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Chapter 6

Immunotherapy in Gynecologic Cancers

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Additional information is available at the end of the chapter

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Abstract

During the last years, significant progress in the understanding of signaling pathways of immune cells has revive the field of immune therapy for cancer. In this chapter, we explain the recent immunotherapy-based strategies for the treatment of gynecological cancers including cervical cancer, endometrial cancer, ovarian cancer, and vulvar cancer. This work will mainly focus on emerging clinical data on immune checkpoint inhibitors. But also data on adoptive T cell therapies and vaccines will be presented. It is anticipated that in future biomarker-guided randomized trials will provide better approaches in terms of response and resistance to immune therapy. The use of combination therapy for gynecological cancer might be one possible approach to overcome resistance.

Keywords: gynecologic cancers, ovarian cancer, endometrial cancer, cervical cancer, immune therapy, immune checkpoint inhibitors

1. Introduction

Gynecologic cancers include vulva, vaginal, cervical, endometrial, and ovarian/tubal/peritoneal cancers, the latter of which are still classified as one disease. As these organ-classified cancers have different characteristics, biology, therapies, and outcomes, during the past decade, approaches have been undertaken to subclassify them as to their heterogeneity and based on next-generation profiling. The main cornerstone of treatment for gynecologic cancer comprises in most cancers of surgical resection with different possibilities of adjuvant further therapy like chemo-, radio-, targeted, and, increasingly, immunotherapy.

In the United States, almost 90,000 women were diagnosed with gynecologic cancers in 2015 and over 29,000 will die from their disease [1]. Many women are cured with combined modalities, however, in ovarian cancer, for example, over 70% of cancers are diagnosed in advanced

International Federation of Gynecology and Obstetrics (FIGO) stage III or IV, thus their five-year overall survival is only 30% [2].

Outcome in ovarian cancer in all stages is the worst of all gynecological cancers with a 10-year overall survival of 30%, followed by vaginal cancer with a 10-year overall survival of 35%. Cervical and vulvar cancers have a 10-year overall survival rate of 65%. Endometrial cancer has the best prognosis, with a 10-year survival rate of 80% [1].

Immunotherapy represents a new alternative and rational approach for the treatment of cancer, including gynecologic cancers [3, 4]. More than a decade ago, it was demonstrated for ovarian cancer that tumor-infiltrating lymphocytes (TILs) play an important role in tumor rejection and prognosis [5]. This was one of the first evidence that immune therapy might be beneficial in ovarian cancer patients. A meta-analysis confirmed the prognostic role of TILs for ovarian cancer patients [6]. Later it was also demonstrated that the ratio of different T cell subtypes plays an important role [7].

A major function of the immune system is to continually seek out and eliminate cancer cells as they arise in a process defined as cancer immunosurveillance [8]. This involves both innate and adaptive immune mechanisms that function complimentarily to promote tumor immunity. Most importantly is that antitumor immune responses can be induced by immunological agents. Various forms of immunotherapies are central components of treatment regimens for a number of malignancies [9]. To eliminate cancer cells by T cells is only one-step in a complex immunity cycle [10].

In general, there are three strategies to treat cancer with immunotherapeutic approaches:

(1) Increase tumor antigen presentation.

(2) Increase T-cell activity.

(3) Targeting the tumor environment (immune inhibitory mechanisms).

Strategies to increase tumor antigen presentation includes vaccinations, use of innate immune activators, oncolytic viruses, type I interferon, and toll-like receptor (TLR) agonists.

Especially for epithelial ovarian cancer (EOC), several vaccination approaches have been applied, e.g., cellular vaccines, dendritic cell (DC) vaccines, and virus-loaded vaccines. Several studies have used overexpressed proteins in EOC as a target, e.g., p53, surviving, and MUC1. Several studies have demonstrated immune response but clinical benefit rate was minimal in all of these studies. The vaccination approach is not used in clinical practice nowadays [11].

To increase T-cell activity, there are several approaches tested including cytokine therapies with IL-2 and IL-12, the use of checkpoint inhibitors, and adoptive T cell therapies [12, 13]. Rosenberg et al. demonstrated in 2015 an elegant new therapeutic approach by generating tumor-associated antigen-specific T cells via expression of T-cell receptor or chimeric antigen receptor (CAR) [14]. With this approach, CD19 targeting CAR therapy for acute lymphatic leukemia of the B cell lineage was applied with a very high remission rate of 90% [15]. In ovarian cancer, adoptive T-cell therapy might be also effective. For example, NY-ESO-1 is

specifically expressed in cancer, 42% expression has been seen in ovarian cancer. This might be an important target for adoptive T-cell therapy [16].

