Application of Immunotherapy in the Gynecological Tumors

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Abstract. Gynecologic neoplasms refer to malignancies affecting the female reproductive system, including endometrial cancer, ovarian cancer, and cervical cancer. In recent years, there has been a consistent rise in the incidence of gynecological tumors in China. Due to its high mortality rate, this disease cannot be overlooked. Immunotherapy, which stimulates the body's immune cells to target and eliminate tumors, has emerged as a promising approach for treating gynecological cancers. The examples provided include endometrial cancer, ovarian cancer, and cervical cancer. Immunotherapy has gradually emerged as the primary or neoadjuvant treatment modality for endometrial cancer, exhibiting a remarkable potential to enhance patient survival and mitigate mortality risks. Immune checkpoint inhibitors have exhibited promising outcomes in ovarian cancer, with experimental evidence showcasing their therapeutic efficacy. Cervical cancer is currently exploring immunotherapy approaches and has made substantial progress, as evidenced by favorable response rates. This article provides an overview of current clinical methods and therapeutic outcomes associated with immunotherapy in gynecological cancer treatment while also exploring future directions for its development.

Keywords: Immunotherapy; endometrial cancer; ovarian cancer; cervical cancer.

1. Introduction

The term cancer, also referred to as malignancy and neoplasms, denotes a pathological condition characterized by the uncontrolled proliferation of aberrant cells that surpass their normal boundaries and have the potential to impact any anatomical region within the human body. The process of metastasis refers to the infiltration of cancer cells into adjacent tissues and organs, followed by their subsequent dissemination to distant sites. The risk of mortality due to the primary tumor is significantly heightened as a result of this spread.

Gynecologic cancers can develop in various organs of the female reproductive system including the vulva, vagina, cervix, uterus, fallopian tubes, and ovaries. Among these malignancies, endometrial cancer is the most prevalent type characterized predominantly by adenocarcinoma histology and commonly diagnosed in women around 60 years old. Ovarian cancer is frequently diagnosed at an advanced stage due to subtle or non-specific symptoms, rendering it highly lethal. The incidence of this disease among women is relatively high in resource-rich countries. Conversely, cervical cancer exhibits a contrasting pattern. Due to the widespread availability of Pap test screening, human papillomavirus (HPV) testing, and HPV vaccination, cervical cancer tends to be more prevalent in low-resource countries [1].

Surgery is a conventional approach for cancer treatment and remains the most effective method for eliminating many types of cancer before lymph node or distant metastasis occurs. However, it may not be the primary choice for all early-stage cancers due to potential risks associated with organ removal or disruption of organ function. Additionally, certain cancers develop in anatomically inaccessible areas that cannot be reached through surgical intervention. Chemotherapy is a commonly employed therapeutic approach aimed at eradicating tumor cells. It operates through the systemic or localized administration of pharmacological agents to impede neoplastic growth or eliminate tumors. Nevertheless, its non-selective cytotoxicity towards both malignant and normal cellular populations gives rise to the customary adverse effects associated with chemotherapy.

Tumor immunotherapy is an active or passive approach to induce a tumor-specific immune response in the body, enabling it to effectively inhibit and eliminate tumor cells. This treatment

method offers the advantages of specificity and efficacy while minimizing harm to the body. Unlike traditional treatments such as surgery, targeting, radiotherapy, and chemotherapy, immunotherapy does not directly kill cancer cells. Instead, it activates immune cells capable of recognizing tumors within the body, enhancing the immune system's ability to combat cancer indirectly. Immunotherapy boasts minimal side effects and ensures safety and effectiveness. With ongoing advancements in tumor immunology theory and technology, it holds great promise for achieving a revolutionary breakthrough in radical tumor treatment and becoming the mainstream approach [2]. The objective of this study is to provide a comprehensive overview of the current application of immunotherapy in treating common gynecologic cancers, while also exploring potential future advancements.

2. Correlation between Cancer and Immunity

The immune system serves as the paramount defense mechanism against pathogen invasion, encompassing immune organs, cells, and molecules. It is categorized into innate immunity and adaptive immunity, with the latter further divided into humoral and cellular immunity. By accurately discerning self from non-self substances, the immune system upholds bodily equilibrium to prevent viral, bacterial, and other pathogenic assaults.

