

World Journal of *Gastrointestinal Oncology*

World J Gastrointest Oncol 2022 June 15; 14(6): 1067-1217



**REVIEW**

- 1067** Circular RNAs in hepatocellular carcinoma: Recent advances
Niu ZS, Wang WH
- 1086** Practical considerations for colorectal cancer screening in older adults
Gornick D, Kadakuntla A, Trovato A, Stetzer R, Tadros M
- 1103** Fibrolamellar hepatocellular carcinoma: A rare but unpleasant event
Abdelhamed W, El-Kassas M

MINIREVIEWS

- 1115** Can dietary flavonoids be useful in the personalized treatment of colorectal cancer?
Pereira-Wilson C

ORIGINAL ARTICLE**Basic Study**

- 1124** Glutamine deprivation impairs function of infiltrating CD8⁺T cells in hepatocellular carcinoma by inducing mitochondrial damage and apoptosis
Wang W, Guo MN, Li N, Pang DQ, Wu JH

Retrospective Cohort Study

- 1141** Does the addition of Braun anastomosis to Billroth II reconstruction on laparoscopic-assisted distal gastrectomy benefit patients?
Li XG, Song QY, Wu D, Li S, Zhang BL, Zhang LY, Guan D, Wang XX, Liu L

- 1148** Contemporary, national patterns of surgery after preoperative therapy for stage II/III rectal adenocarcinoma
Soriano C, Bahnson HT, Kaplan JA, Lin B, Moonka R, Pham HT, Kennecke HF, Simianu V

Retrospective Study

- 1162** Clinicopathological differences, risk factors and prognostic scores for western patients with intestinal and diffuse-type gastric cancer
Díaz del Arco C, Estrada Muñoz L, Ortega Medina L, Molina Roldán E, Cerón Nieto MÁ, García Gómez de las Heras S, Fernández Aceñero MJ

Observational Study

- 1175** Characterizing the patient experience during neoadjuvant therapy for pancreatic ductal adenocarcinoma: A qualitative study
Stevens L, Brown ZJ, Zeh R, Monsour C, Wells-Di Gregorio S, Santry H, Ejaz AM, Pawlik TM, Cloyd JM

Randomized Controlled Trial

- 1187** Biofeedback therapy combined with Baduanjin on quality of life and gastrointestinal hormone level in patients with colorectal cancer
Zhou XD, Wei HG, Ai FL

META-ANALYSIS

- 1199** Does chronic kidney disease affect the complications and prognosis of patients after primary colorectal cancer surgery?
Liu XY, Zhang B, Cheng YX, Tao W, Yuan C, Wei ZQ, Peng D

LETTER TO THE EDITOR

- 1210** Hepatocellular carcinoma and immunotherapy: Beyond immune checkpoint inhibitors
Abushukair HM, Saeed A
- 1213** Insight on BRAF^{V600E} mutated colorectal cancer immune microenvironment
Abushukair HM, Zaitoun SM, Saeed A

CORRECTION

- 1216** Correction to "MicroRNA-320a suppresses tumor progression by targeting PBX3 in gastric cancer and is downregulated by DNA methylation"
Li YS, Zou Y, Dai DQ

ABOUT COVER

Editorial Board Member of *World Journal of Gastrointestinal Oncology*, Tamás Micsik, MD, PhD, Assistant Professor, The First Department of Pathology and Experimental Cancer Research, Semmelweis University Budapest, Budapest h-1085, Hungary. micsikt@gmail.com

AIMS AND SCOPE

The primary aim of *World Journal of Gastrointestinal Oncology* (WJGO, *World J Gastrointest Oncol*) is to provide scholars and readers from various fields of gastrointestinal oncology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGO mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal oncology and covering a wide range of topics including liver cell adenoma, gastric neoplasms, appendiceal neoplasms, biliary tract neoplasms, hepatocellular carcinoma, pancreatic carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, duodenal neoplasms, esophageal neoplasms, gallbladder neoplasms, *etc.*

INDEXING/ABSTRACTING

The WJGO is now indexed in Science Citation Index Expanded (also known as SciSearch®), PubMed, PubMed Central, and Scopus. The 2021 edition of Journal Citation Reports® cites the 2020 impact factor (IF) for WJGO as 3.393; IF without journal self cites: 3.333; 5-year IF: 3.519; Journal Citation Indicator: 0.5; Ranking: 163 among 242 journals in oncology; Quartile category: Q3; Ranking: 60 among 92 journals in gastroenterology and hepatology; and Quartile category: Q3. The WJGO's CiteScore for 2020 is 3.3 and Scopus CiteScore rank 2020: Gastroenterology is 70/136.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Ying-Yi Yuan*; **Production Department Director:** *Xiang Li*; **Editorial Office Director:** *Ya-Juan Ma*.

