The somatostatin receptor-targeted radiotherapeutic [^{90}Y-DOTA-DPhe^1,Tyr^3]octreotide (^{90}Y-SMT 487) eradicates experimental rat pancreatic CA 20948 tumours

Barbara Stolz, Gisbert Weckbecker, Peter M. Smith-Jones*, Rainer Albert, Friedrich Raulf, Christian Bruns

Novartis Pharma AG, Basel, Switzerland

Received 14 January and in revised form 16 March 1998

Abstract. Somatostatin receptor-expressing tumours are potential targets for therapy with radiolabelled somatostatin analogues. We have synthesized a number of such analogues in the past and identified [DOTA-DPhe^1, Tyr^3]octreotide (SMT 487) as the most promising candidate molecule because of its advantageous properties in cellular and in vivo tumour models. In the current paper we describe the radiotherapeutic effect of yttrium-90 labelled SMT 487 in Lewis rats bearing the somatostatin receptor-positive rat pancreatic tumour CA 20948. SMT 487 binds with nanomolar affinity to both the human and the rat somatostatin receptor subtype 2 (sst_2) (human sst_2 IC_{50}=0.9 n*M*, rat sst_2 IC_{50}=0.5 n*M*). In vivo, ^{90}Y-SMT 487 distributed rapidly to the sst_2 expressing CA 20948 rat pancreatic tumour, with a tumour-to-blood ratio of 49.15 at 24 h post injection. A single intravenous administration of 10 mCi/kg ^{90}Y-SMT 487 resulted in a complete remission of the tumours in five out of seven CA 20948 tumour-bearing Lewis rats. No regrowth of the tumours occurred 8 months post injection. Control animals that were treated with 30 µg/kg of unlabelled SMT 487 had to be sacrificed 10 days post injection due to excessive growth or necrotic areas on the tumour surface. Upon re-inoculation of tumour cells into those rats that had shown complete remission, the tumours disappeared after 3–4 weeks of moderate growth without any further treatment. The present study shows for the first time the curative potential of ^{90}Y-SMT 487-based radiotherapy for somatostatin receptor-expressing tumours. Clinical phase I studies with yttrium-labelled SMT 487 have started in September 1997.

Key words: Somatostatin – Octreotide – Receptor targeted radionuclide therapy – Yttrium-90

Eur J Nucl Med (1998) 25:668–674

* *Present address:* University Hospital AHK, Department of Nuclear Medicine, Währinger Gürtel 18–20, A-1090 Vienna, Austria

Correspondence to: B. Stolz, Novartis Pharma AG, K-125.15.14, CH-4002 Basel, Switzerland

Many human tumours express somatostatin receptors with a high incidence [1]. These include neuroendocrine tumours, such as pituitary adenomas, carcinoids, islet cell carcinomas, paragangliomas and phaeochromocytomas, lymphomas [2], small cell lung cancer [1, 3], tumours of the nervous system and breast cancer [4]. The majority of these tumours express the somatostatin receptor subtype 2 (sst_2) [5]. For diagnostic purposes these tumours can be visualized with [^{111}In-DTPA-DPhe^1]octreotide (OctreoScan 111) [6]. In order to make radiotherapeutic treatment of somatostatin receptor-expressing tumours possible, we synthesized a series of octreotide analogues that can tightly chelate beta-emitting rare earths (e.g. yttrium-90). Among these compounds were [DTPA-benzyl-acetamido-DPhe^1,Tyr^3]octreotide [7], [DTPA-benzyl-acetamido-DPhe^1]octreotide, [DOTA-benzyl-acetamido-DPhe^1]octreotide and [DOTA-benzyl-acetamido-DPhe^1,Tyr^3]octreotide (manuscript in preparation).

Since octreotide, as observed with most hydrophilic low molecular weight proteins [8], is accumulated extensively at the proximal tubules of the kidneys, a series of octreotide analogues were synthesized and evaluated that contain cleavable linkers [9]. The basic idea in this study was that those conjugates containing kidney-specific cleavable linkers would be rapidly and selectively cleaved in the kidneys and that the hydrophilic cleavage product would be rapidly excreted without further degradation. Thus the accumulation of the radiotherapeutic drug in the somatostatin receptor-expressing tumours would be enhanced in relation to the amount accumulated in the kidneys. Finally [DOTA-DPhe^1,Tyr^3]octreotide (SMT 487) [10] was selected from among various DOTA-coupled octreotide analogues because of its advantageous properties in tumour models. In the present study we investigated the extension of the concept of receptor-targeted radionuclides to its radiotherapeutic application by using ^{90}Y-SMT 487.

