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Original Article

Improved Quality of Life in Patients Treated with Peptide Radionuclides

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Abstract

Peptide receptor radionuclide therapy (PRRT) has recently been established as an important treatment modality for somatostatin receptor (SSTR)-positive tumors. The purpose of this study was to evaluate the clinical response, side-effects as well as the quality of life following ^{90}Y-DOTA-lanreotide (DOTALAN) and/or ^{90}Y-DOTA-Tyr^{3}-DPhe^{1}-octreotide (DOTATOC) therapy in patients with progressive metastatic disease during a 6-year follow-up period. Following dosimetric evaluation with ^{111}In-DOTALAN and ^{111}In-DOTATOC, 13 patients with estimated absorbed tumor doses of >5 Gy/GBq (carcinoid, *n* = 5; radioiodine-negative thyroid cancer, *n* = 4; gastrinoma, *n* = 1; insulinoma, *n* = 1; glucagonoma, *n* = 1; glomus jugularis tumor, *n* = 1) were assigned for PRRT. A dose of 925 MBq of ^{90}Y-DOTALAN (four patients) or 1.85–3.7 GBq of ^{90}Y-DOTATOC (10 patients) was administered intravenously and repeated every 4–8 weeks. Tumor dosimetry was performed prior to and under therapy, re-staging every 2–3 months. Pain intensity, Karnofsky score and general symptoms were evaluated in order to determine quality of life. Patients were followed until death. Altogether, 53 infusions of PRRT (1.85–14.1 GBq) were administered. After the first follow-up of 3 months of ^{90}Y-DOTALAN therapy, stable disease (SD) was observed in one patient and progressive disease (PD) in three patients. With ^{90}Y-DOTATOC therapy, SD was found in all 10 patients. During the re-evaluation period (4–27 months), one patient had to be shifted from ^{90}Y-DOTALAN to ^{90}Y-DOTATOC therapy due to reduced ^{111}In-DOTALAN uptake after 5.5 GBq. In the first 6 months after PRRT with DOTATOC, SD was found in nine of 10 patients and PD in one patient. Thereafter, SD was observed in two patients and PD in eight patients. Nine of 13 patients after PRRT with either DOTALAN or DOTATOC died. None of the patients had experienced severe acute hematological side-effects. Transient thrombocytopenia or lymphocytopenia was seen in 10 patients after 3.7 GBq, and a skin reaction in one patient. Total accumulated kidney dose ranged between 4 and 64 Gy, with reduced creatinine clearance in two patients. Pain relief was achieved in three of three patients after ~3.7 GBq ERT within 4–6 months. Appetite, weight, Karnofsky score and general well-being had improved in patients with SD during and after therapy. Based on the results of this study conducted on a small group of patients, we conclude that PRRT may offer an alternative treatment option for SSTR-positive tumors, with only mild transient side-effects and a marked improvement in the quality of life.

Keywords: DOTA-octreotide, DOTA-lanreotide, peptide receptor radionuclide therapy, quality of life

Introduction

The high-level expression of peptide receptors (R) on various tumor cells as compared with normal tissues or blood cells has provided the molecular basis for the clinical use of radiolabelled peptides as tumor tracers in nuclear medicine.[1,2] In recent years, the use of radiolabelled somatostatin analogs as specific radiopharmaceuticals for the *in vivo* detection and treatment of somatostatin receptor-positive (SSTR) tumors has been implemented.[3-6] In contrast to ^{111}In-DTPA-D-Phe^{1}-octreotide (OCTREOSCAN®), which binds to human (h)SSTR2 and hSSTR5 of the five known hSSTR subtypes with high affinity (K_d 0.1-5 nM), to hSSTR3 with moderate affinity (K_d 10-100 nM) and does not bind to hSSTR1 and hSSTR4; ^{111}In/^{90}Y-DOTA-lanreotide (DOTALAN) was found to bind to

