TACE plus PD-1 successfully achieves conversion therapy for unresectable HCC with multiple macrovascular invasion: a case report

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Case Report

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Abstract

Background

There is still a lack of effective treatment for patients with advanced hepatocellular carcinoma (HCC) and macrovascular invasion, and surgical resection is technically feasible but difficult to remove the tumor completely, which often leads to early recurrence. In recent years, it has been found that the combination of systematic therapy and locoregional treatment has shown better anti-tumor effect for advanced HCC than a single drug or method. Higher objective response rate with combined therapy brings new hope for conversion therapy as well.

Case presentation

A 32-year-old male patient was diagnosed with giant HCC with tumor thrombus formation in the right branch of the portal vein, inferior vena cava, and right atrium. After receiving 3 times transarterial chemoembolization combined with 7 cycles of PD-1 inhibitors treatment, the tumor significantly shrunk and the tumor thrombus in the inferior vena cava and right atrium disappeared. Finally, the patient underwent radical liver resection successfully. Now a year after surgery, the patient remains in disease-free survival.

Conclusion

TACE plus PD-1 inhibitors may be an ideal conversion regimen for patients with potentially resectable HCC, leading to more surgical resection opportunities. Neutrophil lymphocyte ratio decreased after treatment may suggest that patients respond well to PD-1-based combination therapy.

Background

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the third leading cause of death worldwide, and stage C account predominant diagnosis according to Barcelona Liver Cancer Clinic (BCLC) staging system(1). However, the prognosis is much poor for most BCLC-stage C patients due to missed opportunities for curative surgery. Fortunately, some patients with unresectable HCC may undergo radical liver resection by receiving effective tumor downstaging treatment, while these patients are considered potentially resectable(2).

Potentially resectable HCC can be divided into two categories, one is technically unresectable, such as giant tumor or diffuse multifocal tumors with insufficient future liver remanent (FLR); the other is technically feasible but can't provide significant survival benefits compared to non-surgery, which is referred to as pathologically unresectable, such as macrovascular invasion. These two kinds of patients can be treated with effective conversion therapy or neoadjuvant therapy to achieve tumor downstaging.
and thus undergo radical surgery(2). Transarterial chemoembolization (TACE) has been used as a tumor downstaging strategy for many years as it can sometimes result in tumor necrosis and shrinkage(2, 3). Regrettably, TACE has a limited effect in patients with extensive tumor growth in both lobes or macrovascular invasion(3, 4). In recent years, immune checkpoint inhibitors such as PD-1 inhibitor has become a hot spot for the treatment of malignant tumors, and the combination with TACE for advanced HCC has been tried to achieve better anti-tumor effects. However, whether this combined therapy regimen can bring more surgical opportunities to patients with advanced but potentially resectable HCC remains to be explored.

In this case, TACE plus PD-1 inhibitors allowed a patient with giant HCC and multiple macrovascular invasions to achieve tumor downstaging, and ultimately underwent radical liver resection. Based on this particular case, we summarize the recent advances in PD-1-TACE-based combination regimens in the treatment of advanced HCC and discuss the prospects of combination regimens as conversion strategies.

