Chapter

Immunotherapy in Gynecological Malignancies

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Abstract

Cancer immunotherapy is one of the most upcoming treatment strategies emerging as a fascinating option in the management of advanced gynecological malignancies. The development of immune-based antitumor approaches has led to safer treatment options that give fruitful results in these malignancies. In this chapter we are focusing on immune-based treatment in the management of gynecological cancers like cervical cancer, endometrial cancer, ovarian cancer, and vaginal and vulvar cancer. We are also discussing the clinical studies that have been conducted or are currently underway which are exploring these immune strategies that are developing as a logical overture for the treatment of advanced cancers including gynecological cancers.

Keywords: gynecological malignancy, immunotherapy, immune checkpoint inhibitors, cervical cancer, ovarian cancer, endometrial cancer

1. Introduction

Cancer immunotherapy is emerging as an attractive strategy among different therapeutic options over the past years, and also the treatment of many advanced malignancies has been revolutionized with the development of immune-based antitumor therapies. The advent of targeted immune therapies leading to successful outcomes in other malignancies has led to an increase in the number of clinical trials using these interventional strategies in patients with gynecological cancer. Generally, the role of immunotherapy is either to reactivate the immune response or to diminish the tumor-directed immune inhibition.

There are three stages of the dynamic process of immunoediting, also known as the three Es: an early elimination phase with the activation of an innate and adoptive immune response, an equilibrium phase where the isolated tumor cells are able to endure immune incursion, and an immune escape phase that the cancer cell variants can alter their genomic or antigenic phenotype or they are under the control of immunoregulatory phenomena to survive in the immunosuppressive medium. In order to activate tumor-directed immune responses, recent immune therapies have consisted of several approaches, including adoptive cell transfer (ACT), cancer vaccines, and immune checkpoint inhibitors.

Cervical cancer is unique among gynecologic malignant tumors because of its well-established and causative risk factor, chronic HPV infection. The infectious etiology of cervical cancer has led to effective vaccines for prevention; however, advanced stage/metastatic disease remains a principal cause of gynecologic cancer mortality in much of the world. The implementation of antiangiogenic therapy has greatly improved the treatment for relapsed/advanced disease over the last 5 years. Several clinical trials including CheckMate 358 and KEYNOTE-028 and KEYNOTE-158 are evaluating the role of immune checkpoint inhibitors in the treatment of cervical cancer.

In endometrial cancer, patients with advanced or disseminated recurrent disease have a poor prognosis, and most patients with peritoneal recurrence are considered incurable. Platinum and taxane chemotherapy produces response rates of 40–60%, which decreases to 20% for second-line drugs. So there is a need for development of more effective treatment for patients having advanced disease.

Approximately 25% of endometrial tumors are characterized by defects in the DNA mismatch repair system manifested by errors in DNA replication of trinucleotide repeat regions, commonly referred to as microsatellite instability. These defects in mismatch repair (MMR) also result in a high somatic mutation rate and accordingly increased number of neoantigens in these MMR-deficient tumors. In endometrial cancer, the presence of high microsatellite instability (MSI-H) has become an area of interest for use of immune checkpoint inhibitors.

For several reasons ovarian cancer is an ideal tumor type for which to consider an immunomodulatory management approach. Firstly, there is no negative impact of cancer itself on immunoregulatory cells that may be present within the bone marrow or other body locations. Secondly, while standard cytotoxic therapy of ovarian cancer can result in a depression in the number of immunoregulatory cell, these effects are generally modest in extent and short in duration. Lastly, it is common for patients with ovarian cancer to maintain a quite reasonable performance status and satisfactory nutrition.

A majority of ovarian cancer patients respond to cytotoxic chemotherapy and invariably are free from disease for periods varying from months to several years. This time interval can be exploited for required "activation" of immune defense mechanisms, either by using a tested vaccination strategy or any other form of immune modulation.

Multiple studies involving immune checkpoint inhibitors, conducted in advanced endometrial cancer, ovarian cancer, and cervical cancer, have shown promising preliminary results. But similar to that seen in other tumor types, continued work will need to focus on identifying those subsets of patients that will benefit from these therapies as these treatments are not without significant toxicities.