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hSSTR2-5 with high affinity and to hSSTR1 with lower affinity (K_d 200 nM), and was therefore suggested to be a potential radioligand for tumor diagnosis and therapy.[5,7] Compared with OCTREOSCAN® and ^{111}In-DOTA-Tyr^3-DPhe^1-octreotide (DOTATOC), discrepancies were found in the scintigraphic results with DOTALAN in about one-third of (neuroendocrine) the tumor patients concerning both the tumor uptake and detection. On a molecular level, this divergence seems to be based on the increased high-affinity binding of ^{111}In-DOTATOC to hSSTR2.[8]

In the management of patients with SSTR-positive tumors, these new radiopeptides seem to be a potential alternate treatment option, but their exact role remains to be determined. The best radioligand should be carefully investigated because of the different binding behavior. At present, many treatment protocols exist with different study designs.[9-12] Side-effects, kidney protection and optimal dose of radiopeptide for successful treatment of cancer are still under considerable debate, and long-term results and survival rates are lacking. Furthermore, little attention has been given to the quality of life with these new therapies, which is perhaps the most important gain for patients with end-stage cancer. The aim of our study was to assess the clinical utility as well as side-effects of receptor-based ^{90}Y-DOTALAN/DOTATOC therapy (PRRT) in patients with metastatic SSTR expressing cancer refractory to conventional treatment.

Materials and Methods

Patients

We enrolled 13 patients (median: 66 years, male:female = 7:6) in this study with metastatic tumor disease (five carcinoids, one glomus jugularis tumor, four radioiodine-negative thyroid carcinomas, one gastrinoma, one insulinoma and one glucagonoma) during a period of 6 years. Before PRRT, all 13 patients had surgery. Four patients had undergone chemotherapy, four patients had external radiotherapy and four other patients had radioiodine therapy. Three patients were treated with ^{90}Y-DOTALAN, nine patients with ^{90}YDOTATOC and one patient with both radiopeptides.

Treatment protocols and therapy monitoring

Before starting therapy, 10 patients underwent diagnostic and dosimetric evaluation with ^{111}In-DOTALAN and ^{111}In-DOTATOC. Three patients started therapy with ^{90}Y-DOTALAN without diagnostic ^{111}In-DTATOC scintigraphy because DOTATOC was not yet available at that time. Inclusion criteria were as follows:

1. Positive ^{111}In-DOTALAN/-DOTATOC scintigraphy with tumor uptake >5–10 Gy/GBq.
2. Progressive tumor disease under conventional therapy.
3. Life expectancy >3 months.
4. Karnofsky score >60, age >18 years.
5. Laboratory tests: granulocytes >1500/mm^3, platelets >100,000/mm^3, liver and kidney function <Grade I toxicity according to the WHO-criteria.

Exclusion criteria of the study were pregnancy and severe concomitant illness, including severe psychiatric disorder.

There were two different treatment protocols, one for DOTALAN and one for DOTATOC. For DOTALAN therapy, patients started with two infusions of 0.9 GBq ^{90}Y-DOTALAN each with a time interval of 4-weeks apart. After a further 4 weeks, restaging was performed. If no kidney and/or hematological toxicity and no severe side-effects were found, a further two infusions of 925 MBq ^{90}Y-DOTALAN each with a time interval of 4 weeks apart was administered. The patients were restaged after a further 4 weeks. The end point of the therapy was severe adverse side-effects according the WHO standard criteria, kidney dose >30 Gy/GBq (with two exceptions), no therapeutic success (progressive disease) and/or reduction of ^{111}In-DOTALAN tumor uptake. For DOTATOC therapy, patients were started with two infusions (1.85 GBq each) with a time interval of 4 weeks apart. After a further 4 weeks, restaging was performed. After exclusion of kidney and/or hematological toxicity and severe side-effects, patients with large tumors (>3 cm in diameter) received one infusion of 1.85 GBq/m^2. Two infusions of 1.85 GBq each in a time interval of 4 weeks were applied to patients with small tumors. The re-staging was done after 4 weeks and, depending on the patients' situation, further therapy with one infusion of 1.85 GBq/m^2 for patients with large tumors or two infusions of 1.85 GBq each for patients with small lesions were administered. Laboratory tests (blood count, renal and liver function parameter) were controlled prior to and weekly after starting therapy, tumor markers, which were positive in the pre-study investigation every 4 weeks. The end points of the DOTATOC therapy were similar to the DOTALAN therapy protocol already described.