**Case Presentation**

A 32-year-old man with hepatitis B-related cirrhosis visited the doctor due to fatigue and decreased appetite. Magnetic resonance imaging (MRI) revealed a huge tumor (13.7*12.1cm) in the right lobe of the liver, with tumor thrombus formed in the right branch of the portal vein, inferior vena cava, and right atrium (Fig. 1. a). The Alpha-fetoprotein (AFP)is 509.3ng/ml. According to the imaging features and elevated AFP, the patient was diagnosed with HCC accompanied by macrovascular invasion, liver cirrhosis, portal vein hypertension, gastroesophageal varices, splenomegaly, and ascites. Total bilirubin was 28.8 mmol/L, alanine aminotransferase was 77 U/L, and aspartate aminotransferase was 170 U/L. Serum albumin was 31.2 g/L and the prothrombin time was 15.1s. The Child-Pugh class is B status (score 7). The Eastern cooperative oncology group perform score (ECOG PS) was 2. The patient is considered unsuitable for surgical treatment, and TACE combined with PD-1 may be more appropriate. We chose conventional-TACE (oxaliplatin, epirubicin, and iodized oil), which is likely to be less damaging to liver function. On 2020/11/27, the patient received the first TACE treatment, and about 2 weeks later, the patient received the first cycle of Toripalimab (a PD-1 inhibitor from China, 240mg, intravenous). The patient was expected to receive the second TCAE a month later, and Toripalimab will be given about every three weeks. However, the patient developed severe gastroesophageal variceal bleeding 5 days after receiving the Toripalimab. Fortunately, the bleeding was well controlled by endoscopic varicose band ligation combined with pharmacological therapy which mainly includes octreotide, terlipressin, omeprazole, and antibiotics, in addition, we also administered blood transfusions and fluid support to the patient. Before the second TACE, computed tomography (CT) identified that the tumor shrank greatly (Fig. 1. b), and the tumor thrombus in the right atrium and inferior vena cava retracted (Fig. 1. b). AFP, neutrophil lymphocyte ratio (NLR) has been greatly reduced (Fig. 2. a-b). Then the patient received the second TACE on 2021/1/27, and 3 cycles of Toripalimab from 2021/2/4 ~ 3/25. Subsequent re-examination of the enhanced CT showed that the tumor shrank further and the tumor thrombus in the right atrium disappeared, but still existed in the right branch portal vein and inferior vena cava, and there
was still a little enhancement in the lesion (Fig. 1. c). AFP, NLR decreased to normal value (Fig. 2. a-b). As the patient responded well to the combination treatment, he received the third TACE on 2021/3/26 and 2 cycles of Toripalimab from 2021/4/15 – 5/8 with the aim of further reduction of the inferior vena cava tumor thrombus. At the end of May 2021, MRI identified the diameter of the tumor shrank from 13.7cm to 5cm; without any intra-tumoral arterial enhancement, and tumor thrombus in the inferior vena cava disappeared (Fig. 1.d). The patient’s liver function was Child-Pugh A, ECOG PS was 1 and the 15 mins indocyanine green metabolic rate was 5.4%. We conducted a rigorous multidisciplinary discussion and concluded that the patient was currently suitable and safe for operation. Considering that tumor thrombus might remain in the right branch of the portal vein, the scope of resection needed to be extended, so we planned to perform the right Hemi-hepatectomy with an estimated FLR > 50%. The laparoscopic right Hemi-hepatectomy and cholecystectomy were performed successfully on 2021/6/1. The tumor was completely removed (Figure S1. a). The patient recovered well and was successfully discharged from the hospital on the sixth day after the operation. Pathology prompted all the tumor tissues were necrotic with fibrotic and calcium salt deposition, no residual cancer tissue was found and the incisal margin of the liver was negative (microscopic pathological features are shown in Figure S1. b-c). After surgery, the patient received adjuvant antiviral therapy (entecavir, 0.5 mg daily). Now 1 year after surgery, MRI did not find any signs of tumor recurrence, and AFP was at normal value.

Discussion And Conclusion

New options for potentially resectable HCC

As a local treatment acting directly on the tumor, TACE can induce the release of tumor antigens and some cytokines such as proinflammatory cytokines and VEGF, increasing the expression of $PD-1$ and $PD-L-1$. The change in the local immune microenvironment is conducive to the reactivation of tumor autoimmunity and increases T lymphocytes which allows PD-1 inhibitors to work better(5, 6). Notably, TACE may aggravate tumor tissue hypoxia, which can stimulate tumor angiogenesis and lead to tumor recurrence and metastasis(7). The anti-tumor proliferation and suppressed angiogenesis effect of tyrosine kinase inhibitors (TKIs) such as Sorafenib and Lenvatinib can inhibit the pro-angiogenic effect of TACE. Besides, TKIs can also improve antitumor immune responses by modulating macrophages and myeloid-derived suppressor cells to enhance effector T cell responses, and increase the expression of $PD-1$ on T cells, thus promoting the action of PD-1 inhibitors(8). Based on these basic mechanisms, combination therapy of TACE plus PD-1 with or without TKIs is rational and feasible(3). In the last year, several retrospective cohort studies have demonstrated the superiority of dual (TACE + PD-1) or triple (TACE + PD-1 + TKIs) therapy for advanced HCC, resulting in a higher objective response rate (ORR) of up to 77.4% and conversion resection rates of up to 53.2% (Details are shown in Table 1). The better anti-tumor effects of combined therapy also bring new options and hope for potentially resectable HCC.

