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Transformation of G1-G2 Neuroendocrine Tumors (NETs) to Neuroendocrine Carcinomas (NECs) Following Peptide Receptor Radionuclide Therapy (PRRT): A Case Series

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BACKGROUND

We observed patients with well-differentiated NETs who received PRRT with ^{177}Lu-dotatate and later developed rapid disease progression with biopsy-proven histologic transformation to NECs, an outcome that has not been previously described. In this series, we characterize the clinicopathologic features and outcomes of patients whose tumors underwent poorly-differentiated transformation.

METHODS

After obtaining IRB approval, we conducted a retrospective review of all patients with metastatic well-differentiated G1-G2 NETs who received at least one cycle of PRRT with ^{177}Lu-dotatate at our center from January 1, 2019 to December 31, 2020. Patient's clinical information was extracted from the electronic medical record and a refined search for "transformation", "high-grade" and "neuroendocrine carcinoma" was performed for each patient chart.

RESULTS

Among 152 patients (primary sites: 82 small bowel, 39 pancreas, 14 lung, 17 other/unknown) the median number of PRRT cycles delivered was 4. Among these, we identified 7 patients whose NETs transformed to NECs following PRRT. All had pancreatic primary site (7/39 [18%]; p=0.0009). Median time from start of PRRT to transformation was 256 days (range 79-432 days). Five patients (71%) received treatment with platinum and etoposide after transformation with partial response as best response. All patients with transformation died from progressive disease with median overall survival (OS) after transformation of 3.3 months (95% CI: 2.1-4.4). Median OS from start of PRRT for patients with transformation was 11.9 months (95% CI: 4.2- 19.5) compared to 31.1 months (95% CI: 26.3-35.9) in patients without transformation (hazard ratio, 8.1, 95% CI: 3.5-18.8; p<0.001). No differences in the incidence of transformation were observed according to gender (p=0.43), race (p=0.78), or original tumor grade [G1 vs G2] (p=0.86). Among those with pancreatic NETs, all transformed cases had primary tumors located in the pancreatic tail (0% vs 32%; p=0.01). All transformed cases had prior chemotherapy with alkylating agent, temozolomide. The number of prior lines of therapy were similar between those without and with transformation (mean, 3.5 vs 3.7; p=0.81). No differences in the incidence of transformation among pancreatic NET patients were observed according to prior everolimus (p=0.91), sunitinib (p=0.55), and streptozocin (p=0.97).

CONCLUSIONS

This single-institution case series describes seven cases of poorly differentiated transformation of metastatic NET following PRRT. All transformation following PRRT occurred among patients with pancreatic tail primary site and had prior therapy with alkylating agent temozolomide. Further investigation is necessary to determine best treatment sequence in this patient population.

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