

Autologous Tumor-Infiltrating Lymphocyte Infusion plus Anti-Programmed Cell Death Protein 1 Therapy to Cure Advanced Hepatocellular Carcinoma following Palliative Hepatectomy

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Keywords

Adoptive cell therapy · Tumor-infiltrating lymphocytes · Anti-PD-1 therapy · Palliative hepatectomy · Advanced hepatocellular carcinoma

Abstract

Introduction: Adoptive cell therapy derived from autologous tumor-infiltrating lymphocytes (TILs) has demonstrated promising therapeutic efficacy in several cancers. However, its possible synergistic effects with anti-PD-1 therapy in advanced hepatocellular carcinoma (aHCC) remain unexplored. This study aimed to investigate the efficacy of TIL infusion combined with anti-PD-1 therapy for aHCC. **Case Presentation:** Referring to the current protocol of our clinical trial (NCT03658785), 2 patients with HCC at BCLC stage C were enrolled to receive autologous TIL infusion combined with anti-PD-1 therapy.

They underwent unplanned palliative tumor resection to alleviate pain caused by tumor rupture prior to receiving TIL infusion plus anti-PD-1 therapy. Long-term outcomes and treatment-related adverse events were evaluated. Throughout the entire treatment process, both patients experienced only mild symptoms. Notably, both patients achieved complete responses to the treatment and have remained tumor-free for 2 and 4 years, respectively. **Conclusion:** Autologous TIL infusion combined with anti-PD-1 therapy is a safe and feasible strategy for patients with aHCC. Palliative hepatectomy with maximal tumor burden reduction may significantly improve its efficacy and even results in cure for aHCC patients.

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Tian Xia and Tong Yuan contributed equally to this work.

