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CASE REPORT

Case Report: Successful Surgical Resection of PVTT Vp4 Hepatocellular Carcinoma Following Hepatic Arterial Infusion Chemotherapy Combined with Cadonilimab Plus Donafenib

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Objective: To evaluate the potential and efficacy of hepatic artery infusion chemotherapy combined with the PD-1/CTLA-4 bispecific antibody cadonilimab and the multi-kinase inhibitor donafenib in conversion therapy for unresectable hepatocellular carcinoma (uHCC) with Vp4-type portal vein tumor thrombus(PVTT).

Methods: We present a case report of a 41-year-old male diagnosed with diffuse hepatocellular carcinoma (HCC) in the right lobe of the liver and tumor thrombus involving the main portal vein. Following multidisciplinary team evaluation, the patient received conversion therapy consisting of hepatic artery infusion chemotherapy (HAIC) using oxaliplatin, fluorouracil, and leucovorin, in combination with cadonilimab and donafenib.

Results: Post-treatment imaging demonstrated marked regression of intrahepatic tumors and complete resolution of the portal vein tumor thrombus. Serum alpha-fetoprotein (AFP) levels normalized, and protein induced by vitamin K absence or antagonist-II (PIVKA-II) levels showed a significant decline. Subsequently, a radical right hepatectomy was successfully performed, and post-operative pathological examination confirmed complete response. The patient experienced an uneventful recovery and remained free of tumor recurrence during the one-year follow-up period.

Conclusion: The integrative treatment strategy combining HAIC with cadonilimab and donafenib demonstrates considerable promise as a conversion approach for patients with traditionally unresectable HCC with Vp4-type PVTT. This regimen may substantially improve oncological outcomes and enable curative resection. This case provides compelling evidence to support further clinical investigation of this multimodal therapeutic combination.

Keywords: hepatocellular carcinoma, conversion therapy, interventional therapy, bispecific antibodies, portal vein tumor thrombus, case report

Background

Hepatocellular carcinoma (HCC) is a prevalent malignant tumor worldwide, characterized by a poor prognosis.[1] Due to the asymptomatic nature of early-stage disease, approximately 70% of patients are diagnosed at an advanced stage, missing the opportunity for curative surgical intervention and consequently facing unfavorable outcomes.[2] Portal vein tumor thrombus (PVTT) represents the most prevalent form of vascular invasion in HCC, with approximately 50% of HCC patients presenting with PVTT at the time of diagnosis.[3] Patients with PVTT, particularly those with Vp4-type PVTT, have a median survival of no more than 4 months and have traditionally been deemed ineligible for surgery.[4,5] Although systemic therapies such as tyrosine kinase inhibitors (TKIs) have achieved modest improvements, their efficacy

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remains limited, with objective response rates below 20%.[6,7] In recent years, conversion therapy remains a critical approach for managing unresectable hepatocellular carcinoma (uHCC).[8] Notably, hepatic artery infusion chemotherapy (HAIC) has demonstrated a higher tumor response rate in patients with PVTT.[9,10] Concurrently, Immune checkpoint inhibitors combined with TKIs have shown improved prognosis in patients with uHCC, however, approximately 70% of patients initially do not achieve an ideal response.[11–13] Due to substantial non-response rates and the development of acquired resistance,[14–16] these conversion therapies do not consistently yield optimal therapeutic outcomes. Therefore, a option that provides a better prognosis is eagerly needed. Against this backdrop, we implemented a novel multimodal strategy: building upon the potent local control offered by HAIC, we combined it with cadonilimab, a novel PD-1/CTLA-4 bispecific antibody known for its synergistic immunomodulatory effects,[17] and donafenib, a next-generation TKI that has shown improved survival benefits over sorafenib.[5,18] This integrated approach—combining "local and systemic" therapies with "immunotherapy and targeted therapy"—has exhibited significant translational potential in preliminary studies.[19–21] Nevertheless, successful applications of this regimen in Vp4-type PVTT remain exceedingly rare. Currently, the comprehensive management of HCC has become the predominant approach, necessitating multidisciplinary collaboration to design personalized treatment plans that maximize patient outcomes. This case report aims to provide meaningful insights into therapeutic strategies for such high-risk, advanced scenarios.

