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Original Article

Nephrotoxicity and hematotoxicity one year after four cycles of peptide receptor radionuclide therapy (PRRT) and its impact on future treatment planning — A retrospective analysis☆

Bernhard Nilica[a,*], Anna Svirydenka[a], Josef Fritz[b], Steffen Bayerschmidt[a], Alexander Kroiss[a], Leonhard Gruber[c], Irene Johanna Virgolini[a]

[a] Medical University Innsbruck, Department of Nuclear Medicine, Austria
[b] Medical University Innsbruck, Department of Medical Statistics and Informatics, Austria
[c] Medical University Innsbruck, Department of Radiology, Austria

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ABSTRACT

Purpose: Nephro- and hematotoxicity after peptide receptor radionuclide therapy (PRRT) have been described in multiple studies with heterogeneous cumulative activities, number of cycles or radiolabelled peptides. Though highly differentiated metastasized neuroendocrine tumours (NET) have long progression free survival, they may progress. We analysed long-term side effects in a homogenous treatment schedule in PRRT-patients and their impact on future oncologic treatment in case of progression.
Methods: From our database 89/384 patients receiving the same PRRT (Lu-177-DOTATATE or Y-90-DOTATOC) 4 times every 10–12 weeks and a follow-up at 12 months were analysed. One patient had three and 11 patients had two times four PRRT-cycles resulting in 102 cases. eGFR, Hb, WBC and platelets before the first and one year after the fourth therapy cycle were compared. eGFR-Grading was done according to chronic kidney disease classification (CKD) and grading of hematotoxicity according to CTCAE. Impact of age, gender, cumulative activity, type of PRRT on long-term-toxicity was also assessed.
Results: eGFR grade 1–2 dropped from 87/102 at the baseline to 71 cases at follow-up ($p < 0.001$). Before treatment grade 3a was found in 13, grade 3b in 2 cases, and at follow-up grade 3a in 25, grade 3b in 5, and grade 4 in 1 case. Anaemia prior to PRRT and at follow-up was grade 0 in 63 versus 48 ($p < 0.001$), grade 1 in 36 versus 48, and grade 2 in three versus six cases. In white blood cell count and platelets, there were no significant changes in grading occurring. Subgroup analysis revealed that only in the age group 65 and older was there a higher incidence for anaemia ($p = 0.006$).
Conclusion: In roughly 20% of cases an increase in grading of nephro- or hematotoxicity is observed. In those patients, except in one, toxicity findings were mild or moderate one year after completion of four cycles of PRRT with either Y-90- or Lu-177-SST-analogues. In terms of safety, PRRT has no critical impact on further oncologic treatment options in the case of disease progression.

Nefrotoxicidad y hematotoxicidad un año después de cuatro ciclos de terapia con péptidos marcados con radionúclidos (PRRT) y su impacto en la planificación del tratamiento futuro — un análisis retrospectivo

Palabras clave:
90Y-DOTATATO
177Lu-PRRT
Nefrotoxicidad
Hematotoxicidad

RESUMEN

Propósito: La nefrotoxicidad y la hematotoxicidad después de la terapia con péptidos marcados con radionúclidos (PRRT) se han descrito en múltiples estudios usando diferentes actividades acumulativas, número de ciclos o péptidos marcados con radionúclidos. Aunque los tumores neuroendocrinos (NET) altamente diferenciados con metástasis tienen una larga supervivencia libre de progresión, pueden progresar. Analizamos los efectos secundarios a largo plazo en un esquema de tratamiento homogéneo en pacientes con PRRT y su impacto en el futuro tratamiento oncológico en caso de progresión.
Métodos: De nuestra base de datos se analizaron 89/384 pacientes que recibieron la misma PRRT (Lu-177-DOTATATE o Y-90-DOTATOC) 4 veces cada 10 a 12 semanas y un seguimiento a los 12 meses. Un paciente recibió tres y 11 pacientes recibieron dos veces cuatro ciclos de PRRT, lo que dio lugar a 102 casos. Se

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* Corresponding author.
E-mail address: bernhard.nilica@tirol-kliniken.at (B. Nilica).

