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Efficacy and safety of ^{90}Y-DOTATATE therapy in neuroendocrine tumours

Celowana terapia ^{90}Y-DOTATATE guzów neuroendokrynnych — ocena skuteczności oraz toksyczności

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Abstract

Background: The aim of this study was to assess the efficacy and toxicity of peptide receptor radionuclide therapy (PRRT) with the use of the high affinity somatostatin receptor subtype 2 analogue, ^{90}Y labelled Tyr^3-octreotate, (^{90}Y-DOTATATE) in neuroendocrine tumours (NETs).
Material and methods: 46 patients with disseminated or non-operable NET were enrolled in this study. The ^{90}Y-DOTATATE therapeutic activity was calculated per total body surface area up to a total of 7.4 GBq/m^2 administered in three to five cycles, repeated every four to nine weeks. Before and after the therapy, blood tests for haematology, kidney and liver function, and chromogranin A were performed.
Results: Out of 46 ^{90}Y-DOTATATE treated patients, one died before completing the therapy and 16 died after completing the therapy, among them one due to myocardial infarction. After 12 month follow-up, stabilisation of disease was observed in 47%, partial remission in 31%, and progression in 9% of the 45 patients who completed the therapy. Five patients died before completion of 12 months of follow-up. One of the patients died due to myocardial infarction. In one case, the information after 12 months is incomplete. The progression free survival was 37.4 months. During 12 months follow-up, transient decrease of PLT, WBC and haemoglobin values was observed. A transient increase of creatinine level (within normal ranges) and decrease of GFR values were found.
Conclusions: NETs ^{90}Y-DOTATATE therapy results in symptomatic relief and tumour mass reduction. The mild critical organ toxicity does not limit the PRRT of NETs. **(Pol J Endocrinol 2011; 62 (5): 392–400)**

Key words: *peptide receptor radionuclide therapy, neuroendocrine tumours, targeted therapy*

Streszczenie

Wstęp: Celem pracy była ocena skuteczności oraz toksyczności celowanej terapii receptorowej (PRRT) guzów neuroendokrynnych z wykorzystaniem analogu somatostatyny Tyr^3-octreotate znakowanego ^{90}Y (^{90}Y-DOTATATE).
Materiał i metody: Do badania włączono 46 pacjentów z rozsianym lub nieoperacyjnym guzem NET. ^{90}Y-DOTATATE podawano w 3–5 kursach w odstępach 4–9-tygodniowych. Każdorazowo wyznaczano aktywność terapeutyczną, uwzględniając taką całkowitą powierzchnię ciała, by nie przekroczyć sumarycznej wartości 7,4 GBq/m^2. Przed terapią i po niej wykonano oznaczenia parametrów morfotycznych, nerkowych oraz wątrobowych, a także stężenia chromograniny A.
Wyniki: Spośród 46 leczonych pacjentów jeden chory zmarł przed zakończeniem pełnego cyklu terapeutycznego, a 16 po zakończeniu terapii, w tym jeden z powodu zawału serca. W 12. miesiącu obserwacji stwierdzono 47% stabilizacji, 31% częściowych odpowiedzi oraz 9% progresji wśród 45 pacjentów, którzy ukończyli leczenie. Pięciu chorych zmarło przed 12. miesiącem obserwacji. W jednym przypadku utracono możliwość uzyskania informacji o chorym po 12 miesiącach. Okres czasu bez progresji choroby wyniósł 37,4 miesiąca. W ciągu pierwszego roku od zakończenia terapii zaobserwowano jedynie przejściowe obniżenie wartości morfotycznych krwi oraz przejściowy wzrost stężenia kreatyniny i spadek wartości przesączania kłębuszkowego (GFR).
Wnioski: Celowana terapia receptorowa z użyciem ^{90}Y-DOTATATE może być skuteczną oraz stosunkowo bezpieczną metodą leczenia prowadzącą do częściowej odpowiedzi lub stabilizacji choroby u większości pacjentów. **(Endokrynol Pol 2011; 62 (5): 392–400)**

Słowa kluczowe: *terapia znakowanymi analogami somatostatyny, guzy neuroendokrynne, terapia celowana*

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Introduction

The management of patients with neuroendocrine tumours (NETs) is a challenge to clinicians, inspiring the search for new diagnostic and therapeutic procedures. NETs are usually well differentiated neoplasms with low response to chemotherapy. The main problems with systemic therapy are a lack of selectivity and high toxicity for healthy cells. The advantage of targeted radionuclide therapy is a selective treatment effect with the use of an appropriate ligand carrying the isotope directly to the malignant cell population.