Introduction

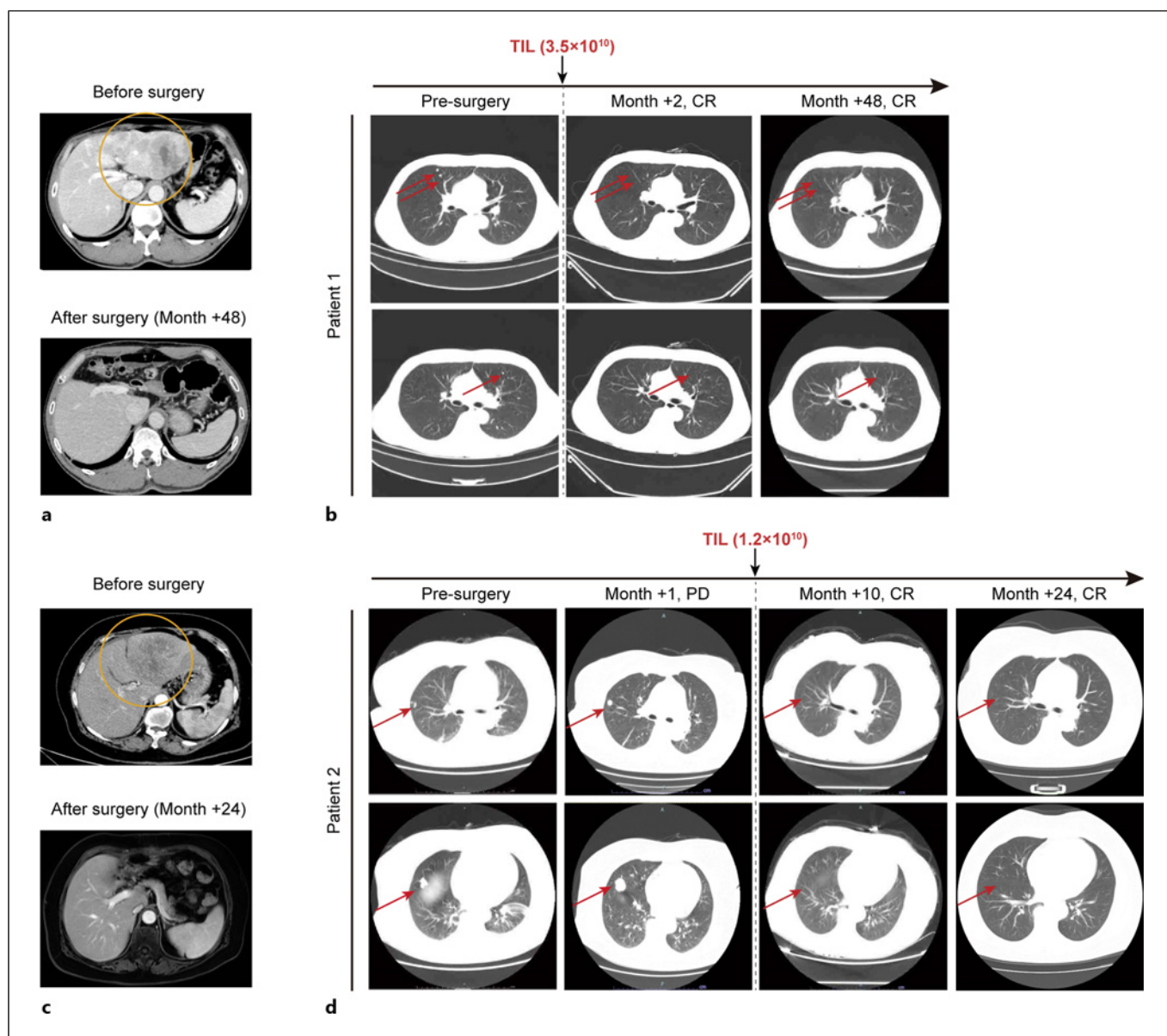
Hepatocellular carcinoma (HCC) is the sixth most common malignancy and the third leading cause of cancer-related death worldwide [1]. More than half of HCC cases are from China, where approximately 55% of HCC cases are initially diagnosed at the advanced stage [2]. According to HCC treatment guidelines such as Barcelona clinic liver cancer (BCLC) [3], National Comprehensive Cancer Network (NCCN) [4], American Association for the Study of Liver Diseases (AASLD) [5], patients with advanced HCC (aHCC) are not suitable for surgical resection and should be treated by systemic therapy, including targeted drugs (lenvatinib and sorafenib, etc.) and immunotherapy. Atezolizumab plus bevacizumab in the IMbrave 150 trial has shown promising efficacy for aHCC, with an objective response rate of 27.3% [6]. However, the median progression-free survival was only 6.8 months. The majority of patients failed to benefit from immunotherapy, and some developed resistance quickly. For these refractory aHCC patients, novel therapeutic strategies are urgently needed.

Adoptive cell therapy using tumor-infiltrating lymphocytes (TILs) isolated and expanded from the patient's own tumor is an individualized immunotherapy approach [7]. TIL therapy offers diverse T-cell clonality, which could recognize tumor antigens, superior tumor homing capacity, and low off-target toxicity [8]. Recently, TIL therapy has shown clinical efficacy with durable responses in advanced melanoma [9, 10], cervical cancer [11], non-small cell lung cancer [12], and breast cancer [13]. In a single-arm, open-label phase 1 trial, 20 metastatic non-small cell lung cancer patients who were refractory to nivolumab treatment demonstrated significant benefits from the combined therapy of TIL and nivolumab [12]. Among the 13 evaluable patients, six exhibited a radiographic response, including two complete responses. The results indicated that combining TIL with anti-PD-1 therapy may further enhance antitumor immune responses in solid tumors that are previously not responsive to anti-PD-1 therapy. In this report, we present 2 aHCC patients with portal vein tumor thrombosis (PVTT) and lung metastases who derived sustained survival benefits from autologous TIL infusion combined with anti-PD-1 therapy following palliative hepatectomy.

