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Neuroendocrine tumors

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

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ABSTRACT

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. The

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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 be also 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 ^{90}Y-DOTA-TATE, ^{177}Lu-DOTA-TATE or mixed ^{90}Y/^{177}Lu-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. ^{90}Y-DOTA-TATE was used in patients with large tumors; ^{177}Lu-DOTA-TATE was given in cases with multiple small changes and mixed ^{90}Y/^{177}Lu-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 insulinoma), 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%. Debulking 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-fluorouracil 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 ^{90}Y/^{177}Lu-DOTA-TATE (total activity 65.86 GBq, mean activity per cycle 3.48 GBq); 2 infusions of ^{177}Lu-DOTA-TATE (total activity 4.26 GBq) and 17 infusions of ^{90}Y-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 (Vamin18) lasting 8–10 h 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 ^{90}Y-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

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