

New forms of radionuclide therapy with ^{90}Y in oncology

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Abstract

BACKGROUND: Currently, there is growing interest in the use of the beta emitter ^{90}Y in systemic therapy in oncology. For successful therapy, an appropriate ligand is chosen to carry the isotope to the place of its action. As well as performing this function, the type of the ligand influences both the course and the side effects of the treatment. For RIT of lymphomas, bone marrow becomes the critical organ; in NET patients treated with labelled somatostatin analogues, increased kidney irradiation can occur. The aim of this study was to evaluate the side effects of therapy using ^{90}Y associated with different ligands, depending on the charge to critical organs after treatment in two groups of patients: those with neuroendocrine tumours and those with non-Hodgkin's lymphomas.

MATERIAL AND METHODS: 32 patients with histopathologically confirmed NET treated with ^{90}Y -DOTATATE (7.4 GBq/m² cumulative dose) and 30 NHL patients treated with ^{90}Y -ibritumomab tiuxetan (1200 MBq max dose) were enrolled in the study.

The kidney function and changes of blood indices were assessed during the course of the therapy.

RESULTS: 59% of NET patients treated with ^{90}Y -DOTATATE displayed transient reduction of blood indices, the largest after cycles III and IV of therapy. After 5 months an increase in creatinine level was noticed, but no statistically important changes in creatinine level and GFR were observed. In the group of patients with NHL, the change of haematological indices after RIT concerned mainly PLT, ANC and WBC. The reduction of the average PLT and WBC values started in the first weeks after the treatment application, reaching nadir in the 6th week and 8th week, respectively. No life threatening infections were observed in either group of patients.

CONCLUSIONS: After treatment with the use of the ^{90}Y radionuclide, no significant treatment toxicity, including disorders involving the critical organs for both types of therapies, was found in the groups of neuroendocrine tumour and non-Hodgkin's lymphoma patients.

Key words: ^{90}Y -DOTA TATE, ^{90}Y -ibritumomab tiuxetan, neuroendocrine tumours, non-Hodgkin's lymphoma, radioimmunotherapy

Introduction

Oncological diseases are still a challenge to clinicians and inspire the search for new diagnostic and therapeutic procedures. Lately, radionuclide therapy with ^{90}Y -labelled compounds has been introduced in the treatment of neuroendocrine tumours (NET) and non-Hodgkin's lymphomas (NHL).

The beta emitter Yttrium-90 is a radionuclide developed from strontium-90 through beta decay. Yttrium-90 decays, with a half-life of 2.7 days (64 hours), to stable Zirconium-90. The beta particles emitted by ^{90}Y have a maximum energy of 2.27 MeV, which gives a maximum range in tissue of 11.3 mm [1, 2].

Yttrium-90 was until recently administered only locally for the purpose of radiosynovectomy and in coronary artery brachytherapy to prevent stent restenosis [3, 4].

^{90}Y has adequate energy to have a cell killing effect in the tumour, and, in addition, the emission of only beta radiation makes the treatment an outpatient procedure. No risk resulting from gamma radiation to other individuals can be expected [1, 5].

For successful therapy, an appropriate ligand should be chosen to carry the isotope to the place of its action. Ligands influ-

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ence both the course and the side effects of the treatment. Yttrium connected by chelating agent Tiuxetan to the monoclonal antibody against antigen CD20+ expressed on the surface of type B lymphocytes is used in non-Hodgkin's lymphoma radio-immunotherapy (RIT). It enables the direct action of the radiation not only on the tumour, but also on the adjacent neoplastic cells not expressing the antigens on their surface (so-called crossfire effect). In the treatment of the NET, a somatostatin analogue labelled with radionuclide is used. Ligand — chelator — [DOTA, Tyr³] octreotate complex is characterised by the greatest affinity to somatostatin receptor type 2, which is expressed in most of the NETs.

