Peptide receptor radionuclide therapy of neuroendocrine tumors: Case series

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SUMMARY

Background: *Peptide Receptor Radionuclide Therapy (PRRT) is novel and efficacious treatment of neuroendocrine tumors (NETs).*

Methods: *Twenty-seven patients (14 females, 13 males, mean age 54.37±11.14 years; range 30-74 years) with progressive, metastatic neuroendocrine tumors, were treated at least once during the period of 31 months (from July the 6th 2009 to February the 6th 2012) with PRRT in Nuclear Medicine Center, Clinical Center Kragujevac. There were carcinoids in 8 cases (6pts had intestinal and 2pts had lung carcinoid), medullary thyroid carcinoma in 5 cases, pancreatic carcinoma in 3 cases, paraganlioma in 2 cases, pheochromocytoma in 2 cases and in 7 cases primary tumors were not detected. We used 56 doses of different kinds of radiopharmaceuticals: 32 doses of 90Y-DOTATOC, 12 doses of 177Lu-DOTATATE, and 12 doses combining the 90Y-DODTATOC and 177Lu-DOTATATE. The PRRT was given in cycles: 12 pts received one cycle, 9 pts two cycles, 4 pts three cycles, 1 patient 4cycles and 2 pts five cycles of PRRT. The radioactivity was 3.2-7.40 GBq per cycle, and intervals between cycles ranged from 6 to 8 weeks.*

Results: *The response to PRRT was assessed by morphological imaging (MSCT and MRI) as well as by tumor marker follow up (CgA, 5-HIAA, catecholamines, CT and CEA). Seven pts (25.9%) had partial response (PR), 17 pts (63.0%) had stable disease (SD), and 3 pts (11.1%) had progressive disease (PD). None of our patients had complete response (CR). All patients received PRRT under renal protection with amino acid infusions. In spite of this precaution, two patients with previously diagnosed diabetes mellitus suffered from serious deterioration of renal function after PRRT.*

Conclusion: *The efficacy and safety of PRRT observed in our case series was in accordance with previously published data.*

Key words: *Neuroendocrine Tumors; Receptors, Peptide; Radioisotopes; Radiopharmaceuticals; Treatment Outcome*

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INTRODUCTION

Neuroendocrine tumors (NETs) are rare neoplasm, originating from dispersed neuroendocrine cells. These cells are able to synthesize, accumulate and secrete numerous bio-active molecules acting like neurohormones, neurotransmitters and neuromodulators (1, 2). Clinical features of NETs are diverse and complex, making correct and timely diagnosis difficult (3, 4). The NETs could emerge anywhere in human organism, but the most frequent site is gastrointestinal tract (4, 5).

Treatment of NETs is complex and multidisciplinary, requiring individual approach according to tumor type, symptoms and disease severity (6, 7). It is necessary sometimes to administer several treatment methods, simultaneously or sequentially (8-10).

Surgical treatment of NETs is primary therapeutic option, if surgical removal is possible (11-13). Methods of interventional radiology are also used, as well as radiofrequency ablation or high-energy focused ultrasound ablation of primary or metastatic tumors (14,15). Drug treatment is based on somatostatin analogues, interferons and chemotherapy (16-24). Due to high expression of somatostatin receptors in NETs, especially of subtypes 2 and 5 (sst2 and sst5) (25,26), the method of Peptide Receptor Radionuclide Therapy (PRRT) with radioactive somatostatin analogues was developed recently. The first attempts to administer PRRT were made in 1990s and during the first part of 2000s, with high doses of ^{111}In-octreotide (27-29). Later on, the other somatostatin analogues were introduced, like DOTA-TOC, DOTA-TATE, DOTA-NOC and DOTABOC-ATE, with different kinetics and distribution, due to differences in affinity for certain subtypes of sst receptors (30-36). Nowadays, the somatostatin analogues are mostly traced with strong beta or beta/gamma emitters, like ^{90}Y and ^{177}Lu. The beta particles kill tumor cells with sst receptors on them, for which radioactive somatostatin analogues were bound.

The radio-traced somatostatin analogues have significant adverse effects, especially nephrotoxicity. These drugs are re-absorbed in proximal tubules, and then retained for long time in renal interstitium (37-39). In order to prevent re-absorption of PRRT drugs, positively charged aminoacids (like L-Lysine and L-Arginine) which concur for drug transporters are administered simultaneously (40, 41).

The aim of our study was to summarize results of PRRT treatment of 27 patients with NETs in Nuclear Medicine Center, Clinical Center Kragujevac.

