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Original Article

Efficacy and safety of transcatheter arterial chemoembolization combined with sorafenib and sintilimab in the treatment of unresectable hepatocellular carcinoma

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Abstract: Objective: To investigate the efficacy and safety of transcatheter arterial chemoembolization (TACE) combined with sorafenib and sintilimab in the treatment of unresectable hepatocellular carcinoma (HCC). Method: This study retrospectively analyzed the clinical data from 50 patients with unresectable HCC treated at Yunhe County People's Hospital of Zhejiang Province from January 2023 to December 2023. The patients were divided into two groups according to treatment regimen: a control group (n=20) treated with TACE alone, and a combination group (n=30) treated with TACE combined with sorafenib and sintilimab. Baseline data, changes in hematological parameters before and after treatment, objective response rate (ORR), disease control rate (DCR), and prognosis were compared between the two groups. Besides, the progression-free survival (PFS) and overall survival (OS) time were also compared between the two groups. Result: The combination group demonstrated significantly lower AFP levels compared to the control group (789.44±23.55 ng/l vs. 1244.65±36.85 ng/l, P<0.05). The ORR and DCR of the combination group were notably higher than those of the control group (56.67% vs. 25.00%, P<0.05; 83.33% vs. 55.00%, P<0.05, respectively). The median PFS and OS of the combined group were significantly longer than those of the control group (12.86 months vs. 5.72 months, P=0.007; 15.63 months vs. 7.05 months, P=0.001, respectively). Moreover, there were no significant differences in grade 1-2 adverse events between the two groups, while the incidence of grade 3 adverse events was significantly lower in the combination group compared to the control group (P<0.05). Conclusion: Our results suggest that the combination of TACE with sorafenib and sintilimab is a feasible treatment option for patients with unresectable HCC, with high efficacy and reasonable safety.

Keywords: Hepatocellular carcinoma, transarterial chemoembolization, sorafenib, sintilimab

Introduction

Liver cancer is a malignant tumor that poses a serious threat to health and life. In China, it has a high incidence rate, accounting for over 50% of cases worldwide [1]. There are two main types of liver cancer: primary hepatocellular carcinoma and intrahepatic cholangiocarcinoma. The former originates from liver cells, while the latter originates from bile duct wall cells. Both types are primarily caused by liver cirrhosis resulting from hepatitis B or C. In the early stages, patients may not exhibit any noticeable symptoms. However, as the disease progresses, patients may experience fatigue, liver pain, weight loss, skin jaundice, hepatomegaly, and other symptoms. By this time, many patients have developed vascular invasion, making surgical resection impossible and eventually progressing to unresectable hepatocellular carcinoma (HCC) [2].

Patients with unresectable HCC can be treated with transcatheter arterial chemoembolization (TACE), provided they have normal liver function. Specifically, chemotherapeutic drugs and embolic agents are directly injected into the tumor artery in the liver through a catheter. This approach allows the chemotherapeutic drugs to directly act on the tumor, improving the therapeutic effect but reducing the adverse reactions caused by drugs [3]. For patients with

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severe liver dysfunction and distant metastasis who are unable to undergo surgical resection, molecular targeted drugs may be selected for treatment, with sorafenib being the most used first-line targeted drug. Sorafenib can directly inhibit the proliferation of tumor cells, block tumor neovascularization, and indirectly inhibit the growth of tumor cells [4]. However, the objective response rate (ORR) of unresectable HCC treated with targeted drugs such as sorafenib alone is low. Therefore, more effective treatment options are needed in clinical practice [5].

In the past decade, studies found that sintilimab offers high affinity and a durable, stable drug effect. By binding to PD-1 and blocking its interaction with PD-1 with PD-L1/PD-L2, sintilimab can relieve immunosuppression, enhance the immune surveillance and killing ability of T cells, and trigger tumor immune responses. PD-1 medicines activate the body's immune system to find and attack cancer cells. They are broad-spectrum drugs effective against multiple metastatic tumor cells in the body, providing significant therapeutic benefits. As a result, they have become one of the treatment options for unresectable HCC [6]. However, patients treated with TACE, sorafenib or sintilimab alone may experience disease progression outside the target volume. Therefore, we evaluated the safety and efficacy of TACE combined with sorafenib and sintilimab in the treatment of patients with unresectable HCC.

