Repeated cycles of peptide receptor radionuclide therapy (PRRT) – Results and side-effects of the radioisotope $^{90}$Y-DOTA TATE, $^{177}$Lu-DOTA TATE or $^{90}$Y/$^{177}$Lu-DOTA TATE therapy in patients with disseminated NET

**Purpose:** PRRT is a known tool in the management of patients with disseminated and inoperable NETs. The aim of study was to assess the effectiveness of the repeated cycles of PRRT in patients with disseminated and inoperable NETs.

**Material and methods:** Eighty nine patients were included in the PRRT. Among them 16 patients (18%) were qualified for a repeated PRRT cycle due to progression of the disease. In one of the patients qualified for the repeated cycle, PRRT was used as neoadjuvant therapy. The results and side-effects of the repeated cycles of PRRT were analyzed.

**Results:** Disease stabilization was observed in 10 patients 6 months after the repeated PRRT cycle and in 5 patients after 12 and 18 months. Ten of the patients who had received repeated PRRT cycles died. In the case of neoadjuvant therapy, further reduction of the tumor size was observed, enabling qualification for surgery. Clinically significant reduction in the mean values of morphological parameters was not observed. Only after 12 and 18 months the mean values of creatinine levels were higher than the normal range (only in 2 patients).

**Conclusions:** The repeated cycles of PRRT did not cause a clinically significant increase of the toxicity of PRRT. The changes in kidney and blood morphology parameters were transient. The repeated cycles of PRRT enabled stabilization of the disease.

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Overexpression of the somatostatin receptors in neuroendocrine tumors has become the molecular basis for the use of somatostatin analogues in diagnosis and therapy of these neoplasms. In recent years, peptide receptor radionuclide therapy (PRRT) with labeled somatostatin analogues, with high affinity to somatostatin receptor subtype 2 (sstr2), has been applied in disseminated and inoperable neuroendocrine tumors (NETs). Somatostatin receptor scintigraphy (SRS) is the standard procedure for staging the patients, qualifying for the PRRT and assessment of treatment efficacy [1]. Development of molecular imaging techniques such as positron emission tomography (PET), single photon emission computer tomography (SPECT), and adoption of hybrid PET/CT modalities with use of newer generation somatostatin analogues improves diagnostics of neuroendocrine tumors [2]. PET-based SRS has shown high sensitivities, specificities, and accuracies in the evaluation of NETs – enables detection of more lesions and is superior in detecting smaller lesions [2]. The use of F18-fluorodeoxyglucose PET in case of neuroendocrine tumors is currently controversial, but there is emerging evidence that the presence of increased glucose metabolism in tumors indicates an increased potency for invasion and metastasis, and overall poorer prognosis [2].

Another therapeutic option in NET, especially in the cases of the neoplasms without somatostatin receptor expression or in high malignancy tumors, is chemotherapy. The combination of streptozotocin and 5-fluorouracil or doxorubicin has been the gold standard for treatment of different types of endocrine pancreatic tumors. The objective response so far has been assessed as 60% of the treated patients, but recent studies using MRI/CT evaluation showed a lower rate of objective responses – 16–30% [3].

PRRT may result in stabilization or regression of the disease. This treatment also improves the quality of life of patients with NET [4]. In cases of primary inoperable tumors, it enables surgical intervention with partial or total resection of the tumor.
response to the therapy and survival rates depends on the tumor stage before treatment and also comorbidity of the patients. If progression of the disease, after effective PRRT, is observed, repeated cycles of PRRT might be considered. Repeated PRRT cycles should also be considered in patients with primary inoperable tumor with partial resection of the tumor performed after the first cycle of PRRT. Repeated doses of radiolabeled somatostatin analogue provide the possibility of obtaining stabilization or regression of the disease. There is, however, probably an increased risk of kidney function impairment and a decrease in blood parameters due to the higher dose of radiolabeled somatostatin analogue used.

The aim of our study was to assess the effectiveness and toxicity of repeated cycles of peptide receptor radionuclide therapy (PRRT) in patients with disseminated and/or inoperable neuroendocrine tumors (NETs).

