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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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EDITORIAL

Present and prospect of transarterial chemoembolization combined with tyrosine kinase inhibitor and PD-1 inhibitor for unresectable hepatocellular carcinoma

Rui Zhang, Yan-Hui Liu, Yu Li, Nan-Nan Li, Zheng Li

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Abstract

In this editorial, we comment on the article (*World J Gastrointest Oncol* 2024; 16: 1236-1247), which is a retrospective study of transarterial chemoembolization (TACE) combined with multi-targeted tyrosine kinase inhibitor (TKI) and programmed cell death protein-1 (PD-1) inhibitor for the treatment of unresectable hepatocellular carcinoma (HCC). Herein, we focus specifically on the mechanisms of this triple therapy, administration sequence and selection of each medication, and implications for future clinical trials. Based on the interaction mechanisms between medications, the triple therapy of TACE + TKI + PD-1 is proposed to complement the deficiency of each monotherapy, and achieve synergistic antitumor effects. Although this triple therapy has been evaluated by several retrospective trials, it is still controversial whether the triple therapy achieves better clinical benefits, due to the flawed study design and heterogeneity in medications. In addition, the administration sequence, which may greatly affect the clinical benefit, needs to be fully considered at clinical decision-making for obtaining better prognosis. We hope that this editorial could contribute to the

design and optimization of future trials.

Key Words: Transarterial chemoembolization; Multi-targeted tyrosine kinase inhibitor; Programmed cell death protein-1 inhibitor; Unresectable hepatocellular carcinoma; Mechanism

Core Tip: This editorial focuses on the mechanisms for combining transarterial chemoembolization with multi-targeted tyrosine kinase inhibitor and programmed cell death protein-1 inhibitor for unresectable hepatocellular carcinoma, administration sequence and selection of each medication, and implications for future clinical trials. Despite several retrospective trials have evaluated the efficacy and safety of this triple therapy, the flawed study design and heterogeneity in medications still arise controversial concerns on the results. Especially, the administration sequence between each medication varied across trials, which could greatly affect the clinical benefit. So, the administration sequence needs to be fully considered in future trials based on the interaction mechanisms between each medication.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common and lethal form of liver cancer[1]. Different treatment modalities have been developed for HCC at different stages. Based primarily on the Barcelona Clinic Liver Cancer (BCLC) staging system, liver transplantation/hepatectomy/local ablation are preferred options for early-stage HCC, transarterial chemoembolization (TACE) is recommended for intermediate-stage HCC, and systemic therapy is the mainstay for advanced HCC[2,3]. Due to the latent property, most HCC is not diagnosed until it is unresectable, making TACE and systemic therapy the only feasible options for most patients.

In practice, TACE is frequently performed across all disease stages, not only HCC at BCLC-B stage[4]. Moreover, systemic therapy is recommended for HCC at BCLC-B stage with extensive bilobar liver involvement and BCLC-C stage. Sorafenib, a multi-targeted tyrosine kinase inhibitor (TKI), became the first effective systemic agent for advanced HCC in 2008[5]. Afterwards, other TKIs, such as lenvatinib and regorafenib, were demonstrated effective for advanced HCC[6,7]. Recently, immune checkpoint inhibitors (ICIs) have shown robust efficacy in the first-line or second-line settings, especially programmed cell death protein-1 (PD-1) inhibitors[8,9]. Indeed, these therapy options have exhibited clinical benefit to patients with unresectable HCC, however, the efficacy of mono-therapy with TACE, TKI or PD-1 inhibitor remains unsatisfactory. Thus, combination treatment exerting synergistic antitumor effects is a promising strategy for achieving improved clinical outcomes[10]. For instance, TACE plus TKI have been evaluated for unresectable HCC by many trials[11], as well as TKI in combination with PD-1 inhibitor[12]. Furthermore, as a potential combination scheme, the triple therapy consisting of TACE + TKI + PD-1 inhibitor has been increasingly evaluated for unresectable HCC.

MECHANISMS OF TACE + TKI + PD-1 INHIBITOR FOR HCC

TACE deprives tumor cells of nutrient supply and concentrates chemotherapeutic agents at tumour site, thus inducing necrosis and apoptosis of tumor cells. Whereas, it hardly guarantees a complete tumour death, meanwhile triggers the deterioration liver function[13]. In addition, TACE aggravates hypoxia in tumor tissues, thus enhancing the expression of hypoxia inducible factor-1α, which in turn upregulates the expression of vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF). These increased growth factors consequently promote tumor angiogenesis, which takes major responsibility for tumor regrowth and extra-hepatic metastasis[14,15]. Naturally, then, this offers a clue that inhibition of VEGF/PDGF receptors may block the effects of proangiogenic factors.