The immune system plays an important role in cancer pathogenesis. Numerous clinical trials and multiple researches dedicated to study therapies that involve the immune system to favorably impact the disease course in various malignancies have not only shown improved patient survival but also diversified the whole cancer management scenario by approval of the use of various immunotherapeutic agents in advanced malignancies [1].

Since cancer immunotherapy has emerged as an effective and appealing therapeutic option among other different therapeutic strategies and has been proven competent against multiple malignancies, it has led to an increase in research on immunomodulatory approaches in gynecological malignancies [2].

The ongoing research on the understanding of tumor biology and immunology has led to improved comprehension of mechanisms of immune recognition, regulation, and tumor escape that has provided new approaches for cancer immunotherapy [3].

2. Role of immune system in cancer

The principal role of the immune system is against foreign pathogens and infections. It is further classified as cellular and humoral immune systems, mediated by T and B lymphocytes and their products, respectively.

The initial innate immunity is nonspecific, and the adaptive immune response is the specialized defense. Both the strategies work in different manner. They employ the cellular immunity which has a rather fast response in eradicating intracellular microbes through the recognition of antigens, activation of antigen-presenting cells (APCs), and activation and proliferation of T cells. They also need humoral immunity mediated via antibodies produced by B cells for neutralizing toxins and act against infections. Where innate immunity works by releasing signals essential to stimulate responses from both T cells and B cells [4], the adaptive immune system is mainly consists of B cells, CD8+ cytotoxic T cells, as well as CD4+ helper T cell [5].

The immune system in tumor cells has a dynamic relationship, in which either it can identify or control tumor cells in a process called cancer immunosurveillance or cause tumor progression through chronic inflammation, immunoselection of poorly immunogenic variants, and suppressing antitumor immunity [6]. There are three stages of this dynamic process called immunoediting. The first is the elimination phase in which innate and adaptive immunity works together to identify and eliminate the cancer cells before they become clinically apparent [7]. If the cancer cells are not eliminated, they enter the second phase which is equilibrium. It can last from months to years. Here the cancer cells persist, but outgrowth is prevented by the immune system. Lastly the escape phase is in which either the cancer cell variants survive in the immunosuppressive microenvironment by altering genetic or antigenic phenotype or under the control of immunoregulatory phenomena. [8] In order to activate tumor-directed immune responses, recent immune therapies have consisted of several approaches, including adoptive cell transfer (ACT), cancer vaccines, and immune checkpoint inhibitors.

Gynecological cancers are a group of malignancies that involve different organs that comprise the female reproductive system. The most common types of gynecologic malignancies are cervical cancer, ovarian cancer, and endometrial cancer. Other less common gynecological malignancies arise from the vagina, vulva, and fallopian tubes [9].

3. Cervical cancer

Cervical cancer represents 6.6% of all female cancers. It is the fourth most common cancer in women with an estimated 570,000 new cases in 2018. Approximately 90% of deaths from cervical cancer occur in underdeveloped and developing countries [10]. Cervical cancer has emerged as a preventable disease due to currently employed screening tests which have highlighted HPV infection as an etiological factor. Although significant progress has been made in screening and prevention of cervical cancer, the 5-year overall survival remains 66% [11]. For cases diagnosed at an early stage, the recurrence rates vary between 10 and 20%, but for advanced cases, the rate of recurrence reaches up to 70% [12]. There is a need to improve outcomes, and immunotherapy could offer this possibility. The recognition of human papilloma virus as an etiological agent has greatly improved the understanding of the disease and led to improved strategies in prevention of cervical cancer [13]. The infectious etiology of cervical cancer has led to effective vaccines for prevention; however, advanced stage/metastatic disease remains a principal cause of gynecologic cancer mortality. Currently there are three licensed HPV prophylactic vaccines, namely, bivalent vaccine cervarix against HPV16/18, Gardasil against HPV-6/11/16/18, and Gardasil9, a nonavalent HPV-6/11/16/18/31/33/45/52/58 vaccine. All are based on on-infectious recombinant type-specific L1 capsid proteins assembled into viral-like particles (VLPs) as immunogens [14].