To determine the quality of life, we evaluated the subjective pain intensity by means of the visual analog score (VAS; 0 = severe pain, 10 = painless), immediately after and every 4 weeks following therapy and by recording the intake of analgesics. The Karnofsky score, general symptoms such as appetite, weight, bowel movement, micturition and sleep pattern were recorded by interviewing the patient before and every 4 weeks under therapy. The overall general well being was rated by 5-point VAS (1 = very poor, 5 = excellent).

Diagnostic and dosimetric evaluation

For diagnostic and dosimetric evaluation, serial whole body scans (anterior and posterior views, matrix 256 x 1024, 15-min each) up to 48 h after intravenous injection of 5.5 GBq ^{111}In-DOTALAN/-DOTATOC were performed as described before by Virgolini *et al.* and Traub *et al*.[6,7]

Preparation and labeling of ^{111}In-/^{90}Y-DOTALAN and ^{111}In-/^{90}Y-DOTATOC

The chemical synthesis, preparation and labeling of ^{111}In-/^{90}Y-DOTALAN and ^{111}In/^{90}Y-DOTATOC were performed according to the procedures described by Virgolini *et al*.[8]

Results

Therapeutic response of ^{90}Y-DOTALAN

Altogether, 14 infusions of the radiolabelled peptide were administered (1.85–5.5 GBq) to four patients [Table 1]. Patients no. 1 and no. 2 receiving 1.85 GBq presented progressive disease (PD) under therapy and died 4 months after starting treatment. In the case of the gastrinoma patient, 5.5 GBq was administered. First, stable disease (SD) over 6 months, then regressive disease (after 5 infusions of ^{90Y}Y-DOTALAN) were observed.[13] Fourteen months after starting therapy, PD in the liver and reduced ^{111}In-DOTALAN tumor uptake were found. Because of the high tumor uptake of ^{111}In-DOTATOC, the patient afterwards received ^{90}Y-DOTATOC therapy ([Table 2], patient no. 9). Patient no.4 presented SD for 10 months with reduction of lung metastases (cumulative activity: 3.7 GBq). However, the patient died 12 months after starting therapy due to pulmonary embolism. An improved quality of life was recorded in the gastrinoma patient with improved appetite, weight gain and overall general sense of well being.

Therapeutic response of ^{90}Y-DOTATOC

Thirty-nine infusions of the ^{90}Y-labelled peptide DOTATOC were administered to a total of 10 patients (3.9–14.1 GBq). Eight of 10 patients were treated following the protocol for large tumors. Under therapy, SD was observed in all 10 patients, with tumor volume reduction in four patients [Figure 1]. Reduced ^{111}in-DOTATOC uptake was seen in three of 10 patients after administration of more than 7.4 GBq of ^{90}Y-DOTATOC [Figure 2]. The follow-up period ranged between 7 and 27 months. Over the first 6 months, SD in nine patients and PD in one patient was observed. Further follow-up recorded SD in two patients and PD in eight patients. In the case of two patients with PD during the follow-up period, we decided to give further therapy as palliative care (patient no. 2 with rapid growth of liver metastases, patient no. 10 with a metastatic glucagonoma after resection of a bone metastasis). Six of 10 patients died Table 2.

Side-effects under therapy

None of the 13 patients developed any acute hematological side-effect. In all four ^{90}Y-DOTALAN patients, we recorded transient drop of thrombocytes, while in six of 10 ^{90}Y-DOTATOC patients transient drop

