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Survival and Response After Peptide Receptor Radionuclide Therapy With [^{90}Y-DOTA^{0},Tyr^{3}]Octreotide in Patients With Advanced Gastroenteropancreatic Neuroendocrine Tumors

Roelf Valkema, MD, PhD,* Stanislas Pauwels, MD, PhD,‡ Larry K. Kvols, MD, PhD,§ Raffaella Barone, MD, PhD,‡ Francois Jamar, MD, PhD,‡ Willem H. Bakker, PhD,* Dik J. Kwekkeboom, MD, PhD,* Hakim Bouterfa, PhD,¶ and Eric P. Krenning, MD, PhD*,†

Because the role of chemotherapy, interferon, or somatostatin analogs as antiproliferative agents is uncertain, currently few treatment options exist for patients with metastatic or inoperable gastroenteropancreatic neuroendocrine tumors (GEP-NET). Fifty-eight patients with somatostatin receptor-positive GEP-NET were treated in a phase I dose-escalating study with cumulative doses of 47 mCi to 886 mCi of the radiolabeled somatostatin analog [^{90}Y-DOTA^{0},Tyr^{3}]-octreotide. At baseline, 47 patients had progressive disease, and 36 were symptomatic. The extent of disease was: 4 patients without liver metastases and 52 patients with liver metastases, including 16 patients with very advanced disease, qualified as "end-stage," and 2 end-stage patients without liver metastases. The objective responses were 5 partial response (PR), 7 minor response (MR), 29 stable disease (SD), and 17 PD. Overall, 33 patients (57%) experienced some improvement in their disease status, including conversion from PD into SD and improvement from SD into MR. Accordingly, 21 of 36 patients (58%) had improvement in Karnofsky performance score or symptoms. The median overall survival (OS) was 36.7 months (95% confidence interval [CI] 19.4-54.1 months). The median progression-free survival in 41 patients who had at least stable disease at the end of the treatment period was 29.3 months (95% CI 19.3-39.3 months). Patients who had SD at baseline had a significantly better OS than patients who had PD at baseline. The extent of disease at baseline also was a significant predictive factor for OS. The OS after therapy with [^{90}Y-DOTA^{0},Tyr^{3}]-octreotide was significantly better than in a historic control group of 32 comparable patients with GEP-NET who had been treated with another radiolabeled somatostatin analog, [^{111}In-DTPA^{0}]-octreotide (median OS 12.0 months, 95% CI 6.2-17.8 months). The difference in OS for both therapies remained highly significant in a multivariate Cox proportional hazard model including progression status and extent of disease at baseline as covariates. Although the objective response after therapy with [^{90}Y-DOTA^{0},Tyr^{3}]-octreotide by standard criteria seems modest, the significantly longer OS compared with historic controls is most encouraging.
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*Department of Nuclear Medicine, Erasmus MC, Rotterdam, the Netherlands.
†Department of Internal Medicine, Erasmus MC, Rotterdam, the Netherlands.
‡Department of Nuclear Medicine, Cliniques Universitaires St Luc, Catholic University of Louvain, Brussels, Belgium.
§GI Tumor Program, H. Lee Moffitt Cancer Hospital, University of Florida, Tampa, FL.
¶Novartis Pharmaceutical Corporation, East Hanover, NJ.
Address reprint requests to Roelf Valkema, MD, Department of Nuclear Medicine, Erasmus MC, Dr Molewaterplein 40, 3015 GD Rotterdam, the Netherlands.
E-mail: r.valkema@erasmusmc.nl

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Most patients with carcinoid tumors and other gastroenteropancreatic neuroendocrine (GEP-NET) tumors have a relatively good prognosis.[1,2] Although many patients have specific symptoms as a result of the overproduction of hormones, other patients have no hormone overproduction or related specific symptoms at all. During the past decades, the advent of drugs that counteract the effects of hormonal overproduction has improved the symptomatic control, as well as the prognosis of selected patients. Proton-pump inhibitors, such as omeprazole, suppress gastric acid production in Zollinger Ellison syndrome, whereas somatostatin analogs, such as octreotide, suppress the hormone production in tumors that express somatostatin receptors, mainly subtype 2 (sst_2). Somatostatin analogs may even stabilize tumor growth in 20% to 50% of cases.[3-5] Despite these advancements, patients with advanced progressive disease, especially with extensive liver involvement, have a significantly worse prognosis than patients with limited disease.[1,2]

Chemotherapy is applied in patients who are not candidates for surgery. Optimistic results indicating a high response rate from some reports[6-8] have later been disputed.[9,10] Chemotherapy therefore generally is not accepted, except in patients with anaplastic tumors, although responses last very short.[11]

Neuroendocrine tumors are not very sensitive to external beam irradiation. However, most GEP-NETs have a high expression of somatostatin receptors, in particular sst_2, which opens the possibility of delivering a high radiation dose specifically to receptor-positive tumor cells. Therefore, direct tumor targeting with high-dose radiolabeled somatostatin analogs was applied in patients, with promising initial results,[12] and the concept was further developed. Peptide receptor radiation therapy (PRRT) with high doses of [^{111}In-DTPA^0]octreotide in patients with neuroendocrine tumors has had limited success as far as objective tumor response is concerned, but the clinical improvement in some patients was striking.[13,14] It also was suggested that the use of PRRT with high doses of [^{111}In-DTPA^0]octreotide improved survival in patients with GEP-NET. The second-generation radiopharmaceutical for PRRT is [^{90}Y-DOTA^0,Tyr^3]-octreotide, with ^{90}Y-emitting beta particles of high energy (2 MeV) and a maximal penetration range of 12 mm. It was developed as ^{90}Y-DOTATOC[15] in parallel to the ^{90}Y-SMT487[16] used in this study. Both compounds are chemically identical. Studies with ^{90}Y-DOTATOC showed a higher objective response rate than those reported for [^{111}In-DTPA^0]octreotide.[17] However, no long-term studies on the survival after PRRT with [^{90}Y-DOTA^0,Tyr^3]-octreotide have been published. The current survival analysis pertains an extended follow-up of an uncontrolled phase-I study of PRRT with [^{90}Y-DOTA^0,Tyr^3]-octreotide. We used the patients with GEP-NET tumors from our previous study on PRRT with [^{111}In-DTPA^0]octreotide[13] as historical controls because these patients were very similar to the patients from the phase-I [^{90}Y-DOTA^0,Tyr^3]-octreotide study.

