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Hepatic complications of peptide receptor radionuclide therapy with Lutetium-177 and Yttrium-90 in patients with neuroendocrine neoplasm

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Abstract

Neuroendocrine neoplasms (NENs) are a heterogeneous group of tumors originating from neuroendocrine cells spread throughout the body, forming the so-called diffuse endocrine system. The gold standard in treating unresectable or disseminated, progressive, and well-differentiated NENs is therapy with radiolabeled somatostatin analogs (peptide receptor radionuclide therapy — PRRT). PRRT is a method based on peptides combined with beta-emitting radionuclides. The study aimed to assess the early and long-term liver complications after administration of Lutetium-177 or Lutetium-177 combined with Yttrium-90. We enrolled 27 patients treated with [^{177}Lu]Lu-DOTATATE with an activity of 7.4 GBq (200 mCi) and 9 patients received the tandem treatment [^{90}Y]Y-DOTATATE + [^{177}Lu]Lu-DOTATATE with an activity of 3.7 GBq (50 mCi + 50 mCi). In the assessment of early as well as long-term complications, no significant effect of the applied treatment on the parameters of liver injury was found. Regarding liver function PRRT was a safe treatment for patients with highly or moderately differentiated, unresectable, or diffuse NENs.

KEY words: neuroendocrine neoplasms; treatment of neuroendocrine neoplasms; radioisotope treatment; PRRT; complications of radioisotope treatment

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Introduction

Neuroendocrine neoplasms (NENs), formerly called neuroendocrine tumors (NETs), constitute a heterogeneous group of neoplasms. They come from neuroendocrine cells spread throughout the body, forming the so-called diffuse endocrine system (DES). They are considered rare neoplasms, but modern imaging techniques have rapidly increased their detection over the last decades [1–4]. Since 1973, in the United States alone, the number of diagnosed cases of NENs has increased over five times. Currently, the overall incidence rate of NENs is 35 cases per 100,000 persons. The most common location of NENs in the human body is the small intestine, in particular the ileum [5], and 70% of NENs are gastroenteropancreatic (GEP NEN), i.e. about 2% of the general population of gastrointestinal neoplasms [6, 7].

Although the endoscopic or surgical removal of the tumor is the only method of treating the patient ultimately [8–10], the most significant progress in the treatment of highly differentiated NENs of the gastrointestinal tract was achieved by introducing somatostatin analogs (SSA) in 1988 [11]. The analogs bind to the somatostatin receptor causing the inhibition of the cell cycle and inducing a proapoptotic effect. They also have an immunomodulating effect, inhibit angiogenesis, and inhibit the secretion of hormones [12]. Treatment with radioisotope-labeled somatostatin analogs (peptide receptor radionuclide therapy — PRRT) has been used for over 20 years. This method uses peptides combined with radionuclides emitting beta or alpha radiation [13, 14]. In Poland, [^{90}Y]Y-DOTATATE was used for the first time in April 2004, and

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in February 2006 tandem treatment [^{90}Y]Y/[^{177}Lu]Lu-DOTATATE was initiated [15].

The current regimen of PRRT treatment consists of 4 administrations of a selected isotope with a specific activity at eight- to twelve-week intervals. The most common side effects are kidney injury and myelosuppression, found relatively rarely in patients treated with PRRT [13]. Acute hematological complications (World Health Organization [WHO] grade 3 or 4) occur in less than 13% of patients receiving Yttrium-90 and 3% of patients receiving Lutetium-177. On the other hand, acute renal complications depend mainly on the radiopharmaceuticals' activity and comorbidities [16–20]. There are limited data on hepatic complications. The Endocrinology and Isotope Therapy Department of the Military Institute of Medicine in Warsaw covers the largest group of patients with NENs undergoing PRRT in Poland and Central and Eastern Europe. Due to the small number of studies and inconclusive results, we decided to assess such complications in this group of patients.

The study aimed to assess the early and long-term hepatic complications after radioisotope treatment using Lutetium-177 or Lutetium-177 in combination with Yttrium-90 in patients with neuroendocrine neoplasm.

Material and methods

Study population

The presented paper is a preliminary study evaluating early and long-term complications of radioisotope treatment in patients with NENs. The study group consisted of 36 patients treated with PRRT due to NENs from November 2017 to June 2019 in the Department of Endocrinology and Isotope Therapy of the Military Institute of Medicine in Warsaw. All patients qualified to PRRT at that time gave their written consent to participate in the study.