^{90}Y-SMT 487 is a radiotherapeutic drug that has been developed for somatostatin receptor-targeted radiotherapy of somatostatin receptor-expressing tumours. In preliminary studies SMT 487 was shown to specifically

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bind to somatostatin receptors with nanomolar affinity [11], and this was confirmed by others using [^{111}In-DOTA-DPhe^{1},Tyr^{3}]octreotide [12]. The chelate stability of ^{90}Y-SMT 487 is of high importance since any free $^{90}Y^{3+}$ is known to mimic Ca^{2+} and will be accumulated by the bones. Therefore, and prior to in vivo experiments, the stability of ^{90}Y-SMT 487 was evaluated. The chelate was stable against isotopic exchange with natural yttrium and transchelation by either DTPA or serum proteins (manuscript in preparation).

The aim of the present work was to investigate the radiotherapeutic effect of ^{90}Y-SMT 487 in rats bearing the CA 20948 rat pancreatic tumour, which has previously been shown to be somatostatin receptor-positive [13].

Materials and methods

Materials. Unless otherwise stated, all reagents and solvents were obtained from commercial sources and were used without further purification. Somatostatin-14, octreotide (SMS 201-995), Tyr^{3}-octreotide (SDZ 204-090) and [DOTA-DPhe^{1}-Tyr^{3}]octreotide (SMT 487) were synthesized at Novartis Pharma AG Basel. ^{90}Y was obtained from the Pacific Northwest National Laboratory (United States) in the form of YCl_3 in a 0.05 *M* HCl solution containing a Sr/Y ratio of 9.0×10^{-9} at calibration. The specific activity of the ^{90}Y was 50 mCi/ml at a reference time of 10 h post delivery. SMT 487 was dissolved in 10 µl of AcOH and 10 µl of MeOH before being diluted with water to create a 1 m*M* solution. Aliquots of this solution were stored at –20°C until required. All buffer solutions used were passed over a Chelex filter to remove any divalent or trivalent metals and stored in polypropylene tubes. All cold solutions were degassed and saturated with either He (HPLC solvents) or N_2 (labelling/binding assay reagents) before use. Analytic high-performance liquid chromatography (HPLC) was performed using an RP_{18} column (Waters Novapak, 4 µm, 3.9×150 mm) with a MeCN/NH_4OAc solvent system initially composed of 100% A, followed by a linear gradient of 100% A (25 m*M* NH_4OAc, pH 4.0) to 100% B (25 m*M* MeCN, 60% MeCN, pH 4.0) over 15 min, and then 100% B for 5 min (flow rates 1.2 ml/min). The eluate was monitored by a UV detector (λ=240 nm) and by a radioactivity detector (B-Ram, Inus, United States) in series. Large amounts of radioactivity were assayed with an ionization chamber (CDC-202, Veenstra Instrumenten, The Netherlands). ^{90}Y activity was determined with an automatic NaI(Tl) counter (No. 1282, Compugamma, LKB, Finland) adjusted to an appropriate counting window. Iodine-125 activity was determined with an automatic NaI(Tl) counter (No. 1274, Riagamma, LKB, Finland).

Radioligand preparation. To prepare ^{90}Y-SMT 487, 40 µl of ^{90}Y was added to 40 µl of 0.15 m*M* NH_4OAc (pH 4.5) and 2 µl of 1 m*M* SMT 487. The reaction mixture was placed in a water bath at 100°C for 15 min. A 1-µl portion was then removed and diluted to 2 ml with 4 m*M* DTPA (pH 4.0) to challenge transchelation of any free ^{90}Y present in the radioligand solution. Fifty microlitres of this solution was then analysed by HPLC to determine the amount of unchelated ^{90}Y. Typically >99.5% of the ^{90}Y was bound to SMT 487. The specific activity was adjusted to 1.0–1.2 Ci/µmol. The radioligand was diluted in HEPES buffer, pH 7.5, containing 1% BSA, and a final volume of 100 µl was injected intravenously. The ^{125}I-labelled Tyr^{3}-octreotide (SDZ 204-090) was prepared using the chloramine T method as described previously [14]. The ^{125}I-Tyr^{11}-somatostatin-14 was obtained from Amersham Switzerland (product no. IM 161).

