Research Article

Role of the prognostic nutritional index in predicting survival in advanced hepatocellular carcinoma treated with atezolizumab plus bevacizumab

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Short Title: PNI in patients with HCC

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Abstract

Introduction: The prognostic nutritional index (PNI) is a multiparametric score introduced by Onodera based on the blood levels of lymphocytes and albumin in patients with gastrointestinal neoplasms. Regarding hepatocellular carcinoma (HCC), its prognostic role has been shown in patients treated with sorafenib and lenvatinib. The aim of this real-world study is to investigate the association between clinical outcomes and PNI in patients being treated with atezolizumab plus bevacizumab.

Methods: The overall cohort of this multicentric study included 871 consecutive HCC patients from 4 countries treated with atezolizumab plus bevacizumab in first-line therapy. The PNI was calculated as follows: 10 × serum albumin concentration (g/dL) + 0.005 × peripheral lymphocyte count (number/mm^3).

Results: Data regarding lymphocyte counts and albumin levels were available for 773 patients, therefore these patients were included in the final analysis. The cut-off point of the PNI was determined to be 41 by receiver operating characteristic (ROC) analysis. 268 patients (34.7%) were categorized as the PNI-low group, while the remaining 505 (65.3%) patients as the PNI-high group. At the univariate analysis, high PNI was associated with longer overall survival (OS) (22.5 vs. 10.1 months, HR 0.34, $p < 0.01$) and progression-free survival (PFS) (8.7 vs. 5.8 months, HR 0.63, $p < 0.01$) compared to patients with low PNI. At the multivariate analysis, high versus low PNI resulted as an independent prognostic factor for OS (HR 0.49, $p < 0.01$) and PFS (HR 0.82, $p = 0.01$). There was no difference in objective response rate (ORR) between the two groups (high 26.1% vs. low 19.8%, $p = 0.09$), while disease control rate (DCR) was significantly higher in the PNI-high group (76.8% vs. 66.4%, $p = 0.01$).

Conclusion: PNI is an independent prognostic factor for OS and PFS in HCC patients on first-line treatment with atezolizumab plus bevacizumab.

Introduction

Hepatocellular carcinoma (HCC) remains the third leading cause of cancer death worldwide [1]. However, the therapeutic armamentarium available has expanded in recent years with the approval of new systemic treatments. Sorafenib was the only available first-line therapy for 10 years based on the results of the two trials, SHARP and Asia Pacific. In these two studies, overall survival (OS) was between 6.5 and 10.7 months, significantly longer than that obtained with placebo [2, 3]. Lenvatinib was the second drug approved in 2017 for the first-line treatment of HCC. The open-label, multicenter, phase III REFLECT trial showed non-inferiority of lenvatinib in OS (13.6 months) compared to sorafenib (12.3 months; hazard ratio (HR) 0.92; 95% confidence interval (CI) 0.79-1.06) [4]. The combination of the anti-programmed cell death ligand-1 (PD-L1) atezolizumab plus the anti-vascular-endothelial growth factor (VEGF) bevacizumab represents the first therapeutic doublet approved for the treatment of HCC in the first-line setting. Indeed, the IMbrave 150 trial showed that this combination can obtain an advantage in OS (19.2 vs 13.4 months; $p < 0.001$) and progression-free survival (PFS) (6.9 vs 4.3 months; $p < 0.001$) compared to sorafenib [5]. Considering the results obtained in phase III trials, atezolizumab plus bevacizumab and lenvatinib are today the most chosen therapies by clinicians in the first-line setting.

With the expansion in available therapies, prognostic factors play an increasingly important role, among which the most relevant in patients with HCC are those indicative of liver function, such as Child-Pugh class and Albumin-Bilirubin (ALBI) grade [6-10]. Recently, there are several evidences in the literature about the fundamental role of both the state of chronic inflammation and the nutritional state in the prognosis of HCC patients [11-18].

The prognostic nutritional index (PNI) is a multiparametric score introduced by Onodera based on the blood levels of lymphocytes and albumin in patients with gastrointestinal neoplasms [19-21]. It initially included 4 parameters (albumin, triceps skinfold, transferrin, and skin test reactivity) and for this reason it was not easy to apply in clinical practice. Subsequently, Onodera simplified it as we use it today, making it an easily accessible tool for the clinician on a daily basis. The prognostic value of PNI is known in patients receiving immunotherapy for various malignancies, such as non-small-cell lung cancers, head and neck cancers, biliary tract cancers, and others [20-25]. Regarding HCC, its prognostic role has been shown in patients treated with sorafenib and lenvatinib, which are currently the other two treatment options available for first-line therapy [12, 14, 17, 18]. The correlation between PNI and survival outcomes has also been shown in second-line settings, such as in patients receiving regorafenib, and in earlier disease settings, such as in patients undergoing local treatments, including hepatectomy and transarterial chemoembolization (TACE) [13, 11, 15]. There is still no data available in the literature regarding its role in patients treated with atezolizumab plus bevacizumab. The aim of this real-world study is to investigate the

association between clinical outcomes and PNI in patients treated with atezolizumab plus bevacizumab.

