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Immunotherapy, an evolving approach for the management of triple negative breast cancer: Converting non-responders to responders

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ABSTRACT

Immunotherapy comprises a promising new era in cancer therapy. Immune checkpoint inhibitors targeting either the programmed death (PD)-1 receptor or its ligand PD-L1 were first approved by the Food and Drug Administration (FDA) for the management of metastatic melanoma in 2011. The approval of this class is being extended to include other types of immunogenic tumors. Although breast cancer (BC) was first categorized as non-immunogenic tumor type, there are certain subsets of BC that showed a high level of tumor infiltrating lymphocytes (TILs). Those subsets include the triple negative breast cancer (TNBC) and HER-2 positive breast tumors. Preliminary data from clinical trials presented promising outcomes for patients with advanced stage/metastatic TNBC. While the objective response rate (ORR) was relatively low, it is still promising because of the observation that the patients who respond to the treatment with immune checkpoint blockade have favorable prognosis and often show a significant increase in the overall survival. Therefore, the main challenge is to find ways to enhance the tumor response to such therapy and to convert the non-responders to responders. This will consequently bring new hopes for patients with advanced stage metastatic TNBC and help to decrease death tolls from this devastating disease. In the current review, we are highlighting and discussing the up-to-date strategies adopted at either the preclinical or the clinical settings to enhance tumor responsiveness to immunotherapy.

1. Introduction

The programmed death (PD)-1 receptor–PD-1ligand (PD-L1) interaction is a key immune checkpoint that is overridden by malignant tumors to escape from the immune surveillance (Zou et al., 2016). PD-1 receptors are normally expressed during the initial activation of T-cells to suppress the unnecessary or excessive immune response that can precipitate autoimmune reactions. The PD-1/PD-L1pathway is engaged by cancer cells to undergo immune evasion. PD-1 receptors suppress T-cell activation upon the interaction of PD-1 with PD-L1ligand proteins. PD-1 is expressed on activated T lymphocytes and myeloid cells, while PD-L1 is mostly expressed on antigen-presenting cells together with other hematopoietic, non-hematopoietic cells and some epithelial cells (Intlekofer and Thompson, 2013). Tumor immune evasion occurs because of the upregulated expression of PD-L1 on tumor cells and on other components of tumor microenvironment (Juneja et al., 2017). Monoclonal antibodies targeting PD-1/PD-L1 immune checkpoints are an evolving approach for the management of cancer. These immune checkpoint inhibitors include PD-1 antibodies such as pembrolizumab and nivolumab or PD-L1 antibodies as avelumab and atezolizumab (Emens et al., 2017). The favorable clinical outcomes in patients receiving PD-1/PD-L1 immune checkpoint inhibitors are mostly associated with upregulated expression of PD-L1. Nonetheless, some studies reported clinical outcomes in patients with tumors that lack PD-L1 expression (Herbst et al., 2014). Tumor infiltrating lymphocytes (TILs) enriched tumor microenvironment is a feature associated with higher response rates to immune checkpoint inhibitors (Wein et al., 2017). Such tumors are called hot or inflamed tumors. It is noteworthy that breast tumors, which exhibit poor prognostic criteria such as estrogen receptor (ER)-negative or progesterone receptor (PR) negative status and lymph node positivity were shown to have higher levels of TILs (Muraro et al., 2011; Wein et al., 2017). Outcomes from clinical trials highlighted that a higher percentage of CD8+ TILs is a feature associated with higher response rates to immune check point inhibitors in triple-negative breast cancer (TNBC) patients (Herbst et al., 2014; Tumeh et al., 2014). Thus, immunotherapy is considered a promising therapeutic option for TNBC which has poor response to conventional therapies and does not have any specific targeted therapy options. The

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response of TNBC to immunotherapy is higher than the response rate of ER- positive breast cancer (Dirix et al., 2015; Savas et al., 2016). Several subsets of TNBC harbor mutations such as ATM and TP53 mutations and alterations in PI3K/MEK and BRCA pathways. The higher incidence of mutations in the tumor cells of TNBC contributes to the increased immunogenicity and boosts the percentage of TILs in TNBC tumors (Anders et al., 2016; Cancer Genome Atlas, 2012). Since advanced TNBC is among the tumors that exhibit high recurrence rate and resistance to the common chemotherapies, clinical trials are in process to evaluate the potential merit of immune checkpoint inhibitors in an effort to find a successful approach for treatment of such hard to treat tumors. The objective response rate (ORR) to pembrolizumab (PD-1 antibody) in patients with advanced PD-L1 + /TNBC was 18.5% (n = 27) (Nanda et al., 2016). Avelumab (PD-L1 antibody) produced an ORR of 44.4% (n = 9) in PD-L1 + /TNBC patients (Dirix et al., 2015). The ORR in PD-L1 + /TNBC patients receiving atezolizumab (PD-L1 antibody) was 13% (n = 71) (Schmid et al., 2017).

While the response was relatively low, it is still promising because of the observation that the patients who respond to treatment with immune checkpoint blockade have favorable prognosis and often show a significant increase in the overall survival with extended anti-tumor immunity. Therefore, the main challenge is to find ways to enhance the tumor response to such therapy and to convert the non-responders to responders. This will consequently help to decrease deaths tolls and open new hopes for patients with advanced stage/metastatic TNBC. In the current review, we are discussing the up-to-date strategies adopted at either the preclinical or the clinical settings to enhance tumor responsiveness to immunotherapy.

