

Peptide receptor radionuclide therapy (PRRT) of neuroendocrine tumors with somatostatin analogues

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Abstract. – **Background:** Clinical experience with the radiolabeled somatostatin analogues ^{90}Y -DOTATOC and, more recently, ^{177}Lu -DOTATATE, is ongoing since more than a decade in few centers.

Dosimetric studies demonstrated that ^{90}Y -DOTATOC and ^{177}Lu -DOTATATE are able to deliver high doses to somatostatin receptor sst2-expressing tumors and low doses to normal organs.

Results and Conclusions: Clinical studies demonstrated that partial and complete objective responses in up to 30% of patients can be obtained, with a great survival benefit in treated patients. Side effects may involve the kidney and the bone marrow and are usually mild. Renal protection is used to minimize the risk of a late decrease of renal function.

Key Words:

PRRT, ^{90}Y -DOTATOC, ^{177}Lu -DOTATATE.

Introduction

Neuroendocrine tumors are quite rare diseases, characterised by the production of amines and hormones. Excluding small cell lung cancer, which can be considered a separate disease, neuroendocrine tumors are mainly represented by tumors of the gastro-entero-pancreatic (GEP) tract. Neuroendocrine tumors usually have a slow growth rate even though aggressive forms exist, and therefore, are diagnosed after they have already spread with metastases. Radical treatment is often difficult to obtain and treatment greatly benefits from a multidisciplinary approach. The best treatment option has to be discussed for each clinical case and might include surgery, interventional radiology, chemotherapy, biotherapy with somatostatin analogues and/or interferon or more recently

with new biotherapy drugs, finally with peptide receptor radionuclide therapy (PRRT) with radiolabeled somatostatin analogues¹.

Neuroendocrine tumors over-express somatostatin receptors, sst₂ in particular, on their cell surface. This constitutes the basis for the therapeutic use of somatostatin analogues. The development of the receptor imaging with ^{111}In -pentetreotide (OctreoScan) allowed the visualization of these tumors², essential diagnosis and put a step forward in the development of a receptor based with radiolabeled analogues.

Theoretical Bases

The aim of the PRRT is to selectively irradiate the tumor cells expressing sst₂ and the surrounding blood vessels, thus also inhibiting the angiogenic response during the treatment³. In the early 90's the first experiences of PRRT were carried out using Auger electron emitters, namely high activities of ^{111}In -pentetreotide, the same radionuclide used for diagnosis. Clinical results were poor, as Auger electron emitters need to be extremely close to the DNA to be effective⁴.

The following logical step was to use emitters, such as ^{90}Y (E_{max} : 2.27 MeV, R_{max} : 11 mm, half-life: 64 h), able to irradiate tissues in an area of few millimetres not only hitting target cells but also the surrounding ones in a "cross-fire" action. A new somatostatin analogue, Tyr³-octreotide, with receptor affinity comparable to the one of original octreotide, was then developed for easy labeling with ^{111}In or ^{90}Y , owing to the tight binding to the macrocyclic chelator DOTA (1,4,7,10-tetra-azacyclododecane-N,N',N'',N'''-tetraacetic acid, ^{90}Y -[DOTA⁰-Tyr³]-octreotide or ^{90}Y -DOTATOC). More recently a new analogue with a higher affinity for sst₂, Tyr³-Thr⁸-octreotide, or octreotate, has been synthesized for labeling with the β and γ emitter ^{177}Lu (E_{max} : 0.49 MeV, R_{max} : 2 mm, half-life: 6.7 days).

Clinical Protocols

Patients eligible for PRRT are those affected by neuroendocrine tumors over-expressing functioning ss_2 receptors. The basis of PRRT, in fact, relies on the internalization of the receptor-radiopeptide complex. A suitable ss_2 expression shown in the diagnostic scans, OctreoScan or ^{68}Ga -octrotide PET/CT, represents the selective criterion to chose patients for treatment. Receptor imaging is the best option to investigate the actual density and functional status of the somatostatin receptors whilst immuno-histochemic findings describe only the scenario *at* the time of the biopsy *in* the site of the biopsy. False positives, such as gall-bladder, accessory spleens, recent surgery or radiation therapy, with the subsequent lymphoid infiltrate mimicking the presence of neuroendocrine disease, must be excluded when analysing a receptor scan (OctreoScan or receptor PET/CT).

On the other hand, false negatives may occur in case of recent chemotherapy or with sub-centimetric disease (although spatial resolution is now increasing with new PET/CT techniques).

