Review

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Effect of transcatheter arterial chemoembolization combined with lenvatinib plus anti–PD-1 antibodies in patients with unresectable hepatocellular carcinoma: A treatment with Chinese characteristics

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SUMMARY Therapies for patients with unresectable hepatocellular carcinoma (uHCC) are currently popular. Current first-line standard-of-care treatments for uHCC are systematic therapies. However, treatments that combine locoregional therapy with systemic therapy are widely accepted in China and have demonstrated high rates of tumor response and conversion to resection with manageable toxicity. A literature review was performed by searching published literature in PubMed and Web of Science up to December 2023 for relevant articles on the use of triple therapy (transarterial chemoembolization combined with lenvatinib and anti–PD-1 antibodies) in uHCC. This review concentrates on the efficacy and safety of triple therapy with Chinese characteristics in patients with uHCC and describes the outcome of conversion surgery, degree of pathological necrosis, and effect prediction. This article will contribute to a comprehensive understanding of the role of triple therapy with Chinese characteristics in patients with uHCC.

Keywords hepatocellular carcinoma (HCC), conversion therapy, transcatheter arterial chemoembolization, lenvatinib, programmed death-1

1. Introduction

Because of the insidious onset of hepatocellular carcinoma (HCC), unresectable HCC (uHCC) accounts for a large proportion of cases (*1,2*). In general, there are two main types of uHCC: surgically and oncologically unresectable (*3*). The definition of surgically uHCC is widely accepted and includes cases where R0 resection cannot be achieved due to extrahepatic metastasis, bilobar tumor locations, main vascular invasion, insufficient residual liver volume, and poor general condition or liver function. However, the definition of oncologically uHCC varies and is controversial; it includes cases that may be technically resectable but have a high risk of recurrence, precluding them from benefitting from surgery. Most references to uHCC usually refer to surgically uHCC.

Recent progress in systematic therapy, the primary treatment for uHCC, and especially the success of the REFLECT and IMBRAVE 150 trials *(4,5*), has greatly improved the treatment of uHCC. The Barcelona Clinic Liver Cancer (BCLC) staging system recommends atezolizumab-bevacizumab/durvalumab-tremelimumab as the first-line standard-of-care treatments for uHCC; if this treatment is not feasible, sorafenib, lenvatinib, or durvalumab is considered (*1*). As shown in Table 1, first-line systemic treatment for uHCC improves prognosis, with a median overall survival (OS) of 6.4–22.1 months and progression-free survival (PFS) of 2.1–7.3 months (*4-12*). However, the outcomes have not been satisfactory.

In China, locoregional therapy (LRT), and especially transcatheter arterial chemoembolization (TACE), plays a critical role in managing patients with uHCC and is widely used for intermediate- and advanced-stage HCC (*13*). LRT combined with systemic therapy has yielded impressive outcomes. The CHANCE 001 study (*14*), a multicenter retrospective matched-cohort study of patients with uHCC from 59 academic hospitals across 22 provinces in China, found that combining TACE with anti–programmed death-(ligand) 1 (anti–PD-[L]1) antibodies and molecular targeted treatments (MTT) significantly improved the objective response rate (ORR),

