

Similar Efficacy Between Atezolizumab Plus Bevacizumab Versus Hepatic Arterial Infusion Chemotherapy For Unresectable Hepatocellular Carcinoma With Portal Vein Tumor Thrombus: A Retrospective Cohort Study

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Abstract. *Background/Aim:* The landscape of treatments for hepatocellular carcinoma (HCC), including immune checkpoint inhibitors, has expanded significantly. However, unresectable HCC patients with portal vein tumor thrombus (PVTT) continue to face a poor prognosis. This investigation examined the survival outcomes and determinants influencing survival rates in advanced HCC patients with PVTT undergoing treatment with atezolizumab plus bevacizumab (ATZ+BEV) or hepatic arterial infusion chemotherapy (HAIC). *Patients and Methods:* Between December 2003 and June 2023, 48 advanced HCC with PVTT underwent treatment with either ATZ+BEV (16 patients) or HAIC (32 patients). *Results:* The analysis revealed no significant disparities in overall survival (OS) or treatment efficacy between the ATZ+BEV and HAIC groups (ATZ+BEV: 10.0 months, HAIC: 15.3 months). Treatment with either ATZ+BEV or HAIC resulted in minimal alterations in the ALBI score and preserved hepatic function. Independent prognostic factors for OS, identified via multivariate logistic regression, included serum α -fetoprotein levels >400 ng/ml [hazard ratio (HR)=1.94; $p=0.001$], the existence of more than five tumors (HR=1.55; $p=0.043$), and the Child-Pugh score (HR=2.53; $p=0.002$). *Conclusion:* This investigation

revealed no significant variance in OS and response rates between patients receiving ATZ+BEV and those treated with HAIC. The survival of advanced HCC patients with PVTT is intricately linked to the preservation of liver function, emphasizing the necessity for additional research to enhance treatment approaches for this patient population.

Globally, hepatocellular carcinoma (HCC) is the sixth most prevalent cancer and holds the position of the third highest cause of death from cancer, with around 900,000 new instances and 830,000 fatalities noted in 2020 (1, 2). The prognosis for patients with unresectable HCC has seen gradual improvements thanks to the development of systemic treatments, encompassing a variety of molecular targeted therapies (MTAs), immune checkpoint inhibitors (ICIs), hepatic arterial infusion chemotherapy (HAIC), and radiation therapy (RT) (3-6).

Nevertheless, the outlook remains bleak for those with advanced HCC, especially for individuals presenting with portal vein tumor thrombus (PVTT), which is evident in 44.0%-62.2% of cases (7). PVTT drastically reduces survival prospects, with life expectancy ranging from 2 to 4 months with only palliative care (8). This highlights the urgent need for more research aimed at improving the outcomes for advanced HCC patients with PVTT.

The IMbrave150 study showcased that combination of atezolizumab and bevacizumab (ATZ+BEV), targeting programmed death ligand 1 (PD-L1) and vascular endothelial growth factor (VEGF) respectively, significantly extends both progression-free survival (PFS) and overall survival (OS) for patients with advanced HCC over sorafenib, making ATZ+BEV the favored initial systemic treatment option for this group (5). On the other hand, several studies have confirmed the efficacy of HAIC in managing HCC with PVTT, with retrospective cohort studies even suggesting that HAIC might be more effective than sorafenib for patients with HCC and PVTT (9-13).

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Key Words: Hepatocellular carcinoma, portal vein tumor thrombus, atezolizumab plus bevacizumab, hepatic arterial infusion chemotherapy.



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To date, no research has directly compared ATZ+BEV with HAIC in advanced HCC patients with PVTT. This investigation seeks to assess and contrast the effects of ATZ+BEV *versus* HAIC in patients suffering from HCC with PVTT.

Patients and Methods

Patients. This was a single-site, retrospective study, conducted at the Aso Iizuka Hospital from December 2009 to June 2023, assessing the impact of systemic treatments on 136 unresectable HCC patients with PVTT affecting the main trunk or major branches of the portal vein. This research adhered to the ethical guidelines of the Declaration of Helsinki and was sanctioned by the Ethics Committee of Aso Iizuka Hospital (Approval No. 24020), with patient consent acquired through an opt-out method.

Evaluation of liver function: ALBI score. The ALBI score, utilized to gauge liver functionality, is determined by the formula: $ALBI\ score = \log_{10}(T-Bil\ [mg/dl] \times 17.1) \times 0.66 + (ALB\ [g/dl] \times 10) \times -0.085$, where T-Bil represents total bilirubin and ALB signifies the level of serum albumin (14).

