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ORIGINAL RESEARCH

Efficacy and Safety of Different Doses of Bevacizumab Combined with Atezolizumab in Unresectable Hepatocellular Carcinoma

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Purpose: To evaluate the efficacy and safety of different doses of bevacizumab combined with atezolizumab in patients with unresectable hepatocellular carcinoma.

Methods: A retrospective analysis was conducted on clinical data from patients receiving Atezo-Bev therapy at our institution. Patients were stratified into standard-dose (SD) and low-dose (LD) groups based on bevacizumab dosage. Comparative analyses evaluated antitumor efficacy and adverse events (AEs) incidence.

Results: A total of 63 patients were included (SD group: n=32; LD group: n=31). Baseline characteristics showed no significant differences between the groups. Median overall survival (OS) was 22.0 months in the SD group and 19.3 months in the LD group, while median progression-free survival (PFS) was 8.0 months and 6.9 months, respectively. No statistically significant differences were observed in OS or PFS between the two groups (P=0.276 and P=0.297, respectively). However, the incidence of bevacizumab-related AEs was lower in the LD group compared to the SD group.

Conclusion: Compared to low-dose bevacizumab combined with atezolizumab, the standard-dose regimen did not demonstrate significant superiority in OS or PFS. Additionally, the low-dose combination may lead to fewer AEs.

Keywords: hepatocellular carcinoma, bevacizumab, atezolizumab, efficacy, adverse events

Introduction

Liver cancer ranks as the third leading cause of cancer-related mortality worldwide, with hepatocellular carcinoma (HCC) accounting for 75–85% of all liver cancer cases.[1,2] Due to its insidious onset and lack of early clinical symptoms, over 50% of HCC patients are diagnosed at advanced stages, rendering them ineligible for curative surgical resection.[3] Encouragingly, systemic therapies, particularly immunotherapy, have achieved remarkable success in recent clinical trials, demonstrating substantial efficacy in treating unresectable HCC (uHCC)[4,5] In the landmark IMbrave150 trial, the combination of atezolizumab (Atezo) and bevacizumab (Bev) significantly extended progression-free survival (PFS) and overall survival (OS) in uHCC patients, with median OS and PFS reaching 19.2 months and 6.2 months, respectively.[6] In addition, among all the Phase III clinical trials related to uHCC, the median OS observed in the IMbrave150 trial is the longest. Given its clinical benefits, Atezo-Bev has been established as a first-line therapeutic regimen. However, in the IMbrave150 trial, 17% of patients in the Atezo-Bev cohort experienced Bev-related adverse events (AEs), resulting in therapy cessation, with gastrointestinal disorders being the most common cause.[7,8] Internationally, debates persist regarding whether Bev dose reduction can mitigate AEs incidence without compromising antitumor efficacy. Yeom et al proposed that uHCC patients experiencing esophageal or gastric variceal bleeding during Atezo-Bev therapy may benefit from Bev dose reduction.[9] Notably, the recent study by Sakai's team demonstrated that reducing the bevacizumab dose in the Atezo-Bev treatment regimen can maintain antitumor efficacy while extending treatment

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duration.[10] A large-scale study by Ball et al (n=354) revealed that for patients with uHCC receiving Atezo-Bev therapy, adjustments in bevacizumab dose intensity during treatment due to any cause did not negatively impact survival outcomes.[11] It is particularly important to emphasize that these aforementioned studies focused exclusively on dose adjustments made during treatment in response to AEs. In contrast, our study innovatively explores the potential advantages of initiating reduced-dose bevacizumab from the very beginning of treatment: we have not only evaluated this strategy's impact on reducing bevacizumab-related AE incidence but also conducted a comprehensive analysis of how dose adjustment affects the antitumor efficacy of the Atezo-Bev combination therapy. This novel study design provides new evidence-based insights for clinical practice.

Materials and Methods

Patients

This study evaluated 63 uHCC patients who received Atezo-Bev therapy at the First Affiliated Hospital of the University of Science and Technology of China between March 1, 2021 and February 1, 2024. uHCC was defined as meeting the following criteria: (1) extensive hepatic involvement with multifocal tumors (>3 lesions) not confined to a single lobe; (2) concurrent extrahepatic metastases; (3) major vascular invasion or tumor proximity to critical vasculature precluding R0 resection; or (4) insufficient predicted remnant liver volume (<40% of standard liver volume in cirrhotic patients or <30% in non-cirrhotic patients). Inclusion criteria: 1) HCC was diagnosed by histopathology or radiology (enhanced computed tomography [CT] or magnetic resonance imaging [MRI]);[12] 2) At least one measurable lesion identified on CT or MRI according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST);3) Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of 0 or 1; 4) Child-Pugh class A or B (7–9 points). Exclusion criteria: 1) Presence of esophagogastric varices on upper gastrointestinal endoscopy or hematologic disorders at initial uHCC diagnosis; 2) Clinical evidence of other primary malignancies, non-HCC metastatic carcinomas, or cholangiocarcinoma; 3) Prior history of systemic therapy for HCC; 4) Lost to follow-up or incomplete clinical data.

