

An Imaging Feature Predicts Efficacy of Atezolizumab Plus Bevacizumab in Unresectable Hepatocellular Carcinoma

AKIFUMI KUWANO¹, MASAYOSHI YADA¹, YOSHIKO MIYAZAKI², KOSUKE TANAKA¹, YUTA KOGA¹, YOSHIHIRO OHISHI², AKIHIDE MASUMOTO¹ and KENTA MOTOMURA¹

¹Department of Hepatology, Aso Iizuka Hospital, Iizuka, Japan;

²Department of Diagnostic Pathology, Aso Iizuka Hospital, Iizuka, Japan

Abstract. *Background/Aim:* Systemic chemotherapy with atezolizumab plus bevacizumab is approved for unresectable hepatocellular carcinoma (HCC). It is necessary to identify probable predictive biomarkers for chemotherapies. HCC with rim arterial-phase enhancement (APHE) has been linked to aggressive tumor activity. *Patients and Methods:* We studied the efficacy of atezolizumab plus bevacizumab for HCC using computed tomography (CT) or magnetic resonance imaging (MRI) imaging features. In total, 51 HCC patients who underwent CT or MRI were classified by the feature of rim APHE. *Results:* Clinical responses to chemotherapy were evaluated, and among those who received atezolizumab plus bevacizumab, there were 10 (19.6%) patients with rim APHE and 41 (80.4%) patients without rim APHE. We found that patients with rim APHE had a better response than those without rim APHE, and patients with rim APHE had longer median progression-free survival compared with those without rim APHE ($p=0.026$). Furthermore, liver tumor biopsy showed that HCC with rim APHE had a higher proportion of CD8+ tumor-infiltrating lymphocytes ($p<0.01$). *Conclusion:* Rim APHE in CT/MRI imaging might be a noninvasive biomarker for predicting response to atezolizumab plus bevacizumab.

Correspondence to: Masayoshi Yada, MD, Ph.D., Department of Hepatology, Aso Iizuka Hospital, 3-83 Yoshio-machi, Iizuka, Fukuoka 820-8505, Japan. Tel: +81 948223800, Fax: +81 948295744, e-mail: myadah1@aih-net.com

Key Words: Hepatocellular carcinoma, atezolizumab plus bevacizumab, rim arterial phase enhancement, tumor-infiltrating lymphocytes, CD8+ T cells.

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Hepatocellular carcinoma (HCC) is the sixth most common neoplasm and the third biggest cause of cancer-related deaths worldwide, with an estimated 900,000 new cases and 830,000 deaths in 2020 (1, 2). Recent progress in systemic chemotherapy for advanced HCC, such as immune checkpoint inhibitors (ICIs) and molecular targeted agents, has improved patient outcomes (3-7).

In the IMbrave150 study, atezolizumab plus bevacizumab, monoclonal antibodies against programmed death ligand 1 (PD-L1) and vascular endothelial growth factor (VEGF), respectively, extended progression-free survival (PFS) and overall survival (OS) in advanced HCC patients compared with sorafenib (3). As a result, atezolizumab plus bevacizumab is becoming the front-line systemic chemotherapy for advanced HCC.

Despite progress in systemic chemotherapy, the prognosis of patients with advanced HCC remains poor. The appropriate choice of chemotherapy may further improve prognosis. It is critical to choose a regimen that is suitable for personalized HCC treatment. For this reason, potential predictive biomarkers and knowledge of the mechanisms of response or resistance to systemic chemotherapies are necessary.

Recent studies showed that CD8+ tumor-infiltrating lymphocytes (TILs) might be linked with clinical responses to atezolizumab plus bevacizumab, although these studies required liver tumor biopsy tissue, and a non-invasive biomarker was needed for prediction of treatment response (8, 9).