Treatment protocol. ATZ+BEV Regimen. Following the IMbrave150 trial's methodology, participants were administered atezolizumab (1,200 mg) and bevacizumab (7.5 mg/kg) *via* intravenous infusion every three weeks (8). This regimen was maintained until the occurrence of disease progression (PD) or the emergence of severe adverse reactions.

HAIC procedures. The study employed two HAIC strategies: a low-dose combination of cisplatin and 5-fluorouracil (low-dose FP) and New FP formulation (15). For HAIC delivery, a 5-Fr-W-spiral catheter was positioned through the right femoral artery, with the tip reaching either the hepatic or gastroduodenal artery. Additionally, a subcutaneous port (Sofa Port, Nipro Pharma Corporation, Osaka, Japan) was installed in the anterior femoral region. Treatment involved the administration of CDDP (30-50 mg) or IA-Call (50 mg) (Nippon Kayaku, Tokyo, Japan) on the first day, succeeded by a 5-day continuous infusion of 5-FU (1,500 mg). Following a two-day interval, the regimen was repeated bi-weekly until significant adverse effects or tumor progression was observed.

Evaluation of efficacy. The effectiveness of the treatments was evaluated at intervals of 6 to 12 weeks through either computed tomography or magnetic resonance imaging, employing the modified RECIST version 1.1 for antitumor response assessment (16). The disease control rate (DCR) comprised complete response (CR), partial response (PR), and stable disease (SD) lasting a minimum of four months. The objective response rate (ORR) combined the instances of PR and CR.

Statistical methods. Statistical analysis was conducted using the JMP Pro version 11 software (SAS Institute, Cary, NC, USA), with results presented as median values. Survival analysis was performed using the Kaplan-Meier method and log-rank test, while the Cox hazard model assessed prognostic factors. Group differences were examined using the Chi-squared or Fisher's exact test, considering $p < 0.05$ as statistically significant.

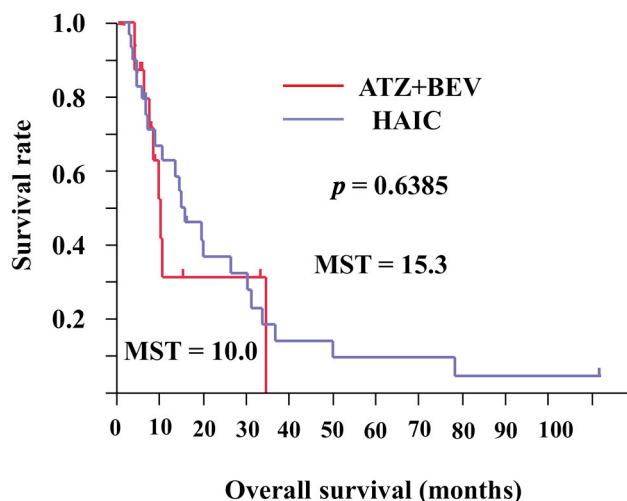


Figure 1. Kaplan-Meier estimates of OS in patients in HCC with PVTT. Significant differences in OS were determined using the log-rank test. Time 0 was defined as the date of administration of systemic chemotherapies. PVTT, Portal vein tumor thrombus; ATZ+BEV, atezolizumab plus bevacizumab; HAIC, hepatic arterial infusion chemotherapy; OS: overall survival.

Results

Patient characteristics. The demographics for the 48 patients receiving ATZ+BEV and HAIC treatments are summarized in Table I. Within this cohort, 37.5% (6/16) under ATZ+BEV treatment and 46.8% (15/32) under HAIC treatment were identified with main trunk PVTT. Parameters such as extent of PVTT, liver function, maximum intrahepatic tumor size, number of lesions, and tumor marker levels indices showed no significant variation between the ATZ+BEV and HAIC treatment groups.

Overall survival. The analysis indicated no substantial variance in OS between the ATZ+BEV and HAIC cohorts (10.0 vs. 15.3 months, $p=0.6385$), as visualized in Figure 1.

Overall response. For those in the ATZ+BEV cohort, a 31.3% (5/16) overall response rate (ORR, CR+PR) was recorded, with a disease stabilization rate (DCR, CR+PR+SD) of 62.5% (10/16). Conversely, in the HAIC cohort, the ORR stood at 34.3% (11/32), and the DCR at 50.0% (16/32). Between the treatments of ATZ+BEV and HAIC, there were no discernible differences in ORR and DCR, as Table II elaborates.

