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Immunotherapy of gynecological cancers

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A B S T R A C T

Oncology treatments have evolved from intuitive, via empiric, to the present precision medicine, with the integration of molecular targeted therapies in our treatment arsenal. The use of the patients' powerful immune system has long been contemplated and recently led to the integration of immunotherapy to overturn the well-documented inhibitory effects of the tumor on the immune system and restore it to a state of activity against the cancer. Recent favorable results have shown the value and effectiveness of immunotherapy against gynecological cancers. In particular, the checkpoint inhibitors, targeting the programmed death-1 (PD-1) pathway, have shown durable clinical responses with manageable toxicity. Several phase II and III clinical trials testing the association of different regimen of chemotherapy and immunotherapy are ongoing in gynecological cancers, and important results are expected. In this chapter, we outline the main principles of immunotherapy for gynecological cancers and summarize the current strategies used in clinical trials.

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Innate immunity: Cells and mechanisms that provide the first line of defense in a nonspecific manner. Innate immune responses are rapid and independent of antigen [1].

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Adaptive immunity: Cells and mechanisms that provide protection that is mediated by B and T lymphocytes following exposure to specific antigen and characterized by immunological memory [2].

Humoral immune response: Transferred by serum. Refer to antibody responses; antibodies are antigen-reactive, soluble, bifunctional molecules composed of specific antigen-binding sites associated with a constant region that directs the biologic activities of the antibody molecule, such as binding to effector cells or complement activation [3].

Cellular immune response: Transferred by cells. Generally, refer to cytotoxic responses mediated directly by activated immune cells, rather than by the production of antibodies T lymphocytes: act as helper cells in the generation of humoral and cellular immune responses and by acting as effector cells in cellular responses [4].

T helper/inducer cells: Express the CD4 cell surface marker, play a main rule in the production of cytokines, and can provide help to B lymphocytes, resulting in antibody production [5].

T suppressor/cytotoxic cells: express the CD8 marker and can directly kill target cells [6].

Major Histocompatibility Complex (MHC): Both CD4 and CD8 T cells respond to antigen only when it is presented in the context of major histocompatibility complex (MHC) molecules on antigen-presenting cells, target cells, or both [7].

B lymphocytes: Cells that produce and secrete antibodies, which are antigen-binding molecules. They also can serve as efficient antigen-presenting cells for T lymphocytes [8].

Macrophages and dendritic cells (DCs): Play a key role in the generation of adaptive, lymphocyte-mediated immune responses by acting as antigen-presenting cells [9].

Natural killer (NK) cells: Have large granular lymphocytic morphology, do not express the CD3 T cell receptor complex, and do not respond to specific antigens [10].

Cytokines: Soluble mediator molecules that induce, enhance, or affect immune responses [11].

Introduction

Cancers are more prevalent in populations who are immunosuppressed (e.g., patients with HIV and organ transplant recipients), suggesting that impaired immunity may contribute to the development of cancer [12]. Considering the immense potential of the immune system to fight “foreign,” many efforts for more than 35 years have attempted to develop strategies for actively stimulating immunological rejection of tumors. In 2017, the Food and Drug Administration (FDA) approved the first two chimeric antigen receptor-T cell therapies for the treatment of patients with refractory or relapsed B-cell leukemia [13].

This chapter will outline the main principles of immunotherapy for gynecological cancers and summarize the current strategies used in clinical trials.

