Receptor-mediated radiotherapy with $^{90}$Y-DOTA-$\text{d-Phe}^1$-$\text{Tyr}^3$-octreotide

Giovanni Paganelli$^1$, Stefania Zoboli$^1$, Marta Cremonesi$^2$, Lisa Bodei$^1$, Mahila Ferrari$^2$, Chiara Grana$^1$, Mirco Bartolomei$^1$, Franco Orsi$^3$, Concetta De Cicco$^1$, Helmut R. Mäcke$^5$, Marco Chinol$^1$, Filippo de Braud$^4$

$^1$ Nuclear Medicine Division, European Institute of Oncology, via Ripamonti, 435, 20141 Milan, Italy
$^2$ Medical Physics Division, European Institute of Oncology, Milan, Italy
$^3$ Radiology Division, European Institute of Oncology, Milan, Italy
$^4$ Medical Oncology Division, European Institute of Oncology, Milan, Italy
$^5$ Division of Radiological Chemistry, University Hospital, Basel, Switzerland

Received 2 October 2000 and in revised form 11 January 2001 / Published online: 7 March 2001 © Springer-Verlag 2001

Abstract. A newly developed somatostatin radioligand, DOTA-$\text{d-Phe}^1$-$\text{Tyr}^3$-octreotide (DOTATOC), has been synthesised for therapeutic purposes, because of its stable and easy labelling with yttrium-90. The aim of this study was to determine the dosage, safety profile and therapeutic efficacy of $^{90}$Y-DOTATOC in patients with cancers expressing somatostatin receptors. We recruited 30 patients with histologically confirmed cancer. The main inclusion criterion was the presence of somatostatin receptors as documented by $^{111}$In-DOTA TOC scintigraphy. $^{90}$Y-DOTATOC was injected intravenously using a horizontal protocol: patients received equivalent-activity doses in each of three cycles over 6 months. The first six patients received 1.11 GBq per cycle and the four successive groups of six patients received doses increasing in 0.37-GBq steps. Toxicity was evaluated according to WHO criteria. No patient had acute or delayed adverse reactions up to 2.59 GBq $^{90}$Y-DOTATOC per cycle (total 7.77 GBq). After a total dose of 3.33 GBq, one patient developed grade II renal toxicity 6 months later. The maximum tolerated dose per cycle has not yet been reached, although transient lymphocytopenia has been observed. Total injectable activity is limited by the fact that the maximum dose tolerated by the kidneys has been estimated at 20–25 Gy. Complete or partial tumour mass reduction occurred in 23% of patients; 64% had stable and 13% progressive disease. It is concluded that high activities of $^{90}$Y-DOTATOC can be administered with a low risk of myelotoxicity, although the cumulative radiation dose to the kidneys is a limiting factor and requires careful evaluation. Objective therapeutic responses have been observed.

Keywords: Receptor-mediated radiotherapy – Somatostatin analogue – $^{90}$Y/$^{111}$In-DOTATOC – Peptides

DOI 10.1007/s002590100490

Introduction

Since the discovery, in the late 1960s, of the inhibitory properties of native tetradecapeptide somatostatin (SS), its extremely short plasma half-life has inspired the synthesis of analogues with more favourable characteristics. The SS analogue octreotide contains the bioactive core of native molecule, consisting in an eight amino acid residue. Recent evidence has shown that the critical portion of any SS analogue is the $\text{d-Trp-Lys}$ fragment. Presently, five specific human G protein-coupled SS receptor subtypes have been cloned and partially characterised. All five receptors bind native SS with high affinity, while octreotide binds with very high affinity only to subtype 2 (sst2) and shows moderately high affinity for sst5 and intermediate affinity for sst3.

High concentrations of sst2 receptors are expressed in numerous tumours, enabling primary and metastatic masses to be localised by scintigraphy after injection of indium-111 labelled octreotide, an SS analogue [1]. In addition to neuroendocrine tumours, SS receptors have been identified on cancers of the central nervous system [2], breast [3], lung and lymphatic tissue [4], and the use of radionuclide-labelled SS analogues shows promise for therapy as well as diagnosis of such cancers [5]. Moreover, sst2 receptors have been observed in peritumoural...
vessels [6, 7], thus enabling an anti-angiogenetic response during radionuclide therapy.

Ongoing multicentre clinical trials, using high doses of $^{111}$In-DTPA-octreotide (Octreoscan) in patients with neuroendocrine tumours [8], have yielded an objective response rate of approximately 15%, with a 66% overall response rate. These results may be ascribed to the Auger and conversion electrons emitted by $^{111}$In. However, yttrium-90 seems more suitable for therapeutic use because of its energetic $\beta$-particles ($E_{\text{max}}=2.27$ MeV) and its long range ($R_{50}=5.94$ mm ($R_{50}$ being the distance within which the $\beta$-particle transfers 95% of its energy to the target tissue)], which allows “cross-fire” irradiation.

Because of the low stability of $^{90}$Y-DTPA linkage, the SS analogue $[1,4,7,10$-tetraazacyclododecane-$N,N',N'',N'''$-tetra-acetic acid $\cdot$ D-Phe$^1$-Tyr$^3$]-octreotide (DOTATOC) was synthesised for stable labelling with $^{90}$Y. DOTATOC has favourable characteristics for potential therapeutic use [9], in that it shows high affinity for sst2 [10, 11] and moderately high affinity for sst5, high hydrophilicity, stable and easy labelling with $^{111}$In and $^{90}$Y [12, 13].

Following a previous bio kinetics and dosimetry study in which $^{111}$In-DOTATOC was administered to estimate absorbed doses during $^{90}$Y-DOTATOC therapy [14, 15], we now report on the toxicity and therapeutic efficacy of $^{90}$Y-DOTATOC in 30 patients with cancers expressing sst2.