In the case of the application of yttrium-labelled somatostatin analogues (ss) in NET, regarding the properties of the ligand which is secreted by glomerular filtration and later reabsorbed in proximal canaliculi, causing its retention in the interstitial area, an increased kidney irradiation can occur [6]. Therefore, kidneys are the critical organs in therapy using ⁹⁰Y-labelled somatostatin analogues. The indications for the radioisotope NET treatment are the presence of disseminated and/or inoperable tumours previously demonstrating positive somatostatin receptor scintigraphy (SRS). The following ⁹⁰Y-labelled SS are the most important: [DOTA, Tyr³] octreotide (DOTA TOC), DOTA-lanreotide (DOTA LAN) and [DOTA, Tyr³] octreotate (DOTA TATE) [6–8].

For lymphomas, bone marrow becomes the critical organ in the given therapy. Bone marrow toxicity depends mainly on the degree of bone marrow infiltration (an absolute counter-indication for RIT is a bone marrow infiltration of > 25%), as well as on the stem-cell reserve (we should expect higher toxicity in patients with poor-cell bone marrow after failures of earlier applied procedures) [9]. The recent ⁹⁰Y ibritumomab tiuxetan (Zevalin) therapy registration refers to patients suffering from relapse after treatment of low degree malignancy follicular lymphoma, or in Rituximab therapy primary resistance [2, 10]. The safety of the substance and the achieved outcome causes Zevalin to be more and more frequently applied in other types of non-Hodgkin's lymphomas.

In those two types of tumours, different activities of ⁹⁰Y are administered. In the group of NET patients treated in our clinics, the maximum calculated total ⁹⁰Y-DOTA TATE activity reached 7.4 GBq per 1 m² of body surface area (BSA), given in 3 to 5 treatment courses. To obtain nephroprotection, a protective arginine and lysine amino acid infusion before and after the administration of the radiolabelled SS was administered, blocking the capture of the tracer. In the case of lymphomas, the ⁹⁰Y-Zevalin was given once, with activity not exceeding 1.2 GBq [11].

The aim of our study was to evaluate the side effects of therapies using ⁹⁰Y associated with two different types of ligands, in two groups of patients: those with neuroendocrine tumours and those with non-Hodgkin's lymphomas.

Material and methods

Thirty-two patients (19 females and 13 males) aged 37–75 years (mean age 58.03 ± 10.75 years) with histopathologically confirmed NET treated in the Endocrinology Department of the University Hospital in Krakow between 2001 and 2007 were included in the

study. Twenty-nine of them were diagnosed to have disseminated disease. In 3 patients the tumour was inoperable, in 1 subject the primary focus was unknown (UPF). The patients with normal laboratory tests: white blood cells (WBC) > 3000/ul, blood platelet level (PLT) > 100'000/ul, urea < 10 mmol/l, creatinine < 160 umol/l, glomerular filtration rate (GFR) > 40 ml/min and positive [^{99m}Tc-EDDA/HYNIC]octreotate somatostatin receptor scintigraphy qualified for the study.

Radioimmunotherapy (RIT) was applied in 30 patients (16 females and 14 males) aged 41–82 years (mean age 58.73 ± 11.26 years) diagnosed to have non-Hodgkin's lymphoma CD 20+ of stage III and IV according to Ann Arbor classification. All patients were followed-up by the Haematology Department of the University Hospital in Krakow. There were 16 patients with NHL and 14 patients with mantle cell lymphoma. RIT was applied either as first-line treatment, after obtaining partial remission (PR) after first- and second-line treatments, or upon relapse following ineffective immunotherapy or chemotherapy. The patients with bone-marrow infiltration > 25%, with PLT < 100,000/μl, WBC < 2,500/μl, after earlier radiotherapy covering > 30% of the body area, after earlier bone-marrow allo- or auto-transplantation, with active HBV, HCV, HIV infections, and kidney or liver failure were excluded. The patients with mantle cell lymphoma received fludarabine, cyclophosphamide and mitoxantrone (FCM) chemotherapy ± Rituximab in 3–6 cycles every 21 days before RIT. After 3 cycles, qualification for further treatment took place. When the patient failed to meet the qualification criteria (neutrophile level (ANC) < 1,500/μl or blood platelet level (PLT) < 100,000/μl), he or she would obtain subsequent cycles of therapy. If the indices failed to increase after 6 cycles of treatment and the CT examination failed to find tumour mass regression (lymph nodes < 30 mm, spleen < 14 cm), RIT was not applied.