Methods

Patient inclusion

The clinical data of 50 patients with unresectable HCC diagnosed at Yunhe County People's Hospital of Zhejiang Province from January 2023 to December 2023 were retrospectively analyzed. The patients were divided into two groups according to their treatment mode: a control group (n=20), treated with TACE alone, and a combined group (n=30), treated with TACE combined with sorafenib and sintilimab.

Inclusion Criteria: Patients aged 28 to 68 years, all meeting the Expert Panel Opinion on Interventions in Hepatocellular Carcinoma (EPOIHCC) expert consensus [7]; Patients with primary lesion evaluated by imaging Modified RECIST (mRECIST) criteria [8]; Patients with physical strength score of 0-2 points; Patients with expected survival more than 3 months.

Exclusion criteria: Patients with indeterminate diagnosis or lesions considered resectable; Patients with common adverse reactions to tumor treatment of grade II or above, myocardial ischemia or myocardial infarction, and/or standard cardiac function grade II-IV; Patients with other systemic malignancies; Patients who had received prior TACE treatment; Patients with brain metastases, severe coagulation disorders, or hematologic diseases; Patients allergic to either of the mentioned drugs; Pregnant or lactating women.

Treatments

TACE in control group: (1) The patient was placed in the supine position, the groin and perineum were disinfected, and local anesthesia was performed. (2) Percutaneous femoral artery puncture was performed using Seldinger technique, and the catheter sheath was placed under X-ray fluoroscopy. (3) Contrast agent was injected into the catheter to perform angiography of the celiac artery and hepatic artery to determine the tumor supply vessels, as well as the tumor size and number. (4) According to tumor blood supply, local perfusion chemotherapy was performed first, with 100 mg oxaliplatin (H20093899, specification: 50 mg) and 2 mg raltitrexed aqueous solution (H20223017, specification: 2 mg). After that, chemoembolization was performed with 10 ml of ultra-liquid iodized oil (Shanghai Wanxiang, H20064893) and 2 mg of aqueous solution of raltitrexed (Macrocrown Bio, H20223017, specification: 2 mg). Finally, embolization was solidified with 150-350 μm polyvinyl alcohol (PVA) particles.

TACE combined with sorafenib and sintilimab in combination group: The treatment method of TACE was the same as that of the control group. Additionally, patients in the combination group were administered with sorafenib after TACE (Hunan Kelen, H20234069, specification: 2 g) at a starting dose of 400 mg/time, twice a day. Dose adjustment or interruption was determined by the clinician based on the sorafenib instruction and the patient's drug-related adverse reactions. In addition to the above treatment, sintilimab was administered, with each injection consisting of 200 mg of sintilimab (Xinda Bio, S20180016, specification: 100 mg (10 ml)/bottle), once every 3 weeks.

Clinical data collection: The hematological indexes of the two groups were collected before

and after treatment, including white blood cell count (WBC), alanine aminotransferase (ALT), aspartate aminotransferase (GOT), blood urea nitrogen (BUN), alpha fetoprotein (AFP).

According to the response evaluation criteria in solid tumors (mRECIST), the treatment effectiveness was classified as: ① complete response (CR): all target lesions disappeared in the arterial phase; ② partial response (PR): the sum of the diameter of all target lesions reduced by ≥30%; ③ progressive disease (PD): the total diameter of all target lesions increased by 20%, with an absolute increase of more than 5 mm, or new lesions appeared. ④ stable disease (SD): the total reduction of target lesions did not reach the PR criteria, and the total increase of target lesions did not reach the PD criteria. Objective response rate (ORR) and disease control rate (DCR) were calculated as follows: ORR = (CR + PR)/(CR + PR + SD + PD) × 100%; DCR = (CR + PR + SD)/(CR + PR + SD + PD) × 100%.

The progression-free survival (PFS) and overall survival (OS) of the patients during the follow-up period were statistically analyzed. PFS was defined as the time from the beginning of treatment to any tumor progression or death from any cause. OS was defined as the time from the start of treatment until the last follow-up or death. Adverse reactions of the two groups were evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE 5.0) [9]. Mild: asymptomatic or mild, requiring no treatment. Moderate: requiring local or non-invasive treatments. Serious: medically important but not immediately life-threatening and prolonging hospital stay. Disability: life-threatening and requiring emergency treatment. Patients were followed up for 18 months after discharge through electronic communication and outpatient review, and other adverse reactions were evaluated and recorded in time.