PATIENTS AND METHODS

Twenty-seven patients (14 females, 13 males, mean age 54.37±11.14 years; range 30-74 years) with progressive, metastatic neuroendocrine tumors, were treated at least once during the period of 31 months (from July the 6th 2009 to February the 6th 2012) with PRRT in Center of Nuclear Medicine, Clinical Center Kragujevac. There were carcinoids in 8 cases (6pts had intestinal and 2pts had lung carcinoid), medullary thyroid carcinoma in 5 cases, pancreatic carcinoma in 3 cases, paraganlioma in 2 cases, pheochromocytoma in 2 cases and in 7 cases primary tumors were not detected (Table 1). We used 56 doses of differ-

ent kinds of radiopharmaceuticals: 32 doses of 90Y-DOTATOC, 12 doses of 177Lu-DOTATATE, and 12 doses combining the 90Y-DODTATOC and 177Lu-DOTATATE (Tables 2 and 3). The PRRT was given in cycles: 12 pts received one cycle, 9 pts two cycles, 4 pts three cycles, 1 patient 4 cycles and 2 pts five cycles of PRRT. The radioactivity was 3.2-7.40 GBq per cycle, and intervals between cycles ranged from 6 to 8 weeks. The patiend were selected for PRRT in accordance with recommendations of the European Neuroendocrine Tumor Society (ENETS) (42). The patients were previously evaluated by the whole body and targeted scintigraphy with 99mTc-Tektrotyd, in order to document expression of the sst receptors in the tumor tissue. The PRRT treatment was administered only to the patients with grade III or IV intensity of radio-tracer accumulation.

Table 1. Types of tumors and number of patients

TUMOR TYPE	patients No
Carcinoid	8*
Medullary thyroid carcinoma	5
Pancreatic carcinoma	3
Paraganglioma	2
Pheochromocytoma	2
Primary tumors were not detected	7
* (intestinal 6 pts, lung 2 pts)	Σ=27

Table 2. Number of cycles of PRRT and number of the patients

No of PRRT cycles	patients No
1	12
2	9
3	4
4	1
5	2
	Σ=27 pts, Σ=56 doses

Table 3. Types of radiopharmaceuticals and number of doses used in our patients

Radiopharmaceuticals for PRRT	No of doses
^{90}Y-DOTATOC	32
^{177}Lu-DOTATATE	12
^{90}Y-DOTATOC/^{177}Lu-DOTATATE	12
	Σ=56 doses

Renal protection

In order to decrease nephrotoxicity of radio-traced somatostatin analogues, slow intravenous infusion of 15% Aminosol (1000 ml of this solution contain 11g L-Lysine and 20 g L-Arginine) was given to each patient, for 60 minutes before somatostatin analogues, for 30 minutes during somatostatin analogues administration, and for 180 minutes after the PRRT.

Contamination and radiation protection

The PRRT was administered by personnel specially educated and trained in regard to radiation protection and prevention of radioactive contamination. The patients were placed in a room specially designed for radionuclide therapy, with lead plates in the walls, special registration instruments and necessary medical and other equipment (survey meter, monitor of vital functions, continuous video surveillance,telephone and Internet access).

The PRRT was administered by slow intravenous infusion, using an infusion pump. Radio-traced somatostatin analogue was injected by a protected syringe to an infusion bottle with 250 ml of physiological saline, placed on a stalk with lead and plexiglas protection (Figure 1). Used bottles, infusion sets and other contaminated materials were kept locked until radioactivity decreased below permitted levels, and thereafter were disposed as medical waste.

Figure 1. The shield used for PRRT application (Lead & Plexyglas)

Post PRRT follow up

Three days after each administration of the PRRT full blood count was made for each patient, and 6 to 8 weeks later, glomerular filtration rate, serum creatinin concentration and clearance of creatinin were measured. Six to eight weeks after each PRRT cycle the patients were scanned by MSCT and MRI, and serum levels of relevant tumor markers were determined (CgA, 5-HIAA, catecholamines, CT and CEA), depending of tumor thype.

RESULTS

Response to the therapy

The assessment of response to PRRT was made by morphological and morphofunctional imaging (MSCT and MRI) as well as by serum levels of tumor markers (CgA, 5-HIAA, catecholamines, CT and CEA), 6-8 weeks following each cycle. The treatment responses of our patients are shown in Table 4, according to the RECIST criteria (Response Evaluation Criteria In Solid Tumors) (43).