The overexpression of somatostatin cell surface receptors on different neoplasms, including NETs, have become the molecular basis for the application of somatostatin analogues in the diagnosis and therapy of these tumours.

In recent years, peptide receptor radionuclide therapy (PRRT) has been tested, using high affinity receptor subtype 2 (sstr2) somatostatin analogues including Tyr^3-octreotate labelled with ^{90}Y or ^{177}Lu or combined therapy using a mixture of somatostatin analogues labelled with ^{90}Y and ^{177}Lu. Tyr^3-octreotate is the most promising radiolabelled peptide for treatment purposes [1].

The following $^{90}Y/^{177}Lu$ labelled somatostatin analogues are the most important: [DOTA, Tyr^3] octreotide (DOTA TOC), DOTA-lanreotide (DOTA LAN), and [DOTA, Tyr^3]-octreotate (DOTA TATE) [2, 3].

The Tyr^3-octreotate (octreotate) differs from the Tyr^3-octreotide (octreotide) in that the terminal threonine replaces threoninol. The terminal threonine provides higher receptor binding, better internalisation, and greater tumour irradiation [4, 5].

Yttrium-90 (T1/2 — 64 hours) is a pure beta emitter with a maximum range of tissue irradiation of 10 mm. The high energy of this radioisotope (935 keV) is sufficient to achieve direct tumour effects. Due to the characteristics of ^{90}Y, patients may be discharged from hospital soon after treatment [6, 7]

The type of ligand used in PRRT influences both the treatment efficacy as well as therapy side-effects. ^{90}Y labelled somatostatin analogues are secreted to glomeruli and reabsorbed in proximal canaliculi, causing tracer retention in the interstitial area with a concomitant increase in kidney irradiation [8, 9]. Therefore, kidneys are the critical organs in the therapy using ^{90}Y labelled somatostatin analogues.

The indications for radioisotope NET therapy are disseminated and/or non-operable somatostatin receptor overexpressed tumours confirmed by positive somatostatin receptor scintigraphy (SRS). The most expected advantage of this therapy is partial or complete remission or stabilisation of disease resulting in prolongation of life and symptomatic relief.

The aim of this study was to evaluate the efficacy and assess the critical organ toxicity of ^{90}Y-DOTATATE therapy in patients with disseminated or non-operable neuroendocrine tumours.

Material and methods

Forty six patients (27 females, 19 males, aged 31–78; mean: 59.7 ± 11.9 years) with histopathologically confirmed NET and positive [99mTc-EDDA/HYNIC] octreotate SRS results were enrolled in the study. There were 26 patients with foregut tumours (18 with pancreatic neuroendocrine tumours), 11 with midgut tumours, two with hindgut tumours, four with medullary thyroid cancer and three with unknown primary focus (PFU).

Twenty two patients suffered from hypertension, 14 patients had a positive history of diabetes, and in ten cases both hypertension and diabetes were observed. Thirteen (28.3%) of the patients received chemotherapy at least six months before PRRT. Metastases were identified in a majority of patients (89.1%), mainly to the liver (71.7%) and to the lymph nodes (32.6%). Other distant metastases (bones, lungs, CSN) were observed in 41.3% of patients. Thirty one patients underwent surgical treatment before PRRT, four patients underwent explorative laparotomy. Eleven patients (24%) were not operated due to the inoperable nature of their tumours or due to cardiac contraindications to the surgery (two patients). Four of the patients who were not operated did not present with distant metastases. Before admission to our department and referral for PRRT, 13 patients received chemotherapy due to disseminated progressive disease or as neoadjuvant therapy (five with streptozotocin/5-FU, one with etoposide/cisplatine, one with cisplatine/vepesid, one with etoposide, one with FDE, two with Gemzar, one with PLFE and one with 5-FU and leucovorine) because of lack of other therapeutic modalities at the time of diagnosis. Three patients underwent local radiotherapy — two women due to eye and thoracic wall metastases, and one man due to bone (spinal column) metastases. Ten patients received a long-acting somatostatin analogue (Sandostatin LAR) due to carcinoid syndrome. The treatment in all cases was no longer than three months.

