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[^{177}Lu-DOTA^{0}-Tyr^{3}]-Octreotate Treatment in Patients with Disseminated Gastroenteropancreatic Neuroendocrine Tumors: The Value of Measuring Absorbed Dose to the Kidney

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Abstract

Background Peptide receptor radiation therapy (PRRT) using [^{177}Lu-DOTA^{0}-Tyr^{3}]-octreotate is a new, promising option for treatment of disseminated gastroenteropancreatic neuroendocrine tumors (GEPNETs).

Methods During 2006-2008, 26 patients with disseminated GEPNETs were treated with ^{177}Lu-octreotate. Radiologic response (RECIST), biochemical response [plasma chromogranin-A (P-CgA)], hematologic toxicity [Common Toxicity Criteria (CTC)], absorbed dose to the kidneys (conjugate view method), and glomerular filtration rate (GFR) were analyzed.

Results ^{177}Lu-octreotate (8 GBq) was given one to five times (median = 3) with a 6-week interval between each. Sixteen of the 26 patients were evaluated radiologically; 6 (38%) had partial response (PR), 8 (50%) had stable disease (SD), and 2 (13%) had progressive disease (PD). Seventeen of the 26 patients were evaluated biochemically; 6 (35%) showed a $\geq$30% decrease, 8 (47%) showed a $\geq$20% increase, and 3 (18%) showed neither a $\geq$30% decrease nor a $\geq$20% increase. The mean absorbed dose to the kidneys was 24 Gy. With a dose limit of 27 Gy to the kidneys, 10 patients did not receive the planned four treatments, while four patients had the potential to receive additional treatment. A significant reduction ($p = 0.0013$) of GFR was observed at follow-up. Three patients experienced CTC grade 3 hematologic toxicity.

Conclusions By using the absorbed dose to the kidneys as a limiting factor, treatment with ^{177}Lu-octreotate can be individualized, e.g., overtreatment can be avoided and patients with the potential to receive additional treatment can be identified. Further studies are needed to define tolerance doses to the kidneys so that treatment can be optimized.

Introduction

The survival of patients with disseminated gastroenteropancreatic neuroendocrine tumors (GEPNETs) has improved during the last few decades. Surgery with excision of the primary tumor, lymph node metastases, and liver metastases is still the only curative treatment available. In selected cases palliative liver resection is indicated [1]. Bilobar hepatic metastases can be treated with hepatic artery embolization to reduce hormonal symptoms and prolong survival in patients with midgut carcinoid [2]. Palliative treatment includes medical therapy for hormonal symptoms, e.g., somatostatin analogs and interferon-α can each be effective agents [3]. Biotherapy with interferon-α has resulted in tumor regression in 15-20% of the patients who received it, but it has not been proven to prolong survival [3–5]. Chemotherapy has resulted in only limited response rates with considerable side effects [6, 7].

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Peptide receptor radiation therapy (PRRT) has recently been developed to treat somatostatin receptor-expressing GEPNET tumors. Promising results have been achieved by using the radiopharmaceutical [^{177}Lu-DOTA^{0}-Tyr^{3}]-octreotate. In a previously published series, [^{177}Lu-DOTA^{0}-Tyr^{3}]-octreotate treatment was found to induce complete response (CR), partial response (PR), or minor response (MR) in 2, 26, and 19%, respectively [8]. The absorbed dose to the kidneys and the bone marrow is the limiting factor for use of PRRT.

To evaluate the radiologic response, examination with computed tomography (CT) using the RECIST criteria offers one established method for evaluation of therapeutic effects [9]. The general neuroendocrine (NE) tumor marker plasma chromogranin A (P-CgA) correlates well with tumor burden [10–12]. Therefore, the biochemical response can be used as a simple but reliable method to evaluate tumor response. Development of a radiopharmaceutical for PRRT has included both new somatostatin analogs with high affinity for sstr and selection of isotopes with a suitable range, e.g., octreotate has a twofold higher affinity for sstr 2 than octreotide, and ^{177}Lu has a suitable range for tumors up to 1 mm in diameter, whereas ^{90}Y is more suitable for larger tumors [13, 14]. One way to optimize PRRT is to measure the absorbed dose to the kidneys. This could ensure that the dose limit is approached but not exceeded.

