Immunotherapy in Ovarian Cancer

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Editorial

Ovarian cancer ranks fifth with a 5-year survival of 40% for patients with advanced disease and remains the most lethal gynecologic malignancy among women [1]. Most patients with advanced disease undergo aggressive frontline treatments with surgery and adjuvant chemotherapy; however, 80% of patients ultimately recur within few months and develop chemoresistant disease [2]. Advances in traditional treatment regimens and addition bevacizumab as a targeted therapy have shown promising results with improved progression-free survival but overall survival rates still remains the unaltered.

Recent in-depth understanding of immune cells and immune regulation of cancer has attracted a significant interest to develop immunotherapy as an alternative treatment in advance diseases. There is extensive evidence that suggest an active immune surveillance in ovarian cancer patients. Taking that in consideration, various clinical trial using immune check point inhibitors have been initiated for the patients with advanced and recurrent ovarian cancer. However, the response rate of these patient remain modest with 10-15 percent remission which along with the side effects of these therapy is not acceptable. Hence there is immense need to discover new approaches for use of these agents to improve the clinical outcome for ovarian cancer patients.

One of the keys approach to attain success with immune checkpoint inhibitors can be using them in combination to other therapies. A combination therapy has the potential to make tumor cells more vulnerable and may overcome the heterogeneity among the cancer cells which makes it difficult to target whole population with single agent. A recent article by Martin et al., [3] revealed that ovarian cancer patients have low mutation burden which may limit the neo-antigen targeted vaccination strategy. They found that although a specific CD4 and/or CD8 T cell response was achieved, none of the vaccines was able to prolong the survival of tumor bearing mice. However, an approach focused on tumor associated antigens (TAAs) seems more promising in this scenario as cancer cells harbor the over expressed or post-translationally modified proteins. In order to recognize by immune system, we need to identify different approach to enhance the TAA presentation on the cancer cell surface. One approach can be to increase the production of TAAs inside the cancer cells. The recent study from our group has revealed that modulating the immunoproteasome expression using interferon and demethylating agents in cancer cells would enhance the quality and quantity of antigen presentation [4]. Recently, interferon has also been shown to control the fibroblast glutathione and cysteine signaling pathway hence overcoming the drug resistance in ovarian cancer [5]. The combination with checkpoint inhibitors can be beneficial for ovarian cancer patients as interferon can serve as an antigen presentation booster alongside inhibiting the therapeutic resistance of cancer cells. Another combination of immune checkpoint inhibitors with radiation therapy can also be of benefit as radiation is well known to increase the neoantigen and TAA production by inducing DNA damage in cancer cells. Combining DNA damage repair targeted drugs with immunotherapy will also be of interest to boost the immunotherapy response rate in patients. Olaparib, Rucaparib and Niraparib are the approved poly (ADP-ribose) polymerase (PARP) inhibitors targeting the dysfunctional homologous recombination repair pathway for ovarian cancer patients who have a germline or somatic BRCA1/2 mutation [6]. All these PARP inhibitors are currently FDA approved for the second-line maintenance therapies in ovarian cancer patients; however their use as a first line therapy along with checkpoint inhibitors is still under investigation [7].

With all these approaches there are also a variety of questions need to be answered: What is the effective approach for a combination therapy, as a front line or follow-up treatment? What combination will be suited for an individual patient? How to identify the patient sub-population for each combination therapy? The last but not the least will be to identify the biomarkers for response to these combinatorial therapies. There is a lot of potential for an immune modulation approach in treatment of ovarian cancer patients, but the promise has yet to be fulfilled. We hope that the ongoing and future studies related to these combinatorial strategies will provide us with an unambiguous clinical utility of this approach.

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