Table 1. First-line systemic treatment for uHCC

Study (*Ref.*)	Regimen	Number of patients	Main characteristics of patients	mOS (months)	mPFS (months)	ORR (RECIST 1.1)	DCR (RECIST 1.1)	Treatment-related adverse effects grade 3/4
SHARP (*6*)	Sorafenib *vs.* placebo	299 *vs.* 303	BCLC-B/C	10.7 *vs.* 7.9	5.5 *vs.* 2.8	2% *vs.* 1%	43% *vs.* 32%	52% *vs.* 54%
REFLECT (*4*)	Lenvatinib *vs.* Sorafenib	478 *vs.* 476	BCLC-B/C	13.6 *vs.* 12.3	7.3 *vs.* 3.6	18.8% *vs.* 6.5%	72.8% *vs.* 59.0%	57% *vs.* 49%
IMbrave150 (*5*)	Atezolizumab-Bevacizumab *vs.* Sorafenib	336 *vs.* 165	BCLC-A/B/C	19.2 *vs.* 13.4	6.8 *vs.* 4.3	27.3% *vs.* 11.9%	73.6% *vs.* 55.3%	56.5% *vs.* 55.1%
HIMALAYA (*7*)	Tremelimumab-Durvalumab *vs.* Sorafenib	393 *vs.* 389	BCLC-B/C	16.4 *vs.* 13.8	3.8 *vs.* 4.1	20.1% *vs.* 5.1%	60.1% *vs.* 60.7%	50.5% *vs.* 52.4%
HIMALAYA (*7*)	Durvalumab *vs.* Sorafenib	389 *vs.* 389	BCLC-B/C	16.6 *vs.* 13.8	3.7 *vs.* 4.1	17.0% *vs.* 5.1%	54.8% *vs.* 60.7%	37.1% *vs.* 52.4%
EACH (*8*)	FOLFOX4 *vs.* Doxorubicin	184 *vs.* 187	BCLC-B/C	6.40 *vs.* 4.97	2.93 *vs.* 1.77	8.15% *vs.* 2.67%	52.17% *vs.* 31.55%	55.74% *vs.* 45.40%
ZGDH3 (*9*)	Donafenib *vs.* Sorafenib	328 *vs.* 331	BCLC-B/C	12.1 *vs.* 10.3	3.7 *vs.* 3.6	4.6% *vs.* 2.7%	30.8% *vs.* 28.7%	57% *vs.* 67%
RATIONALE-301 (*10*)	Tislelizumab *vs.* Sorafenib	342 *vs.* 332	BCLC-B/C	15.9 *vs.* 14.1	2.1 *vs.* 3.4	14.3% *vs.* 5.4%	44.2% *vs.* 50.3%	22.2% *vs.* 53.4%
CARES-310 (*11*)	Camrelizumab-Rivoceranib *vs.* Sorafenib	272 *vs.* 271	BCLC-B/C	22.1 *vs.* 15.2	5.6 *vs.* 3.7	25% *vs.* 6%	78% *vs.* 54%	81% *vs.* 52%
ORIENT-32 (*12*)	Sintilimab plus IBI305 *vs.* Sorafenib	380 *vs.* 191	BCLC-B/C	NR *vs.* 10.4	4.6 *vs.* 2.8	21% *vs.* 4%	72% *vs.* 64%	53% *vs.* 45%

Abbreviations: OS, overall survival; PFS, progression-free survival; ORR, objective response rate; RECIST, response evaluation criteria in solid tumors; DCR, disease control rate; BCLC, Barcelona clinic liver cancer; NR, not reached.

PFS, and OS compared to TACE alone in patients with predominantly advanced HCC. A systematic review and meta-analysis (*15*) also confirmed that combining MTT with anti–PD-1 antibodies and LRT is an effective conversion therapy regimen with a significant ORR, conversion potential, and satisfactory safety profile.

Because of the heterogeneity of MTT, the current study focused on the triple therapy of TACE combined with lenvatinib (an MTT) plus anti–PD-1 antibodies. Searches on PubMed and Web of Science conducted on December 1, 2023 revealed that all articles on triple therapy were written by Chinese researchers (*16-39*). Therefore, this review aims to explain triple therapy with Chinese characteristics and to examine its role in managing uHCC.

2. Triple therapy in unresectable HCC

In 2021, the first-line efficacy of triple therapy for uHCC was analyzed based on triple therapy's clinical presentation (*16*). The study enrolled 62 patients with initial uHCC from four centers in China: 35, 21, and 6 patients with BCLC stages C, B, and A, respectively. Based on the modified Response Evaluation Criteria in Solid Tumors (mRECIST), the ORR was 80.6% per investigator and 77.4% per blinded independent central review. Twenty-nine patients underwent conversion surgery with a median follow-up time of 12.2 months. A pathological complete response (PCR) and major pathological response (MPR) were achieved in 16 and 24 patients, respectively. Because of the relatively short follow-up time, the median PFS and OS times were not reached.

As shown in Table 2 (Online Data: *http://www.biosciencetrends.com/action/getSupplementalData.php?ID=185*), triple therapy resulted in an ORR of 26.1–87.2%, disease control rate (DCR) of 70–100%, median PFS of 6.3–22.5 months, and median OS of 15.7–29 months. Despite a lack of final results from randomized controlled phase III trials, triple therapy was found to be effective, with a median OS comparable to that of current first-line treatment regimens.

Triple therapy in uHCC with portal vein tumor thrombosis. Portal vein tumor thrombosis (PVTT) is a dismal prognostic factor for HCC, with a median survival period of 2.7–4.0 months without treatment (*40*). Despite the short survival, triple therapy's effectiveness was able to be determined in patients with HCC and main trunk PVTT. Our retrospective study (*37*) enrolled 41 patients with main trunk PVTT who received triple therapy as the first-line therapy. The intrahepatic tumor ORR was 68.3% (5 complete responses [CR] and 23 partial responses [PR]) per mRECIST. PVTT was considered to have regressed in 8 patients, and 4 patients had complete necrosis. After a median follow-up of 18 months, the median PFS was 14.5 (range 1.3–27.6) months, and the median OS was 21.7 (range 2.8–30.5) months; 12

patients (29.3%) underwent conversion surgery. Of the 12 patients, three had an intrahepatic tumor PCR and seven had a PVTT PCR as determined by a pathological examination of the resected specimen.

