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CASE REPORT

Successful surgical resection of large hepatocellular carcinoma with portal vein tumor thrombus after conversion therapy with mFOLFOX-HAIC combined with donafenib and sintilimab: two case reports and a literature review*

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Abstract

The aim of our study was to evaluate the clinical efficacy of mFOLFOX-HAIC combined with donafenib and sintilimab conversion therapy followed by surgical resection of large hepatocellular carcinoma with portal vein tumor thrombus (PVTT). The clinical data of two patients with large hepatocellular carcinoma who were admitted to the Second Affiliated Hospital of Kunming Medical University were retrospectively collected. Both patients received mFOLFOX-HAIC combined with donafenib and sintilimab conversion therapy, followed by hepatectomy. Clinical data were reported, and clinical efficacy was evaluated. One patient had a 14.5 × 11.1 cm tumor with a tumor thrombus in the right portal vein. The other patient had a 12.1 × 8.3 cm tumor with portal and hepatic vein tumor thrombi. Both patients had CNLC stage IIIa prior to conversion therapy, which was reduced to stage Ib after conversion therapy. Subsequently, the patient underwent open and laparoscopic right hemihepatectomies. Short-term high-intensity conversion therapy with mFOLFOX-HAIC combined with donafenib and sintilimab is a feasible and effective treatment for patients with large hepatocellular carcinoma with PVTT.

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Hepatocellular carcinoma (HCC) is the third most common malignant tumor worldwide and the second leading cause of death from malignant tumors in China, seriously threatening human life and health [1, 2]. Radical surgery is the primary treatment option for patients with CNLC stage Ia, Ib, and IIa who meet the physical and tumor condition criteria and have good liver reserve function, with the goal of achieving long-term survival [3, 4]. However, the majority of HCC cases (approximately 80%) occur in developing countries, and unfortunately, most of these patients have tumors in the middle and late stages, which means they may have lost the opportunity for radical surgery [5]. The prognosis of these patients is extremely poor, with a median survival time of only approximately two years, and these patients can only receive non-surgical treatments, such as local and systemic treatments. However, the clinical effects of single treatment methods are poor.

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Therefore, a multidisciplinary team approach and a combination of various methods have been explored for the comprehensive treatment of advanced HCC [6].

In recent years, transcatheter arterial chemoembolization (TACE), hepatic artery infusion chemotherapy (HAIC), and other interventional measures, combined with targeted therapy and immunotherapy, have achieved encouraging results in terms of tumor shrinkage, control, and elimination of tumor thrombi, and tumor downstaging. Simultaneously, with these methods, a higher objective response rate (ORR) is obtained during clinical treatment, and the median survival time of patients is significantly prolonged [7]. Here, two patients with large HCC with portal vein tumor thrombosis (PVTT) admitted to the Second Affiliated Hospital of Kunming Medical University were treated with mFOLFOX-HAIC combined with donafenib and sintilimab targeted therapies, as well as with immunotherapy. This combined treatment successfully down-staged the tumor, enabling the patients to undergo right hepatectomy with favorable therapeutic effects. The data is presented below, along with a review of related literature.

Patients and methods

Patient 1

Table 1 presents the data of the patient. A 57-year-old man was admitted to the hospital due to a liver mass detected by physical examination two days earlier. The patient had undergone open appendectomy for acute appendicitis 25 years previously and had a long history of chronic hepatitis B. Contrast-enhanced computerized tomography (CT) examination showed a 14.5×11.1-cm liver tumor in the right lobe and a tumor thrombus in the right branch of the portal vein (Fig. 1a). Other data included positive hepatitis B surface antigen, AFP 2.17 ng/mL, Eastern Cooperative Oncology Group (ECOG) score 0, Child–Pugh grade A, Barcelona Clinic Liver Cancer (BCLC) stage A, and CNLC stage IIIa.