Materials and Methods

Patients

The overall cohort of this multicentric study included 871 consecutive HCC patients from 4 countries (Italy, Germany, Japan, and the Republic of Korea) treated with atezolizumab plus bevacizumab between October 2018 and April 2022. Eligible patients had HCC diagnosis histologically confirmed or clinically confirmed according to international guidelines, and no previous systemic therapy. Data regarding lymphocyte counts and albumin levels were available for 773 patients, therefore these patients were included in the final analysis. Common eligibility criteria for the use of atezolizumab plus bevacizumab were applied. All patients received an upper endoscopy in the six months preceding the start of the treatment according to the IMbrave150 criteria. Not all patients had Child Pugh class A or Eastern Cooperative Oncology Group performance status (ECOG PS) ≤ 1 as indicated by the inclusion criteria of the IMbrave150 trial. This is due to the fact that this is a real world retrospective study which by its nature has less stringent inclusion criteria. Atezolizumab plus bevacizumab was administered as described in the IMbrave150 trial, and all patients received 1200 mg of atezolizumab plus 15mg/kg of body weight of bevacizumab intravenously every 3 weeks [26]. Treatment interruptions and/or bevacizumab dose reductions were allowed to manage adverse events (AEs). AEs were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0 [27].

Statistical analysis

The primary endpoint of this study was the association between OS and PNI, whereas the secondary endpoint was the association between PFS and PNI.

Serum albumin and lymphocyte count on peripheral blood were collected at baseline (the day before the start of treatment). The PNI was calculated as follows: 10 × serum albumin concentration (g/dL) + 0.005 × peripheral lymphocyte count (number/mm^3). The cut-off point of the PNI was determined to be 41 by receiver operating characteristic (ROC) analysis (Supplementary Fig. 1). Categorical variables were compared with the Fisher's exact test.

OS was defined as the time interval from the first day of treatment to the day of death or last follow-up visit. PFS was defined as the time interval from the first day of treatment to the progression of the disease or the day of death for any cause. OS and PFS were estimated by the Kaplan-Meier method and curves were compared by the log-rank test. Unadjusted and adjusted HRs by baseline characteristics were calculated using the Cox proportional hazards model.

MedCalc package (MedCalc® version 16.8.4) was used for statistical analysis.

Results

Study population

Among the 773 patients available for analysis, 622 (80.5%) were males. The median age was 72 years (range 27-94). 574 (74.2%) patients had anECOG PS of 0, 713 (92.2%) patients were Child-Pugh A, and 464 (60.0%) had Barcelona Clinic Liver Cancer (BCLC) C HCC.

The median OS was 15.9 months (95% CI 14.7-22.5), whereas the median PFS was 7.4 months (95% CI 6.6-8.5).

268 patients (34.7%) were categorized as the PNI-low group, while the remaining 505 (65.3%) patients as the PNI-high group. The clinical and laboratory characteristics of each group are shown in Table 1. The groups showed significant differences ($p < 0.05$) in age, etiology of liver disease, Child-Pugh class, ECOG PS, basal alpha-feto-protein (AFP) levels, ALBI grade, and neutrophil-lymphocyte ratio (NLR).

Survival outcomes according to PNI

At the univariate analysis for OS, high PNI was associated with longer OS (22.5 vs. 10.1 months, HR 0.34, 95% CI 0.25-0.45; $p < 0.01$) compared to patients with low PNI (Fig. 1). In addition, BCLC B (HR 0.77, 95% CI 0.59-0.99; $p = 0.04$), Child-Pugh A (HR 0.09, 95% CI 0.05-0.17; $p < 0.01$), baseline AFP < 400 ng/mL (HR 0.48, 95% CI 0.36-0.64; $p < 0.01$), NLR ≤ 3 (HR 0.59, 95% CI 0.45-0.77; $p = 0.01$), and having undergone liver surgery (HR 0.71, 95% CI 0.55-0.93; $p = 0.01$) were associated with better prognosis. Following adjustment for clinical covariates positive in univariate analysis and after correction for the heterogeneous baseline characteristics, multivariate analysis confirmed high versus low PNI (HR 0.49, 95% CI 0.18-0.74; $p < 0.01$) as independent prognostic factor for OS (Table 2).