Therapeutic strategies

Immunotherapy is utilized to overturn the well-documented inhibitory effect of the tumor on the immune system and restore it to a state of activity. The tumor is able to elude immune response through multiple pathways, including the activation of immune checkpoints that inhibit the immune system's ability to target the tumor [14,15]. To activate tumor-directed immune responses, recent immune therapies have utilized several approaches:

1 **Adoptive cell transfer (ACT):** Autologous T cells, meaning the T cells from the patients, undergo either ex-vivo extraction from resected tumor tissue (tumor-infiltrating lymphocytes (TILs)) or from peripheral blood from the patient, and are then expanded in vitro, and infused back into the patient with the purpose that these T cells will attack the cancer cells. In addition, to improve specificity against the cancer, genetically modified T cells, designed to recognize specific tumor-associated antigens, may be included into adoptive cell transfer. These include engineered T-cell receptors that recognize tumor-specific peptides or chimeric antigen receptors (CAR) that allow T cells to recognize tumor surface antigens using an antibody-like recognition module. This technology has provided the best results, to date, in tumor immunotherapy [16,17]. This approach has the capacity

to specifically kill cancer cells and can potentially lead to the complete elimination of residual cancer cells [16].
In the early stages (late 1980s), adoptive cell transfer based approaches used peripheral blood mononuclear cells exposed to IL-2 ex vivo to lead to the formation of what are called lymphokine-activated killer (LAK) cells, to kill cancer cells [18,19]. Although some encouraging responses were originally obtained in human subjects, considerable toxicity was seen with LAK cells and IL-2 treatment [20–24], and adoptive immunotherapy with LAK cells did not become a practical option for the treatment of gynecological cancers.
A more sophisticated approach of adoptive cell transfer consists of ex vivo-stimulated TILs or tumor-associated lymphocytes from ascites, with or without IL-2 [25,26].
Optimization of these adoptive immunotherapies will include improving the cell source, the forms of stimulation, the methods for in vitro expansion, and the cytokines that are given during such treatment.

2 **Cancer vaccines:** Either tumor-specific antigens (supplied as peptides) or antigen-activated dendritic cells are used, in combination with immune-stimulatory adjuvants, to stimulate T-cell responses [27].
The best-known preventive vaccine is the one against the human papilloma virus (HPV), which is highly effective to prevent cervical cancer, vulvar cancer, oro-pharyngeal cancers, and anal cancers [28]. Therapeutic vaccines, on the other hand, are being developed in clinical trials, but no major breakthroughs have occurred to date.

3 **Immune checkpoint inhibitors**: Immune checkpoint proteins are expressed on cytotoxic T cells upon their activation, with the intention to keep the immune response under control, in a sort of "negative feedback loop" to hinder overactivation of the immune response and lessen damage to normal cells. Cancer cells utilize these pathways to evade immune surveillance. To counteract this undesired immune inhibition induced by the checkpoint proteins, monoclonal antibodies against these checkpoint proteins have been developed, including against the cytotoxic T lymphocytes-associated antigen 4 (CTLA-4), the programmed cell death (PD-1) protein, and the PD-1 ligand proteins (PDL-1), and are currently being used successfully in clinical settings [29–31].

Side effects

The most common adverse reactions among patients treated with immune checkpoint inhibitors included fatigue (43%), musculoskeletal pain (27%), diarrhea (23%), pain and abdominal pain (22% each), and decreased appetite (21%). Eight percent of patients discontinue one of these drugs called pembrolizumab due to adverse reactions. Serious adverse reactions occurred among 39% of patients. The most frequent serious adverse reactions reported included anemia (7%), fistula (4.1%), hemorrhage (4.1%), and infections (4.1%) [31,32].

Cervical cancer (Table 1)

Cervical cancer is unique among gynecologic cancers because of its established quasi universal cause, human papillomavirus (HPV), the exact mechanisms whereby HPV proteins interact and disrupt the molecular machinery of the cell, and the existence of a pre-cancerous stage detectable by the pap smear. Of the many types of HPVs, more than 30 infect the genital tract. Of these, 14 are high-risk HPV subtypes, and two of the high-risk subtypes, 16 and 18, are found in up to 62% of cervical carcinomas and 82% of the precancerous diseases [28]. HPV-infected cancerous cervical epithelial cells express two of the viral genes, E6 and E7, that, respectively, interact with and disrupt the function of the p53 and retinoblastoma tumor suppressor gene products. Factors other than infection with HPV, such as cellular immune function, play an important role in determining whether the infection of cervical epithelial cells regresses or progresses to cancer. This has led to the development of prophylactic and therapeutic vaccines to HPV as well as treatment approaches based on the enhancement of host immune function.