Case Presentation

Our study received approval from the ethics committee of The First Affiliated Hospital of Guangxi Medical University (Ethics No: 2025-E0368). Written informed consent was obtained from the patient for participation in this study. A 41-year-old male patient was admitted to the hospital due to recurrent abdominal pain and bloating for over one month On November 12, 2023. The patient was identified as a hepatitis B carrier and had been undergoing regular oral entecavir antiviral therapy for the past month. He had a smoking history, averaging approximately 20 cigarettes per day for 20 years. He had no history of hypertension, diabetes and coronary artery disease. The patient denied any alcohol consumption. On physical examination, his body mass index (BMI) was 25.35 kg/m^2 (weight, 75 kg; height, 172.0 cm). No unremarkable presentations. Contrast-Enhanced of the liver and Contrast-Enhanced Ultrasound of the Liver demonstrated diffuse hepatocellular carcinoma in the right lobe of the liver (9.6 × 8.2cm) and portal vein main branch cancer thrombosis (Figure 1). Laboratory findings included alpha-fetoprotein (AFP): 15.89 ng/mL, protein induced by vitamin K absence or antagonist-II (PIVKA-II): 115,331.27 mAU/mL, HBV DNA: 1.12×10^5 IU/mL, ALT: 60 U/L, AST: 130 U/L. Routine blood

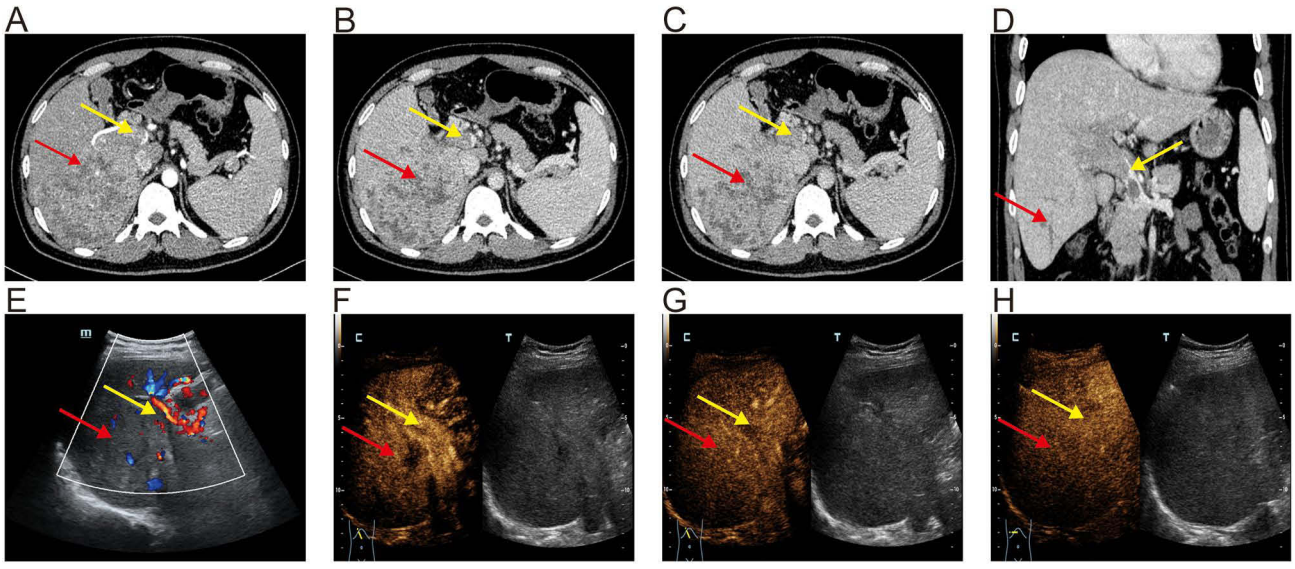

Figure 1 Multistage liver-enhanced CT and contrast-enhanced ultrasound at the first visit. The red arrows indicate intrahepatic tumors. The yellow arrows indicate portal vein tumor thrombus. (**A**) Arterial phase image of the initial CT. (**B**) Venous phase image of the initial CT. (**C**) Delayed phase image of the initial CT. (**D**) Coronal delayed phase image of the initial CT. (**E**) Conventional ultrasound image at the time of diagnosis. (**F**) Arterial phase ultrasonography image at the time of diagnosis. (**G**) Venous phase ultrasonography image at the time of diagnosis. (**H**) Delayed phase ultrasonography image at the time of diagnosis.