**Materials and methods**

**Patient population and inclusion criteria.** We recruited 30 adult patients (18 men and 12 women; age 35–73 years) with histologically confirmed cancer (23 carcinoids, one breast cancer, three medullary thyroid cancers, one meningioma, one grade III astrocytoma and one small cell lung cancer) and documented residual disease or recurrence after conventional treatment. The main inclusion criterion was presence of SS receptors as documented by scintigraphy with $^{111}$In-DOTA TOC. Extension of disease was assessed by computed tomography (CT), magnetic resonance imaging (MRI) or ultrasound. No chemotherapy or radiotherapy was given for at least 1 month before and 2 months after receptor-mediated radiotherapy (RMRT) with $^{90}$Y-DOTATOC. Patient characteristics are shown in Table 1. Exclusion criteria were: (a) pregnancy or lactation; (b) age $<$21 years; (c) Karnofsky performance status $<$60 and life expectancy $<$6 months; (d) presence of a known second neoplasm; (e) white blood cell count $<$2,500/dl, haemoglobin $<$10 g/dl, platelets $<$100,000/dl, bilirubin $>$2.5 mg/dl, and (f) blood urea nitrogen (BUN) $>$45 mg/dl and creatinine $>$1.5 mg/dl. The study was performed at the European Institute of Oncology after approval by the Institute’s Ethics Committee. All patients were informed of the nature, aim and potential risks of the therapy.

**Reagents.** The SS analogue DOTATOC (DOTA: $[1,4,7,10$-tetraazacyclododecane-$N,N',N'',N'''$-tetra-acetic acid]) was synthesised at the Division of Radiological Chemistry University Hospital, Basel according to a published procedure [13]. $^{90}$Y chloride was purchased from AEA Technology (Harwell, UK). Typically, to 30 µl of DOTATOC in 30 µl 0.2 M ammonium acetate (pH 5.0) were added 150 µl of 0.4 M ammonium acetate/gentisic acid (pH 5.0) and 1.11 GBq $^{90}$YCl$_3$ in 0.04 M HCl. The mixture was then heated for 25 min at 90°C. Quality control of $^{90}$Y-DOTATOC employed high-performance liquid chromatography and a Sep-Pak C18 cartridge (Waters, Millipore, Mass., USA), as previously described [16]. Labelling yields of more than 98% were routinely achieved at a specific activity of more than 50 GBq/µmol. A competition binding assay, using rat cortex membranes and $[125I]$-Tyr$^3$ octreotide as specific ligand [13], showed that the receptor binding affinity of the radiolabelled DOTATOC was preserved ($K_D=2.2\pm0.5$ nM).

**Administration protocol.** $^{90}$Y-DOTATOC was injected intravenously over 20 min in 100 ml of physiological saline. A horizontal protocol was used; three equivalent activity doses were administered to each patient with an interval of 8 weeks between each. The first six patients received 30 µg of DOTATOC labelled with 1.11 GBq of $^{90}$Y in each of three cycles over 6 months. The second group of six patients received 40 µg of DOTATOC labelled with 1.48 GBq of $^{90}$Y for the same number of cycles. Major toxicity was not observed in these two groups, so the other three groups received 50, 60 and 70 µg of DOTATOC labelled with 1.85, 2.22 and 2.59 GBq of $^{90}$Y, respectively. The patients were hospitalised for 2–3 days after treatment in rooms set aside for radionuclide therapy, and were discharged only after the level of activity in the urine had fallen below 0.037 MBq/ml.

**Biodistribution and dosimetry.** All patients received an $^{111}$In-DOTATOC diagnostic scan before therapy and dosimetry was performed as previously described [14, 17]. In ten patients whose tumour mass (18 lesions) could be accurately evaluated by CT or MRI, whole body imaging was performed at 30 min, 3-4 h, 24 h and 48 h after injection using a double-head gamma camera (GE MAXXUS) equipped with a medium-energy general-purpose collimator. Single-photon emission tomography scans over the lesions were also obtained 3–4 h after injection and visually matched with the CT and MRI scans.

Regions of interest were drawn manually over the total body, tumour and normal organs, i.e. heart, lungs, liver, spleen and kidneys. Data from the gamma camera were converted to biological time-activity curves [%IA$_{t=0}$] taking into account background, attenuation and physical decay. The SAAM II program was used to fit the observed kinetic data to a compartmental model [18]. After an acceptable fit had been obtained, the program was used to determine the residence times for $^{111}$In and $^{90}$Y in the source organs, assuming that the kinetics of $^{111}$In- and $^{90}$Y-labelled DOTATOC were identical [14, 19].

Dose calculations were performed according to the MIRD formalism, by entering the residence times for all source organs in the MIRDOS 3.1 software and selecting the standard male or female phantom, as appropriate to the sex of each patient, so as to reduce the approximation resulting from considering standard organs [20].

All patients were also scanned at 24 and 48 h after the therapeutic dose of $^{90}$Y-DOTADOC (bremssstrahlung imaging).

**Safety and therapeutic effect.** Toxicity was evaluated according to WHO criteria [21]. After discharge the patients underwent the following tests: renal function, hepatic function, lactate dehydrogenase and uricaemia every 15 days, and complete blood count 3 days after therapy and then weekly for the first 2 months. Tumour markers [5-hydroxyindoleacetic acid (5-HIAA), chromogranin A and others] were assayed 1 day before and 2 days after therapy and once a month for the following 2 months.

Objective therapeutic response was assessed by CT, MRI or both, with and without contrast, 6–8 weeks after the third cycle.