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Case Report

Glypican-3-Targeted CAR T Cell Therapy in An Advanced Hepatocellular Carcinoma Patient: A Case Report

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Abstract

Purpose: Glypican-3 (GPC3) is highly expressed in most hepatocellular carcinomas (HCCs) and represents a promising cancer target. Most previous clinical trials of GPC3-targeted chimeric antigen receptor (CAR) T cells have demonstrated preliminary safety but unsatisfactory tumor response. However, reports on the detailed toxicity and efficacy profile of GPC3 CAR T cells in HCC patients are limited. We aim to report preliminary results of our GPC3 CAR T cells. **Methods and results**: A 66-year-old patient with a history of recurrent HCC had undergone multiple treatments. Immunohistochemistry revealed high GPC3 expression in his tumour tissue. After enrollment in our single-arm, open-label phase I trial (NCT05123209), the patient received fludarabine and cyclophosphamide lymphodepletion before a single infusion of GPC3-targeted CAR T cells. The treatment was well tolerated. Only grade 1 cytokine release syndrome (CRS) was observed on Day 4 post-infusion, manifested by low-grade fever and elevations in IL-6 and IL-10. Symptoms were resolved rapidly with tocilizumab and dexamethasone. No severe adverse events were noted. CAR T cells proliferated and peaked at Day 7 in the peripheral blood. A transient reduction of alpha-fetoprotein (AFP) was observed on Day 21. However, computed tomography on Day 28 demonstrated an enlargement of the primary lesion, accompanied by a rise in AFP, indicating progressive disease (PD). **Conclusions of the study:** This case illustrates that GPC3-directed CAR T cell therapy was safe and feasible for an advanced HCC patient, but did not achieve objective remission within four weeks. Further optimization of treatment strategies was warranted for improved response.

Keywords: Hepatocellular carcinoma; Glypican-3; CAR T-cell therapy; Case report; Cytokine release syndrome

Introduction

Hepatocellular carcinoma (HCC) is a prevalent and highly fatal malignancy worldwide, particularly in East Asia and parts of Africa [1,2]. Although systemic therapies such as sorafenib and other tyrosine kinase inhibitors can extend survival to some degree, the prognosis of advanced HCC remains poor [3].

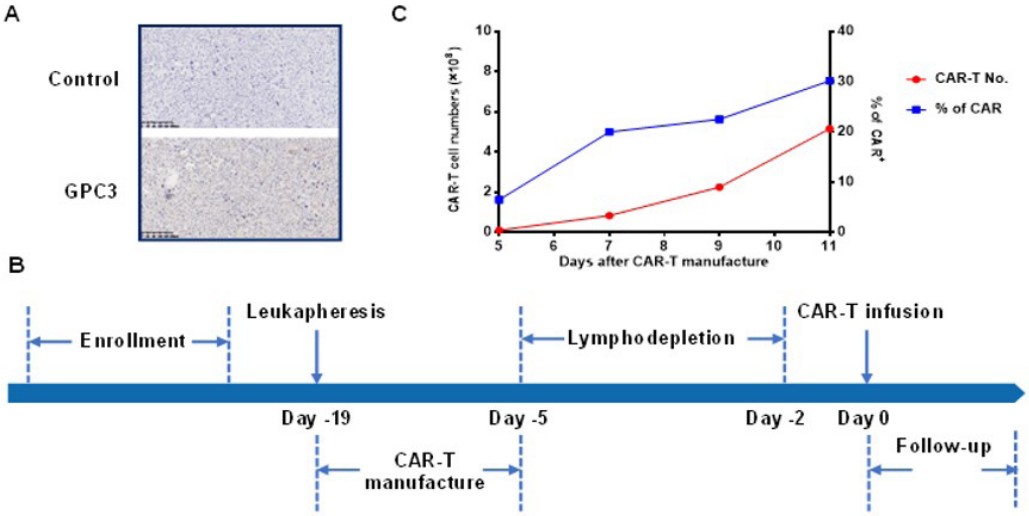
Glypican-3 (GPC3) is a membrane-bound heparan sulfate proteoglycan that is typically absent in normal adult tissue but is overexpressed in most HCCs [4]. Research suggests that GPC3 may promote tumor progression via modulation of the Wnt and other key signalling pathways [5,6]. Given its relatively high tumor specificity, GPC3 has emerged as a promising immunotherapeutic target. Early-phase clinical studies on GPC3-directed monoclonal antibodies and chimeric antigen receptor (CAR) T cell therapies have shown an acceptable safety profile, although with modest

objective response rates so far [7,8]. Moreover, reports on the detailed toxicity and efficacy profile of GPC3 CAR T cells in HCC patients are limited, especially in patients with high tumor burden.