Most HCCs are hypervascular and exhibit diffuse or global hyperenhancement in the arterial phase of computed tomography (CT) or magnetic resonance imaging (MRI) (10, 11). Rim arterial-phase hyperenhancement (APHE) is also reportedly associated with poor prognosis of HCC because it is related to aggressive histopathological features including a more hypoxic and fibrotic tumor microenvironment (12-14). It has been demonstrated that the presence of rim-APHE played an important role in predicting the prognosis of HCC in curative resection, radiofrequency ablation, and transarterial chemoembolization therapy. (12-16).

Table I. Baseline characteristics of patients who received atezolizumab plus bevacizumab.

Characteristics	All	With rim APHE	Without rim APHE	p-Value
Number	51	10	41	
Age, years	73 (67.0-80.0)	71 (62.5-76.8)	73 (67-80.5)	0.494
Sex, n (male/female)	42/9	8/2	34/7	0.830
MVI positive, n	15	4	11	0.422
EHS positive, n	12	3	9	0.598
Intrahepatic max tumor size, cm	4.0 (2.5-7.0)	5.3 (2.9-8.2)	4.0 (2.5-6.7)	0.460
Numbers of tumors >5	32	6	26	0.842
Etiology				0.256
HBV	8	1	8	
HCV	24	7	17	
NBNC	19	2	17	
Child-Pugh				0.176
Child-Pugh score A	39	9	30	
Child-Pugh score B/C	12	1	11	
Alb, g/dl	3.6 (3.2-4.0)	3.9 (3.6-4.1)	3.6 (3.2-3.9)	0.242
T.Bil, g/dl	1.0 (0.9-1.2)	0.9 (0.6-1.1)	1.0 (0.8-1.3)	0.348
ALBI score	-2.25 (-2.61--1.89)	-2.45 (-2.81--2.20)	-2.29 (-2.53--1.83)	0.184
BCLC stage				0.596
A	3	1	2	
B	22	3	19	
C	26	6	20	
Tumor marker				
AFP, ng/ml	80.6 (7.6-922.4)	615.9 (7.5-1,358.9)	44.2 (7.2-528.6)	0.047
PIVKA-II, mAU/ml	628 (81.0-4,348.0)	1,706.1 (49.5-20,040)	557 (84.5-3,170.5)	0.928

Data are expressed as median (interquartile range). APHE: Arterial phase enhancement; HBV: hepatitis B virus; HCV: hepatitis C virus; MVI: microvascular invasion; EHS: extrahepatic spread; Alb: albumin; T.Bil: total bilirubin; ALBI score: albumin-bilirubin score; BCLC stage: Barcelona Clinic liver cancer stage; AFP: α -fetoprotein; PIVKA-II: vitamin K absence or antagonist-II.

In this study, we analyzed rim-APHE using CT/MRI to determine whether it may be a useful biomarker for predicting responses to atezolizumab plus bevacizumab in HCC.

Patients and Methods

Patients. The effectiveness of atezolizumab with bevacizumab in HCC patients with and without rim-APHE in CT or MRI was examined in this single-center prospective trial conducted between December 2020 and February 2023 at Aso Iizuka Hospital. Atezolizumab and bevacizumab combination therapy was administered to 73 individuals in total. We excluded 6 patients who were followed up within 4 weeks, 3 patients who experienced transarterial chemoembolization within 3 weeks prior to chemotherapy, and 13 patients who did not have dynamic CT/MRI prior to treatment. For this investigation, we evaluated 51 patients altogether. Before starting chemotherapy, a liver tumor biopsy was performed on 30 of 51 patients. This study was conducted in accordance with the guidelines of the Declaration of Helsinki and was approved by the Ethics Committee of Aso Iizuka Hospital (approval No. 22008). The opt-out method was used to obtain consent for this study.

