, chemoradiation or a combination. Advanced stage disease is characterized by low treatment response rates, high recurrence rates and overall poor prognosis. Treatment options remain limited for women with advanced stage and recurrent disease. The traditional treatment for metastatic or recurrent cervical cancer is systemic chemotherapy such as cisplatin or topotecan combined with paclitaxel (88). Within the last decade, strides in tumor molecular testing and immunotherapy have provided potential targeted therapeutic options. GOG 240 provided evidence for an added benefit of these regimens in combination with the anti-angiogenesis agent, Bevacizumab (89, 90). Significant barriers to the success of immunotherapeutic approaches in cervical cancer treatment are tumor resistance and immunosuppressive TME.

Cervical cancer vaccines

Prophylactic vaccination strategies have been successful in the prevention of precancerous lesions and cervical cancer in developed nations but less so globally especially in low-income countries. These vaccines generate neutralizing antibodies for the clearance of many HPV subtypes as well as establishing protective immunity. However, these neutralizing antibodies and elicited T cells specific for HPV capsid proteins, such as L1, cannot eradicate the HPV infected epithelial cells which constitutively express the oncogenic proteins, E6 and E7. Thus, current efforts are focused on the development of therapeutic HPV vaccines with the goal of generating anti-tumor T cell mediated immune responses to target early HPV proteins, E6 and E7 antigens and neoantigens in cervical cancer.

Live vector-based vaccines that have shown promise in cervical cancer patients include bacteria-based vectors from listeria and vaccinia. ADXS11-001, a listeria derived vector encoding HPV16 E7, was used in a phase III trial to treat cervical

cancer patients with recurrent or persistent disease (NCT02853604) (91). Human antigen HPV (TA-HPV) is a vaccinia-based vector vaccine that encodes E6 and E7 oncogenes with mutations (92). TA-HPV induced $CD8^+$ T cells specific for HPV in cervical cancer patients (93). Limitations of live vector vaccines include susceptibility to innate immune defenses leading to neutralization prior to antigen expression and subsequently obviating repeated vaccination. Potential solutions involve a heterologous prime-boost approach. In addition, there is a high risk of complications from live vector vaccines in patients with compromised or senescent immune systems.

Most potential therapeutic nucleic acid-based HPV vaccines are DNA vaccines which show tolerability when delivered by electroporation. INO-3112 is a HPV DNA vaccine which encodes the E6 and E7 proteins from HPV16 and 18 in addition to the cytokine, IL-12. In cervical cancer patients undergoing adjuvant chemoradiation, INO-3112 vaccine demonstrated tolerability and immunogenicity (94). A strategy which avoids the potential safety issues and limitations associated with live vector and naked nucleic acid HPV vaccines involves using whole cell based DCs vaccines. DC immunotherapies in cervical cancer have shown mixed efficacy but continue to hold promise. In a phase I trial with stage IB and IIA cervical cancer patients, subcutaneous administration of autologous DCs pulsed with full-length HPV 16/18 E7 combined with KLH showed a good safety profile and tolerability (95). These HPV-DC vaccines elicited humoral and $CD4^+$ T cell responses. In a phase I trial of 14 cervical cancer patients treated with placebo (saline), unprimed autologous DCs or tumor lysate pulsed autologous DCs, CR was noted in 1 patient who received tumor lysate pulsed DCs followed by cisplatin chemotherapy and remained disease free beyond 72 months (96). A current effort is targeting telomerases expressed by HPV associated tumors. The Universal Cancer Peptides vaccine (UCPVax) has demonstrated the ability to stimulate $CD4^+$ T cell responses against tumor cells (97–99). A clinical trial is now investigating the immunogenicity of UCPVax in patients with HPV positive cancers including cervical cancer (NCT03946358). Another ongoing phase I/II trial is testing HPV Vaccine PRGN-2009 combined with α-PD-L1/TGF-Beta Trap (M7824) in HPV positive tumors (NCT04432597).

