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Durable complete response after discontinuation of atezolizumab-bevacizumab therapy in patients with hepatocellular carcinoma with portal vein tumor thrombosis: the first report

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Short title: Durable complete response in advanced HCC

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Abstract

Hepatocellular carcinoma (HCC) with portal vein tumor thrombosis (PVTT) is associated with a dismal prognosis. Atezolizumab plus bevacizumab (atezo-bev) is the recommended palliative treatment, and approximately 10% of the patients may experience a complete response (CR), according to the mRECIST criteria. The treatment duration is until disease progression or unacceptable side effects occur. Long-term continuation can cause potential toxicities and a substantial financial burden, making early treatment discontinuation a viable option. This report describes durable CR after discontinuing atezo-bev treatment in three patients with HCC and PVTT.

Keywords: Cirrhosis, Hepatocellular carcinoma, Immunotherapy, Liver transplantation, Hepatitis C

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Introduction

Hepatocellular carcinoma (HCC) with portal vein tumor thrombosis (PVTT) is a challenging condition with limited treatment options and is associated with a poor prognosis.[1] Atezolizumab (anti-programmed death ligand-1 antibody) plus bevacizumab (anti-vascular endothelial growth factor antibody) is the recommended palliative treatment.[2] Approximately 10% of these patients experience a complete response (CR), and the recommended treatment duration is until disease progression or unacceptable side effects occur. [3] However, long-term continuation of the therapy can cause potential toxicities that affect the quality of life and a substantial financial burden, making early treatment discontinuation a viable option.[4] However, the optimal time or criteria for discontinuing therapy in patients who achieve CR are yet to be determined. Additionally, studies have shown durable objective responses to immune checkpoint inhibitors, even after treatment cessation, in patients with advanced melanoma or non-small cell lung cancer. [5] A recent study also demonstrated that atezolizumab maintained responses after two years of therapy in 13% of alveolar soft part sarcoma patients.[6] However, a long-term durable off-treatment response in advanced HCC has not been reported with atezolizumab plus bevacizumab (atezo-bev) therapy. Here, we describe the first report of a durable CR after discontinuation of atezo-bev treatment in three patients with HCC and PVTT.

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Case report

Case 1:

A 65-year-old male patient with hepatitis B virus-related compensated cirrhosis presented with abdominal pain and weight loss over a 1-month duration. Computed tomography (CT) showed right lobe HCC (15 × 12 cm) with right PVTT and an inferior vena cava tumor thrombus, which was fluorodeoxyglucose (FDG) avid with a maximum standard uptake value (SUVmax) of 8.1 in the positron emission tomography (PET) scan. Investigations revealed an alpha-fetoprotein (AFP) level of 15 ng/ml, a neutrophil-lymphocyte ratio (NLR) of 2.2, portal hypertensive gastropathy on endoscopy, and Child-Pugh class A with a MELD score of 13. The patient achieved radiological CR according to the HCC-specific Modified Response Evaluation Criteria in Solid Tumors (mRECIST) with normal AFP after six doses of atezolizumab (1200 mg) plus bevacizumab (15 mg/kg) were administered once in three weeks and complete resolution of FDG uptake, resolution of IVC thrombus, and decrease in size of HCC, as noted in the PET scan (Figs. 1A & 2). The patient discontinued atezo-bev therapy, given financial constraints, and he refused to take other systemic treatments. He was followed up with three monthly AFP and triphasic CT of the abdomen. The patient is doing well without HCC recurrence 24 months after discontinuing atezo-bev therapy.

Case 2:

A 57-year-old male patient presented with abdominal distension of 1-week duration. The evaluation revealed alcohol-associated cirrhosis with ascites and large HCC (8.5 × 14 cm) with main PVTT (Vp4) (Fig. 1B). HCC was FDG avid with an SUVmax of 8.9 in the PET scan. Investigations showed an AFP level >20000 ng/ml, an NLR of 2.4, small esophageal varices on endoscopy, and Child-Pugh class B 8 with a MELD score of 16. Transarterial radioembolization (TARE) could not be performed due to increased bilirubin and ascites.