The local Bioethics Committee approved the study at the Military Institute of Medicine. All procedures carried out in the study followed the Helsinki Declaration of 1964 and its subsequent changes. Patients to be enrolled had to meet the following inclusion criteria: a) a highly differentiated, progressive neuroendocrine neoplasm defined as Ki-67 $<$ 20% (progression within the last 12 months); b) good expression of somatostatin receptors in a qualifying receptor scintigraphy study (single photon emission computed tomography [SPECT]) or positron emission tomography/computed tomography (PET/CT); c) no more options for surgical treatment possible and d) chronic treatment with long-acting somatostatin analogs. The exclusion criteria were: a) the patient's lack of consent to treatment; b) pregnancy or lactation; c) assessment of the patient's performance status based on the World Health Organization/Eastern Cooperative Oncology Group (WHO/ECOG) status 3 or 4 or the basis of the Karnofsky classification ($<$ 60); d) no uptake of the radiotracer in the somatostatin receptors imaging (SRI); e) bone marrow failure: hemoglobin less than 8 g/dL, platelets less than 80 $\times$ 10^3/μL, leukocytes below 2 $\times$ 10^3/μL, lymphocytes below 0.5 $\times$ 10^3/μL, neutrophils less than 1 $\times$ 10^3/μL; f) creatinine clearance $<$ 30 mL/min, blood urea nitrogen over 45 mg/dL or serum creatinine concentration over 1.8 mg/dL; g) liver injury (3-fold increase in bilirubin); h) systemic infections; i) glomerulonephritis; j) interstitial nephritis; k) obstructive nephropathy or l) urinary tract infection.

Treatment strategies

Patients were given an intravenous infusion of [^{177}Lu]Lu-DOTATATE with an activity of 7.4 GBq (200 mCi) or tandem treatment [^{90}Y]Y-DOTATATE + [^{177}Lu]Lu-DOTATATE with an activity of 3.7 GBq (50 mCi + 50 mCi) (ItraPol and LutaPol, manufacturer: National Center for Nuclear Research, POLATOM Radioisotope Center, Otwock, Poland). In addition, selected biochemical parameters were assessed before and after the radioisotope administration. For two days, patients also received infusions of 10% amino acid solution (Nephrotect, Fresenius Kabi) (1000 mL on the first day, 500 mL on the second day) and Ringer's solution (2 x 500 mL). Treatment with long-acting somatostatin analogs (octreotide - Sandostatin LAR; Novartis and lanreotide autogel — Somatuline; Ipsen) was discontinued for at least four weeks prior to PRRT administration. The time since completion of prior chemotherapy was more than three months.

In total, the therapy (4 courses) lasted on average nine months (7–11 months). After the fourth course, patients were scheduled for follow-up visits, which were performed approximately 18 months from the start of the therapy (10 months from the end of radioisotope treatment). The following parameters were checked at each stage of the study: serum albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin. Detailed procedures are as follows: day 1 — history taking and physical examination, serum albumin, ALT, AST, bilirubin; day 2 — intravenous administration of 1000 mL of positively charged amino acids with a simultaneous infusion of 500 mL Ringer's solution - a continuous infusion of 8 hours, intravenous infusion of radioisotopes [^{177}Lu]Lu-DOTATATE or [^{90}Y]Y-DOTATATE + [^{177}Lu]Lu-DOTATATE (a radiopharmaceutical solution in 100 mL 0.9% NaCl); day 3 — intravenous administration of 500 mL of positively charged amino acids with a simultaneous infusion of 500 mL of Ringer's fluid — a continuous infusion of 4 hours; day 4 — serum albumin, ALT, AST, bilirubin, post-therapeutic scintigraphy, and patient's discharge. Follow-up tests (clinical and laboratory) were performed during a one-day hospitalization. The biochemical tests were performed in the Department of Laboratory Diagnostics of the Military Institute of Medicine using an automatic biochemical analyzer (Cobas C 501, Roche Diagnostics).

Statistical methods

Statistical analyzes were performed with the use of the IBM SPSS Statistics 25. It was used to analyze basic descriptive statistics with the Shapiro-Wilk test, two-factor analysis of variance in a mixed schema, and Mann-Whitney U tests. The classical threshold α = 0.05 was considered the level of significance. Acute complications were assessed during the 1st and 4th course. Long-term complications were evaluated based on comparing the results obtained before the 1st course, before the 4th course, and during the follow-up examination. Data were also analyzed depending on the type of the applied therapy, sex, age, BMI,

comorbidities (chronic kidney disease, diabetes, hypercholesterolemia, hypertension), NEN point of origin, and the history of chemotherapy.