To target the tumor environment, there are also several therapeutic approaches. It has been demonstrated that several immune inhibitory mechanisms are associated with poor prognosis in gynecological cancer and in particular, in ovarian cancer, e.g., tumor infiltrating regulatory T cells, tumor-associated macrophages, expression of indoleamine 2, 3-dioxygenase (IDO) by tumor stromal cells [17, 18]. To target the responsible pathways might be effective, especially in combination with newer programmed cell death ligand-1 (PDL-1) or its receptor programmed cell death protein-1 (PD-1) checkpoint inhibition [19, 20].

For gynecological cancer, in particular for ovarian cancer, there is still an unmet challenge in cell therapy for cancer. The selection of the right target antigen, which is tumor cell-specific and has a robust expression, seems to be very important.

2. Cervical cancer

Cervical cancer is the fourth most common female cancer worldwide, with estimated 528,000 new cases and 266,000 deaths in 2014 [21]. Infection with high risk types of human papillomavirus (HPV) is the most crucial risk factor [22]. Human papillomavirus types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 72, and 82 are associated with high risk of cervical cancer, whereas HPV types 6, 11, 40, 42, 43, 44, 54, 61, 70, 72, and 81 are considered to have low carcinogenic risk [23, 24].

Most common cases are diagnosed in less developed countries, where cervical cancer comprises nearly 15% of cancers in women. In Switzerland, with a small population of only eight million, the incidence is much lower, with about 240 cases diagnosed each year [25].

Better screening methods and vaccination against HPV in the past decades have led to an improvement of cervical cancer prognosis in developed countries, particularly where a broad prevention plan has been put in place [26]. To date, we have an efficacious vaccination available against the nine most important HPV types (HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58) [27]; however, despite better prevention strategies, cervical cancer is still not sufficiently manageable worldwide with a stagnating mortality rate. Most cancers in the developed world present in early FIGO stage IA1–IIA, while primary metastatic disease is uncommon. Surgery including radical hysterectomy including pelvic lymph node resection for staging is the gold standard. Patients with high-risk features including insufficient margins, large tumors, and lymph vascular space invasion receive adjuvant radiochemotherapy (RCTX) with platinum [28]. From stage IIB onwards, patients are treated with combined radiochemotherapy with platinum. This was established in 1999 when five randomized controlled trials demonstrated a 30–50% survival benefit for patients treated with combined radiochemotherapy compared with radiation alone.

A large meta-analysis of chemoradiation trials demonstrated an absolute overall survival (OS) benefit of 12% [29]. Since these trials, no practice changing studies were published until 2014, when the findings of a phase III study with bevacizumab resulted in its approval for late-stage cervical cancer by the Food and Drug Administration (FDA) and European Medical

Agency (EMA). In a large randomized phase III trial, two chemotherapy regimens with cisplatin and paclitaxel or topotecan and paclitaxel plus or minus bevacizumab were examined [30]. Bevacizumab was applied during chemotherapy and as maintenance therapy until disease progression, achieving an increased OS benefit (17.0 months versus 13.3 months; hazard ratio (HR) for death, 0.71; 98% confidence interval (CI), 0.54–0.95; P = 0.004) and a higher response rate (48 versus 36%, P = 0.008). An additional quality of life (QoL) analysis confirmed the low toxicity profile and good tolerability without any deterioration of quality of life [31].

2.1. Immune system and cervical cancer

Most cervical cancers are associated with HPV infection. The cervical epithelium is the ideal area for HPV because of the absence of an inflammatory milieu, which provides a protective niche where the HPV is capable of evading the host immune response for many months. Research has provided some insight into the means of evasion by the virus in cervical cancer [32]. The presence of CD4+ lymphocytes in precursor lesions and CD8+ lymphocytes in malignant tumors in the absence of an effective immune response suggests that T cell cytotoxic responses are impaired [33, 34]. Indeed, the zeta chain of the T-cell receptor is downregulated in CD8+ lymphocytes in cervical cancer, suggesting defective T cell signaling [35]. Furthermore, NKG2D-expressing natural killer and cytotoxic T cells, which have a key role in the elimination of virus-infected and tumor cells, are present at reduced levels in both patients with cervical cancer and cervical intraepithelial neoplasia [36]. Increased T regulatory cell activity has also been reported [37]. The immunoregulatory enzyme, IDO, appears to facilitate the induction of immune escape together with T regulatory cells [38]. Understanding the different mechanisms of immune evasion in cervical cancer is key to establishing new treatments.

