

Application and Challenges of Immune Checkpoint Inhibitors (ICI) in Gynecological Tumors

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Abstract. Gynecological malignant tumors seriously threaten the women's lives and also the health, with cervical cancer, ovarian cancer and endometrial cancer being the most common. Traditional treatment modalities (surgery, chemotherapy, radiotherapy) remain the cornerstone, but their efficacy is often limited by drug resistance and recurrence. New treatment methods need to be explored to save patients' lives. Immune checkpoint inhibitors (ICI) have made breakthrough progress in gynecological malignant solid tumors. By blocking the binding of inhibitory receptors on the surface of T cells (such as PD-1 and CTLA-4) to their ligands, they have reactivated the immune response of T cells to tumors, completely changing the treatment landscape. This article aims to systematically review the current clinical application status, key clinical trial evidence and biomarker roles of ICI in cervical cancer, endometrial cancer and ovarian cancer, deeply analyze the challenges it faces, including the limitations of biomarker prediction, drug resistance, management of immune-related adverse reactions and exploration of combination treatment strategies. In order to provide references for its clinical application and future research.

Keywords: Immune checkpoint inhibitors, cervical cancer, endometrial cancer, ovarian cancer

1. Introduction

Gynecological tumors are one of the major public health issues threatening women's health. According to global cancer data from 2022, there were 1.4734 million new cases of gynecological malignancies worldwide, accounting for 15.25% of all female cancer cases. Among these, cervical cancer was the most severe, with 662,300 new cases, representing 44.95% of total gynecological tumor cases. Endometrial cancer and ovarian cancer followed closely, accounting for 28.53% and 21.99% of total gynecological tumor cases, respectively. In terms of mortality, cervical cancer also imposed a heavy burden, with 348,900 deaths, accounting for 51.28% of all gynecological tumor-related fatalities [1]. These data indicate that cervical, endometrial, and ovarian cancers, as common types of gynecological malignancies and remain a leading cause of female mortality. Traditional treatment modalities are based on surgery, chemotherapy, and radiotherapy. In recent years, the application of targeted therapies such as anti-angiogenic drugs has significantly improved survival rates for some patients. However, overall, treatment options for advanced and recurrent cases remain limited, necessitating new therapeutic strategies.

Tumor immunotherapy, especially immune checkpoint inhibitors (ICI) targeting programmed death protein-1 (PD-1), its ligand (PD-L1), and cytotoxic T lymphocyte-associated protein-4 (CTLA-4), has completely transformed the treatment landscape of various solid tumors [2]. This type of drug reactivates the anti-tumor immune response by relieving the inhibition of effector T cells by the tumor microenvironment (TME). Both at home and abroad, a variety of ICI have been approved for the clinical treatment of gynecological tumors. However, there have been few systematic sorting and analysis of the specific applications of different gynecological tumors yet. Therefore, this article intends to systematically elaborate on the immune pathogenesis of common gynecological malignant tumors, as well as the clinical research progress of monotherapy and combination therapy of ICI. Meanwhile, the core challenges in current clinical applications are analyzed, with the aim of providing more theoretical reference basis for the diagnosis and treatment of common gynecological tumors.

2. Application of ICI in cervical cancer

2.1. Immune pathogenesis of cervical cancer

The immune pathogenesis is a multi-step immune escape process driven by persistent infection with high-risk human papillomavirus (HR-HPV). The core lies in how the virus skillfully disrupts the host's immune surveillance and eventually leads to the malignant transformation of normal cervical epithelial cells. HPV viruses, especially types 16 and 18, infect the epithelial cells of the cervical basal layer through minor trauma and integrate their genomes into the DNA of the host cells. This integration event is a key turning point in cancer development. After integration, the virus continuously expresses two key oncoproteins, E6 and E7. The E6 and the E7 proteins respectively degrade the tumor suppressor proteins p53 and pRB, interfering with the cell cycle regulation and thereby promoting the occurrence and development of tumors. In addition, E7 can significantly up-regulate the expression of histone methyltransferase SUV39H1, thereby catalyzing the enrichment of inhibitory histone markers H3K9me2 and H3K9me3 in the promoter regions of innate immune sensor genes (such as RIG-I, cGAS and STING), leading to epigenetic silencing of these genes. This silence weakens the cells' ability to perceive viral nucleic acids. However, the loss of the immune system is the real driver. The HPV virus has developed sophisticated immune escape strategies during its evolution. The core strategies include inducing an imbalance in the Th1 /Th2 immune response and down-regulating antigen presentation function. Research has found that HPV infection can promote the transformation of the immune response from Th1 type to Th2 type, which is manifested as an increase in the level of Th2-type cytokines (such as IL-10) in cervical lesion tissues, while the expression of Th1-type cytokines (such as IFN- γ , IL-12, etc.) decreases. This immunosuppressive state formed by Th1 response deficiency and Th2 dominance is an important factor promoting the progression of cervical lesions [3,4].

