Prognostic impact of C-reactive protein and alpha-fetoprotein in immunotherapy score in hepatocellular carcinoma patients treated with atezolizumab plus bevacizumab: A multicenter retrospective study

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Research Article

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Abstract

Aim: This study aimed to investigate the utility of C-reactive protein (CRP) and alpha-fetoprotein (AFP) in immunotherapy (CRAFITY) score in hepatocellular carcinoma (HCC) patients receiving atezolizumab and bevacizumab (Atez/Bev).

Methods: This retrospective cohort study included a total of 297 patients receiving Atez/Bev from September 2020 to November 2021 at 17 different institutions and hospital groups in Japan. Patients with AFP≥100 ng/mL and those with CRP≥1 mg/dL were assigned a CRAFITY score of 1 point.

Results: The patients were assigned CRAFITY scores of 0 points (n=147 [49.5%]), 1 point (n=111 [37.4%]), and 2 points (n=39 [13.1%]). AFP≥100 ng/mL and CRP≥1.0 mg/dL were significantly associated with progression-free survival (PFS) and overall survival (OS). The median PFS in the CRAFITY score 0, 1, and 2 groups was 11.8 months (95% confidence interval [CI] 6.4-not applicable [NA]), 6.5 months (95% CI 4.6-8.0), and 3.2 months (95% CI 1.9-5.0), respectively (p<0.001). The median OS in patients with CRAFITY score 0, 1 and 2 was not reached, 14.3 months (95% CI 10.5-NA), and 11.6 months (95% CI 4.9-NA), respectively. The percentage of patients with grade ≥3 liver injury, any grade of decreased appetite, any grade of proteinuria, any grade of fever, and any grade of fatigue was lowest in patients with a CRAFITY score of 0, followed by patients with CRAFITY scores of 1 and 2.

Conclusions: The CRAFITY score is simple and could be useful for predicting therapeutic outcomes and treatment-related adverse events.

Introduction

According to the Imbrave150 trial [1], combination therapy with atezolizumab plus bevacizumab (Atez/Bev), an anti-programmed death ligand 1 (PD-L1) inhibitor and monoclonal antibody targeting vascular endothelial growth factor (VEGF), demonstrated an advantage over the sorafenib in terms of the overall survival (OS) and progression-free survival (PFS). Based on the positive results, Atez/Bev have become the standard of care in first-line treatment in patients with advanced HCC under the recent guidelines [2-4]. However, the objective response rate (ORR) of immune monotherapy for HCC ranged from 17% to 20% [5-8] and only one-third of patients who received Atez/Bev treatment showed an objective response [1]. Numerous biomarkers, including the PD-L1 expression [9], and activated Wnt/β-catenin signaling [10, 11], that may be used to assist in decision-making and guide treatment have been studied; however, the established biomarkers have not been fully validated [12]. A recent study [13] reported the utility of C-reactive protein (CRP) and alpha-fetoprotein (AFP) in immunotherapy (CRAFITY) score in patients treated with immunotherapy. However, more than one-half of patients included in this study were treated with immune monotherapy, and data about the efficacy and safety of Atez/Bev is limited. Accordingly, the aim of the current study is to investigate the utility of the CRAFITY score in HCC patients receiving Atez/Bev.

Methods

Patients

A total of 325 patients with HCC received Atez/Bev from September 2020 to November 2021 at 17 different institutions and hospital groups in Japan. The inclusion criteria of this retrospective study were as follows: (a) HCC diagnosed based on typical enhancement on radiological imaging, including computed tomography and magnetic resonance imaging, or histologically proven in a biopsy specimen or a resected specimen obtained during the clinical course; (b) patients were treated with Atez/Bev; (c) The serum levels of AFP and CRP were measured at baseline. Among these 325 patients, baseline AFP data were missing for 28 patients. Therefore, the remaining 297 patients were included in the present study (Figure 1).

After receiving official approval, this study was conducted as a retrospective analysis of database records based on the Guidelines for Clinical Research issued by the Ministry of Health and Welfare of Japan. The study protocol was granted approval by the Institutional Ethics Committee of Ehime Prefectural Central Hospital (IRB No. 30-66) (UMIN000043219). All procedures were performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients.

Atez/Bev treatment and the evaluation of AEs

After obtaining written informed consent from each patient, all patients received intravenous Atez/Bev every 3 weeks. The Atez/Bev treatment is composed of atezolizumab (1200 mg) and bevacizumab (15 mg/kg body weight). The treatment was discontinued until the development of unacceptable or serious AEs or clinical tumor progression was observed. We used the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 to evaluate the AEs. We carried out dose interruption or discontinuation of each drug based on the guidelines for Atez/Bev treatment provided by the manufacturer.

