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Hepatocellular Carcinoma and Immunotherapy: Beyond Immune Checkpoint Inhibitors

Hepatocellular Carcinoma and Immunotherapy: Beyond Immune Checkpoint Inhibitors

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Abstract

Hepatocellular carcinoma (HCC) is one of the deadliest and most common malignancies in the liver. Considering the rich immune background of carcinogenesis in HCC, efforts have been focused on further understanding the role of the immune system in tumor suppression and promotion. The utilization of immunotherapy in HCC has led to encouraging results that translated to longer survival and better quality of life among patients. The development of novel HCC-tailored regimens such as vaccine therapy and adoptive cellular therapy coupled with a deeper understanding of predictive biomarkers for immunotherapy's response warrant better treatment outcomes.

Key Words: Hepatocellular Carcinoma; Immunotherapy; Biomarkers; Cancer Vaccines; Adoptive Cellular Therapy

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Core Tip: Immunotherapy has changed the treatment landscape in solid cancers. In advanced hepatocellular carcinoma (HCC), immune checkpoint inhibitors became the standard of care following their positive efficacy and safety outcomes. However, primary and acquired resistance are major issues in the treatment paradigm and more research is still needed to understand and identify potential predictors of response in HCC. Other immunotherapy modalities such as vaccine therapy and adoptive cellular therapy could play a prominent role in certain HCC sub cohorts as they are currently being investigated in clinical trials settings.

TO THE EDITOR

We read with great interest the review done by Mattos and colleagues on the immune landscape of hepatocellular carcinoma (HCC) covering the immune aspects and

markers of HCC as well as the immunotherapeutic modalities used in this malignancy [1]. Considering the immunogenicity of HCC, it comes as no surprise that clinical and basic research has been directed to dive deeper into HCC's immune- biological and therapeutic upside, especially with the rise of immunotherapy in oncology.

While the authors thoroughly discussed the therapeutic use of Immune Checkpoint Inhibitors (ICI) such as anti-programmed cell death protein 1 and its ligand (nivolumab, pembrolizumab, and atezolizumab) and anti- cytotoxic T-lymphocyte-associated protein 4 (ipilimumab), we would like to highlight the role of other promising immunotherapeutic modalities in HCC. The first being tumor-associated antigen vaccines, including the oncofetal antigen glypican-3 (GPC3) vaccine which was investigated in adjuvant settings in HCC patients in a phase 2 trial resulting in a 20.1 median overall survival (mOS) [2]. Another potential vaccine antigen is the multidrug resistance-associated protein 3 (MRP3), a highly expressed member of the ATP-binding cassette transporters in HCC tissue [3]. MRP3-derived peptide vaccines resulted in a mOS of 19 mo in a phase 1 trial on 12 HCC patients. Oncolytic virotherapy is another immune modality investigated widely in solid malignancies. Heo *et al* conducted a phase 2 trial assessing the efficacy and safety of high- and low-dose JX-594, an oncolytic poxvirus, in HCC patients [4]. They reported a significantly longer mOS with high-dose JX-594 compared to low-dose (14.1 *vs* 6.7 mo, P = 0.02) [4]. Lastly, adoptive cellular therapy, being a promising option gaining more use in hematological and solid cancers, has been investigated in HCC specifically through genetically modified T cells expressing chimeric antigen receptors for GPC3 in a phase 1 trial on 13 patients which resulted in a mOS of 278 days [5]. **Table 1** includes the characteristics of clinical trials on non-ICI immunotherapeutic options for HCC patients.

Furthermore, we would like to emphasize the importance of identifying predictive biomarkers for immunotherapy response in HCC. As of now, limited evidence exists on this topic, yet there are some preclinical and clinical data pointing to potential targets. For instance, emerging evidence suggests that activated Wnt/Beta-catenin signaling can predict primary immunotherapy resistance in HCC [6]. There is also a growing interest

in the microbiome's predictive value to ICI response in other cancers. For HCC, this is especially relevant since chronic liver disease alters the microbiome components [7]. Established ICI predictive biomarkers in other malignancies such as microsatellite instability and high tumor mutational burden are of limited use in HCC due to their rarity [6], [8].

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2	Christo Kole, Nikolaos Charalampakis, Sergios Tsakatikas, Michail Vailas et al. "Immunotherapy for Hepatocellular Carcinoma: A 2021 Update", Cancers, 2020 Crossref	13 words — 2%

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