The ⁹⁰Y-DOTATATE (Research and Development IAE Radioisotope Centre Otwock-Świerk, Poland) administered activity of 7.4 GBq/m², given in 3–5 treatment cycles every 4–9 weeks, was calculated for each patient, with respect to body area, assessed from body weight and height. In the case of reduced blood indices, the therapy was postponed by 1–2 weeks. An 8-hour infusion of Vitamin 18 (amino acid preparation) was applied before and after treatment.

The ⁹⁰Y-ibritumomab tiuxetan activity was calculated based on blood platelet level and patient body weight. At the blood platelet level of ≥ 150,000/μl or of 100,000–150,000/μl, the patient received 15 MBq/kg or 11 MBq/kg, respectively, with total activity up to 1200 MBq. A dose of 250 mg/m² of Rituximab was administered a week before RIA, as well as 4 hours before ⁹⁰Y-Zevalin injection. The labelling of the CD 20 + antibodies was performed in the Nuclear Medicine Department (Ibritumomab “cool kit” — antibody and tiuxetan (Yttrium chelator) manufactured by Bayer-Pharma-Schering (BSP), ⁹⁰Y radionuclide by CIS bio International, Gif-sur-Yvette Cedex, France). The radiochemical purity of the radiopharmaceutical after labelling was higher than 95% in all cases.

The patients with NET were treated at the Nuclear Medicine Unit of the Endocrinology Department at the University Hospital in Krakow and at the Nuclear Medicine Department of the Medical University in Warsaw in the period from 2003 to 2007. All of them gave their consent prior to inclusion to the study.

Results

Side effects of the therapy

Morphology

During the follow up of the NET patients treated with ⁹⁰Y-DOTATATE, 59% of them displayed transient reduction of blood indices. A reduction in WBC, greatest after cycles III and IV, was observed. In 19 persons, leucocytosis was reduced by at least Grade 1 toxicity, based on the WHO toxicity grading scale. None of the patients displayed Grade 4 toxicity, while 3 persons displayed Grade 3 toxicity. One patient with WBC of 1360/mm³ was administered Neupogen in the third month after treatment application.

A reduction in average blood platelet count with respect to initial values was observed after treatment, while the average values were maintained within the standard. Haematological toxicity grade 3 in the PLT area was found only in one patient.

A reduction of the average values of haemoglobin after subsequent treatment cycles was observed in some patients. The lowest average haemoglobin levels were found in the fourth month after therapy application. Usually, the haemoglobin level corresponded to that of mild anaemia, while serious anaemia (Grade 3) occurred in 3 patients after the first cycle of treatment, a month after the treatment application, and after the second cycle. Two

patients required administration of two units of red blood concentrate. Figures 1 and 2 present the average values of Hb, WBC and PLT in the patients with NET before and after treatment.

In the group of patients with NHL, the change of indices after treatment concerned mainly PLT, ANC and WBC. The reduction of the average PLT values started in the first weeks after the treatment application, reaching nadir in the sixth week after initiation of the therapy. After 6 months, despite the fact that the average PLT values were coming close to the lower standard boundary, the values were still lower than the initial ones. Grade 4 toxicity occurred in 15 patients (50%) and was maintained in the majority of the patients during 2–3 weeks, while it continued for 8 weeks in one person. Grade 3 occurred in 5 patients (16.6%), staying for 5 weeks in two patients, and 11 weeks in one patient. The lowest average PLT values that occurred in the sixth week amounted to 48,000/mm³. Correct PLT values were maintained in 3 patients after treatment. Twelve patients (40%) required platelet mass transfusion, due to low PLT values and haemorrhagic diathesis symptoms.