2.2. Checkpoint-inhibitors in cervical cancers

Despite this new regime, the prognosis for metastatic and locally advanced cervical cancer is still poor, with an OS of 12–17 months [30, 39]. To improve prognosis, new treatment options are urgently needed. One important strategy is to enable the immune system to reject the tumors facilitating checkpoint-inhibitors. An important strategy to improve T cell-dependent tumor attack is by inhibiting immune T cell checkpoints. A checkpoint-inhibitor is a drug that inhibits certain surface proteins made by specific immune cells, such as T cells and cancer cells. These specific proteins control the immune responses and prevent T cells from killing cancer cells. Inhibiting these proteins will remove the natural surveillance of the immune system and T cells will be activated to eliminate cancer cells.

Blocking inhibiting checkpoints like cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) or PD-1/PD-L1 results in activation of T cell proliferation and cytokine production. CTLA-4 begins to be expressed on the naïve T cell 48 hours after activation in lymph nodes and is closely associated with attenuation of these activating T cells [40]. PD-1 is expressed on effector T cells in peripheral tissues and binds with PD-L1 (B7-H1) and PD-L2 (B7-DC) expressed on DCs or tumor cells for attenuation of activated effector T cells [41, 42]. Under normal circumstances, interferon (IFN)-γ upregulates the expression of PD-L1, protecting DCs from

T cell-mediated cytotoxicity [43]. However, in head and neck squamous cell carcinomas associated with HPV, the number of CD8+ T cells expressing PD-1 has been reported to be higher in tumors than peripheral blood. This suggests that the expression of PD-1 by CD8+ T cells starts after entering into the tumor microenvironment.

Currently, there are several studies in the U.S. and EU examining different checkpoint-inhibitors and combinations, e.g., chemotherapy, PARP-inhibitors, or antiangiogenetic agents, in cervical cancer and other solid tumors (**Table 1**). Presently, most studied checkpoint-inhibitors are pembrolizumab, nivolumab, ipilimuab, and durvalumab.

Pembrolizumab, a PD-1 antibody, is approved for patients with advanced melanomas [44]. In cervical cancer, it is currently being investigated in a phase II trial (NCT02628067) based on the phase IB data presented at ASCO 2016 [45]. Patients with stage IVB or nonresectable cervical cancer received 10 mg/kg pembrolizumab every 2 weeks until disease progression or toxicity for a total treatment of 24 months. The overall response rate (ORR) was 17% (95% CI 5–36). While no grade 4 toxicity occurred, two treatment-related discontinuations were observed (grade 3 colitis and grade 3 Guillian-Barré syndrome). The median progression-free survival (PFS) and OS were 2 and 9 months, respectively. The 12 months PFS and OS were 8 and 33%, respectively. Some patients had very long remission rates that are promising and will lead to further evaluation in cervical cancer.

Nivolumab has been approved for metastatic and unresectable lung cancer [46], where it showed a survival benefit compared to conventional chemotherapy treatment. This PD-1 antibody has also been tested in a phase I/II study for patients with HPV-associated tumors, including cervical, vaginal, and vulvar cancer (www.clinicaltrials.gov:NCT02488759).

Ipilimumab is an anti-CTLA-4 antibody and was the first checkpoint inhibitor approved for metastatic melanoma and has significantly improved the OS of this disease [19]. It is at present tested in several other tumors including gynecologic cancers. In cervical cancer, it has been tested in a phase I study following standard radiochemotherapy in patients with

ClinicalTrials.gov Identifier:	Phase	Drug	Situation
NCT02471846	I	GDC-0919 *(small molecule investigational immunotherapy designed to inhibit IDO (Indoleamine 2,3-dioxygenase), a protein often overproduced by many cancer cells)* *plus atezolizumab*	Metastatic tumors including CC
NCT02812875	IB	CA-170 *Oral small molecule inhibiting PD-L-1/2*	Metastatic solid tumors including CC
NCT02635360	II	Pembrolizumab	Combing with RCTX for advanced CC
NCT02834013	II	Nivolumab plus ipilimumab	Metastatic rare tumors including CC

Notes: Ongoing checkpoint-inhibitor studies in cervical cancers. RCTX = radiochemotherapy; CC = cervical cancer.

