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Immunotherapy for Hepatocellular Carcinoma and Its New Development

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Abstract:

Hepatocellular Carcinoma (HCC) is the most common primary liver cancer with high mortality. Because of the limitation on the conventional therapeutic options and immunological characters of this disease, variable immunotherapy strategies for HCC have been designed and investigated. A few of them look promising. In this review, we comprehensively summarized recent and novel immunotherapies for HCC, with a particular focus on clinical trials on the basis of their physiological rationales for these strategies. Insights into these clinical progress and their ideologies are essential to improve efficacy and clinical outcome of these immunotherapies.

Keywords: Hepatocellular carcinoma; Immunotherapy; liver tolerance; Clinical trial

Introduction:

Hepatocellular carcinoma (HCC) is the most common histological type of primary liver cancer, accounting for 85% to 90% of liver cancers. HCC is one of the most morbid cancers in the world. There are approximately 750,000 new cases each year, which represents 5.7% of all new cancer cases, 85% of these new cases reported in sub-Saharan Africa and East Asia. This geographic distribution of HCC overlaps that of chronic viral hepatitis, according to epidemiological data [1]. It is widely accepted that HCC is developed from viral hepatitis B and C, and hepatic cirrhosis at the later stage. Other less common causes are chronic exposure to toxins or inherited liver disease, such as non-alcoholic fatty liver disease. HCC is the fifth most common malignant tumor, but in terms of mortality, it is ranked third in the world. Although there are great advances in medical diagnostic technology and surveillance programs for high-risk populations, only 20% of HCC patients can be diagnosed in phase I, and only these patients are likely to benefit curative therapy (liver transplantation, surgical resection or ablative therapy); most HCC patients with liver dysfunction are not feasible for these aggressive treatments. Therefore, the only reliable treatment option is Sorafenib, which gave a median overall survival of 6.5 to 10.7 months. In addition, tumor recurrence of HCC occurs in 50% to 80% of patients after 5 years of treatment. A significant unmet medical need remains.

Immune checkpoint blockade

The field of cancer immunotherapy is undergoing a renaissance due to a deeper understanding of the immune system and immuno- surveillance. The balance between co-stimulatory signals and immune checkpoints determines T cell activation and the overall intensity of the immune response. Whenever CD80/CD86 from APC cells recognized by CD28 on effector T cells, they deliver co-stimulatory signals to synergize first activation signalling from TCR recognizing antigen/ MHC (Major Histocompatibility Complex) complex; meanwhile, to control the intensity and remission of immune response tightly, T cells also present inhibitory receptors, such as CTLA-4 and PD-1. CTLA- 4 compete CD28 binding to CD80/CD86 and thereby inhibits T-cell activation. PD-1 receptors are expressed on several immune cells, including effector T and NK cells, which associate with PD-L1 from APC or tumour cells. Engaged PD-1 receptors deliver pro-apoptotic signalling to effector immune cells. After astonishing success of clinical trials on CTLA-4 and PD-L1 blockade to treat melanoma patients, similar positive results are highly anticipated in HCC patients.

In a recent pilot clinical trial, 37 patients with HCC or HCV infection were injected with 15 mg/kg of the CTLA-4-blocking antibody tremelimumab for 90 days, to test the anti-tumour and antiviral effect of this antibody. In addition to demonstrating the safety of such approach in patients, a 17.6% partial response rate and a 76.4% disease control rate was achieved. A significant drop in viral load was also observed. Another phase I clinical trial of tremelimumab with percutaneous Radiofrequency Ablation (RFA) or trans-arterial therapy is ongoing (NCT01853618).

The anti-PD-1 antibody based therapy is even more promising than a CTLA-4 blockade. Nivolumab was the first immune drug approved as a second-line treatment for patients with HCC by FDA in September 2017. In the CheckMate040 study, 48 patients with HCC had received nivolumab 0.1-10 mg/kg intravenously for 2 years. The Objective Remission Rate (ORR) was 15%; median Overall Survival (OS) was 15.1 months and the 9 months OS rate was 67%. In a dose-expansion study of nivolumab, 174 patients with HCC received nivolumab 3 mg/kg intravenously. The ORR was 20% and tumor burden was reduced In 68 patients (39%). Besides, in 80 HCC patients treated with nivolumab only, the ORR was 23%; Disease Control Rate (DCR) was 63%; and 40% of patients had stable disease over than 6 months. However, in the group of sorafenib-experienced patients that received nivolumab, 91% (166/182) of patients progressed on sorafenib treatment. The ORR was 16%-19%. Most recently, the efficacy and safety of anti-PD1 therapy of advanced HCC was evaluated on 11 cases, no related adverse effects were noted; the disease control rate reached 81.8% comparing to an objective response of 63.6%, this clinical trial proved promising application of PD-1 in HCC. There are more clinical trials on other immune checkpoint blockade (Figure 2). Greten summarised clinical data of the therapies based on PD-1/PD-L1 blockade under study for the treatment of hepatocellular carcinoma.

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