Peptide Receptor Radionuclide Therapy in the Treatment of Neuroendocrine Tumors

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KEYWORDS

• Neuroendocrine tumor • Carcinoid • Radionuclide therapy • PRRT • Treatment

KEY POINTS

- Peptide receptor radionuclide therapy (PRRT) is a promising new treatment modality for inoperable or metastasized gastroenteropancreatic neuroendocrine tumors patients.
- Most studies report objective response rates in 15% to 35% of patients.
- Progression-free and overall survival compare favorably with that for somatostatin analogues, chemotherapy, or newer, "targeted" therapies.

INTRODUCTION

In patients with inoperable metastasized gastroenteropancreatic neuroendocrine tumors (GEPNETs), therapeutic options are limited. Treatment with somatostatin analogues decreases hormonal overproduction and can relieve symptoms in patients with GEPNETs.[1,2] Furthermore, more recent studies showed that treatment with somatostatin analogues prolongs progression-free survival (PFS) in patients with well-differentiated (grades 1 and 2) GEPNETs.[3,4]

The majority of GEPNETs express somatostatin receptors, mainly somatostatin receptor subtypes 2 and 5.[5] These can be visualized using radiolabeled somatostatin analogues. The first commercially available diagnostic somatostatin analogue was [^{111}Indium-DTPA^{0}]octreotide (Octreoscan; Mallinckrodt, St Louis, MO).[6] Nowadays, newer PET radiopharmaceuticals are available, such as [^{68}Ga-DOTA-Tyr^{3}]octreotide[7] and [^{68}Ga-DOTA-Tyr^{3}]octreotate.[8] A logical sequel to somatostatin receptor imaging for diagnostic purposes was to use the same receptor-binding concept for treatment (**Fig. 1**).

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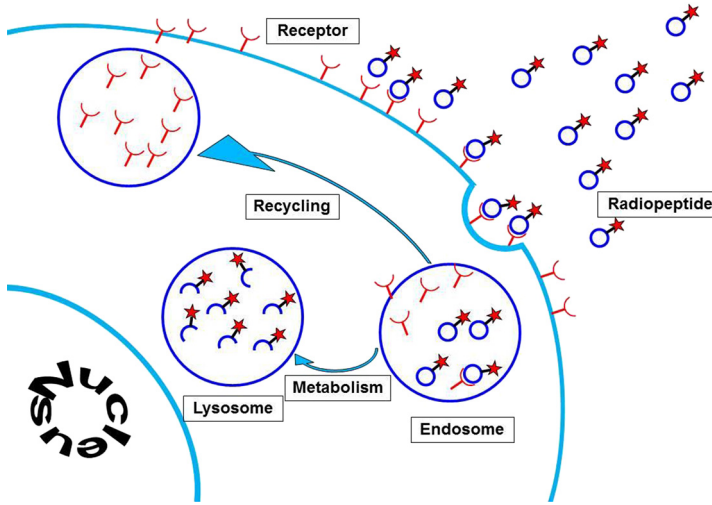

Fig. 1. Mechanism of action of peptide receptor radionuclide therapy. The radiolabeled somatostatin analogues are internalized, and the breakdown products of the radiolabeled peptides are stored in lysosomes, thus enabling a long irradiation of tumor cells.

PEPTIDE RECEPTOR RADIONUCLIDE THERAPY EFFICACY: OBJECTIVE RESPONSE AND SURVIVAL

Because at that time somatostatin analogues labeled with beta-emitting radionuclides were not available for clinical use, early studies in the 1990s used high activities of the Auger electron-emitting [^{111}In-DTPA^{0}]octreotide for peptide receptor radionuclide therapy (PRRT). These treatments often resulted in symptom relief in patients with metastasized GEPNETs, but objective tumor responses were rare (**Table 1**).[9,10]

The next generation of analogues used in PRRT consisted of a modified somatostatin analogue, [Tyr^{3}]octreotide, and a different chelator, DOTA instead of DTPA, which allows stable binding of the β-emitting radionuclide ^{90}yttrium (^{90}Y). Its maximal tissue penetration is 12 mm and its half-life is 2.7 days. [^{90}Y-DOTA^{0},Tyr^{3}]octreotide (^{90}Y-DOTATOC) was used in several phase I and phase II PRRT trials in various countries (see **Table 1**).[11–18] The reported objective responses range from 4% to 33%. Differences in cycle doses and administered cumulative dose, as well as differences in patient characteristics (included tumor types, patient performance status) make it virtually impossible to compare these studies. Different studies report median PFS varying from 17 to 29 months, and median overall survival (OS) from 22 to 37 months (**Table 2**).[15–18] In a report on the treatment effects of ^{90}Y-DOTATOC in a large group of patients, the response to ^{90}Y-DOTATOC was associated with longer survival.[23]

^{177}Lutetium (^{177}Lu) is a medium energy β-emitter, with a maximal tissue penetration of 2 mm. ^{177}Lu also emits low-energy γ-rays, allowing scintigraphy after therapy (**Fig. 2**). The somatostatin analogue [DOTA^{0},Tyr^{3}]octreotate differs from [DOTA^{0},-Tyr^{3}]octreotide only in that the C-terminal threoninol is replaced with threonine, resulting in a higher affinity for the somatostatin receptor subtype 2 than octreotide.[24] The treatment effects of [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate (^{177}Lu-octreotate) therapy were described in a large group of GEPNET patients.[19] Complete remission (CR) was found in 5 (2%) patients, partial remission (PR) in 86 (28%), and minor response in 51 (16%; see **Table 2**). Prognostic factors for predicting tumor remission (CR, PR, or minor