This retrospective study collected patients' clinical data, including gender, age, history of hepatitis virus infection, Child-Pugh score, bilirubin, platelet count, white blood cell count, absolute neutrophil count, serum creatinine, alpha-fetoprotein (AFP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), thyroid function, presence of cirrhosis (clinical or radiological diagnosis), Barcelona Clinic Liver Cancer (BCLC) stage, ECOG PS score, presence of portal vein tumor thrombus, adverse events (AEs) during treatment, and follow-up information.

This study was conducted in accordance with the guidelines of the Declaration of Helsinki and was approved by the Ethics Committee of the First Affiliated Hospital of the University of Science and Technology of China (Approval No.: 2024-RE-488). As this was a retrospective study, the requirement for informed consent was waived.

Atezo-Bev Treatment Protocol and Grouping

Based on the comprehensive evaluation of the patient's specific clinical conditions, all patients received combination therapy with Atezo (1200 mg per dose) and Bev administered intravenously every 3 weeks. The standard dose (SD) of Bev was 15 mg/kg, while a low dose (LD) of Bev (7.5 mg/kg) was permitted in this study. Patients receiving the SD of Bev were assigned to the SD group, and those receiving the LD of Bev were assigned to the LD group. If intolerable AEs occurred during Atezo-Bev combination therapy, temporary treatment discontinuation was allowed.

The decision to implement the LD of Bev regimen was predicated on a comprehensive evaluation of the following critical clinical determinants: 1. Financial constraints: Limited affordability for some patients; 2. Bleeding risk management: Subnormal baseline platelet levels necessitating risk mitigation; 3. Liver function stratification: Inclusion of Child-Pugh B cohort. All 31 patients enrolled in the LD group received the half-dose regimen after providing fully informed consent.

Treatment Efficacy Evaluation and Follow-Up

CT or MRI was performed every 8–12 weeks to assess tumor response following combination therapy. This study applied mRECIST criteria to determine treatment response, specifically including complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). Two radiologists independently evaluated the responses without access to clinical information. In cases of discordant assessments, a third senior radiologist made the final determination. The

objective response rate (ORR) was calculated as the sum of CR and PR percentages, while the disease control rate (DCR) was calculated as the sum of CR, PR, and SD percentages.

AEs during treatment were evaluated and graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. PFS was defined as the time interval from the initiation of combination therapy to tumor progression, or the last follow-up date, whichever occurred first. OS was defined as the time interval from the initiation of combination therapy to death or the last follow-up date, whichever occurred first. The last follow-up date was August 1, 2024.

Statistical Analysis

Continuous variables are presented as mean ± standard deviation or median (interquartile range [IQR]), while categorical variables are expressed as frequency (percentage). Differences between continuous and categorical variables were analyzed using Student's *t*-test (or Mann–Whitney *U*-test) and chi-square test (or Fisher's exact test), respectively. Survival curves were generated using the Kaplan-Meier method and compared with the Log rank test. In all statistical analyses, a P value <0.05 was considered statistically significant. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software (version 26, SPSS Inc., Chicago, IL, USA).

Results

Baseline Characteristics of Patients

We summarized the baseline characteristics of 63 patients who met the inclusion criteria of this study before receiving Atezo-Bev combination therapy (Table 1). The mean age of all patients was 57.0 (range: 31–77) years, with a majority being male (50 patients, 79.4%) and only 13 female patients (20.6%). Hepatitis B virus infection was present in 58 patients (92.1%), and 51 patients (81.0%) had a history of cirrhosis. The numbers of patients with BCLC stage B and C were 18 (28.6%) and 45 (71.4%), respectively. Before receiving Atezo-Bev combination therapy, 28 patients (44.4%) had AFP levels ≥400 ng/mL. Vascular invasion was observed in 33 patients (52.4%), and 19 patients (30.2%) had extrahepatic metastasis. Twenty-six patients (41.3%) had previously undergone HCC-related surgical treatment, and 28 patients (44.4%) had received local therapy. No statistically significant differences were observed in baseline characteristics between the SD and LD groups.