Inclusion criteria for PRRT therapy were:

— progressive disease according to RECIST defined as at least 20% increase in size of at least one neoplasmatic lesion (also in patients after other therapeutic approaches) or inoperable primary tumour and/or lack of symptoms control with biotherapy (somatostatin analogue treatment);
— positive [^{99m}Tc-EDDA/HYNIC] octreotate SRS;

— blood morphology: white blood cells (WBC) > 3,000/μl, platelets (Plt) > 100,000 /μl, Hb > 10 g/L;
— renal parameters: blood urea nitrogen (BUN) < 10 mmol/L, creatinine < 160 μmol/L, and glomerular filtration rate (GFR) > 30 mL/min;
— written informed consent to the therapy.

Exclusion criteria were:

— Karnofsky's performance index < 50;
— pregnant or lactating women. For women of childbearing age and for their partners, effective contraception was required;
— systemic chemotherapy received ≤ 6 months before PRRT.

The patients were treated at the Nuclear Medicine Unit of the Endocrinology Department at the University Hospital in Krakow from 2005–2010.

The ^{90}Y-DOTATATE (IAE, Radioisotope Centre POLATOM, Poland) therapeutic activity was calculated per the total surface area of the patient including weight and height, up to the total of 7.4 GBq/m^2 activity. The treatment schedule was three to five cycles, repeated every four to nine weeks. The most frequent single amount of activity was 3.7 GBq (100 mCi) given usually every six to seven weeks. In the event of transient impairment of the haematological and/or renal indices, the interval period was extended to a maximum of nine weeks. Dosimetry based calculation of the therapeutic doses was not possible because of the technetium labelled compounds used for the pre-therapeutic SRS. The first patients received ^{90}Y-DOTATATE in intravenous infusion lasting 30 minutes; then it was changed and bolus of radiolabelled somatostatin analogue was applied two hours after mixed amino acid administration (Vamin 18, Fresenius Kabi, Germany; containing among others 11.3 g of arginine and 9.0 of lysine/1,000 mL of solution), which was used for kidney protection. The Vamin 18 infusion was continued up to ten hours after ^{90}Y-DOTATATE administration. The PRRT was designed so as not to exceed the permissible accumulated dose for kidney (27 Gy) [10, 11].

Before and after PRRT, all patients received a physical examination, a quality of life assessment (Karnofsky's scale), a questionnaire examination concerning symptoms of disease (e.g. diarrhoea, flush, bronchospasm, etc.), blood testing for haematology (WBC with blood smear, Hb, Plt, and RBC), kidney function (BUN, creatinine, GFR), liver function (ALT) and chromogranin A (CgA). All biochemical indices were assessed after each cycle of the therapy, five and 12 months post-therapy, and every month thereafter. The GFR value was calculated using Cockcroft-Gault's formula. Estimation of GFR values for patients with chronic renal disease was performed in accordance with the recommendations of the Disease Outcome Quality Initiative (K/DOQI)9.

SRS and computed tomography (CT) were performed in all patients before and three, six, 12, 18 and 24 months after PRRT. [99mTc-EDDA/HYNIC]octreotate (740 MBq) single photon emission computed tomography (SPECT) of abdomen and/or chest and whole body (WB) scans were obtained with the use of a dual-head, large view field E.CAM gamma camera (Siemens) equipped with low-energy, high resolution (LEHR) collimators with e.soft operating systems. Semi-quantitative region of interest (ROI) analyses of the focal lesions were performed. Target/non target ratios, up to five focal lesions per scan, were compared before and after therapy.

Most CT examinations were performed with a 10-row helical tomograph (Siemens Sensation 10). Tumour response to PRRT was assessed using Response Criteria In Solid Tumors (RECIST).

Statistical methods

The correlation between the time to progression and the received activity, also the correlation between PLT levels after 12 months from PRRT and the received activity, were assessed using Spearman's rank correlation coefficient. The impact of prior chemotherapy on the time to progression, the bone marrow and the kidney function were analysed using t test. In the subgroup of patients with diabetes and/or hypertension, separate analyses of the influence of these conditions on the kidney were also performed using t test. The Kruskal-Wallis test was used to assess the relationship between the difference of chromogranin A values before and after the PRRT and the response to the treatment. The overall survival, the progression free survival and the event free survival were assessed on the basis of Kaplan-Meier survival curves. In analyses, a 5% (0.05) level of significance was assumed.

Statistical analysis of the data was performed using STATISTICA v. 9.0 (StatSoft, Inc.).