Table 1
Immunotherapies for cervical cancer.

Immunotherpy	Mechanism	Overall response rate
TA-HPV vaccine [54]	Viral vectors expressing HPV-16 or -18 E6 or E7	20–50%
Pembrolizumab [32]	Immune checkpoint inhibitors	<20%
Nivolumab [63]	Immune checkpoint inhibitors	20–50%
HPV-Tumor-infiltrating T cells [65]	Adoptive cell transfer	20–50%

Vaccines

The biologic principle of cancer vaccines is to stimulate an immune response specifically directed against malignant cells. This can be applied prophylactically and therapeutically.

- **Prophylactic Human Papillomavirus Vaccine**

For prophylactic vaccination, the goal is to induce an immune response that will recognize, eradicate, and prevent (pre-)malignant progression.

HPV E6 and E7 are attractive antigens for use in therapeutic vaccines due to the involvement of these HPV-encoded proteins in cellular transformation, and therefore, they are consistently expressed in HPV-positive tumor cells [33–35]. The development of prophylactic vaccination to protect against HPV infection became within the realm of possibility through the development of protein mimics that simulate the exterior protein capsid of the virus, termed virus-like particles (VLPs) [36]. Currently, there are three clinically available vaccines:

1 **Gardasil** (Merck, NJ, USA), a quadrivalent prophylactic vaccine containing the VLPs of four HPV types, 6, 11, 16, and 18. The vaccine was approved by the U.S. Food and Drug Administration (FDA) in 2006 [37].
2 **Cervarix** (GlaxoSmithKline, Middlesex, U.K.), a bivalent prophylactic vaccine containing the virus-like proteins of types 16 and 18, that was approved in 2009 [38].
3 **Gardasil 9** (Merck, NJ, USA), a nonavalent vaccine containing the virus-like proteins of nine HPV types, 6, 11, 16, 18, 31, 33, 45, 52, and 58, that was approved by the U.S. FDA in 2016 [39].

Clinical trials showed that both the bivalent and quadrivalent vaccines are highly efficient in preventing dysplastic and cancerous lesions, especially in patients who were not previously exposed to HPV. The efficacy of Gardasil was 99% for preventing cervical intraepithelial neoplasia grades 2 and 3 caused by HPV 16 or 18 in females who were not previously infected with either HPV 16 or 18 before vaccination; however, efficacy was reduced to 44% in those who were infected prior to vaccination [40–42].

The bivalent and quadrivalent HPV vaccines were approved for females aged 9–26 for cervical cancer prevention with an additional approval of the quadrivalent HPV vaccine for genital warts.

In late 2016, several months after its approval, the nonavalent HPV vaccine became the only available HPV vaccine in the United States given its trial efficacy and broader coverage of oncogenic HPV serotypes. However, globally, vaccine availability is still restricted and varies based on location and vaccine cost, with most countries adopting either the bivalent or quadrivalent HPV vaccine [43].

- **Therapeutic Human Papillomavirus Vaccine**

Cancer vaccines are being developed therapeutically to serve as a “booster” for pre-existing antitumor immune responses or activating antitumor immunotherapies that have been actively administered to the patient. Various therapeutic vaccine strategies have been explored, including live vector, nucleic acid, protein, whole cell, and combinatorial vaccines. However, currently, there

are no HPV therapeutic vaccines approved for use in humans. Nevertheless, there have been numerous and extensive studies that have generated promising vaccine candidates tested in clinical trials [44–46].

Live vector vaccines

Live vector vaccines are recombinant bacterial or viral vectors that can replicate inside the host cells, facilitating the spread of antigens. They can drive antigen presentation through both MHC class I and class II pathways, stimulating $CD8^+$ cytotoxic T-cells and $CD4^+$ helper T-cells, respectively, thus provoking immune-mediated antitumor activity, and in cervical cancer, HPV-specific proteins have been utilized to target HPV-infected cells [47].

