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Methodological and conceptual considerations for examining the α-FAtE scoring in unresectable hepatocellular carcinoma

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We read with great interest the study by Rossari *et al* titled 'α-FAtE: a new predictive score of response to atezolizumab plus bevacizumab for unresectable hepatocellular carcinoma'.[1] This study sheds light on the assessment of treatment response in patients with hepatocellular carcinoma (HCC) receiving atezolizumab plus bevacizumab. However, on evaluating the study, we identified several points that warrant further attention.

The α-FAtE scoring system is based on parameters including AFP, ALP, and blood eosinophil count. While AFP levels are associated with liver damage, it is known that AFP is not a specific test for HCC. In a series of 1158 patients with HCC, only 18% had AFP values above 400 ng/mL, while 46% had normal serum AFP levels (below 20 ng/mL).[2] It has been shown that high AFP levels are more indicative of HCC in patients with chronic liver disease who are not infected.[3] Additionally, chronic viral hepatitis can increase blood AFP levels. Many of the patients included in the study have chronic viral infections, such as HBV and HCV, that can elevate AFP levels. Although subgroup analysis differentiated between viral and non-viral etiologies of HCC, we believe that the unknown AFP levels in these subgroups could affect the α-FAtE scoring system and its results.

Another parameter in the scoring system, ALP, is an enzyme primarily sourced from the liver and is an indicator of cholestasis. Serum ALP levels may increase due to malignant and non-malignant reasons. Moreover, elevated ALP levels are expected in conditions like chronic hepatitis and infiltrative HCC. Given that HCC developed on a background of chronic liver disease in the included patients, prognostic scoring based on ALP levels may not yield optimal results.

Eosinophils have become a focal point in oncology with the emergence of immunotherapy. The accumulation of eosinophils in peripheral blood and tumor tissue, defined as tumor-associated tissue eosinophilia, has been reported as a prognostic marker for better clinical outcomes in cancer patients treated with immunotherapies (ICIs).[4] An increase in absolute eosinophil count in the peripheral blood of melanoma patients treated with immunotherapy is indicative of response to ICIs and correlates with significantly prolonged overall survival.[5 6] The study only examined eosinophil counts at the start of treatment; we think that assessing the relationship between eosinophil counts at both the beginning and the end of follow-up in both arms could better elucidate the prognostic value of eosinophil levels. Additionally, changes in the α-FAtE score from the start to the end of treatment could also contribute to the prognostic significance of the scoring system.

Prothrombin induced by vitamin K absence or antagonist (PIVKA)-II is one of the elevated biomarkers in the blood in HCC. Higher blood levels of PIVKA-II have been associated with larger tumor volumes and more advanced disease stages. In metastatic HCC, PIVKA-II levels are increased compared with non-metastatic disease.[7 8] The combination of PIVKA-II and AFP may serve as a potential indicator for anti-PD-1 therapy response in HCC.[9]

Mutations in the DNA mismatch repair (MMR) pathway are associated with increased microsatellite instability (MSI), elevated somatic mutations, and a higher number of tumor-infiltrating lymphocytes. This process leads to the activation of the PD-L1 pathway in the tumor microenvironment, may play a role in the anti-tumor response. Compared

with other tumors, MSI-H or DNA MMR gene deficiency is less common in HCC, occurring in less than 3% of cases.[10] More data are needed to better understand the role of MSI status in the immuno-oncological response in HCC.

PD-L1 expression is controversial in predicting the response to immunotherapy in HCC. Tumor mutational burden (TMB) has been found to be effective in predicting immunotherapy (IO) responses in several malignancies. However, the role of TMB in predicting IO responses in HCC remains unclear. There are conflicting results regarding the predictive role of TMB in IO responses.

In addition to the α-FAtE scoring system, the evaluation of these potential prognostic biomarkers will provide further insight into understanding the immunotherapy response in HCC.

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