Results

Therapeutic effect

A completed schedule of ^{90}Y-DOTATATE therapy was administered in 45 patients out of 46 treated, one having received only one cycle of PRRT. In this patient with uncontrollable symptomatic disease, diagnosis of NET was made two months prior to therapy. In 45 patients who completed ^{90}Y-DOTATATE therapy, after 12 month follow-up stabilisation of disease was observed in 47%, partial remission in 31%, and progression in 9% of patients. 11% of patients died before the 12 month follow up, one patient due to myocardial infarction. In one patient, the information after 12 months is incomplete. Figure 1 presents SRS results before and after the PRRT in the patient with partial response.

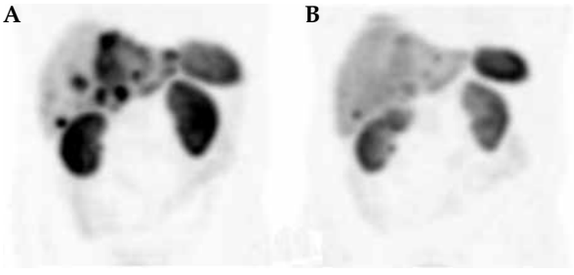

Figure 1. *The SRS results with [99mTc-EDDA/HYNIC]octreotate before and after the PRRT in patient with partial response*

Rycina 1. *Wynik badania SRS z zastosowaniem [99mTc-EDTA/ /HYNIC]Octreotate przed i po terapii znakowanymi analogami somatostatyny u pacjenta z częściową remisją choroby*

The progression free survival was 37.4 months. The event free survival was 31.2 months. Overall survival is not culminate is not reached (the 25th percentile was 20.3). Progression of the disease after 12 months (between 13–60 months after beginning of PRRT, nine patients after two years) was observed in 16 patients, among whom seven patients died between 13 and 40 months after beginning PRRT. Nine patients with progression received additional PRRT cycles between 11 and 47 months after ending the first PRRT cycles. Despite repeated therapy, five of them died, at two, four, 11, 18 and 24 months from starting repeated PRRT cycles. Three patients are still repeating PRRT cycles, one has displayed stabilisation of the diseases after PRRT. A statistically significant correlation between time to progression and the received activity was not observed ($p > 0.05$). The overall survival, the progression free survival and the event free survival after the PRRT are shown in Figure 2.

There was no statistically significant difference in the survival time of patients with or without prior chemotherapy treatment ($p = 0.13$). All symptomatic patients in which PR or SD were achieved, were free of carcinoid syndrome symptoms, although in this group the therapy with long-acting somatostatin analogues was restarted after PRRT.

Side effects of PRRT

After 12 months follow-up, there were no statistically significant changes in the creatinine after PRRT. In this time, creatinine changes grade 1 were observed in 5%, grade 2 in 15%, and grade 4 in 5% of patients. No changes grade 3 in creatinine values were observed in our group of patients. Twelve months into therapy, an increase of mean creatinine values to 80 μmol/L, compared to a baseline of 72 μmol/L, was observed (normal range 45–97 μmol/L). The slightly higher mean increase to 140 μmol/L was seen in four patients 24–28 months after the beginning of PRRT. None of the patients from this group presented symptoms of renal dysfunction. In one patient (a 68 year-old woman) with diabetes, an increased value of creatinine level was observed from six months after PRRT. After ten months, the creatinine value was 313 μmol/L and the patient was referred for dialysis therapy. The next patient, a 63 year-old woman with hypertension, had increases in values of creatinine level 12 months after PRRT (350 μmol/L); 12 months later, this woman was referred for dialysis therapy. In both of these patients, regression of the disease is still observed. The mean creatinine levels are presented in Figure 3.

A transient decrease of blood parameters was observed in 62.5% of patients after PRRT. The highest decrease in WBC was seen after cycles III and IV of the therapy. At different times after PRRT, transient changes grade 3 (according to WHO criteria) in seven patients were observed; no grade 4 was observed. After 12 month follow-up, no grades 3 or 4 according to WHO criteria were observed. Filgrastim was administered to one patient with a WBC level of 1,360/mm^3 three months into therapy. Transient decreases of platelets values grade 3 according to WHO criteria in four patients was observed at different times after PRRT; no grade 4 was observed. After 12 month follow-up, no grades 3 or 4 according to WHO criteria were observed. A transient decrease in platelet level was observed compared to baseline, but mean platelet values were within normal ranges.

Decreased Hb levels were observed during this study, with the lowest mean Hb values noted at the 12 month follow-up following the initiation of therapy (11.2 g/dl) compared to baseline (13.1 g/dl). In most cases, mild anaemia was observed. Transient decreased values of Hb grade 3 according to WHO criteria in three patients were observed at different times after PRRT. Two of them after previous chemotherapy needed blood transfusion. One patient treated with chemotherapy (Gemzar) once monthly for seven years developed MDS. This patient died 12 months after ending PRRT. After 12 month follow-up, no grades 3 or 4 in Hb levels according to WHO criteria were observed.