There is a huge unmet need for the treatment for women having advanced/recurrent cancer after standard chemotherapy and immunotherapy aims to fill that void, through therapies that harness a patient's own immune system to attack the cancer.

4. Cancer vaccines in cervical cancer

Cancer vaccines are used to mediate immune response by activating T cells which can specifically recognize cancer cells by tagging them with tumor-specific antigens E6 and E7. These antigen-tagged tumor cells are recognized by antigen-presenting cells and killed by cytotoxic T cells [15].

Live vector vaccines are highly immunogenic vaccines which can stimulate mucosal as well as humoral and/or cellular systemic immunity. They present E6 and E7 to APC to cause immune response through major histocompatibility complex MHC I [16]. Although they are attenuated vaccines, still care has to be taken before administering it in immunocompromised individuals. ADXS11-001 is a type of live attenuated vaccine that uses *Listeria monocytogenes* (Lm), a gram-positive intracellular bacterium as bacterial vector. It secretes HPV-16 E7 antigen fused to a nonhemolytic fragment of Lm protein listeriolysin O [17].

The following studies have been conducted (**Table 1**):

Study name	Patient cohort	Treatment schedule	Response	Toxicity
Maciag et al. [18] Phase I trial	*n* = 15 Recurrent or metastatic disease	DL1: ADXS11-001 1 × 109 two doses every 21 days DL2: ADXS11-001 3.3 × 109 two doses every 21 days DL3: ADXS11-001 1 × 1010 two doses every 21 days	Stable disease in 7 patients	Pyrexia (100%), vomiting 60%, pain (57%), chills, anemia (53%) Grade 3: 40% (6 pts)
Ghamande et al. [19] Phase I	*n* = 9 Recurrent or metastatic disease	DL1: ADXS11-001 5 × 109 thrice weekly during 12 weeks DL2: ADXS11-001 1 × 1010 thrice weekly during 12 weeks	—	TRAE: 75% AE: 99% Grade 1 and 2 Grade 3: chills, vomit, hypotension, tachycardia, fever, and nausea
Basu et al. [20] Phase II	*n* = 109 Advanced cervical cancer	Arm 1 ADXS11-001 monotherapy Arm 2 ADXS11-001 with cisplatin combination	Median progression-free survival (6.10 vs. 6.08 months) and the overall response rate (17.1% vs. 14.7%) were similar for both groups	More adverse effects in arm 2
Huh et al. [21] (GOG 0265) Phase II	*n* = 26 Recurrent or metastatic disease	ADXS11-001 1 × 109 every 28 days for 3 doses	Mean 12 months survival: 38.5% Median OS: 6.2 months	AE: 91% Grade 1 and 2 TRAE: 38%: nausea, vomiting, chills, fatigue, and fever

Table 1.
Role of vaccination in HPV-associated cervical cancer.

4.1 Peptide-based vaccines in cervical cancer

Refer **Table 2**.

Study name	Patient cohort	Treatment schedule	Response	Toxicity
Welters et al. [22] Phase II adjuvant	*n* = 6 Stage IB1 and HPV16+	HPV16 E6 E7 SLP vaccine	Vaccine-enhanced number and activity of HPV16-specific CD4+ and CD8+ cells	Grade 1 and Grade 2: local pain, fever, flu-like symptoms, swelling, itching, burning eyes
Poelgeest et al. [23] Phase II	*n* = 31 Recurrent or metastatic disease	HPV16 E6-E7 SLP vaccine 300 g for four doses every 21 day	Median OS: 12.6 months no tumor regression or delay of progression	Grade 1 and Grade 2: fever, fatigue, headache, flu-like symptoms, chills, nausea, swelling extremities, rash, vomiting, tingling extremities, and injection site pain

Table 2.
Peptide-based vaccine in cervical cancer.

4.2 Dendritic vaccines in cervical cancer

Refer **Table 3**.