tests and coagulation function showed no remarkable abnormalities. The Child-Pugh score was 5 (grade A), and the indocyanine green test (ICG) indicated an ICG-R 15-minute retention rate of 9.7%. He was diagnosed with (1) primary hepatocellular carcinoma (right lobe of the liver, Child-Pugh grade A, Barcelona Clinic Liver Cancer stage C, China Liver Cancer Staging IIIa, PVTT type Vp4) (2) post-hepatitis B cirrhosis (3) splenomegaly (4) portal hypertension. The case was reviewed by the multidisciplinary team (MDT) of hepatobiliary surgery at the First Affiliated Hospital of Guangxi Medical University. The MDT considered the patient's high tumor burden along with the presence of cancerous thrombosis in the main portal vein and decided to initiate conversion therapy. This approach involved periodic evaluation of surgical feasibility combined with hepatic artery perfusion chemotherapy, targeted therapy, and immunotherapy. The patient agreed to undergo conversion therapy first, followed by an evaluation of surgical treatment. Considering the patient's commercial insurance coverage and confidence in the drugs provided by Zhongshan Kangfang Biomedical Co., Ltd, the patient voluntarily selected the immunotherapy regimen containing cadonilimab (AK104). In conjunction with the first-line recommended treatment regimen outlined in the guideline for diagnosis and treatment of primary liver cancer (2022 edition), the final targeted immunotherapy regimen was determined to include donafenib and cadonilimab. The patient subsequently signed a written informed consent for the treatment. On November 15, 2023, the first HAIC treatment was performed. Specific chemotherapy regimen (FOLFOX regimen): 85 mg/m^2 of oxaliplatin infusion for 3 h; 400 mg/m^2 of leucovorin infusion for 1.5 h; 400 mg/m^2 of 5-FU infusion for 2 h, and 2400 mg/m^2 of continuous 5-FU infusion for 46 h. Following this treatment, patients received donafenib 200 mg twice daily + cadonilimab 10 mg/kg every three weeks. Concurrently, oral entecavir antiviral therapy and hepatoprotective measures were implemented, and the detailed treatment (Figure 2C). After treatment, a follow-up liver-enhanced CT scan revealed shrinkage of the tumor lesion in the right lobe of the liver, reduction in the size of the cancer embolus, and decreased metabolic activity of both the tumor and the embolus. However, partial residual activity of the tumor was still observed. Serologic revaluation indicated an AFP level of 2.64 ng/mL and a PIVKA-II level of 94.21 mAU/mL. After Interventional therapy combined with targeted and immunotherapy, tumor markers demonstrated a significant decreasing trend (Figure 2A and B). According to the Modified Evaluation Criteria for Solid Tumor Efficacy, the patient's right lobe liver tumor achieved partial response (PR); however, imaging studies revealed that the tumor was still partially active (Figure 3A–F). Taking into account the patient's overall clinical condition, the MDT deliberated and recommended a surgical approach involving simultaneous hepatic tumor resection and