Cancer arises from a culmination of aberrations within the body's own responses such as errors in normal cell division or DNA damage. In a sense, cancer cells can be regarded as pathogens; however, they pose greater challenges compared to other invaders due to their ability to employ various disguises like surface-secreted glycoproteins or mucopolysaccharides that evade detection by the immune system. Moreover, differentiating between various types of cancer cells presents varying degrees of difficulty for recognition by the immune system—ultimately fostering a selection effect akin to natural selection in biological species—which drives cancer cell evolution and impedes their identification by immune mechanisms. Additionally, the rapid proliferation rate exhibited by cancer cells contributes significantly to impeding effective clearance by immune cells [3].

Immunotherapy is a cutting-edge systemic cancer treatment modality that harnesses the power of immune cells, enabling them to recognize and target specific cancer cells. Additionally, it augments the body's immune response by providing supplementary substances. Recent clinical trials have demonstrated remarkable efficacy of cancer immunotherapy across various malignancies, including long-term remission and potential cure for select patients with metastatic disease. This therapeutic approach can be categorized into active and adoptive forms.

Active immunotherapy guided by active immunity may involve the administration of vaccines, genetically modified T cells derived from the patient, or specific types of monoclonal antibodies to stimulate the patient's immune system against cancer. Adoptive immunotherapy typically includes administering laboratory-produced monoclonal antibodies to genetically modified T cells or NK cells from healthy individuals to cancer patients. In some cases, these cells are engineered with an anticancer CAR. Other forms of adoptive immunotherapy encompass lymphokines and cytokines such as interferon and interleukins. Currently, the field of immunotherapy for gynecological tumors primarily focuses on immune checkpoint inhibitors (ICI), therapeutic vaccines, and adoptive cell therapy (ACT) [4]. The blockade of immune checkpoint signaling by ICI can restore T cell function and induce tumor eradication by activating immune cells. Tumor vaccines introduce various forms of tumor antigens, such as lysed tumor cells, tumor-associated proteins or peptides, and genes expressing tumor antigens into patients to elicit anti-tumor effects through immune response activation. ACT involves isolating immunocompetent cells from tumor patients, expanding and functionally characterizing them in vitro, followed by infusion back into the patient to directly eliminate tumors or stimulate the body's immune response against malignant cells.

3. The Utilization of Immunotherapy in Gynecologic Cancer

3.1. Endometrial Cancer

Endometrial cancer is typically categorized into two subtypes, with endometrial hyperplasia being the preceding lesion. Type I tumors are commonly observed and usually responsive to estrogen; these tumors have a lower grade, may exhibit microsatellite instability, and harbor mutations in PTEN, PIK3CA, KRAS, and CTNNB1. On the other hand, Type II tumors, also known as aggressive tumors, are generally high-grade with a poor prognosis and prone to significant harm. The staging of endometrial cancer is based on noninvasive versus invasive histology along with the extent of spread including depth of invasion, involvement of surrounding structures or extrauterine/lymph node metastasis; lymphatic space invasion; and molecular classification. For early-stage treatment, surgery and chemotherapy remain the primary approaches, while in advanced stages, a diverse range of treatment modalities are commonly employed [5].

With the rapid advancement of tumor immunotherapy, immunotherapy alone or in combination with other drugs has transitioned from being a subsequent treatment option to becoming a frontline therapy and is now even approaching neoadjuvant therapy. Numerous studies have demonstrated remarkable outcomes. Among gynecologic tumors, endometrial cancer exhibits the highest proportion of MSI-H/dMMR cases. There exist multiple biomarkers for immunotherapy, among which MSI-H/dMMR status is widely acknowledged as an indicator of immune response benefits in solid tumors. The MSI-H/dMMR tumors exhibit a higher tumor mutation burden and increased infiltration of immune cells, indicating an "immune hot tumor" microenvironment state, which is highly favorable for immunotherapy.

