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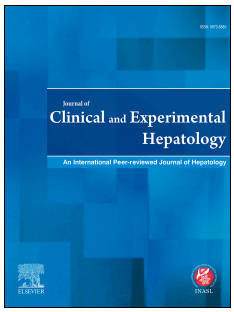

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Lenvatinib maintenance therapy after complete response to Atezolizumab plus bevacizumab in HCC and PVTT: Alternative strategy in a resource-limited setting

We read the article by Jahagirdar et al., which discusses systemic therapies for hepatocellular carcinoma (HCC) and the challenges clinicians encounter in the Indian setting. (1) HCC with portal vein tumoral thrombosis (PVTT) is a challenging condition with limited treatment options and a poor prognosis. (2) Atezolizumab plus bevacizumab (Atezo/Bev) is recommended therapy when there are no contraindications due to its superior overall survival (OS) and objective response rates compared to sorafenib or lenvatinib. (3) There is an increasing number of complete responders (CR) with Atezo/Bev in real-world clinical practice. (4) However, continued use of Atezo/Bev in CR may lead to potential toxicities and pose a significant financial burden to healthcare or families, especially in the Indian setting. Options for patients who achieved CR include either continuing treatment or undergoing curative liver transplantation or resection. (5,6) Therefore, it is vital to have an alternative therapy after Atezo/Bev induction and no evidence exists to treat these responders with multikinase inhibitors. Moreover, several retrospective studies have demonstrated that lenvatinib has a similar OS, making it an attractive alternate treatment option. (7,8) This first report describes lenvatinib maintenance therapy after induction Atezo/Bev therapy in four patients with locally advanced HCC.

Thirty-five patients with HCC and PVTT (BCLC-C) were treated with a combination of Atezo/Bev as a first-line therapy between 2020 and 2023 at Gleneagles BGS Hospital, Bengaluru, Karnataka. Nine (25%) patients achieved a CR according to mRECIST criteria with treatment. Four patients who showed radiological CR and normal AFP discontinued Atezo/Bev therapy due to financial constraints. (Table 1) One patient had a tumour thrombus of the right

portal vein (Vp3), and three had a tumour thrombus extending into the main portal vein (Vp4). None of these patients underwent locoregional/ radiotherapy for HCC. These patients were started on lenvatinib as maintenance treatment after explaining potential risks, including recurrence, and two patients required a dose reduction to 4 mg due to hand-foot syndrome and GI-related side effects. The median OS was 28 (range,18-36) months, and the median PFS after starting lenvatinib was 24.5 (range, 14-31) months. All four patients maintained CR achieved by Atezo/bev therapy without recurrence.

Lenvatinib is a selective inhibitor that targets common and alternative oncogenic pathways, such as VEGFR1-3, FGFR1-4, PDGFR, and KIT. Immune checkpoint inhibitor (ICI) antitumor activity can persist for several months to years even after treatment discontinuation due to durable T-cell response. (9) Therefore, subsequent lenvatinib administration after atezolizumab cessation may have a temporary additive effect attributed to the durability of the complete response. (10) HCC recurrence after discontinuing Atezo/Bev is a concern and necessitates further research. Atezolizumab plus bevacizumab therapy is a “game-changer” for locally advanced HCC patients, and high treatment costs limit its usage. Therefore, early discontinuation of this expensive therapy after achieving CR with lenvatinib maintenance can significantly improve patient outcomes and reduce healthcare-related costs. In summary, the case series suggests that lenvatinib may be considered as a maintenance therapy agent after achieving CR with Atezo/Bev therapy in HCC with PVTT patients in a resource-limited setting.

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Abbreviations

1. HCC - Hepatocellular carcinoma
2. PVTT - Portal vein tumoral thrombosis
3. AFP – Alpha-fetoprotein
4. FDG - Fluorodeoxyglucose
5. SUV - Standardized uptake values
6. PET - Positron emission tomography
7. mRECIST – Modified response evaluation criteria in solid tumors
8. CR – Complete response

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Table 1: Baseline characteristics and treatment response to Atezolizumab/Bevacizumab therapy

Parameter	Patient No.1	Patient No.2	Patient No.3	Patient No. 4
Age/Sex	58/Male	60/Male	55/Male	65/Female
Cause of cirrhosis	Hepatitis C	Alcohol	Hepatitis B	Hepatitis B
Decompensation at presentation	No	No	No	Ascites
Child Pugh class/score	A	B7	A	B8
ECOG Performance status	1	1	0	1
Alpha-fetoprotein (ng/ml)	>3000	916	16	>120000
Esophageal Varices	Small	Small	No	Small
BCLC Stage	C	C	C	C
Tumor Characteristics Size Number Main PVTT IVCTT	 10 cm Solitary Yes No	 12 cm Multifocal Yes No	 8 cm Solitary Yes Yes	 8 cm Two lesions Yes No
PET SUVmax	9.2	7.8	8.1	6
Atezolizumab/bevacizumab doses	3	6	6	5
Response to therapy HCC- specific mRECIST FDG-PET	 CR CR	 CR CR	 CR CR	 CR CR
Adverse events	No	No	Hypothyroidism Cellulitis	Hepatic encephalopathy
Reason for Atezo/Bev withdrawal	Financial	Financial	Financial	Financial
Lenvatinib dose	8 mg	4 mg	8 mg	4 mg
Follow up duration	32 months	24 months	36 months	18 months

ECOG: Eastern cooperative oncology group; BCLC: Barcelona Clinic Liver Cancer; IVCTT: Inferior vena cava tumoral thrombosis; PET: Positron emission tomography; SUV: Standardized uptake Value; CR: Complete response.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: