Chapter 6
Personalized Treatment in Immunotherapy for Gynecologic Cancer

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Abstract Recent cancer treatments have entered a new era with novel types of immunotherapies. In particular, immune checkpoint signals mediated by the immunosuppressive cofactors programmed cell death 1 (PD-1) and PD-1 ligand 1 (PD-L1), are the most promising targets for new cancer treatments.

Several clinical trials of various types of gynecologic cancers have been completed and revealed a modest antitumor effect with monotherapy with immune checkpoint inhibitors (ICIs; anti-PD-1 antibody and/or anti-PD-L1 antibody). However, genetic and/or molecular biomarker-selected endometrial cancer and cervical cancers are more promising for treatment with ICIs. Some ICIs have been approved by the FDA and the combination of ICIs with other agents has yielded good results in trials for these cancers. Therefore, the selection of patients who would benefit from ICI immunotherapy is quite important.

Keywords Immune checkpoint inhibition · PD-1 · PD-L1 · MSI · TMB

6.1 Introduction

In the last decade, cancer treatment has been revolutionized by new types of immunotherapies, mainly immune checkpoint inhibitors (ICIs) such as anti-programmed cell death 1 (PD-1) antibodies and/or anti-PD ligand 1 (PD-L1) antibodies (Table 6.1), which have become standard treatments for several advanced solid tumors [1, 2] (Table 6.2). Based on the mechanism of action of these agents, several biomarkers to measure the response to treatment have been investigated in

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Table 6.1 Immune checkpoint inhibitors (PD-1 signal inhibitors) in gynecologic cancers

Target	Agent	Brand name	Company
PD1	Nivolumab	Opdivo	Bristol-Meyers Squibb/Ono
	Pembrolizumab	Keytruda	MSD
	Dostarlimab-gxly	Jemperli	GSK
	Cemiplimab-rwlc	Libtayo	Sanofi
	Balstilimab		Agenus
PD-L1	Atezolizumab	Tecentriq	Roche
	Durvalumab	Imfinzi	AstraZeneca
	Avelumab	BAVENCIO	Pfizer

Table 6.2 FDA approved PD-1 signal inhibitors in gynecologic cancers

Tumor type	Biomaker	Agent	Company
Cervical cancer	PD-L1	Pembrolizumab	MSD
	PD-L1	Pembrolizumab±TC+Bmab	MSD
Endometrial cancer	MSS	Pembrolizumab+lenvatinib	MSD/Eisai
	dMMR/MSI-High	Dostarlimab-gxly	GSK
Solid tumor	dMMR/MSI-High	Dostarlimab-gxly	
		Pembrolizumab	MSD
	TMB-High	Pembrolizumab	

*MSI-High, microsatellite instability-high; MSS, microsatellite stable; MMRd, mismatch repair deficiency; TC±Bmab, paclitxel±bevacizumab

clinical trials and have led to the approval of ICI-based treatments [3, 4]. More recently, some clinical trials using ICI monotherapy have demonstrated promising antitumor effects for gynecologic cancers such as mismatch repair deficient (MMRd) or microsatellite instability (MSI)-high cases of endometrial cancers and PD-L1-expressing cervical cancer [5]. However, gynecologic cancers, particularly ovarian cancer, represent a heterogenous subgroup of histologies, and thus their responses to ICIs cannot be fully predicted using known biomarkers. Therefore, the optimal biomarkers for specific subtypes of patients with cancer are urgently required [4].

Conversely, combination immunotherapies with other antitumor therapies such as chemotherapy, targeted therapy, radiotherapy, or other immunotherapies have been expected to enhance the antitumor effect of ICIs in gynecologic cancers, and some of these have demonstrated promising synergistic effects.

This chapter highlights the mechanism of action of ICIs and recent clinical trials of ICIs used to treat gynecologic cancers, including specific molecular- or genetic-based personalized immunotherapies (Fig. 6.1).

