Cancer Management and Research

Elevate Series

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CASE REPORT

Durable Control of Multi-Refractory HBV-HCC with Bevacizumab/Sintilimab/Lenvatinib Triplet Therapy

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Background: Advanced HCC progressing after standard first-line immune checkpoint inhibitor (ICI)/antiangiogenic therapy and second-line tyrosine kinase inhibitors (TKIs) has limited treatment options.

Case Presentation: A 67-year-old male with HBV-related HCC (cT2N1M0, Child-Pugh B) exhibited rapid progression after transarterial chemoembolization, bevacizumab/sintilimab, and lenvatinib monotherapy. Salvage triplet therapy with bevacizumab (400 mg IV q3w), sintilimab (200 mg IV q3w), and lenvatinib (8 mg daily) achieved >50% alpha-fetoprotein (AFP) reduction within two cycles and sustained radiologic disease stabilization for 10 months, with only grade 1 fatigue and hemoptysis.

Conclusion: This is the first documented case of bevacizumab/sintilimab/lenvatinib triplet efficacy in triple-class refractory HCC, suggesting potential synergistic mechanisms and feasibility even in Child-Pugh B patients. These findings warrant further investigation in prospective studies.

Keywords: hepatocellular carcinoma, multi-refractory HCC, triplet therapy, salvage therapy, disease control

Introduction

Hepatocellular carcinoma (HCC) is a major global health challenge and ranks as the third leading cause of cancer-related death worldwide. Its incidence is increasing, especially in regions where chronic hepatitis B virus (HBV) infection is endemic, which remains a major cause of the disease and significantly affects treatment outcomes.[1,2] The therapeutic landscape for advanced HCC has been transformed by the introduction of molecular targeted therapies and immune checkpoint inhibitors (ICIs). The current standard first-line therapy for unresectable HCC has shifted toward the combination of atezolizumab (anti–PD-L1) and bevacizumab (anti–VEGF), supported by the landmark IMbrave150 trial, which demonstrated superior survival compared with sorafenib.[3] Alternative first-line options include dual ICI regimens (eg, tremelimumab plus durvalumab) or tyrosine kinase inhibitor (TKI)-based combinations.[4,5]

Despite these advances, a substantial proportion of patients exhibit primary resistance or ultimately develop progressive disease. Effective second-line therapies exist, particularly for patients who progress on or are intolerant to first-line anti-VEGF/ICI combinations. Regorafenib, cabozantinib, and ramucirumab (specifically for patients with baseline AFP ≥400 ng/mL) have demonstrated survival benefits in this setting.[6,7] However, therapeutic options become increasingly limited and less effective beyond the second line, representing a critical unmet need in HCC management. The molecular heterogeneity of HCC, together with acquired resistance mechanisms, makes it particularly challenging to maintain disease control in the later stages.[8]

Preclinical studies and emerging clinical evidence suggest that combining ICIs with either VEGF blockade or multi-target TKIs may provide synergistic therapeutic benefits.[9–11] VEGF blockade can normalize tumor vasculature, potentially enhancing T-cell infiltration and improving the efficacy of ICIs, whereas TKIs exert broad anti-angiogenic and anti-proliferative effects by targeting multiple kinase pathways involved in HCC pathogenesis.[12,13] While triplet combinations are being actively explored in first-line trials (eg, COSMIC-312), data on their use as later-line salvage therapy, particularly after

Received: 20 June 2025
Accepted: 8 September 2025
Published: 13 September 2025

progression on multiple prior lines including ICIs and TKIs, remain sparse and primarily confined to retrospective reports or small series.[14,15] This lack of robust evidence creates significant uncertainty for clinicians managing heavily pretreated patients with preserved performance status.

This case report describes a patient with advanced HBV-related HCC who showed rapid progression after initial transarterial chemoembolization (TACE) and subsequent systemic therapies, including bevacizumab/sintilimab and lenvatinib monotherapy. Faced with limited options and rising AFP, a salvage triplet regimen combining bevacizumab, sintilimab, and lenvatinib was initiated, resulting in a remarkable 10-month period of disease stabilization with manageable toxicity. This case provides valuable real-world evidence on the potential efficacy and tolerability of aggressive salvage triplet therapy in the challenging setting of multiply pretreated advanced HCC, underscoring the need for further prospective evaluation.

