Therapeutic Vaccines for Ovarian Cancer

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Abstract. Ovarian cancer is widely recognized as one of the most aggressive gynecological malignancies. Chemotherapy based on platinum and maintenance therapy following surgery are the cornerstones of treatment for ovarian cancer. However, early detection of ovarian cancer is difficult, frequently resulting in metastasis at the time of diagnosis, which impacts the efficacy of surgical interventions, leading to elevated rates of recurrence and a bleak prognosis. Immunotherapy has demonstrated the potential for improved treatment of ovarian cancer. Currently, cancer vaccines represent a significant immunotherapeutic approach. Cancer vaccines are a therapeutic approach designed to activate the patient's immune system to target and eliminate cancer cells. These vaccines can include tumor antigens, antibodies, cytokines, etc. to stimulate and initiate an immune response against the tumor. In this review, I provided an overview of past research progress in different therapeutic vaccines for ovarian cancer, including their mechanisms of action and advancements in preclinical and translational studies.

Keywords: Ovarian cancer; Immunotherapy; Cancer vaccine.

1. Introduction

Ovarian cancer is considered to be among the most fatal types of gynecological malignancies. In the year 2020 alone, there were approximately 310,000 new cases of ovarian cancer diagnosed worldwide, resulting in approximately 210,000 deaths from this disease [1]. The incidence rate is estimated at roughly 11 cases per 100,000 individuals, while the corresponding mortality rate stands at 6.5 per 100,000 individuals [2]. Despite a slight decline in both incidence and mortality rates, the deadliest gynecological malignancy is still ovarian cancer. This is due to the difficulty of early detection and the absence of effective screening strategies; 75% of patients have advanced diagnoses, which results in a 46% 5-year survival rate. [3].

One of the primary treatments for ovarian cancer is surgery. This procedure entails the removal of the ovaries, fallopian tubes, uterus, and other affected tissues, with the extent of the surgery determined by the extent of tumor spread. Additionally, chemotherapy is also commonly employed for treating ovarian cancer. To control tumor growth and spread, platinum-based chemotherapy drugs (such as cisplatin and carboplatin) are frequently combined with other drugs (such as paclitaxel). Targeted therapy medication, like PARP inhibitors, offer a treatment used for specific ovarian cancer subtypes, particularly benefiting patients with BRCA gene mutations. Current research investigates intraperitoneal chemotherapy perfusion to enhance the drug concentration at the lesion site [4]. While chemotherapy provides considerable benefits to patients, the resistance and severe side effects necessitate the development of novel therapies, such as immunotherapy.

Immunotherapy encompasses various approaches, such as cancer vaccines, immune checkpoint inhibition, and adoptive cell therapy, all of them aimed at enhancing the immune system's capacity to recognize and kill tumor cells. Tumor-infiltrating lymphocytes (TILs) found in the tumor microenvironment have been demonstrated to be associated with better prognoses among ovarian cancer patients. Nonetheless, the activity of anti-tumor T cells was severely suppressed in the ovarian cancer microenvironment. Recent research demonstrated substantial intra-patient heterogeneity in T cell infiltration patterns, T cell receptor repertoires, and immune infiltrates across different tumor sites [5]. This heterogeneity poses an additional challenge for ovarian cancer treatment due to its multifocal nature.

Numerous clinical trials have been conducted on ovarian cancer vaccines in the last thirty years. While some vaccines have generated humoral and cellular immune responses, many have not

exhibited substantial antitumor effectiveness. Nevertheless, recent studies have demonstrated encouraging clinical advantages for ovarian cancer patients through the utilization of innovative vaccines, particularly those utilizing dendritic cell-based antigen presentation or synthetic platforms [6].