The KEYMAT-775 study assessed the efficacy of renvastinib in combination with pembrolizumab in patients with advanced endometrial cancer who had previously undergone at least one platinum-based chemotherapy regimen. The results demonstrated significant enhancements in overall survival (OS) and progression-free survival (PFS), indicating a 32% reduction in the risk of mortality (HR=0.68 [95% CI, 0.56 to 0.84]; p=0.0001). Moreover, there was a substantial decrease of 40% in the risk of disease progression or death (HR=0.60 [95% CI, 0.50-0.72]; $p < 0.0001$) [6]. ACT therapy (includs Tumor-infiltrating lymphocytes (TIL)) has also made advancements in the treatment of endometrial cancer. TIL is a highly heterogeneous population of lymphocytes present within tumor tissues and play a crucial role in the immune response against specific tumor antigens. It was observed that TIL exhibited a positive correlation with improved PFS specifically in patients diagnosed with high-grade endometrial cancer, while no such association was found in those with low-grade tumors. Previous research has demonstrated that TIL have significant implications in tumor development, prognosis, and predicting the clinical efficacy of tumors through immune recognition.

These neoantigens initiate an immune response to eradicate the tumor; however, insufficient data hinders their convincing efficacy. The results of the clinical trial and expert opinions are eagerly anticipated. It is important to note that precise cancer staging and molecular profiling contribute to personalized treatment approaches. For recurrent and advanced tumors, regardless of molecular subtypes, a comprehensive assessment based on clinicopathological and molecular characteristics should be conducted, considering various exploratory therapies such as chemotherapy, radiotherapy, hormone therapy, targeted therapy, immunotherapy or their combinations.

3.2. Ovarian Cancer

The histology of ovarian cancer encompasses various types, each characterized by a distinct genetic composition. Within an individual patient, the cancer may manifest in different locations and consist of multiple subtypes of cancer cells with unique genetic profiles. The most prevalent histology, high-grade serous epithelial ovarian cancer, is considered a unified clinical entity alongside fallopian tube and peritoneal cancer due to shared clinical characteristics. Epithelial ovarian cancer can be categorized into five subtypes: high-grade serous carcinoma, low-grade serous carcinoma, endometrioid carcinoma, clear cell carcinoma, and mucinous carcinoma.Ovarian cancer primarily

affects postmenopausal and perimenopausal women. Risk factors include nulliparity, delayed childbearing, early menarche, delayed menopause, and specific genetic markers. Ultrasonography is commonly used for the detection of early-stage ovarian cancer, while CT or MRI scans are typically employed to assess tumor extent in advanced cases prior to surgery. Elevated levels of CA125 can also indicate the presence of ovarian cancer as a tumor marker [7].

The standard treatment approach involves surgical intervention followed by adjuvant chemotherapy with platinum and paclitaxel. As an emerging treatment modality, immune checkpoint inhibitor (ICI) has demonstrated relatively favorable therapeutic outcomes for ovarian cancer. Similar to a car's braking system, one of the roles and functions of this molecule is to timely "brake" the immune response when activated, thereby maintaining its activation within normal limits and preventing overactivation. The activation of immune checkpoints by tumor cells serves as a "brake" mechanism, hindering the presentation of antigens to T cells and impeding the process of antigen presentation in tumor immunity. By suppressing T cell immune function, tumors can evade surveillance and persist. Immune checkpoint inhibitors alleviate this inhibitory effect, enabling immune cells to reactivate their cytotoxic activity against cancer cells.The two commonly used ICI immunotherapies include Programmed Cell Death Protein 1 (PD-1) and Cytotoxic T-Lymphocyte Associated Antigen 4 (CTLA4) [8].

The PD-1 inhibitor is an immune checkpoint inhibitor currently available on the market, which plays a crucial role in reducing autoimmunity and promoting autoimmune tolerance by inhibiting T cell activation and down-regulating immune response. Its inhibitory effect is achieved through the promotion of apoptosis in lymph node antigen-specific T cells while simultaneously decreasing apoptosis in Tregs. Numerous studies have demonstrated that tumors exploit PD-1 signaling to evade immune detection, underscoring the significance of PD-1 signaling as evidenced by FDA approval for immunotherapy employing PD-1 signaling blockers to induce antitumor responses. The multicohort Keynote-028 trial aimed to assess the safety, tolerability, and antitumor efficacy of pembrolizumab monotherapy in patients with advanced ovarian cancer who express programmed death ligand 1 (PD-L1). Notably, pembrolizumab demonstrated sustained antitumor activity in individuals with PD-L1-positive advanced ovarian cancer [9].

