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Immunotherapy vs Best Supportive Care for Patients With Hepatocellular Cancer With Child-Pugh B Dysfunction

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IMPORTANCE Whether patients with Child-Pugh class B (CP-B) cancer with unresectable hepatocellular carcinoma (uHCC) benefit from active anticancer treatment vs best supportive care (BSC) is debated.

OBJECTIVE To evaluate the association of immune checkpoint inhibitor (ICI)–based therapies vs BSC with overall survival (OS) of patients with uHCC and CP-B liver dysfunction.

DESIGN, SETTING, AND PARTICIPANTS This retrospective, multicenter, international clinical case series examined data of patients with CP-B with uHCC who were receiving first-line ICI-based regimens from September 2017 to December 2022 whose data were extracted from an international consortium and compared with a cohort of patients with CP-B receiving BSC. Patients were treated in tertiary care centers across Europe, US, and Asia in routine clinical practice. After applying the inclusion criteria, 187 and 156 patients were left in the ICI and BSC groups, respectively. The propensity score was calculated for the following variables: age, alpha-fetoprotein levels, Child-Pugh score, extrahepatic spread, portal vein tumor thrombosis, cirrhosis, ascites, and baseline Eastern Cooperative Oncology Group performance status.

EXPOSURES Patients in the ICI group received first-line systemic therapy with either atezolizumab plus bevacizumab (A+B) (n = 141) or nivolumab (n = 46).

MAIN OUTCOMES AND MEASURES OS in the inverse probability of treatment weighting (IPTW) populations was the main outcome, and it was estimated with Kaplan-Meier method; univariable Cox regression test was used to make comparisons between the 2 groups.

RESULTS The median age was 66 (IQR, 61-72) and 73 (IQR, 66-81) years in the ICI (33 women [18%]) and BSC groups (41 women [26%]), respectively. In the IPTW populations, median OS was significantly longer in the ICI group (7.50 months; 95% CI, 5.62-11.15) compared with BSC (4.04 months; 95% CI, 3.03-5.03; hazard ratio, 0.59; 95% CI, 0.43-0.80; $P < .001$). Multivariable analysis confirmed that ICI exposure was associated with a reduction of approximately 50% in the risk of death (hazard ratio, 0.55; 95% CI, 0.35-0.86; $P < .001$), and the presence of portal vein tumor thrombosis, an Eastern Cooperative Oncology Group performance score of greater than 1, and alpha-fetoprotein levels of 400 ng/mL or greater were associated with increased risk of death.

CONCLUSIONS AND RELEVANCE The results of this case series provide comparative evidence of improved survival in association with ICI treatment compared with BSC in patients with uHCC with CP-B liver dysfunction.

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Supplemental content

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Hepatocellular carcinoma (HCC) is the most common primary liver tumor that generally arises via chronic liver inflammation and coexists with liver cirrhosis in up to 70% to 80% of the cases.[1] Liver dysfunction is not only associated with the prognosis, but may also affect the safe delivery of systemic anticancer therapy.[2] Concerns about the metabolism of chemotherapy and targeted therapies have led clinical trials for HCC to exclude patients with Child-Pugh (CP) class B (CP-B) liver dysfunction, promoting the widespread recommendation of best supportive care (BSC) for these patients.[3]

Despite the lack of level 1 evidence, recently published data on immune checkpoint inhibitors (ICIs) have provided encouraging (albeit uncontrolled) evidence for the use of immunotherapy in patients with CP-B liver dysfunction.[4] However, most of the evidence produced to date has been uncontrolled and based on single-arm studies of selected patients with CP-B liver dysfunction, and whether delivering immunotherapy changes the natural history of patients with CP-B liver dysfunction and HCC remains debated. To satisfy this research question, we conducted a retrospective study building on 2 multicenter registries to comparatively evaluate the outcomes of ICI-based regimens with BSC.

Key Points

Question Do patients with unresectable hepatocellular carcinoma (HCC) and suboptimal liver function benefit from immunotherapy vs best supportive care?

Findings In this case series of 343 patients with Child-Pugh class B liver dysfunction, immunotherapy-based systemic therapy was associated with significant reduction in the risk of death compared with best supportive care.

Meaning The results of this study suggest that immunotherapy may be a safe and effective option for patients with unresectable HCC and suboptimal liver function.

Methods

Study Population

Ethical approval was granted by the Imperial College Tissue Bank and by local institutional review boards at each participating institution. Oral consent was provided to use deidentified data. Clinical data of patients affected by unresectable HCC (uHCC) with a CP liver function class B (score, 7-9) at the time of HCC diagnosis were extracted from an international consortium collecting data of consecutive patients with advanced/uHCC receiving ICI-based systemic treatment across Europe, the US, and Asia and from the Italian Liver Cancer dataset (eMethods 1 and eFigure 1 in Supplement 1).

