Clinical usefulness of newly developed prognostic predictive score for atezolizumab plus bevacizumab for hepatocellular carcinoma

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Abstract

Background/Aim: The present study aimed to develop detailed parameters for prediction of prognosis for patients with unresectable hepatocellular carcinoma (uHCC) receiving Atezolizumab plus Bevacizumab (Atez/Bev). Methods: Between September 2020 and January 2023, the patients treated with Atez/Bev were enrolled (n=719, males 577, median age 74 years). Factors involved in overall survival (OS) were extracted and a prognostic scoring system based on hazard ratio (HR) was created. OS and progression-free survival (PFS) were examined retrospectively, and the prognostic ability of the newly system was compared to CRAFITY score using concordance index (c-index) and Akaike Information Criterion (AIC) results. Results: Cox-hazards multivariate analysis showed BCLC classification C/D (HR 1.4; 1 point), AFP [?]100 ng/mL (HR 1.4; 1 point), mALBI 2a (HR 1.7; 1 point), mALBI 2b/3 (HR 2.8; 2 points), and DCP [?]100 mAU/mL (HR 1.6; 1 point) as significant factors. The assigned points were added and used for IMnunotherapy with AFP, BCLC staging, mALBI, and DCP evaluation (IMABALI-De) scoring. For IMABALI-De scores of 0/1/2/3/4/5, OS was not applicable (NA)/NA/26.11/18.79/14.07/8.32 months (P<0.001; AIC 2788.67, c-index 0.699), while for CRAFITY scores of 0/1/2, OS was 26.11/20.29/11.32 months (p<0.001; AIC 2864.54, c-index 0.606). PFS for those IMABALI-De scores was 21.75/12.89/9.18/8.0/5.0/3.75 months (P<0.001; AIC 5203.32, c-index 0.623) and for the CRAFITY scores was10.32/7.68/3.57 months (p<0.001; AIC 5246.61, c-index 0.574). IMABALI-De score had better AIC and c-index results as compared to CRAFITY score for both OS and PFS. Conclusion: The proposed IMABALI-De score may have a favorable prognostic predictive ability for uHCC patients with Atez/Bev.

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Running head: new prognostic predictive score for Atez/Bev

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Results: Cox-hazards multivariate analysis showed BCLC classification C/D (HR 1.4; 1 point), AFP [?]100 ng/mL (HR 1.4; 1 point), mALBI 2a (HR 1.7; 1 point), mALBI 2b/3 (HR 2.8; 2 points), and DCP [?]100 mAU/mL (HR 1.6; 1 point) as significant factors. The assigned points were added and used for *IM* nunotherapy with *A* FP, *B* CLC staging, m*AL* B*I,* and *D* CP *e* valuation (IMABALI-De) scoring. For IMABALI-De scores of 0/1/2/3/4/5, OS was not applicable (NA)/NA/26.11/18.79/14.07/8.32 months (P<0.001; AIC 2788.67, c-index 0.699), while for CRAFITY scores of 0/1/2, OS was 26.11/20.29/11.32 months (p<0.001; AIC 2864.54, c-index 0.606). PFS for those IMABALI-De scores was 21.75/12.89/9.18/8.0/5.0/3.75 months (P<0.001; AIC 5203.32, c-index 0.623) and for the CRAFITY scores was10.32/7.68/3.57 months (p<0.001; AIC 5246.61, c-index 0.574). IMABALI-De score had better AIC and c-index results as compared to CRAFITY score for both OS and PFS.

Conclusion: The proposed IMABALI-De score may have a favorable prognostic predictive ability for uHCC patients with Atez/Bev.

