Yttrium-Based Therapy for Neuroendocrine Tumors

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KEYWORDS

• ^{90}Y-DOTATOC • Peptide receptor radionuclide therapy • PRRT • Neuroendocrine tumors • Dosimetry

KEY POINTS

- Peptide receptor radionuclide therapy (PRRT) finds its main indication in the treatment of inoperable or metastasized neuroendocrine tumors, and G1 and G2 tumors are the ideal candidates.
- After 17 years of experience, PRRT with ^{90}Y-peptides are generally well tolerated; in addition, acute side effects are usually mild.
- Objective responses to ^{90}Y-peptides are registered in 10% to 34% of patients, with a significant impact on survival and quality of life.

INTRODUCTION

Peptide receptor radionuclide therapy (PRRT) finds its main indication in the treatment of inoperable or metastasized neuroendocrine tumors (NETs), particularly of the gastroenteropancreatic (GEP) tract. Well/moderately differentiated G1 and G2 tumors are the ideal candidates.[1]

PRRT was introduced in clinical practice in 1994 as the next logical step of the in vivo localization of a metastatic neuroendocrine tumor with the radiolabeled somatostatin analogue [^{111}In-DTPA0-D-Phe1]-octreotide.[2]

Subsequently, many patients have been treated with high-dose [^{111}In-DTPA0-D-Phe1]-octreotide, exploiting the Auger and conversion electrons of ^{111}In. Partial remissions, however, have been observed only exceptionally.[3]

Higher-energy and longer-range emitters, such as the pure beta emitter ^{90}Y, seemed more suitable for therapeutic purposes. The higher energy (maximum 2.2 MeV) and penetration range (R_{95} 5.7 mm) of β particles from ^{90}Y are advantageous, with a direct killing of somatostatin receptor-positive cells and a cross fire effect that hits nearby receptor-negative tumor cells. A new analogue name, Tyr^3-octreotide, with a similar pattern of affinity for somatostatin receptors was developed at the University of Basel for its high hydrophilicity, simple labeling with ^{111}In and ^{90}Y, and tight binding to the bifunctional chelator DOTA (1,4,7,10-tetra-azacyclododecane-N,N′,N″,N‴-tetra-acetic acid).[4,5]

[^{90}Y-DOTA^0,Tyr^3]-octreotide or ^{90}Y-DOTATOC was first administered in patients affected by metastatic neuroendocrine tumors in 1996. The excellent symptomatic and objective response following several cycles of ^{90}Y-DOTATOC therapy led to high expectations regarding the potential of PRRT for other patients with NET tumors.[6]

Other clinical experiences have been carried out with ^{90}Y-lanreotide, a different somatostatin receptor agonist.[7]

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Somatostatin analogues represent, to date, the prototype and the most successful paradigm of radiopeptide therapy because of the fortunate discovery of a successful class of synthetic peptides, such as octreotide and its variants, and to the inhibiting properties of somatostatin and its analogues, which induce few and limited side effects. The success of the clinical application of the octapeptide somatostatin analogues, such as octreotide, and, subsequently, of their radiolabeled counterparts, such as the [^{90}Y-DOTA^{0},Tyr^{3}]-modified form, was caused by their high affinity for somatostatin receptors subtype 2 (sst2) and moderate affinity for subtype 5 (sst5), perfectly tailored to the prevalent expression of sst2 and sst5 in neuroendocrine tumors.

Since 2000, the new analogue DOTATATE ([DOTA^{0},Tyr^{3},Thr^{8}]-octreotide or octreotate), with a 9-fold higher affinity for sst2 as compared with [DOTA^{0},Tyr^{3}]-octreotide, was introduced in clinical use for its easy labeling to the beta- and gamma-emitting radionuclide lutetium-177.[8]

Owing to its efficacy and reasonably acceptable toxicity, since its introduction, PRRT with ^{90}Y-DOTATOC or ^{177}Lu-DOTATATE has been used in several clinical trials over the following years in many centers, mainly in Europe but also in the United States and Australia.

Seventeen years after its first introduction, despite the lack of homogeneity among the studies, PRRT can be regarded as efficient and reasonably safe.

RADIOBIOLOGIC BASIS OF PRRT

From a dosimetric point of view, the efficacy of PRRT relies on a sufficient radioactivity concentration in tumors. This concentration is related to tumor receptor density as well as receptor affinity and pharmacokinetic characteristics of the radiopeptide used.[9] Predictive factors for tumor shrinkage are, in fact, a high uptake at basal somatostatin receptor imaging, with either Octreoscan or positron emission tomography (PET) with Ga-DOTA-peptides, and a small volume of liver metastases.[10,11] The uptake at basal somatostatin receptor imaging represents a rough estimate of the absorbed dose. The dose is, in fact, predictive of the tumor response.[12] Nevertheless, there is no well-defined threshold dose for tumor control but a certain probability over a range of doses.[13] Besides tumor dose, other modulating factors have to be considered, first of all radiosensitivity (which accounts for the individual, genetically based responsiveness to the treatment), repair, redistribution, reoxygenation, and repopulation (the so-called 5 Rs of radiobiology). Additionally, the nonuniformity of uptake (caused by variable receptor density, vascularization, and interstitial pressure) as well as the tumor volume and the number of clonogenic stem cells must be considered. Finally, the type of radionuclide used, its range, cross fire, and energy deposition within tumor lesions must be taken into account.

To understand the biologic basis of tissue damage after irradiation, we have to consider the type of tissue organization. Tissues may show rapid turnover, like bone marrow, mucosae, and most tumors, with a hierarchical organization, whereby stem cells produce precursors that, in turn, produce mature cells. Damage to these cells is typically acute (<90 days) and evident after the lifespan of the mature cell has elapsed. Acute damage may be reversible. Other tissues, like the kidney whose cells mostly die of senescence, show a slow turnover. In this case, damage is typically delayed and irreversible, associated with vascular changes, fibrosis, and atrophy. However, late effects may also occur in rapidly renewing tissues, such as myelo displastic syndrome (MDS) or acute leukemia, which may occur in irradiated patients.[14]

Kidney radiation toxicity is typically evident several months after irradiation because of the slow repair characteristics of renal cell.

PRRT is a form of continuous radiation delivery with a decreasing dose rate over time. The irradiation produces both lethal and sublethal damage that can be repaired during the irradiation itself, but the differential between creating new damage and the repairing depends on the specific dose rate at any particular time and on the repair capability of the tissue. Low-dose rates, as in PRRT, will spare normal tissues more than the tumor; this may allow benefits as in fractionation in external radiotherapy.[15]

The linear quadratic model interprets mathematically this differential sparing, and the biologic effective dose (BED) concept is used to quantify the biologic effects induced by different patterns of radiation delivery. This model has been recently revised for radionuclide therapy and has been applied in particular to PRRT with the intent of increasing the dose-response correlation.[16] Focusing on the kidney concern, the BED has proven to be a reliable predictor of renal toxicity, which is helpful in the implementation of individual treatment planning.[17] In PRRT, the BED has been shown to correlate with renal injury. However, BED is a relatively young concept applied to nuclear medicine and still has to be fully validated with a wider series of data.

The main radiobiological parameter required in such assessment is the tissue α/β ratio, which gives an indication of the sensitivity of a tumor or