Impact of immune-related adverse events on efficacy of immune checkpoint inhibitors in patients with advanced hepatocellular carcinoma

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Introduction

Immune checkpoint inhibitors (ICI) have been found to be efficacious in the treatment of advanced hepatocellular carcinoma (aHCC). Their use can result in immune-related adverse events (irAEs). Recent studies have demonstrated a positive association between irAEs and improved clinical outcomes in several cancer types - advanced melanoma[1], urothelial cancer[2], renal cell carcinoma[3] and others[4,5]. It remains unknown if such an association exists for aHCC. We aim to explore the association between irAE and ICI efficacy in patients with aHCC and if steroid use was associated with poorer outcomes.

Methodology

Retrospective chart review was performed on 168 patients with advanced HCC who received at least one dose of ICI between May 2015 - Nov 2019 at our centre. Survival outcomes were analyzed in terms of median progression free survival (PFS) and median overall survival (OS) estimated using the Kaplan-Meier method. Log-rank test was done to evaluate for significant differences between survival curves. Univariate and multivariate Cox regression models were used to evaluate the relationship between the incidence of irAEs and survival. Complementary landmark analyses for OS were performed using landmarks of 6 weeks and 12 weeks. Patients who remained alive were censored at the time of last follow-up. irAEs were graded according to Common Terminology Criteria for Adverse Events (CTCAE) v4.03. Response was graded according to Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 and were analyzed in terms of objective response rate (ORR) and disease control rate (DCR). Pearson Chi-Square test was used to evaluate if ORR and DCR were significantly different between groups.

Results

Patient Characteristics

Median duration of follow-up was 25.1 months. Median age was 69 years, 85.7% were male and 57.7% had hepatitis B infection. 60.7% had ECOG PS of 0. 78.0% had Child Pugh A liver cirrhosis. 50% had macrovascular invasion and 65.5% had extrahepatic metastasis. Majority (82.7%) received immunotherapy monotherapy, with anti-PD1/PD-L1 monoclonal antibodies being the most common (80.4%). (Table 1)

Characteristic		Freq (%)	Characteristic		Freq (%)
Age	Median	69	**Child Pugh Score**	5-6	131 (78.0)
	Range	25 - 88		7	23 (13.7)
Gender	M	144 (85.7)		8- 9	14 (8.3)
	F	24 (14.3)			
Ethnicity	Chinese	114 (67.9)	**AFP (ng/mL)**	< 400	91 (54.2)
	Malay	10 (6.0)		≥ 400	76 (45.2)
	Indian	4 (2.4)	**Etiology**	Hepatitis B	97 (57.7)
	Caucasian	2 (1.2)		Hepatitis C	15 (8.9)
	Others	38 (22.6)		Non-viral	56 (33.3)
ECOG	0	102 (60.7)	**BCLC**	B	28 (16.7)
	1	59 (35.1)		C	140 (83.3)
	2/3	7 (4.2)	**Immunotherapy Regimen**	IO only	139 (82.7)
Macro-vascular Invasion	Yes	84 (50.0)		IO-IO	16 (9.5)
	No	84 (50.0)		IO-TKI/mAb	13 (7.7)
Extrahepatic Metastasis	Yes	110 (65.5)	**Immunotherapy (line of therapy)**	1st line	114 (67.9)
	No	58 (34.5)		2nd line	44 (26.2)
ALBI Grade	G1	34 (20.2)		3rd line	9 (5.4)
	G2	119 (70.8)		4th line	1 (0.6)
	G3	13 (7.7)			

Table 1: Demographics and Clinical Characteristics (n=168)

irAE Characteristics

57.7% experienced all-grades irAEs, while 14.3% experienced grade ≥3 irAEs. 2 experienced treatment-related death. The most common irAEs were dermatological (47%), hepatobiliary (14.3%) and endocrine (9.5%). The most common irAEs (grade≥3) were hepatobiliary (7.1%), gastrointestinal (3.0%) and pneumonitis (2.4%). (Table 2). 61 (36.3%) of patients experienced 1 irAE, 22 (13.1%) 2 irAEs, 14 (8.3%) experienced ≥3 irAEs.