Keywords: hepatocellular carcinoma, Atezolizumab plus Bevacizumab, prognosis, modified albumin-bilirubin grade, IMABALI-De score, IMABALI score, CRAFITY score

Introduction

Studies have revealed that hepatocellular carcinoma (HCC) ranks as the sixth most prevalent cancer type globally and stands as the third to fourth leading cause of cancer-related deaths worldwide(1)·(2). Recently, atezolizumab and bevacizumab (Atez/Bev), a recently developed immunotherapy, received approval for unresectable HCC (uHCC) and has shown favorable therapeutic outcomes in real-world clinical practice (3). When possible, it is considered that HCC patients in Barcelona Clinic Liver Cancer stage (BCLC) -C should be treated with Atez/Bev, while it has also been proposed as systemic treatment for earlier stage HCC (BCLC-B) patients, who show transcatheter arterial chemoembolization (TACE) refractoriness status (4) (5). As a result, an assessment tool for detailed prediction of prognosis is needed to provide clinical information regarding prognosis after introducing Atez/Bev for treatment decision making. In past reports, c-reactive protein (CRP) and alpha-fetoprotein (AFP) in immunotherapy (CRAFITY) score has been shown to be a useful prognostic scoring system for Atez/Bev cases(6) (7). Conversely, the prognosis of HCC patients is known to be affected not only by tumor burden and malignant potential (8), but also hepatic reserve function (9). The aim of the present study was to develop a method for detailed prediction of prognosis for patients treated with Atez/Bev based on clinical parameters related to malignant potential of HCC, tumor burden, and hepatic function.

Materials and Methods

Following exclusion of patients without CRP and/or tumor marker data [AFP and/or Des-γ-carboxy prothrombin (DCP)] (n=36), between September 2020 and January 2023, 719 HCC patients treated with Atez/Bev at 25 different institutions, following written informed consent (IC). Every enrolled patient provided written IC. The treatment strategy with Atez/Bev was the same as previously reported and is illustrated in Figure 1 (10). The choice to administer Atez/Bev was made by the physician at each medical center. Patients were given intravenous Atez/Bev, comprising Atez (1200mg) and Bev (15 mg/kg of body weight), in accordance with the manufacturer's recommendations, every three weeks(11). Treatment was discontinued if serious or unacceptable adverse event (AE) occurred, or elseif there was clinical HCC progression. The National cancer institute common terminology criteria for adverse events (ver. 5.0)(12), was employed to assess of AEs. The attending physician was responsible for determining the subsequent course of treatment following the cessation of Atez/Bev.

Following official approval, the retrospective database analysis was conducted in compliance with Japan's Ministry of Health and Welfare Clinical Research Guidelines and the Helsinki Declaration.

Upper gastrointestinal endoscopy prior to Atez/Bev

In order to mitigate the risk of gastrointestinal bleeding as an adverse event associated with Atez/Bev therapy, each patient had an upper gastrointestinal endoscopy within six months of commencing Atez/Bev. This examination aimed to monitor the presence of esophago-gastric varices (EGV), which were categorized into 3 types; small straight (F1; Grade 1), enlarged tortuous (F2; Grade 2), or large coil-shaped (F3; Grade 3). In cases where bleeding was detected or high-risk situations such as EGV grade 2 (F2) or higher, or if the red-color sign was positive, variceal ligation or injection sclerotherapy were performed before commencing Atez/Bev therapy.

Etiology of HCC

HCC due to infection of hepatitis B virus (HBV) was diagnosed based on a positive HBV surface antigen, while the presence of positive anti-HCV antibodies indicated HCC associated with hepatitis C virus (HCV) infection. Nucleotide analogs , such as entecavir, tenofovir, or tenofovir alafenamide fumarate were administered to HBV-infected patients. For patients without HBV or HCV infection but with a history of alcohol abuse ([?]60 g/day), the underlying liver disease was attributed to alcohol (13, 14) . The patients with a documented autoimmune disease history were ineligible for Atez/Bev treatment.

Assessments of hepatic reserve function

Hepatic reserve function was assessed using Child-Pugh classification (15) and albumin-bilirubin (ALBI) score (16, 17) and modified ALBI grade (mALBI): ALBI grade 2 divided into two subgrades (2a and 2b) with an ALBI score of -2.27 as the cut-off value(9).