Table 4. Responses to the PRRT in our patients

Therapeutic response (RECIST criteria)	No of patients
CR	0 (0%)
PR	7 (25.9%)
SD	17 (63.0%)
PD	3 (11.1%)

None of our patients (0%) had complete response (CR). Partial response (PR) was observed in 7 patients (25.9%), further 17 patients (63.0%) achieved state of stable disease (SD), and in 3 patients (11.1%) the disease progressed (PD) even after administration of the PRRT. Example of stable disease (SD) as response to PRRT is shown in Figure 2.

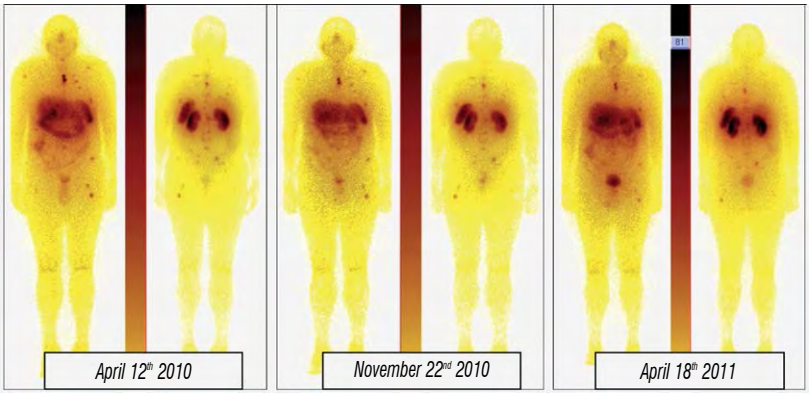

Figure 2. Stable disease (SD) as response to PRRT

Dg: Carcinoid tumor pulmonis atipicum metastaticum in lgl et hepate

- July 3rd 2009 3.70 GBq 90Y-DOTATOC
- September 11th 2009 3.40 GBq 90Y-DOTATOC
- April 9th 2010 5.55 GBq 177Lu-DOTATATE
- November 19th 2010 5.55 GBq 177Lu-DOTATATE
- April 15th 2011 3.40 GBq 90Y-DOTATOC&3.70GBq 177Lu-DOTATATE

During administration of renoprotective aminoacid solution, in 5 cases out of 56 (i.e. in 8.9% of administration attempts) the patients experienced transitory nausea and light anxiety, not requiring treatment. Apart from this, there were no other adverse skin or gastrointestinal reactions to the PRRT. In almost all patients we observed transitory lymphopenia and thrombocytopenia grade 1 or 2, but counts of lymphocytes and platelets became normal after a few weeks unequivocally.

Nephrotoxicity

In spite of receiving the PRRT with renoprotective aminoacids, two patients with previously diagnosed diabetes mellitus experienced decrease of renal function. Their glomerular filtration rate decreased for more than 30%, and their serum creatinin was raised for more than 25%.

DISCUSSION

The radiopharmaceuticals were chosen for PRRT according to physical characteristics of radionuclides ^{90}Y and ^{177}Lu, which are incorporated in somatostatin analogues DOTATOC and DOTATATE. In general, administration of ^{177}Lu-DOTATATE is better option in smaller tumors (up to 2 cm in diameter), due to lower energy and shorter range of its beta corpuscles. The ^{177}Lu-DOTATATE has additional benefit of scintigraphic visualization by gamma camera, because the ^{177}Lu apart from beta corpuscles with energy of 0.497MeV emits also gamma quants with energy suitable for recording at gamma camera (210keV). On the other hand, due to higher energy (2.25MeV) and longer range of beta corpuscles from ^{90}Y, treatment with ^{90}Y-DOTATOC should be used in larger tumors. Regardless of pure beta emitting properties of ^{90}Y, the distribution of this radiopharmaceutical could be recorded by gamma camera using bremsstalhug radiation from ^{90}Y, although such pictures are of lower quality. In patients with both smaller and larger tumors combination of ^{90}Y-DOTATOC and ^{177}Lu-DOTATATE is recommended (44). Since nephrotoxicity of ^{177}Lu-DOTATATE is significantly lower than that of ^{90}Y-DOTATOC (45), it is important to make good balance between maximal efficacy and acceptable safety when choosing and dosing radiopharmaceuticals for PRRT.

In accordance with the abovementioned facts and experiences of the others (44, 46, 47) we made our choices of radiopharmaceuticals for PRRT in our patients (^{90}Y-DOTATOC; ^{177}Lu-DOTATATE or combination ^{90}Y-DOTATOC/^{177}Lu-DOTATATE).

