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Immunotherapy in ovarian cancer

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ABSTRACT

Immunotherapy aims to develop combination approaches that simultaneously augment immunity while preventing local immune suppression. Despite advances in combinatorial chemotherapy regimens and the advent of intraperitoneal chemotherapy administration, current therapeutic options for patients with ovarian cancer are inadequate. Advances in immunotherapy offer a promising frontier for treating ovarian tumors. Multiple immunotherapeutic modalities are currently developed and tested in clinical trials. Antibody-based therapies, immune checkpoint blockade, cancer vaccines, and chimeric antigen receptor–modified T cells have demonstrated preclinical success and entered clinical testing. In this review, we discuss these promising immunotherapeutic approaches and emphasize the importance of combinatorial treatment strategies and biomarker discovery.

Nearly 75% of patients in clinic, present with stage III and IV ovarian cancer.[1] Management of ovarian cancer primarily includes cytoreductive surgery and platinum-based chemotherapy.

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Although clinical remissions are obtainable, most patients relapse and die of disease, with a 5-year survival rate of approximately 30%.[2] Novel therapies need to be integrated into ovarian cancer treatment strategies to achieve durable clinical outcomes.

Dedicated research on ovarian cancer immunogenicity in the past 20 years has led to new immunotherapeutic approaches to the treatment of ovarian cancer. The observation that CD3+ tumor-infiltrating T cells and increased overall survival (OS) were associated was a key finding in establishing the validity of ovarian cancer immunotherapy.[3] The antitumor effector role of tumor-infiltrating lymphocytes (TILs) such as CD3+ and CD8+ T cells was further confirmed recently.[4] A positive correlation among patients with ovarian cancer with preexisting CD3+ or CD8+ intraepithelial T cells at the time of diagnosis and their life span has been observed, suggesting that activation of antitumor immunity can enhance survival. Certain tumor-associated antigens (TAAs) such as (eg, MAGE-A4 and NY-ESO-1), growth-activating receptors (eg, HER2/neu), folate receptor alpha, p53, and CA125 were found to be abnormally upregulated in tumor tissue and ascites of patients with ovarian cancer.[5-7] The presence of these members of the cancer-testis antigen family lent additional support to an immunotherapeutic treatment strategy.

Certain TAAs or growth factor receptors or both that are specifically expressed by cancer cells are targeted by monoclonal antibodies (mAbs). These include erb-b2 receptor tyrosine kinase and epidermal growth factor receptors (EGFRs), which are approved for clinical use. mAbs function as cytostatic or cytotoxic agents by inhibiting trophic signal transduction cascades, and in addition, also employ other immune mechanisms such as complement-dependent cytotoxicity and antibody-dependent cellular cytotoxicity.

The Food and Drug Administration (FDA) has approved immunotherapies for prostate cancer, advanced kidney cancer, lymphoma, and metastatic melanoma, but only recently have immunotherapies targeting ovarian cancer entered clinical testing (Table 1). In this article, we discuss advances in immunotherapeutic approaches to ovarian cancer, dividing the therapeutic strategies into 4 categories such as antibodies, immune checkpoint inhibitors, vaccines, and adoptive cell therapy (ACT).

Antibody therapy

In the past 15 years, antibody-based therapies for hematologic cancers and solid tumors have become well-established therapeutic strategies. After rituximab's 1997 FDA approval for treating chemotherapy-resistant non-Hodgkin lymphomas, 18 other molecular antibodies have gained FDA approval for use in oncologic care.

Antibody therapy is a promising area of research and increasingly antibody therapies are being used in ovarian cancers.

Bevacizumab

Vascular endothelial growth factor (VEGF) is a key mediator of developmental angiogenesis and has been shown to regulate the vascularization of tumors.[8] Anti-VEGF antibody therapy has proven effective in multiple cancer subtypes including metastatic colorectal cancer, glioblastoma, non–small-cell lung cancer, and renal cancers.[9] Bevacizumab (Avastin, Roche) is a humanized mAb that binds to all isoforms of the VEGF receptor ligand. The level of VEGF in serum and ascites is directly related to disease burden, and inversely related to survival, often independent of other established prognostic factors.[10-12]

Ovarian cancer is a promising candidate for VEGF therapy; however, in biopsies from ovarian tumors, VEGF gene expression correlates with a poor prognosis.[13] The results of the phase III AURELIA trial show that the addition of bevacizumab to single-agent chemotherapy leads to increased progression-free survival (PFS) and overall response rate (ORR): PFS increased from 3.4-6.7 months and ORR increased from 11%-27%.[14] However, the intent-to-treat analyses have yet to establish an effect on OS.[13-16]