Diagnosis and evaluation of HCC stage

The diagnosis of the HCC relied on the consensus statement of the Japan society of Hepatology (JSH) (18) and tumor staging was based on BCLC stage (19).The diagnosis specifically considered increased alpha-fetoprotein (AFP), contrast-enhanced ultrasonography with perflubutane (20), dynamic-CT (21), magnetic resonance imaging (MRI) (22, 23), and/or pathological findings during the clinical course.

Evaluation of therapeutic efficacy of Atez/Bev treatment

To evaluate the therapeutic response, the response evaluation criteria in solid tumors (RECIST), ver. 1.1 (24),or modified RECIST (mRECIST)(25) were employed. Progression-free survival (PFS) was determined using RECIST results. The response categories were progressive disease: PD, stable disease: SD, partial response: PR, or complete response: CR. The initial evaluation took place around six weeks after commencing Atez/Bev treatment, utilizing dynamic CT scans. Additional dynamic CT scans were carried out when necessary, and in certain cases, even before the six-week mark, depending on the patient's condition. Subsequent dynamic CT scans were scheduled every six weeks following the initial assessment, with extended intervals of nine to twelve weeks after the first six months (10).

Scoring for assessment of prognosis of uHCC patients treated with Atez/Bev

CRAFITY score (6) (7) and the newly developed *IM* nunotherapy with*A* FP, *B* CLC staging, m*AL* B*I* and *D* CP*e* valuation (IMABALI-De) score, the details of which are presented following, were used to assess the prognosis of patients with Atez/Bev. Because DCP is not available for clinical use in many regions other than Japan, we also proposed IMABALI score without DCP as a sub-score for such region.

Statistical analysis

For statistical analyses, Cox-hazard analysis, Kaplan-Meier method, and log-rank test results were utilized. The log-rank test and Kaplan-Meier method were used to assess overall survival (OS) and PFS following the introduction of Atez/Bev. When median values were provided, the interquartile range (IQR) was also reported. Statistical significance was determined for P values less than 0.05. AIC and c-index results were used for comparisons between both prognostic predictive scores. A graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria), Easy-R (EZR), version 1.61 (Saitama Medical Center, Jichi Medical University, Saitama, Japan)(26),was used to perform all of the statistical analyses.

Results

Clinical features of present cohort

Table 1 displays the fundamental patient characteristics. Of all patients, the median age was 74 (IQR: 69-80) years old and 577 were male (80.3%). The etiology of HCC was HBV in 117 (16.3%), HCV in 239 (33.2%), HBV/HCV co-infection in 1 (0.1%), alcohol in 159 (22.1%), and non-HBV-non-HCV-non-alcohol in 203 (28.2%). The median ALBI score was -2.40 (mALBI grade1: 2a: 2b: 3 = 257: 178: 274: 10), while median AFP was 31 (IQR: 5.45-460.50) and median DCP was 280 (IQR: 43.5-2996.0). A Child-Pugh score of 5/ 6/ 7/ 8/ 9/ 10 was noted in 417 (58.0%)/ 224 (31.2%)/ 57 (7.9%)/ 16 (2.2%)/ 4 (0.6%)/ 1 (0.1%), respectively of the patients, a CRAFITY score of 0/ 1/ 2 was noted in 367 (51.0%)/ 274 (38.1%)/ 78 (10.8%), respectively, and BCLC stage 0/ A/ B/ C/ D was noted in 11 (1.5%)/ 44 (6.1%)/ 257 (35.7%)/ 390 (54.2%)/ 17 (2.4%), respectively. The duration of the median follow-up was 10.34 months (IQR: 5.38-16.17).