Patients and Methods

PRRT with [^{90}Y-DOTA^0,Tyr^3]octreotide

The patients were all veterans of a multicenter phase-I, uncontrolled, open-label vertical (per cycle) and horizontal (number of cycles) dose-escalating study.[18,19] The primary goals were to establish the 1-cycle and 4-cycle maximum tolerated doses of [^{90}Y-DOTA^0,Tyr^3]octreotide (^{90}Y-SMT487, ^{90}Y-edotreotide) and to evaluate the immediate, 6 month, and long-term (18 month) safety profiles. All patients gave written informed consent. The study was approved by the local ethical committees of the 3 participating centers. Before entering the therapy study, all patients had undergone dosimetry using [^{86}Y-DOTA^0,Tyr^3]octreotide and positron emission tomography.[20]

Sixty patients were included in the study, of whom 58 had GEP-NET, including 35 patients with carcinoid tumors (5 foregut, 30 midgut), and 23 with mainly pancreatic neuroendocrine tumors, including 8 patients with functioning islet cell tumors, 10 patients with nonfunctioning islet cell tumors, and 5 patients with unclassified GEP-NET (Table 1). Two patients with glomus tumors were excluded from this analysis on survival. In 52 patients liver metastases were known at the time of inclusion and 18 patients (16 patients with liver metastases, 2 without) were already in a very advanced disease stage. These patients were qualified as "end-stage" by clinical assessment, using the same criteria as in a previous study with therapeutic doses of [^{111}In-DTPA^0]octreotide.[13] Briefly, in patients with a Karnofsky performance status (KPS) $\leq$70%, any 2 of the following criteria were required (1): rapid tumor progression, (2) high tumor load (especially hepatomegaly or ascites), and (3) definite weight loss (>1 kg per month for at least 3 months, or cachexia); in patients with a KPS $\geq$80%, rapid tumor progression and 1 of the other criteria were required.

The initial administered activity of [^{90}Y-DOTA^0,Tyr^3]octreotide was 25 mCi/m^2 (925 MBq/m^2) per cycle. Vertical escalation proceeded as 25 mCi/m^2/cycle intervals for subsequent cohorts of patients. The patients were allowed to receive up to 4 cycles of their cohort activity (horizontal escalation). The interval between treatments was 6 to 9 weeks. In the later phase of the study, the protocol was amended to allow further escalation of the activity per cycle. These patients received then a number of full cohort activities and a final smaller remainder of activity as the last cycle, until their measured cumulative renal radiation dose was reached.

For renal protection purposes, all patients were infused with 1500 mL of a commercially available solution (Aminosteril N-Hepa 8% (Fresenius AG, Bad Homburg, Germany) together with 500 mL of a mineral solution (Ringer lactate, Baxter B.V., the Netherlands). The infused solution contained 124.5 g amino acids (AAs), including 10.88 g of L-lysine and 16.08 g of L-arginine. The AA solution was infused over the course of 4 hours at a continuous rate of 500 mL/min, starting 30 minutes before infusion of [^{90}Y-DOTA^0,Tyr^3]octreotide via a separate line. The position emission tomography dosimetry studies with

Table 1 Baseline Demographic and Clinical Characteristics of the 58 Patients Treated with [^{90}Y-DOTA^0,Tyr^3]octreotide

Age (years)	
Mean ± SD	54.0 ± 9.6
Range	33-75
Sex, n (%)	
Male	33 (57)
Female	25 (43)
Diagnosis, n (%)	
Carcinoid	35 (60)
Foregut	5 (9)
Midgut	30 (52)
GEP-NET	23 (40)
Islet functional	3 (5)
Islet nonfunctional	11 (19)
Unclassified	5 (9)
Extent of disease	
Liver metastases	52 (90)
End-stage*	18 (31)
Time since initial diagnosis (months)	
Median	35.9
Range	6.7-275
Time since diagnosis of liver metastases (months)	
Median	31.4
Range	3.0-158
Previous treatments, n (%)†	
Surgery	32 (55)
Chemotherapy	18 (31)
External beam radiotherapy	7 (12)
Chemo-embolization	9 (16)
Interferon	8 (14)
Octreotide	37 (64)
Progressive at baseline, n (%)	47 (81)
During octreotide treatment	33 (57)
Without octreotide treatment	14 (24)

Abbreviation: GEP-NET, gastroenteropancreatic neuroendocrine tumor.

*The qualification "end-stage" was based on clinical criteria: (1) Karnofsky Performance Status (KPS); (2) high tumor load (especially hepatomegaly and/or ascites); (3) rapid tumor progression; (4) weight loss of more than 1 kg/month for at least 3 months or cachexia. Patients with KPS ≤ 70 required any 2 of the other criteria; patients with KPS ≥ 80 required rapid progression and 1 of the other criteria.

†Cumulative percentages differ from 100, since some patients received more than 1 treatment, while others had no previous treatment at all.

[^{86}Y-DOTA^0,Tyr^3]octreotide also had been performed with concomitant AA infusions as described previously.[20]

Evaluation of Response and Survival Parameters

All patients had at least 1 measurable tumor (assessed by computed tomography [CT], magnetic resonance imaging [MRI], or ultrasound [US]) for the assessment of objective response by standard Southwest Oncology Group (SWOG) criteria.[21] Additional to the standard SWOG criteria of complete response (CR; = disappearance of all tumors, confirmed at 4 weeks) and partial response (PR; ≥50% decrease), we used "minor response" (MR; = 25-49% decrease). Antitumor effects were monitored 6 weeks after the administration of the final treatment dose and at 6-month intervals by CT scan or, when appropriate by MRI or US (including endoscopic US). For the patients who received 4 cycles, the evaluation of the fourth cycle was at about 6 months after the first treatment dose. After the formal 18-month period of the study protocol, continued evaluations at 6-month intervals until death were planned by the 3 participating hospitals. Any MR, PR, or CR was confirmed using the same imaging modality at an interval of at least 4 weeks. The overall survival (OS) was assessed by Kaplan–Meier analysis from day 1 of the first therapy cycle until death or censoring.