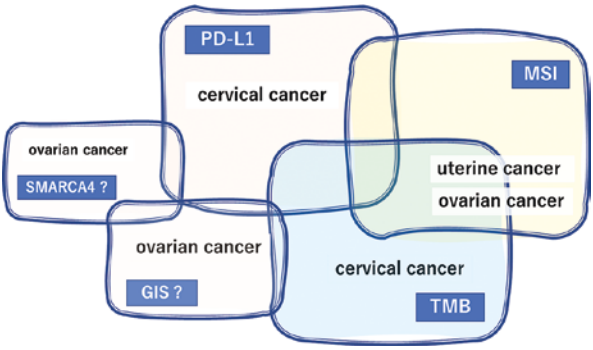

Fig. 6.1 Precision biomarkers in gynecologic cancers. MSI, microsatellite instability; TMB, tumor mutational burden; GIS, genomic instability score; SMARCA4, SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily A, member 4

6.2 PD-1 Signal

PD-1 (CD279) is an immunosuppressive co-inhibitory molecule that belongs to the CD28 family of receptors on T cells. PD-1 was discovered in 1992 and is known to be an induced molecule on T cells undergoing apoptosis [6]. Additional studies demonstrated PD-1 expression on mature hematopoietic cells such as T and B cells, as well as monocytes, following activation [7]. The cognate ligands for PD-1 are the B7-family molecules, PD-L1 (CD274, B7-H1), and PD-L2 (CD273, B7-H2). PD-L1 is expressed in human tonsils, placenta, monocytes, and lungs, where it plays a role in immune tolerance. PD-L2 is mainly expressed in dendritic cells (DCs) under normal physiological conditions [8]. The PD-1/PD-L1/L2 signaling pathway has been shown to control excessive autoimmune and inflammatory responses. This pathway plays a key role in immune homeostasis, together with the B7–1/2/CTLA-4 signaling pathway described above [9]. The CTLA-4 signaling pathway is primarily involved in the process of antigen presentation in lymph nodes, whereas the key role of the PD-1 signaling pathway is to suppress the immune response to target cancer cells in peripheral tissue.

6.3 PD-1 Signal Inhibitors

Several clinical trials have utilized humanized anti-PD-1 antibodies (pembrolizumab, nivolumab, dostarlimab-gxly, cemiplimab-rwlc, and balstilimab) and anti-PD-L1 antibodies (atezolizumab, durvalumab, avelumab) for solid tumors as PD-1 signal inhibitors (Table 6.1). Subsequently, some antibodies have been approved by the FDA for gynecologic cancers (Table 6.2). Pembrolizumab, an anti-PD-1

antibody, was first approved for melanoma in 2014 and dostarlimab-gxly, another anti-PD-1 antibody, has been approved for mismatch repair deficient (MMRd) recurrent or advanced solid tumors. To date, at least 200 clinical studies have been carried out using some type of PD-1 signal inhibitors in gynecologic cancers (ClinicalTrials.gov) [10].

6.4 Personalized PD-1 Signal Inhibitors

Based on the mechanism of action of PD-1 signal inhibitors, several biomarkers for the response to treatment have been investigated in various clinical trials, including gynecologic cancers, and this has led to the approval of PD-1 signal inhibitors. Recent clinical trials of PD-1 signal inhibitors for gynecological cancer have demonstrated promising results in endometrial cancers and cervical cancers. Because gynecological cancers represent a heterogeneous group of tumors, the optimal biomarkers for a specific type of cancer have not yet been fully determined; some biological biomarkers known to be useful for the treatment of gynecologic cancers are shown in Fig. 6.1.

6.5 PD-L1 Expression

PD-L1 protein expression is a predictive biomarker of the efficacy of PD-1 inhibitors in several types of cancer including cervical cancer, but not in endometrial cancer and ovarian cancer, as demonstrated in previous immunotherapeutic clinical trials [11, 12]. PD-L1 gene amplification has been reported in 0.7% of 100,000 cases of more than 100 types of solid tumors, and specifically in 2.7% (10/374) cases of cervical cancer. Furthermore, although the number of cases is small, the response rate (RR) to PD-1 pathway inhibitors was 66.7% (6 responses) in 9 solid tumors with PD-L1 gene amplification [10], and the same has been reported in multiple cancer types including lung cancer and breast cancer. Therefore, PD-1 pathway inhibitors are often recommended for cancers with high PD-L1 gene expression including cervical cancers, and not for endometrial and ovarian cancers.