Case Presentation

Patient 1, a 49-year-old Asian male, was hospitalized due to a ruptured HCC. Computed tomography (CT) scan of the upper abdomen revealed multiple lesions in

the left hepatic lobe, with the largest measuring 71×48 mm. Additionally, the left portal vein was filled with tumor thrombus (shown in Fig. 1a; online suppl. Fig. S1; for all online suppl. material, see <https://doi.org/10.1159/000544163>). Furthermore, a CT scan of the lungs identified several nodules (shown in Fig. 1b). Patient 1 exhibited an alpha-fetoprotein level exceeding 60,500 ng/mL (shown in Table 1). The patient was diagnosed with HBV-related HCC at stage C according to BCLC staging classification. The comprehensive characteristics of the patient are outlined in Table 1. The patient was enrolled in our ongoing phase I study investigating TIL treatment in advanced solid tumors (ClinicalTrials.gov number, NCT03658785). After completing informed consent and eligibility confirmation, patient 1 underwent left hemi-hepatectomy for HCC, yielding fresh tumor tissues for TIL culture [14]. Before the infusion of TIL, the patient underwent lymphodepletion regimen, which included cyclophosphamide for 2 days and fludarabine for 3 days. After 24 days of TIL culture, the patient received a single intravenous infusion of 3.5×10^{10} autologous TIL, consisting of 82.60% CD4+ and 15.00% CD8+ T cells (shown in online suppl. Table S1). This was followed by intravenous interleukin-2 (IL-2) treatment (1.0×10^6 IU/day) for a duration of 9 days. After that, the patient received anti-PD-1 monoclonal antibody (mAb) (toripalimab, TopAlliance Biosciences) injections every 21 days (shown in online suppl. Table S2). However, anti-PD-1 mAb was administered only twice but had to be discontinued due to pandemic restriction and financial reason. Patient 2, a 67-year-old Asian female, was admitted 1 week after undergoing transhepatic arterial embolization at another hospital due to tumor rupture and bleeding. CT scan revealed a sizable mixed signal mass in the left lobe of the liver, measuring approximately 147×79 mm (shown in Fig. 1c). Simultaneously, multiple nodules were observed scattered throughout both lungs, with the largest one situated in the middle lobe of the right lung, measuring about 18 mm in diameter (shown in Fig. 1d). The AFP level was 14,529 ng/mL (shown in Table 1). The patient was diagnosed with HBV-related HCC at stage C. The detailed clinical characteristics are summarized in Table 1. The patient was enrolled in our study and underwent palliative left hemi-hepatectomy. After 29 days of TIL culture, the patient underwent a five-day lymphodepletion treatment, followed by a single intravenous infusion of 1.2×10^{10} autologous TIL (90.60% CD4+ and 7.24% CD8+ T cells) (shown in online suppl. Table S1). Subsequent to the TIL infusion, the patient received IL-2



(Figure continued on next page.)

treatment (1.0×10^6 IU/day) for 12 days. Then, the patient received toripalimab every 21 days for 18 sessions (shown in online suppl. Table S2).

After receiving one session of TIL infusion (3.50×10^{10}) followed by only two sessions of anti-PD-1 mAb, all lung metastases in patient 1 completely disappeared 2 months after hepatectomy and have maintained a tumor-free status up to now (shown in Fig. 1a, b). As depicted in Figure 1d, metastatic lung lesions in patient 2 progressed 1 month after hepa-

tectomy with the initial 18 mm lesion in the right lung increased to 25 mm. However, after receiving one session of TIL infusion (1.20×10^{10}) and regular anti-PD-1 therapy, the lung lesions completely disappeared 10 months after hepatectomy and have maintained a tumor-free status until manuscript submission (shown in Fig. 1c, d). As of now, these 2 patients have survived for more than 24 and 48 months, respectively, and resumed their normal lives without any further antitumor treatment.

