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Elevated Cancer Testis Antigen Expression Corresponds to Immune Activation and Improved Survival in Small Bowel Neuroendocrine Tumors

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BACKGROUND

While immune checkpoint inhibition (ICI) has proven highly effective in management of many solid tumors, its effectiveness in small bowel neuroendocrine tumors (SBNET) remains limited. Elucidation of the tumor immune microenvironment may improve understanding of mechanisms of ICI resistance and drivers of response in SBNET, expanding our treatment options as incidence continues to increase. Thus, we performed bulk transcriptional and digital spatial profiling (DSP) to further characterize the SBNET immune microenvironment and its association with overall survival (OS).

METHODS

Clinicopathologic data and preserved tissue blocks of primary tumors were obtained from patients who underwent surgical resection for well-differentiated SBNET between 2003-2016. A Cox proportional hazards model was used for OS and multivariable analyses (MVA). Using the NanoString PanCancer Immune Panel, bulk transcriptional profiling was performed on RNA from the tissue blocks. A tissue microarray was created, and DSP was performed on 245 regions of interest, segmented using PanCK to delineate tumor from stroma.

RESULTS

Transcriptional analysis of 42 resected SBNET yielded dichotomization into high and low cancer testis antigen (CTA) expression during unsupervised clustering of gene expression. Elevated expression of interleukin and antitumoral chemokines and cytokines was demonstrated in CTA^{high} patients (n=12). Significant improvement in median OS was also observed in CTA^{high} patients (HR 0.211, 95%CI 0.059-0.751) and those with increased IL expression (HR 0.153, 95%CI 0.020-1.153). MVA, controlling for age, sex, metastatic disease, and Ki-67%, confirmed independent association of CTA^{high} status with improved OS (HR 0.183, 95%CI 0.041-0.818.

DSP on regions of tumor and adjacent normal small bowel revealed heterogeneous CTA expression between tumor, tumor stroma, normal tissue, and normal stroma, with elevated CTA expression primarily driven by tumor epithelium. Upregulation of genes involved in immune activation (HLA-DQB1, CD27), interferon response (IFNA4, IFIT3), and epigenetic regulation and chromatin remodeling (KDM6A, WDR5) was demonstrated in CTAhigh tumors. Signals for increased immune cells (CD8+ cytotoxic T cells, activated NK cells) were exhibited in CTAhigh tumor regions and their adjacent stroma. T cell receptor (TCR) profiling demonstrated increased TCR diversity in CTAhigh tumor ($p=0.024$) and adjacent stroma ($p=0.022$) regions

CONCLUSIONS

Consistent with previous studies examining other disease sites, elevated CTA expression in resected SBNET is associated with increased anti-tumor immunity and improved overall survival. Augmentation of the peritumoral immune environment in CTAhigh regions suggests a role for CTA expression in modulating tumor response. Targeted pathways to drive CTA expression may represent an opportunity to improve tumor sensitivity and response to immunotherapy in future trials.

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