Table 1 Baseline Characteristics of All Patients

Characteristics	SD Group (n=32)	LD Group (n=31)	P value	All Patients (n=63)
Age, median (range), years	57.0 (31–77)	59.0 (31–75)	0.563	57.0 (31–77)
Atezo-Bev treatment cycle, median (range)	17.5 (5–34)	17.0 (4–30)	0.789	17.0 (4–34)
ALT, IU/L	34.8 (11.0–142.0)	40.0 (9.0–263.0)	0.496	38.2 (9.0–263.0)
AST, IU/L	45.7 (18.0–296.0)	46.0 (21.0–151.0)	0.885	46.0 (18.0–296.0)
Gender, n (%)			0.805	
Male	25(78.1)	25 (80.6)		50 (79.4)
Female	7 (21.9)	6 (19.4)		13 (20.6)
Etiology, n (%)			0.970	
Hepatitis B virus	30 (93.8)	28 (90.3)		58 (92.1)
Non-hepatitis B virus	2 (6.3)	3 (9.7)		5 (7.9)
Cirrhosis, n (%)			0.561	
Yes	25 (78.1)	26 (83.9)		51 (81.0)
No	7 (21.9)	5 (16.1)		12 (19.0)
ECOG PS, n (%)			0.482	
0	27 (84.4)	24 (77.4)		51 (81.0)
1	5 (15.6)	7 (22.6)		12 (19.0)

(*Continued*)

Table 1 (Continued).

Characteristics	SD Group (n=32)	LD Group (n=31)	P value	All Patients (n=63)
Child-Pugh class, n (%)			0.384	
A	24 (75.0)	26 (83.9)		50 (79.4)
B	8 (25.0)	5 (16.1)		13 (20.6)
AFP, n (%)			0.693	
≥400 ng/mL	15 (46.9)	13 (41.9)		28 (44.4)
<400ng/mL	17 (53.1)	18 (58.1)		35 (55.6)
BCLC stage, n (%)			0.300	
B	11 (34.4)	7 (22.6)		18 (28.6)
C	21 (65.6)	24 (77.4)		45 (71.4)
Vascular invasion, n (%)			0.904	
Yes	17 (53.1)	16 (51.6)		33 (52.4)
No	15 (46.9)	15 (48.4)		30 (47.6)
Extrahepatic metastasis, n (%)			0.721	
Yes	9 (28.1)	10 (32.3)		19 (30.2)
No	23 (71.9)	21 (67.7)		44 (69.8)
Prior HCC surgery, n (%)			0.537	
Yes	12 (37.5)	14 (45.2)		26 (41.3)
No	20 (62.5)	17 (54.8)		37 (58.7)
Prior local therapy, n (%)			0.535	
Yes	13 (40.6)	15 (48.4)		28 (44.4)
No	19 (59.4)	16 (51.6)		35 (55.6)

Note: Data are presented as number (percentage) or mean (range).
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status; Child-Pugh, Child-Pugh liver function classification; BCLC, Barcelona Clinic Liver Cancer staging; HCC, hepatocellular carcinoma; AFP, alpha-fetoprotein.

Treatment Efficacy

Tumor response to Atezo-Bev combination therapy was determined by CT or MRI (Table 2). Among all patients, 9 (25.4%) achieved CR and 22 (34.9%) achieved PR. SD and PD were observed in 25 (39.7%) and 7 (11.1%) patients, respectively. The ORR and DCR were 49.2% and 88.9%, respectively. The median follow-up time for all patients was 13.1 months (95% confidence interval [CI]: 12.4–14.8 months). The overall median OS was 20.0 months and the median PFS was 7.8 months in all 63 patients (Figure 1). In the SD group, median OS and PFS were 22.0 months and 8.0 months, respectively, compared with 19.3 months and 6.9 months in the LD group. No statistically significant differences were observed between SD and LD groups in either OS (P=0.275) or PFS (P=0.297) (Figure 2). Additionally, we conducted comparative analyses of treatment duration across different response categories (CR/PR/SD/PD), as detailed in Supplementary Table 1.

Table 2 Treatment Efficacy According to mRECIST Criteria

Tumor Response	SD Group, n (%)	LD Group, n (%)	All Patients, n (%)
CR	5 (15.6)	4 (12.9)	9 (14.3)
PR	12 (37.5)	10 (32.3)	22 (34.9)
SD	12 (37.5)	13 (41.9)	25 (39.7)
PD	3 (9.4)	4 (12.9)	7 (11.1)
ORR	53.1%	45.2%	49.2%
DCR	90.6%	87.1%	88.9%

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate; SD, standard dose; LD, low dose.