Two studies (Zou *et al*. and Li *et al*.) analyzed triple therapy's safety and clinical efficacy in patients with uHCC and PVTT. In the study by Zou *et al*. (*36*), patients with uHCC and PVTT (53.75% PVTT type I, 46.25% type II/III/IV, per Cheng's classification) after triple therapy had a median OS of 21.7 months and a PFS of 6.3 months. The multicenter prospective study by Li *et al* (39). enrolled 69 patients with uHCC and PVTT (13% PVTT type I, 87% PVTT type II/III/IV, per Cheng's classification). After a median follow-up of 17.3 months, the ORR was 26.1%, and the DCR was 78.3% per mRECIST. The median PFS and OS were 9.3 and 18.2 months, respectively.

Although patients with HCC and PVTT have poor prognoses, promising results are obtained after triple therapy.

3. Triple therapy in conversion surgery

Although participants' baseline characteristics and the definition of conversion to resectable HCC varied among studies, conversion rates were 25–50%, based on the good ORR performance of triple therapy (*16-19*).

A meta-analysis (*15*) evaluating the efficacy and safety of different conversion regimens found that combining LRT and MTT plus anti–PD-1 antibodies resulted in a significantly greater conversion rate (33%, 95% confidence interval [CI] 17–52%) than combinations of LRT and MTT without anti–PD-1 antibodies (12%, 95% CI: 8–17%; $P = 0.01$).

The prognosis after conversion surgery was also a topic worthy of attention. Therefore, we conducted a study that enrolled patients with uHCC who received first-line triple therapy and underwent conversion surgery at five major cancer centers in China (*41*). Ultimately, the study included 70 patients. After a median follow-up of 12.9 months, the 1-year recurrence-free survival (RFS) and OS rates were 68.9% and 97.1%, respectively; the 2-year RFS and OS rates were 54.4% and 94.4%, respectively. The prognosis for patients undergoing conversion surgery was similar to that of patients with initially resectable intermediate-stage HCC (*1,13*).

4. Pathological results of triple therapy

The pathological results of conversion surgery after triple therapy were notable. In our study of conversion surgery (*41*), a PCR after triple therapy was observed in 29 (41.4%) patients and an MPR in 59 patients (84.3%). Achieving a PCR was associated with a favorable RFS (hazard ratio [HR] = 0.113, 95% CI: 0.031–0.409, $P =$ 0001). In other studies (*42,43*) on the degree of tumor necrosis after conversion therapy, an MPR or PCR was suggested to improve the prognosis for conversion surgery. Deep tumor cell necrosis after triple therapy may reduce the risk of recurrence.

Based on the triple therapy responses, many patients had a PCR. Since patients had a CR, whether conversion surgery remains necessary was questionable. Therefore, a clinical study (*44*) was conducted to determine whether conversion surgery offers prognostic advantages for patients with uHCC with a clinical complete response (cCR) after conversion therapy. A cCR was defined as 1) serum tumor marker normalization (α-fetoprotein [AFP] < 7 ng/mL and des-gamma-carboxyprothrombin [DCP] < 40 mAU/mL) for ≥ 4 weeks and 2) radiographic CR per mRECIST for ≥ 4 weeks. Ultimately, the study included 74 patients who had cCR; 52 (70.3%) received triple therapy as described in this review. Propensity score matching (PSM) was performed to minimize the influence of potential confounders. Before PSM, 45 patients (60.8%) underwent conversion surgery; 29 (39.2%) received nonsurgical treatment. No statistically significant differences in disease-free survival (DFS) or OS were noted between the two cohorts (HR = 0.715, 95% CI: 0.250–2.043, $P = 0.531$; HR = 0.980, 95% CI: 0.177–5.418, $P = 0.982$, respectively). After PSM, 26 pairs of patients were matched; no significant differences in DFS and OS were noted between the two cohorts (HR = 1.547, 95% CI: 0.51–4.669, $P = 0.439$; HR = 1.024, 95% CI: 0.168–6.242, $P = 0.979$, respectively). This finding suggests that conversion surgery may not be essential for patients with uHCC with cCR.

5. Prognostic prediction of triple therapy

Despite a high ORR, some patients experience disease progression. Therefore, the early prediction of the prognosis for triple therapy is important.

ORR and OS are closely related; therefore, a nomogram model was developed to predict early ORR in patients with uHCC receiving triple therapy after 3 months (*45*). The ORR was 60.9%, and early ORR was predicted independently by AFP, PVTT, tumor number, and tumor size. The nomogram model was highly consistent and clinically useful in the training cohort (C-index = 0.853, 95% CI: 77.50–93.07%). These findings were confirmed in an external validation cohort from three cancer centers in China (C-index = 0.800, 95% CI: 63.52−87.83%).

