Consistent efficacy of hepatic artery infusion chemotherapy irrespective of PD-L1 positivity in unresectable hepatocellular carcinoma

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Abstract. Atezolizumab/bevacizumab is the first line of treatment for unresectable hepatocellular carcinoma (HCC), combining immune checkpoint inhibitor and anti-VEGF monoclonal antibodies. Hepatic arterial infusion chemotherapy (HAIC) is administered when the above-described combination fails to confer sufficient clinical benefit. The present study aimed to explore the association between tumor programmed cell death-ligand 1 (PD-L1) positivity and HAIC response. A total of 40 patients with HCC who had undergone HAIC with available biopsy samples obtained between January 2020 and May 2023 were retrospectively enrolled. Tumor response, progression-free survival (PFS), disease control rate (DCR) and overall survival (OS) were evaluated. PD-L1 expression in tumor samples was assessed using a combined positivity score. The response rates of HAIC-treated patients with advanced HCC after failure of atezolizumab/bevacizumab combination therapy were recorded. OS (P=0.9717) and PFS (P=0.4194) did not differ between patients with and without PD-L1 positivity. The objective response rate (P=0.7830) and DCR (P=0.7020) also did not differ based on PD-L1 status. In conclusion, the current findings highlight the consistent efficacy of HAIC, regardless of PD-L1 positivity.

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Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver cancer and a major cause of cancer-related mortality (1,2). In 2008, Llovet *et al* (3) showed that sorafenib increased overall survival (OS) compared to placebo, thus introducing an effective systemic therapy for advanced HCC.

In 2018, Kudo *et al* (4) showed that lenvatinib was not inferior to sorafenib in the treatment of advanced HCC, whereafter the former was introduced as a first-line chemotherapy option. Since the introduction of multitarget tyrosine kinase inhibitors (TKIs), such as sorafenib and lenvatinib, markers that may help predict their therapeutic efficacy have been actively explored. Such an attempt was made by Marisi *et al* (5), who did not identify factors predicting sorafenib response. Following the advent of TKIs, a new era of combination therapies has emerged, including combination treatments with TKIs and immunotherapy, such as immune checkpoint inhibitors (ICIs). In 2020, Finn *et al* (6) showed that atezolizumab plus bevacizumab combination therapy resulted in superior overall survival (OS) and progression-free survival (PFS) compared to sorafenib, thereby changing the first-line treatment of patients with unresectable HCC. Markers predicting the efficacy of the atezolizumab plus bevacizumab combination, including programmed cell death ligand 1 (PD-L1), are the subject of active research (7). Both TKIs and ICIs exert immunomodulatory effects on the tumor microenvironment (TME) (8). In 2013, Sprinzl *et al* (9) showed that sorafenib enhances anti-tumor immune responses by regulating macrophages, in addition to its direct effect on tumor cells. In 2019, Kato *et al* (10) demonstrated that lenvatinib reduced

tumor-associated macrophage (TAM) infiltration, thereby enhancing anti-tumor immunity.

The liver TME is defined as the sum of stromal and tumor cells within the extracellular matrix, along with their secretome. Chronic insults from various etiologies, including hepatitis B, hepatitis C, alcoholic and non-alcoholic steatohepatitis, which are characterized by sequelae of inflammation and oxidative DNA damage, promote tumorigenesis through the accumulation of mutations and epigenetic rewiring (11). TKIs interact with tyrosine kinase receptors, inhibiting the autophosphorylation of their cytoplasmic domains to exert their anti-angiogenic effects (12). Sorafenib regulates TAMs and enhances T-cell responses, thereby enhancing anti-tumor immunity (9,13). Lenvatinib was shown to target fibroblast growth factor receptors, leading to greater efficacy of anti-programmed cell death 1 (PD-1) therapy (14). A recent meta-analysis concluded that PD-L1 expression was associated with a superior objective response rate in patients with advanced HCC treated with PD-1 or PD-L1 inhibitors (15).