At the univariate analysis for PFS, high PNI was associated with longer PFS (8.7 vs. 5.8 months, HR 0.63, 95% CI 0.51-0.78; $p < 0.01$) compared to patients with low PNI (Fig. 2). In addition, Child-Pugh A (HR 0.53, 95% CI 0.34-0.83; $p < 0.01$), baseline AFP < 400 ng/mL (HR 0.60, 95% CI 0.48-0.75; $p < 0.01$), NLR ≤ 3 (HR 0.59, 95% CI 0.45-0.77; $p < 0.01$), and having undergone TACE (HR 0.76, 95% CI 0.62-0.94; $p = 0.01$) were associated with better PFS. Following adjustment for clinical covariates positive in univariate analysis and after correction for the heterogeneous baseline characteristics, multivariate analysis confirmed high versus low PNI (HR 0.82, 95% CI 0.66-0.95, $p = 0.01$) as independent prognostic factor for PFS (Table 2).

There was no difference in objective response rate (ORR) between the two groups (high 26.1% vs. low 19.8%; $p = 0.09$), while disease control rate (DCR) was significantly higher in the PNI-high group (76.8% vs. 66.4%, $p = 0.01$).

With regard to AEs, the incidence of hypertension was significantly higher in the PNI-high group (26.9% vs. 19.0%; p = 0.02), conversely the incidence of proteinuria was higher in the PNI-low group (33.6% vs. 25.9%; p = 0.03) (Table 3).

Discussion/Conclusion

This multicenter study is the first to show a significant prognostic value of PNI for both OS and PFS in HCC patients treated with atezolizumab plus bevacizumab.

Mainly two studies have investigated the role of PNI in HCC patients treated with immunotherapy with so far conflicting results. These two studies have in common the fact that they have analyzed the data of patients treated with different immunotherapy drugs and in different lines of treatment. The first of these studies was published in 2020 and showed that serum albumin levels and PNI value are associated with OS and PFS in patients receiving anti-PD1 treatment. Recently, however, a study involving 362 patients treated with immune checkpoint inhibitors failed to show a prognostic value of PNI [28, 29]. The data from our study appear more homogeneous because the population included only patients treated with atezolizumab plus bevacizumab in the first-line setting.

The large sample size allowed to identify two groups with distinct basal characteristics. What stands out is that patients belonging to the PNI-low group presented more frequently also other characteristics that define a worse prognosis and that may have influenced survival outcomes, including Child-Pugh B, ALBI 2, NLR > 3, AFP ≥ 400 ng/mL, and ECOG PS > 1. Moreover, patients with low PNI had a viral etiology more often and were subjected to local therapies, such as surgery, in a lower percentage. These different characteristics are the basis of the fact that PNI could represent an index, easy to calculate, to quickly identify potentially more fragile patients with more advanced disease, both in terms of oncological stage and in terms of impaired liver function. Despite this condition of fragility, there were no notable differences in terms of AEs between the two groups. Our data show that atezolizumab plus bevacizumab is a safe therapy even in the most fragile patients, such as those with low PNI. Of note is the fact that patients with high PNI had a higher incidence of hypertension which is a known factor associated with a better prognosis in patients treated with antiangiogenics such as bevacizumab [10, 30, 31]. This finding could be explained by the fact that patients with high PNI were exposed longer to its hypertensive effects.

Regarding efficacy outcomes, the DCR was higher in patients with high PNI. A higher rate of progressive disease (PD) at the first re-evaluation in patients with low PNI was also reported in the analysis performed by Caputo and colleagues on patients on first-line treatment with sorafenib (40% vs. 15% respectively; p = 0.04). Also in this study, which included 664 patients, PNI was found to be an independent prognostic factor for OS [14]. The role of PNI in patients receiving lenvatinib was investigated by Hiraoka et al in a real-world study that included 375 patients. Again, PNI was found to be an independent prognostic factor for OS,

but no data regarding response rates were reported [12]. In patients treated with lenvatinib, PNI was included within the lenvatinib prognostic (LEP) index, which also includes the BCLC stage and the ALBI grade. This index was recently validated as an independent prognostic factor for both OS and PFS within a study that included 717 patients. Patients classified as low-risk (PNI > 43.3 and undergoing TACE) had a lower rate of PD at first re-evaluation than patients classified as higher risk (low risk 17.6%; medium risk 12.9%; high risk 27.1%; p = 0.003) [17]. Curiously, in our study patients with high PNI showed a better DCR, but a similar ORR compared to patients with low PNI. These results may have been influenced by the fact that patients with high PNI had a non viral etiology that could constitute a negative characteristic for this group in light of recent evidence that patients with this particular etiology appear to be less responsive to immunotherapy [32, 33].