We have used activity of 3.2 to 7.40 GBq per administration, according to the recommendations and experiences of the others (45, 48, 49), because such doses of ^{177}Lu-DOTATATE and ^{90}Y-DOTATOC for treatment of NETs were not followed by serious adverse effects. However, some authors used much lower radioactivities of these preparations per cycle (50, 51). The doses were calculated according to number and size of the tumors, and according to body mass and age, which is satisfactory, but less exact method than dose calculation according to the body surface area (52, 53).

There is no clear recommendation about the PRRT dose fractioning. It remains obscure whether series of lower radioactivity with shorter intervals are better than series of higher radioactivity with longer intervals. The intervals should compromise between therapeutic efficacy and nephrotoxicity of radiopharmaceuticals. We used intervals of 2-3 months between the PRRT sessions, while the others used shorter intervals, 4-6 weeks (50, 53, 54) or 6-9 weeks (4). Longer intervals in our patient series were mostly consequence of problems with the radiopharmaceuticals supply. It was possible to get ^{90}Y-DOTATOC only once per week, and ^{177}Lu-DOTATATE once or twice per month. Besides, there are only two beds available for such patients in our Centre. Finally, some patients had to wait for radiopharmaceuticals because they had received previously non-traced somatostatin or interferon.

Incomplete response to the treatment in our patients could be explained by the fact that majority of our patients received only one or two cycles of the PRRT. Seven patients (25.9%) had partial response (PR), 17 patients (63.0%) had stable disease (SD), and 3 patients (11.1%) had progressive disease (PD). Our results are similar to results of other studies, but total clinical benefit (CR+PR+SD) in our patients was somewhat larger (88.9%) (46, 47, 50, 55-60). These differences were probably caused by small number of patients, by different kinds of radiopharmaceuticals and different doses, as well as by different type and grade of tumors.

In order to prevent re-absorption of the PRRT drugs and their retention in kidney interstitium, positively charged aminoacids (like L-Lysine and

L-Arginine) which concur for drug transporters and decrease irradiation of the kidneys for 9-53% (without decrease of uptake by tumor cells) are administered simultaneously (40, 61, 62). Although pure solutions of L-lysine and L-arginine have larger renoprotective effect, due to restrictions in supply we used available preparation of mixed aminoacids Aminosol 15% (Hemofarm AD, Serbia), containing 11g of L-Lysine and 20 g of L-Arginine per liter. Some studies showed that for successful renoprotection it was more important to prolong duration of aminoacids infusion than to administer certain dose (37, 63, 64). Knowing these facts, we decided to give infusion of aminoacids during the period of 4.5 hours, ie. for 60 minutes before, 30 minutes during and 180 minutes after the PRRT. In some studies duration of infusion was similar (37, 63), but there were some authors who prolonged the aminoacids infusion up to 10 hours and even 2 days after the PRRT (65, 66).

In 8.9% of all administrations of the PRRT with aminoacids our patients experienced temporary nausea and light anxiety, not requiring treatment. The other authors had observed such adverse reactions more frequently, e.g. Bodei and associates (63) registered such reactions to L-lysine and L-arginine in 10% to 69% of cases, depending on the total administered dose.

Blood toxicity of radiopharmaceuticals usually follows the PRRT closely, but it is mostly mild and transient. Bodei and associates (47) had found blood toxicity of grade III or IV in only 13% of patients treated by the ^{90}Y-DOTATOC, and in only 2-3% treated by the ^{177}Lu-DOTATATE. Our patients experienced only mild, transient lymphopenia and thrombocytopenia (grades 1 and 2), without serious consequences.

Since renal function damage after the PRRT is consequence of a long-term process which becomes manifested only after a few months, it is early to make definitive conclusions about renal safety in our patients. The recommended period for follow-up is 6 to 50 months after administration of the PRRT (67-69). During our 31-month follow-up period we have discovered serious renal function deterioration (decrease of GFR for more than 30% and increase in serum creatinin for more than 25%) after 2 months in two patients with NETs and diabetes mellitus. Diabetic nephropathy is an important risk factor for development of renal damage after the PRRT, as shown by Sabet, Bodei, Valkema and Cassady in their studies (39, 51, 63, 68). The others among our patients did not have any kidney problem during the first 31 month after the PRRT.

According to our results with the PRRT therapy of NETs, we could conclude that such therapeutic modality is effective and relatively safe.

Conflict of interest

We declare no conflicts of interest.

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