In addition to such systemic treatments, Tischfield *et al* (16) demonstrated that locoregional therapies (LRTs), such as transarterial embolization, also induce changes in the TME. Hepatic artery infusion chemotherapy (HAIC) is a popular LRT option in Eastern Asia, particularly in South Korea and Japan. Considering the immunomodulatory effects of LRTs reported in multiple studies and reviews (8), the present study set out to determine whether the expression of factors related to the anti-tumor immune response, particularly PD-L1 expression, can predict the efficacy of HAIC in HCC.

Materials and methods

Study design and population. A total of 40 patients diagnosed with HCC who had undergone HAIC and a liver biopsy between January 2020 and May 2023 at Seoul St. Mary's Hospital (Seoul, Korea) were retrospectively enrolled. These patients were diagnosed based on radiological and histological findings, including multiphasic computed tomography and magnetic resonance imaging (17). The patients' hospital records were reviewed and their tumor response, PFS, disease control rate (DCR), objective response rate (ORR) and OS were evaluated. The DCR was defined as the proportion of patients who showed complete response, partial response or stable disease after therapy. The ORR was defined as the proportion of patients that responded either partially or fully to therapy: partial response or complete response. Patients were diagnosed with HCC based on the imaging criteria of the American Association for the Study of Liver Disease, the 2022 Korean Liver Cancer Association and the National Cancer Center Korea practice guidelines (17,18). Biopsy samples were immunohistochemically assessed for PD-L1 positivity using combined positivity scores (CPSs) (19). The study protocol was approved by the Institutional Review Board of Seoul St. Mary's Hospital (Seoul, Korea; approval no. KC23RISI0656). The study conformed to the ethical guidelines of the Declaration of Helsinki.

Immunohistochemistry. Immunohistochemistry was performed on core-needle liver biopsy samples. A 4-μm-thick cross-section of a paraffin-embedded block from the biopsy sample was placed on a glass slide. Deparaffinization, rehydration and antigen retrieval were performed using CC1 antigen retrieval solution (Ventana Medical Systems) and an automated slide stainer (Ventana Medical Systems) for 64 min. The sample was incubated with antibodies against PD-L1 (1:50 dilution; cat. no. M3653; Dako) for 32 min at 37˚C and washed. Finally, the slides were counterstained with hematoxylin I and bluing reagent (Ventana Medical Systems) for 4 min at room temperature. The CPS for PD-L1 expression were determined (19). In the present study, slides with ≥1% PD-L1-positive cells were considered PD-L1-positive samples. Sangro *et al* (20) also used the 1% threshold when determining PD-L1 positivity in their study on the association of inflammatory biomarkers with prognosis in nivolumab-treated patients with HCC.

Response evaluation. Response was evaluated using the modified Response Evaluation Criteria in Solid Tumors (21). All CT and MRI scans of the patients were examined by more than one doctor from The Department of Gastroenterology and Hepatology, and one doctor from The Department of Radiology. Accordingly, tumors with no arterial enhancement were defined as those showing a complete response (CR). Tumors with the sum of the diameters of viable lesions reduced by >30% were defined as showing a partial response (PR). Tumors with viable lesion diameters that had increased by >20% were defined as progressive disease (PD). Tumors that did not meet the criteria for PR or PD were defined as having stable disease (SD).

Statistical analysis. SPSS version 26 software (IBM Corp.) was used for statistical analyses. Categorical variables were analyzed using Fisher's extract test or the Freeman-Halton extension for Fisher's extract test in the case of multiple groups, and continuous variables were analyzed using an independent t-test. Patient survival was analyzed using the Kaplan-Meier method and survival curves were analyzed using the log-rank test. Cox proportional hazards regression analysis was used to analyze factors associated with survival. $P<0.05$ was considered to indicate statistical significance.

