Ovarian Cancer Therapeutic Opportunities

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Among women in the United States, ovarian cancer is the fifth leading cause of cancer deaths, accounting for approximately 5% of all cancer deaths, with an estimated 22,280 new cases this year [1]. There are 239,000 new diagnoses and 152,000 deaths from the disease in 2012 worldwide. The four most common subtypes of ovarian cancer are serous, endometrioid, clear cell, and mucinous carcinoma based on distinct clinical and biological behaviors. Over 60% of ovarian cancer cases are diagnosed at a late stage of distant metastases or invasion due to lack of effective screening for detection. Currently, the standard treatment approach for patient with ovarian cancer is surgical intervention followed by platinum-based drugs plus taxane chemotherapy [2,3]. The 5-year survival rate for ovarian cancer patients with stage III or IV disease is under 20%. No effective therapy is available for relapsed or metastatic disease that has failed first-line chemotherapy [4]. However, this landscape may change because of the remarkable progress in precision medicine and cancer immunotherapy.

Malignancy is considered a multi-factorial disease and the influence of immunologic mechanisms on cancer progression and prognosis has recently received much needed attention. The role of immunotherapy in cancer treatment has been proved with beneficial effect on tumor progression by augmenting immunity through active and passive strategies. Immunotherapies for cancer treatment could be categorized into certain four types, which are therapeutic vaccines, cytokines, immune checkpoint inhibitors, and adoptive T cell transfer. Therapeutic vaccines are designed to treat an existing cancer by inducing the tumor-directed immunity and strengthening the natural immune response against the tumor. Cytokines, as immune modulators, are potent chemical signals that manipulate immunocyte growth and activity to generate the appropriate immune effector cells to eradicate solid tumors. Immune checkpoint inhibitors are drugs, often made of antibodies that prevent cancer cells from turning off functional anti-tumor immunocytes. Adoptive T cell transfer involves the isolation and reinfusion of potent and antigen-specific T lymphocytes into patients to treat cancer.

Recent reports have demonstrated that cancer vaccine using human papillomavirus (HPV)16 synthetic long peptide resulted in complete and partial regression of high-grade HPV16-induced vulvar intraepithelial neoplasia [5,6]. In addition, it was reported that therapeutic vaccination against HPV16 has clinical benefit and potential successful treatment in patients with high-grade premalignant lesions of the cervix [7]. Another example is that HER2 peptide-based vaccination combined with dendritic cells treatment markedly decreases HER2 expression on HER2+ breast ductal carcinoma [8]. These cases indicate that therapeutic vaccine strategies have been successful in enlarging the pool of tumor-specific T cells or reactivating existing tumor-specific T cells. However, the activated T cells might encounter anergic state or failure of homing to tumor without exerting their function within the tumor, resulting in an unmet therapeutic efficacy. Nowadays, a supportive co-treatment during vaccination to achieve high immune response rates and properly polarized T cell immune responses has progressed in ovarian cancer treatment by combining with other therapies, such as immune checkpoint inhibitors [9-11], chemotherapy [12,13] and adoptive T cell therapy [14].

Cytokines, the messengers of the immune system, could be used to activate the immune systems to suppress tumors. The successful cytokine-based cancer therapy should directly stimulate immune effector cells within the tumor and enhance anti-tumor cytotoxic effect. Numerous animal studies have demonstrated the broad antitumor effects of cytokines and this has been further translated into clinical approaches against tumor, such as IL-2, interferon (IFN), and granulocyte macrophage colony-stimulating factor (GM-CSF, essential for generation and expansion of dendritic cell for T cell activation). IL-2 is the first cytokine successfully used in clinical cancer therapy, but only effective in certain types of cancers. More recently, IL-2 has been used as a key cytokine to promote the activation and proliferation of T and NK cells in a combination therapy [15,16]. The therapeutic potential of IFN is to exert a cytostatic effect on tumor cells and promote tumor cell apoptosis [17,18]. Although the antitumor effect of IFN is effective against different types of tumors in animal models, its clinical outcomes show limited therapeutic index. It is believed that IFN may be an important regulator of antitumor activity mediated by other cancer therapies. Likewise, current clinical
trial for GM-CSF is combining GM-CSF with cancer vaccine and/or immune checkpoint inhibitors to enhance antitumor immunity and achieve objective cancer regression in ovarian cancer patients [19,20].

Most studies of cancer immunotherapy to date have focused on augmenting immunity through active or passive strategies. One of the most promising strategies to induce T cells activation is immune checkpoint inhibitors, such as CTLA-4 blockade that has been demonstrated to improve immunity and clinical outcomes [21,22] and the programmed death 1 (PD-1)/PD-L1 interruption that has been found to achieve an immune-modulation approach in the treatment of solid tumors [23,24]. These important studies demonstrate that the concept of reversing immunosuppression in cancer has clinical relevance and provides further evidence that immune-based therapy will eventually find a meaningful place in the anticancer treatment armamentarium. Yet increasing evidence reveals the situation of tumor microenvironment and consistence of tumor-infiltrating T cells are much more complex, as we came to understand the recruitment of regulatory T cells (Tregs) by ovarian cancer [25-27], with poor prognosis [28]. Although the tumor infiltrating Tregs are attenuated by anti-PD-1 and anti-CTLA-4 antibodies [29], the immune checkpoint blockade targeted agents might represent greater therapeutic index by combining with other anti-cancer therapies, such as Treg depletion and adoptive T cell transfer.

Adoptive T cell therapy is a promising strategy to rapidly establish tumor immunity by genetically engineered T cells to harbor special antigen receptors, called chimeric antigen receptors (CARs) that allow the T cells to exhibit an enormous antitumor activity in cancer patients, such as CD19 CAR-T cells [30] and NY-ESO-1-reactive TCR T cells [31]. The clinical trial using adoptive T cell therapy has further tested in patients with ovarian cancer and revealed the potent therapeutic efficacy [32-34]. Although the infusion of engineered T cells can improve antitumor immune response, the presence of suppressive Tregs [35] and severe off-target off-tumor toxicities [36] may not be sufficient to overcome the inhibition. The challenge of controlling T cells in a therapeutic setting highlights the practical necessity to augment current adoptive transfer technology. An opportunity to raise antitumor effect for adoptive T cell transfer therapy might be strategies to combine with other cancer therapies.

In conclusion, the future of immunotherapies for ovarian cancer treatment looks bright. The current successes with immunotherapeutic strategies in other cancers have indicated a better therapeutic index compared to traditional therapies and increase the survival rate of patients with malignancy. These studies and the initial data in early-phase testing (phase I and II) for ovarian cancer immunotherapies suggest the approaches may ultimately prove useful for ovarian cancer treatment. Although the complexity of tumor microenvironment and antitumor immunity still remains elusive, the research of decoding the mechanisms of tumor and immunocytes may further develop better therapeutic strategies.

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