Study name	Patient cohort	Treatment schedule	Response	Toxicity
Ramanathan et al. [24] Phase I	*n* = 14 Recurrent or metastatic disease	Arm 1: placebo three doses every 14 days Arm 2: unprimed DC three doses 1 × 106 cells every 14 days Arm 3: primed DC three doses 1 × 106 cells every 14 days	SD in Arm 3	Grade 1 and Grade 2: itching at injection site, fever, chills, abdominal discomfort, vomit, ALP increased
Ferrara et al. [25] Phase I	*n* = 15 Recurrent or metastatic disease	Analogous dendritic cells pulsed with HPV E7 protein	Serological response in 3 pts Cellular response in 4 pts No objective clinical response	
Santin et al. [26] Phase I	*n* = 10 Stage IB or IIA	DL1: HPV16/18 E7 antigen-pulsed DC5 × 106 for five doses every 21 days DL2: HPV16/18 E7 antigen-pulsed DC10 × 106 for five doses every 21 days DL3: HPV16/18 E7 antigen-pulsed DC15 × 106 for five doses every 21 days	CD4+ T-cell response in all patients	Mild swelling and erythema at the injection site

Table 3.
Dendritic vaccine in cervical cancer.

5. Immune checkpoint inhibitors in cervical cancer

5.1 PD1/PDL1 inhibitors

Programmed cell death protein-1/programmed death ligand-1 immunoregulatory axis is a promising target for cervical cancer treatment [27]. Pembrolizumab is a humanized monoclonal immunoglobulin G4 (IgG4) kappa isotype antibody targeting PD-1 (**Table 4**).

Other ongoing trials of pembrolizumab include PAPAYA Trial [30] which is a phase I study involving Stage Ib to Stage IV cervical cancer. The treatment schedule includes intravenous pembrolizumab followed by cisplatin-based chemoradiotherapy and brachytherapy and additional pembrolizumab after radiation. Another phase II trial with pembrolizumab followed by chemoradiotherapy and brachytherapy is also open for recruitment [31].

Nivolumab is a human IgG4 monoclonal antibody that causes stimulation of PD1 pathway-mediated immune response inhibition by binding to the PD-1 receptor and blocking its interaction with PD-L1 and PD-L2. [32] Checkmate 358 trial is a phase I/II trial by Hollebecque et al. in 19 patients of cervical cancer which studied nivolumab 240 mg every 2 weeks and showed ORR was 20.8% and disease control rate was 70.8%. Responses were observed regardless of PD-L1 expression, HPV status, and number of prior therapies [33].

Other trials of nivolumab include NRG-GY002, a phase II trial in recurrent or metastatic breast cancer [34]. A trial of nivolumab with HPV 16 SLp vaccine in HPV 16 positive cervical cancer is also underway [35].

Other checkpoint inhibitors under investigation include atezolizumab which is a fully humanized monoclonal antibody IgG1 isotype PD-L1. It is being studied to assess the safety and efficacy in combination with cyclophosphamide/carboplatin in gynecological cancer including cervical cancer in phase Ib PRO-LOG study [36]. Another phase II study is ongoing to study the synergistic action of antiangiogenic therapy with immunotherapy by combining bevacizumab with atezolizumab in women with recurrent or metastatic cervical cancer [37, 38],

Durvalumab is a human IgG1 monoclonal antibody that blocks the action of PD-L1 with PD1 and CD 80. It is being studied along with tremelimumab, which is an antibody against CTLA4 in patients who have failed to respond or relapsed to standard treatment [39].

5.2 CTLA-4 inhibitors

Ipilimumab is a fully human monoclonal IgG1κ antibody which acts against the cytotoxic T lymphocyte antigen-4 (CTLA-4). CTLA4 is an immune-inhibitory

Study name	Patient cohort	Treatment schedule	Response	Toxicity
Keynote 028 Frenel et al. [28] Phase Ib	*n* = 24 Patients having metastatic disease in PD L1 > =1%	Pembrolizumab 10 mg/kg every 2 weeks up to 2 years	ORR = 12.5% 6 months PFS 13% OS 66.7% (preliminary results)	75% pts with treatment-related adverse effects 20.8% with Grade 3 toxicity
Keynote 0158 Schellens et al. [29] Phase II	*n* = 47 Metastatic disease	Pembrolizumab 200 mg thrice weekly to 2 years	ORR 17% (independent of tumor PD L1 status)	Not reported

Table 4.
PD1/PDL1 inhibitors in cervical cancer.