Effects on liver function. The intervention with either ATZ+BEV or HAIC was linked to negligible shifts in the ALBI score, thus sustaining liver function, as portrayed in Figure 2.

Table I. Baseline characteristics of patients.

Characteristics	ATZ+BEV	HAIC	p-Value
Number	16	32	
Age, years	69.5 (64-77.3)	68.5 (63.3-74.8)	0.6408
Sex, n (male/female)	15/1	24/8	0.0910
PVTT trunk/1 st or 2 nd branch	6/7	15/17	0.1229
EHS positive, n	2	6	0.5763
Intrahepatic max tumor size, cm	6.0 (3.0-7.0)	5.0 (3.0-9.0)	0.9900
Numbers of tumors >5	7	20	0.2176
Etiology			0.5378
Viral	8	19	
Non-viral	8	13	
Child-Pugh score			
A/B	12/4	20/12	0.3800
Alb, g/dl	3.6 (2.8-3.9)	3.2 (2.9-3.5)	0.1076
T.Bil, g/dl	1.1 (0.8-1.5)	0.9 (0.7-1.6)	0.7485
ALBI score	-2.22 (-2.46-1.54)	-1.92 (-2.25-1.51)	0.1820
Tumor marker			
AFP, ng/ml	235.1 (33.7-10,564.5)	178.3 (7.0-2,105.3)	0.3194
PIVKA-II, mAU/ml	2,198 (70.5-11,025.5)	1586.5 (194.5-6,508.8)	0.2600
With radiotherapy	2	15	0.0135

Data are expressed as median and interquartile range. ATZ+BEV, Atezolizumab plus bevacizumab; HAIC, hepatic arterial infusion chemotherapy; PVTT, portal vein tumor thrombus; EHS, extrahepatic spread; Alb, albumin; T.Bil, total bilirubin; ALBI score, albumin-bilirubin score; AFP, α -fetoprotein; PIVKA-II, vitamin K absence or antagonist-II.

Factors associated with OS. Through univariate examination, the presence of over five tumors, the Child-Pugh score, and serum AFP level surpassing 400 ng/mL were identified as factors linked to OS. The choice of therapeutic approach exhibited no measurable effect on OS of advanced HCC patients with PVTT. Moreover, multivariate analysis revealed serum AFP levels exceeding 400 ng/mL [hazard ratio (HR)=1.94; $p=0.001$], tumor number greater than five (HR=1.55; $p=0.043$), and the Child-Pugh score (HR=2.53; $p=0.002$) as autonomous indicators of OS.

Discussion

The question of optimal treatment for unresectable HCC patients with PVTT remains unresolved, lacking comparative analyses between ATZ+BEV and HAIC prior to this study.

This investigation is the inaugural study to evaluate the comparative efficacy of ATZ+BEV versus HAIC within this patient category. Our results reveal OS of 10.0 months for ATZ+BEV and 15.3 months for HAIC, alongside overall response rates of 31.3% and 34.4%, respectively, indicating negligible differences in treatment outcomes.

The IMbrave150 trial encompassed subjects exhibiting severe disease traits, notably 14% afflicted with PVTT in either the main trunk or main portal branch (8). Contemporary findings indicate a median survival duration of merely 7.6 months for this specific group under ATZ+BEV therapy (17).

Table II. Comparison of responses in patients receiving Atezolizumab plus bevacizumab and those treated with hepatic arterial infusion chemotherapy.

	ATZ+BEV	HAIC	p-Value
Overall response			0.5214
CR	0	1	
PR	5	10	
SD	5	5	
PD	5	12	
NE	1	4	
ORR (CR+PR)	5	11	0.6343
DCR (CR+PR+SD)	10	16	0.3493

ATZ+BEV, Atezolizumab plus bevacizumab; HAIC, hepatic arterial infusion chemotherapy; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluated; ORR, objective response rate; DCR, disease control rate.

The adverse prognosis for advanced HCC with PVTT can be ascribed to factors, such as heightened risk of tumor dissemination, elevated portal pressure, and reduced blood flow through the portal system, which may precipitate liver failure (18). Our findings illustrate that treatment with either ATZ+BEV or HAIC incurs only minor modifications in ALBI scores, thus preserving liver functionality.