Receptor binding. For in vitro somatostatin receptor binding studies ^{125}I-Tyr^{3}-octreotide or ^{125}I-Tyr^{11}-somatostatin-14 was used as the radioligand. Somatostatin-14, octreotide and SMT 487 were used as competitors. Radioligand binding assays with the five human somatostatin receptor subtypes ($hsst_{1–5}$) were performed using cell membrane preparations of CHO and COS cells expressing the respective receptor subtypes. Somatostatin receptor binding studies were also performed using membrane preparations of CA 20948 tumours. The binding of ^{125}I-Tyr^{3}-octreotide and ^{125}I-Tyr^{11}-somatostatin-14 was assayed as described previously [15, 16]. The data from the displacement experiments were analysed according to a one-site model to obtain values for the half-maximal-inhibitory concentration (IC_{50}) of the respective somatostatin analogues. The dissociation constant (K_d) and the number of binding sites (B_{max}) were calculated according to Scatchard [17].

RT-PCR. The CA 20948 tumour was assessed for the presence of somatostatin receptor subtype ($sst_{1–5}$) mRNA to confirm the presence of the target receptor subtype for ^{90}Y-SMT 487, which is mainly the sst_2. Preparation of poly(A)$^{+}$-RNA, Dnase I digestion prior to reverse transcription, and RT-PCR analyses were performed as described in [18]. The following primer pairs were applied: for rat sst_1, RS190 5'-TCAGCTGGGATGTTCCCCAATG-3' and RS190 5-GTCGTCTT GCTCGGCGAACACG-3'; for sst_2, 2A and 2B as described [19]; for sst_3, RS35 5'-CT GGCG AACAGCCTTCATCATCTA-3' and RS39 5'-TAGGAGAGGAA GCCGTAGAGGATGG-3'; for sst_4 RS46 5'-GATGCCACTGT CAACCATGTGTCCCT-3' and RS47 5'-ACGGAGTTGTCCTT GGAGCCAGTCAG-3'; and for sst_5, RS51 5'-GTATTAGTG CCTGTGCTCTACCTGTTGG-3' and RS55 5'-GGCAGATGT GGGTTCCTCGGGCAGTGT-3'.

Tumour cell inoculation and tumour growth assessment. In all animal experiments the "*Principles of laboratory animal care*" (NIH publication No. 86-23, revised 1985) were followed, and the specific Swiss laws "Art. 13a Eidg. Tierschutzgesetz, TschG; Art. 60 bis 62 Eidg. Tierschutzverordnung, TschV" were also applicable. The CA 20948 pancreatic tumours were grown in Lewis rats as previously described [13]. Briefly, male Lewis rats (Iffa Credo, France) were injected subcutaneously into both flanks, each with 1 ml of a 2 mg/ml cell suspension of the CA 20948 tumour. The tumour cells were suspended in F-12 Nutrient Mixture HAM, supplemented with 0.1 g/100 ml $NaHCO_3$ and 10% fetal calf serum. When the experiments started at about 14 days post injection (p.i.), multiple tumours had grown per inoculation site and the total tumour load per rat was approximately 11 000 mm^{3}. The body weight of the rats at this time was approximately 300 g. To those rats that exhibited complete remission, CA 20948 tumour cells were re-inoculated as described above. Control rats of the same age were also inoculated with tumor cells.

Tissue distribution. Seven tumour-bearing rats received each 50 µCi ^{90}Y-SMT 487 in 100 µl HEPES (10 m*M*, pH 7.6, containing 1% BSA) into the v. jugularis under isoflurane anaesthesia. After 24 h p.i. the animals were sacrificed by CO_2 asphyxiation; the organs of interest were removed, weighed and counted in a gamma counter, along with a standard of the injectate. The radioactivity in each tissue was expressed as percent of the injected dose per gram tissue (%ID/g).