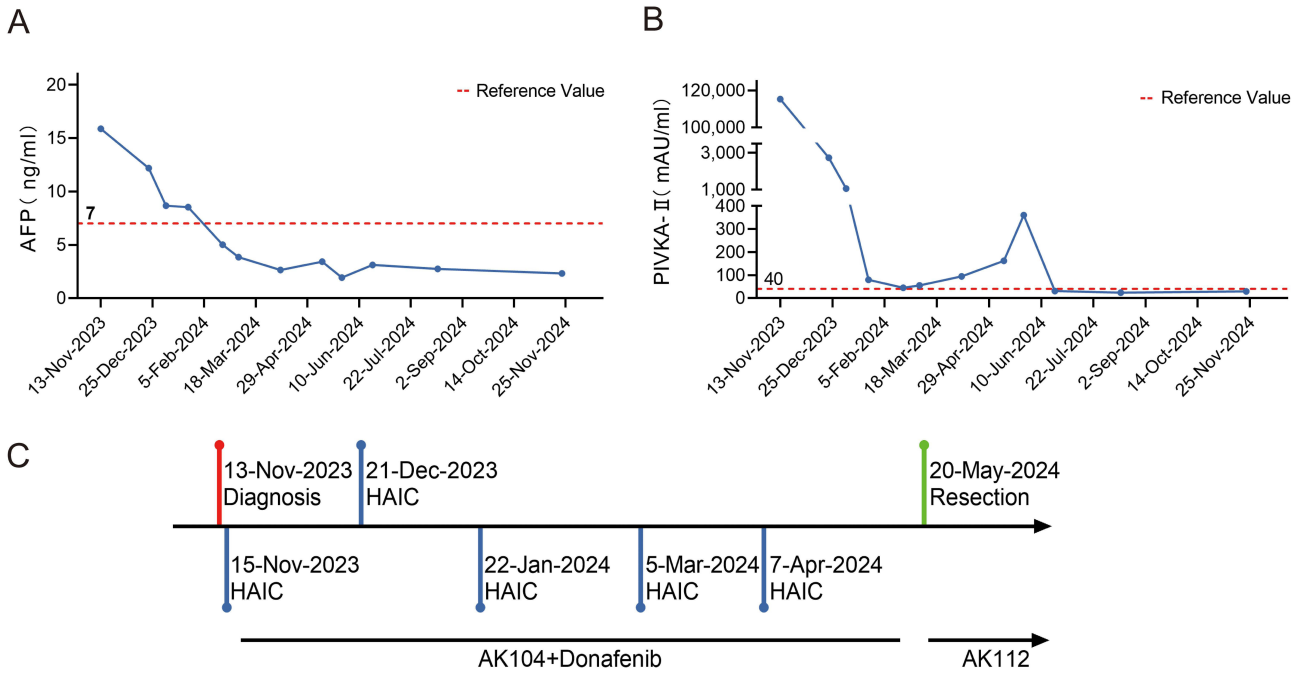

Figure 2 Dynamic changes of tumor marker levels during treatment and the treatment timeline. Graphical representation of dynamic changes in AFP (**A**), PIVKA-II (**B**) throughout the treatment course, along with the treatment timeline (**C**).

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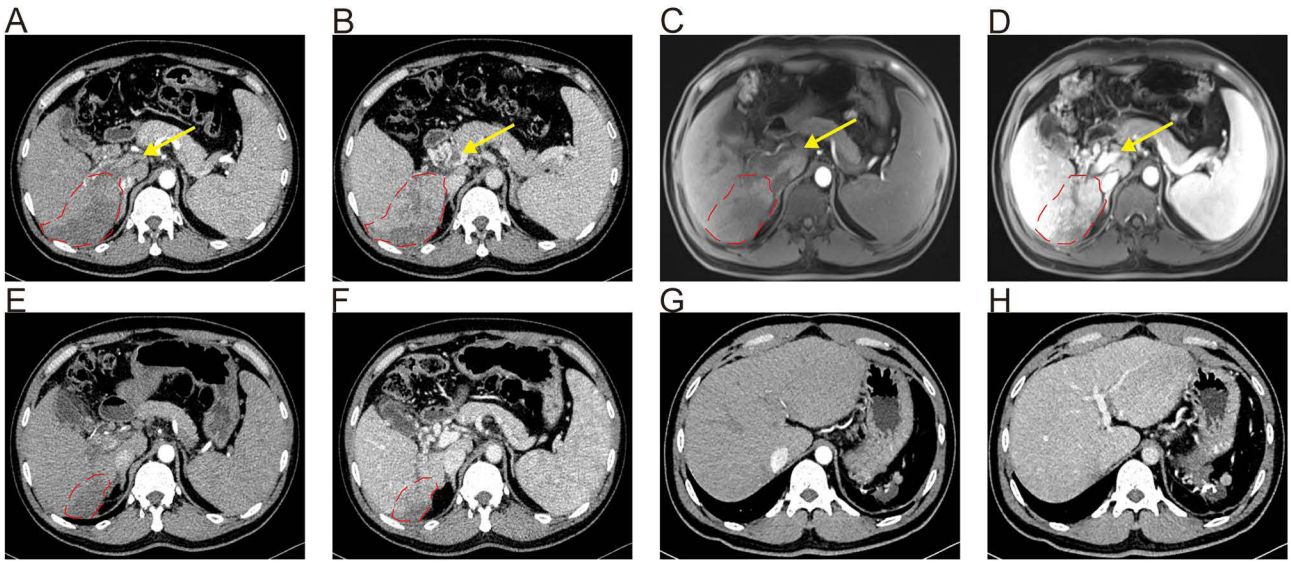