Factor detection and construction of IMABALI-De score

In univariate Cox-hazard analysis findings, CRP[?]1.0 mg/dL [1.884: 95% confidence interval (CI) 1.426-2.488, P<0.001] , AFP [?]100 ng/mL (HR 1.706: 95% CI 1.327-2.194, P<0.001), and DCP [?]100 mAU/mL (HR 2.109: 95% CI 1.573-2.828, P<0.001), as well as BCLC-C/D (HR 1.587: 95% CI 1.219-2.067, P<0.001),

and mALBI 2a (HR 1.726: 95% CI: 1.190-2.501, P=0.004) or 2b/3 (HR 3.233: 95% CI 2.351-4.447, P<0.001) were prognostic indicator for death. Furthermore, prognostic indicator for death in multivariate analysis were AFP ([?]100 ng/mL) (HR 1.392: 95% CI 1.072-1.808, P=0.013) and DCP ([?]100 mAU/mL) (HR 1.619: 95% CI 1.191-2.20, P=0.002), as well as BCLC C/D (HR 1.352: 95% CI 1.029-1.776, P=0.030), and mALBI 2a (HR 1.749: 95% CI: 1.206-2.536, P=0.003) or 2b/3 (HR 2.848: 95% CI 2.053-3.950, P<0.001) (Table 2). According to the results of multivariate Cox-hazard analysis, BCLC C/D, DCP [?]100 mAU/mL, AFP [?]100 ng/mL, and mALBI 2a were each assigned 1 point, while mALBI 2b/3 was given 2 points, with the sum of those point values used as IMABALI-De score. When same analysis was performed without DCP, results was not different (Supplemental table 1). Of the 719 enrolled patients, an IMABALI-De score of 0 was noted in 51, a score of 1 in 115, a score of 2 in 177, a score of 3 in 169, a score of 4 in 132, and a score of 5 in 75. The cut-off values for CRP ([?]1.0 mg/dL) (6), AFP [?]100 ng/mL (27) and DCP [?]100 mAU/mL (27) were set based on previous reports.

Therapeutic response to Atez/Bev treatment according to IMABALI-De score

Best therapeutic response was evaluated in 664 patients (IMABALI-De score 0:1:2:3:4:5 = 48:108:162:160:119:67). Objective response rate (ORR) was 28.3%, and disease control rate (DCR) was 78.6%, respectively. CR:PR:SD:PD for patients with an IMABALI-De score of 0 was 3:14:26:5 (ORR/DCR=35.4%/89.5%), with a score of 1 was 5:27:57:18 (ORR/DCR=29.9%/83.2%), with a score of 2 was 5:46:81:27 (ORR/DCR=32.1%/83.0%), with a score of 3 was 8:34:85:32 (ORR/DCR=26.4%/79.9%), with a score of 4 was 4:33:53:29 (ORR/DCR=31.1%/75.6%), and with a score of 5 was 0:9:32:26 (ORR/DCR=13.4%/61.2%). There was not significantly difference regarding therapeutic response among the patient groups divided by IMABALI-De score (p=0.054).

Overall survival according to CRAFITY score, mALBI grade, Child-Pugh score, and IMABALI-De score

Analysis using IMABALI-De score showed median OS (mOS) was not applicable (NA) (95% CI: NA-NA) for a score of 0, NA (95% CI:21.3-NA) for a score of 1, 26.11 months (95% CI: 17.64-NA) for a score 2, 18.79 months (95% CI: 15.57-NA) for a score 3, 14.07 months (95% CI: 11.57-18.25) for a score 4, and 8.32 months (95% CI: 6.79-12.86) for a score 5 (P<0.001) (Figure 2a). According to CRAFITY score, mOS was 26.11 months (95% CI: 20.14-NA) for a score of 0, 20.29 months (95% CI: 16.43-NA) for a score of 1, and 11.32 months (95% CI: 6.18-13.32) for a score of 2 (p<0.001) (Figure 2b). As for mALBI grade, mOS was NA (95% CI: 24.54-NA) for grade 1, 24.0 months (95% CI: 17.75-NA) for grade 2a, 13.43 months (95% CI: 11.82-15.32) for grade 2b, and 11.0 months (95% CI: 1.11-NA) for grade 3 (p<0.001) (Figure 2c), while for Child-Pugh score, mOS was 26.14 months (95% CI: 24.0-NA) for a score of 5, 16.18 months (95% CI: 13.97-20.07) for a score of 6, 9.36 months (95% CI: 6.54-16.68) for a score of 7, 6.64 months (95% CI: 3.07-NA) for a score of 8, 4.0 months (95% CI: 3.43-NA) for a score of 9, and 1.11 months for a score of 10 (p<0.001) (Figure 2d). AIC results for IMABALI-De score, CRAFITY score, mALBI grade, and Child-Pugh score were 2788.67, 2864.54, 2816.58, and 2829.04, respectively, while C-index results for those were 0.699, 0.606, 0.653, and 0.625, respectively. Regarding OS, IMABALI-De score had better AIC and c-index results as compared to CRAFITY score, mALBI grade, and Child-Pugh score.