Statistical Analysis

The main objective of the study was to compare outcomes of patients with CP-B liver dysfunction who were receiving immunotherapy-based active systemic anticancer treatment or BSC for uHCC. Details about the statistical analysis are reported in eMethods 2 in Supplement 1. Statistical analyses were carried out using R Studio, version 4.1.2 (R Foundation). The 2-tailed α level for all analyses was set at .05.

Results

Baseline Characteristics

We selected 187 patients with CP-B with uHCC who were not amenable to locoregional therapy treated with ICI-based therapies and 158 patients with CP-B with similar staging characteristics who received BSC only. In the ICI group, 141 were treated with atezolizumab plus bevacizumab (A+B), whereas 46 received nivolumab. Baseline characteristics are summarized in **Table 1** and eTable 1 in Supplement 1.

Outcomes for the Study Population

The median follow-up for the population receiving active treatment was 10.63 months (95% CI, 9.30-11.96) and 23.42 months for the BSC cohort (95% CI, 13.22-33.62). Details about outcomes for the whole cohort are reported in eResults 1 in Supplement 1.

IPTW Survival Analyses

In the IPTW populations, patients receiving active treatment reported a significantly longer median overall survival (OS) compared with BSC (7.50 months [95% CI, 5.62-11.15] vs 4.04 months [95% CI, 3.03-5.03]; hazard ratio [HR], 0.59; 95% CI, 0.43-0.80; $P < .001$; **Figure**). The IPTW-fitted multivariable analysis, including the groups of interest and those variables with an standard mean difference of greater than 0.10 after the weighting (eTable 3 in Supplement 1), confirmed ICI exposure to be significantly associated with a reduction in the risk of death (HR, 0.55; 95% CI, 0.40-0.74; $P < .001$), portal vein tumor thrombosis (PVTT), alpha-fetoprotein (AFP) levels of 400 ng/mL or greater, and an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of greater than 1 conferred an increased risk of death (HR, 2.02; 95% CI, 1.53-2.66; $P < .001$; HR, 1.75; 95% CI, 1.32-2.31; $P < .001$; HR, 1.31; 95% CI, 1.00-1.73; $P = .06$; **Table 2**). Barcelona Clinic Liver Cancer stage was not included in the model to avoid collinearity; the single components were included as single variable (PVTT, extrahepatic spread, and ECOG PS). As reported for the unweighted population, the year of diagnosis did not have a prognostic association with the weighted models (eTables 4 and 5 in Supplement 1).

Subgroup Analyses

The benefit from the treatment was preserved in all the subgroups of interest, as well as in those characterized by worse prognosis in the multivariable model. A positive interaction with the treatment was found with AFP levels, albumin-bilirubin grade, and ascites (eTable 6 and eFigure 3 in Supplement 1).

Objective Response Rate and Progression-Free Survival

In the treatment group, objective response rates and disease control rates were 14.3% and 56.2%, respectively. The median progression-free survival for patients receiving active treatment was 3.16 months (95% CI, 2.93-4.34) (eFigure 4A and eResults 2 in Supplement 1).

Table 1. Differences in the Baseline Characteristics in the Active Treatment and Best Supportive Therapy Groups

Characteristic	No. (%)		*P* value	Adjusted *P* value
	Active treatment (n = 187)	BSC (n = 158)		
Age, median (range), y	66 (61-72)	73 (66-81)	<.001	.002
Age, y				
≤69	95 (51)	134 (85)	<.001	.002
>69	92 (49)	24 (15)		
Sex				
Female	33 (18)	41 (26)	.06	>.99
Male	154 (82)	117 (74)	.06	>.99
Origin				
Asia	54 (29)	0	<.001	.002
Outside Asia	133 (71)	158 (100)		
BCLC				
B	33 (18)	13 (8)	.01	.18
C or D	154 (82)	145 (92)		
AFP, ng/mL				
<400	101 (55)	125 (79)	.001	.02
≥400	86 (45)	33 (21)		
Child-Pugh score/class				
7-8	165 (88)	124 (78)	.02	.24
9	22 (12)	43 (22)		
ALBI score				
2	93 (50)	67 (43)	.33	>.99
3	94 (50)	91 (57)		
Cirrhosis				
Yes	168 (90)	152 (96)	.02	.38
No	19 (10)	6 (4)		
Ascites				
Yes	122 (65)	119 (75)	.04	.70
No	65 (35)	39 (25)		
Etiology				
Viral	105 (56)	102 (65)	.11	>.99
Nonviral	82 (44)	56 (35)		
HBV				
Yes	50 (27)	27 (17)	.03	.51
No	137 (73)	131 (83)		
HCV				
Yes	48 (26)	79 (50)	<.001	.002
No	139 (74)	79 (50)		
PVTT				
Yes	115 (61)	63 (40)	<.001	.002
No	72 (39)	95 (60)		
EHS				
Yes	92 (48)	24 (26)	<.001	.002
No	95 (52)	134 (74)		
ECOG score				
>1	21 (11)	82 (52)	<.001	.002
0 or 1	166 (89)	75 (48)		