Figure 3 The multiphase CT and gadoxetate disodium–enhanced MRI scan results at various periods. The red dashed lines denote intrahepatic tumors. The yellow arrows indicate portal vein tumor thrombus. (**A**) Arterial phase CT image after two sessions of HAIC conversion therapy. (**B**) Venous phase CT image after two sessions of HAIC conversion therapy. (**C**) Arterial phase MRI image after three sessions of HAIC conversion therapy. (**D**) Venous phase MRI image after three sessions of HAIC conversion therapy. (**E**) Preoperative arterial-phase CT image. (**F**) Preoperative venous-phase CT image. (**G**) Arterial phase CT image one-year post-surgery. (**H**) Venous phase CT image one-year post-surgery.

splenectomy. Following thorough communication with the patient and his family, the patient consented to the surgical treatment and formally signed the informed consent form. Following the exclusion of surgical contraindications, a right posterior lobe hepatectomy, cholecystectomy, and splenectomy were performed with the assistance of intraoperative ultrasound on May 20, 2024. The tumor was primarily located in the S7 segment of the liver, with dimensions measuring 5.1×4.0 × 5.2 cm^3. The tumor was irregularly oval in shape, firm in consistency, and pale in color, with a pseudo-capsule that remained intact. The borders were clear, there was no hemorrhage in the center, and the tumor did not invade the blood vessels, bile ducts, diaphragm, or adrenal glands. The residual hepatic blood supply following tumor resection was adequate. In the in vitro measurement, the shortest distance between the S7 tumor and the incision margin was 0 cm (Figure 4A and B). Postoperative pathology (mass in segment S7 of the liver): specimen following radical resection post-intervention. Microscopically (Figure 4C and D), the tumor exhibited multifocal necrosis involving 100% of the lesion. Extensive fibrous tissue hyperplasia was observed surrounding the necrotic areas, accompanied by prominent lymphocytic infiltration, foam cell reaction, hemosiderin deposition, and cholestasis. These histopathological changes were consistent with the interventional therapy. No residual viable tumor tissue was detected. Additionally, there were no satellite nodules, no neural invasion, and no microvascular infiltration (MVI) grade: M0. The liver peritoneum and surgical margins were free of tumor involvement. Chronic hepatitis changes (G3S4) were noted in the adjacent hepatic tissues, with an Ishak score indicating inflammation of 12 and fibrosis of 6. Special stains for Ag and PAS corroborated the aforementioned diagnosis. Pathologic evaluation confirmed complete response (CR). The patient recovered well after surgery. The patient received adjuvant therapy with 20 mg/kg of ivonescimab (AK112) every 3 weeks after surgery to date. Adverse reactions occurring during conversion therapy were assessed according to the Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0). The treatment-related adverse events (TRAES) included: (1) diarrhea (CTCAE Grade 1); (2) thrombocytopenia (CTCAE Grade 1–2); (3) fever (CTCAE Grade 2); and (4) rash (CTCAE Grade 2). The patient exhibited no signs of tumor recurrence on follow-up imaging conducted one-year post-surgery (Figure 3G and H). Additionally, both AFP and PIVKA-II levels were within the normal range, and the patient maintained a good general condition.