2.2. Evidence of ICI in cervical cancer

A systematic review and meta-analysis (12 trials) with a total of 523 advanced cervical cancer patients, aimed at evaluating the efficacy and safety of ICIs. The results showed that the objective response rate (ORR) of PD-1 inhibitors was 0.24, the complete response rate (CR) was 0.03, the partial response rate (PR) was 0.20, the disease stability rate (SD) was 0.31, and the disease control rate (DCR) was 0.56. The incidence of adverse events at any level is 0.81, and the incidence of adverse events at or above level 3 is 0.25. The study also pointed out that the number of studies on

PD-L1 and CTLA-4 inhibitors is limited, and the monotherapy efficacy is not significant, but the combination therapy shows potential synergistic effects. Despite limitations such as high heterogeneity and lack of individual patient data, this meta-analysis still provides important evidence for the application of ICIs in advanced cervical cancer [5].

KEYNOTE-826 is a global, phase III, randomized, double-blind, placebo-controlled clinical trial aimed at evaluating the efficacy of pembrolizumab combined with chemotherapy (with or without bevacizumab) in the treatment of patients with persistent, recurrent or metastatic cervical cancer. A total of 617 patients were included in the study, with a focus on analyzing the PD-L1 expression positive population ($CPS \geq 1$) and the intention-to-treat population. The results indicated that in all key subgroups, the addition of pembrolizumab could significantly improve the overall survival and progression-free survival of patients. These subgroups include whether bevacizumab was used in combination, whether carboplatin or cisplatin was selected as a platinum-based drug, whether chemotherapy or radiotherapy had been received only previously, and whether the histological type of the tumor was squamous cell carcinoma or non-squamous cell carcinoma. The hazard ratio data showed a consistent benefit trend. For instance, in the subgroup combined with bevacizumab, the hazard ratio for death was 0.62, while in the non-combination subgroup it was 0.67. In addition, pembrolizumab also significantly increased the objective response rate in each subgroup [6]. That is, regardless of the baseline characteristics or treatment background of the patients, adding pembrolizumab to the standard chemotherapy regimen can bring clinically significant survival advantages, thereby supporting it to become a new first-line standard treatment option for this patient group.

3. Application of ICI in endometrial cancer

3.1. Immune pathogenesis of endometrial cancer

At the molecular level, the immune characteristics of endometrial cancer vary significantly depending on different molecular subtypes. Among them, tumors with mismatch repair dysfunction (dMMR) or high microsatellite instability (MSI-H) will lead to the production of a large number of neoantigens due to the failure of the DNA replication error repair mechanism. These tumor-specific neoantigens are recognized by immune cells, thereby triggering a strong anti-tumor immune response, manifested as the infiltration of a large number of cytotoxic T cells in the tumor microenvironment and the upregulation of immune checkpoint molecules (such as the PD-1/PD-L1) [7,8].

In contrast, most endometrial cancers with normal mismatch repair (pMMR or MMRP) exhibit a different immune landscape. These tumors have a lower burden of new antigens, and their immune escape mechanisms are more complex and elusive. Tumor cells can actively suppress T cell function by upregulating various immunosuppressive signaling pathways, such as sustained high expression of PD-L1. Meanwhile, the tumor microenvironment often exhibits a state of "immune suppression" or "immune rejection", which may be characterized by the enrichment of tumor associated macrophages (TAMs), the regulatory T cells (Tregs) and other cells. The recruitment of macrophages to the local endometrium and polarization is a prerequisite for TAMs to function. Circulating monocytes are an important source of TAMs, and patients with endometrial cancer who have a high number of circulating monocytes have a significantly higher incidence of muscle infiltration and pelvic lymph node metastasis. The loss of LKB1 expression in endometrial epithelial cells can activate the secretion of chemokine CCL2, which recruits TAMs to the local area of endometrial cancer. In addition, Zhao Linlei et al. detected Treg cells and serum IL-10 and TGF-8

levels in endometrial cancer patients and found that all three levels were higher than those in the normal control group, suggesting that Treg and its inhibitory cytokines may be key components involved in tumor immune suppression in the tumor microenvironment [9,10].

