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COMMENTARY

Strengthening the case that elevated levels of programmed death ligand 1 predict poor prognosis in hepatocellular carcinoma patients

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Abstract: Immunotherapy targeting programmed death receptor 1 and programmed death ligand 1 (PD-L1) has shown impressive antitumor efficacy in several solid cancers, including advanced hepatocellular carcinoma (HCC). Since response rates of various cancers to such immunotherapy appear to correlate with PD-L1 expression levels, several studies have examined whether PD-L1 expression correlates with HCC pathology and patient prognosis. In this paper, we analyzed the strength and limitations of a recent meta-analysis of associations of PD-L1 with HCC characteristics and patient prognosis.

Keywords: hepatocellular carcinoma, programmed death ligand 1, hepatic resection, prognoses

Hepatocellular carcinoma (HCC) is a malignant disease with poor prognosis.[1] Its officially recommended treatment is by sorafenib therapy, which is extremely expensive, often causes adverse events, and prolongs overall survival by only 3 months in patients with advanced disease.[2,3] Immunotherapy targeting programmed death receptor 1 (PD-1) and programmed death ligand 1 (PD-L1) has shown impressive antitumor efficacy in several solid cancers,[4–6] including advanced HCC.[7] Since response rates of various cancers to such immunotherapy appear to correlate with PD-L1 expression levels,[8] several studies have examined whether PD-L1 expression correlates with HCC pathology and patient prognosis. As the results obtained were inconsistent, Gu et al[9] initiated to perform the first meta-analysis that focused on the associations of PD-L1 with HCC characteristics and patient prognosis.[9] They concluded that higher PD-L1 levels predict poor differentiation, vascular invasion, higher levels of α-fetoprotein (AFP), and poorer survival. While these results are clinically useful, they should be interpreted with several limitations in mind.

One of the limitations is that the meta-analysis did not include four studies[10–13] involving 384 patients that satisfied the inclusion criteria of this meta-analysis.[9] In addition, one study[14] included in this meta-analysis was based on PD-L1 assays in serum but not in tumor samples. The patients included in this study received both surgery and palliative therapies, while in other studies,[15–20] patients received only surgery. These issues may increase heterogeneity in the pooled data, undermining the reliability of the results. In addition, it is unclear to us how this meta-analysis was able to report survival hazard ratios for the pooled patient population with tumors of any stage, when most studies in the meta-analysis reported survival separately by tumor stages but not in the population as a whole.

The work of Gu et al[9] suggests that higher PD-L1 levels are associated with poorer clinicopathological characteristics of HCC. To extend this finding, we examined eleven

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Table 1 Summary of studies examining potential associations of PD-L1 expression levels with HCC clinicopathological characteristics and patient prognosis

Study	Country	Sample size	*P*-value										
			Gender	Age	AFP	Hepatitis history	Poor tumor differentiation	Tumor size	Satellite nodules	Vascular invasion	Tumor stage	OS	DFS/RFS
Finkelmeier et al[14]	Germany	215	NR	NR	NR	>0.05	NR	NR	NR	NR	**<0.05**	**<0.05**	NR
Gabrielson et al[15]	USA	65	NR	NR	NR	>0.05	>0.05	NR	NR	>0.05	>0.05	0.353	NR
Gao et al[16]	People's Republic of China	240	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	**<0.05**	>0.05	**<0.05**	**<0.05**
Kan and Dong[17]	People's Republic of China	128	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	NR	**<0.05**	>0.05	**<0.05**	NR
Umemoto et al[18]	Japan	80	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	0.051	0.081
Wu et al[19]	People's Republic of China	71	NR	NR	NR	NR	NR	NR	NR	NR	NR	**<0.05**	NR
Zeng et al[20]	People's Republic of China	141	>0.05	>0.05	>0.05	NR	NR	**<0.05**	>0.05	**<0.05**	**<0.05**	**<0.05**	**<0.05**
Calderaro et al[10]	France	217	>0.05	>0.05	**<0.05**	>0.05	**<0.05**	>0.05	**<0.05**	**<0.05**	NR	NR	**<0.05**
Jung et al[11]	Korea	85	>0.05	>0.05	>0.05	>0.05	>0.05	**<0.05**	NR	>0.05	>0.05	**<0.05**	**<0.05**
Shi et al[12]	People's Republic of China	56	NR	NR	NR	NR	NR	NR	NR	NR	**<0.05**	NR	**<0.05**
Wang et al[13]	People's Republic of China	26	>0.05	>0.05	NR	>0.05	>0.05	NR	NR	NR	**<0.05**	NR	NR

Note: Bold values are statistically significant.
Abbreviations: AFP, α-fetoprotein; DFS, disease-free survival; HCC, hepatocellular carcinoma; OS, overall survival; PD-L1, programmed death ligand 1; RFS, recurrence-free survival; NR, not reported.

studies and found that none of the studies reported gender, age, or hepatitis history to be associated with elevated PD-L1 expression (Table 1). Only one study associated high PD-L1 expression with higher preoperative serum levels of AFP, poor tumor differentiation, and satellite nodules;[10] two studies associated it with tumor size;[11,20] four studies associated it with vascular invasion;[10,16,17,20] and four studies[12–14,20] associated it with tumor stage. One study reported no significant association between high PD-L1 levels and overall survival,[15] while another study reported a nonsignificant trend that higher levels were associated with shorter overall survival.[18]

The results in Table 1 and those reported by Gu et al[9] suggest that elevated PD-L1 levels are associated with several HCC characteristics that are also risk factors for early tumor recurrence. Such recurrence can occur through two mechanisms: true metastasis due to primary HCC dissemination before surgery and multicentric occurrence (de novo) in remnant liver due to continuous viral infection and inflammation.[21] HCC treatments are usually effective against one or the other type of recurrence, but not both. In contrast, targeting PD-L1 may inhibit both types simultaneously, since reducing PD-L1 levels can strengthen T-cell responses to hepatitis virus infection.[22,23]

Despite its limitations, the meta-analysis of Gu et al[9] substantially strengthens the evidence that higher PD-L1 levels are associated with poorer clinicopathological characteristics of HCC and poorer prognosis of patients. Further phase I or phase II clinical trials should be performed to investigate anti-PD-L1 treatment for HCC.

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Disclosure

The authors report no conflicts of interest in this work.

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