The mean Hb, PLT and WBC values in patients before and after PRRT are given in Figure 4.

Patients treated previously with chemotherapy had statistically lower baseline and control leukocyte and platelet levels, and higher creatinine levels, than patients who were not treated with chemotherapy. There were no statistically significant differences in creatinine levels 12 months after the therapy in patients with arterial hypertension and diabetes in comparison with patients without these conditions ($p > 0.05$).

A decrease in chromogranin A mean marker values was observed in 35 out of 45 patients who completed the

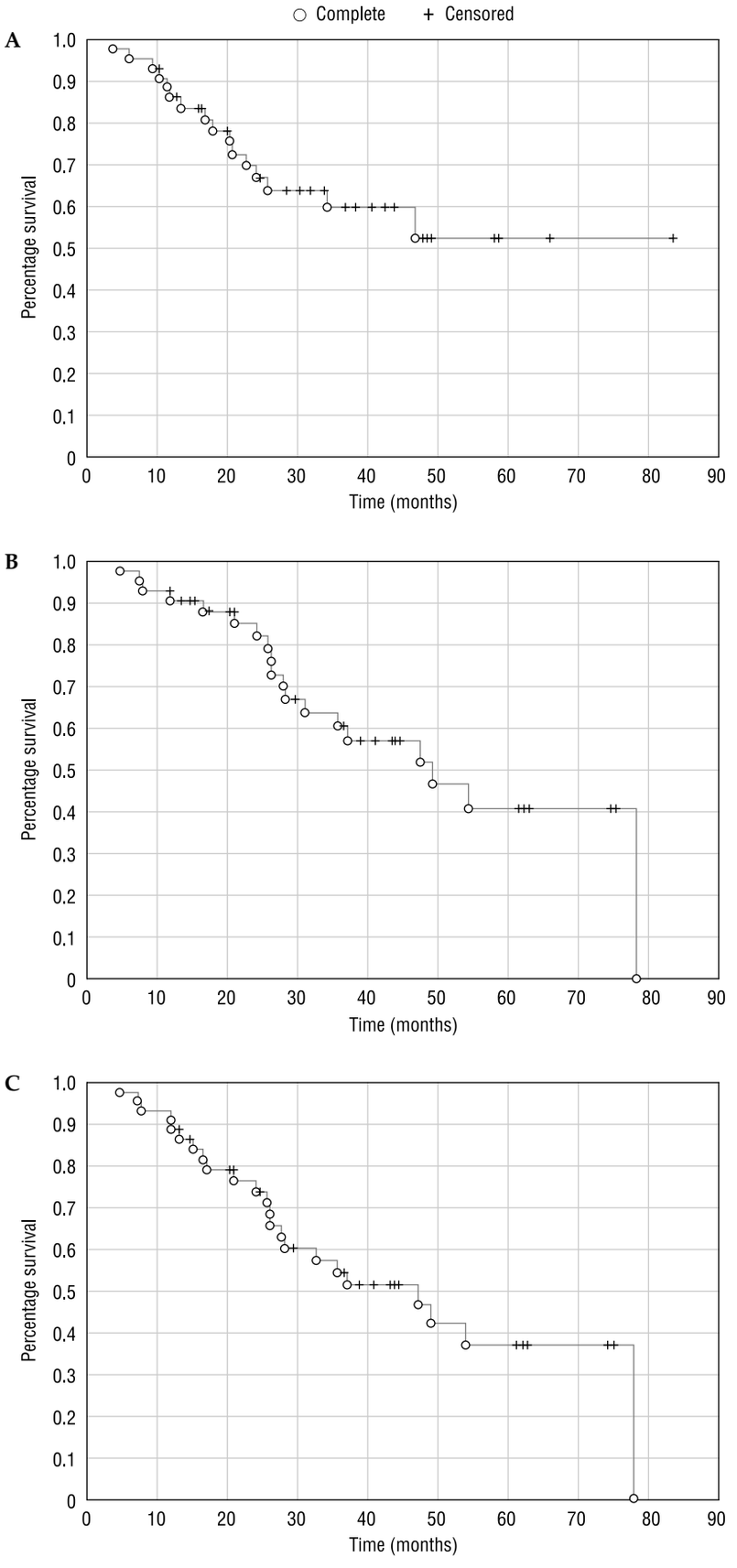

Figure 2. *The Kaplan-Meier survival curves.* **A.** *The overall survival.* **B.** *The progression free survival.* **C.** *The event free survival*
Rycina 2. *Krzywe przeżycia Kaplana-Meiera.* **A.** *Czas całkowitego przeżycia.* **B.** *Czas wolny od progresji.* **C.** *Czas przeżycia wolny od jakiegokolwiek zdarzenia (progresja, śmierć)*