Case Presentation

A 67-year-old male presented to our hospital on March 6, 2023, after the incidental discovery of a hepatic mass during a routine physical examination three days earlier. Initial evaluation at an external facility included a PET-CT scan (February 24, 2023), which revealed a 3.1-cm FDG-avid lesion in segment 8 of the right hepatic lobe, suggestive of HCC. Additional findings included multiple FDG-avid subcapsular nodules in the right inferior hepatic lobe (suspicious for small HCC), numerous intrahepatic short-T1-signal nodules with abnormal FDG metabolism (suggestive of intrahepatic metastases), and enlarged FDG-avid lymph nodes in the hepatic hilum, abdomen, and retroperitoneum (indicative of metastatic involvement). Additional imaging findings included cirrhosis, splenomegaly, and ascites. Serum AFP was markedly elevated at 1028.84 ng/mL. The patient had a 30-year history of chronic HBV infection without prior antiviral therapy, with an admission HBV-DNA level of 10^3 IU/mL. He denied any family history of malignancy, significant comorbidities, smoking, or alcohol use. Physical examination confirmed abdominal distension and shifting dullness. His performance status was ECOG 1. Based on his history of chronic HBV infection, elevated AFP, and corroborative imaging findings, a clinical diagnosis of primary HCC was established. Staging identified cT2N1M0 disease (Stage IVA), with Child-Pugh B cirrhosis (score 8; Table 1) and BCLC stage B disease. Liver biopsy was deferred.

Initial management began on March 8, 2023, with TACE involving intra-arterial infusion of an epirubicin (30 mg)–lipiodol emulsion (4 mL), followed by embolization with polyvinyl alcohol particles. Concurrently, entecavir antiviral therapy was initiated. Systemic therapy began on March 28, 2023, with the combination of bevacizumab (400 mg IV on day 1) and sintilimab (200 mg IV on day 1) administered every 21 days. The treatment was well-tolerated initially, with no significant adverse events recorded. However, after three cycles, restaging abdominal CT on June 13, 2023, showed progressive disease (iuPD per iRECIST criteria; Figure 1A). An additional cycle of bevacizumab plus sintilimab was administered, but subsequent CT on July 20, 2023, confirmed further hepatic progression (icPD, Figure 1B). Therapy was switched to lenvatinib (8 mg orally once daily). Disease progression persisted after two months, as confirmed by abdominal CT on September 13, 2023 (Figure 1C), prompting a second TACE on September 18, 2023, using the same epirubicin–lipiodol/PVA regimen.

Faced with rapid tumor progression and continuously rising AFP levels (Figure 2), alongside the prohibitive cost and low expected response rate of later-line options like ramucirumab, a multidisciplinary team (MDT) discussion was convened.

Table 1 Child-Pugh Score and Subcomponents for the Patient

Parameter (Subcomponent)	Patient Value/Finding	Score*
Hepatic encephalopathy (stage)	None	1
Ascites	Mild, clinically detectable (shifting dullness, diuretics controlled)	2
Total bilirubin (μmol/L)	31 μmol/L (within 34–51 range)	1
Serum albumin (g/L)	32 g/L (within 28–35 range)	2
Prothrombin time prolongation (sec)	+5 sec (within 4–6 range)	2
Total score	8	
Child-Pugh class	B	

Notes: *Scoring: 1–3 points per parameter; total score: Class A = 5–6, Class B = 7–9, Class C = 10–15.