Table 1. Data on immune therapy agents in particular checkpoint-inhibitors in cervical cancer.

locally advanced cervical cancer (www.clinicaltrials.gov: NCT01711515). The trial is currently recruiting patients.

Another phase 2 trial from Princess Margaret Hospital examines the role of ipilimumab in patients with metastatic or recurrent human papillomavirus-related cervical cancer (www.clinicaltrials.gov: NCT01693783).

Durvalumab (MEDI4736), an anti-PD-L1 antibody, is being tested in combination with tremelimumab, an anti-CTLA-4 antibody [47, 48] in a phase I trial for patients with six different types of cancer, including cervical cancer (www.clinicaltrials.gov: NCT01975831). Durvalumab inhibits PD-L1 interaction with PD-1 (IC_{50} 0.1 nM) and CD80/B7.1 (IC_{50} 0.04 nM), allowing T-cells to recognize and kill tumor cells.

Early single agent phase I evaluation in several tumor types, including triple negative breast cancer, showed a disease control rate of 33% and an overall response rate of 10% [49]. There were early (5 weeks) and also durable responses (56+ weeks). PD-L1 expression appears to enrich the response to durvalumab monotherapy. Drug-related events were observed in 46% of patients with 7% of patients reporting a grade ≥3 AE that led in 1% to discontinuation of the treatment. The most common drug-related AEs were fatigue, rash/pruritus, diarrhea, and vomiting.

3. Ovarian cancer

Epithelial ovarian cancer (EOC) is the fifth most common cancer in women and one of the main causes of death in relation to gynecologic cancer worldwide [50]. Ovarian cancer has a poor prognosis, probably as three in four cancers are diagnosed in advanced FIGO stages [51]. The 5-year survival rate is poor, estimated at 20–30% for stage I–IV disease. Not only the tumor stage, but also the histopathological subtype is prognosis defining, with poor differentiated serous cancers having the poorest outcomes [2]. Best prognosis is seen in mucinous subtype. These subtype is mostly localized FIGO stage I disease [52].

Surgery with optimal debulking still has a major influence on the outcome in advanced EOC. Best outcome has been reported for patients achieving maximal cytoreductive surgery without macroscopic residual disease [53].

The most promising novel agents for ovarian cancer are antiangiogenesis-based therapies, e.g., bevacizumab, pazopanib, cediranib, or trebananib and PARP-inhibitors, e.g., olaparib or niraparib [54–60]. Bevacizumab and olaparib are approved in the United States and Europe and demonstrated a PFS benefit of 3–4 months when used during or after platinum-based chemotherapy. In BRCA positive patients, there was a PFS benefit of more than 9 months for patients diagnosed with relapsed serous high grade EOC [61].

Recent data suggest that also patients without a BRCA mutation might benefit from a treatment with the PARP-inhibitor niraparib. In this recent study published by Mirza et al., niraparib was also beneficial in non-BRCA mutated patients [62]. They used homologous recombination deficiency (HRD) score to predict response on niraparib. In this study, non-BRCA mutated patients had also significant difference 9.3 versus 3.9 months in PFS.

Non-BRCA mutated and HRD-positive 12.9 versus 3.8 months (HR 0.38).

HRD positive and BRCA wildtype: 9.3 versus 3.7 months, somatic BRCA mutated 20.9 versus 11.0 months, HRD negative 6.9 versus 3.8 (HR 0.58).

3.1. Vaccination strategies for ovarian cancer

A number of methods have been used to enhance immune response in ovarian cancer to improve prognosis, yet, none of these methods have been approved. Several types of vaccination strategies have been tested, e.g.:

(1) Anti-idiotype AB-based vaccination, for example, Abagovomab.

(2) Peptide-/protein-based vaccination, for example, NY-ESO peptides.

(3) Lymphocytes-based vaccination, for example, Autologous LAK plus IL2.

(4) Carbohydrate-based vaccination, for example, MUC1-Sialyl-TN.

(5) DNA plasmid-based vaccination, for example, Poxviral Vector PANVAC-V.

(6) Combination-based vaccination, for example, with sunitinib.

(7) Vaccination-based on dendritic cells, for example, autologous DC pulsed with MUC1-derived peptides or HER-2/neu.

The following paragraph will focus on anti-idiotype AB-based vaccination only as this type is best developed and also phase III data are available.