ACT in cervical cancer

T lymphocyte-based vaccines including tumor infiltrating lymphocytes (TILs) and T cells with engineered TCRs or chimeric antigen receptors (CAR) are a potential strategy in cervical cancer (100, 101). Studies have shown a promising role for TILs in HPV-associated tumors including cervical cancer. A phase II study investigated the effect of a single infusion of HPV E6/E7 reactive TILs delivered with lymphodepletion and aldesleukin in 9 patients diagnosed with metastatic cervical cancer and previously treated with platinum-based chemotherapy or chemoradiation (102). Treatment responses were observed in 33% of patients and 2 patients had CR lasting 22 and 15 months, respectively. One patient had partial response which lasted 3 months after treatment. The HPV reactivity of the infused TILs correlated positively with clinical response ($p=0.0238$). The frequency of HPV-reactive T cells in the patient's peripheral blood one month after treatment was positively associated with clinical response ($p=0.0238$) (102). Currently, an

ongoing prospective, multicenter, open label, phase II trial is investigating autologous TIL (LN-145) and IL-2 ± pembrolizumab treatment in recurrent, metastatic, or persistent cervical cancer (NCT03108495).

A first in human phase II trial using T cells with genetically modified TCRs specific for HPV E6, lymphodepletion and IL-2 in patients with HPV-associated recurrent or metastatic cervical, anal, and head and neck cancers (103). In another phase II trial of patients with HPV associated cancers including 18 with cervical cancer, 5 women had an objective tumor response to treatment with 2 CR and 3 PR. The 2 cervical cancer patients' CR lasted 67- and 53-months post treatment (104). Subsequently, phase I and II trials are investigating this promising role for immunotherapy in cervical tumors using T lymphocytes with HPV specific TCRs (NCT03578406, NCT02858310, NCT04556669). A phase I/II trial of stage III or IV or recurrent cervical cancer patients is assessing the potential role for CAR-T cell therapy in tumors expressing target tumor associated antigens (TAA) including GD2, PSMA, Muc1 or mesothelin (NCT03356795). The results of these trials are heavily anticipated and will provide insights into optimizing the effectiveness of adoptive T cell therapy in cervical cancer.

Cervical TME

The cervical TME is characterized by a high expression of PD-L1. The advent of ICI, targeting PD-1/PD-L1 and CTLA-4, has been critical for improving the treatment responses for cervical cancer patients. Pembrolizumab was approved in 2018 as a second line therapy for recurrent or metastatic cervical cancer patients with PD-L1 positive tumors. Recently, FDA approved first line pembrolizumab combined with platinum chemotherapy with or without bevacizumab for persistent, recurrent or metastatic cervical cancer (105). In addition, another second line treatment tisotumab vedotin was approved for recurrent or metastatic cervical cancer (106). A number of trials provided supporting evidence for these FDA approvals and led to the paradigm shift in treatment options for cervical cancer patients. KEYNOTE 158 was a phase II basket trial of PD-L1 expressing tumors including 99 previously treated advanced cervical cancer patients given pembrolizumab monotherapy for 2 years or until progression (107). The overall ORR was 12.2% with 3 CR and 9 PR. All treatment responses were observed in patients with PD-L1 expressing tumors. The median DOR was not reached and ranged from 3.7 to ≥18.6 months. KEYNOTE 826, was a phase III trial of Pembrolizumab/placebo with chemotherapy ± Bevacizumab in cervical cancer patients with persistent, recurrent or metastatic disease. Clinical outcomes were determined based on PD-L1 status. In patients with Combined Positive Score ≥10, PFS was 10.4 compared to 8.1 months in placebo groups. Similarly, for CPS ≥1 and the ITT groups, PFS was 10.4 versus 8.2 months in patients treated with pembrolizumab versus placebo. 2-year OS was significantly longer in the pembrolizumab treated compared to control patients.

Further, the EMPOWER-Cervical-1/GOG3016 phase III trial tested Cemiplimab in patients with recurrent cervical cancer and progression on platinum chemotherapy. The median OS in Cemiplimab arm was 12 versus 8.5 months in the chemotherapy controls. The ORR was 16.4% in the total population, 18% in patients with CPS ≥1% versus 11% in CPS <1% expressing tumors (108). The

results of ongoing trials using ICI and classic or targeted treatments are highly anticipated. Current trials are exploring ICI combined with RT (NCT05310305, NCT05310383, NCT05311566, NCT03589339), chemotherapy (NCT04974944, NCT05290935) and targeted therapies (NCT04651127, NCT05086692).