TKIs can inhibit a number of serine/threonine and tyrosine kinases, such as VEGF and PDGF receptor, thereby exerting both anti-angiogenic and direct antitumour effects[14,16]. Therefore, the combination of TACE with TKI is designed to counteract the proangiogenic effect of TACE, meanwhile exert synergistic anti-tumor effects arisen from different action mechanisms[11]. On the one hand, all TKIs with proven efficacy in HCC inhibit VEGF signaling pathway, while anti-VEGF therapy can induce tumuor hypoxia[17]. To sum up, both TACE and TKI can lead to hypoxia in tumor. Hypoxia supports immunosuppression to aid tumor immune escape, especially by upregulating immune checkpoint molecules[18], for instance, up-regulated PD-L1 expression induced by sorafenib[19]. Therefore, there is a rationale for combining TKI with ICI.

In recent years, the advent of ICIs, including the PD-1 and programmed death-ligand 1 (PD-L1), have gradually shifted the direction of research to immunotherapy. Especially, the combination of atezolizumab and bevacizumab have recently outperformed sorafenib as the first-line treatment[20]. ICIs can prevent the recognition escape of tumor cells and reactivate immune responses in the tumor microenvironment, thereby enable T cells to identify and kill tumor cells. So, ICIs can antagonize the immunosuppressive effects caused by TKIs. In turn, TKIs have also been found to enhance the antitumor sensitivity of PD-1 inhibitors[21]. Indeed, TKI in combination with PD-1 inhibitor have been demonstrated to improve anti-tumor efficacy, such as prolonged overall survival (OS)[12]. Additional, TACE-induced necrosis increase the release of tumor antigens, which may further increase the efficacy of immunotherapy[22]. Overall, the combination treatment scheme consisting of TACE, TKI and PD-1 inhibitor is proposed with expectation to complement the deficiency of each monotherapy, and achieve synergistic antitumor effects.

ADMINISTRATION SEQUENCE AND SELECTION OF EACH MEDICATION

Only in recent years, the triple therapy of TACE + TKI + PD-1 inhibitor has been evaluated for its efficacy and safety in unresectable HCC by clinical trials (Table 1). In the study by Qin *et al*[23], TACE + TKI + PD-1 was found to significantly extended progression-free survival (PFS) and increased disease control rate (DCR) as compared to TACE + PD-1, but no significant difference in OS and objective response rate (ORR). For treatment procedure, several chemotherapeutic agents were used in TACE. Concurrent sorafenib and PD-1 inhibitor (sintilimab or camrelizumab) were administered on day 4 after the initial TACE, and then sorafenib at a 4–7-day interval before and after each subsequent TACE. By contrast, in the study of Chen *et al*[24], pembrolizumab and lenvatinib were administered before initiating TACE in which only pharmorubicin was used as the chemotherapy drug. Patients received triple therapy showed significantly longer OS and PFS than that in duplex group (TACE + TKI). Subsequently, Wang *et al*[25] reported a retrospective trial indicating that triple therapy was superior to TKI + PD-1 regarding OS, PFS, ORR and DCR. The treatment procedure differed from the above two trials. Patients received TKI (lenvatinib) after initial TACE, then PD-1 (pembrolizumab, camrelizumab, or sintilimab) within 7 days of initial TKI. The latest retrospective trial by Ma *et al*[26], reported the encouraging efficacy of triple therapy in patients, especially the longest OS (26.43 months) among mentioned trials. In this trial, TACE was initiated before the administration of lenvatinib or PD-1 inhibitors.

In summary, most of the above trials have shown encouraging results of the triple therapy in unresectable HCC, such as extended PFS and OS. The administration sequence of TACE + TKI + PD-1 varied across trials, which may affect the outcomes. Likewise, the selection of each medication was also flexible, especially the diverse PD-1 inhibitors. However, the limitations existed in them may impair the robustness. For instance, all these trials are retrospective, and the sample sizes are small. Therefore, it is still controversial whether triple therapy achieves a better prognosis for patients, meanwhile the randomized controlled trials on large populations are of requisite.

IMPLICATIONS FOR FUTURE CLINICAL TRIALS

TKI administration is scheduled to suppress tumour angiogenesis induced by TACE, thus administration timing is a key factor affecting efficacy. Since it has been reported that serum VEGF reaches maximum concentration on day 1 after TACE[14], immediate administration after TACE or even pretreatment of TKI could contribute to favorable clinical outcomes[11]. Moreover, TACE can increase the release of tumor antigens, thereby contributing to tumor-specific immune response. So, it may favor that scheduling the administration of PD-1 inhibitors closing to TACE to make the most of an immune support environment induced by TACE. Therefore, the administration sequence between TACE, TKI and PD-1 inhibitor is an important variable affecting the clinical benefit, which needs to be fully considered in future trials.