compararon la TFG, la Hb, los glóbulos blancos y las plaquetas antes del primer ciclo de terapia y un año después del cuarto ciclo. La clasificación de la TFG se realizó según la clasificación de la enfermedad renal crónica (ERC) y la clasificación de la hematotoxicidad según el CTCAE. También se evaluó el impacto de la edad, el sexo, la actividad acumulada y el tipo de PRRT en la toxicidad a largo plazo.
Resultados: El grado 1–2 de la TFG se redujo de 87/102 al inicio a 71 casos en el seguimiento ($p < 0{,}001$). Antes del tratamiento se encontró grado 3a en 13, grado 3b en 2, y en el seguimiento grado 3a en 25, grado 3b en 5 casos, y grado 4 en 1 caso. La anemia antes de la PRRT y en el seguimiento fue de grado 0 en 63 versus 48 ($p < 0{,}001$), de grado 1 en 36 versus 48, y de grado 2 en tres versus seis casos. En el recuento de glóbulos blancos y plaquetas no se produjeron cambios significativos en la clasificación. El análisis de subgrupos reveló que sólo en el grupo de edad de 65 años o más hubo una mayor incidencia de anemia ($p = 0{,}006$).
Conclusión: En aproximadamente 20% de los casos se observa un aumento de la gradación de la nefrotoxicidad o hematotoxicidad. En estos pacientes, excepto en uno, los niveles de toxicidad fueron leves o moderados un año después de completar cuatro ciclos de PRRT con análogos de Y-90 o Lu-177-SST. En términos de seguridad, la PRRT no tiene un impacto crítico en las opciones de tratamiento oncológico posterior en caso de progresión de la enfermedad.

Introduction

Peptide receptor radionuclide therapy (PRRT) with either Y-90- or Lu-177-somatostatin receptor (SSTR) targeted agents has been successfully used over the last two decades in patients with neuroendocrine tumours (NETs) following the initial report by Krenning et al.[1] The main indication for PRRT is differentiated, non-resectable or metastatic NET showing SSTR-expression and low proliferation index, i.e. grade 1 and 2 NET.[2] The Phase 3 trial of Lu-177-DOTA-Tyr3-octreotate (Lu-117-DOTATATE) in advanced midgut NETs grade 1 or 2 (NETTER-1) resulted in a markedly longer progression free survival (PFS) and a significantly higher response rate compared to long-acting repeatable (LAR) octreotide alone.[3] A study to evaluate the efficacy and safety of Lu-177-DOTATATE in patients with grade 2 and grade 3 advanced NET (NETTER-2) is currently on the way.[4] The intended treatment regimen of Lu-177-DOTATATE (LUTATHERA®) consists of four intravenous infusions of 7.4 GBq (200 mCi) Lu-177-DOTATATE, 10–12 weeks apart, plus best supportive care including octreotide LAR.[5]

Dosimetry is useful to assess the radiation risk for normal and critical organs, i.e. bone marrow and kidneys after PRRT. Radiolabelled SST-analogues are reabsorbed in the renal proximal tubules, thus, the kidneys are exposed to a relatively high radiation dose. Renal uptake, hence renal radiation exposure, can be reduced by coinfusion of aminoacids during PRRT.[6] The standard activity of 7.4 GBq (200 mCi) Lu-177-DOTATATE (i.e. planned activity) may be reduced in the case of pretherapeutic relevant renal impairment, or low white blood cell count. At our centre we also use Y-90-DOTA- Tyr3-octreotide (Y-90-DOTATOC) with a standard activity of 4 GBq (108 mCi) and 2 GBq (54 mCi) as reduced activity respectively. Over time, a portion of patients with differentiated NET will show progressive disease after initial response to PRRT. In these patients, re-PRRT may be a favourable option.[7,8] When NETs lose their initially high differentiation, the ENETS Consensus Guidelines propose molecular targeted therapies, and in the case of higher de-differentiation, they suggest chemotherapy.[9] These therapies may also require a dose modification in the case of renal impairment, anaemia, leukocytopenia or thrombocytopenia.

Numerous articles have been published on toxicity following PRRT (both Y-90- and Lu-177-labelled SST-analogues) showing that the treatment is safe and beneficial.[3,10–12] Commonly, findings of severe toxicity (any grade greater than grade 2[13]) according to the Common Terminology Criteria of Adverse Events (CTCAE), occur rarely.

But, looking closer at the published studies, populations described were of high heterogeneity regarding several factors. These factors being the administered cumulative activity, the number of applications of the radiopeptide, or the duration of follow-up. In contrast, we investigated chronic nephro- and hematotoxicity following a standardized protocol of PRRT. For renal function we used CKD-Grading[14] as it provides a better distinction than CTCAE in moderate renal impairment. Hematotoxicity was still graded by CTCAE.

It may not be new data that the safety profile of this therapy seems to be good. However not only severe, but even mild to moderate chronic toxicity is often discussed to have an effect on further patient management. For example, eGFR influences the decision of whether to perform computer tomography with or without intravenous iodinated contrast media, or to provide prophylaxis to prevent acute kidney injury respectively.[15] Additionally, moderate chronic toxicity may have an influence on the choice of future oncologic treatment in the case of disease progression.

For long term patient management it is important to know which consequences nephro- or hematotoxicity caused by peptide receptor radionuclide therapy will have, even if they are only mild or moderate.