PRRT is administered systemically, divided in multiple cycles up to the maximum administrable dose to yield a therapeutic effect, without trespassing the dose-limit of 25-27 Gy to the kidneys, dose-limiting organs^{5,6}. An interval of 6-9 weeks between cycles is needed to reduce the possibility of hematological toxicity. In order to lower the kidney irradiation, patients are also co-infused, before and after therapy with positively charged amino acids, such as lysine and/or arginine, that competitively inhibit the renal tubule reabsorption of the radiopeptide⁷. This protocol may reduce the dose to the kidneys by 9% to 53%⁸. The radiopharmaceutical is slowly administered intravenously over 20 minutes, diluted in saline solution. No allergic reactions or fever have been observed after the infusion⁹. A mild nausea, mainly related to the amino acid infusion, may occur.

Phase I studies assessed that the recommended activity per cycle is about 5 GBq for ^{90}Y -DOTATOC (with cumulative activities of 13-18.5 GBq)¹⁰ and about 5.5-7.4 GBq for ^{177}Lu -DOTATATE (with cumulative activities 22.2-29.6 GBq)¹¹.

Efficacy

It is known that an absorbed dose of at least 70-80 Gy must be delivered to obtain a reduction of the tumor mass. Dosimetric studies have as-

essed that such doses are reached by administering cumulative activities of at least 7.4 GBq of ^{90}Y -DOTATOC or at least 20 GBq of ^{177}Lu -DOTATATE¹². In 10 years of clinical trials, phase I and II studies demonstrated that PRRT is able to yield up to 30% objective responses¹³. The most used radiopharmaceutical is ^{90}Y -DOTATOC; although a comparison between the published studies is virtually impossible, as they are not homogeneous, the registered objective responses range from 10% to 30%.

In a study carried out at Basel University, Switzerland, 39 patients affected by neuroendocrine tumors, mainly GEP, were treated with ^{90}Y -DOTATOC, 7.4 GBq/m² in 4 cycles. A 23% objective response was observed with complete remission in 2 patients, partial response in 7, stability of disease in 27. The best objective response (38%) was obtained in 13 patients affected by pancreatic neuroendocrine tumors. Moreover an impressive reduction of symptoms was obtained in the majority of patients¹⁴.

In another multicentric phase I study held in Rotterdam, Louvain and Tampa Universities, 60 patients with GEP neuroendocrine tumors were enrolled. Patients were treated up to 14.8 GBq/m² in 4 cycles or up to 9.3 GBq/m² as a single shot. At the first evaluation, 8% of patients showed a partial response and 13% a minor response. In a following analysis of 58 patients, treated with cumulative activities from 1.7 to 32.8 GBq, a clinical benefit was observed in 57% of cases (including stability and minor response) and true objective response in 20%. The main finding was about the median overall survival of 36.7 months and the median time to progression of 29 months, greatly longer than those of the historical group¹⁵.

A comparable response rate was described by the European Institute of Oncology (IEO) in Milan, Italy, throughout a retrospective analysis on 141 patients treated in phase I and II studies. Patients were affected mainly by GEP neuroendocrine tumors, 80% progressing at baseline and were treated with cumulative activities from 7.4 to 26.4 GBq. Objective response rate was 26% (including partial and complete responses). Moreover, stable patients at baseline showed a better response (32% partial and complete objective response) than those progressing at baseline¹⁶.

The newer radiopeptide ^{177}Lu -DOTATATE, with a greater ss_2 affinity and the possibility of imaging and dosimetry at the same time^{17,18}, was experimented at the University in Rotterdam,

Netherlands. One hundred and thirty-one GEP neuroendocrine patients were enrolled in the study and treated with cumulative activities of 22.2-29.6 GBq. Complete remission was obtained in 2%, partial in 26% and stability in 54% (including 19% minor response). Better response was observed when a higher OctreoScan uptake was present in the basal imaging, or when the metastatic load to the liver was limited. Progression of disease was more common in patients with an extensive disease or in compromised general clinical conditions. The median overall survival was 36 months, a fairly better result than the one of chemotherapy¹¹. Moreover, ¹⁷⁷Lu-DOTATATE showed a significant improvement of the quality of life, with a reduction of clinical symptoms in both responding and non responding patients¹⁹. In addition, ¹⁷⁷Lu-DOTATATE demonstrated an overall survival from start of treatment of 46 months, (128 months from diagnosis). Compared with historical controls, there was a survival benefit of 40 to 72 months from diagnosis²⁰. A phase I-II study has recently been completed at IEO Milan, and the evaluation of safety and efficacy of ¹⁷⁷Lu-DOTATATE is ongoing. In Figure 1 an example of objective response is reported.