Data processing

SPSS 19.0 was used for data analysis, and Prism 8.0.2 was used for figure generation. Normally distributed measurement data were described as $\bar{x} \pm s$ and analyzed using paired or independent sample t-tests for intra- and inter-group comparison. The count data were described by [n (%)] and analyzed by χ^2 test. Survival curves were plotted using Kaplan-Meier. The survival difference between groups was detected by Log-Rank method. $P<0.05$ was considered statistically significant.

Results

Comparison of baseline data between the two groups

The baseline data of the two groups were compared, as shown in **Table 1**. There were no statistical differences in gender, age, WBC, tumor number, maximum tumor diameter, and disease staging based on various criteria (all $P>0.05$), indicating that the two groups were comparable.

Comparison of hematological indexes between the two groups before and after treatment

Before treatment, there were no statistical differences in hematological parameters between the two groups. After treatment, the levels of ALT, GOT, BUN and WBC increased while the level of AFP decreased in both groups; however, there was no significant difference between the two groups in terms of ALT, GOT, BUN and WBC (all $P>0.05$). Notably, the level of AFP was significantly lower in the combination group compared to the control group ($P<0.05$), see **Table 2** and **Figure 1**.

Comparison of curative effect between the two groups

After treatment, 17 cases achieved PR (17/30, 56.66%), 8 cases were SD (8/30, 26.67%), and 5 cases were PD (5/30, 16.67%) in the combination group, with an ORR of 56.67% and a DCR of 83.33%. In the control group, there were 5 cases of PR (25.00%), 6 cases of SD (30.00%), and 9 cases of PD (45.00%), with an ORR of 25.00% and a DCR of 55.00%. The ORR and DCR in the combination group were significantly higher than those of the control group (all $P<0.05$, **Table 3**).

Comparison of survival time between the two groups

By the end of follow-up, the median PFS time was 12.86 months in the combination group and 5.72 months in the control group ($P=0.007$, **Figure 2**). The median OS time was 15.63 months in the combination group and 7.05 months in the control group ($P=0.001$, **Figure 3**).

Table 1. Comparison of baseline data between the two groups (%, $\bar{x}\pm s$)

Information		Combination group (n=30)	Control group (n=20)	*P* value	X^2/t, df
Gender (%)	Male	16 (53.33)	12 (60.00)	0.6469	0.2095
	Female	14 (46.67)	8 (40.00)		
Age (years)		51.22±5.41	50.14±4.87	0.4665	t=0.7346, df=43.73
ECOG PS	0	13 (43.33)	14 (70.00)	0.1191	4.2500
	1	8 (26.67)	4 (20.00)		
	2	9 (30.00)	2 (10.00)		
Child-Pugh grading	A	18 (60.00)	13 (65.00)	0.8012	0.0633
	B	12 (40.00)	7 (35.00)		
BCLC grading	B	17 (56.67)	11 (55.00)	0.7704	0.0854
	C	13 (43.33)	9 (45.00)		
CNLC stage	I_b	5 (16.67)	2 (10.00)	0.4564	2.6071
	II_a	5 (16.67)	2 (10.00)		
	II_b	6 (20.00)	3 (15.00)		
	III_a	14 (46.66)	13 (65.00)		
WBC (10^9/L)		5.77±1.40	5.11±1.22	0.0843	t=1.765, df=44.52
AFP/(ng·1-1)	≥400 ng/mL	16 (53.33)	13 (65.00)	0.4210	0.6476
Tumor number	≤3 a	13 (43.33)	8 (40.00)	0.8012	0.0633
	>3 a	17 (56.67)	12 (60.00)		
Maximum tumor diameter	<7 cm	16 (53.33)	13 (65.00)	0.4210	0.6476
	≥7 cm	14 (46.67)	7 (35.00)		

Note: ECOG PS, Eastern Cooperative Oncology Group Performance Status; BCLC, Barcelona Clinic Liver Cancer; CNLC, China Liver Cancer; WBC, White Blood Cell; AFP, Alpha-fetoprotein; df, degrees of freedom.

