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Leveraging immunotherapy for the treatment of gynecologic cancers in the era of precision medicine

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HIGHLIGHTS

- Cancers evolve mechanisms for evading and suppressing the immune system
- A number of different immunotherapy approaches have been used and show promise in gynecologic cancers
- Emerging data reveal durable responses in some patients with gynecologic cancers

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ABSTRACT

During the past decade significant progress in the understanding of stimulatory and inhibitory signaling pathways in immune cells has reinvigorated the field of immuno-oncology. In this review we outline the current immunotherapy based approaches for the treatment of gynecological cancers, and focus on the emerging clinical data on immune checkpoint inhibitors, adoptive cell therapies, and vaccines. It is anticipated that in the coming years biomarker-guided clinical trials, will provide for a better understanding of the mechanisms of response and resistance to immunotherapy, and guide combination treatment strategies that will extend the benefit from immunotherapy to patients with gynecologic cancers.

1. Introduction

The immune system plays a key role in eliminating and controlling early tumor growth [1,2]. Recognition and elimination of tumors by the immune system involves a series of steps coordinated by the various parts of the innate and adaptive immune system. The immune recognition of cancer begins at the tumor site, where fragments of malignant cells get taken up by professional antigen-presenting cells (APC) such as dendritic cells (DC). Activation of DCs in turn requires several maturation signals, which are in part provided by the "danger" signals released from the dying tumor cells, known as damage-associated molecular patterns (DAMPs) [3]. Following activation, APCs migrate to tumor-draining lymph nodes, where they present tumor-associated antigens (TAAs) in the form of antigenic peptides bound to the major histocompatibility complex (MHC) class I and II molecules. This enables antigen recognition by antigen-specific CD4 and CD8 T cells. In addition to recognition of specific antigenic peptides bound to MHC, activation of T cells requires another immunostimulatory signal, which is provided by engagement of a co-stimulatory receptor such as CD28 on the surface of T cells [4]. Activated T cells then migrate to tumors through the systemic vasculature by following a chemokine gradient [5,6] and extravasate through a series of interaction with adhesion molecules in the tumor endothelium [7]. Finally, recognition of tumor targets proceeds through interaction between the T cell receptor (TCR) and specific antigenic tumor peptide bound to MHC, ultimately leading to T-cell mediated tumor destruction.

Starting with the process of antigen presentation, tumors have evolved a variety of resistance mechanisms that allow for successful escape from immune recognition and elimination [8]. Hence, immunotherapeutic approaches aim to improve recognition of tumors by the immune system and to inhibit the mechanisms of immune escape. Many of these approaches have been explored in gynecologic malignancies, with recent data demonstrating promising activity in various tumor types. Here we will discuss several examples of such modalities,

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primarily focusing on the more recently reported studies, though the list is certainly not exhaustive and multiple other approaches could be considered to be applicable. With emerging data, it is likely that a combination of several different modalities will be needed for optimal activation of anti-tumor immunity and therapeutic efficacy.

1.1. Immunotherapy of ovarian cancer

Epithelial ovarian cancer (EOC) is the fourth most common cancer in women and accounts for the highest number of gynecologic cancer deaths. Although EOC has not been traditionally considered a type of cancer that would be amenable to immunotherapy, multiple lines of evidence have demonstrated that the immune system likely plays a key role in eliminating and controlling ovarian cancer growth. In particular, the presence of tumor-infiltrating lymphocytes (TILs) has emerged as an important prognostic biomarker in EOC, with increased number of TILs predicting longer survival [9,10]. Tumor-reactive antibodies and T cells have been demonstrated to be present in the peripheral blood of EOC patients [11,12], and oligoclonal tumor-directed T cells have been directly isolated from the tumors and ascitic fluid [13–20].

Based on these findings, several immunotherapeutic strategies have been explored in EOC. These approaches can be broadly subdivided into three categories: 1) Direct targeting of tumors with tumor-specific antibodies; 2) modalities that aim to enhance antigen presentation, such as vaccines, toll-like receptor (TLR) agonists, and oncolytic viruses, and 3) strategies focusing on activation of tumor-specific T cells, either through direct adoptive transfer or by targeting of activating and inhibitory pathways in T cells and tumor microenvironment.

1.1.1. Targeting of ovarian tumors with tumor-specific antibodies

Antibodies targeting surface antigens have been demonstrated to be effective against different cancer types [21,22]. While some of these agents target tumor driver pathways (e.g. trastuzumab and cetuximab), some in addition mediate antibody-dependent cellular cytotoxicity (ADCC), allowing for recognition of the antibody-labeled cancer cells with immune effectors, such as natural killer cells. In ovarian cancer, however, such strategies have been more elusive, likely secondary to lack of an optimal surface antigen. Indeed a 2014 Cochrane review of trials in ovarian cancer using antigen-specific targeting failed to establish a conclusive evidence for efficacy of such strategies in EOC [23].