Treatment-related adverse events reported during TIL and anti-PD-1 therapy

Adverse Event	Lymphodepletion		TIL infusion		IL-2 infusion		Anti-PD-1 mAb infusion	
	Patient 1	Patient 2	Patient 1	Patient 2	Patient 1	Patient 2	Patient 1	Patient 2
Neutrophil count decreased								
Platelet count decreased								
Lymphocyte count decreased	Grade 4	Grade 4						
White blood cell count decreased								
Anemia								
Thrombocytopenia								
Transaminase abnormality	Grade 1		Grade 1		Grade 1			
Creatinine increased								
Hypokalemia								
Hypoalbuminemia								
Nausea	Grade 2	Grade 2						
Vomiting	Grade 2							
Diarrhea								
Fatigue			Grade 1		Grade 1		Grade 1	Grade 1
Dyspnea								
Abdominal pain								
Constipation								
Allergy								
Fever			Grade 2	Grade 2	Grade 2	Grade 2		
Chills								
Tachycardia								
Oliguria								
Rash							Grade 1	
Hypertension		Grade 2						

e

Fig. 1. Treatment timeline and treatment-related adverse events of patients 1 and 2. **a** Enhanced CT scan of liver tumor before (upper panel) and after surgery (lower panel) in patient 1. The tumor (yellow circle) was removed by left hemi-hepatectomy in patient 1. **b** CT scans of metastatic lung lesions (red arrows) before surgery, 2 months and 48 months after surgery in patient 1. The metastatic lung lesions were completely disappeared 2 months after hepatectomy. The patient has maintained a tumor-free status for 48 months. **c** Enhanced CT scan of liver tumor before surgery (upper panel) and the enhanced magnetic resonance imaging (MRI) scan after surgery (lower panel) of

patient 2. The tumor (yellow circle) was removed by left hemi-hepatectomy. **d** CT scans of metastatic lung lesions (red arrows) before surgery, 1 month, 10 months, and 24 months after surgery in patient 2. The metastatic lung lesions progressed 1 month after hepatectomy. After receiving TIL therapy, the metastatic lung lesions were completely disappeared 10 months after surgery, and the patient has maintained a tumor-free status for 24 months. **e** The treatment-related adverse events were found during TIL and anti-PD-1 therapy of patients 1 and 2. TIL, tumor-infiltrating lymphocytes; IL-2, interleukin-2; PD-1, programmed cell death protein 1; mAb, monoclonal antibody.

Table 1. Characteristics of 2 patients

Characteristics	Patient 1	Patient 2
Age	49	67
Gender	Male	Female
Primary tumor location	Liver	Liver
Pathology	HCC	HCC
Tumor differentiation	Median	Low
Presence of portal vein thrombosis	Yes	Yes
Extrahepatic metastatic sites	Lung	Lung
BCLC staging	C	C
Child-Pugh score	A6	A6
ALBI score	2	2
ECOG score	1	1
Alpha-fetoprotein levels, ng/mL	>60,500	14,529
Etiology of chronic liver disease	HBV	HBV
Adequate antiviral therapy	Yes	Yes
Tumor rupture history	Yes	Yes
Prior treatments	None	TACE
Tumor PD-L1 expression $\geq 1\%$	No	No
Acquisition of TIL	Liver resection	Liver resection

BCLC staging, Barcelona Clinic Liver Cancer staging; ECOG, Eastern Cooperative Oncology Group; TACE, transhepatic arterial embolization; PD-L1, programmed cell death ligand 1; TIL, tumor-infiltrating lymphocytes.

Treatment-related adverse events were graded according to the Common Terminology Criteria for Adverse Events, version 5.0 (CTCAE v5.0). Hematological toxicities were expected, and grade four lymphocyte count decrease toxicity was noted in both patients, resolving after the cessation of chemotherapy (shown in Fig. 1e). Two weeks after lymphodepletion and TIL infusion, the total white blood cell count, neutrophil count, and lymphocyte count gradually returned to pretreatment levels in both patients (shown in Fig. 2a, b). Additionally, minor to moderate fluctuations were observed in both platelet count and hemoglobin in the patients (shown in Fig. 2c, d). All non-hematologic adverse events, including transaminase abnormality, nausea, vomiting, fatigue, fever, rash, and hypertension were grade one or two (shown in Fig. 1e). Symptoms alleviated at the end of the treatment without the need for medication.