Leucopenia after RIT started as early as during the first week after treatment. Nadir occurred in the eighth week (average values of 1,680/mm³). During the subsequent 4 weeks, the average values of the WBC increased to the level of 3,890/mm³. Grade 4 toxicity occurred in 8 patients (26.6%) and Grade 3 in 11 patients (36.6%). The maximum period of Grade 4 toxicity maintenance was

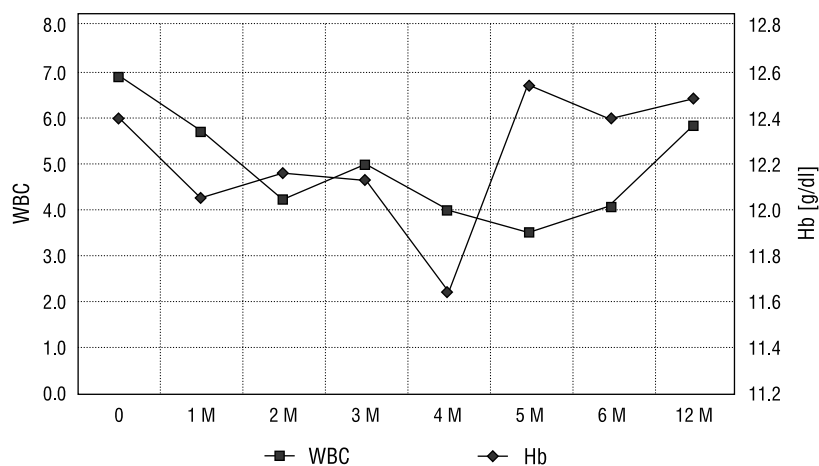


Figure 1. Average haemoglobin (Hb) and white blood cells (WBC) values in patients with neuroendocrine tumours (NET) before, during and after the therapy.

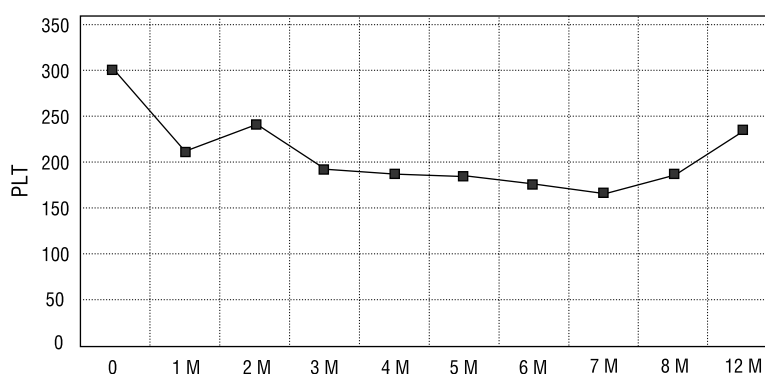


Figure 2. Average blood platelet level (PLT) values in patients with neuroendocrine tumours (NET) before, during and after the therapy.

3 weeks, while in the case of 3 patients, Grade 3 for WBC was maintained for 5 weeks, and 10 weeks in one patient.

The neutrophile value nadir occurred in the sixth week after the treatment application, and the average ANC values amounted to 1010/mm³ at that time. After 4 weeks, the average values of ANC increased to 1,810/mm³. Grade 4 toxicity occurred in 12 patients (40%), while grade 3 occurred in 4 patients (13.3%). In 3 patients, grade 4 toxicity was maintained for 3 weeks. In 6 patients (20%), Neupogen was applied due to leucopenia and granulocytopenia, while 8 patients were treated with antibiotics due to upper respiratory tract infections. Three patients were hospitalised due to infections (pneumonia or neutropenia with fever). None of the patients displayed a life-threatening infection.

Grade 3 toxicity for haemoglobin affected 7 patients (23.3%), while grade 4 occurred in one patient. The haemoglobin nadir, with an average value of 9.77 g/dl, occurred in the eighth week after therapy application. The increase of the average values to the lower standard boundaries was present six months after the treatment application. Ten patients (33.3%) required red blood cell transfusions. Reduced Hb values were maintained during less than 2 weeks, although in one patient they lasted 3 weeks. The Figures present the

average Hb, ANC, WBC (Figures 1, 3) and PLT (Figures 2, 4) values in the patients with NHL before and after treatment.