3.2. Vaccination with idiopathic antibodies: abagovomab and oregovomab

In his theory of clonal selection published in 1974, Neils Jerne described how antibodies (Ab1) generated in response to a particular antigen may themselves be immunogenic [63, 64]. The immunogenic determinants of Ab1 antibodies are termed 'idiotopes'. Ab1 idiotopes can act as antigens, leading to the development of anti-idiotypic antibodies (Ab2) [64]. As idiotopes are largely located in the highly variable region of the antibody that serves as the antigen-binding site, in some cases Ab2 anti-idiotypic antibodies can mimic antigen structure. Indeed, research has shown that exposure to Ab2 anti-idiotypic antibodies can sometimes induce a more pronounced response than exposure to the antigen itself. Exposure to Ab2 anti-idiotypic antibodies may subsequently stimulate the generation of Ab3 antibodies, some of which target Ab2 idiotopes, and are also capable of binding to the antigen.

Abagovomab (ACA-126) is a murine IgG1k monoclonal antibody (Ab2) with an idiotope that imitates CA125. It is under investigation as an anti-idiotypic vaccine for ovarian cancer. CA125 is a mucin-like transmembrane glycoprotein that is upregulated in ovarian cancer and currently represents the most widely used ovarian cancer biomarker [65, 66]. The biological function of CA125 remains poorly understood, with putative roles in cell adhesion, migration, invasion, and possible immunosuppressive properties suggested [67, 68].

In phase I studies in patients with chemotherapy-resistant ovarian cancer, abagovomab was associated with induction of Ab3 and HAMA responses, increased serum levels of interferon (IFN)-γ, and increases in CA125-specific CD8+ T cells postvaccination [69], suggesting the induction of Th1 immune responses [70]. The induction of Ab3 response was confirmed in a phase Ib/II clinical trial with abagovomab in 119 patients with CA125-positive ovarian, tubal, and peritoneal cancer [71]. Ab3 response occurred in 68.1% of patients and was associated with prolonged overall survival (OS) compared with nonresponders (23.4 versus 4 months; $P < 0.0001$), regardless of FIGO stage, first-line chemotherapy, or previous treatment. Antibody-dependent cellular cytotoxicity (ADCC), observed in 26.9% of patients, was also associated with significantly prolonged survival (25 versus 10 months; $P = 0.0126$), suggesting a role for ADCC in the antitumor effect of abagovomab. Nevertheless, abagovomab was not associated with prolonged recurrence-free survival (RFS) or OS compared with placebo when administered as a maintenance therapy to patients ($n = 888$) with first remission of ovarian cancer (FIGO stage III/IV) during the phase III 'Monoclonal antibody Immunotherapy for Malignancies of Ovary by Subcutaneous Abagovomab' (MIMOSA) trial, despite the induction of measurable immune response [72].

Oregovomab (B43.13, OvRex) also targets CA125, binding with high affinity ($K_D = 1.2 \times 10^{10}\ M^{-1}$). This murine IgG1 monoclonal antibody was investigated for the treatment of ovarian cancer after a survival advantage was noted during its initial use as a technetium 99c-labeled agent for the immunoscintigraphic detection of recurrent ovarian cancer [73].

Infusion of the antibody results in the formation of immune complexes with circulating antigen that trigger generation of anti-CA125 antibodies [74]. Indeed, oregovomab appears to induce broad humoral and cellular anti-CA125 responses.

During a phase I trial, multiple infusions of oregovomab were associated with a greater than threefold increase in anti-CA125 antibody levels in nearly half (43%) of patients ($n = 184$) with ovarian cancer (FIGO stages I–IV) [74]. Anti-CA125 antibody response was associated with prolonged survival compared with nonresponse (22.9 versus 13.5 months; $P = 0.0089$), and an increase in T-cell proliferation was noted, which was also associated with prolonged survival. In a phase II study ($n = 20$), T-cell responses to CA125 and/or autologous tumors were also shown to correlate with prolonged survival in oregovomab-treated patients with platinum-resistant recurrent ovarian cancer (FIGO stages I–IV) compared with nonresponders (median not reached versus 51.9 weeks) [75].

While oregovomab elicits tumor-specific T-cell responses, it does not appear to be able to directly inhibit tumor growth. Anti-CA125 antibodies isolated from oregovomab-treated patients with ovarian cancer (FIGO stages I–IV) in one study were able to mediate ADCC in the presence of peripheral blood mononuclear cells, but not CDC [76].