Bacterial vector: Listeria is a promising vector because of properties such as its ability to infect macrophages without being captured by phagocytosis, and its ability to direct antigen processing via MHC I and MHC II pathways; therefore, Listeria monocytogenes (Lm) is of particular interest for vaccine development [48,49]. Promising results started to be published from various phase I, II, and III clinical trials, using bacterial vector vaccines against advanced cervical malignancies, reporting reduction in tumor size, increase in E7 cell-mediated immunity but only modest improvement in overall survival [50–53].

Viral vectors: In clinical trials, recombinant modified vaccinia virus Ankara (MVA) viral vectors expressing HPV-16 or -18 E6 or E7 (TA-HPV) showed HPV-specific cytotoxic T cell (CTL) responses in 28% of patients with advanced cervical cancer in a phase I/II study [54,55], and at least, a 40% reduction in lesions in 83% of patients aged 42–54 with high-grade vulvar or vaginal intraepithelial neoplasia in a phase II study [56]. Most recently, a vaccine based on HPV-16 E2 (MVA E2) was shown to have 90% efficacy in the treatment of HPV-induced anogenital intraepithelial lesions in a phase III study in 1356 patients [57].

However, there remain challenges in the use of live vector vaccines due to potential dominance of the immune response to the bacterial/viral vector instead of the HPV antigen and the potential pathogenicity of the vector, particularly among oncologic patients and immune-compromised individuals [47,58].

Subunit vaccines

Various subunit vaccines have been explored and found to have an effect on cancer cells. Subunit vaccines are antigens delivered in the form of peptides or whole proteins. They are regarded as safer than live vector vaccines as they are present in the host cells transiently, decreasing the chances of toxicity [59–61].

Immune checkpoint inhibitors

In cervical cancer, patients with advanced or disseminated recurrent disease have a poor prognosis and few substantial treatment options are available which make alternative treatment options such as immunotherapy attractive.

Preliminary results from the cervical cancer cohorts of several studies were recently published and included patients with recurrent squamous cell carcinoma and adenocarcinoma of the cervix. In these studies, treatment with anti-PD-1 therapy such as pembrolizumab and nivolumab demonstrated promising antitumor activity in patients with pretreated cervical cancer, without regard to tumor PD-L1 or other tumor biomarker expression [32,62,63]. Recently, based on studies, the FDA approved pembrolizumab (Keytruda, Merck and Co. Inc.) for patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy [64].

Adoptive cell transfer (ACT)

The efficacy of TIL therapy was demonstrated in cervical cancer by Stevanovic et al. [65]. TILs were extracted from cervical cancer tissue, expanded ex vivo, and selected for their ability to recognize the

HPV-associated proteins E6 and E7. This approach resulted in two complete and one partial response in a clinical trial that included nine patients. At the time of publication, the two complete responses were ongoing 22 and 15 months after treatment, respectively.

After examining the T-cell response in patients who underwent complete regression, Stevanovic et al. surprisingly found that the reactive T cells were not directed against virally associated epitopes, but rather against cancer germline antigens (KK-LC1) or neoantigens (mutated SETDP1, METTL7) not previously recognized by the immune system [66]. These observations demonstrate one of the main challenges in T-cell-based therapy, which is the identification of those tumor associated antigens (TAAs) on tumors from individual patients that induce the highest level of T-cells activation at the tumor site.

- **Adverse effects:**

Two main toxicities are associated with adoptive cell transfer:

1 Activation of infused tumor specific T cells can cause cytokine release syndrome [67], which can lead to severe neurologic toxicities, hypoxia, and hypotension that requires immediate treatment with steroids or the anti-IL-6 receptor antibody tocilizumab [68,69].
2 On-target toxicity of normal tissues that express the target antigen and off-target toxicity to tissues that express an unrecognized cross-reactive antigen [70].

