BLOOD-BASED EXTRACELLULAR MATRIX BIOMARKERS ARE CORRELATED WITH PROGNOSTIC AND FIBROTIC-RELATED CLINICAL CHARACTERISTICS AND LIVER FUNCTION MARKERS IN PATIENTS WITH ADVANCED HEPATOCELLULAR CARCINOMA

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Background Immune checkpoint inhibitors (ICI) have demonstrated clinical benefit in advanced hepatocellular carcinoma (aHCC). However, many patients do not respond to these therapies indicating a need for novel non-invasive biomarkers to monitor disease progression and predict treatment outcomes. HCC is a highly fibrotic disease with excessive extracellular matrix (ECM) and collagen remodeling and a reactive stroma that can affect T-cell infiltration and influence response to ICI. Fibrotic processes cause ECM remodeling, during which unique collagen fragments, like PRO-C3, are released into the blood and could be used as a non-invasive measure of the tumor fibrotic activity. Here we investigated if circulating ECM fragments are correlated with prognosis, fibrotic characteristics, and liver function in patients with aHCC.

Methods We performed the analysis on 602 patient sera specimens collected before treatment in the CheckMate 040 study (NCT01658878) of patients with advanced HCC. ELISA assays were used to measure ECM fragments related to fibroblast activity and collagen synthesis including pro-peptides of type III, IV, V, VI, XXVIII collagens (PRO-C3, PRO-C4, PRO-C5, PRO-C6, PRO-C28), cross-linked pro-peptide of type III collagen (PRO-C3X), alpha smooth muscle actin (αSMA) and ECM degradation fragments such as MMP-degraded type I, III, IV, V, VI collagens (rC1M, C3M, C4M, C5M, C6M, TUM), granzyme B-degraded type IV collagen (C4GzB), and citrullinated and MMP-degraded vimentin (VICM). ECM fragments were evaluated for their association with each other, liver function markers (Spearman’s correlation, rho) and clinical characteristics (Kruskal-Wallis test).

Results Of the 15 ECM markers assessed, C3M and C4M (rho=0.82), C6M and TUM (rho=0.82), and PRO-C4 and PRO-C5 (rho=0.78) showed the highest correlation. Higher levels of the circulating collagens including PRO-C3 were associated with poor prognostic factors such as macrovascular invasion (p=4.8e-06) and ascites (p=4.1e-04), as well as poor overall survival. Similarly, PRO-C3 was also associated with fibrosis-related characteristics such as Child-Pugh score and class (p=5.4e-10 and p=5e-06 respectively) and OKUDA stage (p=4.3e-08). Circulating collagen fragments were positively correlated with C-reactive protein, alfa-fetoprotein, aspartate aminotransferase and negatively correlated with albumin levels. Collagen levels were distributed differentially based on viral etiology suggesting underlying biological differences in the TME.

Conclusions Quantifying circulating ECM fragments could enable non-invasive profiling of tumor stroma dynamics during the course of aHCC. Tumor stroma may influence response to ICI; therefore, these biomarkers may have prognostic and/or predictive potential. Further analysis is needed to determine the clinical utility of circulating ECM fragments and their impact on treatment outcomes in aHCC.

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