Imaging acquisition. Contrast-enhanced hepatic CT was performed on the patients. CT was performed in the axial plane with sections

that were 5-7 mm thick using a 256-section (GE Revolution, GE Healthcare, Milwaukee, WI, USA) multidetector CT scanner. After administering a nonionic iodinated contrast agent at a rate of 2 ml/kg of body weight for 20-40 s using an automatic power injector and a bolus-triggered method, hepatic arterial phase scanning was started. The starting times for portal and delayed phase scanning were 70 and 180 s following the initiation of the contrast medium injection. A 1.5-T or 3.0-T MR scanner was used for the MRI (Ingeina; Philips Healthcare, Best, the Netherlands). Primovist (0.25 mmol/ml gadoxetic acid; Bayer Schering Pharma, Berlin, Germany) was infused intravenously per kilogram of body weight for the dynamic investigation. Using the test injection procedure with 1.5 ml gadoxetic acid+8 ml saline flush, the ideal arterial dominant phase, determined as the time of peak enhancement in the abdominal aorta+an extra 10 s of imaging time (16-22 s), was attained. After imaging during the arterial phase, images during the portal and delayed phases were taken at intervals of 20 and 60 s, respectively. All patients' hepatobiliary phases were measured 15 min after injection.

Rim-APHE. In contrast to the capsule appearance, which is a smooth thickened peripheral rim enclosing a background nodule in the portal or delayed phase (17, 18), rim-APHE was defined as an irregularly shaped rim-like peripheral hyperenhancement in enhanced contrast CT or MRI (17, 18). The CT and MR scans were examined independently by four hepatologists. The review orders were randomized for each patient to prevent recall bias caused by

Table II. Comparison of responses to atezolizumab plus bevacizumab between hepatocellular carcinoma with and without rim arterial phase enhancement (APHE).

	All (n=51)	With rim APHE n=10	Without rim APHE n=41	p-Value
Overall response				0.043
CR	1	0	1	
PR	17	7	10	
SD	14	2	12	
PD	19	1	18	
ORR (CR+PR)	18	7	11	0.005
DCR (CR+PR+SD)	32	9	23	0.024

CR: Complete response; PR: partial response; SD: stable disease; PD: progressive disease; ORR: objective response rate; DCR: disease control rate.

each imaging modality. If the patient had numerous HCCs, the imaging analysis was performed on the largest tumor.

Albumin–bilirubin (ALBI) score. The ALBI score was used to evaluate liver function. The formula for calculating the ALBI score was $\log_{10} [\text{T-Bil (mg/dl)} \times 17.1] \times 0.66 + [\text{ALB (g/dl)} \times 10] \times -22.120.085$, where T-Bil is total bilirubin and ALB is the serum albumin level (19).

Treatment protocol. Every 3 weeks, patients underwent intravenous administration of atezolizumab 1,200 mg and bevacizumab 7.5 mg/kg in accordance with the IMbrave150 trial protocol by Chugai Co., Ltd. (Tokyo, Japan) (3). Treatment was continued until disease progression (PD) or intolerable side effects.

Evaluation of efficacy. Every 6 to 12 weeks following the start of treatment, CT or MRI was used to assess the treatment response. Modified RECIST version 1.1 was used to evaluate the antitumor response (20). Complete response (CR), partial response (PR), or stable disease (SD) lasting at least 4 months were all considered to be indicators of the disease control rate (DCR). The definition of the objective response rate (ORR) was PR plus CR. Every 3 to 4 weeks, the patient was examined and treated until PD or until the adverse effects became unacceptable.

Immunohistochemistry (IHC). Liver tumor biopsy specimens fixed in 10% formalin were embedded in paraffin for 10–48 h at room temperature. Serial sections (5 μm) were cut from paraffin blocks and stained with hematoxylin and eosin. The presence of CD8+ T cells was determined by IHC using mouse anti-human monoclonal CD8 primary antibody (clone C8/144B; 1:50; DAKO, Agilent, Santa Clara, CA, USA). After incubation with secondary antibodies, staining reactions were performed using the Bond Polymer System (Leica Biosystems, Buffalo Grove, IL, USA). By inspecting high-power fields (HPFs) chosen for the most confluent areas of CD8+ TILs at 400 $\times$ magnification, IHC staining of CD8+ cell infiltration was evaluated based on the quantity of positively stained CD8+ TILs. An optimal cutoff was obtained using the mean (CD8: 15.9 cells/HPF), as in our previous report (9).