The in vivo persistence of adoptively transferred T cells in the blood at 1 month post-cell transfer is correlated with improved outcomes in melanoma patients treated with ACT [15]. We thus evaluated the in vivo persistence of the infused TIL clones in patients 1 and 2, respectively. We used

single-cell TCR sequencing to quantify the expected frequency of TCR β clonotype sharing the same nucleotide sequence of CDR3. For patient 1, we identified a total of 3,287 (corresponding to 8,675 cells), 6,560 (corresponding to 9,440 cells), and 7,475 (corresponding to 10,772 cells) TCR clones in TIL infusion product, 3 months post-PBMC, and 6 months post-PBMC samples, respectively (shown in online suppl. Table S3). Using the TCR sequence as a molecular tracking barcode, we found that the frequency of CDR3 sharing constituted 9.76% of all TCR clones in PBMC at approximately 3 months after the TIL infusion and 10.50% of all TCR clones in PBMC at 6 months (shown in Fig. 2e). For patient 2, a total of 2,448 clones (corresponding to 7,465 cells), 3,827 clones (corresponding to 8,723 cells), and 3,333 clones (corresponding to 8,380 cells) were identified in TIL infusion product, 3 months post-PBMC, and 6 months post-PBMC samples, respectively (shown in online suppl. Table S4). The frequency of CDR3 sharing observed in PBMC at 3 and 6 months after infusion was 3.63% and 4.02%, respectively (shown in Fig. 2f). These results suggested that the infused TIL persisted in the peripheral blood.