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Measurement of radioactivity. All tissue samples were made up to a 1 ml volume with water to establish a linear relationship between counting rate and tissue size; the samples where counted for 2 min in a gamma counter measuring the bremsstrahlung from the beta decay. The validity of this measuring method was established by Hnatowich et al. [20]. Activity standards (10%, 1%, 0.1% and 0.01% of the injected dose) were prepared from the ^{90}Y-SMT 487 treatment solution for each experiment and measured with each batch of samples to provide an automatic decay correction. A linear relationship between the observed counting rate and the time activity was found.

Experimental radiotherapy. Ten to 12 days following tumour cell inoculation, animals were randomized to control and treatment groups. One treatment group received 5 mCi/kg (n=5) and the other 10 mCi/kg (n=7) as a single dose intravenously (i.v.). The control group received unlabelled SMT 487 (8.3 nmol/kg), the same amount of peptide as present in the radioligand preparation (n=7). The tumours were measured on the day of radioligand administration and every 3–4 days thereafter. Tumour volumes were determined with a caliper in a blinded fashion and were calculated by using the formula for the ellipsoid $V=\pi/6(d_1 \times d_2 \times d_3)$, where d_1, d_2 and d_3 represent the three largest diameters. Individual and mean growth curves were calculated using Excel (Microsoft). Tumour volume refers to the sum of volumes of individual tumours on each animal. The tumour volumes were normalized and expressed as times of their initial volume. This procedure was chosen because of the differences in the tumour size at the start of the study and in the multiplicity of the tumours in a single animal. Excel or Origin statistical procedures were used for data evaluation (Student's t test).

At progressed stages the CA 20948 tumour becomes soft and haemorrhagic; cystic spaces and areas of necrosis are common [13]. In our experiments tumour necrosis was a strict indication to sacrifice the rats.

Results

In vitro pharmacology

Both octreotide and SMT 487 bound with high, subnanomolar affinity to the human somatostatin receptor subtype 2 (hsst$_2$) expressed on COS cells (Table 1). While the affinity of SMT 487 and octreotide was similar for hsst$_2$, there was a 100-fold drop in the affinity of SMT 487 for hsst$_5$ relative to octreotide, indicating increased sst$_2$ specificity of SMT 487. RT-PCR revealed that the CA 20948 rat tumour strongly expressed rat sst$_2$. Furthermore, low expression of sst$_5$ receptor mRNA could be detected (Fig. 1). Receptor binding experiments demonstrated that both octreotide (n=10) and SMT 487 (n=3) inhibited the binding of ^{125}I-Tyr^3-octreotide to CA 20948 tumour membranes in a monophasic manner (Fig. 2), with IC$_{50}$ values for octreotide of 0.22±0.02 nM and for SMT 487 of 0.39±0.02 nM. The Scatchard transformation of the binding data was linear, demonstrating

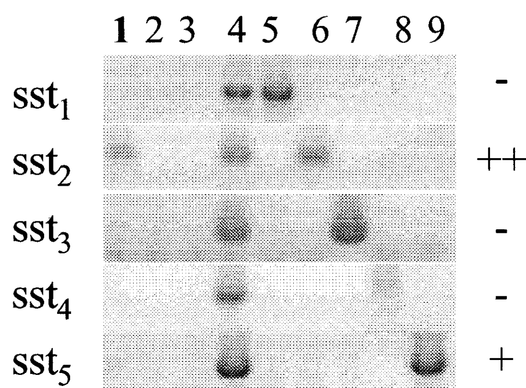

Fig. 1. RT-PCR analyses of sst$_{1-5}$ receptor expression in the CA 20948 rat exocrine pancreatic tumour. *Lane 1*, CA 20948 tumour cDNA. Negative controls: *lane 2*, CA 20948 tumour poly(A)$^+$-RNA without reverse transcription; *lane 3*, water control. Positive control: *lane 4*, rat genomic DNA (since sst receptor genes are intron-less). Further controls: *lane 5*, mouse sst$_1$; *lane 6*, rat sst$_2$; *lane 7*, mouse sst$_3$; *lane 8*, rat sst$_4$; and lane 9, rat sst$_5$ cDNA

