Peptide Receptor Radiotherapy Comes of Age

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KEYWORDS

• PRRT • Neuroendocrine tumor • Peptide receptor radionuclide therapy • NETTER-1 • Carcinoid

KEY POINTS

- Radiolabeled somatostatin analogs are an effective treatment for patients with metastatic, progressive, somatostatin receptor–positive neuroendocrine tumors.
- The NETTER-1 study was the first randomized controlled clinical trial to evaluate the efficacy of peptide receptor radionuclide therapy in metastatic midgut neuroendocrine tumors.
- Short-term risks of radiolabeled somatostatin analogs include cytopenias, which tend to be mild and transient.
- There is a roughly 2% risk of treatment-related myelodysplastic syndrome or acute leukemia.

INTRODUCTION

Neuroendocrine tumors (NETs) are biologically and clinically heterogeneous neoplasms that arise from cells of the endocrine and nervous systems and have the ability to produce and secrete various hormones.[1,2] They are often characterized by the overexpression of somatostatin receptors (SSTR) on the cell surface.[3] The majority of NETs arise from the gastroenteropancreatic and bronchopulmonary tracts, with their incidence and prevalence increasing over the past few decades, attributable to increased awareness and improved diagnostic testing.[4] NETs can result in a wide range of symptoms secondary to the hypersecretion of various hormones including serotonin.[4,5] Therapeutic options have expanded in recent years to include somatostatin analogs (SSAs), mammalian target of rapamycin inhibitors, angiogenesis inhibitors, and new cytotoxic drugs. Peptide receptor radionuclide therapies (PRRT), consisting of radiolabeled SSAs, have exhibited promising treatment results over the past 2 decades, allowing for targeted delivery of radionuclides to tumor cells

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with high SSTR expression.[6] PRRT has been studied in numerous early phase, single-arm clinical trials. However, the NETTER-1 trial (A Multicentre, Stratified, Open, Randomized, Comparator-controlled, Parallel-group Phase III Study Comparing Treatment With 177Lu-DOTA0-Tyr3-Octreotate to Octreotide LAR in Patients With Inoperable, Progressive, Somatostatin Receptor Positive Midgut Carcinoid Tumours) was the first randomized, phase III, clinical trial providing high-level evidence of the efficacy of PRRT in advanced NETs.[7] In this article, we discuss the evolution, clinical efficacy, and future of PRRT in NETs.

EVOLUTION OF PEPTIDE RECEPTOR RADIONUCLIDE THERAPIES

The principle of PRRT in NETs involves attachment of an SSA to a radionuclide, thereby allowing delivery of radiation to SSTR-expressing tumors. In general, low- and intermediate-grade tumors express higher levels of SSTRs than high-grade tumors.[8] Radiolabeled SSAs consist of a radionuclide isotope, an SSA, and a chelator that binds and stabilizes the complex. The most common chelators are DOTA (tetraazacyclododecane-tetra-acetic acid) and DTPA (diethylenetriamine penta-acetic acid). The SSAs octreotide or octreotate, which has a slightly stronger affinity to SSTR subtype 2, are the most common carriers.[9]

Throughout the years, various radionuclides have been used in PRRT, including ^{111}indium (^{111}In), ^{90}yttrium (^{90}Y), and ^{177}lutetium (^{177}Lu). ^{111}In emits Auger and conversion electrons with very short tissue penetration of 0.02 to 10 and 200 to 500 μm, respectively. The earliest experiences with PRRT using ^{111}In-DTPA-pentetreotide resulted in symptom palliation in some cases, but disappointing tumor response results.[10,11] The 2 more commonly used isotopes, ^{90}Y and ^{177}Lu, are beta (electron) emitters, with penetration ranges of 12 and 2 mm, respectively, and a substantially superior therapeutic potential. ^{177}Lu is often regarded as the preferred isotope owing to its lower risk of nephrotoxicity.[12] Because ^{177}Lu also emits gamma rays, it can be used for dosimetry and monitoring tumor response during treatment.[13]

PRRT is administered to patients with evidence of SSTR expression on imaging studies, because increased response rates have been documented in patients with higher levels of radiotracer uptake on SSTR scintigraphy.[14] Patients are screened before treatment with baseline SSTR scintigraphy (OctreoScan), or more recently, ^{68}Ga DOTATOC or DOTATATE-PET scans to assess for receptor expression.[14,15] In 1 study, pretreatment ^{68}Ga-DOTATOC-PET/computed tomography predicted tumor response to PRRT with a sensitivity and specificity of 95% and 60%, respectively, using a threshold maximum standardized uptake value of greater than 16.[15]

Locations of tumor and overall tumor burden have an impact on response rates. For example, patients with pancreatic NETs have higher rates of partial radiographic response compared with patients with midgut NETs.[16] Patients with very large tumors and high hepatic tumor burden are, on average, less likely to respond.[17]

^{90}Y-DOTATOC AND ^{177}LU-DOTATATE

Numerous phase I and II trials as well data from institutional registries have been reported evaluating the tolerability and efficacy of ^{90}Y- and ^{177}Lu-radiolabeled SSAs. It is difficult to compare the studies owing to large variations in eligibility criteria, response assessments, and dosimetries. **Tables 1** and **2** provide a summary of outcomes of ^{177}Lu-based and ^{90}Y-based treatment. The range of overall response rates (ORRs) across studies using ^{90}Y-DOTATOC has varied between 4% and 38% and the median progression-free survival (PFS) ranged from 16 to 29 months.[27] Similar studies