Results

Baseline characteristics. Table I presents the baseline characteristics of the 40 enrolled patients. A total of 36 (90%) of the patients were men and 4 (10%) were women. The mean age was 61.23±14.51 (range, 26-89) years. Hepatitis B infection was the most common cause of HCC [23 (57.6%) patients]. A total of 7 (17.5%) patients had a history of excessive alcohol consumption. Another 10 (25%) patients had no known risk factors for fatty liver disease. The mean tumor size was 9.53±4.43 cm. A total of 5 (12.5%) patients had a single HCC lesion, while 35 (87.5%) had multiple lesions. Furthermore, 31 (77.5%) patients had portal vein invasion, 18 (45%) had extrahepatic metastasis, 32 (80%) had Child-Pugh class A liver function, 8 (20%) had Child-Pugh class B liver function, 18 (45%) had a history of treatment, 6 (15%) had Barcelona Clinic Liver Cancer (BCLC) stage B disease and 34 (85%) had BCLC stage C disease. Table II shows the baseline characteristics of patients with and

Table I. Baseline characteristics of enrolled patients (n=40).

Item	Value
Sex (male/female)	36 (90)/4 (10)
Age, years	61.23±14.51
Etiology	
HBV	23 (57.5)
HCV	0 (0)
Alcohol abuse	7 (17.5)
Unknown	10 (25)
Tumor size, cm	9.53±4.43
Tumor number	
Single	5 (12.5)
Multiple	35 (87.5)
Portal vein invasion	
Yes/No	31 (77.5)/9 (22.5)
Extrahepatic metastasis	18 (45.0)
Child-Pugh score	
A	32 (80.0)
B	8 (20.0)
C	0 (0.0)
Previous treatment history	18 (45.00)
BCLC stage	
B	6 (15.0)
C	34 (85.0)

Values are expressed as n (%) or the mean ± standard deviation. HBV, hepatitis B virus; HCV, hepatitis C virus; BCLC, Barcelona Clinic Liver Cancer.

without PD-L1 positivity. There was a significant difference in enrolled patients with and without PD-L1 positivity in BCLC stage (Table II; P=0.026).

OS and PFS according to PD-L1 expression. OS and PFS did not significantly differ between patients with and without PD-L1 expression (Fig. 1; P=0.9717 and 0.4194, respectively). In addition, no significant differences were noted in the objective response rate (ORR) and disease control rate (DCR) (Table III; P=0.633 and 0.508, respectively). HAIC response also did not differ based on PD-L1 expression (Table III, P=0.595). Specifically, among patients with ≥1% PD-L1-positive cells, 1 (3.3%) showed a CR, 3 (10%) showed a PR, 15 (50%) showed SD and 11 (36.7%) showed PD. Among those with <1% PD-L1-positive cells, 1 patient (10%) showed a CR, 6 patients (60%) showed SD and 3 patients (30%) showed PD. Fig. 2 displays representative immunohistochemical findings for the enrolled patients, including samples with or without PD-L1 expression from patients whose disease did or did not progress (Fig. 2A-D).

Factors associated with prognosis. Table IV shows the results of the Cox regression analysis performed to identify the factors associated with OS and PFS. With regard to OS, the Eastern Cooperative Oncology Group (ECOG) performance status and liver function, represented by the Child-Pugh class, were significantly associated with a better prognosis (P<0.001 and P=0.02, respectively). Multivariate Cox regression analysis revealed a significant association between ECOG performance status and a better prognosis [hazard ratio=4.000 (95% CI: 1.937-8.262), P<0.001]. None of the factors analyzed was significantly associated with PFS.

