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Tumor Microenvironment Remodeling Mediates Resistance to 177Lu-DOTATATE in Metastatic Well-Differentiated Neuroendocrine Tumors

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BACKGROUND

Peptide receptor radionuclide therapy (PRRT) with ^{177}Lu-DOTATATE improves progression-free survival in advanced neuroendocrine tumors (NETs), yet responses remain highly variable. The tumor microenvironment (TME) may be a key determinant of PRRT response. We characterized immune changes within the TME to elucidate immunomodulatory effects and identify potential combination strategies.

METHODS

Tumor tissues were obtained from two patient cohorts treated at UChicago Medicine: one undergoing surgical debulking after PRRT, with lesions classified as non-progressing or progressing, and a second undergoing paired pre- and post-PRRT debulking. Samples included small bowel NET (SBNET) and pancreatic NET (PNET) primary tumors and liver metastases (58 lesions, 13 patients). Six-plex multiplex immunofluorescence (CD4, CD8, CD68, FoxP3, PD-L1, CD31) quantified immune features at single-cell resolution. Tumor-intrinsic features (Ki-67, SSTR2, CA9, γH2AX, and CD31) were assessed by immunohistochemistry. Clinical-grade genomic profiling was performed using the OncoPlus next-generation sequencing panel for all patients. Bulk RNA sequencing with immune deconvolution was performed on 23 liver metastases.

RESULTS

Progressing tumors exhibited elevated CD8$^+$ T-cell infiltration compared with non-progressing tumors in post-PRRT lesions (275.8 vs. 101.3 cells/mm^2; p=0.020), with increased PD-L1 positivity on CD68$^+$ macrophages (0.93% vs. 0.18%; p=0.0047) and on other tumor compartments (0.90% vs. 0.10%; p=0.0085). Spatially, macrophages were

closer to $CD8^+$ T cells in progressing tumors (35.0 vs. 100.8 µm; p=0.0045). Progressing tumors had lower SSTR2 expression in post-PRRT lesions (p=0.0068). CD31 IHC cross-validated mIF endothelial density (p=0.001), positively correlated with macrophage infiltration (p=0.0003), and inversely correlated with $CD8^+$ T-cell density (p=0.001). Transcriptomic profiling identified subtype-specific resistance programs: PNETs were enriched for ECM-receptor interaction (FDR=1.9×10^{-4}) and PI3K-Akt signaling (FDR=4.7×10^{-4}), while SBNETs were enriched for epithelial-mesenchymal transition (FDR=7.1×10^{-9}) and TNFα-NFκB signaling (FDR=0.013). Immune deconvolution confirmed enrichment of fibroblasts, plasma cells, neutrophils, and non-classical monocytes with depletion of endothelial and dendritic cell populations. Tumor mutational burden showed no relation to the derived TME metrics, while mutation-detected SBNETs showed higher endothelial density than mutation-negative SBNETs (275.4 vs. 198.0 cells/mm^2; p=0.029).

CONCLUSIONS

PRRT resistance might operate through a two-hit mechanism: $CD8^+$ T cell infiltrates suppressed by PD-L1-mediated checkpoint engagement, compounded by reduced SSTR2 mediated drug delivery. Tumor vascularity independently drives immunosuppressive macrophage recruitment and T cell exclusion across this cohort. These findings support further pre-clinical investigation of PD-1/PD-L1 checkpoint inhibitor and anti-VEGF combinations with PRRT in patients with progressive NETs.

ABSTRACT ID #36556