Abbreviations: AFP, alpha-fetoprotein; ALBI, albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer; BSC, best supportive care; ECOG, Eastern Cooperative Oncology Group; EHS, extrahepatic spread; HBV, hepatitis B virus; HCV, hepatitis C virus; PVTT, portal vein tumoral thrombosis.

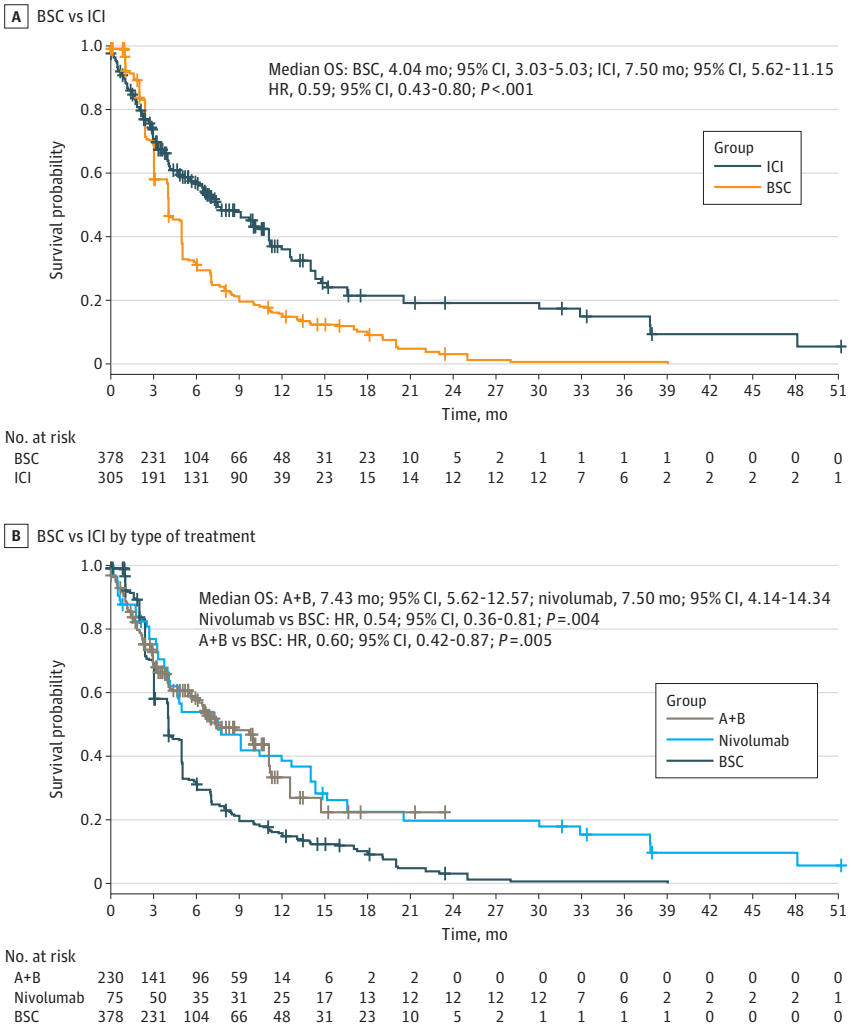
Safety Profile

Overall, in the treatment group, 112 patients experienced at least 1 adverse event (AE); therefore, the incidence of all-cause AEs in treatment recipients was 58.9%. Twenty patients (10.7%) experienced at least 1 grade 3 or higher AE. No grade 5 AEs were reported during the treatment (eResults 3 in Supplement 1).

Discussion

During the last decade, the clinical outcomes of patients with uHCC have substantially improved.[5,6] However, clinical trials testing systemic therapies have consistently excluded those patients falling outside stringent CP class A criteria. There-

Figure. Overall Survival (OS) in the Best Supportive Care (BSC) and Immune Checkpoint Inhibitor (ICI)–Exposed Inverse Probability of Treatment Weighting Populations



B, Stratified according to the type of treatment (nivolumab and atezolizumab + bevacizumab [A+B]). HR indicates hazard ratio.