Patients were censored if they were still alive on October 1, 2005, or had died from other causes than their tumor. Additionally, 2 patients who switched to PRRT with [^{177}Lu-DOTA^0,Tyr^3]octreotate were censored as well because very favorable therapeutic results of this therapy have been reported,[17] and we could not distinguish the contribution of either variant of PRRT on further survival after the first [^{177}Lu-DOTA^0,Tyr^3]octreotate administration. The contribution of additional factors on survival after PRRT with [^{90}Y-DOTA^0,Tyr^3]octreotide was investigated by the Cox regression method with backward stepwise removal of covariates. The survival after PRRT with [^{90}Y-DOTA^0,Tyr^3]octreotide was compared with a historical control group of patients who had been treated in Rotterdam with [^{111}In-DTPA^0]octreotide.[13] This comparison was confined to the subgroup of 32 patients from that study with GEP-NET tumors only.

The progression-free survival (PFS) after PRRT with [^{90}Y-DOTA^0,Tyr^3]octreotide was determined for all patients from day 1 of the first therapy cycle until documented progression according to SWOG criteria or tumor-related death or censoring. Patients were censored if they were still alive without progression on October 1, 2005, or had died from other causes than their tumor without progression.

Historical Control Patients Treated With [^{111}In-DTPA^0]octreotide

All 32 patients with GEP-NET tumors were selected from a group of 50 patients treated with high doses of [^{111}In-DTPA^0]octreotide who participated in a phase-I study in Rotterdam, which has been reported in detail.[13] The relevant patient characteristics were similar to the characteristics of the patients treated with [^{90}Y-DOTA^0,Tyr^3]octreotide (Table 2). Briefly, the treatment protocol comprised multiple administrations of 165 to 300 mCi (6-11 GBq) of [^{111}In-DTPA^0]octreotide, at 2-week intervals with an aim of at least 8 administrations.[13] The actual cumulative administered activity in the 32 GEP-NET patients ranged from 127 mCi (1 cycle) to 4350 mCi (22 cycles).

Results

In 34 patients, 4 equal cycles of [^{90}Y-DOTA^0,Tyr^3]octreotide were planned. Administered activities per cycle ranged from

Table 2 Comparative Characteristics of Carcinoid and GEP-NET Patients Treated with [^{90}Y-DOTA^0,Tyr^3]octreotide (Present Study) or [^{111}In-DTPA^0]octreotide (Historic Controls)

	[^{90}Y-DOTA^0,Tyr^3]octreotide (n = 58)	[^{111}In-DTPA^0]octreotide (n = 32)	*p* Value
Age (years) (mean ± SEM)	54.0 ± 1.3	52.0 ± 2.6	0.46*
Female	25 (43)	16 (50)	0.66†
Male	33 (57)	16 (50)	
Carcinoid	35 (60)	12 (38)	0.05†
GEP-NET	23 (40)	20 (62)	
Progressive at start	47 (81)	28 (88)	0.56†
Stable at start	11 (19)	4 (13)	
KPS ≤ 70	10 (17)	14 (44)	0.01†
KPS > 70	48 (83)	18 (56)	
No liver metastases, no end-stage	4 (7)	1 (3)	0.77‡
Liver metastases, no end-stage	36 (63)	19 (58)	
End-stage	18 (31)	12 (38)	

Note: Values indicate number of patients (%) except as noted. Within categories, percentages may not add to 100 due to rounding.
*_t_ Test.
†Fisher exact test.
‡Pearson chi-square.

19.7 mCi/m^2 to 103 mCi/m^2, and cumulative activities ranged from 222 mCi/m^2 to 403 mCi/m^2. In 24 patients, single-dose escalation from 97.3 mCi/m^2 per cycle to 251 mCi/m^2 per cycle was performed. Their cumulative activities ranged 19.5 mCi/m^2 to 349 mCi/m^2. The treatments were given between January 1998 and August 2002.

Two patients died during the first cycle (1 from pulmonary embolism, 1 from tumor progression). Two patients withdrew their consent after 1 cycle; both died shortly afterward from disease progression. Because of disease progression, 1 patient completed only 1 and another patient only 3 of the 4 planned cycles. The remaining 52 patients received their full individual treatment, either as planned (n = 49), or without the last cycle because of long lasting thrombocytopenia (n = 2), or with 50% decreased cycle doses after creatinine clearance dropped below 40 mL/min due to ureter obstruction by tumor (n = 1).

Two patients had dose-limiting toxicity during the planned observation period of 18 months: 1 patient with transient grade 3 liver toxicity and 1 patient with grade 4 thrombocytopenia. Additionally, 1 patient developed myelodysplastic syndrome 2 years after the start of PRRT and 9 patients had a more than 15% per year decline in creatinine clearance with end-stage renal disease in 2 patients. The toxicity is not reported in detail here, but preliminary results were reported[19] and the renal toxicity was reported in detail previously.[22-24]

The objective responses after PRRT with [^{90}Y-DOTA^0,Tyr^3]octreotide are displayed in Table 3. As assessed at the end of their last treatment cycle, only 2 patients had PR, with an additional 3 patients reaching PR during long-term follow-up. This trend of continued regression in tumor size was seen in many patients who had reached stable disease (SD) after being progressive at baseline or who were already stable at baseline. Overall, 33 patients (57%) experienced any improvement in their disease status, including conversion from progressive disease (PD) into SD, and improvement from SD into MR. Accordingly, 21 of 36 patients (58%) had improvement in KPS or symptoms, wheras 22 patients were already asymptomatic at baseline.

