Immunotherapy And Immune-Related Hepatitis In Hepatocellular Carcinoma: Outcomes And Tissue Biomarker Analysis

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INTRODUCTION

High-grade hepatitis occurs in less than 10% of patients undergoing nivolumab or pembrolizumab. Yet hepatitis remains a relatively frequent immune-related adverse event (irAE) that poses HCC patients at an increased risk, when comparisons are done with other tumor types or when patients receive immune checkpoint inhibitors (ICI) plus targeted agents. Determinants of hepatic irAE (HIRAE) in HCC remain poorly understood and there are insufficient data to establish to which extent the pre-existing organ damage may contribute to an overall increased risk of adverse events during treatment. To the best of our knowledge, studies investigating HIRAE and their outcomes have mainly focused on patients with extra-hepatic primary tumors.

AIM

The objectives of this study were: (i) to assess the prevalence of immuno-related hepatitis in patients treated with ICI alone or in combination with other ICI and/or targeted agents, (ii) to assess the relationship between the development of hepatitis and time to treatment failure (TTF, defined as the interval between first ICI infusion to the earliest date of disease progression, or the day patient came off study because of toxicity or death due to any cause), (iii) to identify clinical and morpho-pathological factors linked to high-grade hepatitis.

METHOD

We included patients with advanced/unresectable receiving PD-1 or PD-L1 antibodies, +/- antibodies targeting CTLA-4, selective TKI or multikinase inhibitors (MKI). Levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, alkaline phosphatase (Alk P), gamma-glutamyltransferase (GGT), international normalized ratio were recorded. Analyses were performed before any immunotherapy injection. HIRAE were categorized as high-grade (CTCAE grades 3–5) or low grade (grades 1 and 2). The criteria for grade ≥3 hepatitis were met if AST/ALT and/or GGT/Alk P raised more than five times the upper limit of normal (ULN) and/or total bilirubin levels raised more than three times the ULN. With increased baseline AST/ALT levels, the criteria for grade ≥3 hepatitis were met if AST/ALT levels raised >3x from baseline and more than five times the ULN, or AST/ALT levels raised >8x ULN, whichever was lower. Oral corticosteroids were administered according to clinical judgment, when two or more consecutive AST/ALT analyses, did not show a decrease of liver enzymes. Tumor progression, or portal vein thrombosis as alternative diagnoses for HIRAE were ruled out by means of radiological imaging

RESULTS

Demographics of advanced HCC patients treated with immune checkpoint inhibitors (*N* = 58)

Age, median (range)	71	(49-83)
Gender, male, N (%)	40	(69)
Previous loco-regional treatments, N (%)	31	(53)
Previous liver surgery, N (%)	22	(38)
Etiology (%)		
-HCV	18	(31)
-HBV	5	(9)
-Non-viral¶	35	(60)
Child-Pugh Score A, N (%)	57	(98)
Albumin-bilirubin grade, N (%)*		
-1	47	(82)
-2	10	(18)
Median time from HCC diagnosis to treatment start with immune checkpoint inhibitors, days (range)	615	(29-8191)
Line of treatment with ICI, N (%)		
-First	19	(33)
-Second	33	(57)
-Third	6	(10)
Treatment received, N (%)		
-Anti-PD-1/PD-L1 monotherapy	20	(34)
-Anti-PD1/PD-L1 + anti-CTLA-4	15	(26)
-Anti-PD1/PD-L1 + anti-CTLA4 + MKI	5	(9)
-Anti-PD1/PD-L1 + MKI/TKI	18	(0.31)

¶Includes: Non-alcoholic fatty liver disease (N = 2), alcohol (N = 12), unknown (N = 15), prior HCV infection achieving sustained viral response under direct antiviral agent treatment (N = 2), other (N =4, including hemochromatosis, hepatitis A, concomitant alcohol and hepatitis C).