Evaluation of the tumor stage, liver function, and efficacy of Atez/Bev

The tumor stage was determined by the Barcelona Clinic Liver Cancer (BCLC) staging system [4]. The liver function was evaluated by Child-Pugh classification and albumin-bilirubin (ALBI) score [14] and modified albumin-bilirubin (mALBI) grade [15]. The radiological response was assessed by the Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST ver.1.1). The ORR was defined as the percentage of the sum of patients with a complete response (CR) or partial response (PR), and the disease control rate (DCR) was defined as the percentage of the sum of patients with CR, PR, and stable disease (SD). Progression-free survival was defined as the time from the day of starting Atez/Bev to the observation of clinical disease progression or death and OS was defined as the time from the day of starting Atez/Bev to death or the last visit.

CRAFITY score

The CRAFITY score was determined by the values of AFP and CRP. According to a previous study [13], patients with AFP ≥100 ng/mL at baseline and those with CRP≥1 mg/dL were assigned 1 point. For example, a patient with AFP <100 ng/mL and CRP <1 mg/dL was assigned to CRAFITY 0 points. A patient who had either AFP ≥100 ng/mL or CRP ≥1 mg/dL was assigned a CRAFITY score of 1 point, and a patient who had both AFP ≥100 ng/mL or CRP ≥1 mg/dL was assigned a CRAFITY score of 2 points.

Statistical analyses

All Statistical analyses were conducted using EZR Ver. 1.54 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) [16]. Continuous data are presented as the median (interquartile range) and categorical data are presented as the number (percentage). The χ^2-test, Fisher's exact, and Mann–Whitney U test were used as appropriate. Cox proportional hazards regression models were used to evaluate the hazard ratio (HR). The number of explanatory variables involved in each model depends on the number of events. We included chronic liver disease, BCLC stage, AFP, CRP, treatment settings, age, and sex as explanatory variables in the analysis of factors associated with PFS. In the analysis of factors associated with OS, we used chronic liver disease, BCLC stage, AFP, CRP, and treatment settings as explanatory variables. Viral infection was defined as hepatitis B virus (HBV) or hepatitis C virus (HCV) infection. Age was dichotomized based on the median value. Because the value of CRP was strongly correlated with the ALBI score (r=0.44, p<0.001; Supplemental Figure 1), we did not adopt the ALBI score as an explanatory variable to avoid multicollinearity. The results obtained with a cutoff value of ALBI score for CRP≥1 mg/dL are shown in Supplemental Figure 2.

Results

Table 1 shows an overview of patient characteristics. The median age of all patients was 73.0 (68.0-78.0) years and 243 patients (81.8%) were men. The PS was 0, 1, and 2 in 238 (80.1%), 49 (16.5%), and 10 patients (3.4%), respectively. The etiology of chronic liver diseases was HCV, HBV, alcohol, and others in 97 (32.7%), 49 (16.5%), 57 (19.2%), and 94 (31.6%) patients, respectively. The Child-Pugh score was 5, 6, and ≥7 in 183 (61.6%), 96 (32.3%), and 18 patients (6.1%), respectively. The median ALBI score was calculated to be -2.43 (-2.70 to -2.13) and the mALBI grades were 1, 2a, 2b, and 3 in 115 (38.7%), 76 (25.6%), 104 (35.0%), and 2 patients (0.7%), respectively. One hundred sixty-nine (56.9%) and 128 patients (43.1%) received Atez/Bev as a front line and later line treatment, respectively. The BCLC stage was classified as early, intermediate, advanced, and terminal in 17 (5.7%), 121 (40.7%), 155 (52.2%), and 4 patients (1.3%), respectively. There were 122 patients (41.1%) with a serum AFP ≥100 ng/mL and 67 patients (22.6%) with serum CRP ≥1.0 mg/dL. Accordingly, the patients were assigned CRAFITY scores of 0 (n=147 [49.5%]), 1 (n=111 [37.4%]), and 2 points (n=39 [13.1%]). The patients with a CRAFITY score

of 0 points showed significantly better PS, better preservation of the liver function, a higher percentage of first-line treatment, and an earlier HCC stage in comparison to those with CRAFITY scores of 1 or 2 points.

The numbers of patients with a confirmed radiological response, as assessed by RECIST ver.1.1, are shown in Table 2. Among the patients with CRAFITY scores of 0, 1, and 2 points, 119, 101, and 37 patients, respectively, showed a confirmed radiological response. The radiological response rate (p=0.20) and ORR (p=0.80) were not significantly different, while a significant difference in the DCR was observed among the three groups (p=0.029).