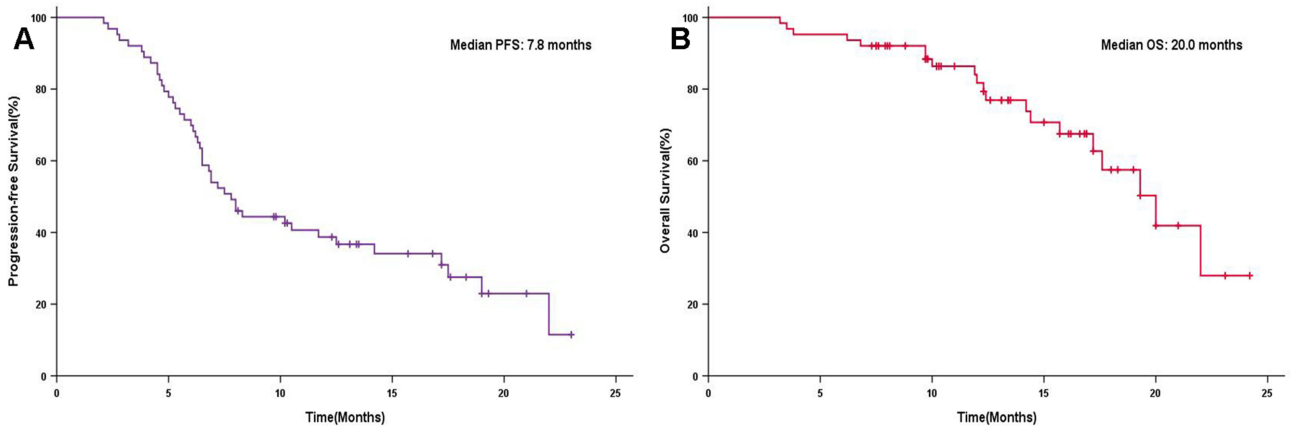

Figure 1 Progression-free survival (PFS) curve (**A**) and overall survival (OS) curve (**B**) for all patients.

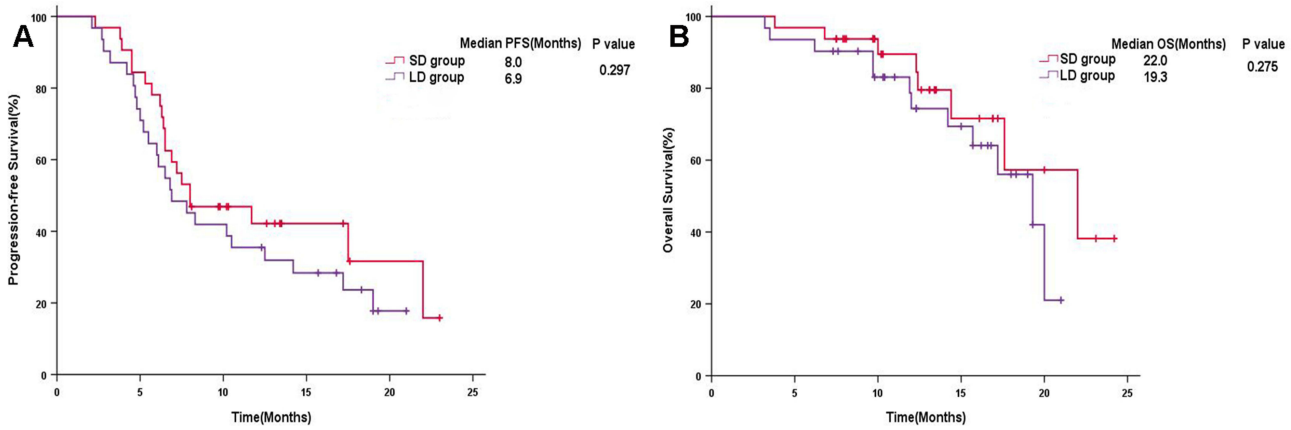

Figure 2 Progression-free survival (PFS) curves (**A**) and overall survival (OS) curves (**B**) for the standard-dose (SD) and low-dose (LD) groups.

Safety Analysis

AEs occurring during Atezo-Bev treatment in both groups were evaluated according to CTCAE version 5.0 (Table 3). The most common AEs among patients receiving combination therapy were hypertension (36.5%) and proteinuria (34.9%), followed by

Table 3 Adverse Events of All Patients

AEs, n(%)	SD Group (n=32)	LD Group (n=31)	P value	All Patients (n=63)	Grade 3/4 AEs (n=63)
Hypertension	15 (46.9)	8 (25.8)	0.082	23 (36.5)	3 (4.7)
Proteinuria	15 (46.9)	7 (22.6)	0.043	22 (34.9)	2 (3.2)
Decreased platelet count	13 (40.6)	7 (22.6)	0.124	20 (31.7)	3 (4.7)
AST increased	10 (31.3)	8 (25.8)	0.633	18 (28.6)	2 (3.2)
Anorexia	10 (31.3)	7 (22.6)	0.438	17 (27.0)	0
Fatigue	9 (28.1)	7 (22.6)	0.613	16 (25.4)	0
Pruritus	9 (28.1)	6 (19.4)	0.414	15 (23.8)	0
Constipation	8 (25.0)	7 (22.6)	0.822	15 (23.8)	0
Diarrhea	8 (25.0)	6 (19.4)	0.590	14 (22.2)	0
Hyperbilirubinemia	7 (21.9)	6 (19.4)	0.805	13 (20.6)	1 (1.6)
Anemia	7 (21.9)	6 (19.4)	0.805	13 (20.6)	0

(*Continued*)

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Table 3 (Continued).