Discussion

In the case of patients with advanced HCC for whom surgical treatment, such as resection, transplantation or LRT, including transarterial catheter embolization, is not an option, systemic therapy with atezolizumab plus bevacizumab is the first line of treatment (22). In Eastern Asia, HAIC is considered when systemic chemotherapy is not effective, particularly in HCC with portal vein invasion (23). The theoretical rationale is that, unlike normal hepatocytes, which receive most of their perfusion from the portal vein, HCC cells receive most of their perfusion from the hepatic artery (24). Transarterial chemoembolization (TACE) is another popular LRT that may damage and impair liver function (25). HAIC is significantly less toxic than TACE (26). In 2015, Song *et al* (27) reported comparable OS and time to progression between sorafenib and HAIC in patients with HCC with portal vein invasion. A study from 2019 suggested that HAIC is effective in patients regardless of portal vein invasion or extrahepatic metastasis (28). Comparable OS and PFS between lenvatinib and HAIC have also been reported by Lee *et al* (29). It is worth noting that lenvatinib has been reported to have similar efficacy to first-line atezolizumab/bevacizumab, particularly in specific cases, such as patients with autoimmune disease or other patients receiving immunosuppressants (30,31). Comparable OS and PFS were also previously reported between atezolizumab/bevacizumab and HAIC (32). Recently, Iwamoto *et al* (33) proposed a new era of multidisciplinary therapeutic strategies encompassing LRT, with an emphasis on the importance of HAIC.

In the current era of personalized medicine, patients are increasingly administered various combination regimens, which include ICIs and LRTs. As ever more treatment modalities become available, identifying biomarkers that predict their efficacy is essential, with extensive research focusing on the TME in this regard. Tischfield *et al* (16) demonstrated that transarterial embolization induces dynamic alterations in the TME. Cell death induced by LRTs results in the release of tumor antigens, which stimulate antigen-presenting cells, triggering an anti-tumor immune response (34). As LRTs may also exert immunomodulatory effects, the present study focused on the association between PD-L1 expression and HAIC efficacy.

In one study, the presence of PD-L1 in patients with HCC treated with ICI was associated with superior outcomes. The KEYNOTE-224 open-label phase II trial using pembrolizumab analyzed the association of PD-L1 with ORR and PFS, reporting a better prognosis in patients with PD-L1-positive tumors (35). In the phase III IMbrave150 trial, PD-L1 expression was associated with superior outcomes of atezolizumab plus bevacizumab combination therapy in terms of PFS and ORR (36). By contrast, in the CheckMate040 randomized clinical trial, PD-L1 expression was not associated with better treatment outcomes (37). PD-L1 is expressed in tumor cells,

Table II. Baseline characteristics of subgroups according to PD-L1 positivity.

Baseline characteristics	PD-L1-positive cells ≥1% (n=30)	PD-L1-positivity <1% (n=10)	P-value
Sex (male/female)	26/4	10/0	0.556
Age, years	59.6±16.20	66.10±5.59	0.067
Etiology			0.122
HBV	20	3	
HCV	0	0	
Alcohol abuse	4	3	
Others	6	4	
Tumor size, cm	9.75±4.49	8.90±4.42	0.747
Tumor number			0.584
Single	3	2	
Multiple	27	8	
Portal vein invasion			0.190
Yes/No	25/6	5/4	
Extrahepatic metastasis	15	3	0.190
Child-Pugh score			0.165
A	22	10	
B	8	0	
C	0	0	
Previous treatment history			0.231
Yes/No	12/18	6/4	
BCLC stage			0.026
B	2	4	
C	28	6	

Values are expressed as n, n (%) or the mean ± standard deviation. HBV, hepatitis B virus; HCV, hepatitis C virus; BCLC, Barcelona Clinic Liver Cancer; PD-L1, programmed cell death ligand 1.