Material and methods

Eighty nine patients with disseminated or inoperable NET were treated with the PRRT in our Departments. Among them, 16 were qualified for a repeated PRRT cycle with 90Y-DOTA-TATE, 177Lu-DOTA-TATE or mixed 90Y/177Lu-DOTA-TATE due to progression of the disease in diagnostic studies (CT, MRI, PET-CT, SPECT) and increasing values of the characteristic marker chromogranin A (CgA). Progression was defined as enlargement of the size of previously visible changes, local recurrence of the disease, or appearance of new lesions (RECIST criteria). In one case, PRRT (the first and also the second cycle) was used as neoadjuvant therapy. 90Y-DOTA-TATE was used in patients with large tumors; 177Lu-DOTA-TATE was given in cases with multiple small changes and mixed 90Y/177Lu-DOTA-TATE in patients with both large and small focuses [5]. In the whole group of patients (7 men, 9 women, mean age 54.3 ± 9.43 years) there were 10 patients with foregut tumors (among them 5 nonfunctioning pancreatic NET, 1 malignant insulina, 6 with midgut tumors, type G2 according to the WHO Classification of Tumors of the Digestive System, 2010). Karnofsky’s index in the whole group of patients was >70%. Debunking surgery was performed in 10 patients before the first cycle of PRRT. Five patients underwent chemotherapy with the use of streptozotocin/ doxorubicin or streptozotocin/5-fluourouracil or gemcitabine HCl (3–24 months prior to the first cycle of PRRT). During the first cycle of PRRT, each patient received 7.4 GBq/m2 of PRRT divided in 4–5 infusions (most often 3.7 GBq per cycle), every 4–8 weeks. A repeated PRRT cycle was performed after 8–37 months after the last infusion of the first cycle of PRRT (mean time was 18.4 months). In the case of 11 patients, repeated cycles were administered after more than 12 months, including 3 patients who received a repeated cycle after 24 months. Patients received 1–4 additional PRRT infusions (1 infusion – 5, 2 infusions – 3, 3 infusions – 6 and 4 infusions – 2 patients). The mean activity administered in the repeated PRRT cycles was approximately 8.14 GBq (Table 1). The total number of repeated PRRT infusions was 37, and there were 19 infusions of 90Y/177Lu-DOTA-TATE (total activity 65.86 GBq, mean activity per cycle 3.48 GBq); 2 infusions of 177Lu-DOTA-TATE (total activity 4.26 GBq) and 17 infusions of 90Y-DOTA-TATE (total activity 58.46 GBq, mean activity per cycle 3.70 GBq).

To assess nephro- and myelo-toxicity each patient had such parameters assayed as creatinine, platelets, leukocytes, and hemoglobin before and every month after treatment. Myelotoxicity was assessed according to WHO classification. During each PRRT treatment (also during additional cycles) aminoacids infusion (Vamidrin® 3.70 GBq) was used for nephroprotection. Patients’ physical condition was assessed during clinical visits after the PRRT – each patient attended at least one visit within 1–4 weeks after each PRRT infusion. Prior to and each six months after the first and repeated cycles, imaging studies (CT, MRI, PET-CT, SPECT) were performed. The response to the therapy was assessed according to RECIST criteria.

Statistical methods

Because of non-Gaussian distribution of the data, the Wilcoxon signed rank test was used to assess the difference between the values of blood count and creatinine at 1, 3, 6, 12 and 18 months after the first and repeated cycles of PRRT. The impact of chemotherapy on these parameters after repeated PRRT cycle was assessed using the Mann-Whitney U test at the same time points. In all analyses, a 5% (0.05) level of significance was assumed.

Results

In the group of 16 patients treated with repeated PRRT cycles during the follow-up disease stabilization was observed in 10 patients 6 months after the repeated PRRT cycle and in 5 patients after 12 and 18 months. Ten of the patients who had received repeated PRRT cycles died, among them disease progression was observed in 1 patient 2 months after the additional PRRT cycle, in 1 patient after 3 months, in 1 patient after 4, in 2 patients after 6, in 1 patient after 7 months, in 2 cases 12 months and in 2 cases 24 months after the repeated PRRT cycle. Among the 6 living patients, one had progression of the disease and received chemotherapy. Four of the living patients had a follow-up of 24 or more months and among them 1 patient had disease progression after 24 and one after 36 months, 2 patients have stable disease. One patient received PRRT as neoadjuvant therapy due to inoperable midgut tumor. The first treatment with total activity of 16.2 GBq caused a decrease in the tumor size from 13 cm to 9.2 cm and enabled surgical intervention. Five months after surgery, the patient received 3 additional 90Y-DOTA-TATE (total dose: 11.1 GBq) infusions with further reduction of the tumor size from 5.2 cm after surgery to 3.5 cm after repeated PRRT cycle. This patient is again qualified for surgery.

The mean time of observation was 36 ± 16 months. The mean time from starting the first PRRT cycle to the first progression was 18 ± 7 months. The mean time from starting the repeated PRRT cycle to the progression was 12 ± 11 months. The mean time from starting the first PRRT cycle to the beginning of the repeated cycle was 22 ± 10 months. The mean time from the end of the first PRRT cycle to starting the repeated PRRT cycle was 18 ± 8 months. The mean time of observation from starting the repeated PRRT cycle till now or to death was 14 ± 10 months. The mean time of observation from starting the repeated PRRT cycle to death was 11 ± 8 months.