Table 1. Latest studies of combination therapy for advanced HCC or as conversion therapy
<table>
<thead>
<tr>
<th>Author/year</th>
<th>Interventions/Sample size</th>
<th>PVTT</th>
<th>BCLC</th>
<th>ORR</th>
<th>CRR</th>
<th>AE*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen, et al.$^{16}$</td>
<td>TACE +Pembrolizumab + Lenvatinib (70) vs. TACE +Lenvatinib (72)</td>
<td>Y</td>
<td>B/C</td>
<td>47.1% vs. 27.8%</td>
<td>25.7% Vs. 11.1%</td>
<td>Elevated AST 17 (24.3%) Elevated ALT 16 (22.9%) Hypertension 13 (18.6%)</td>
</tr>
<tr>
<td>Zhang, et al.$^{17}$</td>
<td>TACE +camrelizumab (46) vs. TACE (46)</td>
<td>Y</td>
<td>B/C</td>
<td>55.1% vs. 22.5%</td>
<td>/</td>
<td>Liver damage Vomiting Nausea</td>
</tr>
<tr>
<td>Liu, et al.$^{18}$</td>
<td>TACE +Lenvatinib + camrelizumab (22)</td>
<td>Y</td>
<td>B/C</td>
<td>72.7%</td>
<td>/</td>
<td>Nausea 10 (45.5%) Abdominal pain 8 (36.4%) Fever 8 (36.4%)</td>
</tr>
<tr>
<td>Wu, et al.$^{19}$</td>
<td>TACE +Lenvatinib +PD-1 (62)</td>
<td>Y</td>
<td>A/B/C</td>
<td>77.4%</td>
<td>53.2%</td>
<td>Elevated AST 38 (61.3%) Decreased appetite 35 (56.5%) Elevated ALT 34 (54.8%)</td>
</tr>
<tr>
<td>Qin et al.$^{20}$</td>
<td>TACE +sorafenib +PD-1 (25) vs. TACE +PD-1(41)</td>
<td>Y</td>
<td>C</td>
<td>59% vs. 50%</td>
<td>/</td>
<td>Hepatocyte dysfunction Post-embolization syndrome Thrombocytopenia</td>
</tr>
<tr>
<td>Cai, et al.$^{21}$</td>
<td>TACE +Lenvatinib +PD-1(41) vs. TACE +Lenvatinib (40)</td>
<td>Y</td>
<td>C</td>
<td>56.1% vs. 32.5%</td>
<td>/</td>
<td>Hypertension 16 (39.0%) Weight loss 14 (34.1%) Diarrhea 13 (31.7%)</td>
</tr>
<tr>
<td>Xiang, et al.$^{22}$</td>
<td>TACE +Lenvatinib +PD-1(56) vs. TACE +PD-1(47)</td>
<td>N</td>
<td>B</td>
<td>64.3% vs. 38.3%</td>
<td>/</td>
<td>Decreased albumin 31(55.3%) Decreased platelet 29(51.8%)</td>
</tr>
</tbody>
</table>
### Hypertension

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>ORR</th>
<th>CRR</th>
<th>AE Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Qu, et al. (&lt;sup&gt;14&lt;/sup&gt;)</td>
<td>TACE + Lenvatinib + PD-1 (56) vs. TACE (54)</td>
<td>Y</td>
<td>B/C</td>
<td>67.9% vs. 29.6%</td>
</tr>
<tr>
<td>Teng, et al. (&lt;sup&gt;23&lt;/sup&gt;)</td>
<td>TACE + Lenvatinib + PD-1 (53)</td>
<td>Y</td>
<td>B/C</td>
<td>54.9%</td>
</tr>
</tbody>
</table>

*<sup>AEs</sup>, The three most common adverse effects with dual or triple therapy*

**Abbreviations:** PVTT, Portal vein tumor thrombosis; BCLC, Barcelona Liver Cancer Clinic; AEs, adverse effects; ORR, objective Response Rate; CRR, conversion resection rate; ALT, alanine aminotransferase; AST, aspartate aminotransferase

