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Spectrum of therapy-related clonal cytopenias and neoplasms after exposure to Lutetium-177-Dotatate

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BACKGROUND

Peptide receptor radionuclide therapy (PRRT) is a form of targeted systemic radiopharmaceutical therapy that has been approved for treatment of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors. Persistent hematologic dysfunction is a recognized potential long-term toxicity after PRRT, including the development of hematologic malignancies and persistent cytopenias. Therapy-related myeloid neoplasms (t-MN) are a well-recognized entity that arise after exposure to DNA damaging therapy for an unrelated condition and are associated with poor outcomes. Therapy-related acute lymphoblastic leukemia and therapy-related clonal cytopenias (t-CC) have also been recognized as clinically distinct entities.

METHODS

We characterized our institutional experience on the spectrum of therapy-related neoplasms/clonal cytopenias in individuals with neuroendocrine neoplasms (NENs) who have received at least one dose of Lutetium-177-Dotatate. Clinical characteristics and outcomes were retrospectively reviewed. Bone marrow biopsies, cytogenetic studies and somatic mutation profiling were reviewed.

RESULTS

A total of 346 patients received at least one dose of PRRT at Mayo Clinic-Rochester. Of these, 8 patients (2.3%) were noted to have an established diagnosis of a therapy-related neoplasm or clonal cytopenia; 1.4% with a therapy-related myeloid neoplasm. The median age at the time of first PRRT treatment was 61 years (range, 51-69) and 62.5% were male. The type of NENs included 3 (37.5%) small bowel, 2 (25%) pancreatic, 1 (12.5%) gastric, 1 (12.5%) unknown primary, and 1 (12.5%) pheochromocytoma. Four patients (50%) also had exposure to an alkylating agent. Five patients (63%) developed a therapy-related myelodysplastic syndrome, 1 patient (12.5%) developed B-cell acute lymphoblastic leukemia, and 2 patients (25%) developed t-CC. The median latency from first PRRT treatment to development of a therapy-related hematologic malignancy or clonal cytopenia was 18.5 months (range, 8-42); the median latency for t-CC and therapy-related neoplasm was 25.5 and 18 months, respectively. All patients received 4 cycles of PRRT. The median latency from time of first alkylator exposure to development of a therapy-related neoplasm was 68.5 months (range, 6-144).

Cytogenetic analyses revealed recurrent high-grade chromosomal damage in 80% of the patients with a t-MN. Somatic mutations were identified in 6 (85.7%) of 7 assessable patients, with the most commonly mutated gene being BCOR (33%). Four patients (50%) were alive at last follow-up.

CONCLUSIONS

Prospective studies are needed to help better understand and predict patients at risk for developing therapy-related neoplasms after PRRT and factors impacting latency for transformation.

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