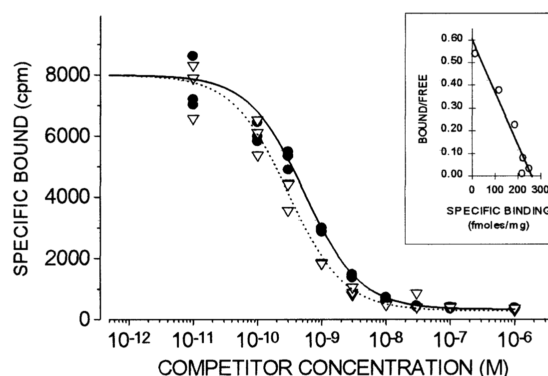

Fig. 2. Binding of ^{125}I-Tyr^3-octreotide to membranes prepared from a CA 20948 rat pancreatic tumour. The membranes (0.33 mg/ml assay mixture) were incubated with the radioligand and increasing concentrations (each in triplicate) of octreotide or SMT 487 (*x-axis*). ●, Single measurements of SMT 487, ∇, single measurements of octreotide. *Inset*: SMT 487 binding data plotted by the method of Scatchard. The maximum binding capacity (B_{max}) was calculated from the intercept on the x-axis

Table 1. Binding affinity of octreotide and SMT 487 to hsst$_{1-5}$ using ^{125}I-SRIF-14 as a specific ligand (n=3, mean; SEM within 10% of mean). Membranes were prepared from transfected CHO or COS cells

Compound	Binding affinity, IC$_{50}$-value (nM)				
	hsst$_1$	hsst$_2$	hsst$_3$	hsst$_4$	hsst$_5$
SRIF-14 (Somatostatin)	0.4	0.1	0.3	0.8	0.6
Octreotide	200	0.6	10	1000	7
SMT 487	>100	0.9	50	>1000	700

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Table 2. Tissue distribution of ^{90}Y-SMT 487 in CA 20948 tumour-bearing rats 24 h post i.v. injection (n=7, average±SEM)

Tissue	^{90}Y-SMT 487 (%ID/g)		
	Average		SEM
Adrenals	5.462	±	0.269
Blood	0.013	±	0.003
Duodenum	0.104	±	0.020
Femur	0.105	±	0.040
Heart	0.014	±	0.003
Kidneys	1.511	±	0.126
Large Intestine	0.305	±	0.045
Liver	0.156	±	0.024
Muscle	0.004	±	0.001
Ovaries	0.013	±	0.002
Pancreas	0.656	±	0.152
Pituitary	2.873	±	0.798
Small Intestine	0.290	±	0.122
Spleen	0.379	±	0.161
Stomach	0.227	±	0.059
Tumour	0.639	±	0.118

the binding of SMT 487 to a single class of high-affinity binding sites in CA 20948 cell membranes (inset in Fig. 2). For SMT 487 the apparent equilibrium dissociation constant K_d was 0.30 nM and the maximum binding B_{max} was 489 fmol/mg. The results from both the RT-PCR and the ex vivo binding experiments indicated that SMT 487 targets selectively sst_2 binding sites with high affinity in the CA 20948 tumour cell inoculates.

Tissue distribution

The tissue distribution of ^{90}Y-SMT 487 was studied in CA 20948 tumour-bearing rats. Twenty-four h after i.v. administration of the radioligand, the amount of activity that accumulated in the tumour was 0.64%±0.12% of the injected dose per gram (%ID/g) (Table 2). Somatostatin receptor-expressing normal tissues like pancreas, stomach and small and large intestine exhibited a low accumulation of the radioligand per gram tissue, whereas the distribution of ^{90}Y-SMT 487 to the adrenals and the pituitary was high, at 5.5%±0.3%ID/g and 2.9%±0.8%ID/g, respectively. The rapid distribution of ^{90}Y-SMT 487 in vivo results in high tumour to tissue ratios at 24 h post injection. For selected organs this ratio was 49.15 (blood), 159.75 (muscle), 6.08 (femur), 4.09 (liver) and 2.20 for the intestines. Except for the kidneys, the relative exposure to ^{90}Y-SMT 487 in somatostatin receptor-negative tissues was low after 24 h.