The median time interval between initial diagnosis and the start of PRRT was 35.9 months (range, 6.7-275). The median OS was 36.7 months (95% confidence interval [CI] 19.4-54.1) after the start of PRRT (Fig. 1). Covariates with potential impact on OS were analyzed by univariate and multivariate regression using a Cox regression model. Gender (P = 0.62), age (P = 0.65), and diagnosis (carcinoid or other GEP-NET, P = 0.16), were nonsignificant univariate factors in predicting OS, whereas extent of disease (no liver metastases, or liver metastases without "end-stage" status, or "end-stage" status, $P < 0.001$), disease status at baseline (PD vs. SD, P = 0.02) and KPS (P = 0.01) were highly significant univariate factors. However, because KPS comprised within our definition of "end-stage" disease, KPS and "extent of disease" are not independent. In multivariate Cox regression models with stepwise entering the factors "progression at start," "extent of disease" and KPS, KPS contributed less than "extent of disease." In a stepwise removal of factors, removal of KPS generated no significant loss upon Chi-square analysis, whereas removal of "extent of disease" was highly significant. Thus, we accepted the model comprising "progression at start" (Fig. 2) and "extent of disease" (Fig. 3) as the best predictive model for OS after PRRT with [^{90}Y-DOTA^0,Tyr^3]octreotide.

The median PFS was 14.3 months (95% CI 8.9-19.7), if all 58 patients are considered, including the 6 patients who did

Table 3 Best Response to Treatment with [^{90}Y-DOTA^{0},Tyr^{3}]octreotide in 58 Patients with Carcinoid or GEP-NET Tumors

	Progressive at Baseline		Stable at Baseline
	Intention to Treat (n = 47)	After Full Treatment* (n = 41)	After Full Treatment* (n = 11)
Best objective response			
Partial response (PR)	5 (11)	5 (12)	0
Minor response (MR)†	5 (11)	5 (12)	2 (18)
Stable disease (SD)	21 (45)	21 (51)	8 (73)
Progressive disease (PD)	13 (28)	10 (24)	1 (9)
Unknown	3 (6)		
Any improvement‡	31 (66)	31 (76)	2 (18)
Symptomatic response			
Symptomatic or KPS < 100 at start	30 (64)	30 (73)	6 (53)
Improvement§	17 (57)	17 (57)	4 (67)
No improvement§	13 (43)	13 (43)	2 (33)

Note: Values indicate number of patients (%). Percentages are relative to totals at column headings, unless otherwise indicated. Due to rounding percentages may not add to 100.

*Full treatment dose denotes either a cumulative dose leading 27 Gy renal radiation dose, or a cumulative dose after which a patient does not qualify for the next cycle.

†Minor response denotes decrease in tumor size between 25% and 50%.

‡Any improvement includes change from PD (at start) to SD or better and change from SD (at start) to MR or better.

§Percentages refer only to patients with symptoms or KPS < 100 at start.

not receive their full amount of activity and the 11 patients who were progressive at the end of their last cycle. In the subgroup of 41 patients with at least SD at the end of the last cycle, the median PFS was 29.3 months (95% CI 19.3-39.3) (Fig. 4).

The median OS in the historical control group of 32 patients treated with [^{111}In-DTPA^{0}]octreotide was 12.0 months (95% CI 6.2-17.8). The difference with the median OS of 36.7 months in the [^{90}Y-DOTA^{0},Tyr^{3}]octreotide patients was highly significant (log rank test, $P < 0.001$). The difference in OS remained significant for [^{90}Y-DOTA^{0},Tyr^{3}]octreotide vs. [^{111}In-DTPA^{0}]octreotide if separate subgroups were considered: "end-stage" patients (median OS 12.3 months vs. 4.2 months, $P = 0.001$), non-"end-stage" patients (median OS not yet reached vs. 18.0 months, $P = 0.017$), patients who were "progressive at start" (median OS 32.1 months vs. 11.4 months, $P = 0.001$), or patients who were "stable at start" (median OS not yet reached vs. 18.0 months, $P = 0.013$). In a multivariate Cox regression model comprising the factors "progressive at start," "extent of disease," and "therapy," the contribution of all 3 factors was highly significant (Fig. 5).

The subsequent phase 2 studies of PRRT with [^{90}Y-DOTA^{0},Tyr^{3}]octreotide were performed with a schedule comprising 3 equal doses of 120 mCi (4.4 GBq), amounting

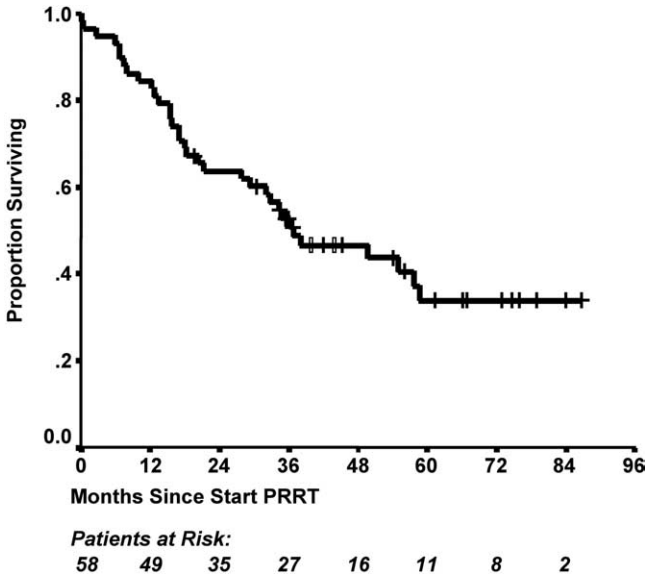

Figure 1 Kaplan Meier curve of overall survival after PRRT with [^{90}Y-DOTA^{0},Tyr^{3}]octreotide. Censored cases are indicated in the curve.