Discussion

Patients with HCC combined with PVTT have limited effective treatment options and face a poor prognosis. Without anticancer therapy, the median survival period is less than four months.[4] For such unresectable cases, conversion therapy

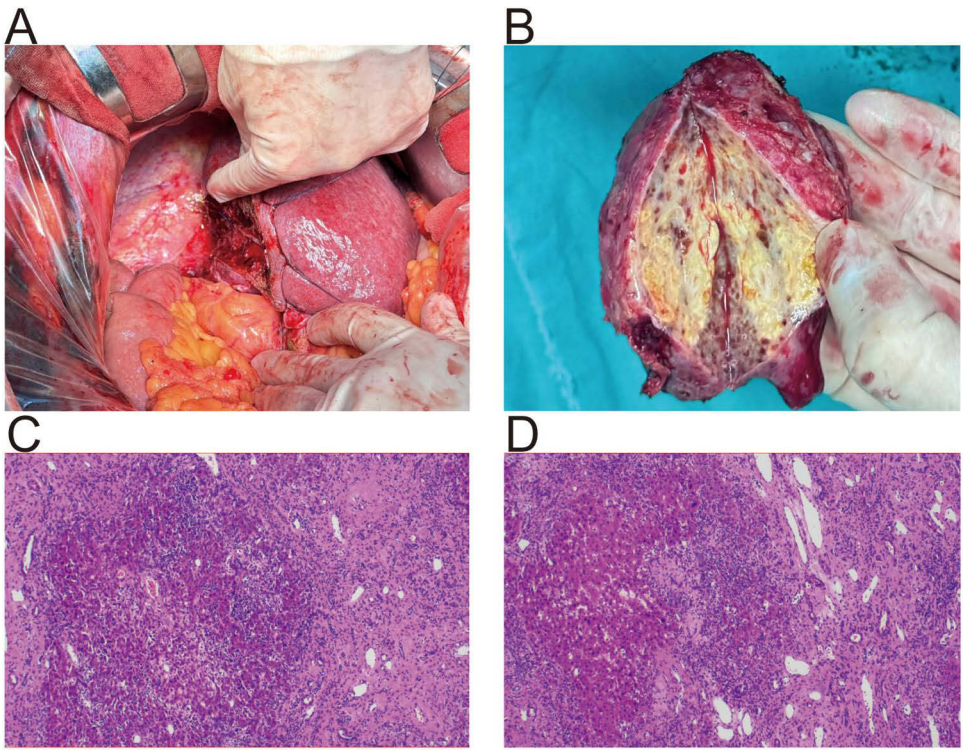

Figure 4 Gross and microscopic pathology of excised specimens. (**A**) Intraoperative observation. (**B**) Gross pathology. (**C** and **D**) Microscopic examination revealed no evidence of residual viable tumor tissue (C:40x magnification, (**D**) 100x magnification).

has emerged as a pivotal strategy to convert initially ineligible patients into surgical candidates and improve long-term outcomes.[5,22] This report presents the first documented case of successful conversion therapy using HAIC with FOLFOX, combined with the PD-1/CTLA-4 bispecific antibody cadonilimab and the multi-kinase inhibitor donafenib, ultimately enabling radical resection, a novel and promising approach for managing this highly refractory HCC subtype.