The aims of the present study were to evaluate the radiologic and biochemical responses to PRRT using [^{177}Lu-DOTA^{0}-Tyr^{3}]-octreotate of 26 consecutive patients with disseminated GEPNETs and to evaluate if measurement of absorbed dose to the kidneys could serve as a tool for optimization of the treatment.

Materials and methods

Patients

Twenty-six patients were treated with [^{177}Lu-DOTA^{0}-Tyr^{3}]-octreotate at our unit during 2006-2008. They all had disseminated GEPNET tumors (10 endocrine pancreatic tumors, 10 midgut carcinoids, 3 rectal carcinoids, 1 pulmonary carcinoid, 1 duodenal gastrinoma, 1 neuroendocrine presacral tumor). Multimodal treatment with combinations of surgery (primary and repeated), chemotherapy, somatostatin analogs, interferon-α, hepatic artery embolization, radiofrequency ablation, external radiation, and, in four patients, liver transplantation was used prior to [^{177}Lu-DOTA^{0}-Tyr^{3}]-octreotate treatment (Table 1).

Indications for treatment

The indications for PRRT were progressive disease despite conventional multimodal therapy and a tumor uptake of the radiopharmaceutical of at least twice the physiologic liver uptake.

Treatment protocol and follow-up

The patients were scheduled for four treatment sessions, each with 8 GBq of [^{177}Lu-DOTA^{0}-Tyr^{3}]-octreotate, 6 weeks apart. The absorbed dose to each kidney was calculated after each session with the conjugate view method. The total absorbed dose limit to each kidney was 27 Gy. The radiologic response was evaluated by measuring tumor size using RECIST criteria [complete response (CR), disappearance; partial response (PR), $\geq$30% decrease; stable disease (SD), neither PR nor PD; progressive disease (PD), $\geq$20% increase together with no CR, PR, or SD documented before PD] on CT scans taken before and after treatment. Biochemical response was evaluated by comparing P-CgA before and after treatment. Hematological toxicity was evaluated according to the Common Toxicity Criteria (CTC) scale. Renal function was assessed by measuring glomerular filtration rate (GFR) by either by Cr-EDTA or iohexol clearance.

Statistical analysis

The change in tumor size according to RECIST criteria and the change in GFR were analyzed using Wilcoxon matched-pairs signed rank sum test; $p < 0.05$ was considered significant.

Results

Absorbed doses to the kidneys

The mean absorbed dose to the kidneys was 24 Gy $\pm$ 5.9 (SEM). Four treatment sessions were given as planned to 11 of the 26 patients. One patient had five sessions, while 10 had fewer than four sessions since they had reached the kidney dose limit after two or three sessions. Four patients did not reach the dose limit and thus could have had additional treatment.

Radiological response

Sixteen of the 26 patients could be evaluated radiologically. Ten either lacked suitable lesions (not measurable on CT, $n = 3$), died of disease before follow-up ($n = 3$), or were due to be followed up ($n = 4$). The radiologic tumor response varied from a 54% increase of tumor size (progression) to a 79% decrease (regression). Six of the 16 (38%) showed partial response (PR) according to RECIST criteria. Eight (50%) showed stable disease (SD) and two

Table 1 Multimodal treatment with combinations of surgery used prior to [^{177}Lu-DOTA^{0}-Tyr^{3}]-octreotate treatment

