Tumor Burden Score: A useful tool to predict immune-related hepatotoxicity during immunotherapy in HCC

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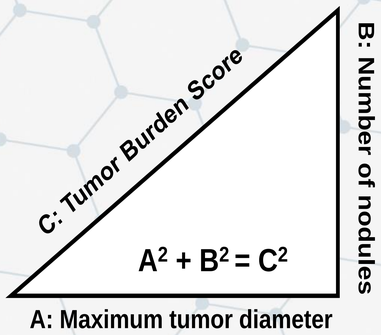
1 Introduction

Treatment with immune checkpoint inhibitors (ICI) is complicated by the development of hepatic immune-related adverse events (HIRAEs) in around 9-20% of cases. While the risk factors for such adverse events are largely unknown, we assessed the role of tumor burden as a determinant for development of HIRAEs.

2 Methods

Our analysis included **36 patients** with HCC treated with a monoclonal antibody (mAb) targeting the programmed cell death receptor-1 or its ligand (PD-1/PD-L1) as single agent (16 patients, 44%) or in combination with a mAb against the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) (20 patients, 56%). The pretreatment **Tumor Burden Score (TBS)** was calculated considering both the **total number of liver nodules (a)** and the **maximum diameter (b)** according to the following formula: $\mathbf{TBS^2 = a^2 + b^2}$. Furthermore, we used a ROC curve to set a TBS threshold which could be used to predict the onset of HIRAEs. HIRAEs were categorized according to CTCAE v. 5.0.

Study Population N=36	
Gender	24 males (67%) 12 females (33%)
Median age (range)	66 years (44-77)
Immunotherapy	16 monotherapy (44%) 20 combo therapy (56%)

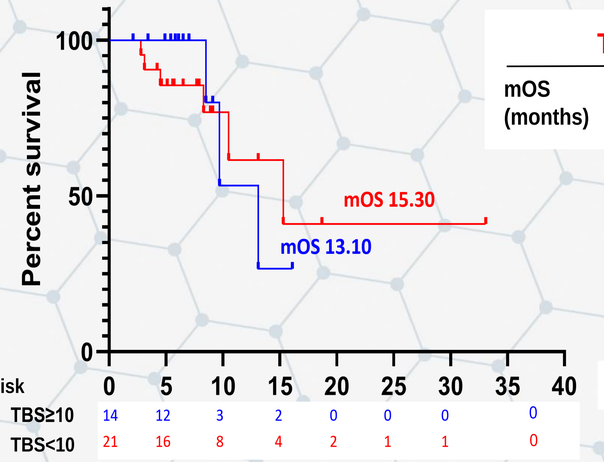


TBS can be used as a measure of the hepatic tumor burden

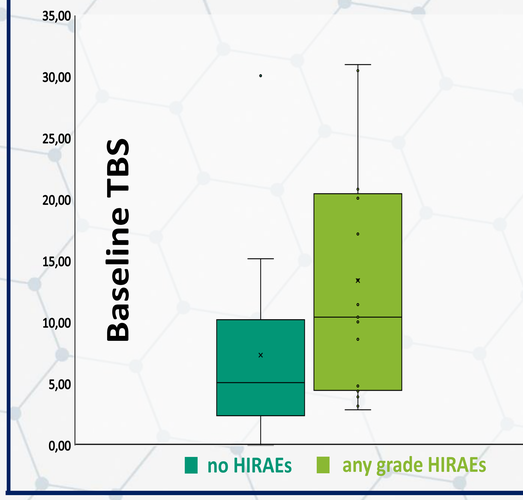
3 Results

18 patients (50%) developed any grade HIRAEs, of whom 5 (18%) developed G3-G4 HIRAEs. No G5 toxicity was registered. No patient permanently discontinued treatment because of HIRAEs. Patients who developed **any grade HIRAEs** had significantly **higher mean values of TBS** compared to patients with no HIRAEs (13.4 [95% CI 8.3 - 18.5] vs 7.3 [95% CI 3.7 - 11.1], p = 0.048). We did not find a significant correlation between the mean baseline TBS value and the development of G3-G4 HIRAEs (12.0 vs 10.1, p=0.70, in patients who developed G3-G4 HIRAEs vs those with a lower grade hepatotoxicity, respectively). From the analysis of the ROC curve, we chose a TBS threshold of 10, with an area under the curve of 0.70 (95% CI 0.52-0.87, p = 0.046). Patients with a **TBS of 10 or more** had a **significantly higher risk of developing any grade HIRAEs** compared to patients with TBS < 10 (Odds ratio = 5 [95% CI 1.1-17.8], p = 0.041). Median overall survival did not significantly differ between patients with TBS<10 and patients with TBS≥10 (7.9 months vs 6.3 months, p = 0.60).

Kaplan-Meier survival curves



	TBS<10	TBS≥10	
mOS (months)	15.30	13.10	p=0.34



	no HIRAEs	any grade HIRAEs	
Mean TBS value	7.3	13.4	p=0.048

***Baseline TBS** differs significantly between patients who develop any grade HIRAEs and those who do not*

4 Conclusion

In HCC patients treated with ICI, **hepatic tumor burden could be a risk factor for the development of any grade HIRAEs**. TBS is a useful tool to measure hepatic tumor burden and it might be used to predict the risk of HIRAEs. The role of TBS in predicting HIRAEs needs to be confirmed and validated in larger cohorts of HCC patients.

5 References

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6 Contact Information

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