Material and methods

Inclusion criteria

We defined the following inclusion criteria for this retrospective study: (a) complete treatment period, i.e. four treatment cycles with the same PRRT compound (Lu-177-DOTATATE or Y-90-DOTATOC) with 10–12 weeks time between each application (Fig. 1); (b) a follow-up period of at least 52 weeks; (c) no additional concomitant oncologic treatment except somatostatin-analogues. Consequently, we excluded patients who had more or fewer than four PRRT cycles, changing substance of PRRT, or those who were lost to follow-up. After exploring database entries from April 2005 to June 2017, we identified 384 patients with at least one cycle of PRRT. Seventy-seven from 384 patients completed one, 11 patients two, and one patient three complete treatment periods and had a follow-up period of at least 52 weeks. Therefore, the total number of analysed anonymized cases is 102 (Table 1). At our site we perform PRRT for over sixteen years and an interval of 10–12 weeks between each application has been established. This interferes with the protocol in the NETTER-1 trial (published January 2017) or the FDA-approval of Lutathera (2018).[3,5] Still for this study we chose the longer interval. In a retrospective setting we have to address the possible selection bias or underestimation of toxicity. Being aware of this, we still chose this strategy to investigate patients with comparable management such as in a “treated per protocol (TPP)” analysis.

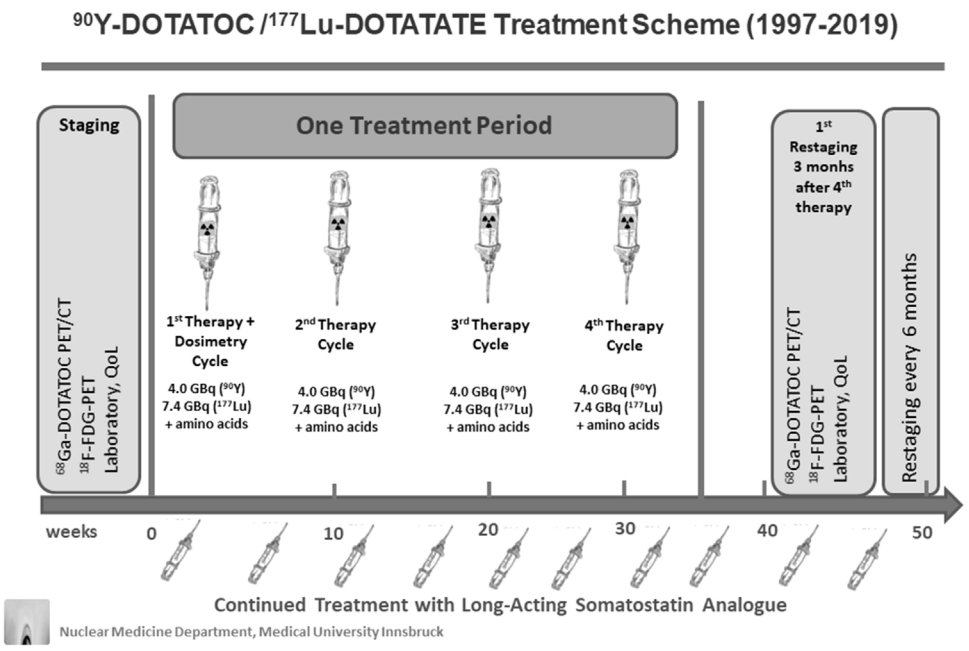

Figure 1. Therapy scheme Innsbruck.

Table 1
Demographic data.

Patient characteristics (n = 102)	Number of cases (%)
Male	67 (65%)
Age ≥ 65 years	44 (43%)
Karnofsky performance status > 70%	102 (100%)
eGFR < 60 at first therapy	15 (14.7%)
Leukocytes < 4.0 G/l at first therapy	13 (12.7%)
Platelets < 150 G/l at first therapy	10 (9.8%)
^{177}Lu-DOTA-TATE	86 (84%)
Cumulative activity ^{177}Lu > 22.2 GBq (600 mCi)	58 (55.8%)
Cumulative activity ^{90}Y > 12 GBq (324 mCi)	13 (12.7%)
Weeks to restaging after last treatment (mean)	68.4 (51.9–103.9; SD 9.1)

Treatment

All patients received ondansetron 4 mg twice daily for two days in the form of prophylactic antiemetic treatment and amino acids (2.5% arginine and 2.5 % lysine in 1000 ml 0.9% saline solution) for renal protection over 5 h starting half an hour prior to the administration of the radiopharmaceutical. The PRRT was administered by a pump system on the opposite arm over 15–20 min. Due to regulatory requirements patients were discharged not earlier than on the third day after PRRT. Dosimetry was performed in all patients along the first therapy cycle. The calculated absorbed radiation dose for kidneys and bone marrow was taken into consideration for individual patient planning, possibly resulting in dose-reduction.