In the KEYNOTE-158 trial of pembrolizumab in previously treated recurrent cervical cancer, the RR was 14.6% in patients with high PD-L1 expression and 0% in patients with low expression. The FDA approved pembrolizumab for PD-L1–positive recurrent cervical cancer in 2018 [13]. The KEYNOTE-826 trial studied the use of pembrolizumab in untreated metastatic/advanced cervical cancer and combined standard chemotherapy with bevacizumab with or without pembrolizumab. This study found that both progression-free survival and overall survival improved in the pembrolizumab group, and following this, the FDA approved

pembrolizumab as a first-line treatment for PD-L1 positive cervical cancer in 2022 [14]. Furthermore, in the randomized phase III EMPOWER-Cervical 1/GOG-3016/ENGOT-cx9 study with the novel anti-PD-1 antibody cemiplimab, cemiplimab demonstrated significantly longer overall survival compared to chemotherapy [11]. In the RaPiDS trial, another anti-PD-1 antibody, balstilimab, also demonstrated that the objective response rate (ORR) in PD-L1-positive patients was 20% and 8% in PD-L1 negative patients. The combination immunotherapy of balstilimab and the CTLA-4 inhibitor zalifrelimab resulted in an ORR of 27% and 11% in the PD-L1-positive and PD-L1-negative cohorts, respectively [15].

On the other hand, previous clinical trials of PD-1 signal inhibitors have shown no significant effect on PD-L1 expression in other gynecologic cancers [16].

6.6 Microsatellite Instability

Recent reports identified the frequency of genetic mutations derived from high microsatellite instability (MSI-High) with DNA mismatch repair deficiency (MMRd) in cancer cells as a candidate biomarker [17]. Many mutated antigens (called neoantigens) produced by MSI expressed on the surface of cancer cells are recognized by T cells and B cells as foreign antigens, either directly or through the APC system. Cancer cells exposed to IFN-γ released from activated T cells express PD-L1, thereby establishing an acquired immune resistance [18]. In this case, PD-1 signal inhibitors are more likely to be effective.

The frequency of MMRd /MSI-High in cancer varies by cancer type. In an analysis of 12,019 patients with MSI with 32 different types of cancer, MSI-High was identified in patients with 24 different carcinomas (2.2%). Endometrial cancer was the most common (17%) cancer with MSI-High, while ovarian cancer (3%) and cervical cancer were rare [5]. Therefore, MMRd/MSI-High endometrial cancer has become the focus of research as a good target for PD-1 signal inhibitors.

In the KEYNOTE-058 study of pembrolizumab in MMRd/MSI-High solid tumors, a high response rate was reported for MSI-H endometrial cancer in 28 of 49 patients (RR: 57%) and also for MMRd/MSI-High ovarian cancer in 5 of 15 patients (RR: 33%). The FDA has approved pembrolizumab for MMRd/MSI-High solid tumors across cancer types [19]. In addition to pembrolizumab, several other PD-1 pathway inhibitors such as dostarlimab-gxly (PD-1) and the antibodies avelumab (PD-L1) and durvalumab (PD-L1) have also been shown to be significantly more effective in patients with MMRd or MSI-High [20–22].

On the other hand, the KEYNOTE146 trial (Phase I/II), which investigated the efficacy of combination therapy of pembrolizumab with the multi-kinase inhibitor lenvatinib, showed a high RR of 57%, and was approved by the FDA for microsatellite stable (MSS)/mismatch repair proficient (MMRp) in 2019. The KEYNOTE-775/309 trial (phase III) demonstrated pembrolizumab in combination with lenvatinib prolonged overall survival, regardless of MMR abnormality [23].

6.7 Tumor Mutational Burden (TMB)

Recent comprehensive genetic mutation analysis of cancer tissues using next generation sequencing has revealed that, among the same cancer types, patients with high somatic gene mutations (tumor mutational burden-high: TMB-High) have high immunogenicity (immunoreactivity) due to the release of neoantigens, and the PD-1 pathway is induced by immune homeostatic reactions. In this situation, PD-1 pathway inhibitors reactivate the antitumor effect with increased immune cell infiltration into the tumor [24].