In summary, the immunopathogenic mechanism of endometrial cancer is the result of molecular variations within the tumor and dynamic evolution of immune components in the tumor microenvironment. A deep understanding of this heterogeneity is the basis for developing effective immune combination strategies, such as combining anti angiogenic drugs.

3.2. Evidence of ICI in endometrial cancer

In a trial studying the efficacy of pembrolizumab in advanced EC(n=24), with 10 mg/kg of pembrolizumab every two weeks for 35 cycles, up to a maximum of 24 months, either until disease progression or severe toxic and side effects occurred. The results showed that the median progression-free survival is 1.8 months, and the 6-month and 12-month progression-free survival rates were 19.0% and 14.3%, respectively. The overall survival rate at 6 months and 12 months were 67% and 51%, respectively. In terms of safety, only 4 patients experienced severe toxic reactions. The efficacy and safety of pembrolizumab were confirmed [11].

The latest Phase 2 study (NCT02912572) evaluated Avelumab (anti-PD-L1 antibody) combined with Axitinib (VEGFR1-3 inhibitor) in recurrent MMRP endometrial cancer patients (n=35). The total ORR reached 40% (14/35). The confirmed ORR is 25.7%. Another 13 cases (37.1%) of patients had stable diseases, and 6 cases (17.1%) showed disease progression. The median duration of response was estimated at 13.8 months, the 6-month PFS rate was 55.8%, and the median progression-free survival was 7 months. In terms of safety, the most common grade 3 and above treatment-related adverse events were hypertension (37.1%), elevated ALT (5.7%), and elevated AST (5.7%). Five cases (14.3%) of patients discontinued treatment due to toxic reactions [12].

4. Application of ICI in ovarian cancer

4.1. Immune pathogenesis of ovarian cancer

Under normal circumstances, the immune system can recognize and eliminate the malignant transformed cells. However, ovarian cancer cells down-regulate the expression of MHC molecules, especially MHC-I molecules, making it difficult for the cytotoxic T cells to recognize tumor-associated antigens, leading to immune escape. Meanwhile, Tregs strongly inhibit the anti-tumor function of effector T cells and the natural killer (NK) cells by secreting inhibitory cytokines such as IL-10 and TGF- β . TAMs, especially in the M2 polarization state, not only secrete various pro-angiogenic factors (such as VEGF) to promote tumor angiogenesis but also consume amino acids necessary for T cell proliferation in the microenvironment by generating metabolic products such as arginase and nitric oxide synthase, thereby inhibiting T cell function at the metabolic level [13].

In addition, during the occurrence and development of ovarian cancer, tumor cells often induce the upregulation of ICPs and their ligands, inhibit the anti-tumor response, and lead to immune escape. Some scholars first discovered and identified a subpopulation of the human NK cells overexpressing PD-1 in the ascites of patients with ovarian cancer. Moreover, the PD-1+ NK cells have a poor proliferation response to cytokine stimulation, showing IFN- γ -mediated degranulation and down-regulation of cytotoxicity [14].

4.2. Evidence of ICI in ovarian cancer

ICI monotherapy is not routinely recommended at present [15]. Most trials of ICI for ovarian cancer are in Phase I to II and the ORR is not high, mostly below 15%. Some of the research results are also acceptable. For instance, nivolumab was administered to 18 patients in the early clinical stage. The disease control rate was 44.0%. Among them, 8 cases had stable conditions, 6 cases progressed, and 4 cases died before the first radiological assessment [16].