At our centre, we aim for a therapeutic regimen as depicted in Fig. 1 with a standard accumulated activity of 29.6 GBq (4×7.4 GBq; 800 mCi = 4×200 mCi) for Lu-177-DOTATATE- and of 16 GBq (4×4 GBq; 432 mCi = 4×108 mCi) for Y-90-DOTATOC-treated patients. If there is evidence of renal impairment with estimated glomerular filtration rate (eGFR) between 35 and 50 ml/min/1.73 m^2 or leukopenia with white blood cell count (WBC) between 1500 and 2500 G/l before the first therapy cycle, the intended cumulative activity was reduced to 50%. If one of the mentioned adverse effects occurred during the course of treatment, we also reduced the intended activity per administration to 50%. If these findings subsided prior to the next planned application, the amount of activity was chosen by the nuclear medicine specialist taking additional aspects into account like general condition, findings in outpatient additional laboratory testing, age or comorbidities. Due to availability and handling of the radiopharmaceutical we had variations of activity administered at each treatment cycle in each patient. Therefore, we decided to define an accumulated activity above 22.2 GBq (600 mCi) for Lu-177-DOTATATE and more than 12 GBq (324 mCi) in Y-90-DOTATOC as standard accumulated activity and, if below, as reduced accumulated activity. This threshold value results from building the mean from standard and reduced accumulated activity.

Analysis of parameters

Blood sampling for eGFR [Modification of Diet in Renal Disease (MDRD) Study equation)], hemoglobin (Hb), WBC and platelets was done one day prior to each treatment cycle and at each restaging. For our statistical analysis we chose the parameters from one day prior to the baseline and from the first restaging visit after a follow-up period of at least 52 weeks (restaging). As secondary parameters, age at date of first administration, gender, type of PRRT and cumulative activity were included for the subgroup analysis.

Usually, we recommend restagings three months after the last therapy cycle and each six-month thereafter if no evidence of progressive disease is found. In a first attempt, we wanted to analyse the data according to first, second, etc. restaging, but the interval between restagings was too widespread for a reliable analysis. The widespread intervals between restagings were caused by patient factors such as travelling distance to our hospital or medical co-attendance at the place of residence. Therefore, we decided to use the data for restaging from a visit at least one year after the 4th and last treatment cycle for analysis.

Toxicity parameters

Hematotoxicity was graded according to CTCAE version 5.0 (Table 2). Normal values (grade 0) are for WBC 4.0–10.0 G/l, platelets 150–380 G/l, Hb for female 120–157 g/l and male 130–177 g/l. Renal impairment was graded according to the Chronic Kidney Disease Classification (CKDC, Table 3) as it offers a more detailed graduation in staging than CTCAE. In CTCAE

Table 2
Common terminology criteria for adverse events.

CTCAE Term	Anemia	White blood cell decreased	Platelet count decreased
Grade 1	Hemoglobin (Hgb) <LLN - 10.0 g/dl; <LLN - 6.2 mmol/l; <LLN - 100 g/l	<LLN - 3000/mm^3; <LLN - 3.0 × 10e9/l	<LLN - 75,000/mm^3; <LLN -75.0 × 10e9/L
Grade 2	Hgb <10.0–8.0 g/dl; <6.2–4.9 mmol/l; <100–80 g/l	<3000–2000/mm^3; <3.0–2.0 × 10e9/l	<75,000–50,000/mm^3; <75.0–50.0 × 10e9/l
Grade 3	Hgb <8.0 g/dl; <4.9 mmol/l; <80 g/l; transfusion indicated	<2000–1000/mm^3; <2.0–1.0 × 10e9/l	<50,000–25,000/mm^3; <50.0–25.0 × 10e9/l
Grade 4	Life-threatening consequences; urgent intervention indicated	<1000/mm^3; <1.0 × 10e9/l	<25,000/mm^3; <25.0 × 10e9/l
Grade 5	Death	Not applicable	Not applicable

Table 3
Comparison of CKD (chronic kidney disease according to The Renal Association) grading categories and CTCAE (Common Terminology Criteria for Adverse Events).

GFR categories (CKD)	GFR categories (CCTCAE)	Range (ml/min/1.73 m^2)	Description
Grade 1		≥90	Normal and high
Grade 2	**Grade 1**	60–89	Mild reduction related to normal range for a young adult
Grade 3a	**Grade**	45–59	Mild to moderate reduction
Grade 3b	**2**	30–44	Moderate to severe reduction
Grade 4	**Grade 3**	15–29	Severe reduction
Grade 5	**Grade 4**	<15	Kidney failure
	Grade 5 (death)		