AEs, n(%)	SD Group (n=32)	LD Group (n=31)	P value	All Patients (n=63)	Grade 3/4 AEs (n=63)
Weight loss	7 (21.9)	5 (16.1)	0.561	12 (19.0)	0
ALT increased	6 (18.8)	5 (16.1)	0.784	11 (17.5)	0
Leukopenia	6 (18.8)	4 (12.9)	0.525	10 (15.9)	0
Neutropenia	7 (21.9)	3 (9.7)	0.185	10 (15.9)	0
Abdominal pain	6 (18.8)	3 (9.7)	0.474	9 (14.3)	1 (1.6)
Ascites	5 (15.6)	4 (12.9)	1.000	9 (14.3)	0
Hypothyroidism	7 (21.9)	2 (6.5)	0.148	9 (14.3)	0
Arthralgia	5 (15.6)	3 (9.7)	0.708	8 (12.7)	0
Nausea	5 (15.6)	3 (9.7)	0.708	8 (12.7)	0
Epistaxis	5 (15.6)	3 (9.7)	0.708	8 (12.7)	0
Creatinine increased	3 (9.4)	4 (12.9)	0.708	7 (11.1)	0
Vomiting	4 (12.5)	3 (9.7)	1.000	7 (11.1)	0
Hypoalbuminemia	3 (9.4)	3 (9.7)	1.000	6 (9.5)	0
Urinary tract infection	2 (6.3)	4 (12.9)	0.426	6 (9.5)	0
Asthenia	3 (9.4)	2 (6.5)	1.000	5 (7.9)	0
Insomnia	2 (6.3)	2 (6.5)	1.000	4 (6.3)	0
Gastrointestinal bleeding	1 (3.1)	1 (3.2)	1.000	2 (3.2)	2 (3.2)
Intestinal perforation	0	1 (3.2)	0.492	1 (1.6)	1 (1.6)

Abbreviations: AEs, adverse events; SD group, standard-dose group; LD group, low-dose group; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

decreased platelet count (31.7%). Hypertension (4.7%) and decreased platelet count (4.7%) were the most frequent grade 3 or 4 AEs. No grade 5 AEs occurred during treatment. Additionally, two patients experienced gastrointestinal bleeding during therapy, requiring temporary discontinuation of Bev for one treatment cycle. Both patients showed symptom improvement after receiving endoscopic hemostasis and other supportive treatments during hospitalization. One patient developed intestinal perforation during treatment, leading to suspension of medication. Emergency perforation repair was performed, and symptoms improved after postoperative nutritional support and symptomatic treatment. In the SD group, both hypertension and proteinuria occurred in 15 patients each (46.9%), being the most common AEs, followed by decreased platelet count in 13 patients (40.6%). In the LD group, both hypertension and AST elevation occurred in 8 patients each (25.8%), being the most common AEs. Proteinuria showed a statistically significant difference between SD and LD groups (P=0.043), while no statistically significant differences were observed for other AEs between the two groups.

Discussion

In our study, the median OS was 22.0 months in the SD group and 19.3 months in the LD group, while the median PFS was 8.0 months in the SD group and 6.9 months in the LD group, with no statistically significant differences in OS or PFS between the two groups. A multicenter, phase Ib study (GO30140 trial) demonstrated that in previously untreated uHCC patients, those receiving Atezo-Bev therapy showed superior PFS compared to those treated with Atezo alone.[13] Hatanaka et al demonstrated in a recent study that early discontinuation of Bev treatment is one of the unfavorable factors associated with PFS and OS.[14] However, during clinical treatment, the incidence of Bev-related AEs remains persistently high, which has attracted widespread attention, especially since grade 3 or higher AEs may force discontinuation of Bev treatment. Although reducing the Bev dose may decrease the incidence of Bev-related AEs, whether dose adjustment would adversely affect the antitumor efficacy of the original treatment regimen remains unknown. In the EAGLE trial, a study of 387 patients with metastatic colorectal cancer found that patients receiving 10 mg/kg Bev did not demonstrate longer PFS compared to those receiving 5 mg/kg Bev.[15] Meanwhile, a retrospective study of 35 uHCC patients receiving Atezo-Bev combination therapy showed that compared to the standard-dose (15 mg/kg) Bev group, the low-dose (7.5 mg/kg) Bev group had a lower incidence of proteinuria, while PFS and tumor response rates were similar between the two groups.[16] Based on these findings, low-dose Bev and standard-dose Bev may demonstrate comparable efficacy in

exerting antitumor effects. Compared with the SD group (15 mg/kg), the LD group (7.5 mg/kg) achieved a remarkable 50% reduction in bevacizumab treatment costs. More importantly, no statistically significant differences were observed between the two groups in terms of OS or PFS (P=0.275, P =0.297). These findings provide important evidence-based rationale for optimizing healthcare resource allocation, particularly for economically disadvantaged patient populations.