Tumor antigens refer to specific proteins, polysaccharides, or other molecules present within tumor cells, which are capable of being recognized as aberrant or anomalous by the immune system, subsequently eliciting an immune response aimed at targeting and eliminating the tumor cells. They can be utilized in the development of cancer vaccines to help elicit immune responses or serve as markers for targeted therapies. Tumor antigens can be classified into two main categories based on the expression pattern of their parental genes: tumor-associated antigens (TAAs) and tumor-specific antigens (TSAs). TAAs are antigens expressed by tumors but less present in normal tissues. They typically arise due to mutations, dysregulation, or overexpression in tumor cells. Examples of TAAs include CA-125, which is found at high levels in ovarian cancer, and HER2, which is highly expressed in breast cancer [7]. These antigens are often found in multiple cancer types, although their expression levels may vary across different cancer types [8]. TAAs can help the immune system identify and eliminate tumor cells. On the other hand, TSAs are antigens that are exclusively expressed on tumor cells and are rarely found in normal tissues. This specificity makes TSAs highly valuable in recognizing and targeting tumor cells without triggering autoimmune responses. Due to their minimal expression in normal tissues, TSAs serve as ideal targets for cancer cell-specific immunotherapies, particularly in individualized treatments. One example of a Tumor-Specific Antigen (TSA is the BCR-ABL fusion protein, which exhibits high expression levels specifically in cases of chronic myeloid leukemia [9]. Tumor antigens are essential components of cancer vaccines, and certain antigens, which may be less prominently presented on the tumor cell membrane surface or less readily identifiable by the immune system, can be augmented using cancer vaccines. Furthermore, the selection of novel antigens for individual patients can be a very promising strategy for personalized cancer treatments.

2. Organization of the Text

2.1. Peptide-based Vaccines

Peptide-based vaccines represent an innovative approach to cancer immunotherapy. These vaccines employ short amino acid sequences (peptides) that mimic cancer antigens or epitopes recognized by T cells. Following administration to the patient, these peptides undergo processing and presentation by antigen-presenting cells (APCs), thereby triggering T cells against cancer cells. In contrast to other vaccine types, peptide-based vaccines have several advantages. These include their specificity towards cancer cells, their potential to establish enduring immune memory, their straightforward production and scalability, and their minimal toxicity [10]. Peptides can specifically bind to surface receptors on cancer cells, enabling targeted diagnostic imaging and treatment. Furthermore, their low immunogenicity and high biocompatibility render peptide-based vaccines safer for ovarian cancer therapy. Additionally, distinguishing peptides present in bodily fluids can serve as diagnostic indicators, providing novel approaches for the detection and diagnosis of ovarian cancer [11].

According to research findings, peptide-based vaccines have demonstrated some efficacy in ovarian cancer treatment. In a specific study, researchers administered peptide vaccines to patients with recurrent gynecologic cancer. The results indicated that the vaccine was safe and had the capability to trigger T-cell responses in these patients [12]. In a separate investigation, scientists administered vaccines containing folate receptor-based peptides to patients with ovarian and breast cancer. The folate receptor is a TAA expressed in various cancer types, including lung cancer, breast cancer, as well as ovarian cancer. This study's findings revealed that all patients exhibited good tolerance to vaccine administration, and in over 90% of the examined patients, the vaccine elicited or enhanced immune responses [13]. In another study, the NY-ESO-1b peptide combined with the

montanide ISA-51 vaccine was used to assess safety and immunogenicity in high-risk recurrent epithelial ovarian cancer patients [14]. The study demonstrated that these peptide vaccines are able to stimulate immune responses in cancer patients. Furthermore, a study combining peptide-based vaccines with other treatment modalities was conducted in platinum-resistant ovarian cancer patients, demonstrating improved clinical outcomes compared to chemotherapy alone [15]. This suggests that peptide-based vaccines have the potential for combination therapy, synergistically enhancing treatment effectiveness when used in conjunction with other therapies like chemotherapy and immune checkpoint inhibitors.