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Atezolizumab (1200 mg) plus bevacizumab (15 mg/kg) was administered once every three weeks, and the patient achieved radiological CR according to the mRECIST criteria after six doses with complete resolution of FDG uptake, normal AFP, and a decrease in HCC size (Fig. 1B & 2). He developed hypothyroidism and initially required large-volume paracentesis for ascites control. The patient refused to continue atezo-bev therapy, given financial constraints, and was started on lenvatinib. However, the patient discontinued lenvatinib therapy within two weeks due to cutaneous and GI-related side effects. The patient refused to take other second-line medications, and close monitoring of HCC recurrence was done with three monthly AFP and triphasic abdominal CT scans. Follow-up imaging revealed continued CR of the lesion and recompensation of cirrhosis. The patient is doing well without recurrence of HCC 24 months after cessation of atezo-bev therapy.

Case 3:

A 55-year-old male patient with hepatitis C virus-related cirrhosis presented with abdominal distension and general weakness over a 1-week period. He was treated for hepatitis C infection elsewhere with direct-acting antivirals. Further evaluation revealed a diagnosis of decompensated cirrhosis with ascites and right lobe HCC with main PVTT (Vp4), which was FDG avid with an SUVmax of 13.5 in the PET scan. Investigations showed an AFP level of 34.7 ng/ml, NLR of 1.9, large esophageal varices on endoscopy, and Child-Pugh class B 7 with a MELD score of 14. TARE could not be performed because of significant lung shunting due to the intratumoral arterioportal shunts. Treatment with atezolizumab (1200 mg) and bevacizumab (15 mg/kg), administered once every three weeks was initiated. The patient achieved radiological CR after six doses of atezo-bev, with complete resolution of FDG uptake, normal AFP, and a decrease in the size of the HCC (Figs. 1C & 2). Treatment course was complicated by the development of hepatic encephalopathy, hypothyroidism, left vocal cord

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paresis, and supraventricular tachycardia, which subsequently recovered with medications. The patient refused to continue atezo-bev therapy given the adverse events and was started on lenvatinib. The patient developed severe GI-related side effects, and thus lenvatinib was discontinued within a week and other second-line treatment options were refused. He showed a continued CR, with the disappearance of lesions, recompensation of cirrhosis, and portal vein thrombosis extending to the superior mesenteric and splenic veins, which did not respond six months after anticoagulation. He continued treatment with tab carvedilol with close monitoring of HCC recurrence, with three monthly AFP and triphasic abdominal CT scans. Thirty months after discontinuing atezo-bev therapy, the patient was doing well without HCC recurrence.

Discussion

PVTT is present in 10–40% of HCC patients at diagnosis, with a median overall survival of 2.7–5 months. [1] Immune checkpoint inhibitors (ICIs) have revolutionized treatment with palliative intent, and a subset of patients with HCC with PVTT derive the highest benefit from atezo-bev therapy in the form of a CR. [3] Recent anecdotal reports have shown that HCC patients with PVTT can undergo successful conversion to curative surgery or definitive liver transplantation for durable cure after downstaging with atezo-bev therapy. [7,8] However, the optimal duration for those who achieve a CR with atezo-bev is unknown, and treatment-free survival is still a reality in patients with advanced HCC. Our case series is the first to show the durability of CR despite the discontinuation of atezo-bev in selected patients with a concomitant lack of recurrence. Atezo-bev therapy is a game-changer with tremendous ability to achieve treatment-free survival in patients with advanced HCC. In addition, early discontinuation of this expensive therapy can significantly improve patient outcomes and reduce healthcare costs.

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Anti-tumor activity was noted in studies for several months to years, even after cessation of ICI, because of the unique adaptive memory of T cell effects compared to the predicted half-life.[9] Experience from treatment of advanced melanoma and non-small cell lung cancer with ICIs, such as pembrolizumab and nivolumab-ipilimumab, indicates that discontinuation of therapy might be a feasible option in patients who experience CR, since durable remissions are reported. A recent study showed durable CR with six months of dosterlimab (PD-1 monoclonal antibody) therapy in patients with mismatch repair-deficient locally advanced rectal cancer, thereby preventing morbid chemoradiotherapy and surgery.[10] Nevertheless, extrapolating treatment protocols is possible despite the inherent differences in tumor biology.