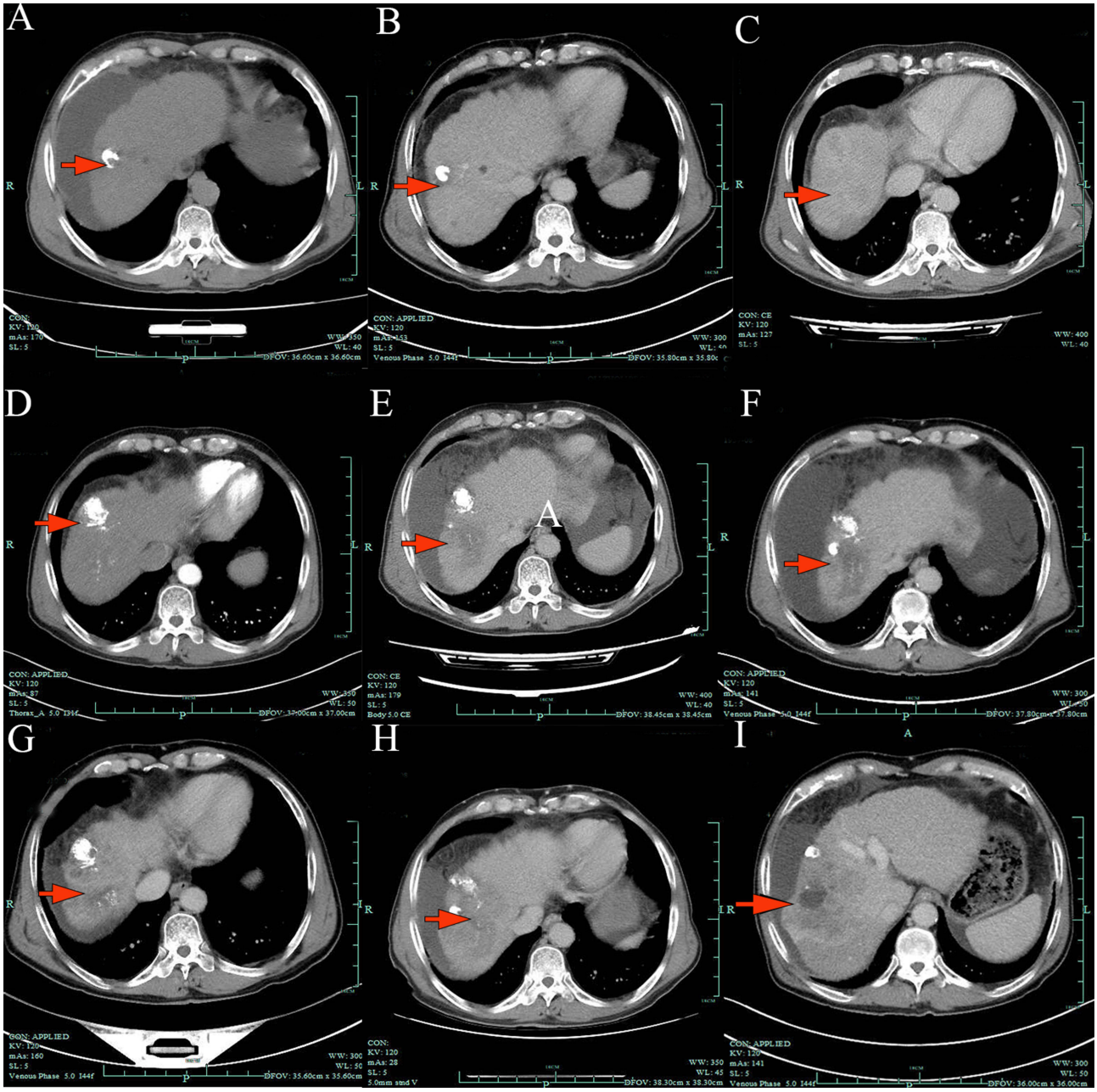

Figure 1 CT variations of intrahepatic lesions during treatment (red arrowheads). (**A**) June 2023. (**B**) July 2023. (**C**) September 2023. (**D** and **E**) November 2023 and January 2024. (**F** and **G**), March and May 2024. (**H**), June 2024. (**I**), July 2024.

Considering the patient's preserved performance status (ECOG PS 1) and relatively good general condition, the decision was made, in consultation with the patient and family, to pursue an aggressive salvage triplet regimen. This regimen consisted of bevacizumab (400 mg IV on day 1) and sintilimab (200 mg IV on day 1) every 21 days, plus lenvatinib (8 mg orally daily). Following initiation of this combination therapy, a dramatic decline in AFP levels was observed (Figure 2).

The patient remained on this bevacizumab/sintilimab/lenvatinib regimen regularly until July 2024. Serial abdominal CT scans during this period demonstrated sustained disease stabilization (Figures 1D–H). Treatment-related adverse events were limited to grade 1 fatigue and grade 1 hemoptysis. Disease progression was eventually documented on abdominal CT in July 2024 (Figure 1I). Subsequent therapy with regorafenib (120 mg orally daily) failed to control the disease, as evidenced by persistently rising AFP levels. Regorafenib was discontinued after two weeks, and the patient transitioned to best supportive care. He succumbed to multiorgan failure two weeks later. Notably, the systemic therapy