Kidney function

No statistically significant difference was found in the creatinine values before and after treatment in either group of patients.

In the NET patient group, a reduction of the average GFR values occurred after Cycle IV of the therapy, from the initial 93.09 ml/min to 88.6 ml/min. After 18 months, the reduction of the average GFR to 85.06 ml/min was clearly visible, while the average value for that point of time was calculated on the basis of 7 measurements, 4 of them showed reductions (64, 70, 72, and 86 ml/min). Figure 5 presents average creatinine values before and after treatment in NET and NHL patients.

The creatinine level after Zevalin treatment was higher than normal range (117 umol/l, 94 umol/l after and before the therapy, respectively) in only one patient.

Response to treatment

In the NET patient group, disease stability occurred in 30% of patients, partial remission in 44%, and progression after complet-

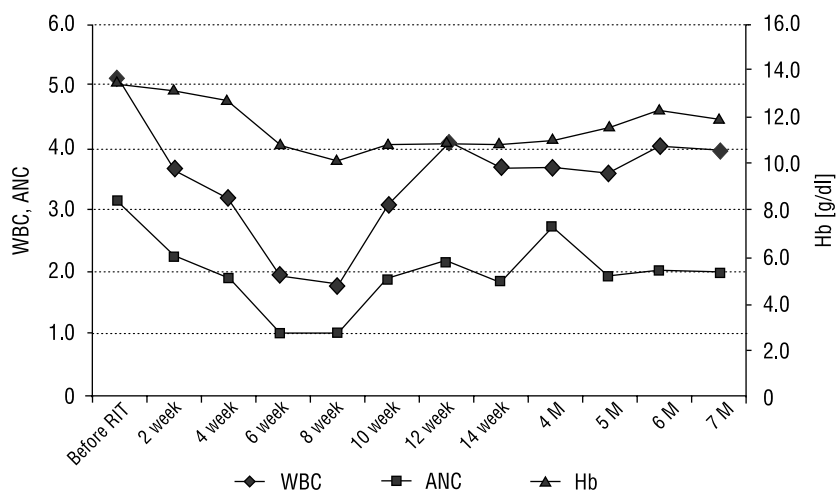


Figure 3. Average haemoglobin (Hb), white blood cells (WBC) and neutrophile level (ANC) values in patients with non Hodgkin's lymphoma (NHL) before and after the therapy.

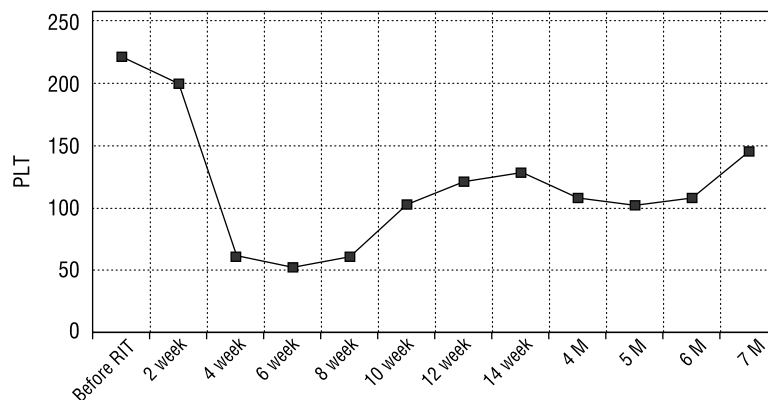


Figure 4. Average blood platelet level PLT values in the patients with non Hodgkin's lymphoma (NHL) before and after the therapy.