Grade 2 (moderate reduction) is defined as eGFR from 59 to 30 ml/min/1.73 m^2, whereas CKD provides in this range two subgrades: Grade 3a from 45 to 59 ml/min/1.73 m^2 (mild to moderate reduction) and Grade 3b from 30 to 44 ml/min/1.73 m^2 (moderate to severe reduction). We decided against taking the albumin-creatinine-ratio into account, because the resulting subgroups would be small and in regard to daily routine the role of this ratio is limited. Exact calculation for eGFR is not provided by our central laboratory since it has been demonstrated that the MDRD study equation[16] underestimates measured GFR (mGFR) at levels of eGFR greater than 60 ml/min/1.73 m^2. This is why we summarised eGFR higher than 60 ml/min/1.73 m^2 as grade 1–2 regarding CKD-classification (grade 1 > 90 ml/min/1.73 m^2 and grade 2 between 60 and 90 ml/min/1.73 m^2). We are aware that this impedes the assessment of reduction in renal function between 120 and 61 ml/min/1.73 m^2, but in general eGFR higher than 60 ml/min/1.73 m^2 does not have relevance for patient management.

Statistical analysis

Statistical analyses were carried out using IBM SPSS Statistics 21 by the Department of Medical Statistics, Informatics and Health Economics. The patients were stratified according to the kind of PRRT (Lu-177-DOTA-TATE or Y-90-DOTA-TOC), the cumulative activity (standard versus reduced), age and gender. We performed paired t-tests to compare t-values from our baseline with year 1. For eGFR above 60 ml/min/1.73 m^2 we exacted this value because it was not provided by our central laboratory, on the one hand, and higher eGFR does not have any impact on clinical routine on the other. We applied other tests such as the marginal homogeneity test for analysis of multivariable models, the McNemar-test for the best grading versus the rest, furthermore Welch's *t*-test and the Cochran-Armitage-trend-test in the subgroup analysis.

Results

Diagnosis

Eighty-two patients suffered from NET (small intestine 33, pancreas 24, unknown primary 6, hindgut 6, caecum 5, lung 5, and stomach 3), three from paraganglioma, three had follicular thyroid cancer and one medullary thyroid cancer. All non-NETs were positive for somatostatin receptor expression.

Treatment

Lu-177-DOTATATE was applied in 86 (84%) and Y-90-DOTATOC in 16 cases. For Lu-177-DOTATATE the median accumulated standard activity was 28.9 GBq (781 mCi) (range 22.12 (597) to 30.55 (824); standard deviation (SD) 2.46 (66.4), 58 cases) and the median accumulated reduced activity 16.8 GBq (454 mCi) (range 12.91 (349) to 20.64 (558); SD 1.69 (45), 28 cases). The Y-90-DOTATOC median standard accumulated activity was 16.1 GBq (435 mCi) (range 12.27 (331) to 16.94 (458); SD 1.24 (33), 13 cases) and median accumulated reduced activity 8.5 GBq (229 mCi) (range 8.43 (227) to 8.70 (235); SD 0.14 (3.7), 3 cases).

Nephrotoxicity

Estimated glomerular filtration rate

The paired *t*-test for comparing t-values from the baseline and year 1 indicated a small significant decrease in eGFR of −1.88 ml/min/1.73 m^2 (95% CI: −3.01 to −0.76, p = 0.001). This result must be seen under the fact that we calculated 60 ml/min/1.73 m^2 for eGFR above 60 ml/min/1.73 m^2. The eGFR was above 60 ml/min/1.73 m^2 (CKD grade 1–2) in the baseline at 87 (85.3%) and in year 1 at 71 (69.6%) cases (Fig. 2).

Before the first therapy cycle already 15 (14.7%) cases had decreased eGFR and one year after the fourth therapy cycle 31 (30.4%). From 15 cases at the baseline with impaired renal function, 2 had normalised eGFR one year after treatment.

Focussing on those 87 cases with CKD grade 1–2 at the baseline, 18 (20.7%) showed higher eGFR impairment (> Grade 2) at the follow-up. Comparing the best grading with the summed other grades (Table 4) the McNemar-test showed significance for decrease in eGFR [p < 0.001, magnitude of effect 15.7% (95% CI: 7.7%–23.7%)].

In regard to the details of grading, we found the CKD grade 3a at the baseline in 13 (12.7%) cases and at year one in 25 (24.5%). grade 3b was observed in 2 cases at the baseline and in 5 (4.9%)

Table 4
Change in grading baseline versus year 1 after treatment.