Although Atezo-Bev demonstrates significant efficacy in treating HCC and provides longer OS for HCC patients compared to sorafenib, its administration is inevitably accompanied by the occurrence of AEs.[17,18] In the IMbrave150 trial, a study of 194 Chinese uHCC patients meeting the inclusion criteria revealed that the most common Bev-related AEs were proteinuria (36.5%) and hypertension (34.9%), and reducing their incidence may bring additional clinical benefits to these patients.[19] Recent clinical studies have demonstrated that *treatment-emergent* proteinuria may serve as a potential indicator for predicting bevacizumab's (Bev) antitumor efficacy. Furthermore, patients who develop hypertension during treatment may show superior OS compared to those without hypertension. These findings suggest that *treatment-emergent* proteinuria and hypertension may hold significant biological implications in Bev's antitumor mechanism.[20,21] In our study, proteinuria (36.5%) and hypertension (34.9%) were also the most frequent AEs, consistent with the aforementioned findings. However, while no statistically significant difference in hypertension was observed between the LD and SD groups, a significant difference in proteinuria was noted between the two groups. This discrepancy may be attributed to the fact that hypertension can be promptly controlled with oral antihypertensive medications, whereas the underlying mechanisms of proteinuria remain unclear, resulting in suboptimal treatment outcomes.[16] Therefore, for uHCC patients receiving Atezo-Bev therapy, adopting a low-dose Bev regimen may significantly reduce the risk of treatment-emergent proteinuria, a finding that carries important implications for clinical practice.

Notably, in our study, the 63 included uHCC patients demonstrated superior OS and PFS compared to the IMbrave150 trial, which may be associated with some uHCC patients receiving transcatheter arterial chemoembolization (TACE) therapy. Atezo-Bev combined with TACE exhibits synergistic effects in treating HCC. TACE can induce necrosis in partial tumor lesions, promote the release of related antigens, further enhance immune stimulation, and improve the antitumor efficacy of Atezo. However, while killing tumor cells, TACE creates a hypoxic environment around tumor cells, which promotes tumor angiogenesis and conversely facilitates the survival of residual tumor cells. Bev reduces tumor angiogenesis by antagonizing the effect of vascular endothelial growth factor in promoting tumor blood vessel formation, thereby partially counteracting the adverse effects of TACE-induced tumor angiogenesis.[22–24] The CHANCE001 trial, involving 826 uHCC patients, demonstrated that compared to uHCC patients receiving TACE monotherapy, those treated with a combination of TACE, programmed death-(ligand) 1 inhibitors and targeted agents showed superior median PFS (9.5 months) and median OS (19.2 months).[25] Subsequent CHANCE2201 trials further confirmed that this triple combination therapy benefits uHCC patients by improving both OS and PFS.[26] However, in these two trials, the incidence of grade ≥3 AEs with the combination regimens was 15.8% and 22.2%, respectively, both higher than those with monotherapy (7.5% and 18.1%, respectively). Although the safety profile of this combination approach remains within an acceptable range, future studies are needed to explore how to minimize the incidence of AEs with combination therapies to benefit more patients.

Our study has several limitations. First, as a single-center, retrospective study, it is prone to selection bias. Second, the relatively short follow-up period may lead to less objective assessments of PFS and OS, and the reported incidence of AEs might also be biased. Therefore, future prospective studies are needed to further evaluate the efficacy and safety of different Bev doses combined with Atezo in uHCC patients, and additional research is required on AEs occurring during Atezo-Bev treatment, particularly grade 3 or higher AEs. Furthermore, exploring biomarkers capable of predicting the efficacy of Atezo-Bev therapy is essential. Although some studies have suggested that the neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio may have some value in predicting Atezo-Bev treatment outcomes, the predictive significance of these ratios still requires in-depth investigation due to the lack of large-scale, multicenter randomized studies.[27,28] It is particularly noteworthy that with the rapid advancement of artificial intelligence and radiomics technologies, emerging evidence has demonstrated the significant clinical value of radiomics-based predictive models in evaluating treatment response to Atezo-Bev therapy.[29,30]

Conclusion

In conclusion, compared with low-dose Bev combined with Atezo, standard-dose Bev combined with Atezo showed no significant advantage in overall OS or PFS. Additionally, the low-dose Bev plus Atezo regimen may result in fewer AEs for patients.