The Kaplan-Meier curves showed that the median PFS was 6.8 months (95% CI 6.0-8.0), with 144 events (48.8%) detected at the time of the analysis (Figure 2a). While the median OS was not reached, the 6-month, and 12-month OS rates were 89.9% (95% CI 85.3-93.1) and 66.1% (95% CI 55.6-74.6%), respectively, with 52 events (17.5%) found at the time of the analysis (Figure 2b). The results obtained from the multivariate analysis are presented in Table 3. The following factors showed a significant association with PFS: AFP≥100 ng/mL (HR 1.97, 95% CI 1.40-2.77, p<0.001) and CRP≥1.0 mg/dL (HR 1.51, 95% CI 1.05-2.19, p=0.028). A statistical analysis of factors related to OS also revealed that AFP≥100 ng/mL (HR 2.74, 95% CI 1.52-4.92, p<0.001) and CRP≥1.0 mg/dL (HR 1.87, 95% CI 1.06-3.31, p=0.032) were predictors of OS. A multivariate analysis was performed using the CRAFITY score as an explanatory variable, and the HRs and 95% CIs of each CRAFITY score are described in Supplemental Table 1.

The PFS and OS for each CRAFITY score are shown in Figure 3. In the CRAFITY 0, 1, and 2 points groups, the median PFS was 11.8 months (95% CI 6.4-not applicable [NA]), 6.5 months (95% CI 4.6-8.0), and 3.2 months (95% CI 1.9-5.0), respectively, (p<0.001). The results of the analysis of PFS in patients with BCLC early and intermediate stage according to the CRAFITY score are shown in Supplemental Figure 2a and those of patients with BCLC advanced and terminal stage are shown in Supplemental Figure 2b. The median OS in patients with CRAFITY score 0 points was not reached while it was 14.3 months (95% CI 10.5-NA) and 11.6 months (95% CI 4.9-NA) in patients with CRAFITY scores of 1 point and 2 points, respectively. There was a significant difference among the three groups (p<0.001). The 6-month and 12-month OS rates were 94.7% (95% CI 88.4-97.6) and 81.1% (95% CI 66.1-89.9%), respectively, in patients with CRAFITY score 0, 92.9% (95% CI 85.6-96.6%) and 63.5% (48.3-75.3%) in patients with CRAFITY score 1, and 63.6% (95% CI 44.5-77.7%) and 33.2% (95% CI 10.5-58.3%) in patients with CRAFITY score 2. The survival curves for patients with BCLC early and intermediate stage, stratified by the CRAFITY score, are shown in Supplemental Figure 3a, while those with BCLC advanced and terminal stage are also shown in Supplemental Figure 3b.

A summary of AEs according to the CRAFITY score is shown in Table 4. The most common AEs in all patients was fatigue (n=75, 25.3%), followed by proteinuria (n=71, 23.9%), decreased appetite (n=70, 23.6%), hypertension (n=58, 19.5%), and liver injury (n=40, 13.5%). Significant differences were observed in grade ≥3 liver injury (p=0.036), any grade of decreased appetite (p=0.002), any grade of proteinuria

(p=0.039), any grade of fever (p=0.011), and any grade of fatigue (p=0.032). The rates of these AEs were lowest in patients with a CRAFITY score of 0, followed by patients with CRAFITY scores of 1 and 2.

Discussion

The major finding of the present study is that AFP ≥100 ng/mL and CRP ≥1.0 mg/dL were found to be predictive factors associated with PFS and OS in patients treated with Atez/Bev. The CRAFITY score, which is composed of AFP and CRP, could stratify the OS of patients treated with Atz/Bev. Because the previous report [13] did not investigate the correlation of the CRAFITY score with PFS and AEs, we revealed that the CRAFITY score could also predict PFS and treatment-related AEs. Accordingly, the CRAFITY score was simple and useful for predicting therapeutic outcomes and treatment-related AEs. To our knowledge, this is the first report assessing the utility of the CRAFITY score in HCC patients treated with Atez/Bev.