The mOS according to IMABALI score was NA (95% CI: NA-NA) for a score 0, NA (95% CI: 21.32-NA) for a score 1, 20.39 months (95% CI: 17.32-26.14) for a score 2, 14.61 months (95% CI: 12.5-20.43) for a score 3, and 9.46 months (95% CI: 7.25-13.21) for a score 4 (P<0.001) (AIC 2799.02, c-index 0.688) (Supplemental figure 1).

Progression-free survival according to CRAFITY score, mALBI grade, Child-Pugh score, and IMABALI-De score

According to IMABALI-De score, median PFS (mPFS) was 21.75 months (95% CI: 10.21-NA) for a score of 0, 12.89 months (95% CI: 10.61-17.57) for a score 1, 9.18 months (95% CI: 6.68-11.79) for a score 2, 8.0 months (95% CI: 6.54-11.0) for a score 3, 5.0 months (95% CI: 3.46-7.0) for a score 4, and 3.75 months (95% CI: 3.14-4.36) for a score 5 (P<0.001) (Figure 3a). CRAFITY score showed mPFS of 10.32 months (95% CI: 8.11-12.25) for a score of 0, 7.68 months (95% CI: 6.25-8.96) for a score of 1, and 3.57 months (95%

CI: 3.0-4.71) for a score of 2 (p<0.001) (Figure 3b). As for mALBI grade, mPFS was 11.96 months (95% CI: 8.64-15.21) for grade 1, 9.50 months (95% CI: 6.96-11.64) for grade 2a, 6.04 months (95% CI: 5.0-7.0) for grade 2b, and 3.43 months (95% CI: 0.39-NA) for grade 3 (p<0.001) (Figure 3c). Finally, mPFS was 10.32 months (95% CI: 8.0-11.89) for a Child-Pugh score of 5, 6.68 months (95% CI: 5.25-7.75) for a score of 6, 5.79 months (95% CI: 3.96-7.04) for a score of 7, 4.18 months (95% CI: 1.54-NA) for a score of 8, 3.43 months (95% CI: 3.0-NA) for a score of 9, and 0.39 months for a score of 10 (p<0.001) (Figure 3d). AIC values for IMABALI-De score, CRAFITY score, mALBI grade, and Child-Pugh score were 5203.32, 5246.24, 5245.61, and 5260.62, respectively, while C-index values were 0.623, 0.574, 0.573, 0.559, respectively. IMABALI-De score showed better AIC and C-index results as compared to CRAFITY score, mALBI grade, and Child-Pugh score, as well as for PFS.

The mPFS according to IMABALI score was 16.25 months (95% CI: 11.96-NA) for a score of 0, 9.57 months (95% CI: 7.0-12.79) for a score of 1, 8.75 months (95% CI: 7.25-12.50) for a score of 2, 6.54 months (95% CI: 4.61-7.75) for a score of 3, and 3.75 months (95% CI: 3.14-4.46) for a score of 4 (P<0.001) (AIC 5217.7, c-index 0.608) (Supplemental Figure 2).