In addition, there are conflicting data on the association between immune response to oregovomab and clinical benefit. A retrospective analysis of 44 patients with recurrent ovarian cancer (majority FIGO stages III and IV) who received technetium 99c-labeled oregovomab reported a significant relationship between immune response and survival [73]. More than 67% of patients had HAMA and Ab2 responses, with 28% of patients experiencing a more than threefold increase in anti-CA125 antibody levels. These immune responses were associated with prolonged survival compared with nonresponders: HAMA (22.6 versus 7.2 months;

P = 0.0016), Ab2 (18.3 versus 9.3 months; *P* = 0.075), and anti-CA125 (18.2 versus 13.1 months; *P* = 0.0896). By contrast, no reduction in tumor burden was detected in 13 oregovomab-treated patients with ovarian cancer during a pilot phase II study, despite measurable T- and B-cell responses in the majority of patients [77]. Furthermore, oregovomab monoimmunotherapy was associated with similar clinical outcomes to placebo during a phase III trial in 375 patients with advanced ovarian cancer (FIGO stage III/IV), despite measurable bioactivity [78].

The potential for combining oregovomab with front-line chemotherapy has been investigated during a phase II clinical trial in 40 patients with advanced ovarian cancer (FIGO stages III/IV) [79]. Patients were randomized to receive oregovomab via two dosing schedules: either on the same day as or 1 week after standard carboplatin-paclitaxel chemotherapy. Primary and secondary endpoints compared antibody and cellular response between the two dosing schedules, but the authors also noted that the immune responses triggered were stronger than those observed in previous studies using oregovomab monoimmunotherapy.

3.3. Immune checkpoint-inhibitors in ovarian cancer

Apart from the vaccination, immune checkpoint-inhibitors such as the programmed cell death 1 protein (anti-PD1)/PD-Ligand1 and CTL-A4 were also under research for ovarian cancer [42] (see also **Table 2**). Tumors with high mutational loads are ideal candidates for therapies with immune checkpoint-inhibitors. In melanoma and lung cancer, these new drugs are already approved [40, 46]. The role of immune checkpoint-inhibitors in ovarian cancer is not so clear so far, although PD1/PD-L1 pathway seems to play an important role in ovarian cancer. In ovarian cancers, PD-1 is expressed on TILs [80]. Expression of PD-L1 on tumors has been shown to be bad prognostic factor [81]. In a preclinical model inhibition of PD1 and PD-L1 demonstrated tumor rejection and reprogramming of tumor microenvironment [82]. In one of first phase I study for an anti-PD-L1 antibody, there were also responses seen for ovarian cancers [83].

First, data from phase a phase II studies demonstrated low response rates but a higher disease control rated and long-term remissions. The patients treated in these trials had poor prognostic disease and were platinum resistant [84]. The assessment of PD-L1 as a prognostic marker for ovarian cancer is less clear. The data from Hamannishi et al. demonstrated that PD-1 was not ideal as prognostic marker [81].

More importantly, the mutational landscape might be important to select the right treatment for the suitable tumor. In general, the mutational burden is lower in ovarian cancer than in other cancers. But ovarian tumors with germline or somatic BRCA1/2 mutations were found to have a higher frequency of exome mutations (67.5 on average) than tumors with wild-type BRCA (49.5 on average) [86].

3.3.1. Ipilimumab

Ipilimumab (MDX-CTLA-4, Yervoy) is a full human IgG1 monoclonal antibody to CTLA-4 approved by the FDA for the treatment of advanced melanoma on the basis of phase III observations of prolonged OS (median 4 months versus tumor vaccine) in patients with unresectable pretreated stages III and IV melanoma [40]. Immune response appears to underlie the antitumor

Drug	Target	Patients	N	PD-L1 Status	ORR (%)	DCR (%)	CR	PR	SD	Literature
Nivolumab	PD-1	Rezidiv platin-resistant	18	All	17	44	2	1	5	[84]
Pembrolizumab	PD-1	Fortgeschrittenes EOC	26	PD-L1+	11,5	34,6	1	2	6	[85]
Avelumab	PD-L1	Platin/Chemo-resistentes EOC	75	All	10,7	54,7	0	8	33	[92]
BMS-936559	PD-L1	Fortgeschrittenes EOC	17	All	1	23.5	0	1	3	[83]

Notes: The clinical data for checkpoint-inhibitors mainly anti-PD-1 in EOC. ORR = overall response rate; DCR = disease control rate; PR = partial remission; CR = complete remission; SD = stable disease; EOC = epithelial ovarian cancer.

