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Letter to the Editor

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Letter Regarding "Impact of Immune-Related Adverse Events on Efficacy of Immune Checkpoint Inhibitors in Patients with Advanced Hepatocellular Carcinoma"

Yinhan Wang Yongfa Huang Huayu Yang Yilei Mao

Department of Liver Surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing, China

Dear Editor,

We read with great interest the article by Kennedy Yao Yi Ng et al. [1] on the relationship between immune-related adverse events (irAEs) and the efficacy of immune checkpoint inhibitors (ICI) in advanced hepatocellular carcinoma (aHCC). Immunologic checkpoint blockade that targets cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) or programmed cell death protein 1 or its ligand (PD-1/PD-L1) has demonstrated efficacy in a variety of malignancies [2, 3]. ICIs, including nivolumab, pembrolizumab, and atezolizumab, have achieved satisfactory treatment responses when combined with tyrosine kinase or VEGF inhibitor and have therefore been listed as first-line treatment in aHCC [4–7]. Apart from antitumor immune responses, immunotherapy can result in irAEs through nonspecific immunologic activation [2, 8]. While the occurrence of irAEs may suggest immunologic disinhibition, whether irAEs predict and participate in antitumor immune responses remains controversial [8].

Considering the paucity of data about irAEs in aHCC, the paper by Kennedy Yao Yi Ng et al. [1] has made a ground-breaking contribution to the field. This retrospective cohort study included 168 patients with aHCC who received at least one dose of any ICI. The large sample size from a single center ensured the data integrity. It was demonstrated that aging, male gender, better performance status, and hepatitis C were identified as independent risk factors for the incidence of irAEs. Severity and multi-system involvement of irAEs positively correlated with treatment responses and survival, which was further confirmed in landmark analysis.

We are, however, concerned about the grouping method in the statistical analysis. According to the Common Terminology Criteria for Adverse Events v4.03 criteria, grade 3 and above irAEs require hospitalization, among which grade 4 means life-threatening and grade 5 equals death [9]. Since the lethality of grade 4 and 5 might be obscured by the extended survival of grade 3 in the current categorizing strategy, we suggest categorizing irAEs into three classes of grade 1–2, grade 3, and grade 4–5. Patients with irAEs of different severity might be allocated with different management strategies, including symptomatic management, ICI cessation, and steroid [5]. As is shown in the study, systemic steroid usage is associated with improved survival in those with irAEs [1], so we wonder if treatment against irAEs was included in the multivariable regression for survival analysis of the whole aHCC-with-ICI population as well. In addition, gender difference in irAEs has rarely been reported in previous ICI cohorts, but a male predilection was reported in this article, which could be a bias due to the male predominance in aHCC. Since irAEs could be censored by disease progression or death, we suggest competing risk analysis

Karger@karger.com
www.karger.com/lic

Correspondence to:
Huayu Yang, dolphinyahy@hotmail.com
Yilei Mao, yileimao@126.com

instead of standard Cox analysis to identify independent risk factors for irAEs.

Another major concern was if it was proper to evaluate the impact of irAEs on survival under traditional Cox regression. As a kind of time-varying exposure, irAEs have varying severity and involved organ systems and should reflect varying risks on prognosis over time, which compromises the proportional hazards assumption. The wide range of time-to-onset of irAEs also questions the applicability of traditional Cox regression, since the interval between onset of irAEs and disease progression or death must be long enough to establish a statistical causality between irAEs and prognosis. In non-small cell lung cancer, for instance, irAEs mostly occurred far ahead of disease progression or death, and multisystem irAEs were associated with improved survival [10]. However, when time-to-onset of irAEs was comparable to those of disease progression or death as it was in advanced melanoma, no progression-free survival (PFS) benefits were observed for irAEs [11].

Time-dependent Cox regression and landmark analysis are powerful tools to adjust for time-varying independent variables in Cox regression if the landmark time is chosen wisely at the turning point of PFS or overall survival (OS) trending [11]. As Figure 1 suggested, the turning points of PFS and OS trending for the aHCC-with-ICI cohort were at 4 months and at 6 months, respectively. We would like to invite the authors to introduce their reasoning process to select 6 and 12 weeks as landmark time. A recent finding that interleukin-6 blockade reduces irAEs and improves antitumor immunity in the meantime implies the potential dissociation between irAEs and treatment response, making one wonder if irAEs could serve as a time-varying confounder instead of an independent variable in the survival analysis [12]. In order to adjust for time-varying confounders, statisticians have developed multiple general linear models, including marginal structural models and structural nested accelerated failure survival time models, to deal with different circumstances [13]. Further studies should be conducted with appropriate general linear models to reveal the exact independent variables behind irAEs, which are expected to correlate to and predict PFS and OS of aHCC-with-ICI effectively and efficiently.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

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