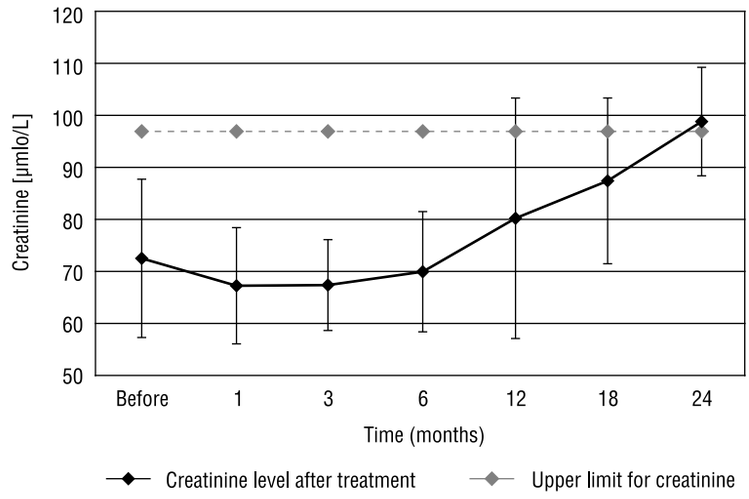

Figure 3. *Creatinine [µmol/L] levels after PRRT*
Rycina 3. *Stężenie kreatyniny [µmol/L] po terapii znakowanymi analogami somatostatyny*

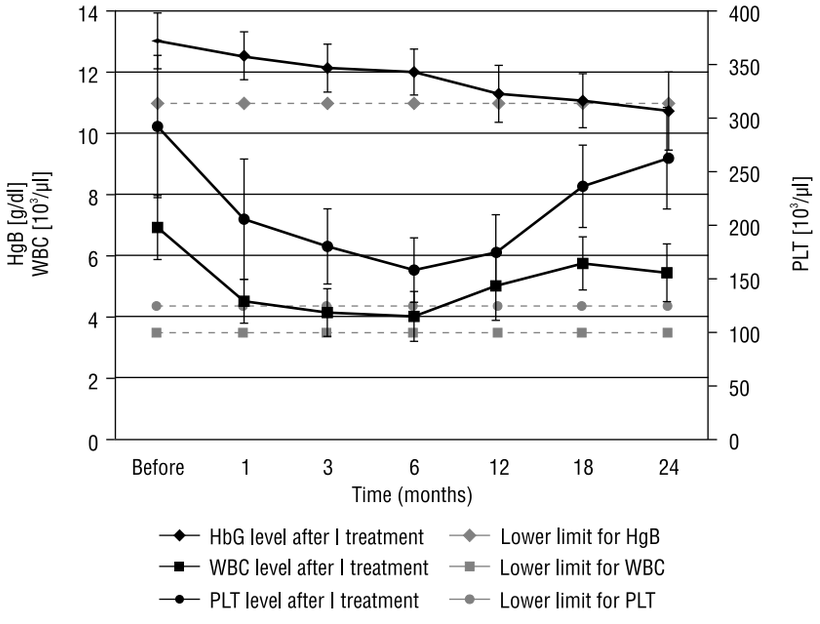

Figure 4. *Hb [g/dl], PLT [10³/µL], WBC [10³/µL] levels after PRRT*
Rycina 4. *Wartości hemoglobiny [g/dl], płytek krwi [10³/µl] i leukocytów [10³/µl] u pacjentów po terapii znakowanymi analogami somatostatyny*

PRRT. No statistically significant relationship between change in chromogranin A level before and after the treatment and response to the treatment was found ($p = 0.31$).

No significant impairment of liver function was seen during or after PRRT.