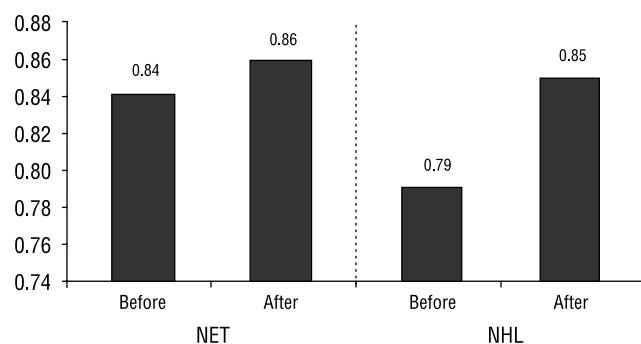


Figure 5. Average creatinine values in patients with neuroendocrine tumours (NET) and non Hodgkin's lymphoma (NHL) before and during 4–6 months of treatment.

ed treatment occurred in 26% of patients. The average time to progression after completed treatment was 17.7 months.

In the NHL patient group, total remission was obtained by 52% of patients, partial remission by 14%, and progression after completed treatment occurred in 34% of patients. The average time to progression after completed treatment was 11.5 months.

Figure 6 presents the proportions of responses to treatment in the NHL and NET patient groups.

Discussion

Radiotherapy toxicity is associated with the influence of ionising radiation not only on tumour cells, but also on healthy cells, although to a lesser degree. As a result of direct irradiation affecting DNA, or the indirect effect resulting from radiolysis of water and the occurrence of free radicals, healthy cells can be destroyed. Doses absorbed by the so-called critical organs after particular types of radiotherapy determine the side effects of radiotherapy when those organs are damaged [9].

The RIT side effects are associated mainly with haematological toxicity, being the largest for blood platelets and neutrophils [11]. In the case of serious neutropenia, patients can obtain a granulocyte growth agent; however, its preventive administration before therapy or in the first several weeks after therapy is not allowed due to the possibility of cell damage induced by irradiation [11]. Based on their analysis of 349 Zevalin treated patients Witzig et al. [11] found that 40% of them displayed grade 1–2 neutropenia, while 30% of them displayed grade 3–4. Despite that, the infection proportion was low, and only 7% of patients required hospitalisation. The analyses conducted by those authors demonstrated that 37% of patients developed mild to medium thrombocytopenia, while 63% developed grade 3–4 thrombocytopenia. The PLT level in 196 patients with grade 3–4 toxicity returned to a value $\geq 50,000/\mu\text{l}$ within 12 weeks after therapy. Anaemia grade 3 and grade 4 occurred in 13% and 4% of subjects, respectively. In the Clayton *et al.* study, red blood cell level reduction (grade 3–4 toxicity) was seen in only 17% of patients [10].

Similarly, in our study the only problem with RIT was haematological toxicity. Leucopenia occurred in 27 patients; 3 patients were free of this side effect. Thrombocytopenia also developed in 27 patients; in 3 patients thrombocytes maintained normal values after treatment. The period of the occurrence of the lowest values

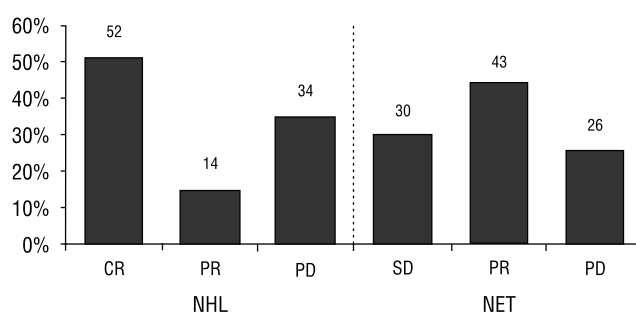


Figure 6. Proportions of response to treatment in patients with neuroendocrine tumours (NET) and non Hodgkin's lymphoma (NHL). CR — complete response; PR — partial response; PD — progression of disease; SD — stabilisation of disease.

of blood indices among our patients, despite the small number of patients in our group, is comparable to the data presented in literature, similarly to the time of maintenance of lowered PLT, WBC and ANC values [11]. The decrease of the blood morphology values started 2–3 weeks after RIT; however, nadir occurred in weeks 7–9. In various groups of lymphomas, we observed a small shift of that period after administration of Zevalin. The period of close monitoring, due to the possibility of the occurrence of agranulocytosis and thrombocytopenia, lasted from 1 to 4 weeks (grade 4 toxicity occurred in 14% and 35% of patients, respectively) [11–13].

