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Lele ZHANG, Jinjian LU

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•Commentary•

Combination strategies for first-line treatment of patients with unresectable hepatocellular carcinoma: prospect of natural products

ZHANG Lele[1*], LU Jinjian[2, 3*]

[1] *School of Basic Medical Sciences, Chengdu University, Chengdu 610106, China;*
[2] *State Key Laboratory of Quality Research in Chinese Medicine, Institute of Chinese Medical Sciences, University of Macau, Macao 999078, China;*
[3] *Department of Pharmaceutical Sciences, Faculty of Health Sciences, University of Macau, Macao 999078, China*

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Liver cancer stands as a significant global health concern, contributing substantially to cancer incidence and mortality, particularly in Asian countries [1]. Hepatocellular carcinoma (HCC) accounts for approximately 90% of all liver cancer cases and is characterized by a high-risk profile and a generally poor prognosis [2]. To address advanced HCC, systemic therapy has been recommended, leading to the approval of a range of treatment regimens in clinical practice. Traditionally, first-line therapy involved the use of multitargeted tyrosine kinase inhibitors (TKIs) such as sorafenib or lenvatinib, while cabozantinib, ramucirumab, or regorafenib were utilized as second-line options [3]. Over the past decade, immunotherapy has revolutionized the therapeutic landscape for various cancer types, particularly through immune checkpoint inhibitors (ICIs) targeting the PD-1/PD-L1 axis. These therapies have achieved unparalleled success due to their ability to provide durable clinical responses and significant survival benefits [4]. As the approval of new first-line and second-line TKIs continues to rise and the field of ICIs-based standard therapies advances, the treatment options for unresectable HCC have diversified significantly. However, it is important to note that the clinical efficacy of current treatment regimens still falls short of expectations, and there remains a pressing need to define optimal systemic therapy regimens for this challenging condition.

The therapeutic efficacy of small molecule TKIs and ICIs faces significant limitations, notably drug resistance and low response rates, respectively [5]. To address these persistent challenges, an increasing number of combination strategies have emerged and been rigorously evaluated for the treatment of various cancers, including unresectable HCC [6, 7]. Alongside established approaches such as radiotherapy, chemoembolization, and other targeted agents, the integration of ICIs with anti-angiogenic drugs has garnered substantial attention over the past five years [8, 9]. This interest is driven by the recognized potential of anti-angiogenic therapy to ameliorate the immunosuppressive tumor microenvironment, consequently enhancing the effectiveness of immunotherapy [10]. Currently, a series of promising phase 3 clinical trials have been conducted to assess the efficacy of combination strategies involving ICIs and anti-angiogenic drugs as first-line treatments for unresectable HCC. In the phase 3 IMbrave150 study, the combination of atezolizumab and bevacizumab exhibited significant improvements in the median progression-free survival (PFS) of unresectable HCC patients, extending it to 6.8 months, compared with the 4.3 months observed with sorafenib. Furthermore, the overall survival (OS) results were striking, with a noteworthy increase to 19.2 months, as opposed to 13.4 months in the sorafenib group. Notably, this first-line regimen gained FDA approval in 2020 [11]. Similarly, findings from the HIMALAYA trial demonstrated that the combination of tremelimumab and durvalumab led to a substantial improvement in the OS of HCC patients compared to those treated with sorafenib [12]. These

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[*Corresponding author] E-mails: zhanglele@cdu.edu.cn (ZHANG Lele); jinjianlu@um.edu.mo (LU Jinjian)
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positive outcomes were further reinforced by the ORIENT-32 trial conducted in China and the global COSMIC-312 trial, both of which confirmed the superior efficacy of PD-1/PD-L1 checkpoint inhibitors combined with anti-angiogenic drugs, in contrast to treatment with sorafenib, for unresectable or advanced HCC [13, 14].