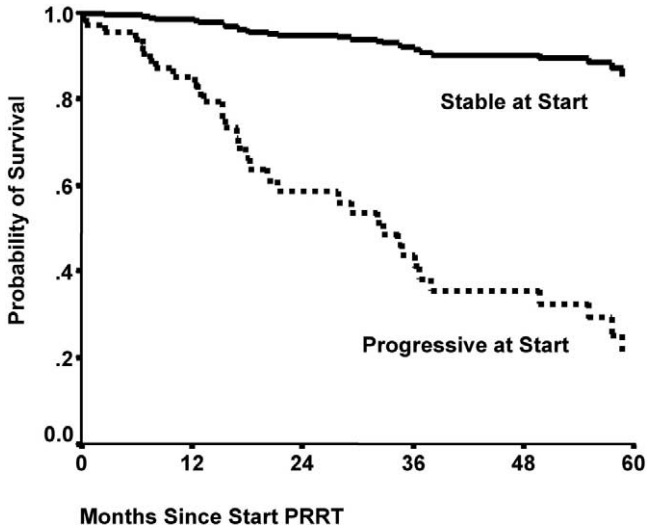

Figure 2 Cox regression model of survival probability after PRRT with [^{90}Y-DOTA^{0},Tyr^{3}]octreotide for patients with SD at start (solid curve) compared with patients with PD at start (dotted curve) ($P < 0.001$).

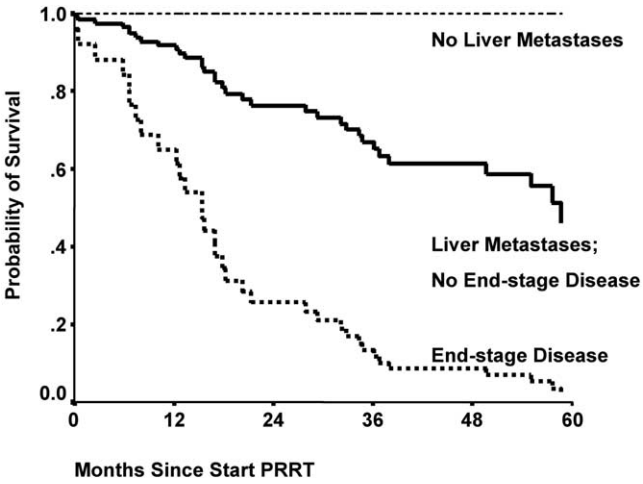

Figure 3 Cox regression model of survival probability after PRRT with [^{90}Y-DOTA^0,Tyr^3]octreotide for patients with no liver metastases (dotted curve, thin), patients with liver metastases but no end-stage disease (solid curve, thick) and patients with end-stage disease (dotted curve, thick) ($P < 0.001$).

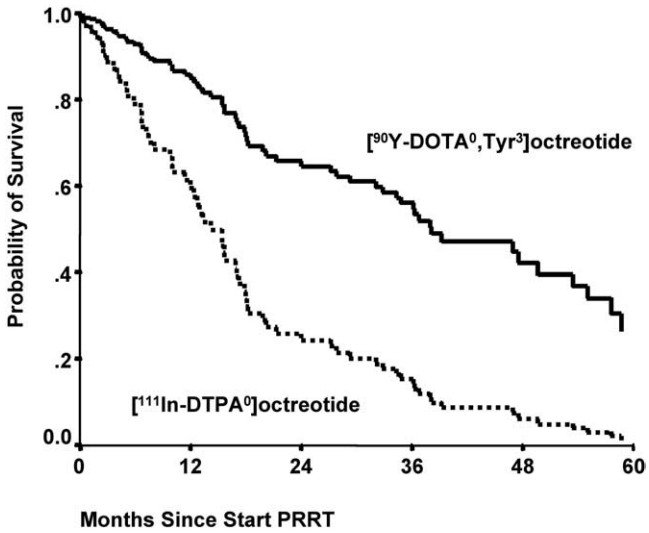

Figure 5 Cox regression model of survival probability after PRRT with [^{90}Y-DOTA^0,Tyr^3]octreotide (solid curve), compared with PRRT after [^{111}In-DTPA^0]octreotide (dotted curve) ($P < 0.001$).

to a cumulative administered activity of 360 mCi (13.3 GBq).[18,25]Within the total group of 58 patients in this study, 25 had received a cumulative activity of less and 33 more than 360 mCi [^{90}Y-DOTA^0,Tyr^3]octreotide. Comparing the baseline characteristics using Chi-square tests, we found no significant differences in age, gender, diagnosis (carcinoid vs. other GEP-NET), or proportion of patients with PD at start. In the group of 25 patients with cumulative activity below 360 mCi, there were 11 patients with "end-stage" disease versus 7 of 33 patients with cumulative activity greater than 360 mCi ($P = 0.08$), and there were 7 of 25 patients with KPS of 70 or lower versus 3 of 33 patients with cumulative activity greater than 360 mCi ($P = 0.06$). Thus, there was a possible trend toward more severe illness in the subgroup who received less than 360 mCi. Moreover, there were 5 patients who did not receive their planned cohort cumulative activity or the activity at their individual limit of toxicity in the group of 25 patients less than360 mCi versus only 1 patient of 33 who received more than 360 mCi ($P = 0.036$). The difference in response was significant: 12 patients with PD, 9 SD, 3 MR, and 1 PR in the patients who received less than 360 mCi versus 5 patients with PD, 20 SD, 4 MR and 4 PR (Pearson chi-square test, $P = 0.045$). These results also were reflected in the median OS of 18.2 months in the patients receiving less than 360 mCi.