Treatment plan of this case rationale integrates local tumor control with systemic antitumor effects.[21,23–26] HAIC based on FOLFOX serves as the cornerstone of local therapy. By continuously infusing high-concentration chemotherapeutic agents through tumor-supplying arteries, it achieves drug concentrations in intrahepatic lesions and portal vein tumor thrombi that far exceed those of systemic intravenous chemotherapy. This enables effective control of high tumor burden and large-vessel tumor thrombi, with relatively lower systemic toxicity and better compared to transarterial chemoembolization.[27–30] Effective local control creates a favorable platform for subsequent systemic treatment. For systemic therapy, we employed cadonilimab in combination with donafenib, which act synergistically through multiple mechanisms: First, the combination of immunotherapy and targeted therapy, donafenib, as a multi-kinase inhibitor, not only inhibits tumor proliferation but also exerts anti-angiogenic effects that promote vascular normalization. This remodeling alleviates hypoxia and reduces immunosuppression in the tumor microenvironment, enhancing T-cell infiltration and improving responsiveness to immune checkpoint blockade.[31] Second, dual immune checkpoint inhibition via cadonilimab simultaneously targets PD-1 and CTLA-4 pathways, two critical regulators of T-cell activation. Compared to PD-1 monotherapy, this dual blockade may elicit a more robust and durable antitumor immune response by promoting broader T-cell priming and effector function.[32,33] Emerging clinical evidence further supports the safety and efficacy of combining bispecific antibodies like cadonilimab with tyrosine kinase inhibitors in advanced HCC.[34–36] Together, HAIC, donafenib, and cadonilimab constitute a multimodal, synergistic regimen that may underlie the achievement of pathological complete remission in this patient.

This case underscores several key considerations in translational therapy. First, timing of surgical intervention is crucial. Current consensus emphasizes seizing the optimal window for resection as early as feasible.[37] The prompt surgical decision following PIVKA-II rebound in this patient highlights the importance of dynamic monitoring and

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MDT-guided management. Second, whether all patients who achieve radiological response require surgical resection remains an open question. While some studies suggest watch-and-wait strategy may be appropriate for those achieving complete imaging response,[38] for high-risk patients, particularly those with Vp4-type PVTT, surgical resection remains the most definitive means of achieving curative intent and obtaining accurate pathological evaluation. In this instance, postoperative pathology confirmed pathological complete response (pCR), whereas preoperative imaging could not reliably distinguish viable tumor from necrotic tissue, reinforcing the irreplaceable role of surgery in current practice.

Postoperative adjuvant therapy remains non-standardized. Clinically, strategies often involve continuing effective preoperative regimens or transitioning to maintenance therapy tailored to individual response and tolerability.[39] Adjuvant treatment is generally recommended for at least six months, with regular monitoring via imaging and tumor markers.[10] Given the patient's high-risk features, including baseline Vp4 PVTT and adverse events during conversion therapy, the postoperative regimen was modified to ivonescimab, a bispecific antibody targeting both PD-1 and VEGF-A. This agent concurrently counteracts immune evasion and suppresses angiogenesis, offering a mechanistically rational and synergistic therapeutic effect.[40] Preliminary data across various solid tumors demonstrate manageable safety and encouraging efficacy signals,[41,42] supporting its potential as an adjuvant option. Nevertheless, optimal post-conversion management—including duration, drug selection, and sequencing—requires further validation through prospective, high-quality studies.

Finally, this study has inherent limitations as a case report, such as involving only a single subject, lacking a control group, and having a relatively short follow-up period. Future studies should validate the resectability rate and safety profile of this approach through prospective clinical trials involving larger, more diverse patient cohorts. Such efforts are crucial for developing more effective and precise multimodal treatment strategies for uHCC, particularly in high-risk patients with Vp4-type PVTT.

Conclusion

Combined therapy of HAIC, donafenib, and cadonilimab showed quick and durable efficacy in an advanced HCC patient. A multidisciplinary and multi-method integrated treatment model represents an inevitable trend in the treatment of uHCC. Regarding the efficacy and safety of the HCC treatment regimen employed in this study, further validation through a larger number of cases will be necessary in the future.

Data Sharing Statement

The raw data supporting the conclusions of this article will be made available by the corresponding author, without undue reservation.

Ethics Approval and Consent to Participate

This study involving patient was reviewed and approved by the Ethics Committee of the First Affiliated Hospital of Guangxi Medical University, and the committee approval to publish the case details. The patient provided his written informed consent to participate in this study.

Consent for Publication

Written informed consent was obtained from the patient to publish this case report.

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Author Contributions

All authors made a significant contribution to the work reported, whether that taking part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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