The KEYNOTE-158 trial of pembrolizumab in multiple solid tumors showed that the RR of the TMB-High group (TMB ≥10 mut/Mb, n = 102) was 29%, while that of the Non-TMB-High group ($n = 688$) was 6% [25]. In 2020, the FDA approved pembrolizumab for TMB-High solid tumors (≥10 mut/Mb), including gynecologic cancers.

The threshold of 10 mut/Mb of TMB-High is open to some debate. Recent research has demonstrated that not all types of TMB-High tumors such as brain tumors, unselected colon cancer, and esophageal cancer have demonstrated a favorable response to PD-1 signal inhibitors [26]. As for gynecological cancers, TMB-H predicts good responses in endometrial cancer but not in cervical cancer and ovarian cancer [27, 28].

6.8 Genomic Instability Score

Genomic Instability Score (GIS) is an algorithmic measurement of loss of heterozygosity, telomeric allelic imbalance, and large-scale state transitions by a next generation sequencing-based in vitro diagnostic test of tumor tissue specimens [29]. The results of the test are used to aid the identification of patients with ovarian cancer with positive homologous recombination deficiency status, who are eligible for treatment with poly (ADP-ribose) polymerase (PARP) inhibitors. It is thought that GIS-high will become a good biomarker of combination immunotherapy for ovarian cancer [30]. In the phase II study of the PARP inhibitor olaparib with the anti-PD-L1 antibody durvalumab (MEDIOLA doublet cohort) for germline BRCA-mutated platinum-sensitive relapsed (PSR) ovarian cancer, high ORR (72%) and disease control rates (81%) were observed with 19% of complete response (CR) cases [31]. Additionally, in the MEDIOLA triplet cohort, the triple combination immunotherapy of olaparib, durvalumab, and the anti-VEGF antibody bevacizumab for non-gBRCAm PSR ovarian cancer demonstrated an incredible antitumor effect in biomarker selected patients. Subgroup analysis revealed that a 100% RR (10 of 10 patients) was reported in GIS-positive cases (Foundation Medicine tumor analysis), while a 75% RR (6 of 8 patients) was reported in GIS-negative patients [32].

6.9 SMARCA4

SWI/SNF-Related, Matrix-Associated, Actin-Dependent Regulator of Chromatin, Subfamily A, Member 4 (SMARCA4) (also known as BRG1) is a subunit of the SWI/SNF chromatin remodeling complex, which regulates the expression of several genes [33]. Alterations in the SWI/SNF complex, and in particular, the loss of SMARCA4 expression, are well documented in several types of cancers including ovarian cancer. Small cell carcinoma of the ovary, hypercalcemic type (SCCOHT), is a rare, highly aggressive form of ovarian cancer seen primarily in younger patients, and has low survival rates for later-stage disease. Although low TMB with high intratumoral immune cell infiltration of SCCOHT would not predict responsiveness to an immune checkpoint blockade, a combination of PD-1 inhibitors with pembrolizumab have shown substantial and durable responses in selected patients [34].

6.10 Summary

Advances in clinical oncology and novel drug discoveries are playing a major role in personalized medicine in gynecologic cancers. The final goal of treatment for cancer is focused on patient specificity so that effective treatment is given to the right patient. The heterogeneity between gynecologic cancers among patients and within the same patient must be accounted for in personalized medicine. Therefore, genomic analyses with next generation sequencing and/or gene expression profiling using DNA microarrays along with bioinformatics will comprehensively reveal the diversity of the genome, epigenome, and expression profiles of gynecologic cancers that can be treated with immunotherapies. In the real-world clinical practice in medical oncology, we should perform reverse-translational research by using patients' samples such as tumor biopsies and/or blood samples to find and develop the next biomarkers or immunoreactive factors [35], which are related not only to antitumor effects but also treatment-refractory/resistant factors to prolong the survival of patients with gynecologic cancers.

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