The efficacy of ICI monotherapy for ovarian cancer is unsatisfactory, and some studies have explored the mode of ICI combined with chemotherapy. The Phase II clinical trial "Neo Pembro" included 33 ovarian cancer patients. They were first treated with one cycle of simple chemotherapy, followed by the addition of pembrolizumab from the second cycle and continued to receive treatment until surgery and one year after surgery. The results showed that after treatment, the number of CD3+ and the CD8+T cells in the tumor significantly increased, the CD8+/FOXP3+ increased and the TNF- α and interferon- γ signaling pathways were enhanced, indicating that chemotherapy combined with pembrolizumab can effectively activate local immune response. In terms of efficacy, 27% of patients achieved primary pathological remission, and their survival outcomes were significantly better than those with secondary remission. At a median follow-up of 52.8 months, 8/9 patients in the primary remission group survived and 6 cases had no recurrence; However, only 4 out of 24 patients in the secondary remission group survived, and only 1 case had no recurrence. Biomarker analysis suggests that high expression of PD-L1 and homologous recombination deficiency status can predict major pathological remission and have the potential to become a patient screening tool. The treatment has good safety and no new safety signals have emerged. Only a few patients have stopped taking the medication due to immune related adverse events [17].

Another study (KGOG 3046/TRU-D) evaluated the efficacy and safety of combining durvalumab and tremelimumab with neoadjuvant chemotherapy in patients with advanced ovarian cancer (n=23). The treatment plan is to first undergo three cycles of "chemotherapy + dual immunotherapy", followed by intermittent cytoreductive surgery, and then receive adjuvant chemotherapy and durvalumab maintenance therapy after the operation. After a median follow-up of 29.2 months, the 12-month PFS rate was 63.6%. Although it did not reach the preset primary endpoint, the longer-term PFS rate at 24 months and 30 months were 45.0% and 40.0%, respectively, indicating a statistically significant improvement. In terms of treatment response, the pathological complete response rate was 17.4%, and the rate of grade 3 chemotherapy response score was 39.1%. These indicators were all superior to the historical data of traditional neoadjuvant chemotherapy. In terms of safety, treatment-related adverse events are controllable. The most common one is rash, and most serious adverse events can be relieved by steroid hormone treatment [18].

5. The challenges currently faced

5.1. Lack of reliable predictive biomarkers

The application of ICI currently faces a core bottleneck, which is the lack of accurate and universally applicable predictive biomarkers. Although the expression level of PD-L1 and microsatellite instability (MSI) have been used in clinical practice, they both have certain limitations. The expression of PD-L1 exhibits spatiotemporal heterogeneity, and the detection methods and interpretation criteria are not consistent, resulting in significant differences in its

predictive value among different cancer types and individuals. Although MSI-H is currently one of the most effective biomarkers, it only appears in a few types of cancer and patients, leading to many patients being unable to benefit from expensive immunotherapy while bearing potential economic and toxic costs, hindering the development of precision immunotherapy. Future research should continue to explore more biomarkers to address the significant individual variability in treatment response, and validate their accuracy through large-scale clinical trials.

5.2. Drug resistance

With the clinical use of ICI, the drug resistance has gradually emerged. Its resistance mechanism is complex and diverse, mainly involving the internal factors of tumors and the regulation of the microenvironment. In terms of the intrinsic mechanisms of tumors, antigen presentation defects (such as down-regulation of MHC-I) and infiltration of immunosuppressive cells lead to T-cell anti-tumor disorders, while epigenetic regulatory abnormalities can promote immune escape by inhibiting the expression of immune-related genes. In terms of the TME, metabolic reprogramming such as tryptophan depletion can activate the immunosuppressive enzyme indoleamine 2, 3-dioxygenase, further weakening T cell function. Tumors can utilize multiple and redundant mechanisms to evade the attack of the immune system. Merely blocking a single pathway of the PD-1/PD-L1 or the CTLA-4 is often insufficient to maintain long-term anti-tumor immunity. Overcoming drug resistance requires a deep understanding of the mechanisms of these dynamic changes and, on this basis, developing combination treatment strategies, such as combined chemotherapy, radiotherapy or targeted drugs, etc., to break immune tolerance [19,20].