Results

The study group consisted of 36 patients, including 16 women (44.5%) and 20 men (55.5%). Details are presented in Table 1. The mean age was 58.1 ± 13.1. Twenty-seven patients received [^{177}Lu]Lu-DOTATATE with an activity of 7.4 GBq (200 mCi), and nine patients received the tandem treatment [^{90}Y]Y-DOTATATE + [^{177}Lu]Lu-DOTATATE with an activity of 3.7 GBq (50 mCi + 50 mCi). Thirty patients completed full treatment (6 dropouts: 2 — disease progression, 1 — myelosuppression, 1 — the death of unknown cause, 2 — withdrawals). Long-term follow-up was not performed in 11 patients because of the Covid-19 pandemic.

The mean body mass index (BMI) was 24.9 kg/m^2, and 50% of patients had normal BMI values. The most common comorbidities were arterial hypertension (41.66%) and diabetes (27.8%). Their frequency was significantly higher in the studied group than in the general population (41.66% vs 31.5% in the case of hypertension and 27.8% vs 9.1% in the case of diabetes). Pancreatic NENs (13/36) and small intestine NENs (11/36) were the most frequent. The percentage of patients with G1 and G2 stages was similar (47.2% vs 52.8%). The median time from disease diagnosis to initiation of radioisotope treatment was 3.4 years (range 0–15 years).

Most patients had liver metastases (91,7%). The three remaining cases had metastases only to lymph nodes and bone, including pulmonary NENs, paraganglioma, and one case with an unknown point of origin. Before PRRT therapy, 6 patients received chemotherapy for: NEN (1 patient — doxorubicin with etoposide, 2nd patient — everolimus, 3rd — capecitabine with temozolomide), breast cancer (1 patient, drug unknown), and colorectal adenocarcinoma (2 patients, unknown drugs). Before PRRT 77,8% of patients had primary NEN lesions surgically removed. Only in 8 cases, the primary tumor was not removed (1 patient did not consent to surgical treatment of a pancreatic tumor, in 6 patients, the lesions were unresectable at the time of diagnosis, one person could not be operated on due to anesthetic contraindications). Additionally, hemihepatectomy was performed in 2 patients, thermoablation — in 2 patients, and liver embolization in — 1 patient.

Table 1. Characteristics of the study population

Characteristics	Value
Age (years)	
Mean	58.1 ± 13.1
Range	23–76
Sex	
Women	19
Men	23
Place of residence	
Village	12
Town < 100,000 citizens	10
City > 100,000 citizens	20
BMI (kg/m^2)	
Mean	24.9 ± 5.2
Range	16.4–41.3
< 18.5	3 (7.1%)
18.5–24.9	21 (50%)
25.0–29.9	12 (28.6%)
≥ 30.0	6 (14.3%)
Comorbidities	
Chronic kidney disease G3	6 (14.3%)
Arterial hypertension	18 (42.9%)
Diabetes mellitus	12 (28.6%)
Hypercholesterolemia	6 (14.3%)
Primary NENs point of origin	
Pancreas	15 (35.6 %)
Jejunum	13 (30.9 %)
Colon	5 (12%)
Others	5 (12%) (2 × ovary, 1 × stomach, 1 × paraganglioma,1 × lung)
Unknown	4 (9.5%)
Grading	
G1	20 (48%)
G2	22 (52%)
G3	0

BMI — body mass index

Acute complications after the 1st course

During the 1st course of PRRT, a slight but statistically significant decrease in the mean serum albumin concentration ($p < 0.001$) and ALT activity ($p = 0.002$), as well as an increase in the mean bilirubin concentration ($p = 0.003$), was observed (Tab. 2). However, these changes remained within the normal ranges. The type of therapy used, age, sex, BMI of the subjects, comorbidities, and the NEN point of origin did not affect the observed changes in hepatic parameters. It was only noted that in patients with a history of prior chemotherapy, the mean concentration of bilirubin slightly decreased after the first administration of radioisotopes ($p < 0.001$).