Moreover, we found that AFP and DCP responses at 6 weeks were predictors for patients with uHCC receiving triple therapy (*46*). After 6 weeks of triple therapy, a > 50% reduction in AFP or DCP levels predicted better treatment outcomes. However, predicting outcomes by the responses of tumor markers remains problematic. Therefore, a prognostic scoring model based on pretreatment baseline levels was developed to predict

outcomes and facilitate earlier treatment decisions (*47*). Patients who received triple therapy at eight centers in China were assigned to training (n = 126) and validation cohorts (n = 84). Baseline patient demographics were collected. In a multivariate analysis, TAE scores (total bilirubin ≥ 17 μmol/L, AFP ≥ 400 ng/mL, and extrahepatic metastasis) were independent predictors of survival in the training cohort. The TAE scoring model was calculated by summing the scores of each of these 1-point risk factors and categorizing the results into three groups: favorable (0 points), intermediate (1 point), and dismal (2–3 points). The TAE score predicted the OS of patients who received triple therapy in both the training (C-index = 0.738, 95% CI: 0.640–0.836) and validation cohorts (C-index = 0.771, 95% CI: 0.689–0.853). The TAE score also stratified PFS well in the training and validation cohorts.

6. The mechanism of triple therapy

Many researchers have sought to explain the potential mechanism of triple therapy (*48-50*). Anti–PD-1 antibodies inhibit the binding of PD-1 and PD-L1, leading to antitumor action by restoring the activity of T cells (*51*). TACE leads to ischemia and tumor tissue necrosis *via* transarterial embolization, and converting "cold" tumors to "hot" tumors by releasing tumor-specific antigens that further enhance the anti-tumor efficacy of anti–PD-1 antibodies. However, a hypoxic microenvironment caused by TACE leads to upward regulation of hypoxia-inducible factor-1, vascular endothelial growth factor, and platelet-derived growth factor receptor, resulting in tumor angiogenesis and progression (*48,52,53*). Lenvatinib is a multi-kinase inhibitor of vascular endothelial growth factors 1-3, fibroblast growth factor receptors 1-4, platelet-derived growth factor receptor alpha, RET, and KIT, which modifies hypoxia and immunosuppression tumor microenvironments by normalizing tumor blood vessels while also enhancing the efficacy of TACE and PD-1 antibodies (*4,54*). The mechanism of triple therapy is complex and synergistic and requires further study to advance our understanding.

7. Treatment-related adverse effects

In addition to the effectiveness of the triple therapy, treatment-related adverse effects (TRAEs) should be considered. Currently, the incidence of grade 3/4 TRAEs in first-line therapy is as high as 37.1–57% (Table 1); the incidence of TRAEs in triple therapy is similar (Table 2). In retrospective cohort studies, no statistically significant differences were noted in the incidence of TRAEs between the triple therapy group and the dual therapy or monotherapy group (*18,19,25-36*).

Identifying the cause of a patient's TRAEs is important since it affects the patient's treatment plan. The most common TRAEs of lenvatinib were hypertension, diarrhea, decreased appetite, and weight loss (*4*). The common TRAEs of TACE included post-thrombotic syndrome (fever, nausea, vomiting, and abdominal pain), liver function damage, allergic reactions, and ectopic embolism (*55*). However, immune toxicities related to the anti–PD-1 antibodies were more extensive (*56*), including almost every organ or system: the skin, endocrine glands (abnormal thyroid function, hypophysitis, primary adrenal insufficiency, type 1 diabetes), lungs (pneumonitis), the gastrointestinal tract (enterocolitis), liver, nervous system, heart, and kidneys. Therefore, scientific monitoring, early detection, correct identification, and effective treatment of TRAEs are very important and could maximize the survival and quality of life for patients with uHCC.

8. Potential problems in triple therapy

Triple therapy has shown promising antitumor activity as a first-line treatment for patients with uHCC; however, several problems remain unsolved. First, triple therapy is not a first-line treatment option because of the lack of randomized phase-III case-controlled trials. Second, combination therapy is not always better than monotherapy. The Leap 002 study (*57*) found that although combining lenvatinib and pembrolizumab showed promising clinical outcomes for uHCC, the OS and PFS for the combination did not meet the prespecified statistical significance compared to lenvatinib monotherapy. Third, triple therapy treatment has Chinese characteristics; the patients in these studies were diagnosed predominantly with hepatitis B virus–related HCC. Therefore, whether triple therapy is as effective for other HCC etiologies requires further investigation. Fourth, the triple therapy in this study combined LRT and MTT plus anti–PD-1 antibodies; the effect of combining other types of LRT or MTT requires further research.

9. Conclusion

Triple therapy shows good clinical outcomes and improves outcomes in patients with uHCC because of its strong antitumor action. However, prospective clinical studies are required to validate triple therapy's effects and provide promising guidance for clinical treatment.

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