Peptide Receptor Radionuclide Therapy using ^{177}Lu octreotate

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Legal aspects
As ^{177}Lu-[DOTA^0-Tyr^3]octreotate (^{177}Lu-Octreotate) is currently not a licensed (radio) pharmaceutical, preparation should meet national regulations.

1. Introduction

In advanced and metastasized neuroendocrine tumours (NET), the use of surgery, external beam radiotherapy and chemotherapy as cytoreductive options is limited. Due to the overexpression of somatostatin receptors, most inoperable or metastasized gastroentero-pancreatic tumours can be treated using non-radioactive somatostatin analogues such as lanreotide and octreotide not only to reduce hormonal overproduction resulting in symptomatic relief, but also to increase time to tumour progression as was demonstrated in a placebo-controlled prospective study in patients with functional midgut neuroendocrine tumours treated with long-acting octreotide. Peptide receptor scintigraphy in humans started with the demonstration of somatostatin receptor-positive tumours in patients using a radioiodinated somatostatin analogue. Later, other radiolabelled somatostatin analogues were developed, and two of these subsequently became commercially available: [^{111}In-DTPA^0]octreotide (Octreoscan) and ^{99m}Tc-depreotide (Neotect).
In the early 1990s, treatment with radiolabelled somatostatin analogues started in patients with NETs. Peptide receptor radionuclide therapy (PRRT) started initially with [^{111}In-DTPA^0]octreotide with promising results such as symptomatic disease control, but partial remissions were rare.
The next generation of PRRT used a modified somatostatin analogue, [DOTA^0-Tyr^3] octreotide, with a higher affinity for the somatostatin receptor subtype-2 (Sstr2) and with a different chelator, in order to ensure more stable binding of the intended β-emitting radionuclide ^{90}Y (^{90}Y-[DOTA^0-Tyr^3]octreotide).
The third generation of PRRT used another modified somatostatin analogue, [DOTA^0,Tyr^3] octreotate, which has three to four times higher tumour uptake compared to [DOTA^0-Tyr^3]octreotide, coupled to the radionuclide ^{177}Lu (^{177}Lu-[DOTA^0-Tyr^3]octreotide). ^{177}Lu is a medium-energy β-emitter with a maximum energy of 0,5 MeV and a maximal tissue penetration of 2 mm. Its half-life is 6,7 days. ^{177}Lu also emits low-energy γ-rays at 208 and 113 keV with 10% and 6% abundance, respectively, which allows scintigraphy and subsequent dosimetry with the same therapeutic compound.

2. Methodology

This guideline is based on available scientific literature on the subject, the previous guideline (Aanbevelingen Nucleaire Geneeskunde 2007), international guidelines from EANM and/or SNMMI if available and applicable to the Dutch situation.

3. Indications

Patients with Sstr2-expressing neuroendocrine tumours of the gastroentero-pancreatic and bronchial tract. Also patients with phaeochromocytoma, paraganglioma, neuroblastoma or medullary thyroid carcinoma which express Sstr2 in sufficient amounts. In general, patients should have one of the following in order to receive PRRT:

a. a progressive tumour assessed by anatomical imaging.
b. non-progressive extensive disease in two or more organs, and progressive disease is likely to be infaust.
c. clinically uncontrollable symptoms using best standard of care.
d. inoperable disease but surgery can be reconsidered after successful PRRT.

4. Relation to other therapies

Therapeutic options for NETs include surgery, SSA, interferon, chemotherapy, molecularly targeted agents, locoregional therapies and PRRT. Surgery with curative intent should be performed whenever feasible. In selected cases, and within a multidisciplinary approach, PRRT may be beneficial as a neoadjuvant therapy to render a patient accessible to surgery, however, most NETs have developed metastases by the time of diagnosis.
As most NET's overexpress somatostatin receptors, medical treatment in the form of somatostatin analogues such as octreotide and lanreotide can be used for symptom relief, as well as for the antiproliferative effect on midgut NETs. Interferon-alpha can also be used to relieve symptoms. Local (chemo-)embolisation and radiofrequency ablation are used to control liver metastases. Symptomatic response rates of 60-95% and biochemical response rates of 50-90% are achieved. A radiological response of 33-80% has been reported. Selective internal radiation therapy (SIRT) has recently been introduced. In a single prospective study in 34 patients the objective response rate was 50%.
Systemic chemotherapy is effective in some patients, especially those with poorly differentiated NETs/neuroendocrine carcinoma or progressive NET of the pancreas. However, in well differentiated midgut NETs the response rates to chemotherapy are low (7-20%). For neuroendocrine carcinoma, chemotherapy usually includes (a combination) of cisplatin, etoposide irinotecan, 5-fluorouracil or capecitabine and oxaliplatin. For pancreatic NETs (a combination of) streptozotocin, 5-fluorouracil and/or doxorubicin can be considered.
Molecular targeted therapies have been introduced recently. The efficacy in pancreatic NETs has been shown for sunitinib and everolimus by a progression free survival of 11,1 vs. 5,5 months and 16,7 vs. 9,7 months respectively, when compared to placebo.