Acute complications after the 4th course

The biochemical parameters assessing liver function obtained during the 4th course are presented in Table 3. There was a slight, statistically significant decrease in serum albumin concentration ($p < 0.001$); however, it remained within the normal limits. There was no correlation between changes in albumin concentration and age, sex, and BMI of the subjects, the presence of chronic diseases, the NEN point of origin, and the type of therapy used. There were also no other significant changes in the parameters of hepatocyte injury.

Table 2. Changes in hepatic parameters during the first peptide receptor radionuclide therapy (PRRT) course

Parameter	Before the 1st course (n = 36)		After the 1st course (n = 36)			[177Lu]Lu-DO-TATATE (n = 27)		[90Y]Y/[177Lu] Lu-DOTATATE (n = 9)			Pancreas (n = 13)		Other locations (n = 23)		
	M	SD	M	SD	p	Δ	SD	Δ	SD	p	Δ	SD	Δ	SD	p
Serum albumin [mg/dL]	4.52	0.51	4.28	0.53	< 0.001	–0.30	0.34	–0.17	0.23	0.275	–0.26	0.40	–0.27	0.28	0.945
AST [IU/L]	25.48	10.97	23.33	9.92	0.086	–2.66	8.52	–0.82	5.12	0.509	–1.23	5.36	–2.59	8.69	0.608
ALT [IU/L]	25.80	18.20	22.20	14.88	0.002	–2.76	8.12	–6.00	4.47	0.220	–4.64	9.11	–3.12	6.42	0.540
Bilirubin [mg/dL]	0.65	0.42	0.76	0.45	0.003	0.09	0.20	0.15	0.25	0.463	0.13	0.23	0.09	0.20	0.611

AST — aspartate aminotransferase; ALT — alanine aminotransferase; M — mean, Δ — change; SD — standard deviation; p — the level of significance

Table 3. Changes in hepatic parameters during the 4th peptide receptor radionuclide therapy (PRRT) course

Parameter	Before the 4th course (n = 30)		After the 4th course (n = 30)			[177Lu]Lu-DO-TATATE (n = 23)		[90Y]Y/[177Lu] Lu-DOTATATE (n = 7)			Pancreas (n = 11)		Other locations (n = 19)		
	M	SD	M	SD	p	Δ	SD	Δ	SD	p	Δ	SD	Δ	SD	p
Serum albumin [mg/dL]	4.57	0.33	4.37	0.33	< 0.001	–0.20	0.26	–0.21	0.22	0.922	–0.16	0.25	–0.23	0.26	0.433
AST [IU/L]	24.34	9.05	22.71	7.71	0.106	–2.22	5.74	0.38	5.90	0.272	–1.91	4.74	–1.50	6.31	0.850
ALT [IU/L]	23.42	12.82	21.56	11.47	0.382	–2.50	5.22	0.43	8.96	0.434	–2.46	7.16	–1.59	5.53	0.690
Bilirubin [mg/dL]	0.62	0.40	0.71	0.48	0.110	0.04	0.14	0.29	1.05	0.557	–0.05	0.28	0.17	0.54	0.196

AST — aspartate aminotransferase, ALT — alanine aminotransferase, M — mean, Δ — change, SD — standard deviation, p — the level of significance

Table 4. Changes in hepatic parameters before treatment initiation and before the 4th peptide receptor radionuclide therapy (PRRT) course

Parameter	Before the 1st course (n = 30)		Before the 4th course (n = 30)			[177Lu]Lu-DO-TATATE (n = 23)		[90Y]Y/[177Lu] Lu-DOTATATE (n = 7)			Pancreas (n = 11)		Other locations (n = 19)		
	M	SD	M	SD	p	Δ	SD	Δ	SD	p	Δ	SD	Δ	SD	p
Serum albumin [mg/dL]	4.61	0.39	4.58	0.33	0.564	–0.09	0.32	0.17	0.38	0.075	–0.05	0.35	–0.02	0.35	0.810
AST [IU/L]	24.82	10.54	24.56	9.09	0.858	–0.69	9.41	1.13	5.38	0.608	0.10	8.06	–0.42	8.96	0.876
ALT [IU/L]	25.91	19.14	23.60	12.96	0.756	–3.41	16.43	1.71	15.87	0.465	–2.00	21.75	–2.57	12.25	0.922
Bilirubin [mg/dL]	0.64	0.43	0.63	0.40	0.685	–0.05	0.29	0.13	0.31	0.159	–0.02	0.36	–0.01	0.27	0.992

AST — aspartate aminotransferase, ALT — alanine aminotransferase, M — mean, Δ — change, SD — standard deviation, p — the level of significance

Chronic complications

1st course vs 4th course — the first assessment of chronic hepatic complications

Before the 4th course, as compared to the tests performed before the 1st course (i.e., after approx. eight months from the start of PRRT), no biochemical features of hepatocyte damage or disturbances in the synthetic function of the liver were found (Tab. 4).

