ISSN 1948-5204 (online)

World Journal of *Gastrointestinal Oncology*

World J Gastrointest Oncol 2024 October 15; 16(10): 4037-4299

Published by Baishideng Publishing Group Inc

World Journal of Gastrointestinal Oncology

Contents

Monthly Volume 16 Number 10 October 15, 2024

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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*.

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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
October 15, 2024

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World J Gastrointest Oncol 2024 October 15; 16(10): 4042-4044

DOI: 10.4251/wjgo.v16.i10.4042

ISSN 1948-5204 (online)

EDITORIAL

Unresectable hepatocellular carcinoma: Transarterial chemoembolization combined with lenvatinib in combination with programmed death-1 inhibition is a possible approach

Fei-Yu Zhao, Dong-Yu Wang, Nian-Song Qian

Specialty type: Oncology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade C
Novelty: Grade B
Creativity or Innovation: Grade B
Scientific Significance: Grade C

P-Reviewer: Aoki H, Japan

Received: February 28, 2024
Revised: May 11, 2024
Accepted: June 11, 2024
Published online: October 15, 2024
Processing time: 211 Days and 7.1 Hours

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Abstract

In this editorial, we review the article "Efficacy and predictive factors of transarterial chemoembolization combined with lenvatinib plus programmed cell death protein-1 inhibition for unresectable hepatocellular carcinoma". We specifically focused on whether transarterial chemoembolization combined with lenvatinib in combination with a programmed death 1 inhibitor could be used in patients with unresectable hepatocellular carcinoma. Since both transarterial chemoembolization as well as lenvatinib in combination with programmed death 1 inhibitors play an important role in the treatment of advanced liver cancer, but the combination of all three therapeutic approaches needs more research.

Key Words: Transarterial chemoembolization; Programmed death 1; Lenvatinib; Hepatocellular carcinoma

Core Tip: This article focuses on the efficacy of transarterial chemoembolization combined with lenvatinib in combination with programmed death 1 inhibitors in patients with advanced hepatocellular carcinoma. Although transarterial chemoembolization as well as lenvatinib in combination with programmed death 1 have both achieved some efficacy in advanced hepatocellular carcinoma, more clinical evidence is needed on the efficacy of all three combinations.

Citation: Zhao FY, Wang DY, Qian NS. Unresectable hepatocellular carcinoma: Transarterial chemoembolization combined with lenvatinib in combination with programmed death-1 inhibition is a possible approach. *World J Gastrointest Oncol* 2024; 16(10): 4042-4044
URL: https://www.wjgnet.com/1948-5204/full/v16/i10/4042.htm
DOI: https://dx.doi.org/10.4251/wjgo.v16.i10.4042

INTRODUCTION

Transarterial chemoembolization (TACE) has emerged as the standard treatment for intermediate-stage hepatocellular carcinoma (HCC)[1]. In addition, lenvatinib and programmed death 1 (PD-1) inhibitors are now classified as first-line systemic therapies for advanced HCC, according to recent guidelines[2]. Is a combination of all three treatments effective for patients with advanced liver cancer? In this editorial, we discussed and analysed an article by Ma *et al*[3] published in the *World Journal of Gastrointestinal Oncology*.

EFFICACY AND BENEFITS

As TACE induces tumour cells to release large amounts of debris as tumour antigens, from causing antigen-presenting cells to mature and ultimately activate systemic anti-tumour immunity, immune checkpoint inhibitors target immunomodulation, and lenvatinib inhibits the kinase activity of vascular endothelial growth factor, thereby inhibiting tumour growth. All three have shown promising results in unresectable HCC.

In this issue, Ma *et al*[3] retrospectively included patients with unresectable HCC treated with TACE combined with lenvatinib combined with PD-1 inhibitors between March 2019 and April 2022. They followed up the overall survival and progression-free survival of these patients and assessed the objective response rate and disease control rate according to the modified response assessment criteria for solid tumours. It was finally concluded that TACE-lenvatinib-PD1 treatment was well tolerated and had good efficacy in patients with unresectable HCC.