NAME OF JOURNAL

World Journal of Gastrointestinal Oncology

ISSN

ISSN 1948-5204 (online)

LAUNCH DATE

February 15, 2009

FREQUENCY

Monthly

EDITORS-IN-CHIEF

Monjur Ahmed, Florin Burada

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/1948-5204/editorialboard.htm>

PUBLICATION DATE

June 15, 2022

COPYRIGHT

© 2022 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>



Hepatocellular carcinoma and immunotherapy: Beyond immune checkpoint inhibitors

Hassan Mohammed Abushukair, Anwaar Saeed

Specialty type: Oncology

Provenance and peer review:

Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0

Grade B (Very good): B

Grade C (Good): C

Grade D (Fair): D

Grade E (Poor): E

P-Reviewer: Elshimi E, Egypt; Limaïem F, Tunisia; Song B, China

A-Editor: Ma LS

Received: December 5, 2021

Peer-review started: December 5, 2021

First decision: December 27, 2021

Revised: December 29, 2021

Accepted: May 12, 2022

Article in press: May 12, 2022

Published online: June 15, 2022



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. asaeeed@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

©The Author(s) 2022. Published by Baishideng Publishing Group Inc. All rights reserved.

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.

Citation: Abushukair HM, Saeed A. Hepatocellular carcinoma and immunotherapy: Beyond immune checkpoint inhibitors. *World J Gastrointest Oncol* 2022; 14(6): 1210-1212

URL: <https://www.wjgnet.com/1948-5204/full/v14/i6/1210.htm>

DOI: <https://dx.doi.org/10.4251/wjgo.v14.i6.1210>

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 <i>et al</i> [2], 2016	GPC3	Phase 2 trial	41	mOS: 20.1 mo (95%CI: 14.7-25.5)
Mizukoshi <i>et al</i> [9], 2015	MRP3	Phase 1 trial	12	mOS: 14 mo (95%CI: 9.6-18.5)
Palmer <i>et al</i> [10], 2009	DCs	Phase 2 trial	35	mOS: 168 d
Butterfield <i>et al</i> [11], 2014	AFP	Phase 1 trial	2	RFS: 9 and 18 mo
Heo <i>et al</i> [4], 2013	JX-594	Phase 2 trial	30	mOS in high- <i>vs</i> low-dose: 14.1 mo <i>vs</i> 6.7 mo
Shi <i>et al</i> [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.

Conflict-of-interest statement: Anwaar Saeed reports research grants from AstraZeneca, Bristol Myers Squibb, Merck, Exelixis, KAHN Medical, and Incyte, and advisory board fees from AstraZeneca, Bristol Myers Squibb, Merck, Exelixis, and Pfizer. The other author has no conflicts of interest to declare.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <https://creativecommons.org/licenses/by-nc/4.0/>