4th course vs follow-up visit – the 2nd assessment of chronic hepatic complications

In the second long-term evaluation, in the control tests compared to the tests before the 4th course (approximately ten months after the end of PRRT), a slight statistically significant (p = 0.007) increase in ALT, remaining within the reference range, was found. This increase was statistically significantly higher in the group of patients receiving tandem therapy (p = 0.010) and in the group of patients with the NEN point of origin in the pancreas (p = 0.049). The increase in ALT was also higher in men (p = 0.015) and patients with diabetes (p = 0.024). However, no disturbances in the synthetic function of the liver were found. Detailed results are presented in Table 5.

1st course vs follow-up visit – the long-term assessment of hepatic complications

In the follow-up at 18 months after the start of treatment, compared to the baseline lab tests before the first course of therapy, in the entire group of patients, no biochemical features of hepatocyte injury or disturbances in the synthetic function of the liver were

Table 5. Changes in hepatic parameters before the 4th peptide receptor radionuclide therapy (PRRT) course and the follow-up

Parameter	Before the 4th course (n = 19)		Follow-up (n = 19)			[177Lu]Lu-DOTATATE (n = 16)		[90Y]Y/[177Lu]Lu-DOTATATE (n = 3)			Pancreas (n = 7)		Other locations (n = 12)		
	M	SD	M	SD	p	Δ	SD	Δ	SD	p	Δ	SD	Δ	SD	p
Serum albumin [mg/dL]	4.60	0.42	4.51	0.40	0.172	–0.06	0.40	–0.30	0.36	0.343	0.09	0.37	–0.20	0.39	0.133
AST [IU/L]	29.42	16.68	25.42	10.00	0.402	5.25	20.51	17.67	11.02	0.329	6.71	8.88	7.50	24.24	0.936
ALT [IU/L]	23.95	14.18	26.95	20.82	0.007	0.44	8.81	16.67	9.29	0.010	9.14	10.75	–0.58	9.00	0.049
Bilirubin [mg/dL]	0.70	0.46	0.64	0.35	0.309	–0.03	0.20	0.17	0.06	0.118	0.06	0.21	–0.03	0.19	0.356

AST — aspartate aminotransferase, ALT — alanine aminotransferase, M — mean, Δ — change, SD — standard deviation, p — the level of significance

Table 6. Changes in hepatic parameters before the initiation of therapy and in the follow-up visit

Parameter	Before the 1st course (n = 19)		Follow-up (n = 19)			[177Lu]Lu-DOTATATE (n = 16)		[90Y]Y/[177Lu]Lu-DOTATATE (n = 3)			Pancreas (n = 7)		Other locations (n = 12)		
	M	SD	M	SD	p	Δ	SD	Δ	SD	p	Δ	SD	Δ	SD	p
Serum albumin [mg/dL]	4.61	0.43	4.51	0.40	0.712	0.19	0.48	0.17	0.25	0.927	0.26	0.44	0.15	0.47	0.629
AST [IU/L]	29.33	17.16	26.11	10.17	0.545	4.69	19.41	17.00	9.54	0.306	4.00	10.52	8.17	22.31	0.651
ALT [IU/L]	26.11	23.70	26.95	20.82	0.232	–0.13	13.58	23.33	22.50	0.023	5.57	22.55	2.42	13.73	0.707
Bilirubin [mg/dL]	0.68	0.36	0.64	0.35	0.505	–0.19	0.36	–0.13	0.55	0.807	–0.33	0.36	–0.10	0.38	0.212

AST — aspartate aminotransferase, ALT — alanine aminotransferase, M — mean, Δ — change, SD — standard deviation, p — the level of significance

found. However, it was noticed that in the group of patients treated with [90Y]Y/[177Lu]Lu-DOTATATE, there was a statistically significant increase in ALT (p = 0.023), and in the group of patients receiving chemotherapy in the past, a slight increase in bilirubin concentration, but within the reference range (p = 0.017) was observed. Detailed results are presented in Table 6.