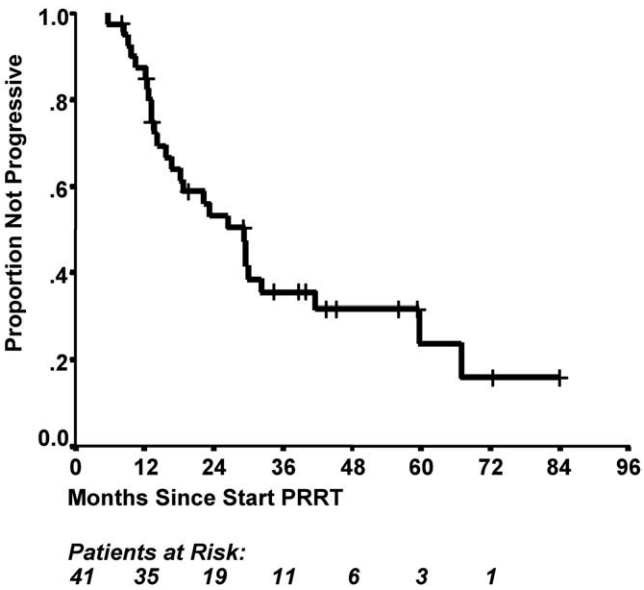

Figure 4 Kaplan–Meier curve of progression-free survival in 41 patients who had at least stable disease after PRRT with [^{90}Y-DOTA^0,Tyr^3]octreotide. Censored cases are indicated in the curve.

To mimic the cumulative activity administered in the phase 2 studies more closely, we also regarded the OS by Kaplan-Meier analysis in a subgroup of 19 patients (17/19 progressive at start) who received a cumulative activity between 270 mCi and 360 mCi, being 75% to 100% of the planned phase 2 cumulative activity. For comparison, we selected 20 patients (18/20 progressive at start) from the [^{111}In-DTPA^0]octreotide group who had received between 540 mCi and 2700 mCi of [^{111}In-DTPA^0]octreotide, being the minimal effective activity and the maximal tolerable activity, respectively.[13] The median OS was 21.3 months for the 19 [^{90}Y-DOTA^0,Tyr^3]octreotide-treated patients, compared with 12.0 months (Log rank test $P = 0.025$) for the 20 [^{111}In-DTPA^0]octreotide-treated patients. The 2 patients with SD within the 19 [^{90}Y-DOTA^0,Tyr^3]octreotide-treated patients are still alive after 39.6 and 61.2 months and the 2 patients with SD within the 20 [^{111}In-DTPA^0]octreotide-treated patients died at 18.0 and 53.4 months, respectively.

Discussion

At first sight, the results of our analysis of response and survival in patients with GEP-NET after PRRT with [^{90}Y-DOTA^0,Tyr^3]octreotide may seem contradictory. As assessed

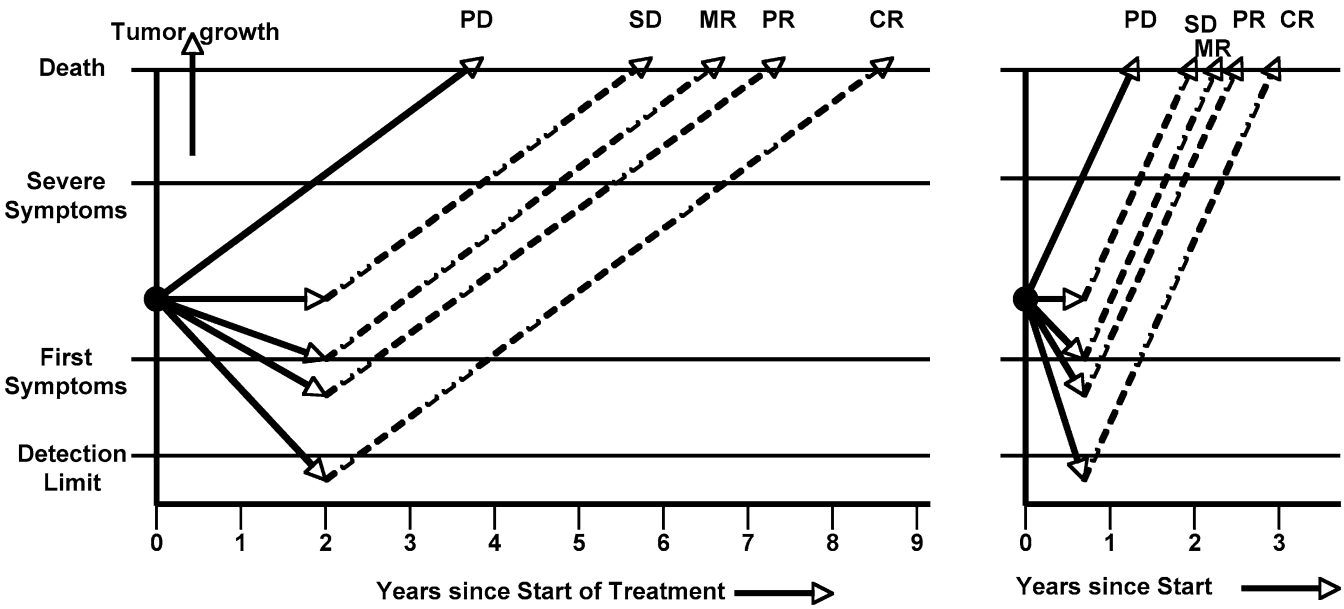

Figure 6 Simplified conceptual model of tumor growth, response to treatment, and survival. The left panel illustrates the potential course of disease for a slowly growing tumor, the right panel for a fast-growing tumor. The tumor growth rate is assumed to be constant in each case, also when the tumor starts growing again after a period of response. For a fast-growing tumor (right panel), there is little time gained when the best response is SD or MR; even the period after relapse from PR or CR until death may be limited. For a slowly growing tumor (left panel), the extra time gained after relapse from MR compared with relapse from SD may be significant. Moreover, the time period between the development of severe symptoms until death would be equal for all response categories from PD to CR, whereas the extra time gained would be in the phase before that.

by standard SWOG response criteria, only 5 of 58 patients (9%) reached PR, and none reached CR. For most tumors, these disappointingly low figures would indicate that the therapy was hardly effective. In contrast, a median OS of 3 years after the start of PRRT and a median PFS of 2.5 years (in the 41/58 patients who were at least stable at the end of the treatment period) are very favorable, as this was accompanied by symptomatic improvement as well. Gastroenteropancreatic tumors generally are slowly growing tumors, with a low sensitivity to radiation. In fast-growing radiosensitive tumors, eg, lymphomas, the effects of external beam radiation become apparent during the course of therapy or soon thereafter. In our group of GEP-NET patients after PRRT with [^{90}Y-DOTA^{0},Tyr^{3}]octreotide we observed only 2 patients with PR at the assessment after their last cycle, but the general trend was a slowly continuing shrinkage of tumor volume on CT over the long-term follow-up after the completion of PRRT. Ultimately, 5 patients reached PR, with an additional 7 patients with MR as best response, and a total of 33 patients (57%) who experienced at least an improvement in SWOG disease status. Moreover, the median PFS in the 41 of 58 patients (71%) was 2.5 years with bearable symptoms, suggesting that an important gain in time may have been achieved for individual patients.