Ovarian cancer (Table 2)

Although >80% of patients with ovarian cancer will initially have a response to frontline treatment (surgery and platinum-based chemotherapy), the majority ultimately recur and eventually develop chemotherapy-resistant disease. The results of recent clinical trials, including trials that incorporate bevacizumab and poly adenosine diphosphate-ribose polymerase (PARP) inhibitors into chemotherapy regimens, suggest that a plateau has been reached for conventional therapies as there is no definitive increase in overall survival. Consequently, new treatment strategies and paradigms are of critical need for these patients.

Vaccines

Therapeutic vaccines for ovarian cancer have been developed and studied in various clinical trials. Currently, ovarian tumor vaccine approaches include:

1 Vaccination with defined tumor-associated antigens or DNA vaccines that encode for tumor-associated antigens.
2 Vaccination with whole tumor cell preparations, with and without the co-administration of antigen-presenting cells.

Table 2
Immunotherapies for ovarian cancer.

Immunotherpy	Mechanism	Response rate
NY-ESO-1 peptide vaccine [76]	Vaccines against specific tumor associated antigens	Activation T-cell immunity
p53 peptide vaccine [77]	Vaccines against specific tumor associated antigens	<20%
Bevacizumab [84]	Recombinant mAb against VEGF-A	20–50%
Oregovomab [85]	Recombinant mAb against CA125	to be confirmed
Pembrolizumab [93]	Immune checkpoint inhibitors	<20%
Nivolumab [89]	Immune checkpoint inhibitors	<20%

Specific tumor associated antigens

Peptide vaccines are designed to stimulate antitumor immune responses against various specific target antigens that are expressed on ovarian cancer, such as NY-ESO-1, p53, WT-1, HER-2, and VEGF [71,72].

- **NY-ESO-1 antigen:**

One of the candidate antigens for vaccine development is NY-ESO-1, which is a highly immunogenic cancer-testis antigen. It is expressed in up to 40% of ovarian cancers [73,74]. Two recent clinical trials have shown the ability of an NY-ESO-1 peptide vaccine with Montanide ISA51 as adjuvant to induce both antigen-specific $CD4^+$ and $CD8^+$ T cell responses in patients with minimal residual ovarian cancer [74]. The second trial used HLA-A*0201-restricted NY-ESO-1b peptide vaccination with Montanide in patients with ovarian cancer in complete clinical remission after first-line treatment [75]. Three of four patients with NY-ESO-1-positive tumors and four of five patients with NY-ESO-1-negative tumors showed T-cell immunity. Three patients with NY-ESO-1-negative tumors remained in complete clinical remission. Approximately 50% of patients showed NY-ESO-1-specific immune responses, resulting in a mean disease-free interval of 19.9 months [76].

While these results should be interpreted with caution, the hypothesis that NYESO-1 targeted therapy may be associated with clinical benefit has become inevitable and would need to be confirmed in randomized clinical trials.

- **p53 peptides:**

Other vaccination strategies have used p53 peptides as the immunogenic antigen because the overwhelming majority of serous cancers overexpress p53. In general, p53 vaccination trials have resulted in the successful generation of p53-specific immune responses, and the vaccines have been well tolerated. Clinical responses have been demonstrated in up to 20% of patients, but these responses have not necessarily correlated with vaccine-mediated anti p53 immunity [77–79].

Whole tumor antigen vaccines

Dissimilar to using specific tumor-associated antigen, whole tumor antigen vaccines can potentially provide an immune response to a wider range of tumor antigens. These vaccines can be created using autologous tumor lysates or tumor-derived RNA and are, in general, administered with adjuvants such as GM-CSF, Montanide ISA-51, or toll-like receptor agonists. Patients may have a better clinical response to whole tumor antigen vaccination [80,81].