Table 2. Data available on immune checkpoint-inhibitors used in ovarian cancer.

effect of ipilimumab. Studies with ipilimumab in melanoma have shown increased absolute lymphocyte counts [87], upregulation of inducible costimulator (ICOS) on CD4+ T cells [88], and enhanced antibody and T-cell responses to cancer-testis antigen NY-ESO-1 that largely correlate with clinical benefit and prolonged survival [88, 89].

Ipilimumab has also been investigated in a small number of patients with ovarian cancer. Findings from two studies in a total of 11 patients with previously vaccinated ovarian cancer (FIGO stage IV) suggest that ipilimumab is generally well tolerated and can trigger a decrease/stabilization of CA125 [90, 91]. Significant antitumor effects were observed in some patients. One patient experienced a marked reduction in serum CA125 levels during ipilimumab treatment with a substantial regression of a large cystic hepatic metastasis, complete resolution of mesenteric lymphadenopathy, and gastrocolic ligament thickening [91]. Increased antibody responses to NY-ESO-1, which is expressed in many ovarian carcinomas, were also detectable and correlated with therapeutic activity. Four additional patients achieved stable disease.

3.3.2. Avelumab

Avelumab (MSB0010718C; anti-PD-L1) is a full human anti-PD-L1 IgG1 antibody currently under clinical investigation for several cancers. It was tested in a phase IB study for chemotherapy refractory EOC. Safety and clinical activity data were reported at ASCO 2016 [92]. Patients with advanced EOC unselected for PD-L1 expression received avelumab 10 mg/kg IV every 2 weeks until progression, unacceptable toxicity, or withdrawal. Tumors were assessed every 6 weeks according to RECIST 1.1. Unconfirmed ORR, PFS, and OS were evaluated and AE graded by NCI-CTCAE v4.0. During a median of 12 weeks (range: 2–54 weeks), 124 patients were treated with AE only occurring in 82 patients (66.1%); most common ones (≥10%) were fatigue (13.7%), infusion-related reaction (12.1%), and diarrhea (11.3%). The ORR was 9.7%. The rate of stable disease was 44.4%. The disease control rate was 54.0%. PD-L1 expression was evaluable in 74 patients with PD-L1+ tumors expressing an ORR of 12.3% and in PD-L1 tumors of 5.9%.

In first line and maintenance setting, avelumab is currently evaluated in a phase III, open-label, international, multicenter study as additional maintenance therapy after debulking surgery (www.clinicaltrials.gov: NCT02718417). The study has three arms. Arm A includes chemotherapy with carboplatin plus paclitaxel (standard of care), arm B includes chemotherapy followed by avelumab in maintenance, and arm C includes chemotherapy in combination with avelumab followed by avelumab in maintenance. The primary endpoint of this study is PFS.

In this platinum-resistant and refractory setting, avelumab is combined with PEGylated doxorubicin versus single-agent PEGylated doxorubicin or avelumab alone (www.clinicaltrials.gov: NCT02580058). The primary endpoint of this study is OS.

4. Vulvar cancers

With approximately 4% of the tumors of the female genital tract, vulvar carcinoma is rare. In 75% of cases, it occurs as type 2 carcinoma in the elderly patient. The median age is 70 years.

As type 1 carcinoma, which is usually associated with HPV, it occurs in younger patients in combination with cervical carcinoma or anal carcinoma. The most important treatment is surgical resection. In approximately 30% of the cases, a complete R0 resection is not possible, and then combined procedures are used before or after surgery with chemotherapy and radiotherapy. For systemic approaches, in general, platinum-based chemotherapy regimens are used, frequently in combination with 5FU, mitomycine-c, taxanes, and ifosfamide [93].

Prognosis for vulvar cancer is still poor and there is a high recurrence rate. The 10-year survival rate is still modest with 65% [1]. Therefore, new treatment options are urgently needed. Standard of care for metastatic situations remains the standard platinum-based chemotherapy [94]. Newer targeted therapy failed to demonstrate a major survival benefit [95]. Immunotherapy especially with checkpoint-inhibitors might therefore be beneficial for squamous cell cancers of the female genital tract.

In anal cancer early data from the first 37 patients having received nivolumab every 2 weeks have recently been presented [96]. Here, two patients (5%) showed a complete response, seven (19%) had a partial response, and 17 (46%) had stable disease. The disease control rate was high with 79% and a median PFS of 3.9 months with 6 patients still remaining on the study at present. However, side effects included fatigue, anemia, rash, and one incident of pneumonitis. For vulvar cancers, currently three trials incorporate checkpoint inhibitors worldwide (www.clinicaltrials.gov: NCT 02858310, NCT02628067, NCT02834013).