Comparison of incidence of adverse reactions between the two groups

At the end of follow-up, there was no significant difference in grade 1-2 adverse reactions between the two groups (*P*>0.05). The incidence of grade 3 adverse reactions or above, such as hand-foot syndrome, hypertension, and loss of appetite in the control group was significantly higher than that in the combined group (*P*<0.05, **Table 4**).

Identification of prognostic factors

Univariate analysis showed that the Child-Pugh score, BCLC stage, tumor size, and treatment modality were related factors affecting the prognosis of patients (all P<0.05). The results of multivariate analysis revealed that treatment modality was an independent factor affecting the prognosis of patients (P<0.05) (**Table 5**).

Discussion

The liver is the largest metabolic organ of human body and the center of blood purification and detoxification. It also has hematopoietic function during the embryonic period and produces coagulation factors, playing a defensive role in the body, making it one of the most vital organs [10-12]. When liver function is compromised, not only is blood purification impaired, but the body also cannot deliver adequate nutrients and oxygen to its organs and tissues, leading to various diseases. Primary liver cancer, a malignant tumor originating in the liver epithelial tissue, does not involve external invasion or metastasis and thus has minimal impact on overall health and liver function in its early stages. As a result, there are typically no obvious clinical symptoms, with only a small number of patients experiencing occasional dull pain and discomfort in the liver region. This pain is usually paroxysmal and does not last long because the liver itself lacks relevant receptors [13-16]. By the time symptoms become apparent, most patients are already in the middle to late stages, with serious conditions such as vascular invasion and extrahepatic metastasis, making surgical res-

Table 2. Comparison of hematological indexes before and after treatment between the two groups

Group	n	ALT/(μmol·1^{-1})		GOT/(μmol·1^{-1})		BUN/(mmol·1^{-1})		WBC/(×10^{9}·1^{-1})		AFP/(ng·1^{-1})	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group	20	45.40±2.479	52.8±7.634	48.15±2.621	50.15±0.7592	6.450±1.75	5.450±0.7592	5.400±0.6806	6.200±0.6156	5537±4.465	1243±0.8507
Combination group	30	46.9±2.510	57.97±6.156	49.87±2.177	51.60±1.773	5.767±1.223	4.733±1.230	4.933±0.5833	6.733±0.8277	5513±44.22	787.7±7.948
t, df		t=2.085, df=41.22	t=2.528, df=34.76	t=2.424, df=35.57	t=2.165, df=30.50	t=2.436, df=47.83	t=2.546, df=47.79	t=2.512, df=36.44	t=2.609, df=47.34	t=2.987, df=29.88	t=310.9, df=29.99
p		0.0433	0.0162	0.0206	0.0383	0.0186	0.0142	0.0165	0.0121	0.0056	0.0001

Note: ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; BUN, Blood Urea Nitrogen; WBC, White Blood Cell; AFP, Alpha-fetoprotein; df, degrees of freedom.