5.3. Immune-related adverse events

While ICIs generate anti-tumor immune responses, they also attack their own normal tissues, leading to a series of adverse reactions, known as immune-related adverse events (IrAEs), which can affect almost all organ systems, the skin (incidence rate 34% to 45%), the digestive system (incidence rate 13% to 32%), the liver (incidence rate 4% to 8%), and the endocrine system (incidence rate 7% to 8%) [21]. The challenge lies in the following: Firstly, IrAEs can occur at any stage of treatment, even after the treatment is completed, and their severity ranges from mild to life-threatening. Secondly, the IrAEs spectra caused by different immunosuppressants vary. Thirdly, to control severe IrAEs, high-dose glucocorticoids or other immunosuppressants are usually required, but this may weaken the anti-tumor immune effect and affect the long-term efficacy of patients.

6. Conclusion

ICI has brought revolutionary changes to the treatment of common gynecological tumors, with significant efficacy in endometrial and cervical cancer, but poor efficacy in ovarian cancer. The current challenges - heterogeneity of therapeutic efficacy, prevalence of drug resistance, limitations of biomarkers, and unique adverse reactions - are the focus of future research. By deepening the understanding of tumor immune interactions, developing innovative combination therapy strategies, and utilizing more precise biomarkers to guide clinical practice, it is expected to overcome existing barriers and enable more gynecological cancer patients to benefit sustainably from immunotherapy, ultimately achieving the grand goal of transforming deadly cancer into controllable chronic diseases.

Although clinical trial data on combination therapy is still limited, there are indications that this therapy, as a new treatment modality, demonstrates encouraging safety and therapeutic potential, and

has good clinical application prospects. In the actual clinical promotion process, it is necessary to strictly grasp its indications, carefully exclude contraindications, and ensure the rationality of patient choices. At the same time, medical personnel need to fully understand the series of adverse reactions that ICIs may cause and establish a sound monitoring and response mechanism to ensure patient medication safety. During the treatment process, it is also necessary to dynamically and comprehensively evaluate efficacy by combining imaging, serological indicators, and changes in clinical symptoms. In addition, the optimal chemotherapy regimen, treatment timing, immunotherapy drugs, and treatment sequence are still to be explored. Believing in the future, with the continuous accumulation of evidence-based medicine evidence, combination therapy is expected to provide more precise and effective treatment options for more patients.