Tumour growth

The tumours of the animals in the control group grew either excessively (Fig. 3a), with a doubling time of 11 days, and became necrotic; consequently, those rats had

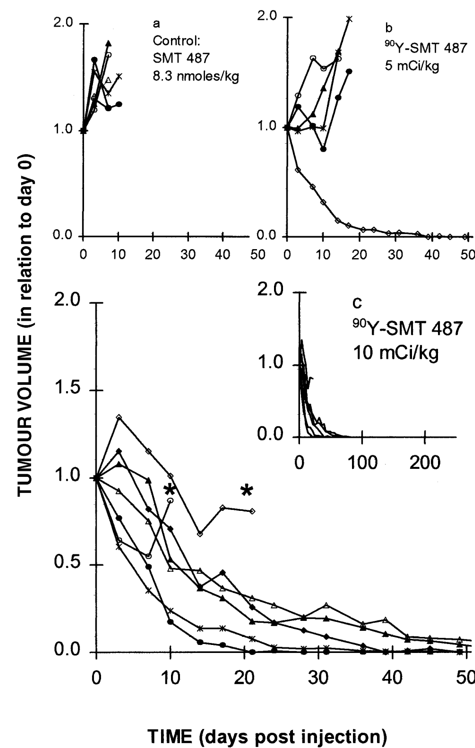

Fig. 3. Effect of ^{90}Y-SMT 487 (single i.v. administration of 5 or 10 mCi/kg at day 0) on tumour growth in Lewis rats bearing CA 20948 tumours. Mean start volume at day 0 was 12 805±1140 mm^3. The tumour volume change in single animals is plotted against time post injection (n=4–7/group). **a** Tumor growth in animals of the control group (SMT 487, 8.3 nmol/kg); **b** tumour growth in rats treated with ^{90}Y-SMT 487, 5 mCi/kg; **c** tumour growth in rats treated with ^{90}Y-SMT 487, 10 mCi/kg. The *asterisks* indicate that these rats had to be sacrificed because of tumour necrosis. *large figure*: 0–50 days post injection; *inset*: 0–200 days post injection

to be sacrificed 10 days post injection (p.i). The tumour-bearing rats were treated with either 5 or 10 mCi/kg i.v. since similar radiotherapeutic doses had been successfully used in tumour-bearing nude mice [7]. This treatment induced a partial to complete tumour remission. After administration of a single i.v. dose of 5 mCi/kg ^{90}Y-SMT 487 in one out of five rats the somatostatin receptor-expressing tumours disappeared 3 weeks after injection (Fig. 3b). In three rats of this group a tumour growth delay of about 1 week was observed. Interestingly, in the 10 mCi/kg group all tumours started to shrink at 5 days p.i. In five out of seven animals the tumour disappeared at seven weeks p.i. In these rats no regrowth of the tumours occurred over the entire observation period of 8 months. Two rats out of this group (Fig. 3c, asterisks) had to be sacrificed 3 weeks p.i., because the tumours became necrotic, which is a common observation of advanced stages of this exocrine pancreatic tumour. Necrosis was not observed in any of the tumours that exhibited complete remission.

Both the 5 mCi/kg dose and the 10 mCi/kg dose were well tolerated, with only transient loss in body weight.

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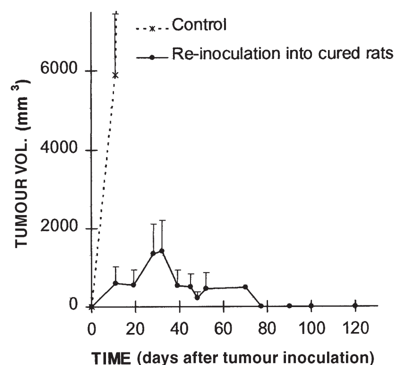

Fig. 4. Effect of re-inoculation of CA 20948 tumour cells into rats that previously exhibited complete remission (Fig. 3) (*n*=5/group). For comparison the same amount of CA 20948 tumour cells was inoculated into previously untreated rats (control). *, Tumour growth in control rats; ●, tumour growth in rats that previously exhibited complete remission

The nadir in body weight loss was on day 7 p.i. (10%–15% of initial weight). Those rats, that showed complete remission gained up to 200% of their initial body weight.

After those 8 months during which the animals were free of tumour, CA 20948 cells were re-inoculated into the same rats. Untreated control rats received the same amount of tumour cells. Upon re-inoculation of CA 20948 tumour material into the cured rats, in five out of seven animals no tumour growth occurred, whereas in those rats exhibiting moderate tumour growth the tumour disappeared after 3–4 weeks without any further treatment (Fig. 4).

