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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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LETTER TO THE EDITOR

Combinations of lenvatinib and immune checkpoint inhibitors plus transarterial chemoembolization, is it the prime time for unresectable hepatocellular carcinoma?

Natalia Centrone, Pedro Luiz Serrano Uson Junior

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Abstract

Hepatocellular carcinoma (HCC) is a lethal disease and unfortunately, most patients will be diagnosed with unresectable/advanced stages and the overall prognosis is poor. For patients with initially unresectable HCC (uHCC), transarterial chemoembolization (TACE) was the mainstream treatment. Lately, the incorporation of immune checkpoint inhibitors and antiangiogenics for the treatment of metastatic disease has paved the way for significant improvements in the treatment of initially uHCC. In this editorial we will discuss an article that evaluated ICI combinations with lenvatinib and TACE for the treatment of uHCC patients, and highlight future advances in the field.

Key Words: Hepatocellular carcinoma; Liver cancer; Lenvatinib; Immunotherapy; Checkpoint inhibitors

Core Tip: Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide and the third most common cause of cancer-related death, accounting for approximately 8% of overall cancer deaths. For patients with initially unresectable HCC (uHCC), transarterial chemoembolization is being evaluated associated with systemic treatments including immune checkpoint inhibitors and antiangiogenics. The synergism of these strategies can improve outcomes for patients deemed unresectable and ineligible for transplantation. In this article we will discuss a very interesting combination evaluated in uHCC patients, and highlight new studies and trials coming forward.

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TO THE EDITOR

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide[1]. However, is the third most common cause of cancer-related death, accounting for approximately 8% of overall cancer deaths[1]. Unfortunately, many patients will be diagnosed with unresectable/advanced stages and the overall prognosis is poor[2]. For patients with initially unresectable HCC (uHCC), transarterial chemoembolization (TACE) was the mainstream treatment[3]. The treatment of uHCC was defined by the Barcelona Clinic Liver Cancer (BCLC) staging, with most cases unfit for liver transplantation or resection included in the BCLC B grade[3]. However, in the few last years, the landscape of the HCC BCLC B patients has dramatically changed[4]. Potent downstaging treatments, with new molecules including immune checkpoint inhibitors and antiangiogenics, associated with local treatments including radiotherapy, TACE and ablation are changing the prognosis and improving survival[4,5]. In this article we will discuss a very interesting combination evaluated in uHCC patients[5].

The article by Ma *et al*[5] assesses the efficacy and safety of a new strategy to treat uHCC, consisting of a combination of the locoregional therapy with TACE, and two first-line systemic treatments, lenvatinib and anti-PD-1 antibodies. This new approach is based on the theory that lenvatinib can modulate vascular endothelial growth factor (VEGF)-mediated immunosuppression, promote cytotoxic T-cell infiltration and inhibit the mechanism of post-TACE recurrence, hypoxia-induced tumor angiogenesis, while the anti-PD-1 antibodies help the patient's immune system to attack the cancer cells, therefore fighting the cancer from multiple angles.

This study consists of a retrospective analysis of 102 patients with uHCC treated with at least one dose of lenvatinib plus anti-PD-1, between March 2019 and April 2022 at the Chinese People's Liberation Army General Hospital (Beijing, China). The included patients were over 18 years old, BCLC stage B or C with an Eastern Cooperative Oncology Group (ECOG) score of 0 or 1. Those with organ disfunctions; other malignances or brain metastasis; previous immunotherapy or treatment with radiotherapy, chemotherapy or thermal ablation within 3 weeks were excluded. The treatment was based on the TACE procedure, according to protocol, followed by the administration of lenvatinib and anti-PD-1 antibodies. TACE consists of intra-arterial injections containing agents to block arterial flow (such as gelatin sponge particles, polyvinyl alcohol particles and polyacrylamide microspheres), causing tumor necrosis, and a high dose of chemotherapy, which maintains a prolonged contact with the tumor while minimizing the systemic effects of chemotherapy[6]. Lenvatinib was administered orally at 12 mg/day for ≥ 60 kg patients or 8 mg/day for patients less than 60 kg; while anti-PD-1 antibodies were administered intravenously at different dosages depending on the drug (for example pembrolizumab 200 mg IV every 3 weeks)[7]. It is important to note that Ma *et al*[5] used five different anti-PD-1 drugs (sintilimab, nivolumab, camrelizumab, pembrolizumab, toripalimab) depending on the patient's choices based on the guideline recommendations and individual financial situation.

The patients were then assessed for tumor responses and adverse events (AE) at a 4 to 8 weeks interval, until death or end of the study, before each treatment or contrast-enhanced computed tomography/magnetic resonance imaging. The median follow-up was 12.63 months, tumor responses were confirmed 4 weeks after the initial evaluation and the alpha fetoprotein level was assessed every 4 weeks. The outcomes of this study were: Tumor response, objective response rate (ORR), disease control rate, median progression-free survival (PFS), median overall survival (OS) and AEs. To evaluate the tumor response, physicians used the modified Response Evaluation Criteria in Solid Tumors, that was then classified into 4 categories: Complete response, partial response, stable disease or progressive disease.

Additionally, PFS was determined by the time between TACE and disease progression of any cause, while OS was defined as the interval between TACE and death/last follow-up. Concurrently, AEs were evaluated based on the Common Terminology Criteria for AE Version 5.0 and examinations. In an attempt to determine the prognostic factors for survival and disease progression, Ma *et al*[5] further analyzed a number of variables including: Sex, age, performance status (0 or 1), BCLC (B or C), etiology (hepatitis B virus or other), tumor size (≤ 6.8 cm or > 6.8 cm), multiple tumors (≤ 3 or > 3), portal vein invasion, extrahepatic metastasis, Child-Pugh (A or B), alpha-fetoprotein (AFP), des-gamma-carboxy prothrombin (DCP), neutrophil-to-lymphocyte ratio (NLR) and lactate dehydrogenase.