Discussion

In the present cohort, IMABALI-De score showed a favorable stratification of prognosis of patients with Atez/Bev. The items of the IMABALI-De scoring system for Atez/Bev treatment for uHCC include tumor burden (BCLC) and malignant potential (AFP, DCP), the same as CRAFITY score, while hepatic reserve function (mALBI 1, 2a, 2b/3) is also used. This point is considered to be the main reason for the superiority of IMABALI-De as compared to CRAFITY score found in this study.

A recent report noted that overall response rate and PFS (weighted Pearson correlation coefficient = 0.71, 95% Cl=0.52-0.84 and 0.62; 95% Cl=0.35-0.84, respectively) demonstrated a good correlation with OS (28). However, post-progression treatments have also been reported to be significant prognostic factors in regard to immunotherapy for HCC (29). Rates presented for post-progression treatment after Atez/Bev failure are comparatively favorable, ranging from 74.2% to 88.2% (30) (31) (32). At the time of writing, post-progression treatment is considered to be primarily dependent on available multi-targeting agents (MTAs); sorafenib, lenvatinib, regorafenib, ramucirumab, and cabozantinib, thus consideration regarding how to prolong prognosis with sequential post-progression treatments is important. Terashima previously noted that post-progression survival (PPS) had a strong relationship with OS in patients who received sorafenib treatment for HCC (r=0.834, P<0.001), and found that the PPS rate for those classified as Child-Pugh A was better as compared to those as Child-Pugh B (54.8±17.4 vs. 32.0±11.6, P=0.015)(33). Needless to say, better hepatic function at the time of introducing an MTA is a required factor for obtaining improved prognosis following Atez/Bev failure.

Systemic therapy for uHCC is mainly performed for Child-Pugh A patients. In the past 30 years, a relative change in hepatic reserve function in patients with chronic liver disease has led to an increased rate of Child-Pugh A from 52.1% to 84.8% (34), thus an assessment tool with greater detail has recently been considered necessary for clinical practice. Philip et al. developed a new tool termed ALBI grade, the only established tool based on a statistical process, and its clinical efficacy has been reported (16, 17), while the prognostic importance of ALBI grade has been elucidated for patients HCC undergoing immunotherapy (29). However, the ALBI grade 2 covers a wide range of patients, which is thought to be a clinical issue. We established a modified tool for assessment of hepatic function termed mALBI, in which the middle grade is divided into two sub-grades(2a, 2b), based on a cut-off value of indocyanine green retention rate at 15 minutes (ICG-R15) of 30% (9). Several reports have noted that mALBI grade plays a great role to predict the prognosis of patients with HCC who underwent treatment with MTA (35) (36) (37) (38) (39). In the same way, hepatic function is thought to be an important requirement for detailed assessment of prognosis of HCC patients with Atez/Bev. Therefore, this score is more focused on hepatic function, not to mention tumor burden and the malignant potential of HCC. In addition to the CRAFITY score, which focuses more on the malignant potential of HCC, we compared IMABALI-De score with mALBI grade and Child-Pugh score, which are indicators of hepatic function, and confirmed the usefulness of the IMABALI-De score. Our research group

has also reported the usefulness of nutritional indices such as NLR (40), prognostic nutritional index (PNI) (41), and neo-GPS (42) as prognostic predictors of Atez/Bev. Because the present study focused on hepatic function and tumor status, prognostic scores predicted by nutritional indicators were not included in the comparison. A study will be conducted to determine which of these various scores and the current score is most useful in predicting Atez/Bev prognosis after a sufficient observation period. In addition, specific subsets such as exhausted CD8+ T cells and regulatory T cells are preferentially enriched and potentially clonally expanded in HCC, unlike peripheral blood (43). Accordingly, peripheral blood fraction count alone is not necessarily a sufficient nutritional immune-biomarker, there is a need to establish a simple prognostic index combined with tumor burden, tumor malignant potential and hepatic function in the future.