Abbreviations

HCC, hepatocellular carcinoma; uHCC, unresectable hepatocellular carcinoma; Atezo, atezolizumab; Bev, bevacizumab; OS, overall survival; PFS, progression-free survival; AEs, adverse events; CT, computed tomography; MRI, magnetic resonance imaging; mRECIST, modified Response Evaluation Criteria in Solid Tumors; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; AFP, alpha-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; SD, standard dose; LD, low dose; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate.

Data Sharing Statement

The datasets generated and analyzed during the present study are available from the corresponding author upon reasonable request.

Ethics Approval and Informed Consent

This study was approved by the Ethics Committee of the First Affiliated Hospital of the University of Science and Technology of China, by the 1975 Declaration of Helsinki (Ethics number:2024-RE-488). This is a retrospective study, and it was confirmed that the privacy and personal information of the involved patients were kept confidential. Therefore, the Ethics Committee waived the requirement for informed consent.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took 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 they have no conflict of interest.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71(3):209–249. doi:10.3322/caac.21660
2. Xu H, He A, Liu A, Tong W, Cao D. Evaluation of the prognostic role of platelet-lymphocyte ratio in cancer patients treated with immune checkpoint inhibitors: a systematic review and meta-analysis. *Int Immunopharmacol*. 2019;77:105957. doi:10.1016/j.intimp.2019.105957
3. Rumgay H, Arnold M, Ferlay J, et al. Global burden of primary liver cancer in 2020 and predictions to 2040. *J Hepatol*. 2022;77(6):1598–1606. doi:10.1016/j.jhep.2022.08.021
4. Sankar K, Gong J, Osipov A, et al. Recent advances in the management of hepatocellular carcinoma. *Clin Mol Hepatol*. 2024;30(1):1–15. doi:10.3350/cmh.2023.0125
5. Yim SY, Lee SH, Baek SW, et al. Genomic biomarkers to predict response to atezolizumab plus bevacizumab immunotherapy in hepatocellular carcinoma: insights from the IMbrave150 trial. *Clin Mol Hepatol*. 2024;30(4):807–823. doi:10.3350/cmh.2024.0333
6. Kudo M, Aoki T, Ueshima K, et al. Achievement of complete response and drug-free status by atezolizumab plus bevacizumab combined with or without curative conversion in patients with transarterial chemoembolization-unsuitable, intermediate-stage hepatocellular carcinoma: a multicenter proof-of-concept study. *Liver Cancer*. 2023;12(4):321–338. doi:10.1159/000529574
7. Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. *N Engl J Med*. 2020;382(20):1894–1905. doi:10.1056/NEJMoa1915745
8. Kudo M, Tsuchiya K, Shao YY, et al. Impact of bevacizumab being skipped due to adverse events of special interest for bevacizumab in patients with unresectable hepatocellular carcinoma treated with atezolizumab plus bevacizumab: an exploratory analysis of the phase III IMbrave150 study. *Liver Cancer*. 2024;13(4):401–412. doi:10.1159/000535501

