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Contents

Monthly Volume 14 Number 6 June 15, 2022

REVIEW

MINIREVIEWS

ORIGINAL ARTICLE

Basic Study

Retrospective Cohort Study

Retrospective Study

Observational Study

World Journal of Gastrointestinal Oncology

Monthly Volume 14 Number 6 June 15, 2022

Contents

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Monthly Volume 14 Number 6 June 15, 2022

Contents

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LETTER TO THE EDITOR

Hepatocellular carcinoma and immunotherapy: Beyond immune checkpoint inhibitors

Hassan Mohammed Abushukair, Anwaar Saeed

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Hassan Mohammed Abushukair, Faculty of Medicine, Jordan University of Science and Technology, Irbid 22110, Jordan

Anwaar Saeed, Division of Medical Oncology, Department of Medicine, The University of Kansas Cancer Center, Kansas City, KS 66205, United States

Corresponding author: Anwaar Saeed, MD, Division of Medical Oncology, Department of Medicine, The University of Kansas Cancer Center, 2330 Shawnee Mission Pkwy, Kansas City, KS 66205, United States. asaeed@kumc.edu

Abstract

Hepatocellular carcinoma (HCC) is one of the deadliest and most common malignancies of 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 has 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 biomarkers predictive of the response to immunotherapy will lead to better treatment outcomes.

Key Words: Hepatocellular carcinoma; Immunotherapy; Biomarkers; Cancer vaccines; Adoptive cellular therapy

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

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TO THE EDITOR

We read with great interest the review by Mattos *et al*[1] on the immune landscape of hepatocellular carcinoma (HCC), which covered the immune aspects and markers of HCC as well as the immunotherapeutic modalities used in this malignancy. Considering the immunogenicity of HCC, it comes as no surprise that clinical and basic research has been directed to dive deeper into the immune-biological and therapeutic upside of HCC, especially with the rise of immunotherapy in oncology.

While the authors thoroughly discussed the therapeutic use of immune checkpoint inhibitors (ICIs), 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 and resulted in a median overall survival (mOS) of 20.1 mo[2]. Another potential vaccine antigen is the multidrug resistance-associated protein 3 (MRP3), a member of the adenosine triphosphate-binding cassette transporters highly expressed in HCC tissue[3]. MRP3-derived peptide vaccines resulted in a mOS of 19 mo in a phase 1 trial of 12 HCC patients. Oncolytic virotherapy is another immune modality that has been widely investigated in solid malignancies. Heo *et al*[4] conducted a phase 2 trial assessing the efficacy and safety of high- and low-dose JX-594, an oncolytic poxvirus, in HCC patients[4]. The investigators reported a significantly longer mOS with high-dose compared to low-dose JX-594 (14.1 mo *vs* 6.7 mo; $P = 0.02$). Lastly, adoptive cellular therapy, which is a promising option that is being used more 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 d[5]. Table 1 includes the characteristics of the clinical trials on non-ICI immunotherapeutic options for HCC patients.

We would also like to emphasize the importance of identifying biomarkers predictive of the immunotherapy response in HCC. To date, limited evidence exists on this topic, yet some preclinical and clinical data point 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 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].

Table 1 Clinical trials characteristics on vaccine therapy, oncolytic virotherapy, and adoptive cellular therapy in hepatocellular carcinoma patients

Ref.	Intervention	Study design	Sample size	Survival outcomes
Sawada *et al*[2], 2016	GPC3	Phase 2 trial	41	mOS: 20.1 mo (95%CI: 14.7-25.5)
Mizukoshi *et al*[9], 2015	MRP3	Phase 1 trial	12	mOS: 14 mo (95%CI: 9.6-18.5)
Palmer *et al*[10], 2009	DCs	Phase 2 trial	35	mOS: 168 d
Butterfield *et al*[11], 2014	AFP	Phase 1 trial	2	RFS: 9 and 18 mo
Heo *et al*[4], 2013	JX-594	Phase 2 trial	30	mOS in high- *vs* low-dose: 14.1 mo *vs* 6.7 mo
Shi *et al*[5], 2020	CAR-GPC3 T-cell	Phase 1 trial	13	mOS: 278 d (95%CI: 48-615)

AFP: Alpha fetoprotein; CAR: Chimeric antigen receptor; CI: Confidence interval; DCs: Dendritic cells; GPC3: Glypican-3; mOS: Median overall survival; MRP3: Multidrug resistance-associated protein 3; RFA: Radiofrequency ablation; RFS: Recurrence-free survival.

FOOTNOTES

Author contributions: Abushukair HA drafted the manuscript and conceptualized the concepts; Saeed A conceptualized the core concepts and critically revised the draft.

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Country/Territory of origin: United States

ORCID number: Hassan Mohammed Abushukair 0000-0002-0068-5201; Anwaar Saeed 0000-0001-8024-9401.

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