We herein reported a case of advanced, recurrent HCC in a patient who received GPC3-targeted CAR T cell therapy after multiple previous treatments had failed. We described his clinical course, adverse effects, pharmacokinetics, early efficacy assessment, and change of biomarkers, providing insights into both the feasibility and limitations of this approach in heavily pre-treated patients.

Case Presentation

A 66-year-old male (weight, 58.9 kg) was diagnosed with primary HCC 15 years ago. Over the course of his disease, he underwent repeated local ablative therapies (radiofrequency ablation and chemical ablation), hepatic arterial infusion chemotherapy (HAIC), transcatheter arterial chemoembolization (TACE), surgical resection, and multiple systemic therapies (antiangiogenic therapy and immune checkpoint therapy). In late 2020, computed tomography (CT) revealed multiple intrahepatic and peritoneal lesions with a maximum diameter of approximately 7.3 cm (Table 1, Table 2). Serum alpha-fetoprotein (AFP) exceeded 3,000 ng/mL. Pathological analysis of newly biopsied tumor tissue demonstrated high GPC3 expression (Figure 1A). According to the inclusion criteria of an ongoing phase I trial (NCT05123209), the patient's Eastern Cooperative Oncology Group (ECOG) performance status was 1, and baseline liver, kidney, and hematologic parameters were within acceptable limits. He provided written informed consent.



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Testing Items	Results
% T cells transduced	30.2%
Cell viability	75%
Dose of CAR-T	8×10^6/kg
Sterility	Negative
Endotoxin	Negative
Mycoplasma	Negative

Figure 1: Immunohistochemical examination of GPC3 expression, study timeline and the quality control parameters of the GPC3 CAR T formulation. A. Immunohistochemical staining for Glypican-3 (GPC3) in tumour tissue obtained before enrolment (upper = negative control; lower = GPC3-positive; scale bar = 100 μm). B. Clinical timeline showing enrolment, leukapheresis (Day -19), lymphodepletion chemotherapy (Days -5 to -3), GPC3-CAR-T infusion (Day 0) and planned follow-up (Days 7, 14, 28, 56). C. In-vitro expansion profile during manufacture: blue line = total viable T-cell number; red line = percentage of CAR-positive (CAR^+) T cells (flow-cytometry) on culture Days 5–11. D. Quality control of the final GPC3-CAR-T product (30.2 % transduction efficiency, 75 % viability, 8×10^6 kg^{-1} dose; sterility, endotoxin and mycoplasma all negative).

Subject ID	Age (years)	Sex	†ECOG score	‡CNLC stage	HCC History (years)	Disease stage	Metastasis	Cirrhosis	Previous lines of treatment	GPC3 expression	CAR-T cell dose
GI0101	66	M	1	IV	15	Relapsed	Yes	Yes	2	+	4.71×10^8
†ECOG, Eastern Cooperative Oncology Group; ‡CNLC, China liver cancer staging system.											

Table 1: Baseline characteristics of the patient.

Date	Treatment	Response
2004.05.25	†CT-guided chemical ablation	‡PR
2004.07.01	hepatic arterial infusion chemotherapy plus transcatheter arterial embolization	PR
2004.07.15	CT-guided chemical ablation	PR
2004.10.29 2005.01.12	hepatic arterial infusion chemotherapy plus transcatheter arterial embolization	PR
2015.04.23	transcatheter arterial embolization	PR
2018.06.11	radiofrequency ablation	PR
2018.11.13	surgical removal of the tumor tissue plus microwave ablation	PR
2019.05.10	hepatic arterial infusion chemotherapy plus transcatheter arterial embolization	PR
2019.11.21 2020.01.14 2020.04.16	transcatheter arterial embolization	PR
2020.03.06-2020.08	Sorafenib, 400mg bid, 5 cycles	§PD
2020.09.09-2020.12	Regorafenib (80 mg bid) plus Toripalimab (180mg, q3w), 2 cycles	¶SD
†CT, computed tomography; ‡PR, partial response; §PD, progressive disease; ¶SD, stable disease.		

Table 2: Previous Treatments of the Patient.