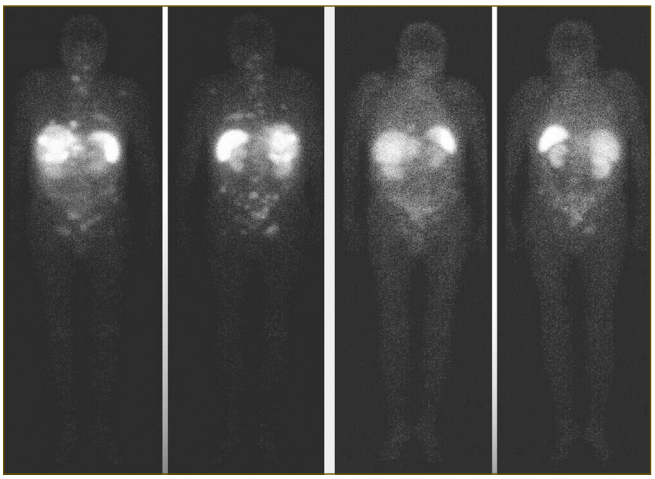

Figure 1: ^{111}In-DOTATOC whole-boy scans of patient no. 3 prior to (left panel) and after (right panel) 9.3 GBq of ^{90}Y-DOTATOC. Reduced radiopeptide uptake in the liver and bone was consistent with decreased size of metastatic tumor lesions

Table 1: Response to therapy with ^{90}Y-DOTALAN

ID diagnosis	Cumulative activity (GBq)	Tumor location	Tumor dose (Gy/GBq)	Cumulative tumor dose (Gy)	Accumulated kidney dose (Gy)	Response/Comments
01-KH	1.85 (2)*	Liver	15	30	4	No response (PD), death 4 months after first therapy
Carcinoid		LNN	15	30		
02-WE	1.85 (2)	Local rec	70	140	3	PD after 3 months with consecutive external radiation, death after 4 months
Follicular thyroid ca		Lung mts	60	120		
03-WW	5.5 (6)	Local rec	56	240	12	SD over 6 months, then RD (after 5) infusions, but PD (liver) 14 months after starting PRRT with consecutive swith to ^{90}Y-DOTATOC
Gastrinoma		Liver mts	4-10	18-59		
04-TJ	3.7 (4)	Local rec	20	80	9	SD over10 months with partial response (lung), than PD, death after 12 months
Hurtel cell ca		Lung mts	15	60		

*Number of treatment cycles in parenthesis, PD: Progressive disease, SD: Stable disease, RD: Regressive disease, PRRT: Peptide receptor radionuclide therapy

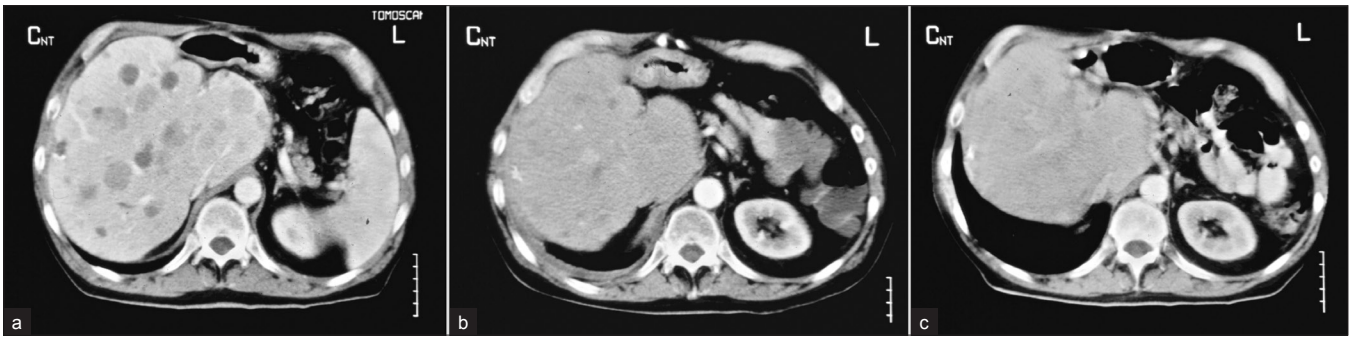

Figure 2: Liver computed tomography images of patient no. 3 with multiple liver metastases: prior to (a), after 9.3 GBq of ^{90}Y-DOTATOC (b) and after 6 months follow-up (c) with response to the liver metastases