Similarly to other reports [10, 11], lower haemoglobin values were not an essential side effect of radioimmunotherapy.

In order to determine the maximum therapeutic activity, literature quotes the data concerning the evaluation of the biodistribution of radiolabelled ^{111}In ibritumomab tiuxetan (^{111}In is a gamma radiation and Auger electron emitter), using MIRDose 3 software. Based on the results of the respective studies, it was calculated that the average absorbed doses of radiation for particular organs, after administration of Zevalin labelled with ^{90}Y at the radioactivity levels of 15 MBq/kg and 11 MBq/kg, in accordance with the Medical Internal Radiation Dosimetry (MIRD), were as follows: 7.42 Gy for spleen, 4.5 Gy for liver, 2.11 Gy for lungs, 0.23 Gy for kidneys, 0.62–0.97 for bone marrow and 0.57 for the whole body. Since no correlation was observed between the dosimetric calculations and haematological toxicity, the dosimetric results do not have a predictive value in the area of the Zevalin toxicity, and that is why the use of dosimetric results is generally not recommended. The estimated doses of radiation absorbed by the healthy organs were much lower than the generally assumed upper boundary values. Based on respective studies, it was found that toxicity correlated with the bone marrow reserves [12]. Nevertheless, that basis was used to establish the maximum activity of the administered ^{90}Y at 1.184 MBq.

Haematological toxicity did not constitute, in general, a serious problem in the case of neuroendocrine tumours. However, among the side effects which may occur after the treatment with radio-labelled somatostatin analogues is bone marrow suppression, most often associated with the application of large doses of radiotherapy (estimated absorbed dose was ca. 3 Gy for bone marrow). Leucopenia with granulocytopenia and thrombocytopenia in grades III or IV of haematological toxicity occurred relatively rarely and were usually of a temporary nature [14]. However, even

when the absorbed dose is lower than the threshold dose for toxicity (mainly in bone marrow), especially in cases of repeated doses, lesions indicating haematological toxicity can occur. Severe grade 3 and 4 haematological toxicity can occur after the [^{90}Y -DOTA 0 , Tyr 3] octreotide treatment, and sporadic cases of myeloblastic syndrome occur after each of the radionuclides [15]. Most frequently, however, similarly to our study group, temporary reduction of blood morphology low indices was observed (grade I and II toxicity) [16].

In the studies by Paganelli et al. [17], among the patients who obtained a cumulative activity of ^{90}Y -DOTA TOC at a level of 6.66–7.77 GBq, 41.7% developed grade 2 haematological toxicity in leukocytes, but the values returned to normal in all cases within 4–6 weeks. Most toxicity in the range of grade 0–1 occurred in doses greater than 5.55 GBq; this was the result of a very low dose being delivered to the bone marrow, as was estimated in dosimetric examinations [18]. In most other published data, reversible haematological toxicity was observed [16, 19, 20]. In the report presented by Otte et al. [21], no significant haematological toxicity (\leq grade 2 toxicity) was observed in 24 out of 29 patients; after treatment with a cumulative activity of \geq 7.4 GBq, 2 out of 5 patients developed anaemia (grade 3) and thrombocytopenia (grade 4) that required treatment.

In our study group, the majority (59%) displayed a temporary reduction of blood indices, especially regarding leukocytes. The WBC values were reduced during subsequent therapies; however, grade 3 haematological toxicity was seen in only 3 patients. Grade 1 and 2 toxicities dominated, as in the specific literature, and were of a temporary nature [14, 16, 17]. Only in one person were reduced leukocyte counts maintained for several months without any clinical symptoms. The reduced leukocyte counts appeared several days after the therapy was applied, but between subsequent cycles their values came back to levels that allowed further treatment, similarly to the results of Waldherr et al. [16]. The values of the remaining indices after the ^{90}Y -DOTA TATE treatment behaved similarly, both for blood platelets and haemoglobin, which were reduced after subsequent therapy cycles, and, similarly to leukocytes, increasing between subsequent cycles and returning to the standard boundaries after completion of the treatment. Our results agree with those available in literature, indicating the temporary nature of the blood morphology changes [14], which could be the result of a low dose delivered to bone marrow [17].