PNI, being calculated based on the lymphocyte count and serum albumin levels, is considered an index of the inflammatory and nutritional status of cancer patients [16, 34]. There have been numerous meta-analyses that have shown its validity from a prognostic point of view in the context of all neoplastic pathologies. Even today we do not know exactly the biological mechanisms underlying its prognostic role, but we know with certainty, thanks to the numerous literature data, that patients with low PNI have the worst outcomes in all disease settings, both in the context of locoregional treatments and in the context of systemic therapies [16]. From this point of view, the results of our study appear fully in line with the available literature. As for HCC patients, three meta-analyses have highlighted its prognostic role, even because, in patients with HCC, alterations in serum albumin levels may also be due to liver dysfunction resulting from cirrhosis [11, 35, 36]. In these patients, prognostic factors related to liver function are those that have been shown to have the greatest influence on prognosis, both in the early and in the advanced disease setting [6-10]. This is also highlighted by our results in which patients with low PNI presented worse OS and PFS certainly due to the worst baseline characteristics indicative of worse liver function. Literature data indicate that having sufficient muscle mass and a good state of nutrition are fundamental factors that can affect response to therapies, tolerability of treatments, and maintenance of a good quality of life [37-41]. Furthermore, there is always a greater interest from patients and their caregivers in finding the best nutritional condition to be maintained during therapies. Therefore, it becomes more and more useful for the clinician to use tools such as the PNI to correctly frame HCC patient and, possibly, direct him towards a multidisciplinary management that also includes the nutritional evaluation. The attention paid to patients with cirrhosis on this aspect is additionally justified by the fact that the etiology of this disease has been changing considerably in recent years. Today, thanks to antiviral therapies, the number of cirrhotic patients diagnosed with NASH/NAFLD linked to the metabolic syndrome is becoming increasingly prevalent [42, 43]. The population of our study is also in line with this phenomenon. In fact, the non-viral etiology characterizes 47.4% of patients with low PNI and 56.8% of those with high PNI. Therefore the possibility of a

nutritional screening in clinical pratice is becoming rapidly more desirable for all these patients and, even more so, for those who develop HCC.

Our study has some limitations, first of all, represented by its retrospective nature. The more favorable prognostic characteristics of the patients in the high PNI group may have influenced survival outcomes, constituting also a limitation of this study. Furthermore, there are no standardized cut-offs for PNI in the literature. However, the large sample in our study made it possible to identify a realistic cut-off through ROC analysis. It would be interesting to analyze the predictive role of PNI in future studies, comparing cohorts of HCC patients treated with the different therapeutic options available in first-line setting, such as atezolizumab plus bevacizumab, lenvatinib, and sorafenib. In conclusion, PNI is an independent prognostic factor for OS and PFS in HCC patients on first-line treatment with atezolizumab plus bevacizumab and could become an useful tool for clinicians to identify patients who could benefit most from this therapy in terms of DCR, upon confimation of these results in a validation cohort.

Statements

Statement of Ethics

All patients provided written informed consent before the enrollment in the study. The study was approved by IRCCS San Raffaele Hospital Ethic Committee, approval number 113/INT/2021, complied with the provisions of the Good Clinical Practice guidelines and the Declaration of Helsinki and local laws, and fulfilled the Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data.

Conflict of Interest Statement

Masatoshi Kudo has received grants from Taiho Pharmaceuticals, Chugai Pharmaceuticals, Otsuka, Takeda, Sumitomo Dainippon-Sumitomo, Daiichi Sankyo, AbbVie, Astellas Pharma, and Bristol-Myers Squibb; has received grants and personal fees from MSD, Eisai, and Bayer, and is an adviser for MSD, Eisai, Bayer, Bristol-Myers Squibb, Eli Lilly and ONO Pharmaceutical.

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The other authors declare no conflicts of interest.

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Data Availability Statement

All data generated or analyzed during this study are included in this article and its supplementary material files. Further enquiries can be directed to the corresponding author.

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Figure Legends

Fig. 1. Kaplan-Meier curves for OS in PNI-low group (green) versus PNI-high group (blue).

Fig. 2. Kaplan-Meier curves for PFS in PNI-low group (green) versus PNI-high group (blue).