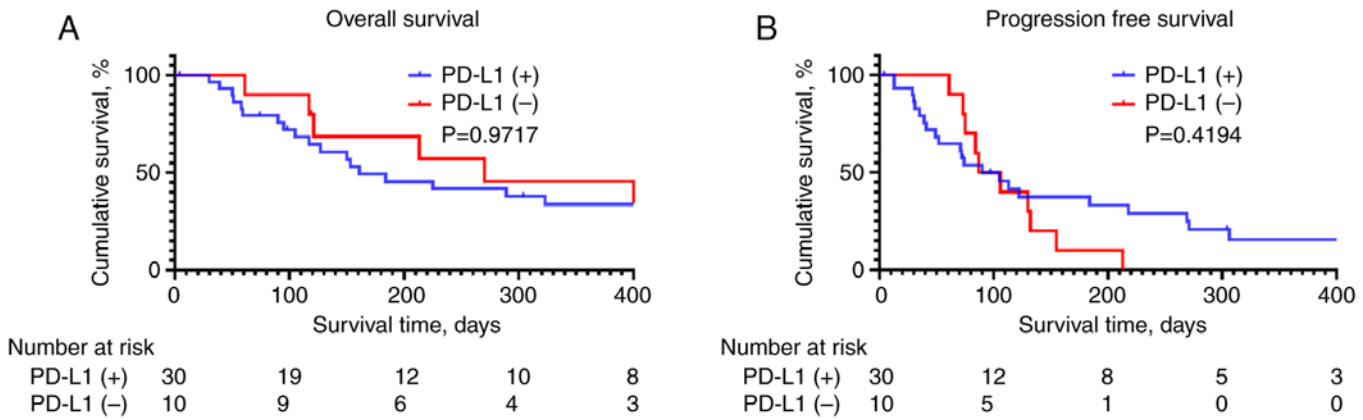

Figure 1. Kaplan-Meier survival curves. (A) Overall survival and (B) progression-free survival of patients with hepatocellular carcinoma based on PD-L1 positivity. PD-L1, programmed cell death ligand 1.

normal hepatocytes, sinusoidal cells and Kupffer cells (38). PD-L1 expression by neoplastic cells is associated with poor prognosis and characteristics include macrovascular invasion and poor differentiation (39). PD-L1 is known to be expressed on TAMs as well as on tumor cells in HCC. Furthermore, PD-L1-expressing TAMs are associated with tumor immunogenicity (40). A previous study by our group demonstrated that PD-L1 is highly expressed in TAMs and cancer-associated fibroblasts in the TME of HCC (41).

In the current study, patients diagnosed with advanced HCC who were treated with HAIC showed similar outcomes in terms of OS, PFS, ORR and DCR, regardless of PD-L1 positivity. Considering the compelling evidence that PD-L1 positivity elicits significantly superior outcomes in patients treated with

Table III. Treatment response of enrolled patients according to PD-L1 positivity.

Parameter	PD-L1-positive cells ≥1% (n=30)	PD-L1-positive cells <1% (n=10)	P-value
Treatment response			0.595
Complete response	1 (3.3)	1 (10)	
Partial response	3 (10)	0	
Stable disease	15 (50)	6 (60)	
Progressive disease	11 (36.7)	3 (30)	
Objective response rate	4/30	1/10	0.633
Disease control rate	19/30	7/10	0.508

Values are expressed as n (%). PD-L1, programmed cell death ligand 1. For ORR and DCR, values are expressed as n/total.

Table IV. Univariate and multivariate analyses of factors associated with overall and progression-free survival of enrolled patients.

	Overall survival			Progression-free survival		
Variable	Univariate P-value	Multivariate P-value	HR (95% CI)	Univariate P-value	Multivariate P-value	HR (95% CI)
PD-L1 positivity	0.706	-		0.622		
Sex (male vs. female)	0.363	-		0.602		
Age[a]	0.353	-		0.480		
Etiology[b]	0.099	-		0.186		
Tumor size[a]	0.366	-		0.827		
Multiple tumor lesions	0.435	-		0.413		
Portal vein invasion	0.806	-		0.790		
Distant metastasis	0.525	-		0.447		
ECOG performance status[a]	<0.001	<0.001	4.000 (1.937-8.262)	0.226		
Child-Pugh class A	0.020	0.062	2.670 (0.953-7.479)	0.510		
Previous treatment	0.625			0.567		

PD-L1, programmed cell death ligand 1; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio. [a]Calculation was made per increment. [b]All etiologies mentioned above (alcohol abuse, hepatitis B, hepatitis C, unknown etiologies) were compared.