	Baseline	→	Year 1		Magnitude of effect
			Best grading	All other grades	
eGFR					
Best grading	87	→	69	18	
All other grades	15	→	2	13	15.7 % (95 % CI: 7.7%–23.7%)
Leukocytes					
Best grading	89	→	76	13	
All other grades	13	→	7	6	5.9% (95% CI: −2.6% to 14.4%)
Thrombocytes					
Best grading	92	→	81	11	
All other grades	10	→	3	7	7.8% (0.8%–14.9%)
Hemoglobin					
Best grading	63	→	45	18	
All other grades	39	→	3	36	14.7% (95% CI: 6.4%–23.0%)

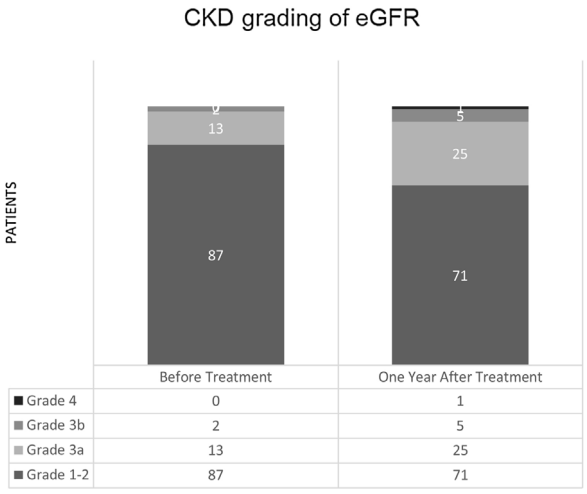

Figure 2. Estimated glomerular filtration rate (eGFR) in CKD-grading before and one year after treatment.

cases after one year. grade 4 was not found at the baseline but in 1 case after one year. CKD grade 5 (eGFR < 15 ml/min/1.73 m^2) was never observed (Fig. 2). In the total of 102 cases no change in CKD-grading was observed in 78 (76.5%), an impairment in 21 (20.6%) and an improvement in 3 (2.9%) cases (Table 5).

Hematotoxicity (Fig. 3; Table 6)

Hemoglobin

At the baseline Hb was normal in 63 (61.8%) and at year one in 48 (47.1%) cases. Anaemia was found in 39 cases at the baseline, of which 3 cases resolved one year after therapy. Of 63 cases with normal Hb before therapy, 18 (28.5%) then developed anaemia (any grade) thereafter (Table 4). Again, comparing the best grading with the summed other grades the McNemar-test showed significance for decrease of Hb [p = 0.001, magnitude of effect 14.7% (95% CI: 6.4%–23.0%)]. By looking at the details, grade 1 (CTCAE) could be observed at the baseline in 36 (35.3%) versus 48 (47.1%) cases at year one. Grade 2 was found at the baseline in 3 (2.9%) and at year one in 6 (5.9%) cases. No toxicity higher than grade 2 occurred. No change in CTCAE-grading was observed in 78 (76.5%), an impairment in 21 (20.6%) and an improvement in 3 (2.9%) cases, (same numerical values as for kidney grading; sic).

Leukocytes

White blood cell count was normal at the baseline in 89 (87.3%) cases and at year one in 83 (81.4%). No statistically significant decrease was observed in the McNemar-test (best versus rest, p = 0.263). Grade 1 at the baseline showed up in 12 (11.8%) and after one year in 13 (12.7%) cases. Grade 2 was observed in 1 (1.0%) case at visit one and in 6 (5.9%) after one year. We did not find toxicity higher than grade 2. No change in CTCAE-grading was observed in 80 (78.4%), an impairment in 15 (14.7%) and an improvement in 7 (6.9%) cases.

Thrombocytes

Platelet count was normal at the baseline in 92 (90.2%) cases and at year one in 84 (82.4%). Here also no statistically significant decrease was observed in the McNemar-test (best versus rest, p = 0,057). Grade 1 could be observed at the baseline in 10 (9.8%) versus year one in 18 (17.6%) cases. No toxicity higher than grade 1 was observed. No change in CTCAE-grading was observed in 88 (86.3%), an impairment in 11 (10.8%) and an improvement in 3 (2.9%) cases.

Subgroup analysis

We found that only in cases where the subject was 65 years old or older was there a significant correlation to the development of anaemia after the completion of PRRT (p = 0.006). In this group, the mean Hb decreased from 132.4 (SD 12.2, range 107–160) to 123.5 mg/dl (SD 13.6, range 95–148). Besides anaemia, subgroup analysis showed that no other factor [i.e. gender, age above 65 years, accumulated activity or kind of treatment (Lu-177-DOTA-TATE versus Y-90-DOTA-TOC)] had a significant impact on nephrotoxicity or hematotoxicity one year after the last treatment. In 12 patients with PRRT, no change in grading one year after the last therapy was observed.

Paired t-*test*

Although this test does not show the impact on grading of toxicity, a significant decrease of all observed parameters by comparing mean values at the baseline and one year after the last therapy could be observed. The eGFR decreased by −1.88 ml/min/1.73 m^2 (SD 5.73, p = 0.001), Hb −5.43 g/l (SD 11.234, p < 0.001), WBC −0.68 G/l (SD 1.73, p < 0.001) and platelets −23.85 (SD 54.69, p < 0.001).

