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Mini Review

Immunotherapy for Hepatocellular Carcinoma

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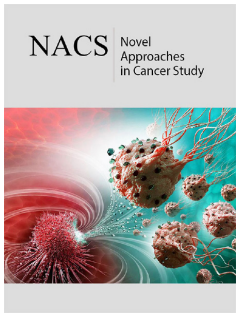
ISSN: 2637-773X



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Submission: January 29, 2020
Published: February 07, 2020

Volume 4 - Issue 1

How to cite this article: Zheng Wenjing, Wei Xiaolin, Li Xiaowu. Immunotherapy for Hepatocellular Carcinoma. Nov Appro in Can Study. 4(1). NACS.000580.2020. DOI: 10.31031/NACS.2020.04.000580

Introduction

Hepatocellular carcinoma (HCC) has always been a difficult medical problem for the increasing mortality rate. According to the World Health Organization (WHO), hepatocellular carcinoma (HCC) is the fourth-leading cause of cancer related deaths worldwide [1] and is considered as a highly refractory cancer. Surgery is the most effective treatment to HCC, but HCC is resistant to conventional chemotherapy. In recent years, immunotherapy has been attracting growing attention as a promising therapeutic method to HCC. Immunotherapies to HCC including chimeric antigen receptor T cells (CAR-T), immune checkpoint inhibitor and oncolytic virus have become research hotspots.

CAR-T therapy means killing tumor cells by chimeric antigen receptor T cells, which are isolated from patient blood, and reinfused into the patient's blood after being genetically engineered to recognize specific TAAs [2]. In 2017, tisagenlecleucel, become the first CAR-T therapy attained the approval of U.S. Food and Drug Administration (FDA) as a promising treatment approach to certain acute lymphoblastic leukemia. Up till now, four generations of CAR-T have been developed. The fourth and last CAR-T generation enables the recruitment of NK cells and macrophages to attack even the antigen-negative cells, by activating T cell signaling and the release of IL-12 [3]. *In-vivo* studies and patient-derived xenograft (PDX) tumor models have revealed CAR-T is an effective therapy in solid tumors with tumor-associated antigens [4]. A study in 2014 observed that GPC3-targeted CAR-T cells could specifically kill GPC3-positive HCC cells, and improve the survival of HCC xenograft model. But there are still several difficulties remain to be solved, such as trafficking in T cells, penetration of CAR-T cells into tumor sites and immunosuppression of tumor microenvironment [3]. More than 10 clinical trials evaluating CAR-T cells therapy in HCC are still ongoing [5]. Recently, a phase I clinical study firstly tested CAR-T directed CD133 (CART-133) in HCC antitumor therapy and its feasibility, controllable toxicity and efficacy were demonstrated [6].

There are several immune checkpoint inhibitors (ICIs) used in HCC treatment, including antibodies targeting CTLA-4 and PD-1/PD-L1. The way PD-1 acts in T cell activation is in the effector phase, mainly in the peripheral tissues. This is different form CTLA-4, which mainly acts in the priming phase of T cell activation. Therefore, compared to CTLA-4, PD-1 engagement can affect a higher number of T cell signaling pathways and is probably more powerful in anti-tumor therapy. Consequently, various kinds of PD-1/ PD-L1 inhibitors were invented and under clinical evaluation in recent years. In clinical trials, PD-1 immune checkpoint inhibitors have produced encouraging results, especially in combination therapy with traditional targeting therapies. According to the previous studies, antiangiogenic effects have been proved to be important in HCC antitumor therapy [7]. So, the mostly tested combination regimen was anti-PD1/anti-PDL1 plus antiangiogenic agents. Such combination regimens as lenvatinib plus pembrolizumab, atezolizumab and bevacizumab, have been proven to have significantly promoted the overall survival (OS) and the progression-free survival (PFS) in HCC patients [8,9]. While in some studies, not all antiangiogenic agents could show good synergistic antitumor efficacy with anti-PD-1 therapy as expected, and some patients could not tolerate the recommended dosage because of the adverse effects [10]. The exploration of other combination regimens is developing at a remarkable speed. Anti-PD-1/anti-PD-L1 in combination with various targeting agents are being tested, including targeting agonists of T cell activation or T cell exhaustion, anti-CD38, MET inhibitors and TGF-b or IDO1 inhibitors,

cytokine network modulators [11]. Meanwhile, pre-clinical models of HCC contributed a lot to the identification of the most effective combination strategies and accelerate facilitating appropriate clinical trial designs [12]. Growing number of immuno-oncology agents got the approval of FDA, brought hope to HCC patients, but also raised concerns about safety evaluation. When treated with ICIs-based combinations, liver-related adverse events, rare but life-threatening toxicity may occur in HCC patients [13,14]. Therefore, our understanding about the adverse effects and toxicity of the ICIs still need more extensive investigations.

Oncolytic viruses (OVs) have been recently reported to be a promising treatment approach in HCC [15]. OVs could selectively attack and lyse cancer cells, in this way OVs replicate and survive [16]. Besides tumor regression, OVs could also activate dendritic cells (DCs) and antigen-presenting cells (APCs), which provided key signals could initiate antitumor immune response [17]. OVs can also be genetically engineered to carry certain functional genes (e.g. granulocyte macrophage colony-stimulating factor), which could recruit various kinds of immune cells and strengthen the immune response to tumor cell [18]. Adenovirus and vaccinia virus used in HCC patient's treatment were still in clinical trials [19,20]. In the future, new immunotherapy approaches for HCC will be established to overcome the limitations of conventional therapies. New biomarkers to diagnose HCC at the early stage and detect the progression of the tumor will be very helpful in the immunotherapy for HCC.

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