VULVAR CANCER

Vulvar carcinoma is a rare malignancy accounting for 4–5% of all gynecologic malignancies. The vulvar cancer incidence rate was estimated to be 2.6 per 100,000 women with a mortality rate of 0.6 per 100,000 women (109). In elderly women, the incidence of vulvar cancer is increasing. The advent of HPV vaccination is linked to the decreasing incidence of vulvar cancer in younger women (110). The most common histology is squamous cell carcinoma (SCC) and accounts for 80–90% of all vulvar cancers. Vulvar SCC can be subdivided into 3 distinct subsets including HPV-associated and HPV negative with either wildtype or mutated *TP53* (111, 112). HPV associated vulvar SCC arises most commonly in younger women and is characterized by p16 overexpression. The precursor lesions for this subtype are vulva HSIL. By contrast, HPV independent vulva SCC is related to persistent dermatoses, especially lichen sclerosis. The precursor lesion for the HPV negative, p53 mutant vulvar SCC subset is usually p53-muant differentiated vulvar intraepithelial neoplasia. These HPV independent subtypes are commonly diagnosed in postmenopausal women. The median age at diagnosis for vulvar cancer is 69 years. Treatment of early-stage vulvar cancer consists of radical surgical resection with sentinel or inguinofemoral lymphadenectomy followed by adjuvant radiation with or without radiosensitizing chemotherapy. Unfortunately, significant morbidity and mortality is associated with radical surgery. Whereas less morbidity, improved response rate, PFS and OS has been demonstrated with neoadjuvant chemoradiation treatment for locally advanced vulvar cancer (113, 114). In patients with advanced stage, recurrent or metastatic vulvar cancer, the treatment options are limited leading to poor prognosis. The 5-year survival for patients with metastatic vulvar cancer is estimated to be 15–30%. After primary platinum-based treatment, patients with recurrent disease show poor response to any subsequent treatment. There is a requirement for improving vulvar cancer patient survival with the development of novel therapeutics including immunotherapy.

ACT in vulvar cancer

Analyses of an immunogenic signature in vulvar tumors revealed an independent positive association between high $CD3^+CD4^+$ and $CD8^+$ T cell intra-tumoral infiltration and survival (115). A phase I/II trial is investigating the safety and efficacy of E7 TCR cells combined with Aldesleukin in patients with metastatic $HPV16^+$ cancers including cervical and vulva carcinoma (NCT02858310). Further studies may illuminate the mechanisms underlying TIL function and effectiveness in vulvar cancer. The rarity of this disease presents a challenge for robust and randomized trials.

Vulva cancer TME

Vulvar SCC tumors exhibit upregulation of immune pathways and increased expression of diverse checkpoint proteins such as PD-1 and PD-L1 (116). Given the link between HPV and vulvar SCC, ICI could be a promising therapy for metastatic or recurrent disease similar to cervical and other HPV related cancers. Several trials involving vulvar SCC patients have demonstrated promising responses to immunotherapy. In KEYNOTE 028, patients with PD-L1 expressing tumors including 18 vulva SCC were treated with the PD-1 inhibitor, Pembrolizumab (117). In this phase 1B multi-center cohort study, the vulva SCC patients had an ORR of 7%. One patient had a partial response, 7 had SD and 6 had progression of disease. No CR was reported. The median PFS for vulvar SCC patients was 3.8 months, and the PFS rates were 20% and 7% at 6 months and 12 months respectively. OS rates were higher at 42% and 28% at 6 months and 12 months respectively. In addition, 8 out of 18 patient tumors showed a significant correlation between the PD-L1 CPS and ORR ($p<0.05$) as well as PFS ($p = 0.005$) (117).

Studies involving vulvar, cutaneous, and cervical SCC demonstrated significant clinical benefit from immune checkpoint inhibitors. This led to FDA approval for specific patient populations such as pembrolizumab monotherapy in patients with metastatic/recurrent tumors expressing high tumor mutation burden (TMB-H) or MSI-H/dMMR. In addition, FDA approval was granted for PD-L1 expressing persistent, recurrent, or metastatic solid and cervical cancers. A phase II study, KEYNOTE 158, was a prospective, single arm, open-label, multi-cohort study conducted to assess the effect of Pembrolizumab on survival in patents with 27 different solid tumors who had metastatic, unresectable disease or progression on chemotherapy. ORR was 34.3% for the entire cohort. Survival analyses showed a median PFS 4.1 months and median OS of 23.5 months. The authors also investigated a link between molecular biomarkers, TMB-H or MSI-H/dMMR and clinical outcomes. Seventy-one vulvar SCC patient tumors were analyzed for TMB status and 12 had TMB-H compared to 59 with no TMB. Two patients from each group achieved objective treatment responses. The median OS for patients with TMB-H tumors was 10.8 months compared to 5.3 months in those with non TMB-H tumors. Thus, a potential benefit may exist in patients with TMB-H tumors undergoing treatment with Pembrolizumab. The MSI-H/dMMR cohort of 223 patients included one with vulvar SCC and thus a correlation could not be established for vulvar cancer. While these molecular biomarkers seem predictive of a good clinical outcome with Pembrolizumab treatment, their status is rarely reported in vulvar tumors. Thus, further studies will contribute to our understanding of the role for molecular biomarkers in immune checkpoint inhibitor treatment responses.