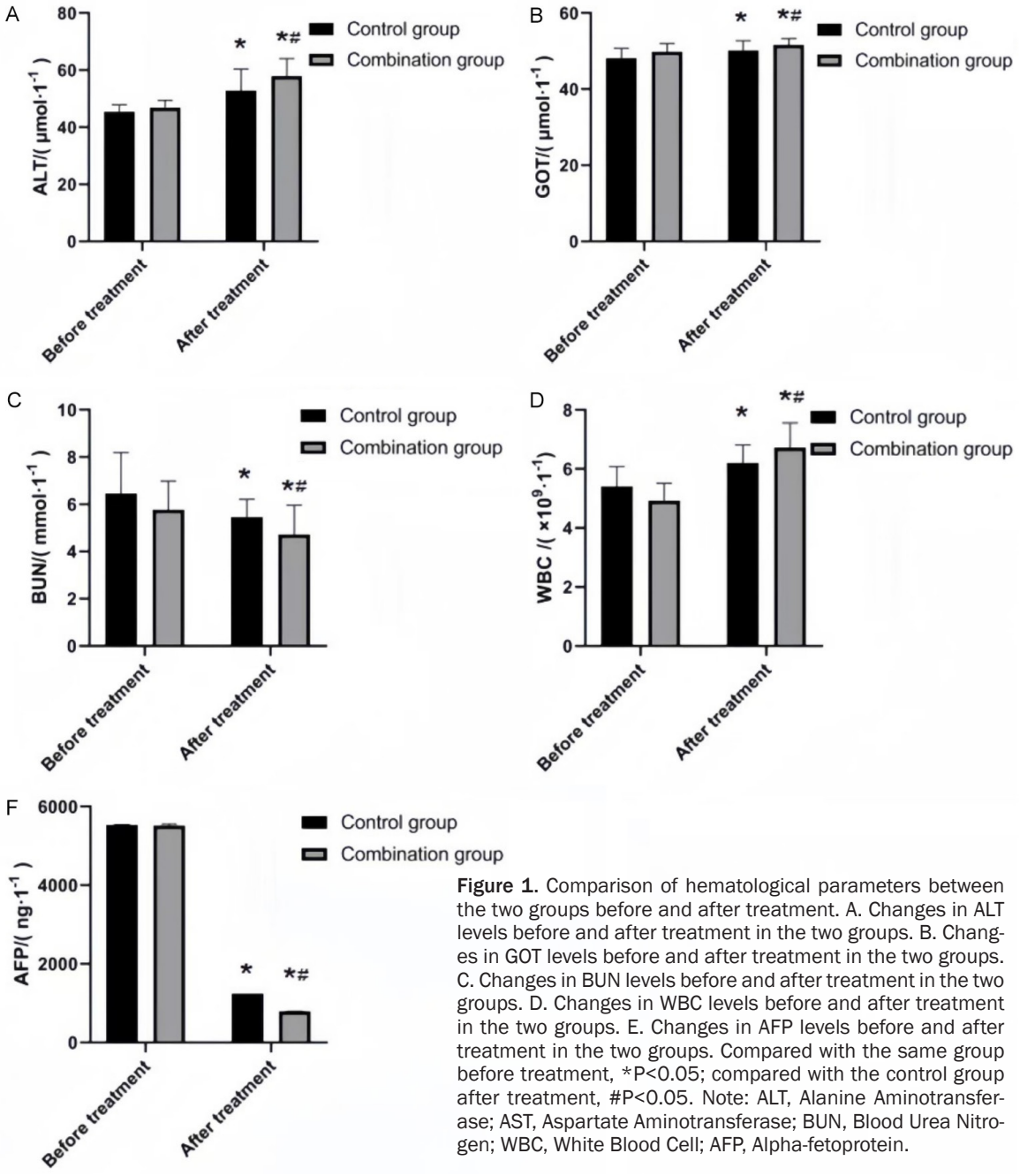

Figure 1. Comparison of hematological parameters between the two groups before and after treatment. A. Changes in ALT levels before and after treatment in the two groups. B. Changes in GOT levels before and after treatment in the two groups. C. Changes in BUN levels before and after treatment in the two groups. D. Changes in WBC levels before and after treatment in the two groups. E. Changes in AFP levels before and after treatment in the two groups. Compared with the same group before treatment, *P<0.05; compared with the control group after treatment, #P<0.05. Note: ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; BUN, Blood Urea Nitrogen; WBC, White Blood Cell; AFP, Alpha-fetoprotein.

Table 3. Comparison of efficacy between the two groups (%)

Tumor response	Combination group (n=30)	Control group (n=20)	X^2	*P* value
CR	0 (0.00)	0 (0.00)		
PR	17 (56.66)	5 (25.00)		
PD	8 (26.67)	6 (30.00)		
SD	5 (16.67)	9 (45.00)		
ORR	17 (56.67)	5 (25.00)	4.8214	0.0281
DCR	25 (83.33)	11 (55.00)	4.8000	0.0285

Note: CR, Complete Response; PR, Partial Response; PD, Progressive Disease; SD, Stable Disease; ORR, Objective Response Rate; DCR, Disease Control Rate.

ection no longer viable and resulting in a poor prognosis [17-19]. The clinical treatment methods for such patients are diverse, including transcatheter arterial chemoembolization (TACE), targeted drug sorafenib, and immune sintilimab treatment. However, according to the findings of Schneeweiß S [20], while single treatments can improve patient