Patient no.	Surgery	LTX	Chemotherapy	Octreotide	Interferon	HAE	RF	Ext Rad
1	X		X					X
2	X			X	X			
3	X		X		X			
4			X		X			
5			X	X				
6	X	X	X					X
7	X	X						
8		X						
9	X		X		X			
10	X			X	X			
11	X			X	X			
12	X			X	X			
13	X	X	X			X	X	
14	X		X	X	X	X		
15	X			X	X	X	X	
16	X			X	X			
17	X			X	X	X		
18	X							
19			X		X			
20			X					X
21	X			X	X			
22	X			X	X		X	X
23	X					X		
24	X							
25	X			X				
26	X				X	X		

LTX liver transplantation, *HAE* hepatic artery embolization, *RF* radiofrequency ablation, *Ext Rad* external radiation

(13%) showed progressive disease (PD). No complete remissions (CR) were observed. The radiologic response was not significant, $p = 0.15$ (Fig. 1).

Biochemical response

Seventeen of 26 patients were evaluated biochemically by measuring P-CgA. Nine patients either did not have elevated P-CgA before treatment ($n = 4$), died of disease before follow-up ($n = 3$), or were due to be followed up ($n = 2$). Six (35%) showed a ≥30% decrease, eight (47%) showed a ≥20% increase, and three (18%) showed neither a ≥30% decrease nor a ≥20% increase (Fig. 2).

Adverse effects

Three patients experienced CTC grade 3 hematologic toxicity with low platelet counts. Nadir values were 12, 19, and 38 × 10^{9}/l and appeared at 40–45 days after treatment. The mean GFR before treatment was 80 ml/1.73 m^2/min ± 4 (SEM). At follow-up the mean GFR was 70 ml/1.73 m^2/min ± 4 (SEM). The decrease in GFR was significant, $p = 0.0013$.

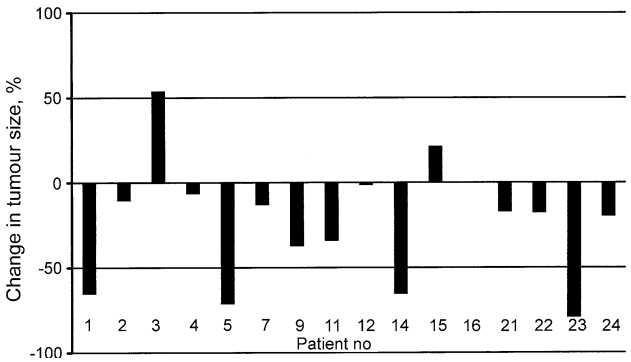

Fig. 1 Sixteen of 26 patients could be evaluated radiologically. The radiologic tumor response varied from a 54% increase of tumor size (progression) to a 79% decrease (regression). Using the RECIST criteria, 6 of 16 patients (38%) showed partial response (PR), 8 of 16 (50%) showed stable disease (SD), and 2 of 16 (13%) showed progressive disease (PD)

Discussion

PRRT with [^{177}Lu-DOTA^{0},Tyr^{3}]-octreotate has recently been introduced as a palliative treatment for patients with GEPNETs [8]. This radiopharmaceutical binds specifically

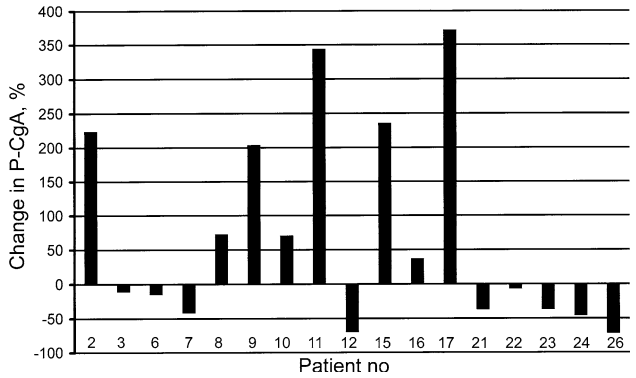

Fig. 2 Seventeen of 26 patients could be evaluated biochemically. The biochemical response varied from a 372% increase to a 72% decrease of P-CgA values. When applying the same response limits as in the RECIST criteria to the biochemical response, 6 of 17 patients (35%) showed partial response (PR), 3 of 17 (18%) showed stable disease (SD), and 8 of 17 (47%) showed progressive disease (PD)