A small number of vulva SCC patients were included in a phase I/II multicenter, open-label, multi-cohort trial. CheckMate358 analyzed the effectiveness of Nivolumab for neoadjuvant therapy or treatment of metastatic or recurrent HPV-associated cancers. In the 5 patients with vulvar/vaginal SCC, two had HPV associated tumors and the ORR was 20%. One patient with a HPV-independent tumor showed complete response lasting 5 months. Whereas SD was achieved in 3 patients and progression was observed in 1 patient. Limitations of this trial included low frequency of HPV associated vulvar tumors attributed to utilization

of different sensitivities of the HPV assays (108). Another phase I/II open-label, multicenter trial was conducted on the effect of Cemiplimab in 59 patients with metastatic cutaneous SCC not including primary vulvar SCC. The ORR was 47% comprising CR in 4, PR in 24, SD in 9 and progression in 11 patients. Treatment response lasting more than 6 months was shown in 57% of patients. Interestingly, 87% patients showed response to treatment at the time of data cutoff. While cutaneous SCC encompasses vulvar SCC, there is a difference in the etiology and molecular markers such as UV light exposure versus persistent viral infection/dermatoses. Thus, the effectiveness of immune checkpoint inhibitors, Nivolumab and Cemiplimab, in vulvar cancer has been approved based on extrapolation from HPV-associated cervical and cutaneous SCC data.

Current ongoing trials involving vulvar SCC are investigating the effectiveness of combination therapies including Pembrolizumab with Cisplatin and RT (NCT04430699), Durvalumab, Tremelimumab and stereotactic body RT (NCT03452332), a phase II basket trial of Pembrolizumab and a HDAC inhibitor, Virinostat (NCT04357873), Nivolumab and Ipilimumab (NCT02834013), durvalumab and MEDI0457 (INO 3112) vaccine (NCT03439085) and Atezolumab combined with a VEGF-TKI, Tivozanib (NCT05000294).

CONCLUSION

The exponential increase in clinical trials testing multi-target immunotherapies may lead to effective tumor destruction, recurrence prevention and, ultimately, prolonged survival of gynecologic cancer patients. Vaccine design and development in gynecologic malignancies will benefit from new and evolving technologies for developing unique tumor neoantigens, oncolytic viral therapies, optimization of adjuvants and immune cell-based vaccines. In ovarian cancer patients, immunotherapy is playing an increasingly prominent role resulting in improved clinical outcomes. The challenges of immunotherapy include high costs, labor intensive extraction and expansion of TILs, limited efficacy of some monotherapies, and concern for toxicities associated with combination therapies. Research is actively underway to address these issues with new design and generation of CAR T cells, CARs, exploration of exogenous TILs development from "normal matched" donors, identification of new TAAs and enhancing peptide and cell-based vaccines.

The endometrial cancer treatment landscape has been revitalized by the new molecular classification of POLE hypermutated, MSI-H, copy number-low or -high tumors. The endometrial TME's high mutation and neoantigen burden presents a unique opportunity to generate tumor associated antigens for vaccines. The immunosuppressive endometrial TME is partially abrogated with ICI mediated therapies. In addition, the characteristic high TIL frequency in endometrial tumors is curtailed by upregulation of various immunosuppressive pathways which are another attractive target. Studies show that the endometrial TME has increased expression of CTLA-4, LAG-3 and IDO, especially in *POLE*-ultramutated and MSI-H tumors. Thus, further studies involving genomic analyses and immunosuppressive pathways inhibitors could present interesting developments for targeted and combined immunotherapy in endometrial cancer patients.

In HPV associated cancers such as cervical and vulvar SCC, immunotherapy with ICI is well studied and becoming increasingly part of first line therapy for recurrent disease. Studies with ICI combined with existing treatments will help inform optimization of a multimodal therapeutic approach in cervical and vulvar SCC patients. It is important to identify robust biomarkers and immunogenic signature to facilitate patient selection for efficacy and improved clinical outcomes.

Conflict of Interest Statement: The authors declare no potential conflict of interest with respect to research, authorship and/or publication of this chapter.

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