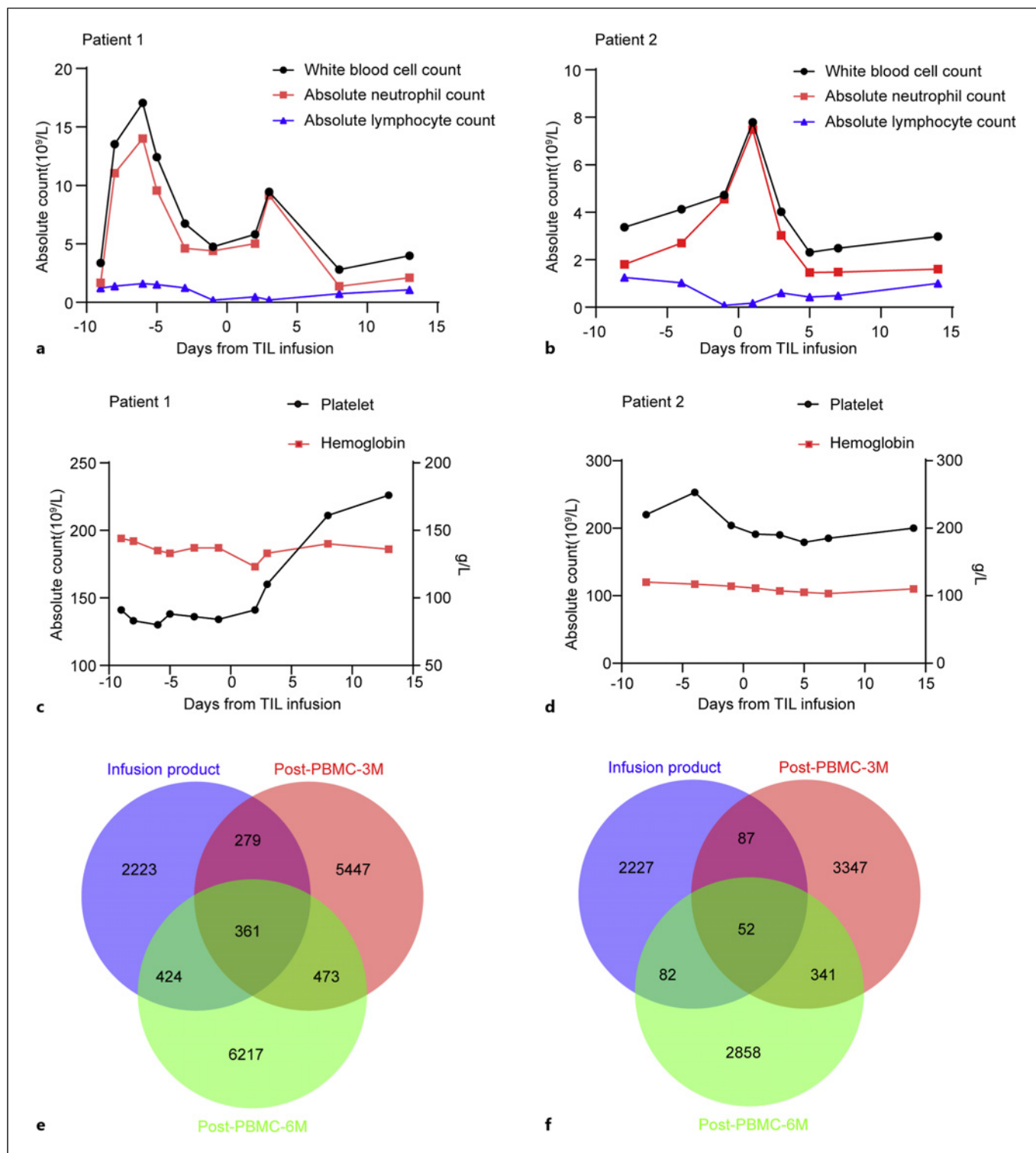


Fig. 2. Changes of peripheral blood cell counts and characteristics of TIL during treatment. **a** Changes of absolute count of cells in blood after lymphodepletion and TIL infusion in patient 1. **b** Changes of absolute count of cells in blood after lymphodepletion and TIL infusion in patient 2. **c** Fluctuations of platelet

count and hemoglobin level during treatment in patient 1. **d** Fluctuations of platelet count and hemoglobin level during treatment in patient 2. **e** Venn diagram of shared clonotype frequency in patient 1. **f** Venn diagram of shared clonotype frequency in patient 2. M, months.

Discussion

Our study demonstrated that TIL infusion in combination with anti-PD-1 therapy for aHCC was feasible, with manageable adverse effects. To the best of our knowledge, this is the first report demonstrating the efficacy of TIL infusion combined with anti-PD-1 therapy in aHCC patients. Interestingly, we unexpectedly found that palliative hepatectomy with maximal removal of tumor burden may benefited the efficacy of TIL infusion plus anti-PD-1 therapy and even resulted in cure. Two patients with PVTT and lung metastases have achieved a tumor-free status for 24 and 48 months, respectively, after a combined treatment strategy. They have resumed their normal lives without further anti-tumor treatment. Considering the median disease-free survival and overall survival of those HCC patients with macrovascular invasion undergoing hepatectomy are approximately 5 and 15 months, respectively [16, 17]. It is reasonable to consider that both of them have achieved a cure.

Tumor burden is a crucial factor for judging the therapeutic effect of immunotherapy. For the most part, lower tumor burden before immunotherapy is relative to better immunotherapeutic outcome [18]. An increasing number of myeloid-derived suppressor cells, regulatory T cells, and tumor-associated macrophages infiltrate the tumor microenvironment as the tumor burden increased, and these cells are related to tumor immune tolerance [19]. In multiple mouse models, tumor resection prior to immunotherapy to reduce tumor burden has been shown to improve control of tumor growth [20, 21]. Chen et al. [22] proposed a new classification system on the tumor immune microenvironment for predicting the efficacy of immunotherapy. Using a cutoff value of PD-L1 expression $\geq 1\%$ to determine PD-L1 positivity, patients who test positive have a higher objective response rate compared to those who test negative [23]. PD-L1-negative tumors without TIL infiltration are considered immunologically ignorant [22]. Unfortunately, most HCC are negative in PD-L1 expression, which significantly impede the effectiveness of anti-PD-1 therapy. In our study, PD-L1 expression was negative ($<1\%$) in these 2 patient specimens as determined by immunohistochemical staining (shown in Table 1). Nevertheless, by palliative hepatectomy in combination with TIL infusion plus anti-PD-1 therapy, the patients still achieved excellent survivals. Thus, we assume that by both increasing TILs through ACT and removing as much tumor burden as possible may improve the efficacy of immunotherapy in patients with negative PD-L1 expression.