https://doi.org/10.2147/CMAR.S547885

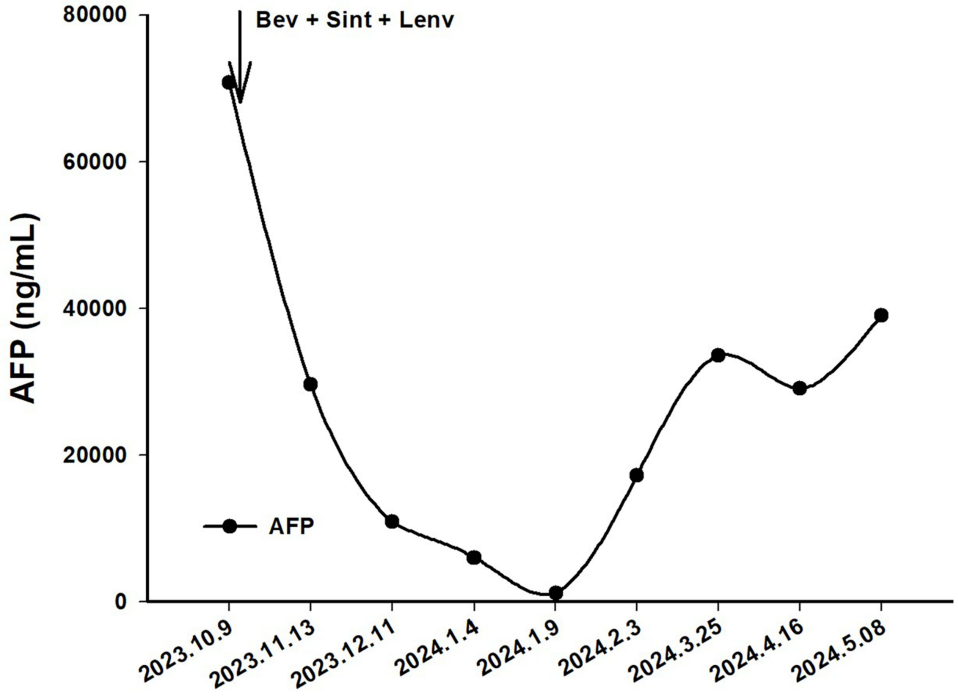

Figure 2 Serum AFP levels (normal <20 ng/mL) from March 2023 to July 2024.

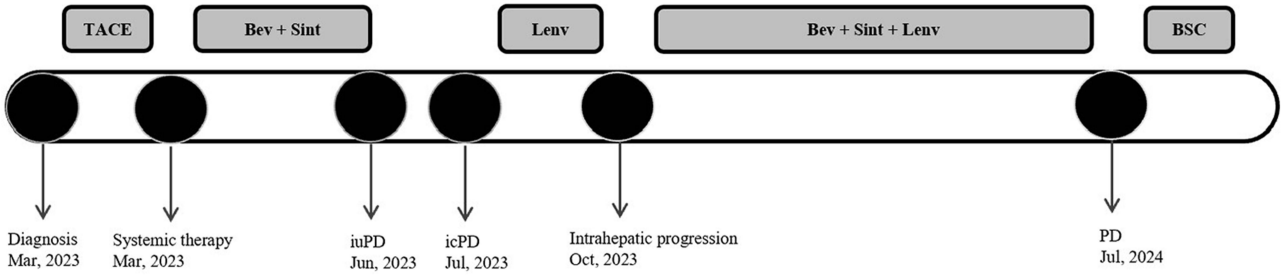

Figure 3 The overview of the approaches to diagnosis and treatment regimens for each regimen.

that provided the greatest clinical benefit was the novel bevacizumab/sintilimab/lenvatinib triplet, which achieved 10 months of disease control. The overall treatment timeline is summarized in Figure 3.

Discussion

This case report describes the successful application of an aggressive salvage triplet regimen—bevacizumab, sintilimab, and lenvatinib—in a patient with advanced HBV-related HCC who experienced rapid disease progression despite multiple prior lines of therapy, including TACE, bevacizumab/sintilimab, and lenvatinib monotherapy. Achieving 10 months of sustained disease stabilization with manageable toxicity (grade 1 fatigue and hemoptysis only) in this challenging clinical scenario provides valuable insights into the potential of later-line combination strategies and warrants further consideration.

The patient's disease course underscores the aggressive nature of HBV-related HCC and the limitations of sequential monotherapies or standard dual combinations in the post–first-line setting. Initial progression on the bevacizumab/sintilimab regimen, which mimics the standard-of-care atezolizumab/bevacizumab backbone,[3] and subsequent failure of lenvatinib monotherapy,[5] highlights the development of resistance mechanisms commonly encountered in advanced HCC.[8] The molecular heterogeneity of HCC and the evolution of resistance pathways under therapeutic pressure pose significant challenges to sustaining disease control, particularly in later lines.[8,16] Faced with rapidly rising AFP levels and diminishing

options, the multidisciplinary team's decision to combine all three agents previously used separately represented a rational, albeit unconventional, salvage approach.