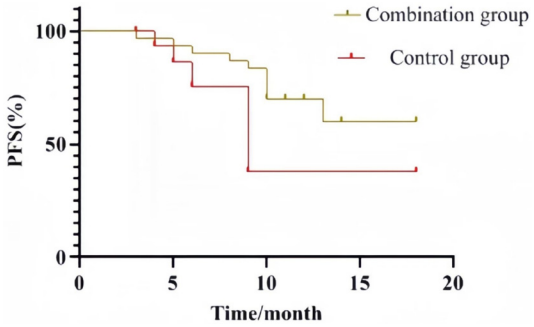

Figure 2. PFS analysis of the two groups after treatment. Note: PFS, Progression-Free Survival.

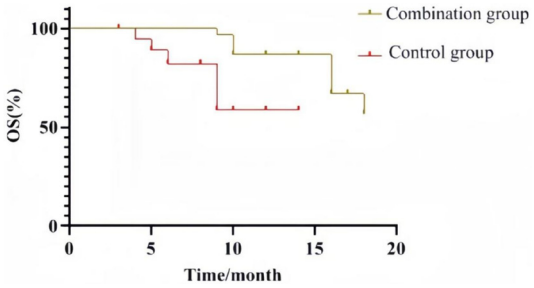

Figure 3. OS analysis in the two groups after treatment. Note: OS, Overall Survival.

outcomes to some extent, they do not significantly enhance survival rates. Current research trends focus on improving and prolonging the overall survival of patients with unresectable HCC while reducing adverse reactions [21-23]. Therefore, this study evaluated the clinical efficacy and safety of TACE combined with sorafenib and sintilimab in patients with unresectable HCC.

TACE is the preferred method for the clinical treatment of advanced liver cancer. The Seldinger method is mainly used for percutaneous arterial puncture, in which a short guide wire is placed into the catheter sheath, and the catheterization is carried out under X-ray fluoroscopy. The catheter is first selectively inserted into the tumor-feeding artery, and then angiography is performed to fully understand the distribution of the feeding artery and tumor blood vessels. Transcatheter infusion of chemotherapeutic drugs or embolization drugs can cause ischemia and necrosis of tumor cells, thereby delaying the growth rate of tumor cells [24, 25]. TACE can block the feeding artery using embolization drugs, while utilizing high concentrations of chemotherapy drugs to locally kill the tumor. However, the effect is relatively limited. In addition, during surgery, the embolization of the tumor artery causes hypoxia of the tumor tissue, which leads to an increase in the secretion of pro-angiogenic factors, tumor angiogenesis and residual cell proliferation, resulting in a heavier tumor burden. This recurrence and metastasis of tumor cells lead to a poor prognosis, similar to the findings of Chua TC et al. [26]. Based on this, the effect of TACE combined with systemic therapy on the clinical efficacy of unresectable HCC has been studied at home and abroad. In this study, 30 patients with unresectable HCC were treated with TACE combined with sorafenib and sindilumab, and 20 patients were treated with TACE alone. The results showed that the ORR and DCR of the combination group were 56.67% and 83.33%, which were higher than those of the control group treated with TACE alone (25% and 55%). These results indicate that TACE combined with sorafenib and sintilimab is an effective treatment for patients with unresectable liver cancer.

At the same time, the median PFS (12.86 months) and median OS (19.43 months) of the combination group were significantly longer than those of the control group (5.35 months, 12.36 months). The likely reason is that sorafenib, as a new multi-target anti-tumor drug, plays a dual inhibitory effect on cell proliferation and angiogenesis of liver tumors, resulting in significant anti-tumor effect [27]. Sintilimab can suppress the tumor growth caused by the hypoxic response to TACE, thus achieving complementarity in mechanism and having a synergistic effect [28].