Most clinical guidelines recommend only systemic therapy as the first-line treatment for aHCC patients [3, 24, 25]. However, some studies indicated that surgical resection achieved better outcomes compared with systemic therapy [16, 17]. For patients with Vp3 PVTT, the median recurrence-free survival after surgery was only 0.56 years [26], and it is even worse for those patients with macrovascular invasion and lung metastases [16]. From the perspective of clinical practice, performing palliative hepatectomy for these 2 patients may not be advisable. However, we conducted palliative hepatectomy to address the unmanageable pain resulting from the rupture of tumors and also to obtain material for subsequent TIL cultivation. To our surprise, the lung metastatic tumors disappeared after palliative hepatectomy followed by TIL infusion and anti-PD-1 therapy. Our study suggested that for patients with vascular invasion, TIL infusion plus anti-PD-1 therapy has the potential to completely eliminate those unfound small tumor lesions or circulating tumor cells if the tumor burden of the patients can be maximally removed. Our study sheds light on a clinical scenario where hepatectomy can be granted for better outcomes for patients with aHCC, if TIL infusion and anti-PD-1 therapy follows.

Although the initial outcomes in report are encouraging, the study is characterized by important limitations. First, enrolled patients were treated with complex medication regimens and the precise mechanism underlying the observed antitumor responses remains under investigation. Second, due to the impact of the COVID-19 pandemic, the entire research treatment decision-making and treatment plan were unable to be strictly implemented according to the experimental design. For instance, for safety reasons, patient 1 could not undergo a biopsy of the lung lesion to confirm the presence of lung metastases. Additionally, for patient 2, the long-term combination therapy based on TIL and anti-PD-1 mAb makes it impossible to rule out the interference of anti-PD-1 mAb, IL-2, and non-myeloablative chemotherapy on the evaluation of TIL efficacy. A direct comparison within the cohort against anti-PD-1 mAb therapy would be more convincing to demonstrate the superiority of TIL combined with anti-PD-1 mAb.

In summary, based on our initial findings, combining autologous TIL infusion with anti-PD-1 therapy appears to be a safe and feasible strategy for patients with aHCC. Meanwhile, performing palliative hepatectomy to achieve maximal tumor burden reduction before initiating immunotherapy strategy has the potential to enhance its efficacy and might even lead to a cure for some patients.

However, further research on a larger scale is needed to enhance the completeness and durability of clinical responses.

Acknowledgments

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Statement of Ethics

The study was approved by the Institutional Review Board at Tongji Hospital (S1230). All the patients have written consent forms signed for the treatment received. All procedures were conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from the patients for the publication of their medical case details and any accompanying images.

Conflict of Interest Statement

The authors declare no potential conflicts of interest.

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Author Contributions

T.X. and Z.H. designed the study, secured grants, and revised the manuscript. X.C. contributed to manuscript revision. T.Y. and L.C. collected and interpreted the data and drafted the manuscript. C.W., M.W., E.Z., B.L., and Z.Z. were responsible for data collection. All authors contributed to the article and approved the submitted version.

Data Availability Statement

The data supporting the findings of this study are not publicly available because the clinical project is still ongoing, with patient enrollment and follow-up in progress. Sharing these data could potentially compromise the privacy of research participants. However, the data can be obtained from the corresponding author, Dr. Huang, upon reasonable request. Please contact Dr. Huang at huangzy@tjh.tjmu.edu.cn for data access.

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