Table 1 Clinical data of the patients

Indicators	Patient 1	Patient 2
Age (years)	57	62
Sex	Male	Male
Chronic hepatitis B	Yes	No
AFP (ng/mL)	2.17	285.04
ECOG score	0	0
ChildPugh	A	A
Before conversion therapy		
Tumor size (cm)	14.5 × 11.1	12.1 × 8.3
Portal vein tumor thrombus	Yes	Yes
Hepatic vein tumor thrombus	No	Yes
CNLC stage	IIIa	IIIa
After conversion therapy		
Tumor size (cm)	11.1 × 8.4	7.1 × 4.5
Portal vein tumor thrombus	No	No
Hepatic vein tumor thrombus	No	No
CNLC stage	Ib	Ib
ICG-R15 (%)	4.7	5.3

Patient 2

Table 1 presents the data of the patient. A 62-year-old man was admitted due to upper abdominal pain for three days. Their 10-year history of hypertension was well controlled with nifedipine and irbesartan. Their 5-year history of diabetes was well controlled with acarbose. The patient had undergone open cholecystectomy for gallstones with cholecystitis 20 years prior. Contrast-enhanced CT showed a tumor in the right lobe of the liver measuring approximately 12.1 × 8.3 cm in size. The portal and hepatic veins adjacent to the tumor were invaded, and a tumor thrombus was identified (Fig. 2a). Other data included AFP 285.04 ng/mL, ECOG score 0, Child–Pugh grade A, BCLC stage A, and CNLC stage IIIa.

Treatment

After examining the patients' liver and renal functions, blood cell analysis results, and coagulation function data, these two cases were treated with mFOLFOX-HAIC (oxaliplatin, 85 mg/m^2 intra-arterial infusion; formyltetrahydrofolate, 400 mg/m^2 intra-arterial infusion; fluorouracil, 400 mg/m2 intravenous injection, and 2400 mg/m^2 continuous intravenous drip) every 21 days. Donafenib tosilate tablets were administered orally at a dose of 200 mg twice a day. Sintilimab was administered intravenously at a dose of 200 mg with 100 mL of normal saline for the same 21-day treatment cycle. Contrast-enhanced CT data were reviewed every three cycles, and the patients' liver function, liver reserve, general condition, and tumor condition were comprehensively evaluated. Surgical treatment was performed if the patient's tumor shrank, the portal vein tumor thrombus disappeared, and the tumor was down-staged to meet the surgical conditions. Otherwise, the conversion therapy was continued.

Results

Patient 1

Table 1 presents the data of the patient. Contrast-enhanced CT showed that the tumor in the right lobe of the liver had shrunk to 11.1 × 8.4 cm, with multiple areas of necrosis within the tumor and no tumor thrombus in the portal vein, inferior vena cava, or hepatic artery (Fig. 1b). Other data included AFP 2.85 ng/mL, INR 1.14, PT 13.0 s, PLT 219 × 10^9/L, TBIL 14.2 μmol/L, no cirrhosis, body mass index (BMI): 24.39 kg/m^2, ICG 15 min retention test 4.7%, ECOG Score 0, Child–Pugh

grade A, BCLC stage A and CNLC stage Ib. An open right hemihepatectomy was successfully performed.

The postoperative pathological results revealed that the liver specimen had a 11.4 × 9.0 cm tumor with hemorrhage and massive necrosis (Fig. 1c). Pathological diagnosis: (right liver) hepatocellular carcinoma, grade II–III, trabecular type and mass type; significant necrosis after embolization (95%); and hepatic resection margins without tumor involvement (Fig. 1d).

Patient 2

Table 1 presents the data of the patient. Contrast-enhanced CT showed that the tumor in the right lobe of the liver had shrunk to 7.1×4.5 cm, with multiple areas of necrosis within the tumor and no tumor thrombus in the portal vein, inferior vena cava, or hepatic artery (Fig. 2b). Other data included AFP 76.26 ng/mL, INR 1.01, PT 13.1 s, PLT 125 × 10^9/L, TBIL 12.0 μmol/L, ICG 15-min retention test 5.3%, ECOG Score 0, Child–Pugh grade A, BCLC stage A and CNLC stage Ib. Laparoscopic right hemihepatectomy was successfully performed.

The postoperative pathological results showed a tumor in the liver specimen measuring 7.0 × 4.5 × 4.0 cm, with a soft texture and gray-brown cut surface, accompanied by significant necrosis (Fig. 2c). Pathological diagnosis: the right liver tumor tissue showed significant infarction and necrosis, and only cell remnants were observed; however, based on the immunohistochemical labeling results, it was diagnosed as hepatocellular carcinoma, and no cancer was found in the resection margin (Fig. 2d).