After the treatment we did not observe clinically significant reduction in the mean values of blood count parameters, such as platelet (PLT) and leukocyte (WBC) count and hemoglobin (Hb) level. Differences between the values of these parameters after first and repeated PRRT cycles at each time point were statistically insignificant (p > 0.05) (Fig. 1).

In one patient, transient grade III toxicity in platelet level was observed 1 month after the first PRRT cycle (PLT count – 26,000/μl). In one patient, transient grade IV toxicity in platelet level was observed 3 months after the repeated PRRT cycle (PLT – 23,000/μl). In two other patients, grade III toxicity in platelet level was observed 3 and 6 months after the repeated cycle (PLT – 45,000/μl, 49,000/μl respectively). The clinical observation of these patients was completed after 7 (2 patients) and 11 months due to death as a result of the disease’s progression. In one patient, grade III toxicity in leukocyte level was observed 1 month after the first
PRRT cycle (WBC = 1860/μl). This was the patient with coexistent thrombocytopenia. The clinical observation of this patient was completed after 11 months due to death as a result of the disease’s progression.

In three patients, transient grade III toxicity in hemoglobin level was observed 1 and 3 months (2 patients) after the repeated cycle (Hb = 7.3 g/dl, 7.4 g/dl, 7.9 g/dl, respectively). We have not observed grade IV toxicity in hemoglobin level so far.

There was no necessity for additional hematological treatment of patients with low platelet or leukocyte levels. One patient required a blood transfusion due to low hemoglobin level.

Differences between the values of creatinine after the first and repeated PRRT cycles at each time point were statistically insignificant ($p > 0.05$). (Fig. 2) After 12 and 18 months the mean values of creatinine levels were higher than the upper limit of the normal range, but only in 2 patients with normal values after the first PRRT cycle the levels of creatinine were higher after the repeated cycle. There was no necessity for additional nephrological treatment of hemodialysis. Maximum creatinine level was 133.7 μmol/l (in one assay after 6 months).

No statistically significant impact of chemotherapy on the morphological parameters and creatinin level analyzed after repeated PRRT cycle was found.

The chromogranin A as a marker of clinical activity of the disease decreased after the first and repeated PRRT cycles. The medians were 349.7 U/l (min 71.0; max 11477.0) prior to and 208.8 U/l

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**Table 1**

<table>
<thead>
<tr>
<th>Initials</th>
<th>PRRT cycle</th>
<th>Activity [GBq]</th>
<th>Time between I treatment end and II treatment start [months]</th>
<th>PRRT cycle</th>
<th>Activity [GBq]</th>
<th>6 months</th>
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<th>24 months</th>
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<td>PD</td>
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<tr>
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<td>Y90/Lu177</td>
<td>11.1</td>
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<td>PD</td>
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<td>14</td>
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<td>8</td>
<td>Lu177 + Y90/Lu177</td>
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<td>SD</td>
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<tr>
<td>K.K.</td>
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<td>22</td>
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<td>7.4 + 1.85</td>
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<td>Death</td>
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<tr>
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<td>Y90</td>
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SD – stable disease.
PD – progressive disease.
PR – partial response.

**Fig. 1.** Morphological parameters levels at the time of first and second PRRT cycle. Error bars indicate SD.
Discussion

As we try to show above, the repeated PRRT cycles in 15 patients with progression of the disease after first PRRT cycle resulted in disease stabilization or regression in five cases. One of those patients died, but not due to disease progression. We would also like to emphasize the usefulness of repeated PRRT cycles as neoadjuvant therapy which enables partial or probably even total surgical resection of primary inoperable tumors, which was observed in our study in the case of one patient with primary inoperable tumor. The other ten patients died due to progression of the disease. Whether the repeated PRRT cycle prolonged their survival remains without answer. But in cases of patients with carcinoid syndrome, PRRT was effective in relieving symptoms of the disease.

In our group, among 89 patients treated originally with PRRT, 16 patients (18%) needed retreatment due to progression of the disease. But we would like to emphasize that in case of 11 patients (60%) progression was observed more than 12 months after the first cycle of PRRT and in 3 cases this period without progression lasted 24 months, what might confirm the effectiveness of PRRT. This relatively long time interval might probably also result from the natural history of neuroendocrine tumor, which are usually slowly growing tumors [6]. However, as it is presented in the Results section, the risk of death is relatively high in the group of 16 patients qualified to the second radioisotope therapy. This is probably connected with the advanced stage of the disease of those patients. Four patients who died within 6 months after the second PRRT cycle presented with disease progression 12, 18, and 24 (2 patients) months after the first PRRT cycle, respectively. However at the beginning of the second radioisotope therapy they already were in the advanced stage of the disease with multiple, also extrahepatic, distant metastases.