In our opinion, attaining SD or MR in patients with slow-growing tumors, especially if maintained for long periods, represent useful therapeutic effects instead of failure to therapy. This concept is illustrated in a simplified model (Fig. 6). The mechanism of direct cell kill after radiation in the sensitive phase of cell division may not be the most important mechanism of tumor response in PRRT with [^{90}Y-DOTA^{0},Tyr^{3}]octreotide. Because GEP-NET tumors are generally well vascularized, we speculate that progressive vascular damage with resulting ischemia and subsequent partial necrosis may play a role, which could be analogous to the late effects of PRRT with [^{90}Y-DOTA^{0},Tyr^{3}]octreotide on the renal function that we observed during the long-term follow-up in some patients,[22] especially in those who received a high biological equivalent radiation dose on their kidneys.[24] We postulated that the continued loss of creatinine clearance with a constant percentage per year was compatible with progressive glomerular damage, ultimately a vascular process.[22]

We observed a median survival of more than 3 years after the start of PRRT with [^{90}Y-DOTA^{0},Tyr^{3}]octreotide, compared with less than 1 year in patients who had been treated with [^{111}In-DTPA^{0}]octreotide in a different study.[13] Both groups of patients were comparable (Table 2), except for a higher proportion of patients with KPS greater than 70 in the [^{90}Y-DOTA^{0},Tyr^{3}]octreotide group. However, the extent of disease at start (no liver metastases, liver metastases but not "end-stage" and "end-stage") and the proportion of patients with PD at start appeared to be equally distributed; therefore, we regarded the [^{111}In-DTPA^{0}]octreotide patients as historical controls. Important predictive factors for survival appeared to be the PRRT with [^{90}Y-DOTA^{0},Tyr^{3}]octreotide, in addition to progressive or stable disease at start, and the extent of disease at start. It is encouraging that in all subgroups of patients, whether or not progressive, whether or not classified as "end-stage,"

PRRT with [^{90}Y-DOTA^0,Tyr^3]octreotide appeared to contribute to the survival, when compared with PRRT with [^{111}In-DTPA^0]octreotide. However, the estimated benefit in OS of 3 year versus 1 year became less prominent (21.3 months) if only the patients were considered who received 75% to 100% of the 360 mCi cumulative activity, as used for the subsequent phase 2 trials with [^{90}Y-DOTA^0,Tyr^3]octreotide,[18] which suggests a dose–effect relationship, although the true radiation dose in the tumors is relevant, rather than the administered activity.[23] It also indicates that, if patients receive PRRT with [^{90}Y-DOTA^0,Tyr^3]octreotide based on careful individual dosimetry,[20] many of them may receive more than 360 mCi with a possible longer survival than when treated in a fixed schedule of 3 cycles of 120 mCi.

Other uncontrolled studies using PRRT with [^{90}Y-DOTA^0,Tyr^3]octreotide have been performed in Basel[26-28] and in Milan.[29] The tumor responses in patients with GEP-NET tumors from these studies have been compared recently.[17] In Milan[29] the responses in 21 patients were 6 (29%) patients with PR, 11 (52%) with SD, and 4 (19%) with PD. The median duration of the response was 9 months. The responses in one study with 74 patients from Basel[26,27] were 3 (4%) CR, 15 (20%) PR, 48 (65%) SD, and 8 (11%) PD, and in another study with 33 patients[28] 2 (6%) CR, 9 (27%) PR, 19 (57%) SD, and 3 (9%) PD. Compared with the present study, there were differences in treatment schedules, and the follow-up time was much shorter in these studies. Therefore, no long-term survival is known from these studies. It is unknown whether the baseline characteristics of the patients in the Basel and Milan studies were comparable to the patients in the present study, especially considering the significant importance of progression status and extent of disease at baseline in our study.

Anthony and coworkers[14] reported tumor responses in 26 patients treated with [^{111}In-DTPA^0]octreotide. They observed PR in 2 (8%) patients, SD in 21 (81%) and PD in 3 (8%) patients. However, they did not strictly adhere to SWOG or equivalent criteria to define response. Importantly, they reported a median survival of 18 months (range, 3 to >54), which compared favorably with the 3 to 6 month expected survival of historic controls who received chemotherapy in an earlier study[30] or unlabeled octreotide.[31] Although no formal comparison was made between the patient characteristics between the patients treated with [^{111}In-DTPA^0]octreotide and the historic controls treated with chemotherapy, the authors assumed that all patients had advanced disease and they claimed that treatment with [^{111}In-DTPA^0]octreotide prolongs survival.[14]

Recently, the results of 131 GEP-NET patients treated in Rotterdam with [^{177}Lu-DOTA^0,Tyr^3]octreotate were reported.[32] In this phase 1/phase 2 study the cumulative activity administered was 600 mCi to 800 mCi, mainly in 200 mCi cycles. Although toxicity was low, the objective responses were very encouraging. Three patients (2%) had CR, 32 (26%) PR, 24 (19%) MR, 44 (35% SD and 2 (18%) PD. The median PFS in the 103 patients who had either SD or tumor regression was more than 36 months. The follow-up time in most of these patients is still too short to allow a reliable assessment of survival, the proportion of patients who have died thus far is very low. Because the inclusion and exclusion criteria for this study are similar to the criteria applied for the present study with [^{90}Y-DOTA^0,Tyr^3]octreotide, we do not expect major differences in baseline disease state of the patients. This indicates, that PRRT with [^{177}Lu-DOTA^0,Tyr^3]octreotate in patients with GEP-NET may be more effective than PRRT with [^{90}Y-DOTA^0,Tyr^3]octreotide. Another study evaluated the quality of life (QoL) in 50 patients with metastatic GEP-NET tumors treated with [^{177}Lu-DOTA^0,Tyr^3]octreotate.[33] A significant improvement in the global health status/QoL scale was observed after completion of the therapy, with associated decreases in symptom scores for fatigue, insomnia and pain. Patients with tumor regression most frequently had an improvement of QoL domains.[33] Future controlled studies are planned to compare PRRT with ^{90}Y-labeled and ^{177}Lu-labeled somatostatin analogs.