Discussion

Lu-177-DOTATATE is used for PRRT and was FDA-approved in January 2018 for the treatment of SSTR-positive GEP-NETs. The results of this retrospective analysis show that the vast majority of patients shows either none or only a mild to moderate decrease in kidney function as well as hematotoxicity one year after completion of standardized PRRT with four treatment cycles of either Y-90- or Lu-177-PRRT. We have to address that there may be a sampling bias due to the retrospective setting. Being aware of this, we still focussed on these rigid inclusion criteria as most of

Table 5
Changes in grading 1 year after treatment.

	eGFR		WBC		Hb		Platelets	
	N	%	N	%	N	%	N	%
Impairment in grading	21	20,6	15	14,7	21	20,6	11	10,8
No change	78	76,5	80	78,4	78	76,5	88	86,3
Improvement in grading	3	2,9	7	6,9	3	2,9	3	2,9
Total	102	100,0	102	100,0	102	100,0	102	100,0

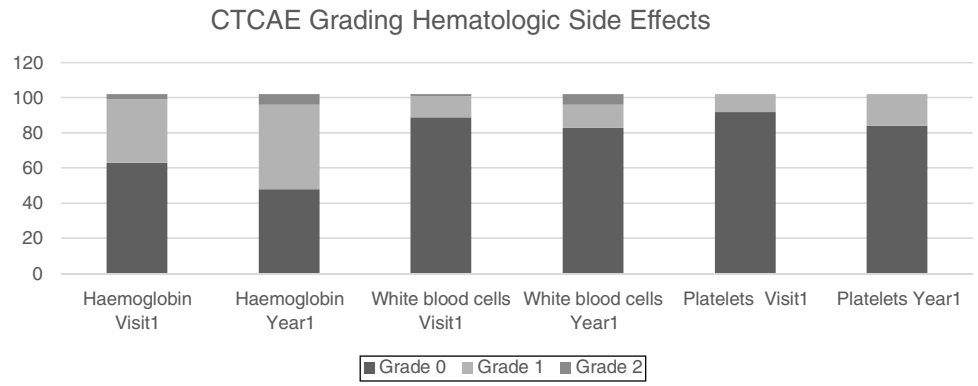

Figure 3. CTCAE grading hematologic side effects; Visit 1 = before treatment; year 1 = 1 year after the last treatment.

Table 6
Hematotoxicity.

	Grade 0		Grade 1		Grade 2	
	Baseline	Year 1	Baseline	Year 1	Baseline	Year 1
Hemoglobin	63	48	36	48	3	6
White blood cells	89	83	12	13	1	6
Platelets	92	84	10	18	0	0

the studies focussing on safety and toxicity of PRRT were of high heterogeneity regarding factors such as the administered accumulated activity, administrations, radiopharmaceutical, or duration of follow-up.[10–12,17]

Bodei et al. reported nephrotoxicity of any CTCAE grade in 279/807 (34.6%) and grade 3 and 4 in 12/807 (1.5%) for a very inhomogeneous cohort of patients studied at IEO Milan between 1997 and 2013. Recently, Rudisile et al.[18] reported no CTCAE grade 3 or 4 nephrotoxicity or relevant decrease in renal function at 12 months of follow-up after 4 cycles of initial Lu-177-DOTATATE PRRT and re-PRRT with a median total cumulated dose of 44 GBq (1189 mCi) [range 33.5 (905)–47 (1270)]. The annual decrease of tubular extraction rate determined by 99mTc-MAG3 renal scintigraphy was $2.25 \pm 0.48\%$ (i.e. 8 ± 12 ml/min/1.73 m^2). In terms of hematotoxicity WBC, erythrocytes and platelet count decreased after the initial four PRRT cycles and after salvage PRRT. Using up to 60 GBq (1621 mCi) of Lu-177-DOTATATE as salvage-therapy Bergsma et al.[12] reported a similar safety level for re-PRRT as for the initial PRRT without grade 3 or 4 nephrotoxicity after re-treatment and no higher incidence for AML or MDS. In a personalized PRRT-setting with an injected activity reaching a prescribed renal absorbed dose of at the maximum 23 Gy Del Prete et al.[19] did not observe severe renal subacute toxicity. Zhang et al.[20] treated 69 patients with grade 3 NENs without observing hematotoxicity CTCAE grade 4. Only one patient presented leukocytopenia grade 3. No grade 3 or 4 anemia or nephrotoxicity was observed. Still the possible impact on future treatment planning of mild to moderate toxicity is not emphasized in these publications.

In our study cohort we found nephrotoxicity of any CTCAE-grade in 31 (30.4%) of 102 cases and severe (CTCAE grade 3/4) in only 1 patient. In this particular patient, the absorbed dose calculated for the kidneys was 17.9 Gy. This patient, aged 73 years at start of PRRT, suffered from intermittent claudication and was on dual therapy for hypertension. This observation is in line with the significant association between hypertension and nephrotoxicity reported by Bodei et al. Contrarily, Bergsma et al. found that hypertension (and other risk factors) did not have a significant effect on the estimated rate of change in the annual decrease in the creatinine clearance of patients treated with Lu-177-DOTATATE.