All patients in this study achieved a complete radiological response with normal AFP with six doses of atezo-bev. Two patients experienced decompensation at presentation in the forms of ascites, jaundice, hepatic encephalopathy, and HCC response to atezo-bev therapy, leading to the recompensation of decompensated cirrhosis. This could be due to an improvement in liver function and portal hypertension caused by a decrease in tumor size. Based on limited experience, atezo-bev treatment may be discontinued in patients who achieve a CR after six doses, along with improved liver function.

While the observations made are interesting, it is essential to note that they should only be considered as the basis for further research rather than as conclusive evidence. However, fixed-duration therapy may be challenging in patients with HCC with PVTT because of limited complete CR rates and lack of biomarkers that can predict response and precise patient selection. Moreover, additional studies are necessary to explore the criteria for discontinuing atezo-bev combination therapy and establish a long-term follow-up protocol. Lastly, it is worth mentioning that the treatment of HCC recurrence after discontinuation of therapy is a concern,

given the lack of data. However, the possibility of retreatment with atezo-bev or alternative systemic treatments remains to be explored in cases of recurrence.

In conclusion, early discontinuation or a fixed duration of atezo-bev treatment in advanced HCC may be feasible in patients who achieve a CR. However, prospective trials are essential to assess treatment-free survival with fixed-duration treatment and identify relevant biomarkers.

Conflicts of interest

The authors have no conflicts of interest to declare.

Ethics Statement

All procedures were conducted according to the Declaration of Helsinki. The patients provided written informed consent for the publication of the details of the medical case and accompanying images. Institutional review board approval was obtained from Gleneagles BGS Hospital (BGSGGH IRB: 10/2023).

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Data Availability statement

The authors will make the raw data supporting this article's conclusions available without undue reservation. This article includes all data generated or analysed during this study. Further inquiries can be directed to the corresponding author.

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Data curation: PK, SR

Writing- Original draft: PK,

Writing- Reviewing: PK, RM, NC

Supervision: SR

Abbreviations

1. HCC - Hepatocellular carcinoma
2. PVTT - Portal vein tumoral thrombosis
3. LT - Liver transplantation
4. ICIs - Immune checkpoint inhibitors
5. LDLT - Live donor liver transplantation
6. AFP – Alpha-fetoprotein
7. FDG - Fluorodeoxyglucose
8. SUV - Standardized uptake values
9. PET - Positron emission tomography
10. MELD - Model for end-stage liver disease
11. mRECIST – Modified response evaluation criteria in solid tumors
12. MMF - Mycophenolate mofetil
13. PD-L1 - Programmed death ligand 1