to sstr 2 and 5 resulting in uptake and internalization of the radionuclide. The first attempts of systemic treatment with [^{111}In-DTPA^{0}]-octreotide resulted in symptomatic relief and reduction in biochemical markers but rarely a radiologic response [15–17]. [^{90}Y-DOTA,Tyr^{3}]-octreotate improved the results and led to partial regression in 7–24% of treated patients [18–20]. Treatment using [^{177}Lu-DOTA^{0},Tyr^{3}]-octreotate has, so far, shown the most promising results, with tumor response in up to 47% of treated patients [8].

The present study describes the outcome of [^{177}Lu-DOTA^{0},Tyr^{3}]-octreotate treatment in 26 consecutive patients evaluated radiologically (RECIST criteria) and biochemically (P-CgA). The follow-up time was relatively short (mean = 5 months). The rate of partial response (38%) is in line with that of previous reports. We observed a weak correlation between radiologic and biochemical responses. A possible explanation for this could be the relatively short follow-up time, i.e., because the P-CgA value reflects both the functional status of the tumor cells and tumor volume, the biochemical responses and radiologic responses can be anticipated not to be synchronous [11]. P-CgA levels are also affected by renal function, which, as shown in the present study, is affected by PRRT [21]. The adverse effects of PRRT reported by other centers have generally been mild. However, the significant reduction in the GFR observed in the present study indicates the importance of the kidney as a dose-limiting organ.

A prerequisite for successful PRRT is high expression of sstr in the tumors. Usually, the selection of suitable patients is based on tumor uptake on octreotide scintigraphy. The cutoff limit for treatment in the present study was a tumor-specific uptake of at least twice the physiologic uptake in the liver, a method that has been widely used. However, this type of visual or semiquantitative evaluation of the concentration of the radiopharmaceutical in the tumor should be avoided. One major reason is that the interindividual variation in the concentration of ^{111}In-octreotide is large, up to a factor of 4 (and liver is not the most critical organ in this treatment). Another reason is that properties and limitations of the scintigraphic technique will give misleading results if these limitations are not dealt with. Instead a more careful determination of tumor uptake, an absorbed dose should be determined.

Several more specific methods for the selection of patients for this treatment have been proposed. Tumor-to-blood (T/B) ratios of the radiopharmaceutical give a relatively accurate measurement of the tumor-specific uptake [22, 23]. Quantification of sstr expression in tumor biopsies gives a precise profile of the sstr subtypes expressed [24, 25]. A suitable radiopharmaceutical with a high affinity for the particular subtypes expressed can be selected in order to obtain an optimal tumor-specific uptake. In the future, a combination of pharmacologic treatment and tumor-specific PRRT may result in better response rates in patients with NE tumors [26].

The tumor burden of our patients was relatively large and the patients had undergone several modalities of conventional treatment before PRRT. Careful selection of patients with regard to sstr expression could be one way to treat patients with smaller tumor burdens, e.g., as completion therapy after surgical resection.

In an animal model of a human carcinoid tumor (GOT 1), a very high rate of CR was accomplished [27, 28]. The GOT 1 tumors have preserved T/B ratios and sstr profiles compared to the original tumor. The results from this model suggest that a higher response rate could be achieved if the amount of activity administered, using an optimal treatment schedule, could be increased. In the present study, measurement of the absorbed dose to the kidneys identified four patients who could have received additional treatment without exceeding the dose limit of the kidney. Our results therefore indicate that such measurements could contribute to individualized treatment. Further studies to define tolerance doses to the kidneys and development of more precise methods for determination of the absorbed doses to the kidneys could contribute to optimization of treatment schedules.

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