Study name	Patient cohort	Treatment schedule	Response	Toxicity
Lheureux et al. [41] Phase I/II	*n* = 42 Recurrent or metastatic disease	Phase I: ipilimumab 3 mg/kg every 21 days for four doses Phase II: ipilimumab 10 mg/kg every 21 days for four doses and four cycles (same dose) every 12 weeks	Median PFS 2.5 months	Grade 3 toxicity: diarrhea, colitis
GOG9929 study Mayadev et al. [42] Phase I	*n* = 34 FIGO IB2/IIA or IIB/IIIB/IVA, positive nodes	Weekly cisplatin 40 mg/m^2 during 6 weeks and extended field radiotherapy. If no progression 2–6 weeks after DL1: ipilimumab 3 mg/kg for four doses every 21 days DL2: ipilimumab 10 mg/kg for four doses every 21 days DL3: ipilimumab 10 mg/kg for four doses every 21 days	1 year DFS 74%	Grade 1 and Grade 2: rash, endocrinopaties, gastrointestinal toxicity Grade 3: 16% including lipase increased, neutropenia, and rash

Table 5.
CTLA4 inhibitors in cervical cancer.

molecule which is expressed in activated T cells and in suppressor T regulatory cells [40] (**Table 5**).

5.3 Adoptive cell transfer therapy

Adoptive cell transfer therapy using autologous tumor-infiltrating lymphocytes is emerging as a promising treatment modality in immunotherapy for various cancers. There are two types of adoptive cell therapy which includes chimeric antigen receptor T-cell (CAR T-cell) therapy and tumor-infiltrating lymphocyte (TIL) therapy.

Chimeric antigen receptor (CAR) T-cell therapy involves genetically engineered patient's autologous T cells that causes them to express a CAR specific for a tumor antigen. These cells are extracted, further divided, and reinfused back into the patient [43].

A trial was conducted by Lu et al. which evaluated adoptive CD4+ T-cell therapy in solid metastatic cancer. It had two patients of metastatic cervical cancer, out of which one patient had objective complete response [44].

There is a trial ongoing to test the safety, feasibility, and efficacy of CAR T-cell immunotherapy in patients who have GD@, PSMA, Muc1, mesothelin, or positive cervical cancer markers by Chang et al. [45].

TIL therapy predates the CAR T-cell therapy, and the basic principle involves the ex vivo culture of tumor specimens which have been resected and expansion of tumor-infiltrating lymphocytes (TILs) with interleukin-2. Selected T cells of a preferred antigen specificity and phenotype can be identified in vitro and divided. The number of antigen-specific T cells in peripheral blood after this method usually exceeds by far that possible by current vaccine treatment strategies alone. In addition, adoptive T cells appear more effective in inducing tumor regression than lymphocytes generated by vaccines, suggesting greater ability to overcome tumor-mediated immune evasion mechanisms [46].

Stevanovic et al. [47] conducted a trial on 17 patients of metastatic cervical cancer who received high-dose lymphocyte-depleting chemotherapy followed by aldesleukin. Patients were treated with a single infusion of human papillomavirus (HPV) E6 and E7 reactivity (HPV-TILs). Three of nine patients experienced objective tumor responses (two complete responses and one partial response).

6. Endometrial cancer

Endometrial cancer is the 4th most commonly occurring cancer in women and the 15th most commonly occurring cancer overall. There were over 380,000 new cases in 2018 [48]. In women with advanced and recurrent cancer, the prognosis is considered very poor. Unfortunately, there are limited treatment options for advanced or recurrent endometrioid endometrial cancer. However, with the advent of immunotherapy, immune checkpoint inhibitors have shown promising results in these cases.