2.2. Dendritic cell-based vaccines

Dendritic cells (DCs), as antigen-presenting cells (APCs), exerting significant influence over innate immune responses and initiating adaptive immunological responses. DCs exhibit a heightened capacity for antigen capture, processing, and presentation compared to other APCs, including monocytes, B cells, and macrophages [16]. DC vaccines aim to elicit an antitumor immune response by restoring the antigen-presenting ability of DCs. Within the ovarian cancer microenvironment, certain signals from tumors have an immune-suppressive effect, leading to dysfunction in dendritic cells. These signals impact both the immune functions and metabolic processes of dendritic cells. As a result, the dendritic cells become less effective at presenting antigens, potentially contributing to tumor progression. However, dendritic cell vaccines offer a promising solution for ovarian cancer patients. These vaccines provide functional dendritic cells, which can help overcome the dysfunction caused by tumor immune-suppressive signals. This approach has the potential to be a safe and effective immunotherapeutic strategy for addressing ovarian cancer. The operational procedure of DC cell vaccination involves the collection of dendritic cells (DC cells) from the patient's body or a donor source. This can be accomplished through the retrieval of DC cells from peripheral blood, bone marrow, or their cultivation from monocytes using macrophage differentiation factors such as GM-CSF and IL-4. Subsequently, the harvested DC cells undergo processing and activation in the laboratory, achieved through various methods, including their association with specific antigens, and their activation with signaling molecules such as cytokines (e.g., TNF-α, IL-1β) to enhance their immunostimulatory capabilities. Following processing and activation, the DC cells are reinjected into the patient's bod. These DC cells carry the presented antigens and are responsible for presenting them to T cells, initiating the immune response.

DC vaccines have demonstrated encouraging outcomes in clinical trials, leading to improvements in progression-free survival and overall survival rates among ovarian cancer patients. These promising results highlight the potential of DC vaccines as a viable therapeutic option for this lethal gynecologic malignancy [17]. And DC vaccines can be personalized based on next-generation sequencing to target individual neoantigens. This personalized approach enhances the specificity and effectiveness of the vaccine, potentially leading to better clinical outcomes [18]. Furthermore, combination therapies with DC vaccines are being explored, which may include their combination with chemotherapies, targeted therapies, immunotherapies, etc. The synergistic effects of different chemotherapy drugs, such as paclitaxel and cyclophosphamide, when combined with DC vaccines, may strengthen the antitumor effect and improve treatment outcomes [18]. However, it's important to note that most patients participating in DC vaccine trials have already completed their primary chemotherapy regimens. As a result, there is limited available evidence to assess the concurrent effects of DC therapy and chemotherapy [19].

In a clinical experiment examining the efficacy of dendritic cell-based vaccination, 90% patients with advanced ovarian cancer displayed an impressive three-year survival rate. In contrast, patients who received cyclophosphamide did not exhibit any notable improvement in survival rates when compared to the control group [20]. This suggests that dendritic cell-based vaccination could be a promising and more effective treatment option for advanced ovarian cancer patients compared to the use of cyclophosphamide. Although dendritic cell vaccination elicited a certain degree of immune response, patient survival rates were reasonably assured. In another study, a low dose of IL-2 was

introduced as an immune adjuvant after each DC vaccine administration. Among the 10 patients, three maintained complete remission (CR) after treatment, and one patient experienced complete tumor disappearance following DC vaccination, with recurrence occurring approximately 50 months later [21].

DC vaccines also encounter several challenges in in the treatment of ovarian cancer, primarily attributed to the deactivation of DC within the tumor microenvironment. In the tumor microenvironment, DCs often exhibit downregulated expression of costimulatory molecules and a weaker antigen-presenting ability, leading to DC tolerance. This tolerance hinders the effective activation of T cells and the initiation of antitumor immune responses [22]. The ovarian cancer microenvironment induces dysfunction in DCs, marked by their inability to mature and secrete suppressive immune factors such as IL-10 and TNF-a. Insulin-like growth factor (IGF) signaling also contributes to DC dysfunction [23]. These dysfunctional DCs fail to elicit effective antitumor immune responses. There are various factors produced by ovarian cancer cells, such as vascular endothelial growth factor (VEGF), indoleamine 2,3-dioxygenase (IDO), and transforming growth factor-beta (TGF-β), that contribute to the immunosuppressive tumor microenvironment. These factors directly affect the function and maturation of DCs, impairing their ability to initiate effective immune responses. A Clinical trial has reported that IDO inhibitors result in a reduction in IDO product levels within solid tumors and can serve as adjunctive agents in DC immunotherapy [24], indicating the use of IDO inhibitors in conjunction with DC immunotherapy is an exciting approach in the field of cancer treatment.