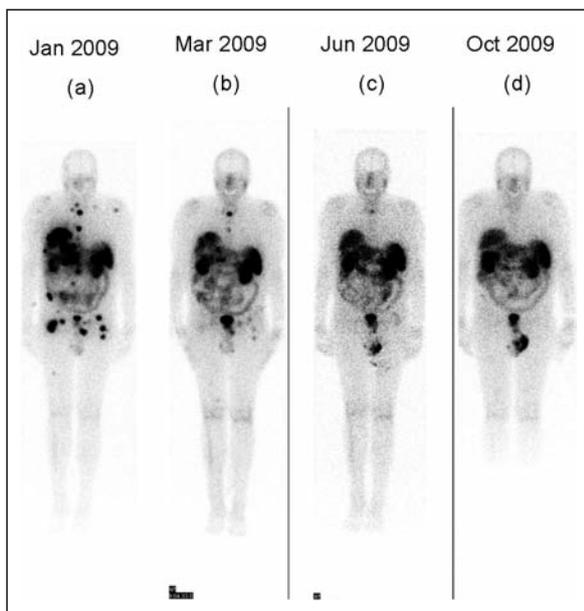


Figure 1. Objective response in a patient affected by neuroendocrine pancreatic carcinoma with multiple liver metastases, abdominal lymph nodes, bone metastases and peritoneal carcinosis, treated with 4 cycles (a-d) of PRRT (Tot. 13.05 GBq). Patient also suffers of carcinoid syndrome. Comorbidity: hypertension, low platelet count.

Toxicity

Dosimetric studies established that it is possible to deliver high adsorbed doses to the tumor with a relative sparing of normal organs such as bone marrow and the kidney.

If the administered activity is below the MTD (maximum tolerated dose, namely activity) per cycle, severe hematologic toxicity is a rare event, while, more frequently, toxicity is a mild and transient event^{10,13}. Kidneys are the dose limiting organs in PRRT, being the maximum tolerated dose about 25-27 Gy. Renal toxicity originates from the proximal tubular reabsorption and interstitial retention of the radiopeptide, resulting in local irradiation. The administration of positively charged amino acids, such as lysine or arginine, which competitively inhibit this phenomenon, is a strategy that proved to reduce renal dose by 9% to 53%¹⁶. However, a loss of kidney function may occur months after the end of the treatments. Even if kidney toxicity does not appear, a decline of creatinine clearance is observed in patients treated with ⁹⁰Y-DOTATOC (with a median decline of 7.3% per year) and ¹⁷⁷Lu-DOTATATE (with a median decline of 3.8% per year). End-stage renal failure requiring dialysis is a particularly untoward event reported in literature in few cases of high dose treatments without kidney protection^{13,21}. Severe renal toxicity is more common in patients with risk factors such as long history of diabetes or hypertension. In these patients the bio-effective dose threshold (a more accurate parameter than the simple adsorbed dose) falls to 28 Gy, whilst it is around 40 Gy for patients with no risk factors. A clinical screening and a dosimetric evaluation of these patients is therefore essential^{22,23}.

Cases of severe hematological toxicity (WHO grade 3 or 4) are quite uncommon and represent not more than 13% of patients treated with ⁹⁰Y-DOTATOC and 2-3% with ¹⁷⁷Lu-DOTATATE¹³. In “dose finding” phase I studies, the maximum tolerated activity per cycle is lower than 2.59 GBq when using ⁹⁰Y-DOTATOC without renal protection. While it rises up to 5.18 GBq when protection is administered^{10,24}.

Treatment with ¹⁷⁷Lu-DOTATATE has shown to be more tolerable, compared to ⁹⁰Y-DOTATOC, but the safety and efficacy are still under observation in a specific phase I-II study carried out at IEO in Milan²⁵.

Finally, it is important to remember that neuroendocrine tumors may cause endocrine syndromes related to hormonal hyper-secretion that

can be exacerbated shortly after the treatment, mainly due to acute cell rupture. Therefore, syndromes such as hypoglycemia, carcinoid syndrome, Zollinger-Ellison must be recognized and suitably treated²⁶.

Conclusions and Future Perspectives

PRRT with ⁹⁰Y-DOTATOC or ¹⁷⁷Lu-DOTATATE proved to be effective, with up to 30% objective responses. PRRT demonstrated to be relatively safe for renal doses below 25-27 Gy, with an acceptable toxicity, both renal and hematological, if an adequate protection is performed. Moreover, PRRT showed an important impact on patient's survival.

External-beam radiotherapy has limited applications in neuroendocrine tumors, such as the palliative treatment of bone metastases.

However, phase II studies are needed to establish the effectiveness of PRRT in the various tumor subtypes. In addition, randomized studies comparing ⁹⁰Y-DOTATOC and ¹⁷⁷Lu-DOTATATE, could precisely assess the possible differences in safety and efficacy.

Nowadays, following the recent tendencies in oncology, PRRT can be considered with chemotherapy agents, such as the radio-sensitizer capecitabine, in order to increase the anti-tumor effect²⁷.

Finally the expression of different classes of receptors, such as gastrin, bombesin or substance P, constitutes the basis for new therapy applications with proper radiopeptides, in a multi-receptor targeting that could be possibly extended to cover other non neuroendocrine tumors²⁸.

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