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Figure legend

Figure 1A

Figure 1B

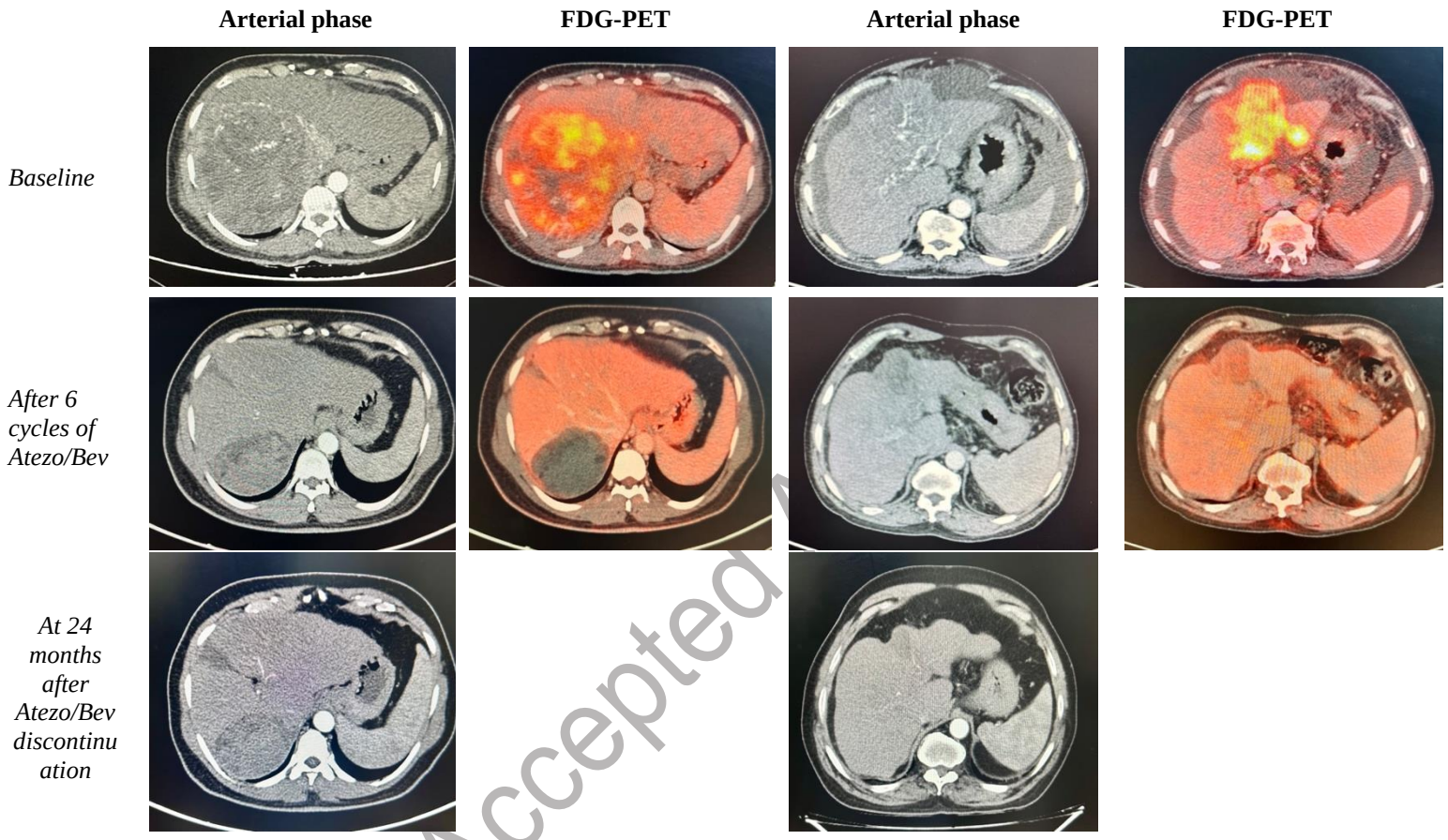

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Figure 1C

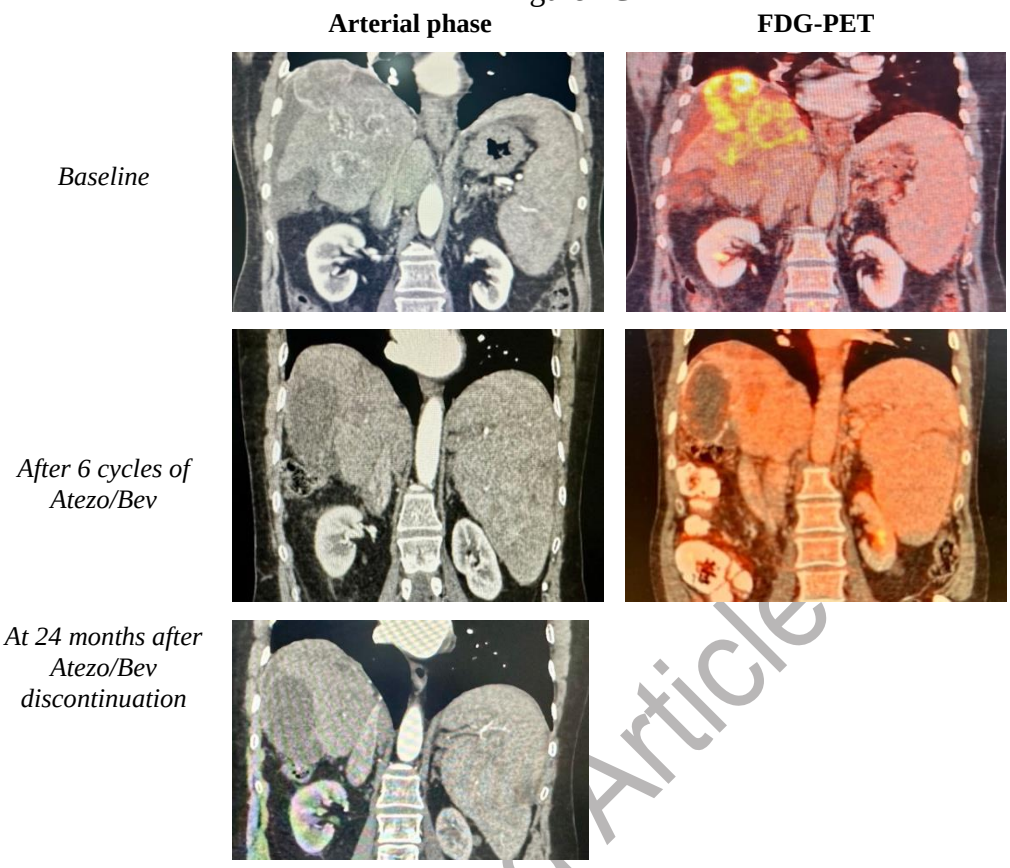

Figure 1. Complete response of hepatocellular carcinoma after treatment with atezolizumab plus bevacizumab, i.e., disappearance of tumoral arterial enhancement in the arterial phase of triphasic CT abdomen