2.3. mRNA Vaccines

mRNA vaccines use synthetic messenger RNA (mRNA) to trigger the immune system to generate an immune response against specific pathogens, such as viruses, in order to protect the human body from infection. The outbreak of the novel coronavirus to some extent has propelled the development of mRNA vaccines and provided a wealth of clinical data for subsequent research and development. The principle behind mRNA vaccines involves embedding the genetic information encoding specific proteins of the pathogen into synthetic mRNA. Once this mRNA enters human cells, the cells use its information to produce proteins related to the pathogen. These proteins can be recognized as foreign antigens to prompt the host immune system to produce antibodies and mount an immune response. mRNA is a genetic material that is non-infectious and non-integrating, posing no genetic risk [25]. Despite the relatively higher expense associated with mRNA synthesis, mRNA vaccines prove to be cost-effective when compared to conventional vaccines and offer the potential for accelerated development.

Currently, there are laboratories using cancer cells obtained from resected tumors of late-stage ovarian cancer patients to study nanoparticles carrying siRNAs targeting mechanisms of chemotherapy resistance overexpressed in ovarian cancer cells [26]. Research into mRNA vaccines targeting new antigens for breast cancer and ovarian cancer CA-125, designed through computer simulations, is also underway. Some researchers have used immunoinformatic tools to predict T-cell epitopes for novel antigens driven by somatic mutations in CA-125 expressed breast cancer and ovarian cancer. They have constructed self-amplifying mRNA vaccines with CD40L and MHC-I targeting domains to enhance the cross-presentation of these new epitopes by DCs. Using the computer ImmSim algorithm, the post-immunization immune responses were estimated, revealing that these mRNA vaccines can drive the IFN-γ expression of CD8+ T cells [27].

2.4. Cancer stem cell vaccination

Cancer stem cell vaccines are an investigational approach to cancer therapy that seeks to elicit an immune response targeting the cancer stem cells residing within malignant tumors. These stem cells constitute a minority population within the tumor and exhibit stem cell-like characteristics, including the ability for self-renewal and differentiation into various cell types. They are considered pivotal in

tumor growth since they can withstand conventional cancer therapies like chemotherapy and radiation, which often results in tumor recurrence and advancement.

The therapeutic strategy of the cancer stem cell vaccine is to stimulate the patient's immune system to generate an immune response against the cancer stem cells. This typically involves obtaining cancer stem cells from the patient's own body or from other sources and using them to prepare the vaccine. This vaccine is then administered back into the patient's body, activating the immune system to identify and combat these cancer stem cells. The hope is that this approach can reduce or prevent cancer recurrence.

Research has shown that different immunotherapies have varying degrees of therapeutic efficacy in ovarian cancer. However, the presence of cancer stem cells (CSCs) in ovarian cancer may be a primary contributor to its eventual recurrence [28]. Studies have developed cancer stem cell vaccines using human ovarian cancer cell lines SKOV3 and HO8910, as well as mouse ovarian cancer cell line ID8. The effectiveness of CSC vaccines against ovarian cancer was evaluated through the analysis of tumor growth and mouse survival rates. It is noteworthy that cancer stem cell vaccines exhibited robust anti-ovarian cancer effects in experiments, resulting in tumor volume reduction, increased cytotoxicity, enhanced antibody production, and extended lifespan in ovarian cancer mice. Furthermore, the number of cancer stem cells in ovarian cancer tissue significantly decreased following vaccine administration [29]. In conclusion, immunotherapy for ovarian cancer through cancer stem cell vaccines holds significant potential.