Results

CAR T Cell Manufacturing and Infusion

Peripheral blood mononuclear cells were collected by leukapheresis. T cells were activated with anti-CD3/CD28 magnetic beads, followed by lentiviral transduction with a construct encoding the humanized GPC3-specific single-chain variable fragment (scFv), CD28 costimulatory domain, and CD3ζ signaling domain. After 11 days of ex vivo expansion, CAR T cells were harvested, with a transduction efficiency of approximately 30.2% and viability of 75% (Figure 1B–1D). The patient received cyclophosphamide (250 mg/m^2/day) plus fludarabine (25 mg/m^2/day) for 3 days as lymphodepletion therapy, and then received a single CAR T cell infusion (total dose of 4.71×10^8).

Adverse Events and Efficacy Assessment

The patient was closely monitored for changes in vital signs, laboratory parameters, and serum cytokines including interleukin (IL)-2, IL-6, IL-10, interferon (IFN)-γ, etc. On Day 4 post-infusion, he experienced low-grade fever (<38.5°C) alongside elevated IL-6 and IL-10, consistent with Grade 1 cytokine release syndrome (CRS) **(Figure 2A, 2B)**. Symptoms were resolved promptly following administration of tocilizumab (IL-6 receptor blocker) and dexamethasone. No neurotoxicity or other severe adverse events were observed (Table 3). Flow cytometry revealed an obvious expansion of CAR T cells in the peripheral blood, with the peak number on Day 7 and subsequent decrease to a low level (Figure 2C).

Subject ID	†CRS grade	Neurotoxicity	Use of Tocilizumab	Use of Dexamethasone
GI0101	1	No	Yes	Yes
†CRS, cytokine release syndrome				

Table 3: CAR T Cell Therapy Related Adverse Events and Management.