The observed efficacy of the bevacizumab/sintilimab/lenvatinib triplet can be interpreted through the lens of synergistic mechanisms targeting multiple facets of HCC biology. Preclinically, VEGF inhibition by bevacizumab promotes vascular normalization, which may reduce immunosuppression and enhance T-cell infiltration into the tumor microenvironment, thereby potentially overcoming resistance to ICIs such as sintilimab (anti–PD-1).[12,17] Allen et al demonstrated that combined anti-VEGF and anti-PD-L1 therapy could stimulate tumor immunity through high endothelial venule (HEV) formation, facilitating lymphocyte access.[13] Concurrently, the multi-kinase inhibitor lenvatinib provides potent anti-angiogenic effects (targeting VEGFR1-3, FGFR1-4, PDGFRα, RET, KIT) and direct anti-tumor activity,[5,18] potentially addressing escape pathways that single-agent TKIs or VEGF blockade alone may not overcome. The significant and rapid decline in AFP observed after initiation of the triplet therapy strongly suggests a profound biological impact on the tumor.

Our findings resonate with emerging, albeit limited, clinical data exploring triplet regimens in HCC. While large Phase 3 trials like COSMIC-312 (cabozantinib + atezolizumab vs sorafenib) focused on the first-line setting and yielded complex results,[14] they demonstrate the feasibility of combining TKIs and ICIs. The rationale for adding VEGF inhibition to this backbone is supported by the IMbrave150 success[3] and preclinical synergy.[12,13,17] However, robust data on triplet combinations specifically in the *salvage* setting, especially after progression on prior ICI and TKI therapies, are exceedingly scarce. Most evidence comes from retrospective series or small prospective studies reporting variable outcomes.[19,20] A retrospective analysis by Scheiner et al suggested potential benefit from ICI rechallenge combined with TKIs and/or locoregional therapies in selected patients.[19] Our case adds to this emerging body of evidence by documenting a significant and durable response (10-month PFS) to a specific triplet combination in a heavily pretreated patient who had clearly progressed on both an ICI/anti-VEGF combination and TKI monotherapy.

The manageable toxicity profile observed (grade 1 fatigue, grade 1 hemoptysis) is a crucial aspect of this case. Combining agents with overlapping toxicities, particularly the risks of hypertension, proteinuria, bleeding, and immune-related adverse events (irAEs) associated with bevacizumab, lenvatinib, and ICIs, raises significant safety concerns.[3,5,21] The absence of high-grade toxicities in this patient suggests that careful patient selection (good ECOG PS 1, adequate organ function, absence of significant comorbidities or history of severe irAEs) and vigilant monitoring may allow for the safe administration of such aggressive regimens. This aligns with the safety profile reported in trials exploring doublet ICI/TKI combinations[14,22] and suggests that adding a third agent may not inevitably lead to unacceptable toxicity in well-managed settings. However, larger cohorts are needed to fully define the safety profile of salvage triplets.

Several limitations inherent to a single case report must be acknowledged. The response could potentially reflect delayed effects of prior therapies; however, the temporal association with triplet initiation and the immediate AFP decline argue against this explanation. The absence of molecular profiling limits our ability to identify specific biomarkers predictive of response to this regimen. Furthermore, the generalizability of this experience is uncertain. The prohibitive cost of such combinations and the lack of predictive biomarkers pose significant challenges for widespread adoption. The subsequent rapid progression after discontinuing the triplet, together with the failure of regorafenib, underscores the relentless nature of advanced HCC and the need for a better understanding of resistance mechanisms to combination therapies.[8,16]

This case highlights a critical unmet need: the lack of established, effective options for patients with advanced HCC who progress on standard first-line and second-line therapies.[8,16] While guidelines offer options like regorafenib (if first-line was sorafenib), cabozantinib, or ramucirumab (for AFP-high) in the second line,[6,7,23] evidence for third-line and beyond is weak. Our experience suggests that carefully selected patients with preserved performance status may derive substantial benefit from aggressive salvage triplet regimens combining mechanisms previously used separately. This strategy warrants further investigation in prospective clinical trials or well-designed retrospective cohorts. Future research should focus on identifying biomarkers to select patients most likely to benefit from such intensive approaches and on optimizing sequencing and combination strategies to maximize efficacy while minimizing toxicity and cost.

Ethics Statement

This study was approved by the Ethics Committee of Quzhou People's Hospital. The approval explicitly covered the publication of the case details. The studies were conducted in accordance with the local legislation and institutional

requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Acknowledgments

The authors thank the patient for his participation and agreement to publication of the report. Written informed consent was obtained from the individual for the publication of any potentially identifiable images or data included in this article.

Funding

The study was supported by Instructional Project of Quzhou (2020057, 2021005), Science and Technology Key Project of Quzhou (2022K48, 2022K138), "New 115" Talent Project of Quzhou, and "258" Talent Project of Quzhou.

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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