Table III. Comparison of histologic differentiation and CD8+ tumor-infiltrating lymphocytes (TILs) between hepatocellular carcinoma with and without rim arterial phase enhancement (APHE).

	All (30)	With rim APHE n=7	Without rim APHE n=23	p-Value
Well/Moderated/Poorly	4/19/17	1/4/2	3/15/5	0.817
CD8+ TILs high/low	12/18	7/0	5/18	<0.01

Statistical analysis. JMP Pro version 11 statistical software (SAS Institute Inc., Cary, NC, USA) was used for all analyses. Data are presented as medians (interquartile ranges). Significant differences between groups were examined by chi-square test. Kaplan-Meier analysis was performed for statistical analysis of PFS. Significant differences in PFS were determined using the log-rank test, and statistical significance was determined at $p < 0.05$.

Results

Patient characteristics. Characteristics of the 51 patients who received atezolizumab plus bevacizumab are shown in Table I. We classified the enrolled patients with rim-APHE HCC and without rim-APHE HCC using CT or MRI.

There were 10 patients with rim-APHE HCC and 41 without rim-APHE HCC. Among the patients with rim-APHE HCC, one was Barcelona Clinic Liver Cancer (BCLC) stage A, three were BCLC stage B, and six were BCLC stage C. Among the patients without rim-APHE HCC, two patients were BCLC stage A, 19 were BCLC stage B, and 20 were BCLC stage C ($p=0.596$). Serum α -fetoprotein (AFP) in patients with rim-APHE was higher than in patients without rim-APHE ($p=0.047$). Age, sex, etiology, Child–Pugh grade, ALBI score, tumor size, number of intrahepatic lesions, microvascular invasion, extrahepatic spread, and protein induced by vitamin K absence or antagonist-II (PIVKA-II) levels were similar between the two groups.

Efficacy of atezolizumab plus bevacizumab in patients with and without rim-APHE HCC. Among patients who received atezolizumab plus bevacizumab, the ORR (CR+PR) was 7/10 (70.0%) in patients with rim-APHE HCC and 11/41 (26.8%) in patients without rim-APHE HCC ($p=0.005$). The DCRs (CR+PR+SD) were 9/10 (90.0%) and 23/41 (56.1%) in patients with and without rim-APHE HCC, respectively ($p=0.020$) (Table II). Therefore, there was a higher response rate in the patients with rim-APHE HCC compared with that in the patients without rim-APHE HCC following atezolizumab plus bevacizumab therapy.

PFS. The median PFS of all patients who received atezolizumab plus bevacizumab therapy was 6.3 months.

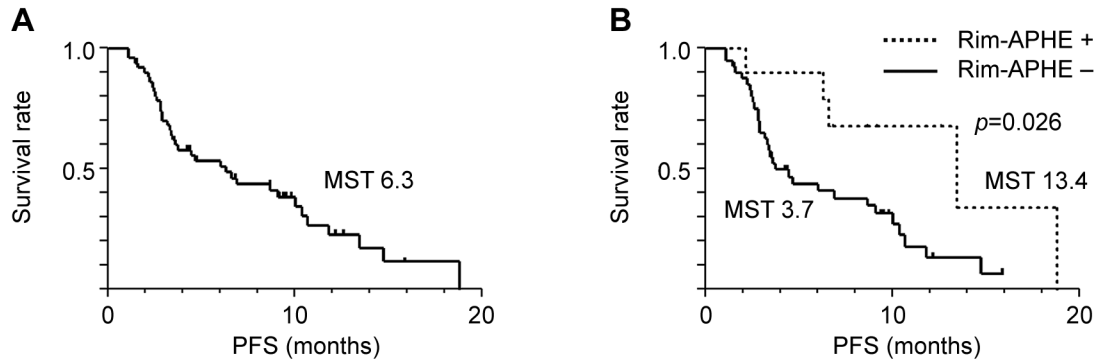


Figure 1. Kaplan-Meier estimates of progression-free survival (PFS) in patients with hepatocellular carcinoma treated with atezolizumab plus bevacizumab. (A) All patients. (B) Patients with and without rim APHE. Significant differences in PFS were determined using the log-rank test. Time 0 was defined as the date of administration of atezolizumab plus bevacizumab.