References

- [1] Liu Yunqi, Zhang Dong, Gao Linzhi, et al. Research Progress on the Role of Small Activating RNA in Common Gynecological Malignant Tumors [J/OL] *Modern Medicine and Health*, 1-9 [2025-09-27].
- [2] Zou Y, Xu Y, Chen X, Zheng L. Advances in the application of immune checkpoint inhibitors in gynecological tumors. *Int Immunopharmacol*. 2023 Apr; 117: 109774.
- [3] Gulinigar Toheniyazi, Du Rong. Research Progress on the Immune Regulatory Mechanism of cervical HPV infection [J]. *Chinese Journal of Family Planning and Obstetrics and Gynecology*, 25, 17(09): 48-52.
- [4] Lo Cigno I, Calati F, Borgogna C, et al. Human Papillomavirus E7 Oncoprotein Subverts Host Innate Immunity via SUV39H1-Mediated Epigenetic Silencing of Immune Sensor Genes. *J Virol*. 2020 Jan 31; 94(4): e01812-19.
- [5] Wang W, Bi X, Feng Y, et al. Efficacy and Safety of Immune Checkpoint Inhibitors on Advanced Cervical Cancer: A Systematic Review and Meta-analysis. *J Immunother*. 2025 Feb-Mar 01; 48(2): 78-88.
- [6] Tewari KS, Colombo N, Monk BJ, et al. Pembrolizumab or Placebo Plus Chemotherapy With or Without Bevacizumab for Persistent, Recurrent, or Metastatic Cervical Cancer: Subgroup Analyses From the KEYNOTE-826 Randomized Clinical Trial. *JAMA Oncol*. 2024 Feb 1; 10(2): 185-192.
- [7] Post CCB, Westermann AM, Bosse T, Creutzberg CL, Kroep JR. PARP and PD-1/PD-L1 checkpoint inhibition in recurrent or metastatic endometrial cancer. *Crit Rev Oncol Hematol*. 2020 Aug; 152: 102973.
- [8] Mestrallet G, Brown M, Bozkus CC, Bhardwaj N. Immune escape and resistance to immunotherapy in mismatch repair deficient tumors. *Front Immunol*. 2023 Jul 10; 14: 1210164.
- [9] Lu Qiaoying, Zhao Hongbo, Chen Xiaojun. Advances in Immune Regulatory Mechanisms of the tumor microenvironment of endometrial cancer [J]. *Journal of Fudan University (Medical Science)*, 2016, 43(04): 475-478.
- [10] Zhao Linlei, Wang Ting, Feng Chaohui, et al. The correlation between CD4+CD25+Treg, IL-10, TGF- β levels and the occurrence and development of endometrial cancer [J]. *Chinese Journal of Eugenics and Child-rearing*, 2012, 18(04): 237-240.
- [11] Barber EL, Chen S, Pineda MJ, Robertson SE, Hill EK, Teoh D, Schilder J, O'Shea KL, Kocherginsky M, Zhang B, Matei D. Clinical and Biological Activity of Chemoimmunotherapy in Advanced Endometrial Adenocarcinoma: A Phase II Trial of the Big Ten Cancer Research Consortium. *Cancer Res Commun*. 2022 Oct; 2(10): 1293-1303.
- [12] Lee EK, Xiong N, Krasner C, Polak M, Campos S, Wright AA, Liu JF, Shea M, Yeku O, Castro C, Porter R, Stover EH, Koppermann L, Smith J, Sawyer H, Hayes M, Zhou N, Cheng SC, Bouberhan S, Pfaff KL, Rodig SJ, Jones S, Penson RT, Moroney J, Fleming GF, Matulonis UA, Konstantinopoulos PA. Phase 2, two-stage study of avelumab and axitinib in patients with mismatch repair proficient recurrent or persistent endometrial cancer. *Gynecol Oncol*. 2025 Jul; 198: 1-8.
- [13] Chen Junchen, Peng Yanzhen, Cheng Jiumei. Research Progress on the Immune Escape Mechanism of Ovarian Cancer [J]. *Chongqing Medical Journal*, 2022, 51(10): 1769-1773.
- [14] Ji Chunya, Bushalaimu Muhamai, Pu Jiawen, etc. Research Progress on the Function and Mechanism of Natural Killer Cells during Immune Escape in Ovarian Cancer [J] *Journal of Clinical Oncology*, 2024, 29(07): 720-725.
- [15] Kong Beihua, Liu Jihong, Yin Aijun, et al. Clinical Application Guidelines for Immune Checkpoint Inhibitors in Gynecological Tumors (2025 Edition) [J]. *Progress in Modern Obstetrics and Gynecology*, 2025, 34(06): 401-424.
- [16] Normann MC, Tüürzer M, Diep LM, Oldenburg J, Gajdzik B, Solheim O, Rud E. Early experiences with PD-1 inhibitor treatment of platinum resistant epithelial ovarian cancer. *J Gynecol Oncol*. 2019 Jul; 30(4): e56.
- [17] Aronson SL, Thijssen B, Lopez-Yurda M, et al. Neo-adjuvant pembrolizumab in stage IV high-grade serous ovarian cancer: the phase II Neo-Pembro trial. *Nat Commun*. 2025 Apr 14; 16(1): 3520.

- [18] Park J, Lee JB, Lim MC, Kim BG, Kim JW, Kim S, Choi CH, Kim HS, Park SY, Lee JY; KGOG investigators. Phase II study of durvalumab and tremelimumab with front-line neoadjuvant chemotherapy in patients with advanced-stage ovarian cancer: primary analysis in the original cohort of KGOG3046/TRU-D. *J Immunother Cancer*. 2023 Oct; 11(10): e007444.
- [19] Zhou X, Ni Y, Liang X, Lin Y, An B, He X, Zhao X. Mechanisms of tumor resistance to immune checkpoint blockade and combination strategies to overcome resistance. *Front Immunol*. 2022 Sep 15; 13: 915094.
- [20] Perrier A, Didelot A, Laurent-Puig P, Blons H, Garinet S. Epigenetic Mechanisms of Resistance to Immune Checkpoint Inhibitors. *Biomolecules*. 2020 Jul 16; 10(7): 1061.
- [21] Yan Zhenying, He Jianxia Research Progress on the Pathogenesis of Immune Checkpoint inhibitor-related Adverse Immune Reactions [J]. *Anhui Medicine*, 2025, 29(10): 1914-1918.