Discussion

Although the liver is supplied with blood by both the hepatic artery and portal vein, the blood supply to HCC tumor tissues primarily originates from the hepatic artery, while the portal vein is mainly involved in the blood supply to the tumor capsule and its surrounding area. This theory [8] has been the basis for the continuous development and improvement of transcatheter arterial embolization. In 1983, Yamada [9] first reported 120 cases of unresectable HCC treated with hepatic tumor arterial embolization combined with drug injection, which caused ischemia and hypoxia of the tumor tissue, produced cytotoxic effects, and induced tumor cell necrosis. This is called TACE, and the 1-year, 2-year, and 3-year survival rates for this treatment are 44%, 29%, and 15%, respectively. Since then, TACE has gradually become the standard treatment for medium-stage HCC (BCLC stage B) worldwide [10-15]. The Chinese guidelines for the diagnosis and treatment of HCC published in 2022 [3] suggest that all HCC patients with clinical stages from IB to IIIB should be included in the treatment indication range of TACE. As a palliative treatment, TACE has certain limitations, including a low complete necrosis rate and a high postoperative recurrence rate for HCC with

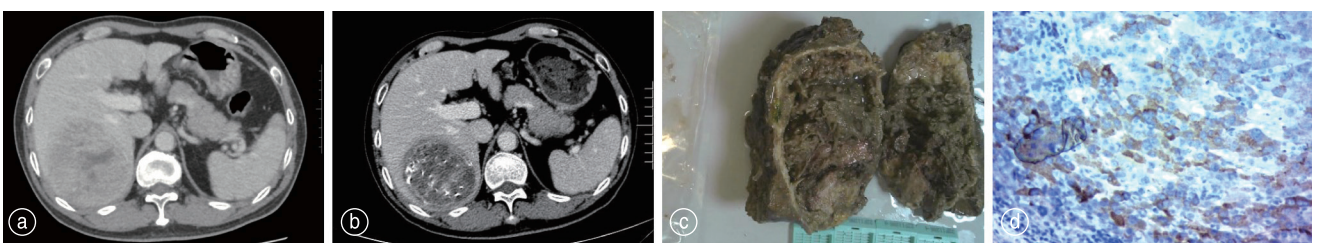

Fig. 1 Patient 1. (a) Preoperative computerized tomography (CT) showed a very large tumor in the right lobe of the liver, with invasion of the right branch of the portal vein and tumor thrombus formation; (b) After conversion therapy, the tumor was significantly reduced, and the portal vein tumor thrombus disappeared; (c) Surgically resected tumor specimen with a large amount of necrotic material inside the tumor; (d) Postoperative pathology (immunohistochemistry) showed hepatocellular carcinoma

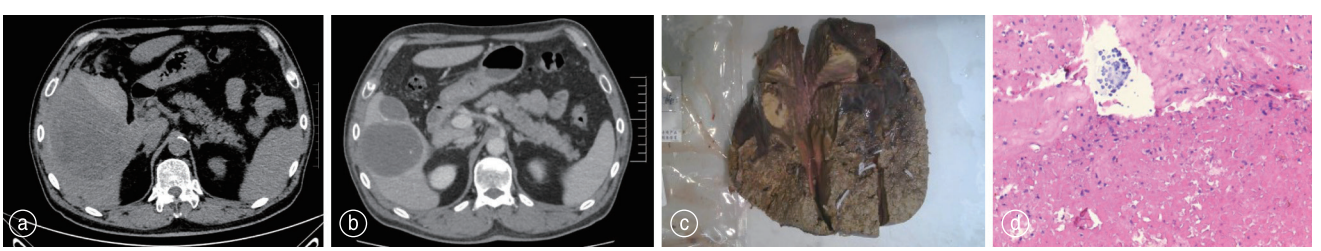

Fig. 2 Patient 2. (a) Preoperative computerized tomography (CT) showed a very large tumor in the right lobe of the liver, with invasion of the right branch of the portal vein and the inferior vena cava with tumor thrombus formation; (b) After conversion therapy, the tumor was significantly reduced, and the portal vein and inferior vena cava tumor thrombus disappeared; (c) Surgically resected tumor specimens; (d) Postoperative pathological results showed hepatocellular carcinoma

a large tumor burden. Additionally, owing to the strong heterogeneity of advanced HCC, its long-term efficacy is not ideal [16]. Therefore, there is an urgent need to develop improved treatment strategies for patients with advanced HCC.