Most trials are single-center studies and limited by the relatively small sample size. Future studies should be multicentered and conducted on large populations. In addition, the varied kinds of each medication may affect the consistency of treatment regimens. The agents used in each therapy should be consistent or well balanced, and subgroup analysis should be conducted if needed in future trials. Although most trials are double-arm studies, the control arms across trials are differed, *i.e.*, TACE + TKI, TACE + PD-1, TKI + PD-1. The control arm should be carefully designed in future trials since it contributes significantly to the results.

CONCLUSION

This work introduces the interaction mechanisms of TACE + TKI + PD-1 inhibitor, reviews the administration sequence and selection of each medication across trials, and discusses the implications for future clinical trials. We hope that this editorial could contribute to the design and optimization of future trials.

Table 1 Characteristics of clinical trials evaluating the transarterial chemoembolization combined with multi-targeted tyrosine kinase inhibitor and programmed cell death protein-1 inhibitor for unresectable hepatocellular carcinoma

Ref.	Study design	Sample size	Hepatocellular carcinoma stage	TACE	TKI	PD-1	Administration sequence	Outcomes
Qin *et al* [23], 2022	Retrospective, double-arm	25 (TACE + TKI + PD-1) *vs* 41 (TACE + PD-1)	Advanced	Pirarubicin, epirubicin, loplatin, raltitrexed	Sorafenib	Sintilimab or camrelizumab	TKI+PD-1 after initial TACE, TKI before and after each subsequent TACE *vs* PD-1 after initial TACE	OS: 21.63 months *vs* 16.43 months, P = 0.103; PFS: 7.63 months *vs* 2.9 months, P = 0.034; ORR: 59.09% *vs* 50%, P = 0.761; DCR: 95.45% *vs* 72.72%, P = 0.095
Chen *et al* [24], 2022	Retrospective, double-arm	70 (TACE + TKI + PD-1) *vs* 72 (TACE + TKI)	Unresectable	Pharmorubicin	Lenvatinib	Pembrolizumab	TKI+PD-1 before initial TACE *vs* TKI before initial TACE	OS: 18.1 months *vs* 14.1 months, P = 0.004; PFS: 9.2 months *vs* 5.5 months, P = 0.006
Wang *et al* [25], 2023	Retrospective, double-arm	46 (TACE + TKI + PD-1) *vs* 59 (TKI+PD-1)	Unresectable	Epirubicin, raltitrexed, oxaliplatin	Lenvatinib	Pembrolizumab, camrelizumab, or sintilimab	TKI after initial TACE, then PD-1 within 7 days of initial MKI *vs* TKI+PD-1	OS: 20.5 months *vs* 12.6 months, P = 0.015; PFS: 10.2 months *vs* 7.4 months, P = 0.035; ORR: 54.3% *vs* 25.4%, P = 0.002; DCR: 82.6% *vs* 64.4%, P = 0.038
Ma *et al* [26], 2024	Retrospective, single-arm	102 (TACE + TKI + PD-1)	Unresectable	Epirubicin, oxaliplatin, 5-fluorouracil, calcium folinate	Lenvatinib	Sintilimab, nivolumab, camrelizumab, pembrolizumab, toripalimab	TKI+PD-1 after initial TACE	OS: 26.43 months; PFS: 10.07 months; ORR: 61.76%; DCR: 81.37%
Dong *et al* [11], 2023	Retrospective, double-arm	228 (TACE + MKI + PD-1) *vs* 228 (TACE)	Unresectable	NA	Sorafenib, lenvatinib, donafenib, regorafenib, apatinib, anlotinib, bevacizumab	Atezolizumab, pembrolizumab, nivolumab, camrelizumab, sintilimab, tislelizumab, toripalimab	PD-1 at least 3 days before or after TACE, TKI within two weeks before or after TACE	OS: 19.2 months *vs* 15.7 months, P = 0.037; PFS: 9.5 months *vs* 8.0 months, P = 0.015; ORR: 60.1% *vs* 32.0%, P < 0.001

DCR: Disease control rate; TACE: Transarterial chemoembolization; TKI: Tyrosine kinase inhibitor; PD-1: Programmed cell death protein-1; MKI: Multikinase inhibitors; OS: Overall survival; ORR: Objective response rate; PFS: Progression-free survival.

FOOTNOTES

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