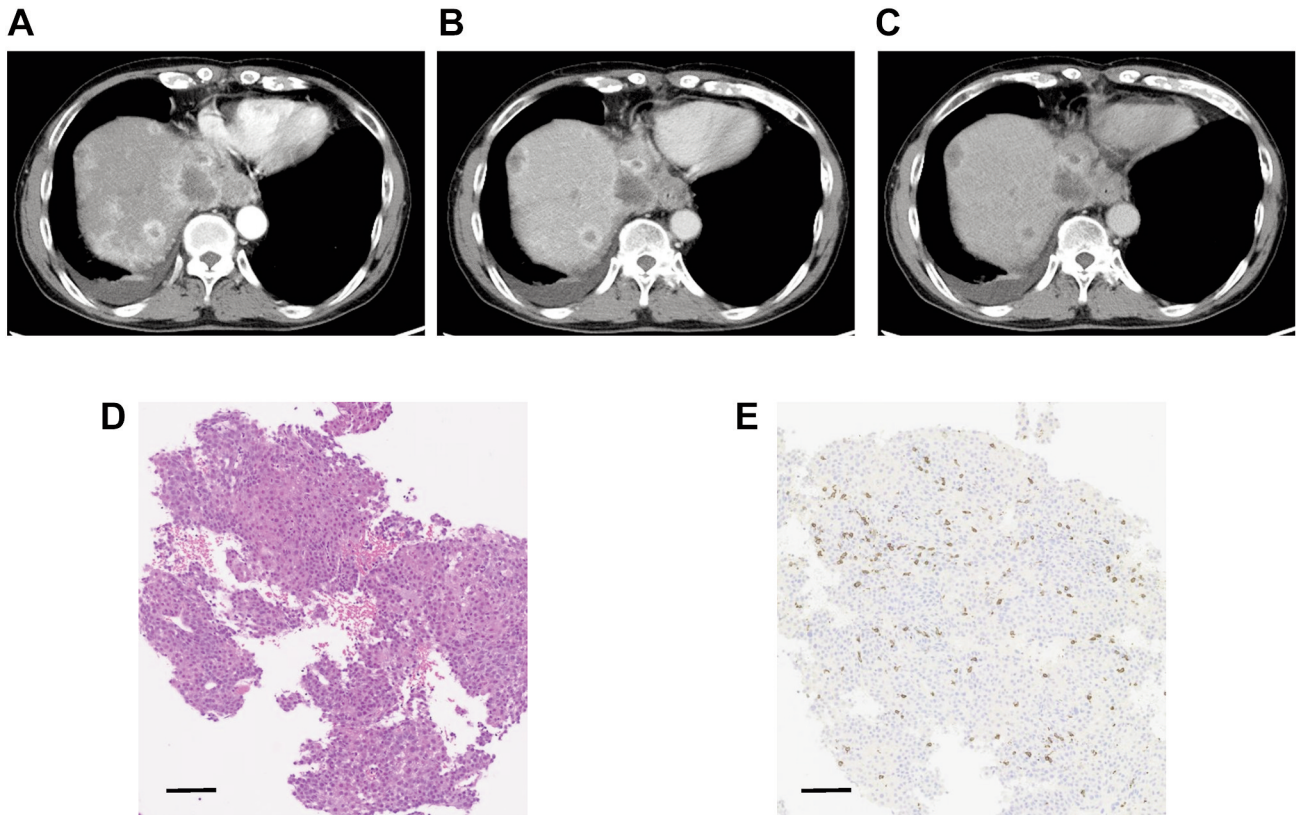


Figure 2. Typical case of HCC with rim APHE. (A) Computed tomography (CT) image prior to treatment. (A) Arterial phase. (B) Portal phase. (C) Equilibrium phase. (D) Hematoxylin and eosin staining of liver specimens (magnification: 100×; scale bar: 100 μm). (E) Immunohistochemistry for CD8+ T cells was evaluated in liver specimens (magnification: 100×; scale bar: 100 μm).