There is no doubt that with the exploration of HCC treatment methods, TACE has also been continuously improved, and a variety of new treatment methods have been developed. As an example, conventional TACE (cTACE) is based on the use of an iodized oil drug emulsion assisted by gelatin sponge particles, microspheres, polyvinyl alcohol, or other solid particles for embolization to achieve tumor ischemic necrosis and cytotoxicity. Moreover, in recent years, drug-eluting bead-TACE (DEB-TACE), which uses pre-loaded chemotherapeutic drugs for continuous and slow release of chemotherapeutics in local tumors, has been developed. Through this method, a high local concentration of chemotherapeutic drugs can be maintained in the tumor, and the peak concentration of blood drugs entering the peripheral circulation can be reduced [10]. Notably, several studies have shown that DEB-TACE has better clinical efficacy than c-TACE [17, 18]. The technique was subsequently developed into transarterial radioembolization (TARE) using yttrium-90 microspheres. This method delivers high doses of β-rays at close range to kill tumor cells [19, 20]. However, the clinical efficacy of this technique remains unsatisfactory.

In recent years, an old technique called HAIC, which was proposed and performed by Japanese doctors in 1995, has received renewed attention [21]. Some studies have reported that HAIC is more effective in patients with advanced HCC who are suitable for TACE [7]. A phase III randomized controlled trial involving 315 patients [5] showed a median overall survival of 23.1 months (95% CI: 18.5–27.7) in the FOLFOX-HAIC group compared to 16.1 months in the control group (95% CI: 14.3–17.9) (hazard ratio 0.58; 95% CI: 0.45–0.75; $P < 0.001$). In addition, the ORR was higher with FOLFOX-HAIC than with TACE [73 (46%) *vs.* 28 (18%); $P < 0.001$], and longer median progression-free survival rates were also observed in the treatment group [9.6 months (95% CI: 7.4–11.9) *vs.* 5.4 months (95% CI: 3.8–7.0), $P < 0.001$]. In addition, the rate of serious adverse events was higher in the TACE group than in the FOLFOX-HAIC group (30% *vs.* 19%, $P = 0.03$). Therefore, compared with systemic chemotherapy, HAIC improves the local drug concentration and tumor uptake rate of drugs and minimizes chemotherapy toxicity [22].

Sorafenib, a tyrosine kinase inhibitor, was approved in 2007 as the first-line targeted therapy for unresectable HCC and showed an overall survival of 10.7 months. Since then, this drug has gradually been approved by the drug regulatory authorities of many countries and regions worldwide and has been recommended by HCC clinical treatment guidelines and expert consensus proceedings. Sorafenib has revolutionized the field of targeted therapy for advanced HCC, establishing its position as the first-line treatment for this condition [4, 23]. However, recent studies have highlighted the emergence of new, promising options for HCC treatment. For instance, lenvatinib has been found to achieve an overall survival (OS) of 13.6 months in the treatment of HCC, demonstrating the effectiveness of targeted therapy in managing advanced HCC [24]. Additionally, donafenib, a new multi-target, multi-kinase inhibitor, represents the latest class of small-molecule targeted drugs with therapeutic potential for HCC. This drug inhibits the RAF/MEK/ERK pathway and the tyrosine kinase activity of VEGFR/PDGFR in tumor cells. As a new deuterated derivative of sorafenib and lenvatinib, it has the advantages of reduced metabolism by hepatic drug enzymes, increased plasma exposure, and a longer half-life [25]. Moreover, it has better pharmacokinetic characteristics and stronger anti-tumor activity [26]. Finally, data from the ZGDH3 study [27] showed that patients with advanced HCC had significantly longer

Table 2 Results of studies related to local treatment, targeted therapy and immunotherapy for HCC

Study	Study type	Year	Treatment	Number of patients	ORR	PFS	DFS	OS
[17]	retrospective cohort study	2021	DEB-TACE or cTACE	71	60.0% *vs* 29.7%	3.3 *vs* 2.1 months	NR	7.8 *vs* 5.7 months
[20]	RCT phase II	2022	90-Y TARE or DEB-TACE	72	NR	NR	NR	30.2 *vs* 15.6 months
[7]	RCT phase III	2022	FOLFOX-HAIC or routine follow-up	315	NR	NR	20.3 *vs* 10 months	(3 years OS)80.4% *vs* 74.9%
[5]	RCT phase III	2022	FOLFOX-HAIC or TACE	315	NR	9.6 *vs* 5.4 months	NR	23.1 *vs* 16.1 months
[27]	RCT phase II-III	2021	Donafenib or Dorafenib	668	NR	3.7 *vs* 3.6 months	NR	12.1 *vs* 10.3 months
[29]	Clinical trial	2017	Nivolumab	262	20%	NR	NR	NR
[31]	retrospective cohort study	2022	pembrolizumab-lenvatinib-TACE or lenvatinib-TACE	142	NR	9.2 *vs* 5.5 months	NR	18.1 *vs* 14.1 months

NR: not reported

OS with donafinib than with sorafenib (12.1 months vs. 10.3 months, respectively; HR = 0.831. 95%CI: 0.699–0.988, $P = 0.0363$) [27, 28].