1.1.1.1. CA-125. The extensive expression of CA125 and its cell-surface precursor MUC16 in the majority of ovarian carcinomas prompted several trials targeting CA125 [24–26]. Oregovomab, an antibody targeting CA-125 has been evaluated in several studies, with early studies demonstrating the development of anti-CA-125T cell responses [27–29]. However, a randomized placebo-controlled phase III trial in patients with advanced EOC in first clinical remission failed to demonstrate benefit to oregovomab therapy, with no significant difference between the placebo and oregovomab groups [30].

1.1.1.2. EpCAM. Epithelial cell adhesion molecule (EpCAM) is a surface integrin receptor commonly overexpressed on cancer cells and appears to be associated with worsened prognosis in ovarian cancer [31]. Catumaxomab is a bispecific antibody recognizing EpCAM and T cell antigen CD3. In addition, catumaxomab possesses an ADCC-mediating Fc region, making it a trifunctional antibody. Catumaxomab mediates anti-tumor effect through two different immune mechanisms: via recruitment and activation of T cells to the EpCAM expressing tumor cells and via binding to Fc receptor-expressing effectors such as NK cells. In a phase II/III trial randomizing patients with advanced cancer with malignant ascites to standard paracentesis or paracentesis with intraperitoneal catumaxomab, catumaxomab delayed ascites re-accumulation, but had no impact on overall survival [32]. A variation on this strategy has been recently developed using bispecific T cell engagers (BiTE) recognizing EpCAM and CD3. This strategy has been demonstrated to be effective in xenograft models of human colorectal and ovarian cancer [33]. More recently, in preclinical models of ovarian carcinoma, a novel EpCAM-CD3 BiTE solitomab has demonstrated significant activity against human ovarian tumor cells in vitro and ex vivo [34,35].

1.1.1.3. FRa. Folate receptor alpha is expressed in high frequency in epithelial ovarian cancer [36]. Farletuzumab, a monoclonal ADCC-mediating antibody against folate receptor alpha, was evaluated in several studies, with earlier studies demonstrating promising efficacy [37,38]. Despite these findings, later larger studies in combination with chemotherapy in platinum-sensitive and resistant patients, however, failed to meet the primary endpoints (NCT00849667, NCT00738699). More recently, data from phase I study using IMGN853, a folate receptor alpha targeting antibody-drug conjugate in patients with FRa positive epithelial ovarian cancer and other Fra positive solid tumors demonstrated clinical benefit rate of 25–33% depending on schedule, with responses seen in different treatment schedule groups [39]. While this strategy is certainly promising, it is unclear whether there is any contribution of the immune system to the observed effect and further studies would be needed to answer this question.

1.1.2. Enhancement of recognition of tumor antigens by the immune system vaccines

Several different vaccination approaches have been explored in ovarian cancer [40–44]. Those include simple vaccine preparations consisting of specific peptides and proteins, as well as more complex strategies, such as engineered cellular vaccines, DC vaccines, virus-vectored vaccines, and oncolytic viruses [45–54]. A comprehensive review of different vaccination strategies that have been explored in ovarian cancer is published elsewhere [55]. The majority of the vaccines have focused on using cancer-testis antigens (e.g. NY-ESO-1), and proteins known to be overexpressed in EOC (e.g. p53, survivin, MUC1). In general, while the majority of the studies demonstrated evidence of cellular and antibody response to the antigens, clinical benefit afforded by vaccination has unfortunately been marginal at best. Since most of the strategies have relied on self-antigens, it is likely that vaccination alone is not sufficient to overcome the T cell tolerance and combinatorial therapies may be necessary. Indeed, studies in preclinical models indicate that combination of vaccines with immune checkpoint blockade result in enhancement over either approach alone [56–63], thus generating rationale for exploration of similar strategies in human trials.

1.1.2.1. TLR agonists. Toll like receptors (TLR) are a class of proteins recognizing signature molecules that are broadly shared by various pathogens, and play a role in the innate immune response and tumor antigen processing and presentation by APC. Ligands for various TLRs are actively being explored as anti-cancer agents and there is a rationale for using such ligands in ovarian cancer [64]. VTX-2337 (motolimod) is a small molecule agonist of TLR8, which stimulates a strong innate immune response. VTX-2337 has been evaluated with systemic administration in combination with liposomal doxorubicin in animal models and in phase I study in patients with advanced ovarian cancer. The combination appeared to be safe, with evidence of immune activation and clinical benefit [65]. A phase 2 study evaluating motolimod in combination with liposomal doxorubicin is ongoing (NCT01666444). Another phase 1/2 study using combination of motolimod with liposomal doxorubicin and anti-PD-L1 antibody MEDI4736 is upcoming (NCT02431559).

1.1.2.2. Type I IFN. Type I IFN is an innate immune response cytokine, which plays a role in antiviral immune response. In addition, recent studies have demonstrated a critical role for the type I IFN pathway in anti-tumor immune response [66,67], where type I IFN was demonstrated to be indispensible for tumor antigen cross-presentation by dendritic cells. Studies with systemic or intraperitoneal IFNα in patients