In the study, 10 patients achieved complete response, 53 achieved partial response, while 20 and 19 patients had stable disease and progressive disease, respectively. The overall response rate was an encouraging 61.76%. The median progression-free survival was reported as 10.07 (95% confidence interval: 8.50-11.65) months, and the median overall survival was 26.43 months (95% confidence interval: 17.00-35.87).

It was ultimately concluded that patients with BCLC stage B disease, early neutrophil-to-lymphocyte ratio response (reduction) and early alpha-fetoprotein response (> 20% reduction) could achieve better clinical outcomes with the proposed triple combination therapy. The triple combination therapy is well-founded in other studies, and similar conclusions were obtained in a similar study by Li *et al*[4]. The LePD1-TACE triple combination therapy was well-tolerated in patients with advanced HCC, and the efficacy was encouraging. Patients with tumour number < 3, neutrophil-to-lymphocyte ratio ≤ 2.165 and with tumor complete response as well as tumor partial response may have more clinical efficacy[4]. There are many other studies that have come to similar conclusions. This implies that TACE combined with lenvatinib and PD-1 in the treatment of HCC can effectively control tumour progression and prolong the survival time of patients. It is well known that HCC is prone to portal vein metastasis and formation of cancer thrombus, and I noticed that 29 patients (28.43%) developed portal vein tumour thrombosis in this study[5], and TACE combined with lenvatinib combined with PD-1 inhibitor in the treatment of HCC combined with portal vein thrombosis was also efficacious in the study of Zou *et al*[6], which suggests that the combination of all three treatments may be beneficial to more advanced HCC patients[6].

PROSPECTS AND SHORTCOMINGS

For cancer patients, adverse event (AE) adverse medical events and side effects of drug therapy are of concern, in this study, no patient died from AE, most of which were grade 1-2 (62/102, 60.78%) AE without medical intervention, which is a desirable result, which fully confirms the safety of the combination of TACE with lenvatinib and PD-1 in the treatment of HCC. As for the side effects, although it is a combination of three different treatments, the toxicity is not multiply superimposed because the treatment principles of the three are different, hepatic arterial infusion chemotherapy is local administration of chemotherapeutic agents, lenvatinib is anti-angiogenesis, and PD-1 monoclonal antibody is immunotherapy to achieve the synergistic effect of the three on each other. However, it has been reported that the combination of PD-1 and lenvatinib can lead to hand-foot syndrome and hypertension[7]. So whether the combination of

TACE, lenvatinib, and immune-checkpoint inhibitors will increase each other's side effects also needs to wait for more studies to confirm.

Beyond clinical outcomes, the cost implications of combination therapy is a critical consideration. In addition, the cost of combination therapy may be higher, including the cost of drugs, monitoring and management during treatment. However, such costs may be justified if future studies with larger sample sizes confirm that combination therapy significantly increases survival or improves quality of life.

The promising results of this preliminary study pave the way for future research. However, larger-scale, multicentre randomised controlled trials are essential to firmly establish the efficacy and safety of this therapeutic strategy. Conclusively, the combination of lenvatinib with TACE and PD-1 monoclonal antibody represents an innovative and potentially more effective option for treating certain HCC patients. Nonetheless, selecting this treatment should involve careful patient assessment, consideration of therapeutic feasibility, cost-effectiveness, and a joint decision-making process between patients and their healthcare providers.

TACE combined with lenvatinib and PD-1 in the treatment of HCC can effectively control tumour progression and prolong the survival time of patients. We hope that this editorial will raise awareness of triple therapy for advanced liver cancer. This will potentially provide a reliable and effective treatment modality for patients with advanced liver cancer.

CONCLUSION

TACE combined with lenvatinib and PD-1 in the treatment of HCC can effectively control tumour progression and prolong the survival time of patients. We hope that this editorial will raise awareness of triple therapy for advanced liver cancer. This will potentially provide a reliable and effective treatment modality for patients with advanced liver cancer.

FOOTNOTES

Author contributions: Qian NS came up with the idea for the article; Zhao FY carried out the writing of the article; and Wang DY was responsible for revising the article.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

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S-Editor: Wang JJ
L-Editor: A
P-Editor: Zhao S

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