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Changes in the Tumor Microenvironment of Well-Differentiated Metastatic Neuroendocrine Tumors might mediate resistance in patients treated with 177Lu-DOTATATE

Rahil Ummar Faruk Abbu[1]; Kevin S. Tanager, MD[2]; Campbell Herring[1]; Olga Lakiza[1]; Namrata Setia, MD[2]; Andy Liao, MD[3]; Ralph Weichselbaum, MD[4]; Xavier M. Keutgen, MD[1].

[1]Division of General Surgery and Surgical Oncology, Department of Surgery, University of Chicago, University of Chicago Medicine, Chicago, IL, USA; [2]Department of Pathology, University of Chicago, University of Chicago Medicine, Chicago, IL, USA; [3]Department of Hematology and Oncology, University of Chicago, University of Chicago Medicine, Chicago, IL, USA; [4]Department of Radiation Oncology, University of Chicago, University of Chicago Medicine, Chicago, IL, USA.

BACKGROUND

Peptide receptor radionuclide therapy with ^{177}Lu-DOTATATE (PRRT) improves outcomes in well-differentiated neuroendocrine tumor (NETs). However, heterogeneous responses and relapse suggest that features within the tumor microenvironment (TME) might mediate treatment resistance. We investigated immune- and stromal remodeling pre- and post PRRT across metastatic NET lesions, correlating findings with clinical response and genomic features to identify determinants of PRRT efficacy.

METHODS

We analyzed 34 tumor samples from 12 patients with pancreatic (PNET, n=5) and small bowel NETs (SBNETs, n=7) treated with PRRT that underwent subsequent surgical debulking. Tumor samples included matched pre/post-PRRT tissues from liver metastases categorized as responding, stable, or progressing. Multiplex immunofluorescence profiling enabled TME phenotyping, spatial analysis, and quantification of immune-stromal interactions. Ki-67 proliferation indices and OncoPlus next-generation sequencing were also performed to evaluate somatic mutations and tumor mutational burden (TMB).

RESULTS

Median time between PRRT and surgical debulking was 10.5 months. Four patients had progression in some, 5 patients in all and 3 patients in none of the liver tumors after PRRT and prior to debulking. Across all samples, PRRT increased CD8$^+$ T cell infiltration (20%, $p = 3.9\times10^{+31}$), CD31$^+$ vascular remodeling (18%, $p < 1\times10^{+10}$), and PD-L1 upregulation (5%, $p = 1.3\times10^{+4}$). Spatial analysis confirmed post-PRRT CD8$^+$ proximity to PD-L1$^+$, FoxP3$^+$, and CD31$^+$ cells, indicating immune exclusion.

Progressing PNET liver metastases showed an immune-silent baseline with CD4$^+$ dominance (90%, $p < 1\times10^{+10}$) and minimal CD8$^+$ (5%), CD31$^+$ (2%), and FoxP3$^+$ (0%) cells. In contrast, responding PNET liver metastases exhibited elevated CD8$^+$ (20%), CD31$^+$ (18%), and PD-L1$^+$ (5%) infiltration, while exhausted CD8$^+$PD-L1$^+$ subsets remained unchanged (3%, $p = 0.50$). Stable SBNET liver metastases had elevated

FoxP3$^+$ (16%) and CD68$^+$PD-L1$^+$ (1%) macrophages while progressing SBNETs showed higher CD8$^+$ (56%), PD-L1$^+$ (9%), and CD8$^+$PD-L1$^+$ (2.2%) infiltration. Genomically, PNETs harbored higher Ki-67 indices (~11.33% vs. ~8.9%), a greater number of somatic mutations (average 2.8 vs. 1.5 mutations), and higher TMB (4.54 vs. 3.44 mutations/Mb).

CONCLUSIONS

PRRT induces CD8$^+$ infiltration and angiogenic remodeling but is limited by immunosuppressive features. SBNETs exhibiting cytotoxic infiltration and PD-L1 expression after PRRT may benefit from immune checkpoint blockade. In contrast, PNETs characterized by CD4$^+$ and CD68$^+$ dominance with minimal checkpoint expression may require priming with multikinase inhibitors to remodel the TME prior to checkpoint inhibition to enhance PRRT efficacy.

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