Study name	Patient cohort	Treatment schedule	Response	Toxicity
Ott et al. [53]	*n* = 24 Locally advanced or metastatic PD-L1-positive endometrial cancer	Pembrolizumab 10 mg/kg every 2 weeks for up to 24 months or until progression or unacceptable toxicity	Three (13%) patients achieved confirmed partial response. Three additional patients achieved stable disease, with a median duration of 24.6 weeks	Grade 3 treatment-related AEs were reported in four patients
Makker et al. [54] Phase II	*n* = 53 Metastatic endometrial cancer unselected for microsatellite instability or PD-L1	20 mg oral lenvatinib daily plus 200 mg intravenous pembrolizumab every 3 weeks, until progression or unacceptable toxicity	Patients had an objective response at week 24	Serious treatment-related adverse events occurred in 16 (30%) patients, and one treatment-related death was reported (intracranial hemorrhage)
Santin et al. [55]	*n* = 2 Pretreated polymerase ε (POLE) ultramutated and MSH6 hypermutated recurrent endometrial tumors refractory to surgery, radiation, and chemotherapy	Anti-PD1 immune checkpoint inhibitor nivolumab 3 mg/kg biweekly	Both patients demonstrated a remarkable clinical response to the anti-PD1 immune checkpoint inhibitor nivolumab	No Grade 3 or higher side effects reported
Fleming et al. [56]	*n* = 15 Previously treated recurrent endometrial cancer	Atezolizumab 1200 mg or 15 mg/kg IV q3w was administered until toxicity or loss of clinical benefit	ORR was 13% (2/15) Of the remaining pts, two had SD, nine had PD, and two were non-evaluable	Seven (47%) pts had any related AE, mainly G1-2 (5 pts). No G4-5-related AEs occurred

Table 6.
Immunotherapy in endometrial cancer.

Microsatellite instability-high (MSI-H) status, tumor mutation burden, and high PD-L1 expression have been associated with higher response rates to this therapy [49].

Approximately 25% of endometrial cancer show microsatellite instability which is caused by defects in mismatch repair genes. These defective MMR genes lead to high somatic mutation rates, thereby increasing the number of neoantigens in MMR-deficient tumors [50].

Endometrial cancer has been subdivided into four prognostically distinct molecular subgroups based on the findings of the cancer genome atlas, namely, polymerase epsilon (*POLE)* ultramutated, MSI hypermutated, copy-number (CN) low, and CN high [51].

The ultramutated POLE subgroup and MSI hypermutated subgroup have immune-rich microenvironment and high mutation load. Evidence has supported over-expression of the PD-1/PD-L1 pathway in these molecular subtypes, and therefore, PD1/PD L1-targeted immunotherapy has a role in these tumors [52] (**Table 6**).

An ongoing phase II, two group trials are studying the role of avelumab in POLE-mutated endometrial cancer and MSS-mutated endometrial cancer. Avelumab is administered at 10 mg/kg as 1-hour IV infusion every 2 weeks until disease progression or unacceptable toxicity. Sixteen patients are enrolled in each cohort in the first stage. The preliminary results are yet to be published [57].

6.1 Anticancer vaccines in endometrial cancer

The following studies have been conducted (**Table 7**).

7. Ovarian cancer

Ovarian cancer accounts for 2.5% of all malignancies among females but 5% of female cancer deaths because of low survival rates, largely driven by late-stage diagnoses [60]. There were nearly 300,000 new cases in 2018. Ovarian cancer is considered to be an ideal type of tumor which can be dealt with immunomodulatory

Study name	Patient cohort	Treatment schedule	Response	Toxicity
Ohno et al. [58], phase II	*n* = 12 WT1/human leukocyte antigen (HLA)-A*2402-positive gynecological cancer	Intradermal injections of a HLA-A*2402-restricted, modified 9-mer WT1 peptide every week for 12 weeks	Stable disease in three patients and progressive disease in nine patients. The disease control rate was 25.0%	Local erythema occurred at the WT1 vaccine injection site
Coosemans et al. [59]	*n* = 6 Pretreated patients with uterine cancer	Four times weekly vaccines of autologous dendritic cells (DCs) electroporated with WT1 mRNA	Three out of four human leucocyte antigen-A2 (HLA-A2)-positive patients showed an oncological response. Two HLA-A2-negative patients did not show an oncological or an immunological response	One patient had a local allergic reaction