5. Endometrial cancers

In the group of gynecologic cancers, endometrial cancers have the best outcome with a five-year overall survival rate of 80% [97]. In general, the disease can be cured with surgery including staging procedures and radiotherapy [98, 99]. For type II cancer and advanced stage disease, chemotherapy with carboplatin and paclitaxel is included in standard of care treatment [98, 99]. For relapsed disease and stage IV disease, surgery can be applied, but in general, standard of care is systemic therapy, including endocrine therapy such as medroxy-progestine, tamoxifen, or aromatase inhibitors [100]. Furthermore, combination chemotherapy with carboplatin and paclitaxel is used [101]. For further progression, agents like doxorubicin or topotecan have minimal activity [102, 103].

For advanced and relapsed endometrial cancer, new treatment options are urgently needed. Beside targeted therapy including combinations with endocrine therapy and CDK4/6 inhibitors or VEGF-(R) inhibitors or FGFR-inhibitors, application of immunotherapy might have strong impact in that stage of disease [104, 105].

The cancer genome atlas has recently classified endometrial cancers in four distinct subgroups [106, 107]:

(1) POLE-ultramutated.

(2) Microsatellite instability (MSI) hypermutated.

(3) Copy number low.

(4) Copy number high.

In endometrial cancers, there are only few data available for a specific immunotherapeutic approach, despite the knowledge that high mutational load tumors are expected to respond well. There are some data about dendritic cell vaccination [108–110] and about checkpoint inhibition, particularly in view of mismatch repair-deficient cancers [111]. In this phase II study, the authors examined the efficacy of pembrolizumab in several tumor types (n = 41), including two endometrial cancers. For mismatch repair-deficient colorectal cancers, the immune-related objective response rate was 40 versus 0% for mismatch-repair-proficient colorectal cancers. Patients with other mismatch repair-deficient tumors had comparable response rates. Whole-exome sequencing showed a much higher rate of somatic mutations for mismatch repair-deficient tumors (mean number of somatic mutations: 1782 versus 73 in mismatch repair-proficient tumors (P = 0.007)). The noncolorectal cohort included nine mismatch repair-deficient cancers including gastric cancer, ampullar or cholangiocarcinoma, small bowel cancer, and endometrial cancer. The objective response rate was 71% (95% CI 29—96) with a median time to response of 12 weeks (95% CI 10–13 months). The treatment was well tolerated; most common side effects (all grades) were rash, pruritus, diarrhoea, allergic rhinitis, and pain. The authors conclude that the treatment was well tolerated and the evaluation of mismatch repair deficiency might be a useful marker, independent of underlying tumor type.

6. Conclusion

There has been a tremendous success for immunotherapy in certain tumor types (e.g., melanoma, lung cancer etc.), in particular, for immune checkpoint-inhibitors. In gynecological cancers, the situation is less clear although there are some promising data, especially for treatment with anti-PD1 or anti-PD-L1 antibodies. Early clinical trials showed encouraging disease control rates in heavily pretreated patients. A combination of checkpoint-inhibitors, e.g., anti-PD-1 with CTLA-4 or anti-PD-1 with LAG3 or combinations with chemotherapy might overcome resistance in this type of disease. Current trials aim to examine the combination between immune checkpoint-inhibitors and VEGF inhibitors like bevacizumab or PARP-inhibitors like olaparib and niraparib. An important role of these combination trials is to improve quality of life for patients. Another important goal is the incorporation of appropriate biomarkers to identify new immunotherapeutic approaches. The situation about immunotherapy in other than ovarian cancer has to be called scarce, and no conclusion can be drawn from the data in these cancers up to date.

Abbreviations

AE Adverse event

AB Antibody

CAR	T-cell receptor or chimeric antigen receptor
CC	Cervical cancer
CD	Cluster of differentiation
CR	Complete remission
DC	Dendritic cells
EMA	European Medical Agency
EOC	Epithelial ovarian cancer
FDA	US Food and Drug Administration
FIGO	International Federation of Gynecology and Obstetrics
HPV	Human papillomavirus
IC_{50}	Half maximal inhibitory concentration
IFN-α	Interferon-alpha
IFN-γ	Interferon-gamma
nM	Nanomol
ORR	Overall response rate
OS	Overall survival
PD-1	Programmed death cell ligand 1
PFS	Progression free survival
PR	Partial remission
QoL	Quality of life
RCTX	Radiochemotherapy
RR	Response rate
TLR	Toll-like receptor

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