AFP is a well-known, novel tumor biomarker, that is widely used in the clinical setting. An elevated serum level of AFP was associated with a poor prognosis across all stages of HCC [12]. Some studies revealed that AFP was a prognostic factor in patients treated with surgical resection [17], liver transplantation [18], radiofrequency ablation [19, 20], and transarterial chemoembolization [21]. In addition, AFP was also associated with a high rate of recurrence after liver transplantation [22]. Due to the prognostic significance of AFP in advanced HCC patients, the pretreatment AFP concentration has been adopted as a stratification factor in recent phase 3 trials [1, 23, 24]. With regard to the molecular HCC classes, Hoshida's HCC subclasses (S1-S3) are associated with various parameters, such as tumor size, tumor differentiation, and AFP [25]. Among these subclasses, the S2 subclass is associated with high serum AFP [25]. Moreover, the expression of AFP and EpCAM (a hepatic stem cell expression marker) were used to characterize the progenitor cell group (S2 subclass) [26]. Recently, AFP was also shown to be associated with the activation of the tumor VEGF pathway [27, 28]. VEGF reduces the therapeutic effect of immune checkpoint inhibitors (ICIs) via some mechanisms, including inhibition of the maturation of dendritic cells [29, 30], stimulation of lymphocyte rolling [31, 32], intra-tumoral T-cell infiltration [33], and expansion of immunosuppressive myeloid-derived suppressor cells (MDSCs) [34, 35]. Given these previous studies, patients with high AFP levels (≥100 ng/dL) showed a poor prognosis and shorter PFS in comparison to those with low AFP levels in the present study.

Inflammation is considered a hallmark of cancer progression and a key component of the tumor microenvironment [36, 37]. C-reactive protein is an acute protein and is mainly regulated by interleukin-6 [38]. To date, many studies reported that CRP is a novel prognostic marker in HCC patients [39-41]. Regarding ICI treatment, an elevated CRP level has been reported as an unfavorable factor in some types of cancers, including non-small cell lung cancer [42, 43] and melanoma [43, 44]; however, few reports have investigated the relationship between the single determination of CRP and ICI efficacy in HCC patients. An association between CRP and immunosuppression was recently reported. CRP binds to T-cells and has a profound suppressive effect on immunity in patients [45, 46]. CRP also regulates the

development and suppressive actions of MDSC [47]. These previous reports support the present findings that CRP is a predictive factor for PFS and OS.

With regard to AEs, the clear mechanism underlying the association between AEs and the CRAFITY score remains unknown. One possible reason is that cancer-related symptoms, such as appetite loss, weight loss, and fatigue, are associated with not only the tumor burden or aggressive types of tumors, but also the presence of inflammation [48]. Obviously, elevated AFP was frequently observed in patients with advanced or aggressive HCC, and elevated CRP reflects the presence of inflammation. Indeed, elevated CRP is associated with AEs in melanoma patients treated with ICI [49]. Accordingly, the CRAFITY score, which is composed of AFP and CRP, could predict AEs in patients receiving Atez/Bev.

Regarding the analysis of the radiological response, although statistical significance was not observed in the analysis of the ORR, it was observed in the analysis of the DCR. A previous study [13] by Scheiner et al. showed that CRAFITY score predicted the ORR and DCR. This difference may be associated with the short observation period of the present study. A further study with long-term observation is needed to confirm the correlation between the CRAFITY score and the ORR and DCR of patients treated with Atez/Bev.

The present study was associated with some limitations. This study was conducted in a retrospective manner. Although the present study included a larger number of patients in comparison to previous studies [13], the observation period of the present study was short. Further prospective studies with long-term follow-up are warranted.

In conclusion, the CRAFITY score is simple to determine and could be useful for predicting therapeutic outcomes and treatment-related AEs.

Declarations

Author contributions

TH, SK, AH, TTad, AN, and TK conceived the study, and participated in its design and coordination. TH, SK, AH, TTad, MH, KKar, JT, MA, KTak, EI, SF, KTs, TI, KTaj, HOc, SY, HT, CO, TNi, NS, KKaw, TTan, HOh, KN, AM, AT, TNa, NI, TO, TA, MI, AN, YK, SN, KJ, HI, and YH performed data curation. TH performed statistical analyses and interpretation. TH, SK, AH, TTad, AN, TK, HK, and MK drafted the text. All authors have read and approved the final version of the manuscript.

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Compliance with ethical standards

Conflict of interest

Takeshi Hatanaka received lecture fees from Eisai. Atsushi Hiraoka received lecture fees from Bayer, Eisai, Eli Lilly, Otsuka, and Chugai. Takashi Kumada received lecture fees from Eisai.

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Tables

Tables 1-4 are available in the Supplemental Files section.

Figures

Figure 1

Flow chart of the selection of HCC patients treated with Atez/Bev. Atez/Bev, atezolizumab plus bevacizumab; CRP, C-reactive protein; HCC, hepatocellular carcinoma.

Figure 2

Kaplan-Meier curves for progression-free survival (a) and overall survival (b) in all patients.

Figure 3

Kaplan-Meier curves for progression-free survival (a) and overall survival (b) according to the CRAFITY score.

CRAFITY score, C-reactive protein and alpha-fetoprotein in immunotherapy.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- AtezBevCRAFITYSupplementalTable2021Dec28.xlsx
- SuppFig1.png
- SuppFig2.png
- SuppFig3.png
- AtezBevCRAFITYTable2021Dec28.xlsx