Based on the clinical importance of hepatic reserve function, the present proposed scoring system is thought to be reasonable. However, therapeutic response was not significantly different among the IMABALI-De scores, except for a score of 5. On the other hand, PFS grading with IMABALI-De score showed a good separation, other than between the score of 2 and 3. Although these results suggest that Atez/bev can serve as an effective treatment regimen for uHCC, the response duration became shorter as IMABALI-De score increased. During the clinical course of HCC, assessment with the present scoring system should be considered so as to not to lose the opportunity of introduction of Atez/Bev for improving prognosis within a short time after BCLC-B status or greater is noted. While systemic therapy is the only treatment for BCLC-C HCC, TACE is one of major option for BCLC-B HCC, as well as systemic therapies. Atez/Bev has been reported to provide clinical benefit to TACE unsuitable patients with BCLC-B HCC beyond the up to 7 criteria (44). Therefore, clinicians should consider switching to Atez/Bev, especially when the IMABALI-De score is as low as possible, to obtain more therapeutic benefit with Atez/Bev. Namely, the present IMABALI-De score might be a useful indicator to switch treatment in BCLC-B HCC patients initiating TACE before the poor prognostic benefit of treatment with Atez/Bev is predicted.

The present study has some limitations. Firstly, while the results were obtained from multiple institutions, they were retrospectively analyzed. Second, because there were some patients with missing data including number of neutrophil and lymphocyte cells, comparisons among previous reported prognostic indicators were not performed in this study. Further prospective studies using long-term follow-up findings are needed to confirm the usefulness of the present IMABALI-De score and to compare it with other prognostic indicators. In near future, it is desirable to continue to search common clinical factors specific to this combined immunotherapy.

In conclusion, the proposed IMABALI-De score, which consists only of common clinical items including mALBI grade, is considered to have a good prognostic predictive ability for uHCC patients treated with Atez/Bev. With considerations based individual case factors, introduction of Atez/Bev at the lowest possible IMABALI-De score is recommended to improve prognosis.

Statements

[Declarations and Ethical Statements]

The entire research protocol received approval from Ehime Prefectural Central Hospital Institutional ethics committee: No. 2022-46. After receiving official authorization, this study proceeded as a retrospective study of database records, following the Ministry of Health and Welfare of Japan's Clinical Research Guidelines and adhering to the principles of the Helsinki Declaration. To protect patient confidentiality, all data were anonymized before analysis. Before treatment, written IC was obtained from all patients. Ethical approval was granted for employing an opt-out approach due to the minimal risk to participants.

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[Conflicts of interest]

Atsushi Hiraoka, MD, PhD; for lecture fees from Chugai, AstraZeneca, and Eli Lilly. Takashi Kumada, MD,

PhD; for lecture fees from Eisai.

Toshifumi Tada, MD, PhD; for lecture fees from Abbvie, Eisai.

Takeshi Hatanaka MD, PhD; for lecture fees from Eisai.

The rest of the authors do not possess any potential conflicts of interest to disclose.

[Authors' contributions]

Conceived the study, participated in its design and coordination was performed by Hironori Ochi, Atsushi Hiraoka, Takashi Kumada. Data curation was performed by Atsushi Hiraoka/ Hideko Ohama/ Masashi Hirooka/ Toshifumi Tada/ Hidenori Toyoda / Kazuya Kariyama/ Takeshi Hatanaka/ Masanori Atsukawa/ Joji Tani/ Koichi Takaguchi/ Takashi Nishimura/ Kazuto Tajiri/ Kunihiko Tsuji/ Hidekatsu Kuroda / Ei Itobayashi/ Toru Ishikawa/ Satoshi Yasuda/ Chikara Ogawa/ Tomomitsu Matono / Fujimasa Tada/ Shinya Fukunishi/ Satoru Kakizaki/ Atsushi Naganuma/ Noritomo Shimada/ Kazuhito Kawata/ Kazuhiro Nouso/ Hisashi Kosaka/ Yutaka Yata/ Asahiro Morishita/ Takuya Nagano/ Keisuke Yokohama/ Akemi Tsutsui/ Norio Itokawa/ Taeang Arai/ Tomomi Okubo/ Yohei Koizumi/ Hiroko Iijima/ Hiroki Nishikawa/ Michitaka Imai/ Shinichiro Nakamura/ Masaki Kaibori/ Yoichi Hiasa. Atsushi Hiraoka conducted statistical analyses and interpretation. The manuscript text was drafted by Hideko Ohama and Atsushi Hiraoka. All authors have reviewed and endorsed the manuscript's final version.