Table 2: Response to therapy with ^{90}Y-DOTATOC

ID diagnosis	Cumulative activity (GBq)	Tumor location	Tumor dose (Gy/GBq)	Cumulative tumor dose (Gy)	Accumulated kidney dose (Gy)	Response/ Comments
01-PF Carcinoid	14.1 (6)*	LNN clavicular LNN abdominal Liver	20 20 ne	387 171	64	SD over 16 months with partial response of LNN after 6 months, then PD (bone), death 21 months after starting therapy
02-SM Carcinoid	10.7 (4)	Liver	14	150	9	SD over 12 months under and after 3 cycles, than PD in spite of further PRRT, death after 22 months
03-HW Carcinoid	9.3 (5)	Liver Lung Bone LNN	90-180 90-180 ne ne	279-535 430-490	25	SD over 16 months with partial response of the liver after 5 months, pain relief over 5 months, end of PRRT because of reduced ^{111}In-DOTATOC uptake (liver, bone), death after 21 months
04-PL Carcinoid	7.4 (3)	LNN mediastinal Liver	10	56	21	SD over 13 months, than PD (liver) and reduced ^{111}In-DOTATOC uptake (lung), death after 32 months
05-RS Glomus jugularis tumor	3.9 (2)	Intra-/ Extracranial	5 15	20 60	26	SD over 13 months, pain relief (6 months), congenital cystiy kidneys
06-KH Follicular thyroid ca	7.4 (3)*	Local rec Lung	15 0.14	111 1	33	SD over 8 months with partial response of the local rec after 3 months, then PD
07-DI Papillar thyroid ca	7.2 (2)	Bone/muscle Lung	10 0.8	72 2.2	18	SD over 5 months, than PD, death after 22 months, pain relief (4 months)
08-SJ Insulinoma	10.7 (5)	Local rec Liver	30 15-20	274 127-163	24	SD over 15 months with partial response of the liver after 2 months, then PD, death after 23 months
09-WW Gastrinoma	5.7 (4)	Local rec Liver	20 20	120 150	12	SD over 17 months with altering gastrin levels, cumulative kidney dose of 5.5 GBq ^{90}Y-DOTALAN 12 Gy
10-OM Glucagonoma	10.3 (5)	Liver Lung	5-7 5	66-86 40	17	SD over 9 months, then PD (bone) with consecutive 5th PRRT cycle

*Number of treatment cycles, SD: Stable disease, PD: Progressive disease, Ne: Not evaluated, PRRT: Peptide receptor radionuclide therapy

of lymphocytes was observed in the first 2 weeks after dose administration. One patient developed skin rash 1 week after the 5th dose (cumulative activity: 10.4 GBq), which was not considered as a side-effect. However, immediately after the 6th infusion, the skin rash appeared again and, hence, therapy was terminated.

In 11 of 13 patients, we did not observe any renal dysfunction under therapy. Three patients presented cumulated kidney dose of more than 30 Gy. The patient with the glomus jugularis tumor having congenital cystic kidneys received 3.9 GBq ^{90}Y-DOTATOC with a cumulated kidney dose of 26 Gy, and did not show any impairment of kidney function under therapy as well as during follow-up. A reduced creatinine clearance was seen in two patients after doses of 7 and 14.1 GBq (accumulative kidney dose: 18 Gy in patient no. 7 and 64 Gy in patient no. 1).

Quality of life

Three of 13 patients experienced pain relief after ~3.7 GBq of ^{90}Y-radiolabeled peptide within a period of 4–6 months. In the case of the carcinoid patient (patient no. 3 of ^{90}Y-DOTATOC therapy) with pain from multiple bone metastases, pain relief lasted for 5 months. During

this time, the patient significantly reduced his intake of analgesics, was able to take longer walks and was feeling generally better, with reduced flush and diarrheal symptoms. The Karnofsky score changed from 60 to 70, and the general well being from 3 to 1 during this time [Table 3]. The glomus jugularis tumor patient with extra- and intracranial tumor lesions showed pain relief for 6 months. Symptoms such as headache and pressure from the tumor manifestation were reduced. In the case of patient no. 7 of ^{90}Y-DOTATOC therapy with bone- and muscle-infiltrating metastasis of the hip, pain relief was observed for 4 months with concomitant reduction of pain medication. She reported deeper and longer sleep, longer and more painless walks as well as weight gain and improved appetite.