Table 7.
Anticancer vaccines in endometrial cancer.

approach as the disease does not negatively affect the immunoregulatory cells in the bone marrow or other locations of the body, and the patients suffering from ovarian cancer maintain a relatively good performance status even in later stages, so immunotherapy can be used as a potential treatment option in these patients. Cytotoxic chemotherapy given in ovarian cancer can negatively impact the immunoregulatory cells, but the effect is short lasting. Further the patients who are in advanced stages, if they respond to standard treatment of ovarian cancer, have a relatively long disease-free period which is substantial for the activation of immune defense mechanism either by cancer vaccines or by immunomodulator drugs [61].

7.1 Immune checkpoint inhibitors in ovarian cancer

The first published data supporting checkpoint inhibitors as a potentially valuable therapeutic option in ovarian cancer were observed in the trials of the anti-PD-1 antibody nivolumab and the anti-PD-L1 antibody BMS-93655 [62]. Other studies are as follows (**Table 8**).

Study name	Patient cohort	Treatment schedule	Response	Toxicity
Hamanishi et al. [63] Phase II	*n* = 20 Platinum-resistant ovarian cancer	IV nivolumab every 2 weeks at a dose of 1 or 3 mg/kg	Overall response rate was 15%, and the disease control rate was 45%	Grade 3 or 4 TRAE in 40% patients
Disis et al. [64] Phase Ib	*n* = 124 Recurrent/refractory ovarian cancer	Avelumab 10 mg/kg IV every 2 weeks	ORR was 9.7% based on 12 partial responses; 6 were ongoing. Stable disease was observed in 55 pts (44.4%); disease control rate was 54.0%	Grade 3 or 4 TRAEs were reported in 6.5%
Varga et al. [65] Phase Ib	*n* = 26 Advanced ovarian cancer	Pembrolizumab 10 mg/kg was given every 2 weeks for up to 2 years or until confirmed progression or unacceptable toxicity	The best overall (confirmed) response was 11.5%. 6/26 (23.1%) had evidence of tumor reduction; 3 had a tumor reduction of at least 30%	Drug-related AEs occurred in 69.2% of pts
Lee et al. [66] Phase I/II	*n* = 12 BRCA positive with ovarian cancer	Durvalumab at 1500 mg every 4 weeks plus olaparib at 300 mg twice daily and durvalumab at 1500 mg every 4 weeks plus cediranib at 20 mg 5 days on/2 days off per week	ORR of 17% and disease control rate of 83%	Grade 3 or 4 TRAEs were reported in 75% patients

Table 8.
Immune checkpoint inhibitors in ovarian cancer.

Ongoing trials include JAVELIN Ovarian 200 is the first phase III trial, which is a three-arm trial, comparing avelumab administered alone or in combination with pegylated liposomal doxorubicin versus pegylated liposomal doxorubicin alone in patients with platinum-resistant/refractory recurrent ovarian cancer [67].

NCT02839707 is undergoing trial which is comparing pegylated liposomal doxorubicin with atezolizumab and/or bevacizumab in refractory ovarian cancer [68].

A phase II study by Wenham et al. [69] is studying combination of weekly paclitaxel and an anti-PD-1 (pembrolizumab). The primary endpoint of this study is a 6-month progression-free survival rate.

ATALANTE trial is an ongoing phase III study to assess the efficacy of atezolizumab in combination with platinum-based chemotherapy plus bevacizumab administered concurrent to chemotherapy and in maintenance [70].

CheckMate 032 study trial to study the safety and efficacy of nivolumab as a single agent or in combination with ipilimumab is currently underway [71].

Similar trial in which nivolumab with or without ipilimumab in treating patients with persistent or recurrent epithelial ovarian is being studied by the National Cancer Institute [72].