Type	Total (%)	Grade 1-2 (%)	Grade ≥3 (%)
Any irAE	97 (57.7)	90 (53.6)	24 (14.3)
Dermatological	79 (47.0)	77 (45.8)	2 (1.2)
Hepatobiliary	24 (14.3)	12 (7.1)	12 (7.1)
Endocrine	16 (9.5)	14 (8.3)	2 (1.2)
Gastrointestinal	15 (8.9)	10 (6.0)	5 (3.0)
Pneumonitis	9 (5.4)	5 (3.0)	4 (2.4)
Others	18 (10.7)	15 (9.0)	3 (1.8)

Table 2: Incidence of Immune-related adverse events

Association between irAE and Response

Patients with all-grades irAEs had a significantly higher ORR (27.8% vs 11.3%, p=0.009) and DCR (67.0% vs 28.2%, p=<0.001) than those without irAEs. ORR was significantly different for patients with grade≥3 irAE vs grade 1-2 irAE vs no irAE (ORR 50.0%, 20.5%, 11.3% respectively, p<0.001) while DCR was significantly different for patients with grade≥3 irAE vs grade 1-2 irAE vs no irAE (87.5%, 60.3%, 28.2% respectively, p<0.001).

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Association between irAE and Survival

Median PFS was significantly longer for patients with all-grades irAEs than those with no irAE (5.5 m vs 1.3 m), for those with grade≥3 irAE vs grade 1-2 irAE vs no irAE (8.5 m vs 3.6 m vs 1.3 m, p<0.001) and those with ≥2 irAE vs 1 vs no irAE (10.1 m vs 2.8 m vs 1.3 m, p<0.001).
Median OS was significantly longer for patients with all-grades irAEs than patients without irAEs (16.2 m vs 4.6 m), for those with grade≥3 irAE vs grade 1-2 irAE vs no irAE (26.9 m vs 14.0 m vs 4.6 m, p<0.001) and for those with ≥2 irAE vs 1 vs no irAE (20.7 m vs 13.9 m vs 4.6 m, p<0.001). (Figure 1)