according to the mRECIST criteria and loss of FDG activity in PET scans

HCC Hepatocellular carcinoma, FDG-PET ^{18}F-fluorodeoxyglucose–positron-emission tomography, CT Computed tomography, mRECIST Modified Response Evaluation Criteria in Solid Tumors

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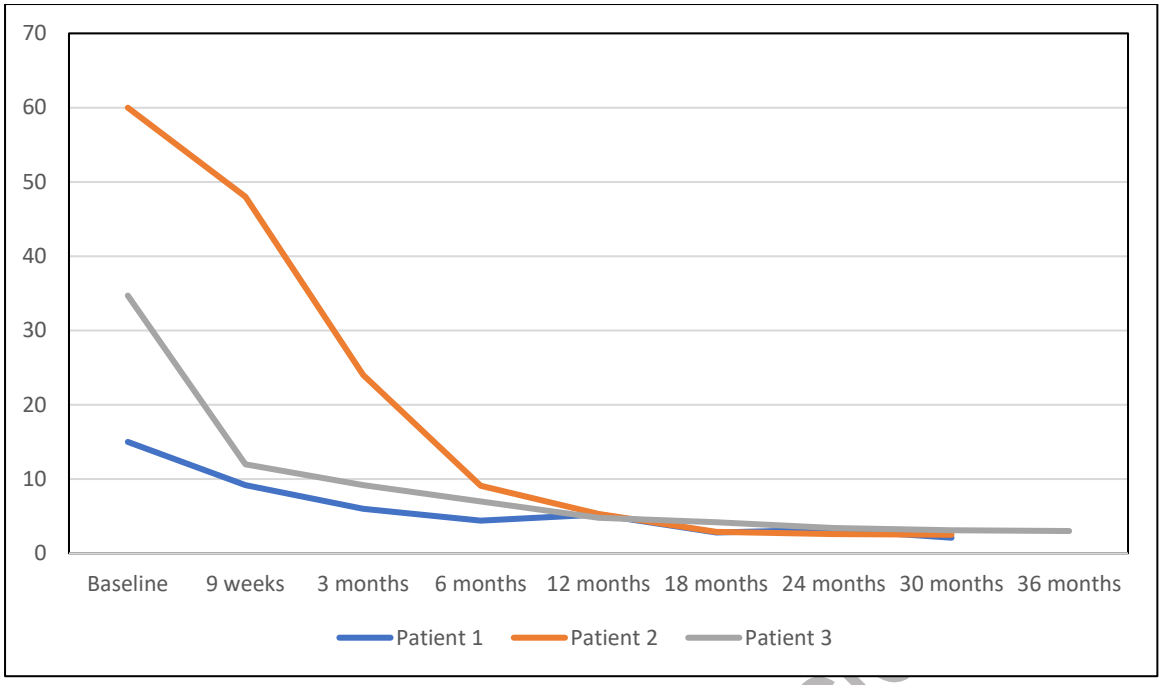

Figure 2: Dynamic changes in alpha-fetoprotein (AFP) levels during treatment and follow-up