Country/Territory of origin: United States

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

S-Editor: Fan JR

L-Editor: Filipodia

P-Editor: Fan JR

REFERENCES

- 1 **Mattos ÂZ**, Debes JD, Boonstra A, Vogel A, Mattos AA. Immune aspects of hepatocellular carcinoma: From immune markers for early detection to immunotherapy. *World J Gastrointest Oncol* 2021; **13**: 1132-1143 [PMID: 34616518 DOI: 10.4251/wjgo.v13.i9.1132]
- 2 **Sawada Y**, Yoshikawa T, Ofuji K, Yoshimura M, Tsuchiya N, Takahashi M, Nobuoka D, Gotohda N, Takahashi S, Kato Y, Konishi M, Kinoshita T, Ikeda M, Nakachi K, Yamazaki N, Mizuno S, Takayama T, Yamao K, Uesaka K, Furuse J, Endo I, Nakatsura T. Phase II study of the GPC3-derived peptide vaccine as an adjuvant therapy for hepatocellular carcinoma patients. *Oncoimmunology* 2016; **5**: e1129483 [PMID: 27467945 DOI: 10.1080/2162402X.2015.1129483]
- 3 **Mizukoshi E**, Honda M, Arai K, Yamashita T, Nakamoto Y, Kaneko S. Expression of multidrug resistance-associated protein 3 and cytotoxic T cell responses in patients with hepatocellular carcinoma. *J Hepatol* 2008; **49**: 946-954 [PMID: 18619700 DOI: 10.1016/j.jhep.2008.05.012]
- 4 **Heo J**, Reid T, Ruo L, Breitbach CJ, Rose S, Bloomston M, Cho M, Lim HY, Chung HC, Kim CW, Burke J, Lencioni R, Hickman T, Moon A, Lee YS, Kim MK, Daneshmand M, Dubois K, Longpre L, Ngo M, Rooney C, Bell JC, Rhee BG, Patt R, Hwang TH, Kim DH. Randomized dose-finding clinical trial of oncolytic immunotherapeutic vaccinia JX-594 in liver cancer. *Nat Med* 2013; **19**: 329-336 [PMID: 23396206 DOI: 10.1038/nm.3089]
- 5 **Shi D**, Shi Y, Kaseb AO, Qi X, Zhang Y, Chi J, Lu Q, Gao H, Jiang H, Wang H, Yuan D, Ma H, Li Z, Zhai B. Chimeric Antigen Receptor-Glypican-3 T-Cell Therapy for Advanced Hepatocellular Carcinoma: Results of Phase I Trials. *Clin Cancer Res* 2020; **26**: 3979-3989 [PMID: 32371538 DOI: 10.1158/1078-0432.CCR-19-3259]
- 6 **Pinter M**, Scheiner B, Peck-Radosavljevic M. Immunotherapy for advanced hepatocellular carcinoma: a focus on special subgroups. *Gut* 2021; **70**: 204-214 [PMID: 32747413 DOI: 10.1136/gutjnl-2020-321702]
- 7 **Keenan BP**, Fong L, Kelley RK. Immunotherapy in hepatocellular carcinoma: the complex interface between inflammation, fibrosis, and the immune response. *J Immunother Cancer* 2019; **7**: 267 [PMID: 31627733 DOI: 10.1186/s40425-019-0749-z]
- 8 **Kole C**, Charalampakis N, Tsakatikas S, Vilas M, Moris D, Gkotsis E, Kykalos S, Karamouzis MV, Schizas D. Immunotherapy for Hepatocellular Carcinoma: A 2021 Update. *Cancers (Basel)* 2020; **12** [PMID: 33020428 DOI: 10.3390/cancers12102859]
- 9 **Mizukoshi E**, Nakagawa H, Kitahara M, Yamashita T, Arai K, Sunagozaka H, Iida N, Fushimi K, Kaneko S. Phase I trial of multidrug resistance-associated protein 3-derived peptide in patients with hepatocellular carcinoma. *Cancer Lett* 2015; **369**: 242-249 [PMID: 26325606 DOI: 10.1016/j.canlet.2015.08.020]
- 10 **Palmer DH**, Midgley RS, Mirza N, Torr EE, Ahmed F, Steele JC, Steven NM, Kerr DJ, Young LS, Adams DH. A phase II study of adoptive immunotherapy using dendritic cells pulsed with tumor lysate in patients with hepatocellular carcinoma. *Hepatology* 2009; **49**: 124-132 [PMID: 18980227 DOI: 10.1002/hep.22626]
- 11 **Butterfield LH**, Economou JS, Gamblin TC, Geller DA. Alpha fetoprotein DNA prime and adenovirus boost immunization of two hepatocellular cancer patients. *J Transl Med* 2014; **12**: 86 [PMID: 24708667 DOI: 10.1186/1479-5876-12-86]



Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

Telephone: +1-925-3991568

E-mail: bpgoffice@wjgnet.com

Help Desk: <https://www.f6publishing.com/helpdesk>

<https://www.wjgnet.com>