Table 2. Inverse Probability Treatment-Weighted Univariable and Multivariable Cox Regression Models for Overall Survival

	Univariable		Multivariable	
Characteristic	HR (95% CI)	*P* value[a]	HR (95% CI)	*P* value[b]
Treatment (active treatment -BSC)	0.59 (0.43-0.80)	<.001	0.55 (0.40-0.74)	<.001
Age (≤69 y to >69 y)	0.94 (0.68-1.30)	.70		
Sex (male-female)	1.31 (0.90-1.90)	.16	1.18 (0.86-1.61)	.31
BCLC (C/D-B)	1.25 (0.87-1.80)	.24		
AFP (≥400 to <400)	1.67 (1.15-2.43)	.01	1.75 (1.32-2.31)	<.001
ALBI grade (3-2)	0.89 (0.65-1.22)	.46	NA	NA
Child-Pugh (9 to 7/8)	1.07 (0.68-1.68)	.78	NA	NA
Cirrhosis (yes-no)	0.64 (0.36-1.15)	.14	NA	NA
PVTT (yes-no)	2.04 (1.47-2.82)	<.001	2.02 (1.53-2.66)	<.001
EHS (yes-no)	1.35 (0.95-1.83)	.10	1.12 (0.81-1.54)	.48
Viral (yes-no)	0.92 (0.62-1.36)	.66	1.01 (0.75-1.31)	.93
Ascites (yes-no)	1.18 (0.88-1.58)	.28	0.90 (0.68-1.20)	.47
ECOG score (>1 to 0/1)	1.10 (0.74-1.62)	.65	1.31 (1.00-1.73)	.06

Abbreviations: AFP, alpha-fetoprotein; ALBI, albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer; BSC, best supportive care; ECOG, Eastern Cooperative Oncology Group; EHS, extrahepatic spread; HR, hazard ratio; NA, not applicable; PVTT, portal vein tumoral thrombosis.

[a] Harmonic mean *P* value for the model: *P* = .001.

[b] Harmonic mean *P* value for the model: *P* < .001.

fore, treatment allocation for patients with moderate liver dysfunction (CP-B) remains controversial.[7] To fill this gap, we comparatively assessed clinical outcomes of patients with CP-B who were receiving ICIs vs BSC whose data were in large, multicenter, international registries.

In our IPTW analyses, treatment with A+B or nivolumab was associated with a statistically significant improvement in OS vs BSC independently from baseline characteristics. In the double-adjusted multivariable model, presence of PVTT and AFP levels of 400 ng/mL or greater emerged as independent factors that were associated with an increased risk of death. Patients with PVTT and AFP levels of 400 ng/mL or greater represent a population characterized by poorer survival even in the context of combination immunotherapy studies[8] but who still benefit from ICI combinations in the presence of well-preserved liver function.[9] Our subgroup analyses, despite being merely exploratory, suggested that the benefit of active treatment was maintained even in the presence of PVTT and elevated AFP levels, with a positive interaction between the treatment and AFP levels. From one side, this indicates that immunotherapy could be effective in the presence of more advanced oncological features; from the other, it suggests stratification factors for future trials enrolling patients with CP-B. As previously shown, our study confirmed that anti-programmed cell death 1 and anti-programmed cell death 1 ligand 1/vascular endothelial growth factor combination therapy was characterized by an acceptable safety profile, with incidence and severity of AEs consistent with data in patients with CP class A.[5,10,11]

Treatment discontinuations secondary to AEs were less than 10%, the proportion of grade 3 or higher AEs was 11%, and bleeding events were 13.2%, suggesting that patients with CP-B can tolerate immunotherapy without significant concerns. Even if direct comparison between A+B vs nivolumab was outside the scope of this article, a significant difference in efficacy between the 2 strategies did not emerge from our data in terms of OS, progression-free survival, and overall treatment duration.

Limitations

There were several limitations that applied to our study: the retrospective design was accompanied by an inherent risk of selection bias and unmeasured confounders that cannot be fully addressed even after adopting stringent statistical adjustments. Furthermore, in the absence of central adjudication of efficacy and safety outcomes, toxic effects and radiologic response data may have experienced interrater heterogeneity. Lastly, without prospective allocation and randomization, positive associations between treatment allocation and survival cannot be interpreted as causative.

Conclusions

To our knowledge, this case series was the first to provide a comparative assessment in the efficacy of ICI-based therapies in patients with advanced HCC and CP-B liver dysfunction. In the absence of high-quality, prospective, comparative data against placebo, our results, strengthened by stringent propensity score weighting methods, potentially provide a useful benchmark for estimating survival benefit in patients with CP-B to further assess ICI-based therapies in dedicated prospective studies.

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