Therefore, all patients with SD under PRRT and in the follow-up period recorded improved appetite, weight gain and an overall general sense of well being. One patient with carcinoid (patient no. 1) started ^{90}Y-DOTATOC therapy in a reduced general health because of his PD and gastric symptoms (pain). After treatment of his gastritis, and after the first two cycles of PRRT, re-evaluation revealed significant improvement in appetite, gain in weight, greater feeling of well being and SD. Later, PD was accompanied by reduced appetite, weight loss and discomfort [Table 3]. Similar results were also obtained for the Karnofsky score, which was higher in two patients of the ^{90Y}Y-DOTALAN protocol and in four patients of the ^{90}Y-DOTATOC protocol during the course of therapy compared with prior results.

Table 3: General well being, Karnovsky score, appetite and weight of patients treated with Y-90-DOTATOC

ID	Quality of life	Prior to therapy	After 3.7 GBq	After 7.4 GBq	After > 7.4 GBq	Follow-up (6months)	Follow-up (> 6 months)
01-PF	GWB	2	5	5	4	4	4, 3, 2
	KS	70	70	70	70	70	50, 40
	Appetite	Reduced	Reduced	Good	Good	Good	Reduced
	Weight	79	74	76	77	76	73
02-SM	GWB	5	5	5	1	3	1
	KS	80	80	70	50	70	50, 40
	Appetite	Good	Good	Reduced	Reduced	Bad	Bad
	Weight	90	90	85	75	75	73
03-HW	GWB	3	5	5	5	5	3, 2, 1
	KS	50	70	70	70	70	50, 30-20
	Appetite	Reduced	Good	Good	Good	Good	Good, reduced
	Weight	62	63	64	64	64	60, 50
04-PL	GWB	3	4	4		3	1
	KS	70	70	70		60	60, 50
	Appetite	Good	Good	Good	–	Good	Reduced
	Weight	91	91	92		92	Ne
05-RS	GWB	3	4			3	3
	KS	70	70			60	60
	Appetite	Reduced	Good	–	–	Good	Good
	Weight	60	60			62	61
06-KH	GWB	1	3	4		3	3
	KS	70	80	80		70	70
	Appetite	Good	Good	Good	–	Good	Good
	Weight	95	95	95		95	95
07-DI	GWB	1	4	5		3	3,2,1
	KS	60	70	70		60	50, 30-20
	Appetite	Good	Good	Good	–	Bad	Bad
	Weight	73	73	73		60	Ne
08-SJ	GWB	5	5	5	5	3	3, 2, 1
	KS	80	80	80	70	70	60, 50
	Appetite	Good	Good	Good	Reduced	Bad	Bad
	Weight	70	70	68	–	60	Ne
09-WW	GWB	5	5	5	5	5	5, 3
	KS	90	90	90	90	90	90
	Appetite	Good	Good	Good	Good	Good	Good
	Weight	84	84	84	84	84	84
10-OM	GWB	1	4	5	3	3	3, 2
	KS	70	80	80	60-50	60-50	60
	Appetite	Reduced	Good	Good	Bad	Good	Bad
	Weight	65	67	68	65	68	65

GWB: General well being rated by visual analog score from discomfort (1) to comfortable feeling (5), KS: Karnovsky score, weight in kg, Ne: Not evaluated.