[Data availability]

Given the nature of this study, it was not feasible to contact the participants to seek their permission for public sharing of the findings. Consequently, the supporting data, such as datasets generated or analyzed for this study, are not accessible to the public.

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Figure legends

Figure 1. Approach employed for the management of hepatocellular carcinoma (HCC) using atezolizumab in combination with bevacizumab (Atez/Bev).

TACE; Transarterial chemoembolization, ECOG PS; Eastern Cooperative Oncology Group performance status, BSC: best supportive care

Figure 2. Overall survival of patients with hepatocellular carcinoma with atezolizumab plus bevacizumab according to score.

1. Median overall survival (OS) was not applicable (NA) (95% CI: NA-NA)/NA (95% CI:21.3-NA)/26.11 (95% CI: 17.64-NA)/18.79 (95% CI: 15.57-NA)/14.07 (95% CI: 11.57-18.25)/8.32 (95% CI: 6.79-12.86) months for IMABALI-De score 0/1/2/3/4/5 ($p<0.001$).
2. Median OS was 26.11 (95% CI: 20.14-NA)/20.29 (95% CI: 16.43-NA)/11.32 (95% CI: 6.18-13.32) months for CRAFITY score 0/1/2 ($p<0.001$).
3. Median OS was NA (95% CI: 24.54-NA)/24.0 (95% CI: 17.75-NA)/13.43 (95% CI: 11.82-15.32)/11.0 (95% CI: 1.11-NA) months for modified albumin-bilirubin (mALBI) grade 1/2a/2b/3 ($p<0.001$).
4. Median OS was 26.14 (95% CI: 24.0-NA)/16.18 (95% CI: 13.97-20.07)/9.36 (95% CI: 6.54-16.68)/6.64 (95% CI: 3.07-NA)/4.0 (95% CI: 3.43-NA)/1.11 months for Child-Pugh score 5/6/7/8/9/10 ($p<0.001$).

Figure 3. Progression-free survival of patients with hepatocellular carcinoma with atezolizumab plus bevacizumab according to IMABALI-De score.

1. Median progression-free survival (PFS) was 21.75 (95% CI: 10.21-NA)/12.89 (95% CI: 10.61-17.57)/9.18 (95% CI: 6.68-11.79)/8.0 (95% CI: 6.54-11.0)/5.0 months (95% CI: 3.46-7.0)/3.75 (95% CI: 3.14-4.36) months for IMABALI-De score 0/1/2/3/4/5 ($p<0.001$).
2. Median PFS was 10.32 (95% CI: 8.11-12.25)/7.68 (95% CI: 6.25-8.96)/3.57 (95% CI: 3.0-4.71) months for CRAFITY score 0/1/2 ($p<0.001$).
3. Median PFS was 11.96 (95% CI: 8.64-15.21)/9.50 (95% CI: 6.96-11.64)/6.04 (95% CI: 5.0-7.0)/3.43 (95% CI: 0.39-NA) months for modified albumin-bilirubin (mALBI) grade 1/2a/2b/3 ($p<0.001$).
4. Median PFS was 10.32 (95% CI: 8.0-11.89)/6.68 (95% CI: 5.25-7.75)/5.79 (95% CI: 3.96-7.04)/4.18 (95% CI: 1.54-NA)/3.43 months for Child-Pugh score 5/6/7/8/9/10 ($p<0.001$).

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