37 COLLAGEN REMODELING BIOMARKERS IN PATIENTS WITH LOCALLY ADVANCED PANCREATIC CANCER TREATED WITH STEREOTACTIC BODY RADIOTHERAPY PLUS INTRADERMAL HEAT-KILLED MYCOBACTERIUM OBUENSE (IMM-101) VACCINATION

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Background Pancreatic ductal adenocarcinoma (PDAC) is one of the deadliest cancers and several clinical trials with new therapies are being conducted in an attempt to increase the survival. In the LAPC-2 trial, patients with non-progressive locally advanced pancreatic cancer (LAPC) after treatment with FOLFIRINOX, were included. In the study, eligble patients were treated with stereotactic body radiotherapy (SBRT) and intradermal heat-killed mycobacterium obuense (IMM-101) vaccination. Treatment with SBRT/IMM-101 was found to induce immune activation in the peripheral blood, that correlated with improved progression-free survival. We explored the predictive value of three circulating collagen biomarkers reflecting tumor fibrosis (PRO-C3), T cell infiltration (C4G), and tumor invasion (C4M) for response during SBRT/IMM-101 in patients with LAPC.

Methods Type III collagen formation (PRO-C3), granzyme B degraded type IV collagen (C4G), and MMP degraded type IV collagen (C4M) were measured at baseline and at five time points during treatment with immunoassays in serum from 36 patients with LAPC who were treated with SBRT and six intradermal vaccinations of IMM-101. In addition, we compared levels of collagen biomarkers to those in of 43 healthy controls.

Results Both PRO-C3 ($p<0.0001$) and C4M ($p=0.0008$) were significantly elevated in patients with LAPC at baseline compared to healthy controls. The median PRO-C3 levels decreased after 3 ($p=0.020$), 4 ($p=0.023$), and 5 ($p=0.002$) doses of IMM-101. In contrast, median C4G increased after one dose of IMM-101 ($p=0.0017$), and the levels stayed high during the treatment, while C4M levels did not change. Interestingly, when evaluating the C4G/C4M ratio, the ratio increased after one dose of IMM-101 ($p=0.022$). The highest increase during treatment was found in patients with partial response compared to patients with stable and progressive disease.

Conclusions In this study, treatment with SBRT in combination with IMM-101 led to decreased levels of the tumor fibrosis biomarker PRO-C3 and increased T cell infiltration biomarker C4G levels. Moreover, the treatment resulted in increased levels of the C4G/C4M ratio in patients with partial response suggesting that this biomarker ratio – high T cell infiltration (C4G) relative to tumor invasion (C4M) – could reflect clinical response. If validated, this suggests that collagen remodeling biomarkers could have a predictive value in pancreatic cancer patients treated with immunomodulatory therapy such as SBRT in combination with IMM-101.

Ethics Approval The study was approved by the Central Committee on Research involving Human Subjects (NL68762.078.19) as defined by the Medical Research Involving Human Subjects Act.

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