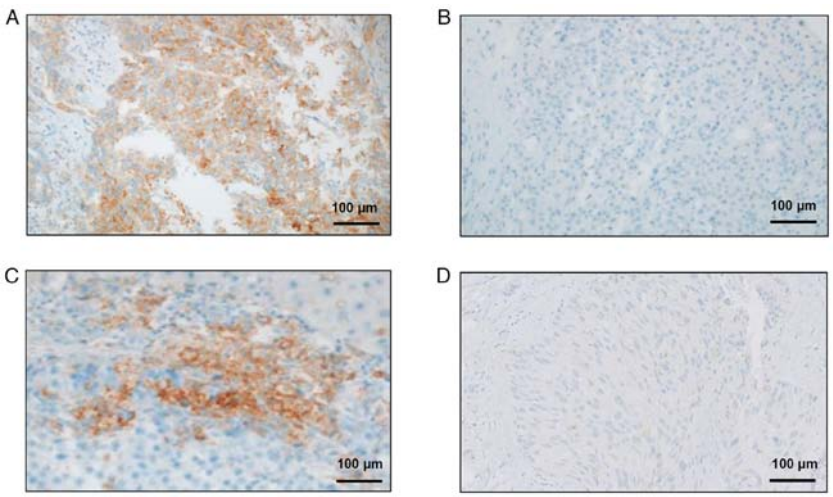

Figure 2. Representative images of PD-L1 immunohistochemistry of biopsy samples. (A) Sample of a patient with PD-L1 positivity who exhibited a poor response (PD-L1-positive progressor). (B) Sample of a case with no PD-L1 positivity who exhibited a poor response (PD-L1-negative progressor). (C) Specimen of a patient with PD-L1 positivity who exhibited a response (PD-L1-positive non-progressor). (D) Sample of a case with no PD-L1 positivity who exhibited a response (PD-L1-negative non-progressor). Brown staining suggests positivity and the counterstained blue are the nuclei (scale bars, 100 μm). PD-L1, programmed cell death ligand 1.

atezolizumab plus bevacizumab combination chemotherapy, HAIC should be acknowledged as a favorable treatment option for patients diagnosed with advanced HCC, particularly those with portal vein invasion without PD-L1 positivity.

The present study had certain limitations, owing to the retrospective nature of its design, which included selection bias. The small number of cases was also a limitation, considering its effect on the statistical power of the results. In addition, there was a significant difference in BCLC stage between patients with and without PD-L1 expression, which was ignored due to the small sample size of the current study. Furthermore, the lack of a longer follow-up duration represents an additional limitation to the present study. Finally, biopsy samples were obtained at a single timepoint per patient, thus not recapitulating the heterogeneity and dynamics of PD-L1 expression in tumors. Ideally, a prospective study with a larger patient pool would yield more meaningful results.

In conclusion, OS and PFS did not differ based on PD-L1 expression between patients with advanced HCC, suggesting that HAIC shows consistent efficacy, irrespective of PD-L1 status. A multidisciplinary approach including various systemic and locoregional treatment options is globally employed for the treatment of advanced HCC, in parallel to an emphasis on monotherapy. There is considerable interest in uncovering positive and negative factors predicting treatment response. The current findings support the use of HAIC in patients with advanced HCC with portal vein tumor thrombosis whose tumors lack PD-L1 expression.

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Availability or data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

JHK, YHK, SL and PSS contributed to the conception and design of the study, data interpretation, writing the first draft of the paper and critical revision of the manuscript. JWH, HCN, SK, CK and JWJ contributed to the study design and data analysis. JSY, JSO, HJC, JYC and SKY contributed to the data interpretation and critical revision of the manuscript. PSS and SHL conceived the idea of this study and contributed to the study conception, study design, data interpretation and critical revision of the manuscript. JK and PSS checked and confirm the authenticity of the raw data. All authors contributed to the manuscript and have read and approved the submitted version.

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Seoul St. Mary's Hospital (Seoul, Korea; approval no. KC23RISI0656). Patient consent was waived owing to the retrospective nature of the study and the analysis used anonymous clinical data.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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