Hepatic complications of PRRT according to CTCAE version 5.0

According to the Common Terminology Criteria for Adverse Events (CTCAE v 5.0) of the US National Cancer Institute, early and late hepatic complications are presented in Tables 7 and 8. Grade 3 and 4 (G3, G4) hepatic complications were not observed after the first administration of radioisotopes. On the other hand, a slight decrease in albumin concentration was found, which caused an increase in adverse event grade 1 and 2 groups. After the first PRRT course, an increase in bilirubin concentration was also noticed, as a result of which an increase in G1 and G2 groups was also found (Tab. 7). In the evaluation of long-term complications, no grade 2, 3, or 4 (G2, G3, G4) hepatic complications were found (Tab. 8).

Discussion

In the presented study, no hepatotoxicity of the applied radioisotope treatment was found in both short and long-term follow-up. The presence of metastatic lesions in the liver, which occurred in 91.7% of the patients, prior chemotherapy and previous locoregional treatment aimed at metastatic lesions in the liver also did not affect the deterioration of liver parameters. The slight increase in ALT activity was associated with tandem therapy, the location of the NENs primary origin in the pancreas, and the diagnosis of diabetes at the follow-up visit.

In the available literature, hepatotoxicity is also a rare complication of PRRT. It has been most frequently reported in patients with large and extensive hepatic metastases (size > 5 cm) [21, 22]. In the NETTER-1 study, the elevation of AST activity of grade 3 or 4 according to CTCAE v 5.0 was found in 4.5%, ALT — in 3.6%, and bilirubin concentration — in 1.8% of patients [23]. Brabander et al. [24], in a study assessing long-term efficacy, survival, and safety of [177Lu]Lu-DOTATATE, noticed the elevated activity of AST and/or ALT (grades 3 or 4 CTCAE v 4.0) only in 3% of patients.

In the literature, patients with NENs with little or no hepatic metastases showed no evidence of significant liver injury [25–27]. However, severe liver damage may occur in a group of patients with extensive liver metastases and/or abnormal liver function. In other words, the safety of using PRRT in a patient with 25% liver involvement is not the same as the safety of treating a patient with 50%, or even 75%, organ involvement. They should also be considered in the case of preexisting liver disease or conditions affecting liver function. Then it is important to choose the right radioisotope and its activity. In such cases, Lutetium-177 labeled peptides are recommended, and the reported activity should be appropriately

Table 7. Early complications according to the Common Terminology Criteria for Adverse Events (CTCAE v 5.0) classification

	Before the 1st course		After the 1st course			In total before the 1st course (%)	In total after the 1st course (%)
	G1 (%)	G2 (%)	G1 (%)	G2 (%)	G3 (%)		
Serum albumin [mg/dL]	2 (5.6)	1 (2.8)	3 (7.7)	2 (5.1)	0	3/36 (8.4)	5/36 (12.8)
AST [IU/L]	5 (13.9)	0	2 (5)	0	0	5/36 (13.9)	2/36 (5)
ALT [IU/L]	6 (16.7)	0	4 (10)	0	0	6/36 (16.7)	4/36 (10)
Bilirubin [mg/dL]	1 (2.8)	1 (2.8)	3 (7.5)	2 (5)	0	2/36 (5.6)	5/36 (12.5)

AST — aspartate aminotransferase, ALT — alanine aminotransferase

Table 8. Long-term complications according to the Common Terminology Criteria for Adverse Events (CTCAE v 5.0) classification

	Before the 1st course		Follow-up			In total before the 1st course (%)	In total at follow-up (%)
	G1 (%)	G2 (%)	G1 (%)	G2 (%)	G3 (%)		
Serum albumin [mg/dL]	2 (5.6)	1 (2.8)	1 (5.3)	0	0	3/36 (8.4)	1/19 (5.3)
AST [IU/L]	5 (13.9)	0	5 (26.3)	0	0	5/36 (13.9)	5/19 (26.3)
ALT [IU/L]	6 (16.7)	0	3 (15.8)	0	0	6/36 (16.7)	3/19 (15.8)
Bilirubin [mg/dL]	1 (2.8)	1 (2.8)	1 (5.3)	0	0	2/36 (5.6)	1/19 (5.3)