Based on tumor immunology research, the activation of T cells can upregulate the expression of programmed death receptor 1 (PD-1). However, the binding of PD-1 to PD-ligand 1 (PD-L1) on the surface of tumor cells inhibits the effect of effector T cells. Consequently, immune tolerance is induced, which promotes tumorigenesis. Based on this theory, PD-1/PD-L1 monoclonal antibody drugs have attracted considerable attention in tumor immunotherapy. The first PD-1/PD-L1 monoclonal antibody, pembrolizumab, was approved for marketing in the United States in 2014. Since then, 10 different drugs have been approved for the immunotherapy of various tumors worldwide. For instance, sintilimab, a PD-1/PD-L1 monoclonal antibody produced in China, was approved for marketing in 2018, which is of landmark significance in the "Chinese innovation era" of anti-tumor immunotherapy. This also brings new hope for the treatment of HCC. Furthermore, the CheckMate-040 study [29] showed that the PD-1 checkpoint inhibitor nivolumab showed good tolerance and safety in patients with advanced HCC.

The ORR of sintilimab combined with bevacizumab for the treatment of advanced HCC is 20% [30], and it should be noted that the effect of single-agent immunotherapy is poor. Nevertheless, the combination of immunotherapy and targeted therapy has shown good therapeutic effects [15, 30]. Although targeted therapy combined with immunotherapy has achieved certain clinical treatment effects, the overall ORR is not optimistic. On the other hand, TACE/HAIC is an important treatment method for patients with unresectable middle- and advanced-stage HCC. However, TACE/HAIC alone cannot completely eliminate tumor activity and often results in tumor progression and distant metastasis. Therefore, for unresectable advanced HCC, TACE/HAIC-based local treatment combined with targeted treatments and immunotherapy may demonstrate a "1+1 > 2" therapeutic effect [31]. Furthermore, numerous studies have demonstrated the superior efficacy of this combination therapy, with overall response rates (ORR) exceeding 60% in patients with advanced HCC, particularly in those with PVTT [32].

Since Hermann reported in the 1970s [33] that giant hepatoblastomas shrank after chemoradiotherapy and were successfully surgically resected, many studies have explored translational therapies for HCC [34]. In the Second Affiliated Hospital of Kunming Medical University, two patients with CNLC stage IIIb HCC achieved satisfactory therapeutic effects in terms of tumor shrinkage and tumor thrombus elimination through two cycles of mFOLFOX-HAIC combined targeted therapy and immunotherapy; following this treatment, the tumor descending stage (CNLC stage Ib) was achieved, and radical surgery was finally performed. Studies from many medical centers worldwide have also shown the excellent performance of HAIC combined with targeted therapy and immunotherapy for the treatment of HCC [31, 32, 35]. This combination therapy has been particularly effective in treating HCC patients with PVTT, who are classified as having CNLC stage IIIa, and for whom surgical resection is not the first choice. Therefore, this treatment approach can be considered as an alternative option for these patients.

Surgical operations often need to be combined with vascular thrombectomy, which is difficult to perform and can easily cause vascular embolism, massive bleeding, and even sudden death during and after surgery. During surgery, the risk of recurrence and metastasis is also high. However, through high-intensity conversion therapy using various methods and drugs, tumor shrinkage, tumor thrombus control or disappearance, and tumor downstaging can be achieved in a short time. Simultaneously, it can reduce the risk of surgery and increase the success rate of surgical resection to achieve longer survival times in patients. However, continuous follow-up is necessary to understand the prognosis of patients and ensure the timely implementation of relevant treatments. More data on patients who received such treatment will be collected to continuously understand the conversion therapy of patients with HCC with PVTT and explore better clinical treatment options.

In conclusion, in patients with large HCC complicated by PVTT, aggressive and high-intensity mFOLFOX-HAIC combined with donafenib and sintilimab can achieve tumor shrinkage, tumor thrombus control or disappearance, and tumor downstaging, reduce the risk of surgery, and increase the chance of surgical resection in a short time. However, these preliminary findings need to be further verified in large-sample randomized controlled trials and prospective clinical studies.

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Conflicts of interest

The authors indicated no potential conflicts of interest.

Author contributions

All authors contributed to data acquisition, data interpretation, and reviewed and approved the final version of this manuscript.

Data availability statement

Not applicable.

Ethical approval

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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