

Immune Checkpoint Markers and Immune Response in Well Differentiated Neuroendocrine Tumors (NET) of the Small Intestine and Pancreas

Annacarolina da Silva¹; Zhirong Qian¹; Sui Zhang¹; Yohei Masugi¹;
Scott Rodig²; Lauren Brais¹; Trevor Dutton¹; Jennifer Chan¹; Stephen Hodi¹;
Shuji Ogino¹; Matthew Kulke¹

¹Dana Farber Cancer Institute; ²Brigham and Women's Hospital

Background: Immune checkpoint (ICP) inhibition has emerged as a promising treatment approach in human malignancies. The potential for neuroendocrine tumors (NET) to respond to ICP inhibitors is unknown, and the immune environment of NET remains relatively unexplored. We aimed to determine the expression profile of PD-1, PD-L1 and PD-L2, in both small intestine neuroendocrine tumors (SINET) and pancreatic neuroendocrine tumors (pNET) and to describe the associated immune response.

Methods: We retrospectively analyzed the clinical and molecular characteristics of 85 well differentiated NET (64 SINET, 21 pNET). We assessed tumor and associated stromal expression of ICP markers using the murine monoclonal antibodies anti-PD-1 (EH33), anti-PD-L1 (9A11) and anti-PD-L2 (9E5). We assessed tumor infiltrating lymphocytes using the T-cell markers CD45RO (UCHL1), CD3 (7.2.38), CD8 (C8/144B) and FOXP3 (206D). We interpreted expression based on published criteria.

Results: Among low grade NET (64 SINET, 21 pNET), tumoral PD-L1 expression was observed in 0/64 (0%) SINET and 2/18 (11%) pNET and tumoral PD-L2 expression in 52/64 (88%) SINET and 19/21(90%) pNET. PD-1-positive stromal lymphocytes were present in 27/60 (45%) SINET and 9/19 (47%) pNET; PD-L1-positive stromal lymphocytes in 33/59 (55%) SINET and 3/18 (17%) pNET, and PD-L2-positive stromal lymphocytes in 52/61(85%) SINET and 19/21 (90%) pNET. T-cell infiltrates, as measured by CD45RO, CD3, CD8 expression, were more abundant in pNET than in SINET. FOXP3+ cells were rare in both. No obvious differences in ICP marker expression or T-cell infiltrates were observed between 5 CDKN1B mutated and 22 wild type SINET.

Conclusion: Expression of the ICP marker PD-L1 is uncommon in pNET and SINET, whereas both tumor types express PD-L2. T-cell immune infiltrates are present in both tumor types, appearing to be more prominent in pNET. CDKN1B mutational status does not appear to influence ICP marker expression or immune response in SINET. Assessment of mutational status of pNET is ongoing.