^{111}In-pentetroctreotide was the first PRRT with clinical efficacy. Partial remissions were rare with this agent, and leukaemia and myelodysplastic syndromes were found in patients who received high cumulative doses. Currently, ^{90}Y-[DOTA^{0}-Tyr^{3}]octreotide is used for PRRT next to or in combination with ^{177}Lu-Octreotate. Post-treatment scintigraphy after ^{90}Y-[DOTA^{0}-Tyr^{3}]octreotide is hampered as only Brehmstrahlung can be detected. The direct gamma emission of ^{177}Lu however, provides information on the intensity of uptake and extent of the disease, and can therefore be used to assess the response to the prior therapy cycles.

5. Medical information necessary for planning

Eligibility and clinical decision making should be based on multidisciplinary discussion. As these tumours are relatively rare, treatment in a Centre of Excellence is recommended.
Eligibility criteria:

a. Medical history report from the (referring) physician, containing a summary of all previous treatments (surgery, RFA, chemotherapy, radiotherapy, current medication etc.)
b. NET proven by histopathology (immunohistochemistry)
c. Tumour uptake on the OctreoScan should be at least as high as normal liver uptake, as judged from planar images. Comparable uptake to other somatostatin receptor imaging modalities may apply, but direct correlation is not available. Octreoscan should not be older than 6 months.
d. Adequate anatomical imaging (e.g. CT and/or MRI), not older than 3 months, preferably less than 2 months
e. Life expectancy at least 3-6 months
f. Karnofski Performance Score >50%, or ECOG Performance Score <4
g. Signed informed consent

Contraindications

a. Pregnancy and lactation
b. Renal impairment (i.e. creatinine clearance <50 ml/min, measured in 24 h urine collection)
c. Impaired haematological function, i.e. Hb <5 mmol/l; platelets <75 x 10^9/l; WBC <2 x 10E9/l
d. Severe hepatic impairment, i.e. total bilirubin >3 times upper limit of normal, or albumin <30 g/l with an increased prothrombin time.
e. Severe cardiac impairment

6. Radiopharmaceutical

Tracer:	^{177}Lu-[DOTA^0,Tyr^3]-octreotate
Nuclide:	Lutetium-177
Activity:	7400 MBq per cycle; four cycles with a 6-12 week interval
Administration:	i.v.

7. Radiation safety

Pregnancy is an absolute contraindication
Lactation is a relative contraindication due to the radiation exposure to the child. Breast uptake can be seen on the pre-treatment ^{111}In-octreotide scan, and if present discontinuation is strongly advised. Milk preservation is no option.

8. Patient preparation/essentials for procedure

a. Renal protection: as the kidneys are critical organs, positively charged amino acids, such as L-lysine and/or L-arginine, are co-infused to competitively inhibit the proximal tubular reabsorption of the radiopeptide, thereby reducing the renal retention. A solution of 25 g of lysine and 25 g of arginine in 1 l normal saline is infused over 4 h, starting 30-60 min before PRRT.
b. Adequate anti-emetic medication should be given.
c. Somatostatin analogues should be discontinued prior to PRRT as they might interfere with receptor targeting. Long-acting somatostatin analogue formulations should be stopped 6 weeks before PRRT, and patients should be switched to short-acting formulations up to 1 day before PRRT. Somatostatin analogues should be restarted one day after therapy.
d. Therapeutic interventions should be undertaken to treat functional syndrome effects or exacerbation (e.g. carcinoid syndrome/hypotension, hypoglycaemia, hypergastrinaemia, hypertension, hypotension, WDHA syndrome, electrolyte imbalance).

9. Acquisition and processing

Planar imaging:

Whole body, 1024x256 matrix, 10-20 min scanning, medium energy collimator, 208 (and 113) keV.

SPECT, if indicated:

128x128, 120 views, 3◦/view 30 seconds/view, Medium energy collimator SPECT/CT recommended.

10. Interpretation

a. Evaluation of all post-treatment scans to assess adequate uptake in all known lesions.
b. If lesions do not show any uptake of the radiopharmaceutical, further diagnostic evaluation to exclude a second primary tumour is recommended. In that case, a multidisciplinary meeting should be used to determine which tumour is treated first.
c. More intense uptake and/or more lesions after the first post-treatment scan might be due to radiopharmaceutical characteristics, and not to tumour progression. If this is the case in later post-treatment scans, tumour progression might be the reason, and interim scanning should be considered to evaluate anatomical tumour progression.
d. A decrease in intensity or number of lesions between post-treatment scans of different cycles, might be the result of tumour response.

11. Report

The report should be a summary of:

1. Current health information
2. Physical examination
3. Administered and cumulative activity and exposure levels
4. Current medication
5. Information about the treatment procedure
6. Global information with regards to follow-up and/or post-treatment evaluation

12. Literature

- D. Kwekkeboom, E. Krenning, R. Lebtahi et al. ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumours: Peptide Receptor Radionuclide Therapy with Radiolabeled Somatostatin Analogs. Neuroendocrinology, 2009;90:220-6.
- J. Zaknun, L. Bodei, J. Mueller-Brand et al. The joint IAEA, EANM, and SNMMI practical guidance on peptide receptor radionuclide therapy (PRRNT) in neuroendocrine tumours. Eur J Nucl Med Mol Imaging, 2013;40(5):800-16.