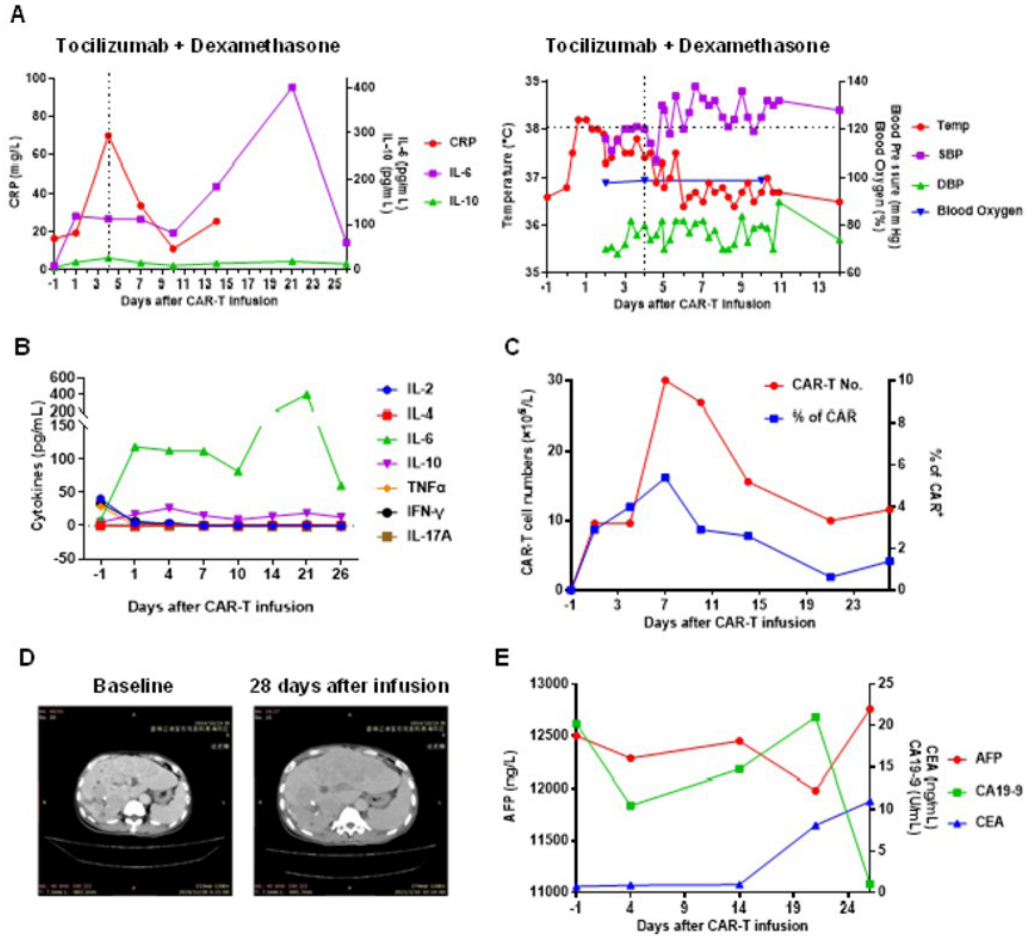

Figure 2: Safety, pharmacodynamics and early efficacy after GPC3 CAR T infusion. A. Left: C-reactive protein (CRP, purple) and interleukin-6 (IL-6, red) kinetics; right: vital-sign trends (body temperature, Temp; systolic/diastolic blood pressure, SBP/DBP; peripheral oxygen saturation, SpO_2) before and after tocilizumab + dexamethasone given for Grade 1 cytokine-release syndrome (dotted lines). B. Additional serum cytokines (IL-2, IL-4, IL-10, TNF-α, IFN-γ, IL-17A) from Day -1 to Day 26. C. Circulating GPC3-CAR-T cells (% CAR^+ of $CD3^+$, blue; absolute CAR-T count × 10^3 μL^{-1}, red) peaking on Day 7 and declining thereafter. D. Contrast-enhanced CT at baseline (left) and Day 28 (right) showing enlargement of the dominant hepatic lesion. E. Serum tumour-marker dynamics (AFP, CEA, CA19-9) from baseline to Day 56; AFP rose continuously, consistent with progressive disease.

A CT scan performed on Day 28 revealed further enlargement of the primary lesion (maximal diameter increasing from 7.3 cm to 9.6 cm), indicating progressive disease (PD). Monitoring of the HCC biomarkers including AFP, CA19-9, and carcinoembryonic antigen (CEA) showed a transient reduction of AFP on Day 21 and a decrease of CA19-9 on Day 28. However, elevations in both AFP and CEA levels were observed on Day 28, accompanied with the tumor progression (Figure 2D, 2E).

Discussion

This patient had an extremely long disease course (15 years) with a high tumor burden, having previously received multiple local and systemic interventions. Following GPC3-targeted CAR T cell therapy, the overall safety profile was consistent with reported data in similar trials: only mild CRS occurred, and it was rapidly controlled by tocilizumab plus low-dose steroids [8,9]. This underscores the manageable toxicity of CAR T-cell therapy when rigorous monitoring and timely interventions are employed [10].

Nonetheless, short-term assessment (4 weeks) showed tumor progression both by imaging and AFP levels. Several factors may account for the limited clinical response:

High Tumor Burden: Multiple lesions of substantial size may exceed the immediate cytotoxic capacity of a single CAR T infusion at the dose of 4.71×10^8.

Insufficient CAR T-Cell Persistence: Despite initial in vivo expansion, the detected CAR T cell peak was modest and short-lived, potentially inadequate for clearing bulky disease. The peak number was as less as 1/100 of CD19 CAR T or BCMA CAR T cells in hematologic tumor patients. Therefore, a sufficient effector-to-target ratio of GPC3 CAR T cells was not achieved in this patient.

Immunosuppressive Tumor Microenvironment: Advanced HCC often exhibits immunosuppressive features within the hepatic milieu, limiting the efficacy of T-cell-based therapies. Investigating combinations with immune checkpoint inhibitors or other synergistic approaches could be beneficial.

These observations reinforce that while GPC3 is a promising target for HCC therapy, further efforts are required to enhance clinical outcomes. Strategies may include optimizing cell dose, improving CAR design for better expansion and persistence, patient selection based on GPC3 expression levels, and combining CAR T cells with other treatments such as PD-1/PD-L1 inhibitors.

Conclusions

In conclusion, GPC3-targeted CAR T- cell therapy exhibited an acceptable safety profile in this heavily pretreated advanced HCC patient, presenting only manageable Grade 1 CRS. However, short-term imaging and biomarker evaluations indicated disease progression. This case highlights the need for continued optimization-through dose escalation, enhanced CAR T- cell persistence, or combination regimens-to achieve meaningful tumor control in patients with high tumor burden and aggressive disease. Larger, prospective clinical trials will help define the optimal treatment settings, dosing schedules, and patient subgroups most likely to benefit.

Declarations

Ethics Approval and Consent to Participate

All procedures were approved by the Ethics Committee of Panjin Liaoyou Gem Flower Hospital (Approval No. PJLYBSHYY-2020YJZ (001)) and complied with the Helsinki Declaration. The patient provided written informed consent prior to participation.

Consent for Publication

The patient granted permission for publication of this case report and all accompanying data.

Availability of Data and Materials

All data generated or analyzed in this case report are included within the article. Additional details are available from the corresponding author upon reasonable request.

Competing Interests

The authors declare that they have no competing interests.

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Authors' Contributions

Lili Kan and all coauthors contributed to the study design, data collection, analysis, and manuscript drafting.

All authors reviewed and approved the final version of the manuscript.

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