Nine patients (15.5%) developed grade ≥3 immune-related hepatitis after a median time of 0.9 months from treatment start. Additional grade ≥3 irAEs consisted in increased amylase levels and vasculitis (one patient each). Upon resolution of hepatitis to grade ≤1 (or liver function tests to baseline patient's values), treatment was eventually resumed in six out of nine patients, none of whom experienced the recurrence of HIRAE

Patient	Gender	Age	HCC etiology; prior treatments for viral hepatitis	Treatment	Baseline ALT levels (IU/L)	Time between treatment start and Grade ≥3 hepatitis (days)	Treatment Management	Steroids and doses	Time to resolution of hepatotoxicity (Grade ≤1, days)	Best Overall Response	Survival status from start of treatment
#1	Male	76	Alcohol	Anti-PD-1 + anti-CTLA4 + MKI	39	46	Permanently discontinued	MP 2mg/kg	45	SD	Died after 9.4 months
#2	Male	73	HCV¶	Anti-PD-1 + TKI	147	85	Permanently discontinued	PDN 0,5mg/kg	Not resolved	SD	Died after 10.6 months
#3	Female	78	HCV*	Anti-PD-1 + anti-CTLA4 + MKI	88	14	Temporarily suspended	-	15	SD	Alive at 11.6 months, PD after 8.1 months
#4	Female	58	Unknown	Anti-PD-1 + anti-CTLA4	123	27	Temporarily suspended	-	14	PR	Alive after 12.8, treatment ongoing
#5	Male	65	HBV°	Anti-PD-1 + MKI	13	70	Temporarily suspended	-	12	SD	Alive after 12.6, PD after 2.7 months
#6	Male	72	HCV¶	Anti-PD-1 + MKI	92	14	Permanently discontinued	-	14	SD	Died at 9.4 months, PD after 6.6 months
#7	Male	64	HCV*	Anti-PD1	29	28	Temporarily suspended	PDN 2mg/kg	2	SD	Alive after 4.1 months, treatment ongoing
#8	Female	84	HCV*	Anti-PD1 + anti-CTLA4	103	20	Temporarily suspended	-	28	PR	Died after 9.6 months
#9	Female	71	HCV*	Anti-PD1 + anti-CTLA4	62	30	Temporarily suspended	-	28	SD	Alive after 2.8 months, treatment ongoing

HCC, hepatocellular carcinoma; HCV, chronic hepatitis C; HBV, chronic hepatitis B; PD-L1, programmed cell death receptor ligand 1; PD-1, programmed cell death receptor; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; TKI, tyrosine kinase inhibitors; MKI, multikinase inhibitors; MP, methylprednisolone; PDN, prednisone ; SD: stable disease; PR, partial response *Detectable HCV RNA at screening and at hepatitis onset; ¶No detectable HCV RNA at screening; °No detectable HBV DNA at screening.

No statistically significant differences in terms of TTF were seen according to grade ≥3 hepatitis vs lower grades (3.25 vs 3.91 months, respectively; p = 0.81). However, TTF was significantly shorter in patients discontinuing treatment because of an AE than in patients experiencing liver failure or progressive disease: 2.3 vs. 3.4 months, respectively (p = 0.034).

Twenty-seven patients had an available pre-treatment liver biopsy. At morphology level, 33% were G3/G4 HCC, 22% showed tumoral necrosis and 11% had TLS easily detectable on H/E section. At phenotypical level, GS immunoreactivity was strong and diffuse (14 cases), moderate and diffuse (6 cases), patchy and faint (3 cases), and absent (4 cases). Beyond those cases with TLS already detectable on H/E sections, rare CD3+ and CD79+ cells were found in one additional case. VETC was observed in 69% of patients. According to morphological and phenotypical features, HCC samples were grouped into a T-cell exclusion class (*N* = 23, 85%) or an Immune class (*N* = 4, 15%).Cases developing grade ≥3 hepatitis segregated into the T-cell exclusion class, frequently characterized by the presence of intra-tumoral necrosis and usually better differentiated. Conversely, none of the four cases falling into the Immune class did develop high-grade hepatitis.

CONCLUSIONS

- Six out of nine patients were able to resume treatment upon resolution of hepatitis to grade ≤1: none of them had a recurrence of hepatitis. This is in contrast with a report suggesting that 10% of melanoma patients might experience recurrent (or de novo) hepatitis once the anti-PD-1 inhibitor is resumed..
- We did not detect any impact on subsequent outcomes in terms of TTF according to hepatitis severity. Nevertheless, patients who permanently discontinue treatment because of AE (including hepatitis) have a significantly shorter TTF than patients who experience liver failure or progressive disease.
- In the event of high-grade hepatotoxicity patients could be reassured that further doses of immunotherapy can be deferred without reducing the possibilities of treatment benefit. In contrast, current practice guidelines, in a more general disease setting, recommend to permanently discontinue treatment.
- Cases with paucity of lymphocytes and GS expression were more prone to develop high-grade hepatitis.

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