- **Dendritic cells**

Dendritic cells are highly effective antigen-presenting cells and play a central role in the induction of both CD4 and CD8 T cell responses. Dendritic cells can be pulsed with tumor antigen peptides or can be produced to express tumor antigens, allowing their use to enhance antitumor immunity. Exposure of T cells to dendritic cells pulsed with ovarian cancer-derived antigenic preparations has resulted in the generation of cytolytic effector T cells that are capable of killing autologous tumor cells in vitro [82].

- **Monoclonal antibodies**

Monoclonal antibodies can potentially induce antitumor responses in various ways:

1 Complement system activation

2 Interaction with tumor cell surface signaling molecules and inducing antiproliferative effects.
3 Enhancing the activity of phagocytic cells.

Bevacizumab

The only monoclonal antibody-based drug, which is currently FDA-approved for the treatment of ovarian cancer, is bevacizumab (Avastin) [83]. Bevacizumab is a recombinant-humanized monoclonal antibody that inhibits vascular endothelial growth factor A (VEGF-A). The FDA approval is based on the phase III GOG-0218 trial, in which the bevacizumab regimen reduced the risk of disease progression or death by 38% compared with chemotherapy alone. The median progression-free survival was 18.2 months versus 12.0 months, respectively (HR, 0.62; 95% CI, 0.52–0.75; $P < .0001$) [84].

Oregovomab

Oregovomab is a murine monoclonal antibody to CA125 that has been studied as a complementary treatment for ovarian cancer. In studies published in 2008–2009, Oregovomab showed survival benefit as maintenance therapy in patients with ovarian cancer after first-line treatment. A subgroup of patients with favorable prognostic factors had a significantly longer time to relapse compared to patients in the placebo group [85–87]. Oregovomab was also studied in combination with carboplatin and paclitaxel during the first-line treatment and might provide immune adjuvant properties in this setting [88]; however, these trials were published by one group a decade ago, and no further data have emerged.

Immune checkpoint inhibitors

Although immune checkpoint blocking antibodies have shown significant promise in mediating tumor regression in cervix, vulvar, and some endometrial cancers, the response rates in ovarian cancer have been modest. The first published data supporting checkpoint inhibitors as a potentially valuable therapeutic approach in ovarian cancer were observed in trials of the anti-PD-1 antibody nivolumab and the anti PD-L1 antibody BMS-93655 [31]. In the study reported by Hamanishi et al. [89], a phase II trial of nivolumab (an anti-PD-1 antibody) in 20 patients with platinum-resistant epithelial ovarian cancer showed a response rate of 15% (3/20) and a disease control rate of 45% (9/20). In this study, two patients experienced a complete response. Although small, the presence of complete responses in platinum-resistant, heavily pretreated patients with an overall poor prognosis is promising.

Two additional immune checkpoint trials using avelumab (anti-PD-L1 antibody) and pembrolizumab (anti-PD-1 antibody) were presented at the 2015 ASCO annual meeting; Avelumab [90] showed an objective response rate (ORR) of 9.7% and a stable disease (SD) rate of 44.4% in platinum-resistant ovarian cancer patients [91], and pembrolizumab was shown to have an 11.5% ORR and 34.6% SD rate in advanced ovarian cancer with positive PD-L1 status [92].

The results of the KEYNOTE-028, a Phase-1b study of pembrolizumab in 26 heavily pre-treated ovarian cancer patients, showed one complete response, two partial responses, and six patients with SD, corresponding to a disease control rate of 34.6% [93].

Ongoing or planned phase 3 trials in ovarian cancer with immune checkpoint inhibitors include NCT02718417 (Javelin Ovarian 100), ENGOT-ov29-GCIG (ATALANTE), NCT02580058 (Javelin Ovarian 200), and NRG-GY009. These trials are testing combinations with chemotherapy and/or bevacizumab, or the potential efficacy as maintenance therapy.