The important issue, not only in our study, is the assessment of the response to the radioisotope therapy. We would like also to...
emphasize here that the response to the therapy was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST), which includes measurement of the longest diameter of every measurable lesion on axial CT slices and calculation of the sum of the longest diameters (SLD) for all selected target lesions [7,8]. But in some cases CT is not efficient in diagnostics process of NET. In some cases somatostatin receptor scintigraphy (SRS) localizes primary neuroendocrine tumor and also the metastatic lesions better than other diagnostic studies and enables also assessment of the advancement of the disease. With SRS small primary tumors and their metastases, not visible in CT scans, might be revealed. For better response evaluation CT scans should be compared with SRS results based on fusion of CT/SRS images. Moreover neuroendocrine tumors are usually well vascularized and PRRT treatment might cause changes not only in tumor size, but also in contrast enhancement and attenuation [9]. Therefore tumor size changes in CT scans taken into consideration while using RECIST criteria seem to be not sufficient to assess response to the therapy in NET. Results of fusion images and assessment of tumor size, contrast enhancement, and attenuation changes in CT scan provide more precise information about results of the treatment. Moreover, as it was suggested also by other authors, anatomic imaging alone using standard RECIST criteria have limitations, particularly in assessing the activity of newer cancer therapies, whereas PET appears particularly valuable in such cases [10].

Treatment with radiolabeled somatostatin analogues is a known tool in the management of patients with disseminated and inoperable NETs. But this treatment has also side-effects connected with absorbed radiation dose to the kidneys and the bone marrow [11]. The radiolabeled compound used in PRRT is bound to the receptor, internalized, and metabolised in the lysosomes. The retaining metabolites cause prolonged local irradiation in the cells with the expression of somatostatin receptors type 2. The radiolabeled somatostatin analogues that are used in PRRT are cleared by the kidneys and, due to reabsorption by the proximal tubular cells, prolonged kidney irradiation and subsequent renal function impairment may be observed. Therefore, the kidney absorbed radiation dose is the major dose-limiting factor [11]. Data on kidney radiation doses at which toxicity appears are still limited, and in PRRT internal assessment is needed to establish the maximum safe dose to the kidneys [5–8]. However, there are known factors which increase the risk of kidney failure such as age over 60, hypertension, diabetes, and previous chemotherapy [11,12,14,15]. There are also clinical indications that usually renal toxicity becomes overt one year or later after PRRT [13,15–17]. In this study no significant difference in the parameter levels analyzed by group of patients with and without previous chemotherapy was found. However, this may be associated with the small number of the patients (five cases) with previous chemotherapy. To protect kidneys during PRRT and enable administration of higher cumulative doses of radiolabeled somatostatin analogues, solutions of aminocids, which reduce the proximal tubular reabsorption of low molecular weight proteins and peptides, are used [11,15,18–23]. Dose fractionation and longer intervals between cycles are also very important nephroprotective factors [12,15]. However, in our study we did not find significant correlation between the time from starting the first PRRT cycle to the beginning of the repeated cycle and creatinin level. Moreover there are data suggesting that dose fractionation may improve the anti-tumor efficacy due to higher expression of somatostatin receptors on regrowth tumors after radiation treatment/irradiation [15,24].

As mentioned above, in our Center we were also using amino-acid formula Vamin 18, before and after each infusion of PRRT, for nephroprotection. During the follow-up after the repeated PRRT cycle we observed only slight elevation of the creatinin level, and there were no cases of overt renal failure after that time. The increased creatinin level was observed for the first time 12 or 18 months after the repeated PRRT cycle, which is in accordance with other authors’ observations [13–17]. But these increasing values did not differ significantly from the values at the same points of the first PRRT cycle.

Bone marrow is the second critical organ during PRRT. However the subsequent anemia, leukopenia, and/or thrombocytopenia are usually reversible [4,15]. In our study if there were grade III or IV (according to WHO) toxicity of the platelet, leukocyte, and hemoglobin levels observed, it was also only transient and patients did not need additional hematological treatment except blood transfusion in one case of low hemoglobin level.

Conclusions

Results of our study show the possibility of safety use of repeated PRRT cycles in patients with progressive disease who previously presented with response to the first PRRT cycle. In the patient with primary inoperable tumor and without metastases, the repeated cycles of PRRT enabled surgical intervention.

Conflict of interest statement

All authors disclose any financial and personal relationships with other people or organizations that could inappropriately influence this work.

References