Returning to CKD-grading, in our cohort of 102 cases, 21 (20.6%) had a decrease of eGFR to a more severe grade one year after treatment. From 87 cases with eGFR CKD grade 1–2 prior to PRRT 18 (20.7%) had a decrease in grading of eGFR at the one-year follow-up (Table 4). Summing up all gradings versus the best, we found a significant decrease in the number of cases with best grading from the baseline to follow up in our “standardized” treatment regimen in both eGFR and Hb. Nevertheless, when focussing on eGFR, we found that still 69.6% (71/102) were grade 1–2 and 24.5% (25/102) had a decrease to grade 3a (mild to moderate). This was the most common finding in roughly 80% (25/31) of the cases. Of those 31 cases, 5 (16%) showed a grade 3b in CKD-classification which is defined as moderate to severe reduction and significantly increased risk to end stage renal disease or cardiovascular event compared to grade 3a. In comparison, CKD grade 3a and b is grade 2 in CTCAE meaning “moderate; minimal, local or non-invasive intervention indicated; limiting age appropriate instrumental activities of daily living”.[13,14]

PRRT had no statistically significant impact on leuko- and thrombopenia in our cohort. No hematotoxicity greater than grade 2 according to CTCAE was observed. However, by comparing best versus all other (“rest”) gradings in Hb we found significance;

still the measured decline was to grade 1 in 48/54 (88.8%) and to grade 2 in 6/54 (11.1%) cases only. The subgroup analysis showed that in patients aged >65 years anaemia may develop after PRRT ($p = 0.006$). In this group, the mean Hb decreased from 132.4 mg/dl to 123.5 mg/dl.

Long-term side effects of PRRT are a topic in the planning of treatment in patients with well differentiated NETs grade 1–2. Because of the long course of the disease and possible changes in differentiation, a large number of NET-patients will develop progression over the course of the disease, and thus will need a more aggressive treatment regimen.[21] Therefore, the question arises whether even mild to moderate renal impairment and/or hematotoxicity after PRRT will restrict future oncologic therapy such as SST analogues, mtor inhibitors, receptor tyrosine kinase inhibitors, interpheron α or chemotherapy. SST analogues do not require dose adjustment to decrease eGFR or anaemia.[22] Targeted therapy with inhibitors of mtor and tyrosine kinase are registered for progressive metastatic pancreatic NET and mtor inhibitors for progressive metastatic small intestinal NET.[9] Mtor inhibitors do not require dose adjustment due to renal impairment.[23] Still we have to pay attention to the common side effect of mtor inhibitors such as anaemia and aggravation of pre-existing anaemia. These facts also apply to receptor tyrosine kinase inhibitors.[24] However, it is unlikely that previous PRRT interferes with targeted therapy because the observed anaemia after PRRT is mild to moderate in most cases. Despite playing a minor role in the treatment of NET interferon alpha 2b[25] and PEGylated interferon alpha 2b[26,27] may be indicated in some patients. The dose, especially in PEGylated interferon, should be reduced by 25% if the GFR is between 30−50 ml/min/1.73 m^2 and by 50% under 30 ml/min/1.73 m^2. Therefore, also for interferon-based therapy it is unlikely to have a contraindication after PRRT.

In case of dedifferentiation, higher grade, bulky or 18F-FDG-avid neuroendocrine neoplasms (NEN) chemotherapy may become an option. The integration of PRRT into multi-modality therapy protocols might improve response to treatment. Especially the use of radiosensitizing chemotherapy in combination with Y-90- or Lu-177-SST-analogues has shown an additive value.[28] The ENETS-guidelines[29] mention numerous different substances such as platinum-based agents, irinotecan, streptozotocin, temozolomide, or 5-fluorouracil and its prodrug capecitabine. Furthermore, the combined use of various radionuclides, sequentially or concomitantly, may optimize the treatment outcome. Finally, broadening horizons with alpha-emitting isotopes such as 225Ac-DOTATATE may increase the attention for the safety profile. In fact, the first data published by Ballal et al.[30] were quite beneficial regarding not only efficacy but also safety. Still, as stated above in our study the decrease in eGFR and Hb is mild to moderate by CTCAE in the majority of patients. Therefore, PRRT will most likely not impede the use of chemotherapy after subsequent progression.

Conclusion

In roughly 20% of all cases an increase of nephro- or hematotoxicity grade was observed. Nevertheless, in those patients, except in one, toxicity findings were mild or moderate one year after completion of four cycles of PRRT with either Y-90- or Lu-177-SST-analogues. In terms of safety, PRRT, including re-PRRT, had no critical impact on further oncologic treatment options in the case of disease progression.

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