The sample consisted mainly of males (87.25%) aged between 34 and 91 years (mean: 57.64 years). Both categories of ECOG and BCLC stage were well and almost equally distributed. Furthermore, chronic hepatitis B virus infection was the prevalent etiology (78.43%), as was Class A Child-Pugh (91.18%). Portal vein tumor thrombosis was observed in 28.43% of patients, 41.18% showed distal metastasis, 48.04% had an AFP level > 400 ng/mL and 87.25% had a DCP level > 40 mAU/mL.

With regard to the safety of this new strategy, 93.13% of the patients developed AEs. Most of the AEs (60.78%) were graded 1-2 (mainly asthenia and hand-foot syndrome). Hypertension and rash were the most common grade 3-4 manifestations. The median PFS of the entire cohort was around 10 months, with an OS of 26.4 months. The ORR was high, with more than half of patients (61.7%) presenting objective responses. Furthermore, as expected, patients with worse BCLC staging presented worse OS. Finally, it was observed that better PFS and OS was related to an early NLR response and AFP response (Table 1).

Table 1 Study summary

Item	Parameter value
Efficacy - clinical outcomes. At the end of the study, 77.45% of the patients were alive, %	
CR	9.80
PR	51.19
SD	19.60
PD	18.62
Objective response rate	61.76
Disease control rate	81.37
Median progression-free survival	10.07 months
Median overall survival	26.43 months
Positive factors related to overall survival	
BCLC stage	B
LDH	≤ 198.52 U/L
Early NLR response	Decrease
Early AFP response	> 20 ng/mL
Positive factors related to progression-free survival	
BCLC stage	B
Early NLR response	Decrease
Early AFP response	> 20 ng/mL

Patients with low tumor burden either at baseline or in response to treatment effects had a better prognosis. CR: Complete response; PR: Partial response; SD: Stable disease; PD: Disease progression; BCLC: Barcelona Clinic Liver Cancer staging; LDH: Lactate dehydrogenase; NLR: Neutrophil-lymphocyte ratio; AFP: Alpha-fetoprotein.

DISCUSSION

This study has some limitations. Importantly, it is a retrospective study with a small sample size from a single center and with a short follow-up. This could indicate a lower generalizability of the results, as only 102 patients were included with a short observation time; thus, it is very unlikely that all types of patients with this condition and possible outcomes are well represented, which in turn, could mean that the study's conclusion does not apply to all patients with this condition. Also, it is important to note that there were five types of anti-PD-1 antibodies used and, as each drug may have its own pharmacodynamic and pharmacokinetic characteristics that could lead to different efficacy rates, the interpretation of the overall effect of this potential new line of treatment could be affected. However, overall, the analysis proved the efficacy and safety of the TACE, lenvatinib and anti-PD-1 antibodies combination for the treatment of uHCC. In addition, compared with other studies, this study presented higher OS and ORR. The better results in terms of survival could be attributed to the super-selection and complete embolization of collateral vessels, the fact that 10 patients received conversion therapy and that many patients underwent various subsequent treatments to improve the OS.

Despite these limitations, the study is very important and is in alignment with the improvements in the treatment of patients with BCLC B uHCC. In the EMERALD-1 trial, the combination of TACE with durvalumab (an anti-PD-L1 antibody) and bevacizumab (an anti-VEGF A antibody) improved PFS *vs* TACE alone, median PFS was 15 months with the combination of TACE-durvalumab-bevacizumab *vs* 8.2 months with TACE alone, with a hazard-ratio (HR) of 0.77, and a *P* value of 0.032, reaching statistical significance[4]. More recently, at ESMO 2024, data from the LEAP 012 trial confirmed these results. Approximately 500 patients with intermediate-HCC were randomized to lenvatinib, pembrolizumab and TACE or placebo plus TACE. At this first interim analysis, median PFS was significantly improved in patients treated with lenvatinib plus pembrolizumab *vs* placebo (HR, 0.66; *P* = 0.0002); 14.6 months *vs* 10.0 months. With 151 events (47.5%), OS is still immature, and data are not published yet. These studies are paving the way for future combinations in uHCC[4]. Investigations into the use of other arterially directed therapies, to compare different types of anti-PD-1 antibodies and to explore the non-inferior relationship between this new proposal and the current regimes recommended by the guidelines will be important.

Finally, it is also important to note, that lenvatinib associated with TACE proved to be superior to lenvatinib alone, in patients with advanced HCC, based on the results of the LAUNCH trial, suggesting an additional effect of the combination of local treatments with lenvatinib, a potent antiangiogenic multi-kinase tyrosine inhibitor[8]. All these data suggest that TACE combined with systemic treatments is an effective strategy to improve ORR and survival in inter-

mediate stage uHCC.

Overall, the results of this study confirm that these combinations should be evaluated in larger cohorts and randomized trials to better understand the best upfront approach for BCLC B uHCC. Multiple randomized phase 3 trials are underway to evaluate potent combinations for uHCC including TACE, such as EMERALD-3 [TACE plus durvalumab, tremelimumab and lenvatinib (NCT05301842)], Checkmate 74W [TACE plus nivolumab and ipilimumab (NCT04340193)], TACE-3 [DEB-TACE plus nivolumab (NCT04268888)] and others. With all these exciting new trials, it seems that the current landscape of treatment for BCLC B HCC patients is already changing.

FOOTNOTES

Author contributions: Centrone N and Serrano Uson Junior PL wrote the article, reviewed and approved the final manuscript.

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