Recently, Prof. QIN and colleagues conducted a clinical evaluation of a combination strategy for unresectable HCC using the anti-PD-1 antibody camrelizumab and VEGFR2-TKI rivoceranib. Their study findings were published in *The Lancet* under the title of "Camrelizumab plus rivoceranib versus sorafenib as first-line therapy for unresectable hepatocellular carcinoma (CARES-310): a randomized, open-label, international phase 3 study" [15]. In this study, 543 patients with unresectable or metastatic HCC, who had not previously undergone systemic therapy, were randomly assigned to receive either camrelizumab–rivoceranib combination therapy or sorafenib monotherapy, with PFS and OS established as the primary endpoints. The results of the study unveiled significant clinical benefits associated with the camrelizumab–rivoceranib combination therapy compared with sorafenib monotherapy. Patients receiving the combination therapy experienced notable increases in median PFS (5.6 months *vs* 3.7 months) and OS (22.1 months *vs* 15.2 months). Furthermore, in comparison with sorafenib monotherapy, the camrelizumab–rivoceranib combination therapy demonstrated a 38% reduction in the risk of death and a 48% reduction in the risk of progression. The OS of 22.1 months achieved with this combination strategy represents a significant milestone, as it is the longest OS reported in randomized, open-label, international phase 3 clinical trials for unresectable HCC to date. Furthermore, the safety profile of this combination strategy proved to be manageable, with no identification of new safety concerns. Briefly, Prof. QIN's work highlights the potential of the camrelizumab–rivoceranib combination therapy as a highly effective first-line therapeutic strategy for patients with unresectable HCC. Based on the positive benefit-to-risk profile observed in this study, the camrelizumab–rivoceranib combination therapy has received approval from the National Medical Products Administration (NMPA) in China for use as a first-line treatment for patients with advanced HCC.

Natural products, owing to their diverse chemical structures and rich sources, have emerged as a valuable resource in the search for novel anticancer candidates [16]. These compounds have displayed exceptional anticancer potential *via* the induction of cytotoxicity, regulation of cancer-driver targets or immune checkpoints, and modulation of immune cells [17]. To date, in the treatment of HCC, several natural products isolated from herbal medicines have shown promise, with some already undergoing clinical evaluation or being licensed for clinical use, such as icaritin, ginsenoside Rg3, and silibinin [18]. Icaritin, an isopentenyl flavonoid glycoside mainly isolated from the famous traditional Chinese medicine *Epimedium brevicornum* Maxim., stands out for its multifaceted anticancer activity against HCC *via* various mechanisms, including the induction of apoptosis, modulation of cell cycle progression, suppression of angiogenesis, inhibition of metastasis, and immunomodulation [19]. Data obtained in phase 3 clinical trials have provided evidence of icaritin's significant improvement in OS for patients with advanced HCC. Consequently, it received approval from NMPA in China in 2022 as a treatment option for patients with unresectable HCC who have not previously undergone systemic therapy. Furthermore, the exploration of novel therapeutic strategies for HCC treatment has gained momentum. Specifically, combining natural products with ICIs or small molecule TKIs emerges as a promising direction. Recent research has highlighted the potential of natural products, such as ginseng polysaccharides and isotoosendanin, in significantly enhancing the efficacy of ICIs, presenting exciting prospects for combination strategies in cancer treatment [20, 21].

Over the past five years, combination strategies involving ICIs and anti-angiogenic drugs, particularly the combination of PD-1/PD-L1 inhibitors and VEGF/VEGFR TKIs, have heralded a paradigm shift in the first-line treatment of advanced HCC. This innovative approach represents a significant milestone in the quest for more effective therapies. As our understanding of the unique features of the tumor microenvironment deepens and prognostic and predictive biomarkers continue to be defined, there is ample cause for optimism regarding the future of HCC treatment. Ongoing research in this field holds great promise, and it is expected that upcoming combination strategies will bring about substantial enhancements in the treatment landscape for unresectable HCC. Moreover, we anticipate that further breakthroughs will emerge in the development and application of natural products, adding another dimension to the arsenal of therapeutic options for this challenging cancer.

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