Discussion

The fact that malignant cells express a high number of peptide receptors has provided the basis for new therapeutic approaches in nuclear medicine. The discovery of somatostatin receptor subtypes on various neuroendocrine tumors has stimulated the development of somatostatin analog-based scintigraphy and therapy.[3,4,7] However, the exact role of this novel therapeutic approach remains to be determined. Also, its ability to improve quality of life has not been addressed so far. In our study, two different somatostatin analogs were used: DOTALAN in the first phase, when it was the only available somatostatin analog and DOTATOC thereafter. In the first phase, little experience with dose application, kidney toxicity, blood abnormalities and other side-effects existed. This is why we administered only a single dose of 925 MBq of ^{90}Y-DOTALAN per cycle to the patients. After introduction of the DOTATOC protocol, all patients underwent dosimetric evaluation with both radiolabelled peptides prior to PRRT. Therefore, the administered activity was adapted to the tumor manifestation with higher dose per cycle of radiolabelled peptide for larger tumors. Although our study group is small and heterogeneous in regard to tumor entity and tumor manifestation, we could observe partial tumor response or SD under therapy with either ^{90}Y-DOTALAN or ^{90}Y-DOTATOC.

These findings are remarkable because all patients had PD when entering the treatment phase and had already undergone chemotherapy, surgery and radiotherapy. Our results of SD and partial tumor response under therapy and during the first 6 months of follow-up are comparable with results of other studies reported in the literature.[9,10,12.14]

When we started PRRT in the late 90s, no information existed about radiolabelled peptide therapy. From the long-term follow-up of our patients, it can be inferred that both the tumor load, especially that of the liver, as well as the performance status influence the outcome of receptor radionuclide therapy. Although preclinical studies in rats have shown the dependence of treatment response on tumor size,[15] ^{90}Y-DOTATOC seems to give a higher response rate of larger tumor lesions, while Auger-emitting analogs, such as ^{177}Lu-Tyr^3-octreotate, act on smaller lesions.[15] Earlier introduction of therapy and/or a "cocktail therapy" may thus potentially influence the outcome of PRRT.

Concerning the side-effects in our study, neither acute nor severe hematological ones were observed. The reported nephrotoxicity after more than 7.4 GBq in two patients, who died ~2 years after stating PRRT because of PD, did not require further treatment.

When directly compared, discrepancies concerning both the tumor uptake and the detection of the tumor lesions were found between ^{111}In-DOTALAN and ^{111}In-DTPA-DPhe^1-octeotide or ^{111}In-DOTATOC in about one-third of the neuroendocrine tumors patients.[8] In this study, we could observe a change of the SSTR profile on the tumor cells following therapy. In case of the gastrinoma patient, we found a higher tracer uptake for ^{111}In-DOTATOC compared with ^{111}In-DOTALAN after ^{90}Y-DOTALAN therapy (cumulative dose: 5.5 GBq). This change of SSTR subtype expression profile caused the shift from ^{90}Y-DOTALAN to^{90}Y-DOTATOC.

The patients started PRRT when disease was progressive and refractory to conventional treatment options. After stabilization of metastatic disease, patients reported weight gain, improved appetite, sleep and general well being for several months. The Karnofsky score was higher during the course of therapy than prior therapy in six of 13 cases. Pain as a physical component of quality of life was closely related to the psychological component of general well being. Pain relief with reduction of analgesic medication led to fewer side-effects, to more physical activity, improved appetite, better sleep and weight gain. This symptomatic benefit from the PRRT was judged by the patients as an improvement in quality of life. Recently, other working groups with different study designs of receptor-mediated radionuclide therapy reported on the clinical benefit.[9,12,14] Waldherr *et al*.[9] described improvement of clinical signs such as flush, diarrhea, vomiting and pain, with an overall clinical benefit of 63%. However, they did not describe the general well being of the patients. Similar results have also been reported by Bombardieri *et al*.[14]

In cancer patients, sources of satisfaction and self-esteem can be compromised. Fearfulness, therapeutic side-effects and the possibility of treatment failure and death are always present. These aspects may affect health-related quality of life, which includes both physical and psychological components. Thus, improvement in quality of life is an important goal of oncological treatment beyond, and perhaps independent of, the curative one. The main finding of our small study is that PRRT may result in a substantial improvement of quality of life parameters, even when there is only minor effects on tumor shrinkage.

Finally, we conclude that the benefit from PRRT in patients with SSTR-positive tumor disease refractory to conventional therapy may extend to an important improvement in quality of life. Further studies are warranted to prospectively establish the role of PRRT in this regard.

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