A phase II trial to determine the median immune-related progression-free survival (irPFS) in combination of an anti-CTLA-4 antibody (tremelimumab) with an anti-PD-L1 antibody (durvalumab) versus their sequential use in platinum-resistant epithelial ovarian cancer is also currently ongoing [73].

Multiple other trial are using immune checkpoint inhibitors in initial therapy to improve progression-free survival like durvalumab or pembrolizumab with standard paclitaxel and carboplatin therapy, where pembrolizumab is used as adjuvant therapy after surgery [74]. The role of immune checkpoint inhibitors as maintenance therapy is also under investigation with JAVELIN Ovarian 100 phase II study of avelumab (anti-PD-L1) as maintenance after standard therapy or in combination with standard therapy and then continued as maintenance treatment [75].

7.2 Cancer vaccines in ovarian cancer

Various types of cancer vaccines are studied for the treatment of ovarian cancer.

The cancer testis antigen, NY ESO1, is most frequently expressed in epithelial ovarian cancer, and vaccine against it has shown induced T-cell-specific immunogenicity [76]. Since NY-ESO-1 is regulated by DNA methylation, it was hypothesized that DNA methyltransferase (DNMT) inhibitors may augment NY-ESO-1 vaccine therapy. Decitabine is a hypomethylating agent that inhibits DNA methyltransferase. A phase I trial was conducted to study dose escalation of decitabine in addition to NY-ESO-1 vaccine and doxorubicin liposome in 12 patients with relapsed epithelial ovarian carcinoma. The results showed stable disease or partial response in six patients [77].

Sabbatini et al. conducted a phase I trial in 28 patients which showed that in order to enhance the immunogenic response to NY-ESO1, the addition of immune modulation agents to the vaccine preparation such as Montanide and immunostimulants such as the toll-like receptor (TLR) ligand poly-ICLC (polyinosinic-polycytidylic acid—stabilized by lysine and carboxymethylcellulose) can be considered [78].

Other antigen under investigation is Her/neu2, which is expressed in 90% of epithelial ovarian cancers. A phase I/II study conducted BY Chu et al. demonstrated a 90% 3-year overall survival response in patients with advanced ovarian cancer who were remission for vaccination with monocyte-derived dendritic cells (DC) loaded with Her2/neu, hTERT, and PADRE peptides, with or without low-dose intravenous cyclophosphamide [79].

In a phase I/II study by Baek et al., 10 ovarian cancer patients with minimal residual disease were treated with dendritic cell vaccination with IL2. Three out of 10 patients showed maintenance of complete response, and one patient showed stable disease [80].

A phase II study was conducted to study the efficacy of personalized peptide vaccine (PPV) for recurrent ovarian cancer patients by Kawano et al. [81]. The patients enrolled in this study showed an overall survival (OS) of 39.3 months in platinum-sensitive cases and 16.2 months in platinum-resistant cases. This was attributed to be secondary to the stabilization of disease and the prolongation of tumor progression rather than disease regression.

7.3 Adoptive cell transfer in ovarian cancer

Adoptive cell transfer therapy is not widely studied in ovarian cancers. In a Japanese study by Fujita et al., 13 patients with epithelial ovarian cancer were treated with tumor-infiltrating lymphocyte therapy. Eleven patients served as control group who received only chemotherapy following primary operation. The estimated 3-year overall survival rate of disease-free patients in the TIL group and in the control group was 100 and 67.5%, respectively [82].

Vulvar and vaginal cancer: Immunotherapy has shown promising results in advanced gynecological cancer. Checkmate 358 trial has shown that nivolumab has encouraging clinical activity in cases of HPV-positive vulvar and vaginal malignancies. A lot of research is warranted to establish immunotherapy as emerging treatment option in these cancers.

8. Conclusion

Immunotherapy is emerging as a viable treatment modality in multiple cancers, and its safety and efficacy are under investigation in advanced gynecological malignancies. Immune checkpoint inhibitors have shown promising preliminary results in advanced ovarian, cervical, and endometrial cancer.

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