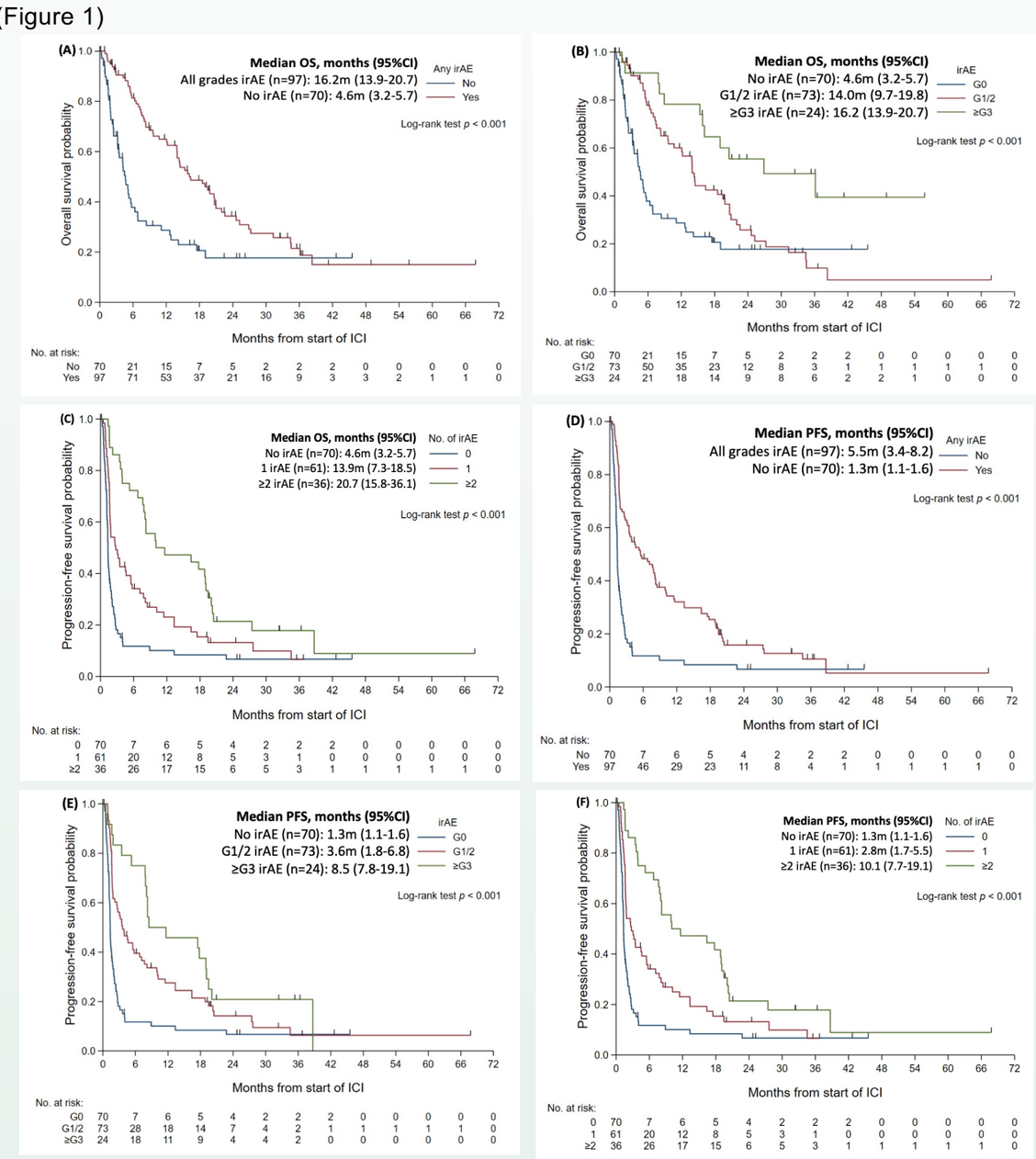

Figure 1: Kaplan–Meier curves for (a) OS (any irAE) (b) OS (Grade≥3 irAE) (c) OS (≥2 vs 1 vs no irAE) (d) PFS (any irAE) (e) PFS (Grade≥3 irAE) (f) PFS (≥2 vs 1 vs no irAE)

Multivariable Cox regression

Multivariable analysis showed that all-grades irAE, grade≥3 irAE, ≥2 irAEs, 1 irAE and dermatological irAEs were associated with a significantly longer median PFS and OS. (Table 3).

irAE Category	Multivariate HR (PFS)	p-value	Multivariate HR (OS)	p-value
Any irAE	0.48 (0.33, 0.69)	0.001	0.49 (0.32, 0.74)	<0.001
Grade ≥3 irAE	0.57 (0.34, 0.95)	0.030	0.40 (0.21, 0.76)	0.005
Dermatological	0.52 (0.35, 0.76)	<0.001	0.50 (0.33, 0.75)	<0.001
Pneumonitis	0.46 (0.21, 1.01)	<0.001	0.43 (0.17, 1.07)	0.069
Endocrine	0.48 (0.26, 0.88)	0.019	0.69 (0.35, 1.36)	0.288
1 irAE vs no irAE	0.57 (0.38, 0.84)	0.005	0.59 (0.37, 0.92)	0.020
≥2 irAE vs no irAE	0.36 (0.22, 0.59)	<0.001	0.35 (0.20, 0.62)	<0.001

Table 3: Cox regression analysis on irAE and survival outcomes

Steroid use: 27 (16.1%) of patients received systemic steroids for treatment of irAEs. Those who did, had a trend towards longer PFS (9.9m vs 3.4m, p=0.238) and OS (20.7m vs 14.3m, p=0.064) than those who did not.

Discussion and Conclusion

Our study found that the presence of all-grade irAEs, severity of irAE and multisystem involvement may be key prognostic markers in patients with aHCC treated with ICI. This supports the hypothesis that patients who experience higher grades and more sites of irAE have higher T-cell activity and hence better anti-tumor outcomes. *Shankar et al.* described similar results in a multi-centre cohort of patients with NSCLC[6].

In addition, *Quach HT et al.*[7] showed that dermatological irAE was associated with longer survival in patients with metastatic melanoma. One would hypothesize that in HCC, presence of hepatobiliary irAE would be associated with increased ICI efficacy but our study showed only a trend towards longer survival. Dermatological irAE was however associated with longer survival. More work is hence required to ascertain the influence of irAE site.

Significantly, patients who received systemic corticosteroids for treatment of irAEs had a trend towards longer OS and PFS as compared to those who did not. This correlates with other studies that steroid use was not associated with poorer outcomes.[8]

Limitations and strengths: This is a single-centre, retrospective study. It included predominantly hepatitis B-associated HCC (precluding its generalization to non-hepatitis B-associated HCC). However, it is the largest study describing such association in patients with aHCC to date, has a long median followup (25.1 m) and its use of landmark analysis accounted for immortal bias.

Conclusion: The presence of irAEs may be a potential prognostic biomarker in patients with aHCC treated with ICI. Patients with more severe irAEs and multisystem involvement have better prognosis. Prompt usage of systemic corticosteroids to treat irAEs is also key to ensure best long-term outcomes.