Kaplan-Meier analysis revealed that the median PFS in the patients with rim-APHE HCC (13.4 months) was increased compared with that in the patients without rim-APHE HCC (3.7 months) ($p=0.026$) (Figure 1).

Histological differentiation and CD8+ TILs in HCC tissues associated with rim-APHE. Histological differentiation and CD8+TIL levels were assessed using IHC prior to chemotherapy in 30 patients (Table III). There was no

significant difference in histological differentiation between patients with and without rim-APHE ($p=0.817$). Seven of seven patients with rim-APHE had high levels of CD8+ TILs, while 5 of 23 patients without rim-APHE HCC had low levels of CD8+ TILs ($p<0.01$). A typical case of moderately differentiated HCC is shown in Figure 2.

Discussion

For patients with advanced HCC, the combination of ICI and VEGF inhibition using atezolizumab plus bevacizumab is approved as systemic therapy (3). In patients with HCC who have received nivolumab, gene expression analysis of immune-related transcripts has recently been used to correlate the objective tumor response with survival, and it has been revealed that non-inflamed HCC with immune exclusion is resistant to ICIs (21-24). Prior to treatment, it is crucial to assess the immunological status of HCC patients because this could further improve prognosis. Precise identification of patients who will benefit from ICI is essential in the era of personalized medicine. As a result, predictive biomarkers are needed for each therapy.

It has been reported that CD8+ TILs could be a biomarker for predicting response to systemic chemotherapy using liver biopsy samples (8, 9). However, these are tissue-based biomarkers that require invasive biopsies and do not reflect the heterogeneity of tumors.

Radiomics is an emerging noninvasive approach and has been shown to improve diagnostic, prognostic, and predictive accuracy in HCC (25-29). Radiomics can also be used to forecast how HCC patients will respond to ICIs and transcatheter arterial chemoembolization (30-32). According to one study, Gd-EOB-DTPA-enhanced MRI-based combination radiomics may be helpful in individual pretreatment immunoscore predictions, including CD8+TILs, to direct precise immunotherapy and accurate prognosis prediction for HCC patients (33). These studies suggested that imaging tests such as CT or MRI could serve as biomarkers for predicting the clinical response to HCC treatment. The presence of APHE that is most obvious in the observational periphery is known as rim-APHE (17, 18). It is linked with a higher risk of tumor recurrence, quick tumor growth, and poor prognosis following surgery, ablation, or transarterial chemoembolization. Rim-APHE has been associated with aggressive tumor biology, such as microvascular invasion, poor differentiation, and hypoxic and fibrotic tumor microenvironments, and can serve as a histopathological marker for proliferative HCCs (12, 15, 34). According to reports, rim-APHE was identified in 5%-31.4% of HCCs that had curative resection or radiofrequency ablation (35, 36). In our investigation, rim-APHE was present in 10 out of 51 individuals (19.6%), matching these studies. Our results showed that atezolizumab plus bevacizumab produced a better response in patients with rim-APHE than in patients without

rim-APHE. The presence of CD8+TILs in HCC with rim-APHE could have led to this outcome.

The limitations of this study include the small number of HCC patients who underwent liver tumor biopsy because of its single-center nature. Because of the small number of cases, we were unable to evaluate OS because liver function and HCC stage were not matched.

Conclusion

Rim-APHE may be a biomarker to predict how an individual would react to atezolizumab with bevacizumab. Our results point to the recommendation of atezolizumab plus bevacizumab as a preventative measure for HCC with rim-APHE. To enhance the prognosis of patients with advanced HCC, more research on chemotherapy selection is required.

Conflicts of Interest

All 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., Y.K., K.T., and Y.M. assisted with the data analyses. Y.M. and Y.O. performed the pathological examinations including immunostaining. 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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