Letter to the Editor

Is immunotherapy-related liver injury more common in patients with hepatocellular carcinoma than in other advanced solid tumors?

Liang Wang^, Yonggang Wei, Ming Zhang^

Division of Liver Surgery, Department of General Surgery, West China Hospital, Sichuan University, Chengdu, China

Correspondence to: Ming Zhang, MD. Division of Liver Surgery, Department of General Surgery, West China Hospital, Sichuan University, No. 37 Guoxuexiang, Chengdu 610041, China. Email: Zmhxdoctor@wchscu.edu.cn.

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We are very interested in the Italian prospective multicenter cohort study by Celsa *et al.* (1) on the occurrence of immune-related liver injury (irLI) in patients with hepatocellular carcinoma (HCC) versus other solid tumors treated with immune checkpoint inhibitors (ICIs). The authors concluded that patients with HCC had a greater incidence and earlier onset of irLI than those with other solid tumors but were characterized by higher remission rates and a lower need for corticosteroid therapy. However, after careful reading, we raised several questions regarding this multicenter study as follows:

First, are there specific diagnostic criteria for irLI. If not, how can liver injury caused by immune damage be confirmed? In addition, doctors at each treatment center have different levels of evaluation of irLI, and the level of transaminase elevation before the occurrence of irLI should be considered. How can the accuracy of the irLI incidence be determined? While this study revealed that elevated aminotransferase levels are associated with viral hepatitis, disease progression in patients with HCC patients is also associated with elevated aminotransferase levels (2,3). However, liver injury due to disease progression cannot be ruled out. As shown in *Tab. 1* of the original article, in the HCC cohort, the alpha-fetoprotein (AFP) levels of the 43 patients who developed any grade of irLI were significantly higher than those of all the HCC patients and the HCC patients who did not develop irLI (P=0.03), which also suggests that it is possible that part of the reason for the occurrence of hepatic impairment in the 43 patients was tumor progression. In a study by De Martin *et al.* (4) in irLI, liver biopsies are routinely performed when irLI is evaluated. However, in the original article (1), the authors neither provided the tumor characteristics of the patients in the HCC cohort nor provided evidence that the 43 patients who developed any grade of irLI did not experience tumor progression. Moreover, in the HCC cohort, of 375 patients with unresectable or advanced HCC, 14.9% had metabolic dysfunction-associated steatotic liver disease (MASLD) (1). However, the etiology of HCC affected the therapeutic response to ICIs: non-viral HCC, particularly nonalcoholic steatohepatitis (NASH)-HCC, might be less responsive to immunotherapy, probably due to NASH-related aberrant T-cell activation leading to tissue damage and thus impaired immune surveillance (5), which might lead to a higher incidence of irLI. In addition, in patients with non-viral HCC, there was a significant difference in overall survival (OS) between MASLD and non-MASLD patients, and

^ ORCID: Liang Wang, 0009-0004-7238-7088; Ming Zhang, 0009-0001-3424-0446.

Table 1 Immune-related adverse events and rate of steroid treatment in 220 patients with unresectable/advanced HCC treated with atezolizumab plus bevacizumab as first-line systemic therapy

Event	Atezolizumab + bevacizumab (N=220), n (%)	
	Any grade	Grade 3–4
Platelet count decrease	28 (12.7)	10 (4.5)
Blood bilirubin increase	27 (12.3)	6 (2.7)
Hypertension	58 (26.4)	24 (10.9)
Diarrhea	51 (23.2)	5 (2.3)
Nausea	34 (15.5)	4 (1.8)
Pyrexia	35 (15.9)	5 (2.3)
Abdominal pain	45 (20.5)	7 (3.2)
Pruritus	65 (29.5)	0
Decreased appetite	56 (25.5)	3 (1.4)
Rash	32 (14.5)	4 (1.8)
Cough	23 (10.5)	0
Fatigue	46 (20.9)	8 (3.6)
Aminotransferase increase (ALT/AST)	68 (30.9)	24 (10.9)
Steroid treatment	28/68 (41.2)	–

HCC, hepatocellular carcinoma; ALT, alanine transaminase; AST, aspartate aminotransferase.

the OS of HCC patients was significantly higher in the MASLD group than in the non-MASLD group (6). It also indirectly indicated that the incidence of various immune-related adverse reactions in patients with advanced HCC and MAFLD may be affected after treatment with targeted therapies and/or ICIs.

Second, the baseline characteristics of the two cohorts differed widely, as shown in *Tab. 1* and *Tab. 2* (1), and the incidence of cirrhosis (72% of patients in the HCC cohort had cirrhosis, whereas the incidence of liver metastases was only 10.2% in the INVIDIa-2 cohort) and the incidence of liver function test abnormalities [baseline bilirubin levels and baseline alanine transaminase (ALT) level >1.5 times the normal upper limit were 6.4% and 19.7% in the HCC cohort, respectively, compared with 2.1% and 2.5% in the INVIDIa-2 cohort]. In addition, the therapeutic intervention regimens of the two cohorts were inconsistent [dual-agent treatment with atezolizumab plus bevacizumab in the HCC group, and first-line programmed death 1 (PD-1)/programmed cell death ligand 1 (PD-L1) checkpoint inhibitor monotherapy in the INVIDIa-2 group]. In a study by Finn *et al.* (7) of atezolizumab in combination with bevacizumab for the treatment of HCC, the proportion of patients receiving atezolizumab in combination with bevacizumab who experienced an adverse event of elevated transaminase levels was greater than 10%. Although bevacizumab does not directly cause liver injury, it is unknown whether bevacizumab increases the hepatic injurious effects of atezolizumab when combined with atezolizumab. While this study corrected for the incidence of irLI based on the duration of exposure to ICI therapy, the effects of the large intrinsic differences in baseline characteristics, the varying responsiveness of different tumors to ICI therapy, and the different intervention regimens made us unsure of the reasonableness of the conclusions of this study (8).

Third, glucocorticoids are the mainstay of treatment for most immune-related adverse events and should be administered early when needed, which may affect the regression of some immune-related adverse events (9,10). However, only 7 of the 43 patients in the HCC cohort who developed any grade of irLI received steroid therapy (1). As shown in *Table 1*, in our study, 220 patients with HCC received atezolizumab plus bevacizumab as a first-line systemic therapy, of which 68 patients developed any grade of irLI and had a high rate of steroid treatment (41.2%). There was also a significantly higher incidence of secondary hypertension and pulmonary and cutaneous (cough, pruritus, rash) immune-related adverse events. Doctors may have subjectively judged that elevated aminotransferase levels were related to tumor progression rather than immune-associated liver injury; therefore, they deliberately avoided steroid treatment, contributing to the low rate of corticosteroid requirement in the HCC cohort.

Finally, we thank Celsa *et al.* for their study on the clinical question of the outcome of irLI in patients with different tumors treated with ICIs, which has helped deepen our understanding of ICIs for HCC and has been an important guide for the development of related studies.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of West China Hospital, Sichuan University (No. 2022-690) and individual consent for this retrospective analysis was waived.

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