The reported response rates for single-agent and combination chemotherapy in patients with GEP-NET tumors are conflicting. High response rates, with 40% to 60% of patients with PR or CR have been reported in older series,[6-8] but this was based also on biochemical responses (change in serum levels of tumor markers) and physical examination for evaluation of hepatomegaly. More recently, investigators failed to confirm such high response rates.[9,10] In a recent phase 2/3 study of doxorubicin with fluorouracil compared with streptozotocin with fluorouracil or dacarbazine in a total of 240 patients with advanced carcinoid tumors, the observed response rates were 8% to 16%, median PFS 4.5 to 5.3 months and median OS 12 to 24 months between the different treatment arms, with the longest OS for the streptozotocin/fluorouracil group.[34] Despite conflicting response rates, a survival benefit of streptozotocin containing regimens has been reported by others.[9,10,35]

Biotherapy with unlabeled or "cold" somatostatin analogs in patients with neuroendocrine tumors is used widely, and there is no doubt about the wide therapeutic index and the high efficacy of somatostatin analogs in the symptomatic control of neuroendocrine tumors.[5,36] Objective tumor responses by radiological criteria are infrequent, and the biochemical responses, as reported in many studies, more likely reflect an effect on the overproduction of hormones and other substances than a cell killing effect. However, tumor stabilization can be observed with somatostatin analog treatment.[3] In a large observational study, an improved survival in patients with advanced carcinoid tumors was observed since 1992, when cold octreotide was introduced.[37] The authors argued that treatment with octreotide might be the cause of the improved survival. However, an additional factor, not mentioned in the report, may have been the improved diagnostic possibilities, mainly the introduction of peptide receptor scintigraphy with ^{111}In-pentetreotide.[38,39] It is possible that patients are now correctly staged as metastasized earlier in the course of their disease than before 1992, and that this lead-time bias is (partially) responsible for the observed longer period from diagnosis to death.

In our PRRT studies, the majority of patients were progressive despite being on treatment with unlabeled somatostatin

analogs, which were continued after the start of PRRT for symptomatic control.

Interferon-alpha can provide symptom control, and can lead to disease stabilization in 35% and PR in 11% of patients, but its use is limited by side-effects.[36] In controlled studies, the response rates after treatment with interferon or interferon in combination with somatostatin analogs were not different from the response after treatment with somatostatin analogs alone.[4,40]

It is difficult to relate the reported response rates, PFS and OS of the many old and new chemotherapy and biotherapy studies with those of PRRT with [^{90}Y-DOTA^0,Tyr^3]octreotide, or other somatostatin analogs because the selection of patients and other parameters are probably different. However, it is unlikely that the patients in the [^{90}Y-DOTA^0,Tyr^3]octreotide or [^{111}In-DTPA^0]octreotide PRRT groups had much less advanced disease than the patients in the chemotherapy studies. In that perspective, the median PFS of 29.3 months and median OS of 36.7 months that we observed for PRRT with [^{90}Y-DOTA^0,Tyr^3]octreotide are encouraging, and the results as reported for PRRT with [^{177}Lu-DOTA^0,Tyr^3]octreotate[32] most promising. Additionally, the relative low rate of toxicity in our PRRT studies[13,19,32] compares favorably with the reported toxicity of chemotherapy, especially of doxorubicin and streptozotocin containing regimens.[34,35]

Limitations

This was a phase 1 study, mainly directed at finding the tolerable dose of [^{90}Y-DOTA^0,Tyr^3]octreotide in a vertical and horizontal escalation schedule. As such, it was uncontrolled and different cumulative activities were administered to the participating patients. However, follow-up was continued by the three participating hospitals as much as possible beyond the 18-month period that was defined in the study protocol. The patient group appeared to be comparable to the patients from an earlier PRRT study with [^{111}In-DTPA^0]octreotide in Rotterdam, so that these could be used as historic controls. Nevertheless, no definitive conclusions can be drawn concerning the objective response rates, PFS or OS after PRRT with [^{90}Y-DOTA^0,Tyr^3]octreotide from this study.

Conclusions

The objective response rate according standard SWOG criteria after PRRT with escalating doses in a phase 1 setting [^{90}Y-DOTA^0,Tyr^3]octreotide was low with PR in 5 of 58 patients (9%). With slowly growing tumors, however, any improvement in response parameters, including conversion from PD into SD or attaining MR, may reflect an important gain for the patient (Fig. 6). Therefore, in our opinion 33 of 58 patients (57%) have had a response (Table 2). The median OS of 36.7 months and median PFS of 29.3 months after PRRT with [^{90}Y-DOTA^0,Tyr^3]octreotide are encouraging and significantly better than after PRRT with [^{111}In-DTPA^0]octreotide, compatible with a true therapy related effect, apparent in patients with progressive or stable disease at start, and also apparent in patients with or without end-stage disease. The median OS was 21.3 months in a subgroup of patients who received a cumulative activity of 75% to 100% of the fixed 360 mCi activity as used in the phase 2 studies with [^{90}Y-DOTA^0,Tyr^3]octreotide. In the future, controlled studies are required to evaluate which variant of PRRT with radiolabeled somatostatin analogs is the most effective, with acceptable toxicity.

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