Discussion

Neuroendocrine neoplasms are a relatively rare group of tumours and their overall incidence appears to have increased over the past 30 years, due in large part to an improvement in the diagnostic tools used for their detection [12]. The potential malignancy of NETs might be independent of their size. The clinical course is often unpredictable and the evidence of metastases may be the only indicator of malignancy [13]. When a tumour is disseminated or nonoperable, the possibility of radical treatment is decreased. Poor sensitivity of NETs to chemotherapy has led to a search for more effective therapies. Recent clinical studies have proven the high effectiveness of PRRT in NET treatment. In a multicentre

study by Valkema et al., 60 patients received increasing activities of [^{90}YDOTA0Tyr^3] octreotide to a total activity dose of 14.8 GBq/m^2 in four cycles or 9.5 GBq/m^2 in a single cycle [14]. Partial response (PR) was seen in 8% of patients and a minor response in 13%, with an observed tumour mass reduction of 25–50%. The mean time to progression was 30 months in 44 patients with stable disease (SD), partial, or minor response to treatment. In the study by Waldherr et al. complete response (CR) was seen in 24% of patients treated with 6–7.4 GBq ^{90}Y-DOTATOC in four cycles [15, 16]. In another trial where an activity of 7.4 GBq/m^2 was administered in two greater intervals between cycles, CR or PR were achieved in 33% of 36 patients, without an increase in side effects [17]. When using a 7.4 GBq activity in four cycles each given six weeks apart, a CR was observed in two of 39 patients, PR in 18%, SD in 69%, and disease progression in 8%. Two patients died three months after treatment due to progression of disease and liver dysfunction. In one of these cases, there was liver damage resulting from bacterial cholangitis following the third cycle of therapy [16].

In our study, the treatment response was evaluated at 12 months following the onset of therapy. After excluding the patient who died before completing the PRRT, the progression free survival was 37.4 months. Varying time periods of response to treatment from 9-30 months have been reported in the literature [15, 18–19]. In the study by Valkema et al., there were increasing activities of ^{90}Y-DOTATOC to a total activity of 14.8 GBq in four cycles or 9.5 GBq in a single cycle. Despite the protracted time of response to treatment, merely 8% of patients had PR after maximal activity was used [14].

However, when different protocols of ^{90}Y-DOTATOC treatment are used, the response to treatment (CR, PR) increases to 10–30%. This is a better result in comparison with other therapies, including therapy with ^{111}In-DTPA-octreotide. Upon comparing our results with those of Waldherr et al. which used the same intravenous cumulative activity, we observed a higher percentage of disease remission, but a lower percentage of disease stabilisation [16]. There was a similar percentage of patients with progression of disease in our study, but a higher number of participants who died before the end of therapy (12 month follow-up). This could be related to delayed diagnosis, with patients admitted to the trials who were in more advanced stages of disseminated disease. Among patients who received the whole planned therapy regimen, the response to treatment was 78% (remission and stabilisation).

In a case of advanced neoplastic disease, this is a very good response in comparison with the methods used thus far in the treatment of NETs [16]. When analysing the group of patients with disease progression, where most progression was between 12 and 24 months (nine patients) after PRRT, it appears that our treatment regimen can prolong life.

Recent reports have shown the effectiveness of octreotide LAR in reducing the risk of neuroendocrine tumour progression (the PROMID study) [20].

In our study, in ten patients receiving a long-acting somatostatin analogue, we were not able to assess the impact of the treatment as the therapy was no longer then three months.

Renal injury is the most serious side effect of PRRT. The renal radiation dose clearly limits the level of isotope activity which can be used safely. The long-term monitoring of renal function post-therapy is very important to evaluate the risk of clinically significant renal failure [9]. Renal injury following PRRT was observed during early studies with somatostatin analogue therapy where issues of kidney protection were not addressed. In 1997, Otte et al. used increasing doses to a cumulative activity of 6 ± 1.34 GBq/m^2 in patients with GEP-NET.

In 83% of patients, no significant renal dysfunction occurred at cumulative activities ≤ 7.4 GBq. In five patients, there was toxic renal injury observed at cumulative activities ≥ 7.4 GBq. Increased creatinine levels were observed two to four months following the final treatment cycle [17,18]. Sporadic cases of delayed renal failure or terminal renal failure were observed by Brans et al. in patients who received activities > 7.4 GBq/m^2 [19].

Bodei et al. monitored patients treated with 90 Y- DOTATOC for up to eight years and reported creatinine toxicity in nine out of 23 patients' cases within one to five years following radionuclide therapy. Eight of the nine patients demonstrating toxicity had pre-existent risk factors. Higher (> 30%) losses of creatinine clearance occurred in patients showing toxicity [21].

The infusion of arginine and lysine reduces the dose absorbed by kidneys by 9–53% [22, 23]. The protective effect of arginine and lysine administered both before and after therapy with different ^{90}Y-DOTATOC activities of up to 5.55 GBq activity per cycle was observed by Bodei et al. [22].