For giant HCC, surgical resection often results in insufficient FLR and thus induces post hepatectomy liver failure and mortality. Portal vein embolization or associating liver partition and portal vein ligation for staged hepatectomy are two approaches that were commonly used to increase FLR. Both approaches require several weeks to induce compensatory hypertrophy of the contralateral hepatic lobe, while the tumor may progress during this period. In contrast to increasing the volume of the FLR, reducing the extent of resection by shrinking the tumor volume is also a possible route. In this case, we observed a substantial reduction in tumor size (from 13.7cm to 5cm) with combination therapy, thus radical resection can be performed safely and quick recovery after surgery. On the other hand, for patients with portal vein or inferior vena cava tumor thrombosis, although surgical resection is technically feasible, complete removal of residual tumor thrombus and cells in the vascular is a great challenge, which is difficult to achieve by surgery alone and often leads to early recurrence. Shrinking or eliminating the tumor thrombus before surgery may be an effective solution to reduce recurrence. In addition, for hepatitis B-related HCC, adjuvant antiviral therapy is also helpful to prevent postoperative recurrence. Moreover, some studies found that hepatitis B surface antigen-positive cancer patients may experience hepatitis B virus reactivation after PD-1 treatment(<sup>9</sup>). Therefore, for hepatitis B-related HCC patients who are treated with PD-1, adjuvant antiviral therapy is necessary. In this case, the patient did not experience tumor recurrence or viral reactivation one year after surgery.

### Adverse Effects
In this case, the patient suffered upper gastrointestinal hemorrhage 5 days after receiving the first cycle of PD-1 inhibitors therapy. However, reports of treatment-related gastrointestinal bleeding were rare in the nine studies about combination therapy (Table 1). Hepatic impairment and hypertension were the most frequently observed adverse effects (AE) (Table 1). In addition, after 5 cycles of PD-1 treatment, the patient developed mild leukocytopenia (Fig. 2.c), which is also one of the common AEs of combination therapy. No combination therapy-related deaths have been reported in the published studies, and grade-4 AEs are rare. However, it is worth noting that the overall probability of AEs is higher with triple or dual therapy than with monotherapy, which suggests that more closely monitor is necessary for combined therapy(10).

**Factors That May Predict The Effect Of Pd-1**

It is of great importance to identify the population at risk of failure to PD-1-based combined therapy, so as to change the treatment regimen in time. Previous studies found that the expression of PD-L1 and TGF-β, tumor-infiltrating lymphocytes and tumor mutational burden et al. may predict the action of PD-1 inhibitors(11). However, most results are based on complex basic experiments, which makes it difficult to carry out large-scale validation and application in clinical practice. Lower levels of NLR associated with a better survival prognosis in advanced HCC patients treated with PD-1 inhibitors have been found in recent years(12). A recently published study on combination therapy (TACE + PD-1 + Lenvatinib) seems to confirm this, patients with low NLR (≤ 3.11) had longer overall survival(13). In this case, however, we observed that the patient's initial NLR value was relatively high, while NLR significantly decreased (from 6.5 to 1.75, Fig. 2. c) after receiving 5 cycles of PD-1 inhibitors and 1TACE treatment. At the same time, the tumor diameter was drastically reduced and the tumor thrombus almost disappeared (Fig. 1.c). Therefore, the decrease in NLR may also suggest that the patient responded well to the PD-1-based combination therapy. Similarly, a latest study on advanced or metastatic esophageal squamous cell carcinoma found that after 6 weeks of PD-1 treatment, patients with NLR < 3 had a better prognosis(14). However, how long to see a decline in NLR is of significance after PD-1 therapy, and the cutoff value of NLR needs further exploration.

**Abbreviations**

HCC, hepatocellular carcinoma; BCLC, Barcelona Liver Cancer Clinic; FLR, future liver remanent; TACE, transarterial chemoembolization; MRI, magnetic resonance imaging; AFP, alpha-fetoprotein; ECOG PS, Eastern cooperative oncology group perform score; CT, computed tomography; NLR, neutrophil lymphocyte ratio; TKIs, tyrosine kinase inhibitors; ORR, objective response rate; AEs, adverse effects

**Declarations**

**Ethics approval and consent to participate**

Written consent for participation was obtained. No ethics approval was
Consent for publication

Written consent for publication of images and necessary data was obtained.

Availability of data and materials

All data generated or analysed during this study are included in this published article [and its supplementary information files].

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

Bin Guo, design of the work, data collection, drafting the article, regular follow-up

Yi Zhou, data collection, drafting the article

Tianhua Ouyang, data collection, organize information, create images and tables

Zhicheng Liu, critical revision of the article

Feng Xia, critical revision of the article

Qian Chen, critical revision of the article

Xiaoping Chen, critical revision of the article

Zhenyu Xiao, design of the work, critical revision of the article, final review of the article

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Not applicable

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Figures
Figure 1

Figure legend not available with this version.
Figure 2

Figure legend not available with this version.

Supplementary Files

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• FigureS1.jpg