AST — aspartate aminotransferase, ALT — alanine aminotransferase

reduced. In 2015 there were published the results of a retrospective study in which 17 patients from the United States of America (USA) were treated with a radioisotope in a Swiss center in Basel. The study evaluated 93 patients with confirmed NENs with liver metastases. Seventeen subjects (18%), after confirming disease progression despite using other traditional therapies available in the USA at that time, were qualified for PRRT treatment in various regimens using various radioisotopes: Yttrium-90, Lutetium-177, Indium-11, or tandem therapy (Lutetium-177 with Yttrium-90). The two study groups (treated or not with PRRT) did not differ in sex, age, baseline laboratory parameters, prior exposure to treatment, or disease duration. In the group not subjected to PRRT, 23 of 76 (30%) patients had increased liver injury markers associated with the use of traditional GEP NET therapy (surgery, chemoembolization, treatment [^{131}I]I-meta-iodobenzylguanidine). In 10 of 17 (59%) patients treated with PRRT, biochemical features of liver injury were found, while ascites occurred in 41% of patients in this group, compared with 6.5% in the second cohort. The higher incidence of hepatotoxicity in that group treated with radioisotope therapy, significantly higher than the one reported so far, could result from the delayed duration of PRRT use (this therapy was not available in the USA at that time) and the previous use of locoregional therapy (surgical treatment, chemoembolization or thermoablation of focal lesions in the liver, [^{131}I]I-MIBG treatment), causing more radiation damage to the liver [28].

In the study published in 2020 by Spanish researchers, one patient (out of a total of 36 treated with [^{177}Lu]Lu-DOTATATE) with extensive liver metastases present had a significant degree of liver injury. Liver parameters deteriorated within weeks after the first administration of the radioisotope, and the patient died of liver failure five weeks later. In the remaining 35 subjects, however, no signs of liver injury were observed [29]. Therefore, there are concerns regarding the safety of radioisotope therapy in patients with high liver involvement by metastatic lesions due to the possibility of radiation hepatitis. However, data published in 2020 from the NETTER-1 study did not support this hypothesis. The increase in liver injury markers was rare and did not appear to correlate with the extent of the neoplastic disease [30]. In the NETTER-1 study, the subgroup of patients with extreme liver parenchymal involvement (> 90%) was not defined; therefore, no detailed safety analysis could be made in this subgroup.

In many patients, NENs are detected when the disease is already advanced. Often, however, it is limited to the liver only, where it is metastasizing from the intestines. In some cases, it is suggested to combine selective internal radiotherapy and PRRT by administering a somatostatin analog conjugated with Lutetium-177 or Yttrium-90 directly through the hepatic artery [31]. Theoretically, this ensures the delivery of higher radioisotope activity to the tumor itself (improving the effectiveness of treatment) while reducing its activity in the systemic circulation (reducing side effects). Initial results of such therapy show that it can be successfully used [31]. Moreover, radioembolization of metastatic lesions in the liver after systemic radionuclide treatment was also shown to be safe, and liver damage induced by this procedure was shown to be rare [32]. However, studies directly comparing these forms of therapy with systemic PRRT administration have not been conducted so far [33].

In our study, we did not observe any significant deterioration of liver parameters. This is most likely since PRRT has been used in Poland for almost 20 years and is a therapeutic option started in the early stages of NEN progression when there is no significant involvement of the liver parenchyma by metastatic lesions. In the presented study, five patients underwent prior locoregional treatment (hemihepatectomy — 2 patients, thermal ablation — 2 patients, or embolization of liver lesions — 1 patient) before starting PRRT, which may have somewhat reduced the adverse events of PRRT on liver function in our study. Furthermore, both in our study and the available literature, the type of radioisotope therapy used did not deteriorate liver parameters and function.

Study limitations

The presented paper, although preliminary, is one of the few prospective studies; however, it has some limitations. First, the study was conducted on a relatively small number of patients. Despite almost two years of recruitment, and in the center with a large number of isotope therapies per year, and the low incidence of neuroendocrine neoplasms, it was impossible to collect the larger group. The COVID-19 pandemic also played a significant role in this regard, due to which some patients did not survive to the end of the study or follow-up visit. Nevertheless, the presented group allowed obtaining many important and interesting results that undoubtedly require further research.

Conclusions

Our study showed that radioisotope treatment and its type did not affect the liver parameters in both early and long-term follow-up. Regarding liver function, treatment of NENs using Lutetium-177 or Yttrium-90/Lutetium-177 isotopes appeared to be safe.

Conflict of interest

None declared.

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