CTLA-4, a member of the immunoglobulin superfamily, is predominantly localized in intracellular vesicles as a transmembrane glycoprotein and functions as a negative regulator. It is expressed in various non-T cells, including both normal and tumor cells, to down-regulate or terminate T cell responses. In this study, patients were administered first-line standard chemotherapy with either nivolumab plus ipilimumab (NIVO+IPI) or pemetrexed/platinum, based on data from Checkmate 743 trial. The findings revealed that the NIVO+IPI group exhibited significant improvement in median OS and a 26% lower risk of mortality compared to the chemotherapy group [10].

In patients with ovarian cancer, particularly those diagnosed with epithelial ovarian cancer, immunotherapy alone generally demonstrates efficacy but exhibits limited sensitivity to relevant immune checkpoint inhibitors such as pembrolizumab and nivolumab, which are commonly employed as second-line treatment options. Notably, the integration of ICI with chemotherapy and a poly (adenosine diphosphate-ribose) polymerase inhibitor has exhibited statistically significant enhancements in progression-free survival when compared to standard chemotherapy among women presenting newly diagnosed advanced or recurrent disease.

3.3. Cervical Cancer

Cervical cancer is predominantly squamous cell carcinoma, while adenocarcinoma is less common and typically follows cervical intraepithelial neoplasia (CIN). In cases where the tumor has not metastasized beyond the parametrial region or advanced stages, surgical intervention or radical radiotherapy may be considered. The current state of ICI immunotherapy, exemplified by the PD-1 monoclonal antibody, has witnessed significant advancements in the management of recurrent and metastatic cervical cancer. It is widely acknowledged that long-term HPV infection plays a significant role in the pathogenesis of cervical cancer; hence, it comes as no surprise that ICI have emerged as

promising potential treatments for this condition. HPV infection can induce an upregulation of PD-L1 protein expression, which exhibits a positive correlation with disease severity. Based on research data statistics, it was found that 46.9%-60.8% of cervical cancer patients exhibited PD-1 positive expression in tumor stroma, while 34.4%-96% of patients showed PD-L1 positive expression. The enhanced activation of anti-tumor T cells through immune modulation further underscores the potential therapeutic efficacy of PD-1/PD-L1 inhibitors in treating HPV-infected cervical cancer. Clinical trials investigating pembrolizumab have demonstrated outstanding antitumor efficacy and safety in relation to cervical cancer, while the objective response of the study has also confirmed the antitumor efficacy of nivolumab.

The KEYNOTE-158 study investigated the application of pembrolizumab monotherapy in patients with cervical cancer. A total of 24 patients with recurrent/unresectable advanced cervical cancer received treatment with pembrolizumab at a dose of 10mg/kg every two weeks. The objective response rate (ORR) achieved was 17%, and the six-month PFS rate was 13% [11]. Additionally, the six-month OS rate reached 66.7%. Another notable study, CheckMate-358, examined single-agent Nivolumab in 19 treated patients with recurrent/metastatic cervical cancer and demonstrated an objective response in five patients, resulting in an ORR of 26.3% [12].

4. Conclusion

The immune system serves as the primary defense mechanism against pathogen invasion. However, cancer cells have developed various strategies to evade detection and elimination. Immunotherapy is an advanced cancer treatment that enhances the ability of immune cells to recognize and target specific tumor cells. In gynecological tumors, immunotherapy primarily focuses on immune checkpoint inhibitors, therapeutic vaccines, and adoptive cell therapy. Remarkable outcomes of immunotherapy have been observed in endometrial cancer, particularly in cases with MSI-H/dMMR status. TILs were found to be positively associated with improved PFS in patients with high-grade endometrial cancer, indicating their potential role in treatment. Immune checkpoint inhibitors have demonstrated promising therapeutic effects by activating immune cells to effectively target ovarian cancer cells. PD1 and CTLA4 are commonly used ICI immunotherapies that modulate T-cell activation and regulate T-cell responses to reduce autoimmunity while promoting autoimmune tolerance. ICI treatment can significantly prolong OS and PFS in ovarian cancer cases. Cervical cancer is closely linked to HPV infection, where PD-1/PD-L1 inhibitors exhibit therapeutic potential. Currently, numerous ICIs have been approved for clinical use and achieved favorable results; thus, immunotherapy has gradually become a first-line treatment option. In the future, exploring combination therapies based on immunotherapy will offer possibilities for patient recovery.

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