There were no differences in baseline characteristics of patients including liver function at start of treatment and etiology between the ATZ+BEV and HAIC treatment groups,

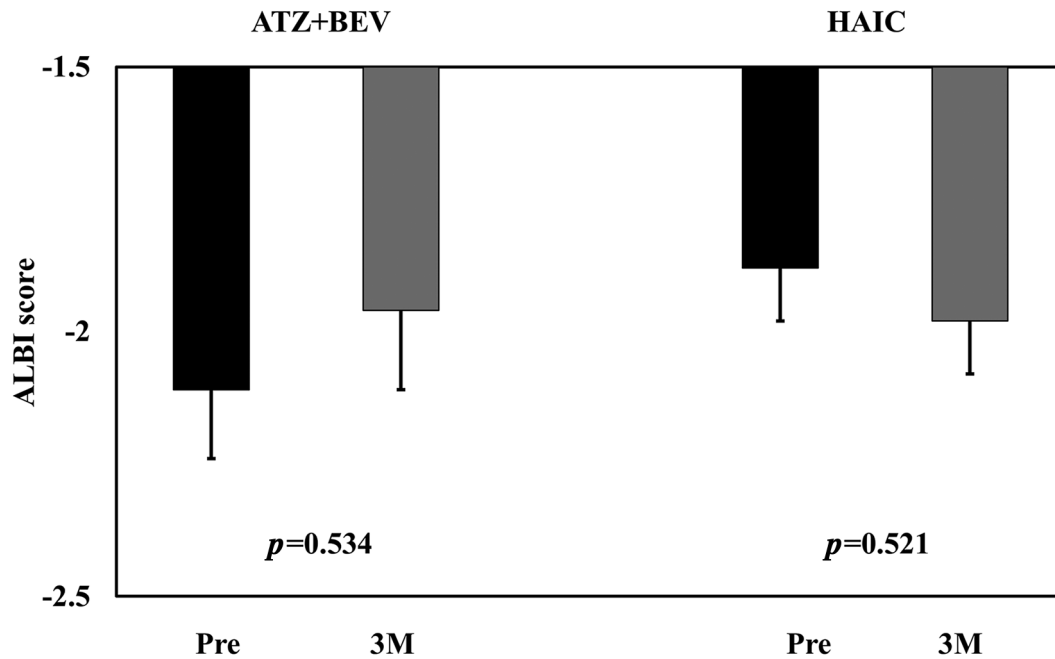


Figure 2. The change of ALBI score in ATZ+BEV and HAIC. ALBI, Albumin-bilirubin score; ATZ+BEV, Atezolizumab plus bevacizumab; HAIC, hepatic arterial infusion chemotherapy.

but most patients in our study with HCC who received HAIC had active hepatitis C virus (HCV) infection before the introduction of direct-acting antivirals. We have reported the crucial role of HCV eradication in the survival outcomes of advanced HCC patients treated with sorafenib (19). Given the historical context, HAIC might be more effective than ATZ+BEV for HCC with PVTT.

Kosaka Y *et al.* have previously highlighted that the synergy of HAIC and radiation therapy could improve outcomes for HCC with the main trunk PVTT (20). Despite this, our analysis revealed no disparity in median survival rates irrespective of radiation therapy inclusion (data not shown).

The study's limitations include its single-center nature and a limited number of participants. The diversity across stages of HCC and varied treatment timelines adds complexity to the analysis. Ideally, aligning participant groups based on liver function, stage of HCC, and line of treatment would refine the study, though this proved impractical with the small cohort size. An evaluation of adverse events linked to the treatment modalities was beyond the scope of this study.

Tailored and interdisciplinary treatment approaches stand as pivotal for enhancing prognoses in advanced HCC patients with PVTT. Recent findings by Simose S *et al.* suggest that combining lenvatinib with transcatheter intra-arterial therapy may improve prognosis over lenvatinib monotherapy in advanced-stage HCC patients (21). Consequently, a combination therapy involving both

ATZ+BEV and HAIC might emerge as a highly efficacious treatment strategy.

Conclusion

No significant differences in OS and response rates were observed between ATZ+BEV and HAIC treatments. Further research is necessary to identify the optimal treatment approach for advanced HCC with PVTT.

Conflicts of Interest

The Authors declare no competing interests in relation to this study.

Authors' Contributions

A.K., M.Y., A.M., and K.M. designed the study. A.K., Y.K., S.N., K.T., and M.Y. assisted with the data analyses. A.K. wrote the initial draft of the manuscript. M.Y. contributed to the analysis and interpretation of the data. M.Y., A.M., and K.M. assisted in the preparation and critical review of the manuscript. All Authors approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

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