Immune checkpoint inhibitors are further being investigated among BRCA mutation carriers suffering from ovarian cancer, in combination with PARP inhibitors. Specifically, a phase I study of olaparib (PARP inhibitor) and durvalumab (anti-PD-L1) found an ORR of 17% and a disease control rate of 83% [94].

Adoptive cell therapy (ACT)

As with other immunotherapy approaches, ACT has been most broadly utilized in melanoma where response rates around 50% have been reported [95]. Furthermore, CAR-T cells have also demonstrated encouraging results of inducing complete response in 70%–90% of patients with relapsed or refractory B-cell acute lymphoblastic leukemia [96]. When it comes to ovarian cancer, there are only few reports regarding the efficacy of ACT, and some of them are promising; when ovarian cancer TIL therapy was administered after surgery and primary adjuvant chemotherapy, the results showed 100% 3-year survival in patients who received TIL versus 67.5% in those who did not [97].

There are several ongoing trials evaluating TILs in ovarian cancer (NCT02482090, NCT01883297). Phase I studies of engineered T cells targeting MUC16 (NCT02498912), mesothelin (NCT01583686), and NY-ESO-1 (NCT01567891, NCT02457650) are ongoing. Although remarkable responses have been observed, most clinical responses are short-lived with eventual tumor relapse.

In summary, the data suggest a strong biological and clinical rationale for testing TIL therapy in ovarian cancer, but further clinical trials are needed.

Endometrial cancer (Table 3)

Endometrial cancer ranks as the most common gynecological cancer [98]. Early diagnosis and the prognosis are often very good from this increasingly common malignancy, but unfortunately, minimal progress has been made to improve survival for women suffering from advanced or recurrent disease with poor outcome [99].

Immune checkpoint inhibitors

Programmed cell death-1 (PD-1) and its ligand PD-L1 are expressed in up to 80% of primary endometrial cancers and are expressed in as much as 100% of metastatic cases [100]. Additionally, microsatellite instability-high (MSI-H) tumors have been found to correlate with higher expression of PD-1 and PD-L1 [101].

At the 2017 annual meeting of the American Society of Clinical Oncology (ASCO), new data from the phase Ib KEYNOTE-028 trial were presented evaluating anti-PD-1 (pembrolizumab) therapy in PD-L1-positive solid tumors and included a subgroup of patients with advanced endometrial cancer (MSI testing was not performed) [102]. Patients in this study had failed standard therapy and had received at least two prior lines of treatment. The tumors were required to have positive PD-L1 expression defined as at least 1% positive staining by immunohistochemistry. Out of 24 patients, three (12.5%) had a partial response and three had SD. This group included patients with all histologies and only one patient had an MSI-H tumor. Overall, pembrolizumab was well tolerated and there was no discontinuation of therapy due to toxicity. Preliminary findings of a phase Ib/II study of pembrolizumab and lenvatinib, a VEGF receptor kinase inhibitor, in 23 patients with metastatic endometrial cancer demonstrated an impressive ORR of 48% [103].

In 2017, subsequent to the publication of the study by Le et al. [104], showing the high sensitivity of MMR-deficient cancers to immune checkpoint blockade with objective radiographic responses in 53% of patients and complete responses in 21% of patients, pembrolizumab was FDA-approved for use in MSI-H or MMR-deficient solid tumors that have progressed on standard therapy and have no alternate therapeutic option, becoming the first drug to gain FDA approval based on genomic characterization rather than tumor site.

Table 3
Immunotherapies for endometrial cancer.

Immunotherpy	Mechanism	Response rate
Pembrolizumab [104]	Immune checkpoint inhibitors	(MMR-deficient) >50%
Pembrolizumab + lenvatinib [103]	Immune checkpoint inhibitors + VEGF receptor kinase inhibitor	>50%

As we await the final results from these trials, additional early phase studies are currently recruiting patients to further assess the clinical benefit in women with advanced and recurrent endometrial cancer:

- (NCT02549209): Pembrolizumab in combination with standard treatment (carboplatin and paclitaxel) for patients with recurrent or advanced disease.
- (NCT02899793): Pembrolizumab in patients with polymutated, hypermutated, or MSI-H tumors, as this group was shown to be a promising targeted cohort.
- (NCT02982486): Combination immune checkpoint inhibitors (anti-PD-1 (Nivolumab) and anti-CTLA-4 (Ipilimumab) are also being investigated in patients with advanced grade 3 endometrial cancers and high-risk histologies (serous, clear cell, and mixed histology).