The results of this study showed that the hematological indexes of the two groups changed after treatment, with the AFP level significantly lower in the combination group than the control group. AFP, as an internationally recognized auxiliary diagnostic index of liver cancer, has diagnostic significance for the recurrence of patients, and the AFP level can well reflect the tumor size. TACE combined with sorafenib and sintilimab can reduce the postoperative recurrence rate in patients. Additionally, the liver and kidney function and routine blood indexes of the two groups were increased after treatment,

Table 4. Adverse reactions in the two groups (%)

Adverse reactions	Grade 1-2 adverse reactions		X^2	P	≥ Grade 3 adverse reactions		X^2	P
	Combination group (n=30)	Control group (n=20)			Combination group (n=30)	Control group (n=20)		
Hand-foot syndrome	5 (16.66)	7 (35.00)	2.2114	0.1370	0 (0.00)	3 (15.00)	4.7857	0.0287
Hypertension	7 (23.33)	6 (30.00)	0.2774	0.5984	1 (3.33)	5 (25.00)	5.3333	0.0209
Diarrhea	8 (26.66)	6 (30.00)	0.0615	0.8041	1 (3.33)	2 (10.00)	0.9450	0.3311
Decreased appetite	11 (36.66)	9 (37.50)	0.3472	0.5558	1 (3.33)	5 (25.00)	7.0875	0.0078
Proteinuria	10 (33.33)	8 (40.00)	0.2313	0.6306	0 (0.00)	0 (0.00)	-	-
Elevated ALT	5 (16.67)	4 (20.00)	0.0909	0.7630	0 (0.00)	1 (5.00)	1.5313	0.2159
Thrombocytopenia	5 (16.67)	3 (15.00)	0.0242	0.8764	0 (0.00)	0 (0.00)	-	-
Renal injury	4 (13.33)	3 (15.00)	0.0273	0.8687	0 (0.00)	0 (0.00)	-	-
Elevated creatinine	7 (23.33)	8 (40.00)	1.5800	0.2088	0 (0.00)	0 (0.00)	-	-
Thrombocytopenia	4 (16.66)	3 (15.00)	0.0591	0.8079	0 (0.00)	1 (5.00)	1.5313	0.2159
Hypothyroidism	2 (8.33)	1 (5.00)	0.0594	0.8072	0 (0.00)	1 (5.00)	1.5313	0.2159

Note: ALT, Alanine Aminotransferase.

Table 5. Univariate and multivariate analysis of prognostic factors in patients with unresectable HCC

Univariate analysis						
Factors	β	SE	Wald	*P* value	HR	95% CI
Gender	0.211	0.402	0.276	0.599	1.235	0.562-2.713
Age	0.434	0.401	1.172	0.280	1.543	0.703-3.386
Child-Pugh score	0.901	0.401	5.048	0.024	2.461	1.123-5.395
BCLC stage	0.785	0.390	4.048	0.044	2.192	1.020-4.708
Tumor size	0.952	0.401	5.632	0.018	2.591	1.181-5.683
Treatment modality	-1.283	0.431	8.855	0.003	0.277	0.119-0.645
Multivariate analysis						
Factors	β	SE	Wald	*P* value	HR	95% CI
Child-Pugh score	0.723	0.418	2.996	0.083	2.062	0.910-4.674
BCLC stage	0.347	0.416	0.695	0.407	1.414	0.624-3.206
Tumor size	0.524	0.427	1.509	0.218	1.692	0.732-3.911
Treatment modality	-1.131	0.447	6.400	0.011	0.323	0.135-0.775

Note: HCC, Hepatocellular Carcinoma; β, regression coefficient; SE, standard error; Wald, Wald chi-square value; HR, Hazard Ratio; CI, Confidence Interval; BCLC, Barcelona Clinic Liver Cancer.

but there was no significant difference between the two groups, indicating that the two treatment schemes have certain feasibility.

In terms of adverse events, the incidence of grade 1-2 adverse events was basically the same in both groups. For grade ≥3 adverse events, the incidence of hand-foot syndrome, hypertension, and anorexia in the control group treated with TACE alone was higher than that in the combined group, which was similar to a previous study [29]. This may be due to transient liver function impairment following treatment, which can be mitigated by dose reduction or symptomatic treatment. Patients may recover in a short time after symptomatic treatment.

Conclusion

TACE combined with sorafenib and sintilimab is a feasible treatment for patients with unresectable liver cancer with high safety and efficacy. There are some limitations in this study, such as short follow-up time, small sample size, and lack of long-term efficacy observation. The results still need to be verified by large-sample, multi-center randomized controlled trials.

Disclosure of conflict of interest

None.

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