In our study, lysine and arginine infusion was begun two to three hours before radioisotope therapy, and continued for ten hours. No noticeable acute renal failure was observed after therapy, which we believe was due to the protective effect of amino acids in addition to the fact that the maximum activity did not exceed 7.4 GBq during the entirety of the treatment regimen, with a cumulative dose for kidneys of under 27 Gy [17–19, 22]. We also observed increased creatinine levels and decreased GFR during prolonged observation following treatment. According to the

literature, toxic renal failure can occur from two to five months or up to several years after therapy [16, 17, 22, 23]. Prolonged observation was performed in all of the living patients in our study and all of these patients are still in the observational group.

For patients treated with ^{90}Y-DOTATOC, hypertension, age, diabetes and renal radiation dose > 14 Gy per cycle are considered risk factors for a decline in creatinine clearance (CLR) of > 20% and an associated high risk of ESRD (defined as CLR < 15 mL/min/1.73 m^2) within five years of therapy [24]. In our study, there was no observed influence of coexisting diabetes and hypertension on renal parameters.

The haematological toxicity of grades 3 or 4 (WHO criteria) of leucocytes, granulocytes, or platelets occurs relatively rarely and is usually transient. Myelotoxicity due to bone marrow suppression is observed following high doses of PRRT where the estimated radiation dose for bone marrow is 3 Gy. However, even with an absorbed dose lower than the anticipated limit dose for toxicity (particularly in bone marrow), repeated doses may produce haematological toxicity. Acute haematological toxicity of grades 3 and 4 might occur after [^{90}Y-DOTA0,Tyr^3] octreotide therapy, and sporadic cases of myelodysplastic syndrome may occur following administration of any of these radionuclides [19].

Paganelli et al. described transient lymphocytopenia after ^{90}Y-DOTATOC treatment in nearly all patients. There was no correlation between the dose and the degree of lymphocytopenia, and eventual return to normal levels was observed in all patients. Toxicities at grades 0 to 1 occurred at activities greater than 5.55 GBq. Among patients who received activities within the range of 6.66–7.77 GBq, 41.7% demonstrated haematological toxicity at grade 2 but, in all cases, values returned to normal within four to six weeks. This observation was probably due to the low dose delivered to the bone marrow which was estimated by dosimetric examination [25].

Chinol et al. used increasing activities of ^{90}Y-DOTATOC, with a cumulative activity of 7.4–21.3 GBq. Reversible haematological toxicity at grade 3 was observed in 43% of patients who received 5.2 GBq, and was defined as the maximum tolerated activity per cycle [26]. In the Valkema et al. study, myelodysplastic syndrome was seen in three of six patients after a whole cumulative activity of 100 GBq (2.7 Ci). In one case, chemotherapy was introduced before the radioisotope therapy and this may explain the severe side effect [27].

In our study, 62.5% of patients had a transient decrease in blood parameters, particularly leucocytes. Toxicities of grades 1 and 2, usually of transient nature, were dominant, as reported elsewhere [1, 16, 25]. One patient in the present study experienced a decrease in leukocyte levels lasting five to six months, but there were no symptoms of severe myelotoxity, including infections, observed in any of the patients. Similarly to the Waldherr et al. study, we observed decreased leukocyte values for several days post-therapy, but values normalised between treatment cycles and all patients were able to continue therapy [16]. Lower primary levels of leucocytes and platelets were seen among patients who had received chemotherapy prior to this study. As in the Paganelli et al. study, there was no correlation between the received activity and the degree of leucopenia after 12 months after the therapy [25].

Platelet numbers decreased following each cycle of therapy, but the effect was transient for leukocytes. In the majority of patients, decreases in platelet levels were present only compared to baseline values, with levels remaining within normal ranges. The same effect was seen for haemoglobin values and there was no need to suspend radiotherapy [16]. One of our patients developed MDS, perhaps as a consequence both of the chemotherapy (used for a long time i.e. repeated every month for seven years) and of the PRRT.

As in other published studies, in our study, liver toxicity was transient and occurred particularly when liver metastases were present [1].

Conclusions

Our study suggests that therapy of neuroendocrine tumours with ^{90}Y-DOTATATE can result in symptomatic relief and tumour mass reduction. Further studies on the influence of PRRT on patient survival are needed. The mild critical organ toxicity observed does not limit the PRRT of NETs.

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Disclosure statement

None of the authors have disclosed any relevant financial interest.

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