Discussion

The present study demonstrates that the new radiotherapeutic ^{90}Y-SMT 487 has the potential to induce complete tumour remission in somatostatin receptor-expressing tumours. This tumour expresses rat sst_2, as demonstrated by RT-PCR. The human sst_2 is 95% homologous to the rat sst_2 [21]. The latter subtype is most abundant in human somatostatin receptor-expressing malignancies [5]. SMT 487 targets sst_2 binding sites with nanomolar affinity in the CA 20948 tumour cell inoculates, as demonstrated by in vitro binding studies on ex vivo tumours (Fig. 2). In vivo ^{90}Y-SMT 487 rapidly accumulated in the tumour tissue, with a high tumour-to-blood ratio of 49.15 at 24 h post injection. The amount of activity accumulated in the tumour (0.64%ID/g, 24 h p.i.) was higher than reported for ^{123}I-Tyr^3-octreotide (0.007%ID/g [22]) in the same tumour model. This might be due to a deiodination process in the case of ^{123}I-Tyr^3-octreotide. After 24 h p.i. 180%±50%ID/g of ^{123}I-Tyr^3-octreotide was found in the thyroid [23], an organ which is known to take up free iodine avidly. Normal rat tissues such as adrenals, pituitary and kidneys are exposed to comparably high radiation doses after administration of ^{90}Y-SMT 487. In order to estimate the potential side-effects that may arise from the irradiation of healthy somatostatin receptor-expressing organs (anterior pituitary, adrenal cortex) or organs through which the radiotherapeutic is excreted (kidneys), a preliminary side-effect profile of ^{90}Y-SMT 487 has been generated in normal rats.

In this study various parameters were measured, including blood cell counts, endocrine profile, urine biochemistry and the histology of various organs (data not shown). No marked impairment of the health of the animals upon a single (30 mCi/kg) or fractionated treatment (3×10 mCi/kg) with ^{90}Y-SMT 487 was observed in rats (manuscript in preparation). The comparatively high exposure to activity in the kidneys presumably may be lowered by a prior injection with L-lysine. In a mouse tumour model the kidney load with ^{90}Y-SMT 487 was reduced by 60% by prior administration of 2 g/kg L-lysine, and this finding was also confirmed by others using [^{111}In-DOTA-DPhe^1,Tyr^3]octreotide in the CA 20948 rat tumour model [12]. The latter effect is in accordance with the reduction of kidney exposure to OctreoScan 111 after an amino acid infusion that is high in L-lysine in patients [24].

In the radiotherapeutic experiment a single intravenous administration of 10 mCi/kg ^{90}Y-SMT 487 resulted in complete remission of the tumours in five out of seven CA 20948 tumour-bearing Lewis rats. No regrowth of the tumours occurred 8 months post injection. The radiotherapeutic effect was dose dependent, since the administration of 5 mCi/kg ^{90}Y-SMT 487 resulted in complete tumour remission in only one out of 5 tumour-bearing rats. The time to tumour progression was delayed for about 1 week in the other animals of the same group. In the same tumour model Anderson et al. reported on a somatostatin receptor-targeted radiotherapeutic approach using a copper-64 labelled TETA-octreotide analogue [25]. Copper-64 emits β^- (0.571 MeV) and β^+ (0.657 MeV) particles which are accompanied by a γ-line of 1.34 MeV. The physical half-life time of ^{64}Cu is 12.7 h. With a single dose of 40 mCi/kg ^{64}Cu-TETA-octreotide a tumour growth delay of about 1 week was observed. The repeated administration of ^{64}Cu-TETA-octreotide (cumulative dose of 60 mCi/kg, Anderson et al.'s study) gave a maximum tumour growth delay of about 2 weeks and thereafter tumour regrowth was observed. For comparison, in our own studies with a single dose of 10 mCi/kg ^{90}Y-SMT 487 complete tumour remission was induced. This demonstrates that both the choice of the chelating moiety (DOTA) and the radionuclide (^{90}Y, β^-_{max}=2 MeV) in ^{90}Y-SMT 487 make it the preferable compound for radiotherapeutic treatment of somatostatin receptor-positive tumours.

The number of binding sites for somatostatin expressed by the CA 20948 rat tumour (489 fmol/mg) is similar to previously reported data for this tumour type [13], and comparable to the number of binding sites that

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