Summary

Immunotherapies represent a novel approach to treat gynecological cancers and offer the potential for extended benefits even in advanced disease. Currently, antibodies against immune checkpoints are the most common representatives of this treatment modality. An improvement in the understanding of the immune system in tumor immunosurveillance has resulted in the development of a new generation of immunotherapeutic agents. Combination with chemotherapy, molecular-targeted therapy and radiotherapy could also be viable treatment options. Many clinical trials are ongoing and will eventually give further insight into immunotherapy's proper place in gynecological cancers treatment.

Practice points

Immunotherapy is utilized to suppress the well-documented inhibitory effect of the tumor on the immune system and restore it to a state of activity, utilizing:

Monoclonal antibodies: The only monoclonal antibody-based drug which is currently FDA-approved for the treatment of ovarian cancer is bevacizumab (Avastin).

Cancer vaccines: Tumor-specific antigens (supplied as peptides) or antigen-activated dendritic cells, in combination with immune-stimulatory adjuvants, to stimulate T cell responses against cancer. Anti-HPV bivalent and quadrivalent vaccines are highly efficient in preventing dysplastic and cancerous lesions, especially in patients who were not previously exposed to HPV.

In addition, bacterial vector vaccines have been developed against cervical malignancies, and reported reduction in tumor size, increase in E7 cell-mediated immunity, but only modest improvement in overall survival.

Checkpoint inhibitors: To counteract the immune inhibition induced by the checkpoint proteins, monoclonal antibodies against these checkpoint proteins have been developed, including against the cytotoxic T lymphocyte associated antigen 4 (CTLA-4), the programmed cell death (PD-1) protein, and the PD-1 ligand proteins (PDL-1), and are currently being used in clinical settings.

In May 2017, the checkpoint inhibitor Keytruda^{R} (pembrolizumab) was approved by the FDA for the treatment of patients with unresectable or metastatic solid tumors including endometrial, which have been identified as having a biomarker referred to as MSI-H or mismatch repair deficient (dMMR)." In June 2018, the FDA granted a full approval to KEYTRUDA^{R} for patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1. Response rates, including complete responses, have been described with other anti-PD-1 antibodies in patients with platinum-resistant epithelial ovarian cancer.

Adoptive cell transfer: Autologous T-cells activated and expanded ex-vivo from TILs or from peripheral blood from the patient, and infused back into the patient so these T cells will attack the cancer cells.

Research agenda

The thought of exploiting the immune system to treat cancer has been pursued for the last three decades. Only recently has this powerful strategy finally moved to the front stage of oncology. This huge advancement is the consequence of years of meticulos work by pioneering scientists.

Oncologists are rushing to amplify the use of immunotherapy to benefit more cancer patients. Hundreds of clinical trials are under way to see whether improved responses can be attained by combination therapy approaches. Understanding the dynamics of the response to immunotherapy will assist in finding ways to overcome immune suppression, and counter-regulation will lead to development of effective personalized targeted approaches to treat cancer as part of standard of care for cancer patients.

The aims of this chapter are to:

- ✓ To discuss the recent advancement in immunotherapies that include cancer vaccines, cell-based therapy, and immune checkpoint blockade.
- ✓ To summarize the current strategies used in clinical trials.
- ✓ To explore future directions for utilizing immune based therapies for long-lasting durable cure.

Conflict of interest statement

The authors declare no financial or personal relationships with other people or organizations that could inappropriately influence (bias) the content of this article.

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