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Review

Cellular immunotherapy in ovarian cancer: Targeting the stem of recurrence

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HIGHLIGHTS

- Review immune system in ovarian cancer and state of cellular immunotherapy
- Present cancer stem cells as targets for clinical application of immunotherapy
- Postulate the use of adjuvant DC vaccination to complement current treatment

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ABSTRACT

Ovarian cancer is a devastating disease with a high relapse rate. Due to a mostly asymptomatic early stage and lack of early diagnostic tools, the disease is usually diagnosed in a late stage. Surgery and chemotherapy with taxanes and platinum compounds are very effective in reducing tumor burden. However, relapses occur frequently and there is a lack of credible second-line options. Therefore, new treatment modalities are eagerly awaited. The presence and influx of immune cells in the ovarian cancer tumor microenvironment are correlated with survival. High numbers of infiltrating T cells correlate with improved progression free and overall survival, while the presence of regulatory T cells and expression of T cell inhibitory molecules is correlated with a poor prognosis. These data indicate that immunotherapy, especially cell-based immunotherapy could be a promising novel addition to the treatment of ovarian cancer. Here, we review the available data on the immune contexture surrounding ovarian cancer and discuss novel strategies and targets for immunotherapy in ovarian cancer. In the end the addition of immunotherapy to existing therapeutic options could lead to a great improvement in the outcome of ovarian cancer, especially when targeting cancer stem cells.

Contents

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Introduction

Epithelial ovarian cancer (EOC) is the most lethal gynecological cancer. Approximately 22,000 new cases of ovarian cancer were diagnosed in 2014 in the US alone. Annually, ovarian cancer results in over 14,000 deaths [1]. Over the last 20 years only a small decrease in those figures was seen. The median age at the time of diagnosis is 63 years [2], although women with a high risk genetic predisposition typically develop ovarian cancer 10 years earlier [3]. Due to a lack of reliable screening tools in the early phase of the disease, which is usually asymptomatic, more than 75% of patients are diagnosed in an advanced stage International Federation of Gynecology and Obstetrics (FIGO) stages III–IV [4].

The current standard for first-line therapy of ovarian cancer consists of cytoreductive surgery and adjuvant chemotherapy based on platinum drugs in combination with Taxanes. Unfortunately, a large proportion of patients (20–40%) do not respond to first-line chemotherapy [2]. Furthermore, recurrence rates are 25% in early stage patients and higher than 80% in advanced stage patients [4]. The median survival time of patients with advanced stage disease is 65 months. Current second-line therapies are generally not curative, resulting in short-term progression-free survival for most patients [2]. The route of administration of adjuvant chemotherapy also has an effect on therapy outcome. Intraperitoneal chemotherapy leads to a longer progression-free and overall survival compared to intravenous chemotherapy. However, it is not widely adopted due to toxic side effects, intraperitoneal delivery problems and other complications [5]. Intensification of the treatment by addition of a third chemotherapeutic or extended duration of platinum or Taxane chemotherapy showed no further improvements in clinical outcome in phase 3 trials. The sequence of treatment modalities was also studied. Initial treatment with chemotherapy (neoadjuvant therapy) followed by surgical cytoreduction had no clinical benefit over surgical cytoreduction followed by chemotherapy [2].

Looking back at the last 30 years, no substantial decrease in death rates has been achieved. Thus, there is a desperate need for novel treatment strategies for ovarian cancer. One such strategy involves activating the patient's own immune system for therapeutic benefit in cancer, referred to as immunotherapy [6]. Immunotherapy has shown considerable clinical promise in recent years and has the potential for a life-long cure of cancer. In this review, we examine the immunological contexture in ovarian cancer, evaluate the clinical promise of immunotherapeutic approaches and discuss innovative combination modalities.

Rationale for cellular immunotherapy

Although not considered as an 'immunogenic' tumor such as melanoma, clinical evidence hints at a role for the immune system in EOC. Infiltration of $CD3^+$ immune cells in ovarian tumors correlates with improved progression free survival [7], suggesting that ovarian cancer is vulnerable to immunological attack. The presence and activation state of other immune effector cells such as Natural Killer (NK) cells and γδ-T cells also correlate with improved clinical outcomes. There is accumulating evidence suggesting that surgery and chemotherapy also modulate the immune system. Surgery can significantly reduce the numbers of suppressive regulatory T cells (Tregs) in EOC patients leading to an improvement in the ratio of CD8/Treg. Additionally, peripheral $CD8^+$ T cells in these patients produce higher levels of IFNγ after surgery [8]. Recent studies demonstrate that chemotherapeutic compounds trigger the immune system [9,10]. These chemotherapeutic compounds, including the platinum-based compounds, can induce tumor cell stress and death that leads to the induction of an anti-tumor immune response. Platinum compounds were also shown to enhance the recognition and killing of tumor cells by immune cells, as well as, enhancing dendritic cell (DC) function [11–13]. Additionally, patients that have $CD3^+$ T cells present in the tumor have improved responses to chemotherapy and are more frequently optimally debulked [7].

Natural killer cells

Natural killer (NK) cells are the cytotoxic cells of the innate immune system, which are involved in the killing of tumor cells. NK cells can be divided in two subsets, based on expression of surface molecule CD56 [14]. $CD56^{bright}$ $CD16^-$ NK cells produce high amounts of cytokines upon activation, but exhibit low cytotoxicity. $CD56^{dim}$ $CD16^+$ NK cells produce low amounts of cytokines, but exhibit high cytotoxicity and the ability to mediate antibody-dependent cellular cytotoxicity (ADDC) through CD16. NK cells recognize and eliminate allogeneic or stressed cells, such as infected or tumor cells [14]. EOC exploits various mechanisms to limit NK cell-mediated tumor killing. Firstly, low numbers of NK cells infiltrate primary EOC [7]. Secondly, infiltrating NK cells are enriched for the less cytotoxic $CD56^{bright}$ cells compared to autologous peripheral blood (32% versus 10%) [15]. Furthermore, EOC also suppresses NK cells through the expression of surface molecules or secretion of soluble factors like CA-125, which shields tumor cells from cytotoxicity [16,17]. Surprisingly, the presence of $CD16^+$ NK cells was significantly correlated with decreased overall survival of ovarian cancer patients [18]. In summary, although it is still unclear whether the presence of NK cells has a beneficial effect on the outcome of EOC, there are several mechanisms in the tumor microenvironment that abolish NK cell anti-tumor immunity.

$CD8^+$ T cells

$CD8^+$ T cells are the cytotoxic effector cells of the adaptive immune system responsible for killing of tumor cells. A seminal study by Zhang and colleagues showed that the presence of tumor-infiltrating lymphocytes (TILs) correlates with favorable clinical outcome [7]. The median progression-free survival of these patients was 22.4 months and median overall survival 50.3 months. In contrast, patients without TILs had a median progression-free survival of 5.8 months and a median overall survival of 18 months. Only a small percentage (4.5%) of these survived up to 5 years, whereas this percentage was significantly higher (38%) in