9. Yeom KM, Song YG, Yoo JJ, Kim SG, Kim YS. Reduced-dose or discontinuation of bevacizumab might be considered after variceal bleeding in patients with hepatocellular carcinoma receiving atezolizumab/bevacizumab: case reports. *Medicina*. 2024;60(1):157. doi:10.3390/medicina60010157
10. Sakai M, Iwamoto H, Shimose S, et al. Dose-reduction of bevacizumab in atezolizumab plus bevacizumab therapy extends treatment duration with disease control in patients with hepatocellular carcinoma. *Oncology*. 2025;103(4):265–276. doi:10.1159/000541082
11. Ball D, Nault JC, Vithayathil M, et al. Survival in patients receiving reduced dose intensity of bevacizumab for unresectable hepatocellular carcinoma. *NPJ Precis Oncol*. 2025;9(1):129. doi:10.1038/s41698-025-00908-7
12. Llovet JM, Villanueva A, Marrero JA, et al. Trial design and endpoints in hepatocellular carcinoma: AASLD consensus conference. *Hepatology*. 2021;73(Suppl 1):158–191. doi:10.1002/hep.31327
13. Lee MS, Ryoo BY, Hsu CH, et al. Atezolizumab with or without bevacizumab in unresectable hepatocellular carcinoma (GO30140): an open-label, multicentre, phase 1b study. *Lancet Oncol*. 2020;21(6):808–820. doi:10.1016/s1470-2045(20)30156-x
14. Hatanaka T, Hiraoka A, Tada T, et al. Association of early bevacizumab interruption with efficacy of atezolizumab plus bevacizumab for advanced hepatocellular carcinoma: a landmark analysis. *Hepatol Res*. 2022;52(5):462–470. doi:10.1111/hepr.13748
15. Iwamoto S, Takahashi T, Tamagawa H, et al. FOLFIRI plus bevacizumab as second-line therapy in patients with metastatic colorectal cancer after first-line bevacizumab plus oxaliplatin-based therapy: the randomized phase III EAGLE study. *Ann Oncol*. 2015;26(7):1427–1433. doi:10.1093/annonc/mdv197
16. Lee YC, Huang WT, Lee MY, Tsao CJ, Feng YH. Bevacizumab and atezolizumab for unresectable hepatocellular carcinoma: real-world data in taiwan-tainan medical oncology group H01 trial. *Vivo*. 2023;37(1):454–460. doi:10.21873/invivo.13099
17. Imai K, Takai K, Aiba M, et al. Adverse events in targeted therapy for unresectable hepatocellular carcinoma predict clinical outcomes. *Cancers*. 2024;16(18):3150. doi:10.3390/cancers16183150
18. Li D, Toh HC, Merle P, et al. Atezolizumab plus bevacizumab versus sorafenib for unresectable hepatocellular carcinoma: results from older adults enrolled in the IMbrave150 randomized clinical trial. *Liver Cancer*. 2022;11(6):558–571. doi:10.1159/000525671
19. Qin S, Ren Z, Feng YH, et al. Atezolizumab plus bevacizumab versus sorafenib in the chinese subpopulation with unresectable hepatocellular carcinoma: phase 3 randomized, open-label imbrave150 study. *Liver Cancer*. 2021;10(4):296–308. doi:10.1159/000513486
20. Moisuc DC, Marinca MV, Gafton B, Alexa-Stratulat T, Pavel-Tanasa M, Cianga P. Antiangiogenic drug-induced proteinuria as a prognostic factor in metastatic colorectal cancer. *Curr Oncol*. 2022;29(6):3996–4011. doi:10.3390/curroncol29060319
21. Shimose S, Iwamoto H, Tanaka M, et al. Association between adverse events and prognosis in patients with hepatocellular carcinoma treated with atezolizumab plus bevacizumab: a multicenter retrospective study. *Cancers*. 2022;14(17):4284. doi:10.3390/cancers14174284
22. Du C, Wu H, Zhong T, et al. Interventional therapy combined with tyrosine kinase inhibitors with or without immune checkpoint inhibitors as initial treatment for hepatocellular carcinoma with portal vein tumor thrombosis: a systematic review and meta-analysis. *Discov Oncol*. 2024;15(1):164. doi:10.1007/s12672-024-01026-9
23. Peng Z, Fan W, Zhu B, et al. Lenvatinib combined with transarterial chemoembolization as first-line treatment for advanced hepatocellular carcinoma: a phase III, randomized clinical trial (LAUNCH). *J Clin Oncol*. 2023;41(1):117–127. doi:10.1200/jco.22.00392
24. Zhao C, Xiang Z, Li M, et al. Transarterial chemoembolization combined with atezolizumab plus bevacizumab or lenvatinib for unresectable hepatocellular carcinoma: a propensity score matched study. *J Hepatocell Carcinoma*. 2023;10:1195–1206. doi:10.2147/jhc.S418256
25. Zhu HD, Li HL, Huang MS, et al. Transarterial chemoembolization with PD-(L)1 inhibitors plus molecular targeted therapies for hepatocellular carcinoma (CHANCE001). *Signal Transduct Target Ther*. 2023;8(1):58. doi:10.1038/s41392-022-01235-0
26. Jin ZC, Chen JJ, Zhu XL, et al. Immune checkpoint inhibitors and anti-vascular endothelial growth factor antibody/tyrosine kinase inhibitors with or without transarterial chemoembolization as first-line treatment for advanced hepatocellular carcinoma (CHANCE2201): a target trial emulation study. *EClinicalMedicine*. 2024;72:102622. doi:10.1016/j.eclinm.2024.102622
27. Matoya S, Suzuki T, Matsuura K, et al. The neutrophil-to-lymphocyte ratio at the start of the second course during atezolizumab plus bevacizumab therapy predicts therapeutic efficacy in patients with advanced hepatocellular carcinoma: a multicenter analysis. *Hepatol Res*. 2023;53(6):511–521. doi:10.1111/hepr.13886
28. Wu YL, Fulgenzi CAM, D'Alessio A, et al. Neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios as prognostic biomarkers in unresectable hepatocellular carcinoma treated with atezolizumab plus bevacizumab. *Cancers*. 2022;14(23):5834. doi:10.3390/cancers14235834
29. Vithayathil M, Koku D, Campani C, et al. Machine learning based radiomic models outperform clinical biomarkers in predicting outcomes after immunotherapy for hepatocellular carcinoma. *J Hepatol*. 2025. doi:10.1016/j.jhep.2025.04.017
30. Yan HT, Zu QQ, Hua HJ, et al. MRI-based quantification of intratumoral heterogeneity predicts response in hepatocellular carcinoma treated with atezolizumab-bevacizumab and TACE/HAIC. *Acad Radiol*. 2025. doi:10.1016/j.acra.2025.06.025