2. Nab-paclitaxel

Taxanes exhibit distinctive modulatory effects leading to activation of several subsets of immune cells (Zagozdzon and Golab, 2001). Low–dose metronomic paclitaxel therapy induces TLR4-mediated activation and maturation of dendritic cells in mouse models. It can also promote the production of proinflammatory cytokines from CD4 + with subsequent priming of CD8 + tumor antigen specific T −cells (Machiels et al., 2001; Pfannenstiel et al., 2010). Evaluation of cellular immunity in breast cancer patients that received taxane treatment after surgery indicated that T-cell blastogenesis and natural killer cell cytotoxic function were enhanced in patients that received taxanes compared to patients that did not administer taxanes (Carson et al., 2004). Therefore, taxanes appeared to be promising candidates for immunotherapy combinations. Nab-paclitaxel (Abraxane®) is the agent of choice to be combined with immunotherapies. It does not require corticosteroid pretreatment because it is a solvent-free preparation that does not elicit hypersensitivity reactions (Robinson and Keating, 2006). Therefore, the patients' immunity will be preserved. Combined treatment of the PD-L1- antibody atezolizumab (840 mg every 2 weeks) with nab-paclitaxel (100 mg/m^2 weekly) resulted in a marked improvement in the ORR in patients with metastatic TNBC. The confirmed ORR was 66.7% in patients receiving the combined treatment (Adams et al., 2016). The enrolled patients were unselected for PD-L1 and did not receive prior treatment for advanced TNBC. Therefore, the combination was tested as a frontline therapy regardless to the status of PD-L1 in the tumor microenvironment. Improved antitumor responses were reported in patients with or without PD-L1 expression (Adams et al., 2016). Based on these promising results, a phase III double-blinded, randomized clinical trial IMpassion 130 was initiated to study the effect of atezolizumab combination with nab-paclitaxel as a front-line therapy in a larger population of patients with metastatic TNBC (NCT02425891).

3. CDK4/6 inhibitors

Abemaciclib is a CDK4/6 inhibitor that showed promising outcomes in the clinical setting for patients with breast cancer and non-small cell lung cancer (NSCLC). Dempsey et al. reported that abemaciclib pretreatment synergized the antitumor effects of PD-L1 immunotherapies in a preclinical model of NSCLC in immuno-competent mice bearing CT26 tumors. The combination produced a superior anti-tumor effect with about 55% complete tumor regression compared to 0% in groups treated with monotherapies. Interestingly, the mice co-treated with abemaciclib/PD-L1 showed the development of anti-tumor-immune memory as they maintained complete tumor regression after the treatment has stopped and resisted CT-26 cells re-challenge (Dempsey et al., 2017). Data generated from this study encourages the initiation of similar studies on breast cancer models and the extension to the clinical setting after careful consideration of the probable toxic reactions.

4. Stimulator of interferon genes (STING) agonists

The stimulator of IFN genes (STING) is an adaptor molecule that plays a key role in cytosolic DNA sensing. STING signaling in dendritic cells (DCs) is usually activated by tumor-derived DNA, leading to increased type I interferon (INF) production and activation of DCs. Activated DCs lead to subsequent activation and cross-priming of tumor cytotoxic CD8 + T cells which attack and eliminate the tumor cells (Demaria et al., 2015). Local injection of ADU-S100, a synthetic cyclic dinucleotide STING agonist, into the tumor site exhibited significant antitumor activity in various *in vivo* models including 4T1 TNBC model (Corrales et al., 2015). A recent study by Foote et al., indicated that treatment with ADU-S100 was successful in delaying tumor progression in immune tolerant nue/N transgenic mouse model of HER2 + breast cancer (Foote et al., 2017). Nevertheless, ADU-S100 monotherapy failed to induce activation and expansion of CD8 + tumor antigen specific T cells. The triple combination of PD-1 antibody and OX-40 activator synergized the effect of ADU-S100 resulting in a successful priming of CD8 + T cells, overcoming immune tolerance and led to tumor clearance in 40% of mice compared to 10% in ADU-S100-only group (Foote et al., 2017). In a separate study, combined treatment by STING agonist and PD-L1 antibody elicited successful antitumor effects in squamous cell carcinoma preclinical model (Gadkaree et al., 2017).

5. Indoleamine 2,3-deoxygenase (IDO) inhibitors

Myeloid-derived suppressor cells (MSDCs) in the tumor microenvironment together with the tumor cells, produce metabolic enzymes such as indoleamine 2,3-deoxygenase (IDO) and arginase (Godin-Ethier et al., 2011; Munder, 2009). These enzymes consume the amino acids essential for the proper functioning of T-cells from the tumor microenvironment and therefore plays an important role in the tumor immune escape. The up-regulated levels of the immunosuppressive enzyme IDO1 in a wide-range of neoplasms is correlated with poor prognosis (Godin-Ethier et al., 2011). Inhibition of IDO is thus suggested to augment anti-tumor immunity and to enhance the responsiveness to immune checkpoint inhibitors. Preliminary data from phase I/II study of combined treatment of IDO1 inhibitor epacadostat together with pembrolizumab in patients with advanced stage tumors showed a promising clinical activity. The ORR in evaluable patients with melanoma was 57% (4 out of 7). The ORR was 40% (2 out of 5) in evaluable patients with renal cell carcinoma(RCC) (Gangadhar et al., 2015).

6. Epigenetic modifiers

Epigenetic silencing of immune recognition and antigen processing genes is one of the mechanisms of tumor immune escape (Choudhary et al., 2009; Hellebrekers et al., 2006). Epigenetic reprogramming *via* small molecule inhibitors of histone-deacetylases(HDAC) has shown significant anti-tumor effects in a variety of cancer types including breast cancer (Bai et al., 2011; Trapani et al., 2017). HDAC inhibitors can also prime the anti-tumor immune response (Terranova-Barberio