Toxic renal lesions were not observed as side effects of the radioimmunotherapy. Based on the results of the dosimetric examination, it was estimated that the average absorbed dose of radiation in the kidneys amounted to 0.23 Gy (calculated using MIRD methodology), while Zevalin secretion in urine was limited and displayed insignificant differences among the patients. In case of the NET tumours, the administration of the doses estimated for the tumours could be limited by a high dose absorbed by the kidneys [18], while the cumulated dose for kidneys exceeding 27 Gy could become a reason for renal failure. Reduction of renal efficiency may occur even several days after therapy, which is why, after a period of patient observation, it is necessary to evaluate renal function for a longer period after therapy to evaluate the long-term risk of clinically significant renal function deficiency [22]. As a protective action, amino acid infusions are applied to reduce reabsorption of the radiolabelled analogue in proximal canaliculi. A positive charge of arginine and lysine deters reabsorption of the radiolabelled analogue

through renal tubules and its retention by interstitial cells, providing nephroprotection and allowing the administration of higher radionuclide activity [23]. In the study by Otte et al., 5 patients without nephroprotection developed toxic renal lesions after treatment with a cumulative activity of \geq 7.4 GBq. In two of them, stable renal failure developed, while 2 patients given higher cumulative activities required haemodialysis. The increase of creatinine levels was still observed about 2–4 months after the last cycle of treatment.

The study by Jamar et al. [24] demonstrated that 10 hours of an amino acid mixture infusion gave an increase in nephroprotection after [^{90}Y -DOTA 0 -D-Phe1-Tyr 3] octreotide treatment.

A similar experience was described in the results of the work by Rolleman et al. [25]. The studies by Bodei et al. [23] showed the protective action of arginine and lysine amino acid infusions directly before and after therapy, with the infusion of various activities of ^{90}Y -DOTATOC up to a total of 5.55 GBq per cycle. Activity of 5 GBq per cycle is recommended for ^{90}Y -DOTATOC, and amino acids must be applied for nephroprotection. Brans et al. [15] reported that sporadic cases of delayed kidney failure or final stages of the disease that required haemodialysis were observed especially in patients who were treated with activity exceeding 7.4 GBq/m 2 .

In our study group, no essential deterioration of renal function was observed after treatment. This could be explained by protective amino acid infusion and the administration of activity not exceeding 7.4 GBq per patient during the whole treatment cycle [15, 20, 21, 23, 26]. That in turn allowed the cumulative dose for kidneys to be kept at levels below 27 Gy [22]. According to other reports, toxic renal lesions may appear not at the beginning of observations but later; 2–4 months [20, 21], 5 months [16] and even several years after the completion of therapy [22, 27]. In our study group, no kidney failure symptoms occurred with renal function stabilisation; however, the patients remain under observation.

Conclusions

1. After treatment with the use of the ^{90}Y radionuclide, no significant treatment toxicity, including disorders involving the critical organs for both types of therapies, was found in the groups of neuroendocrine tumour and non-Hodgkin's lymphoma patients.
2. Therapy with the application of ^{90}Y radio-labelled somatostatin analogues is a well-tolerated method of neuroendocrine tumour treatment, with the possibility of obtaining clinical outcomes in the form of reduced tumour weight and patient lifespan prolongation.
3. Zevalin is a safe and effective means of therapy in cases of relapsed or resistant non-Hodgkin's lymphoma and in cases of patients with mantle cell lymphoma, influencing the consolidation of the chemotherapeutic effect. This allows the prolongation of patient lifespan with the use of non-arduous therapy.

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