2.5. Viral vector-based vaccines

Oncolytic viruses are a class of viruses that can selectively infect and destroy cancer cells, making them a promising approach to cancer therapy. It can also release antigens after tumor cell lysis, indirectly enhancing anti-tumor immunity through the activation of inflammatory responses within the tumor microenvironment [30]. These characteristics render oncolytic viruses a promising vector for the development of cancer immunotherapies. Oncolytic viruses have several notable advantages. For instance, viruses possess a high degree of immunogenicity, enabling rapid activate the immune system, which is conducive to guiding the immune response toward the target antigen. Moreover, viral vectors typically have the capability to enter human cells, thus inducing cellular immunity, including the generation of cytotoxic T cells (CTLs). CTLs play a pivotal role in eliminating infectious pathogens and tumor cells. Additionally, viral vectors can carry multiple antigens, making them suitable for the development of multivalent vaccines that provide immune protection against cancers. However, the safety of viral vector vaccines must undergo assessment, including considerations of immunogenicity and genetic stability, among other factors [31]. Currently, some clinical researches have indicated the sufficient safety profile and anti-tumor efficacy of certain oncolytic virus therapies, such as OrienX010 [32].

In the context of ovarian cancer treatment, viral vector-based vaccines have demonstrated significant potential. In one study, the use of chimeric virus-like particles expressing the lymphocytic choriomeningitis virus glycoprotein resulted in tumor regression in murine models of subcutaneous and orthotopic ovarian cancer [33]. The combination of these chimeric virus-like particles with the JAK1/2 inhibitor ruxolitinib enhanced therapeutic efficacy. In a distinct research study, scientists employed recombinant vaccinia-NY-ESO-1 (rV-NY-ESO-1) and recombinant fowlpox-NY-ESO-1 (rF-NY-ESO-1) vaccines for the treatment of patients with tumors expressing the NY-ESO-1 antigen [34]. Among the 22 patients, 14% had previously demonstrated CD8+ T cell responses, a percentage that rose to 45% after vaccination.

3. Summary

This review has outlined diverse therapeutic vaccine strategies for ovarian cancer, encompassing peptide-based vaccines, dendritic cell-based vaccines, mRNA vaccines, cancer stem cell vaccines, and viral vector-based vaccines. Remarkably, these vaccine modalities have exhibited encouraging

findings in both preclinical and clinical investigations, instilling optimism for enhanced outcomes in ovarian cancer patients.

Peptide-based vaccines, with their specificity and minimal toxicity, have shown efficacy in stimulating immune responses and enhancing clinical outcomes. Dendritic cell-based vaccinations, which are tailored to individual patients using next-generation sequencing techniques, have demonstrated the capacity to enhance rates of progression-free survival and overall survival. mRNA vaccines, driven by advancements in synthetic mRNA technology, have opened new avenues for targeting novel antigens, including CA-125, and have been accelerated by the experience gained from mRNA COVID-19 vaccines. Cancer stem cell vaccines, designed to combat tumor recurrence by targeting cancer stem cells, represent an innovative approach with encouraging preclinical results. Viral vector-based vaccines offer significant advantages, including high immunogenicity, cellular immunity induction, and the ability to carry multiple antigens. Nonetheless, it's crucial to conduct thorough evaluations of their safety, immunogenicity, and genetic stability. Meanwhile, challenges remain in harnessing the full potential of these vaccines.

Certainly, the ongoing research and clinical trials in the field of vaccines are likely to yield further insights and breakthroughs for the detection and treatment of ovarian cancer. The continued refinement of vaccine design, the incorporation of innovative adjuvants, and a deeper understanding of the immune microenvironment within ovarian tumors will contribute to optimizing vaccine strategies. Moreover, the utilization of advanced technologies, including immunoinformatic and viral vector-based vaccines, holds tremendous potential for enhancing the immunotherapeutic arsenal against ovarian cancer. Additionally, the combination of vaccine therapies with other treatment modalities, such as chemotherapy and immunotherapies, holds significant promise for augmenting treatment efficacy.

In conclusion, ovarian cancer vaccines represent a beacon of hope in the battle against this devastating disease. Despite ongoing challenges, recent advancements emphasize the capacity of immunotherapy to revolutionize the field of ovarian cancer treatment. As we venture into the unexplored realm of cancer vaccines, cooperation among researchers, clinicians, and pharmaceutical entities will be essential in fully unlocking the potential of these groundbreaking therapies, ultimately providing newfound optimism for individuals with ovarian cancer.

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