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Clinical Study

Radiolabeled Somatostatin Analogues Therapy in Advanced Neuroendocrine Tumors: A Single Centre Experience

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The aim of this study was to assess the efficacy of PRRT in patients with advanced neuroendocrine tumors (NETs). *Patients and Methods*. From January 2007 to August 2011, we enrolled 65 patients (m/f 38/27; mean age 65 years, range 33–83) with advanced NETs having enhanced SSTR expression, treated with PRRT. The enhanced expression of SSTR was assessed using ^{68}Ga-DOTATOC/DOTATATE PET/CT. Among all the enrolled patients, 6 of them were excluded from the present analysis since they voluntarily interrupted treatment. Mean activity/cycle of 2.6 GBq (^{90}Y-DOTATOC/DOTATATE) or 6.0 GBq (^{177}Lu-DOTATOC/DOTATATE) was administrated intravenously (max 9 cycles). *Results*. Complete response (CR) was found in 1/59 (2%) patients, partial remission (PR) in 24/59 (40.5%) patients, stable disease (SD) in 24/59 (40.5%), and progression (PD) in 10/59 (17%) patients. The overall tumor response rate (CR + PR) was 42.5%. In 40.5% of patients, the disease could be stabilized. Overall, 49 out of 59 patients had no tumor progression (83%). Twelve patients out of 59 (20%) had grade 2-3 hematological side effects including anemia, thrombocytopenia, and leukopenia. Long-term nephrotoxicity was observed in 3 patients (2 moderate, 1 severe). *Conclusions*. PRRT is a promising perspective for patients with advanced NETs.

1. Introduction

Neuroendocrine tumors (NETs) are considered a class of rare neoplasms accounting <5% of all tumors. However, diagnosis of NETs has increased substantially over the last decades and prevalence is now greater than that of any other upper gastrointestinal tumor [1]. These tumors originate from dispersed neuroendocrine cells, distributed almost ubiquitously in the body [2], and occur in 5/100,000 people per year [1].

The most frequent sites of NETs are gastroenteropancreatic tract (GEP NETs), followed by lungs; less frequently skin. Different nomenclature systems and classifications have been used for NETs.

Current pathological staging and grading differ between Europe and USA; however, both classification systems are centered on the primary site of the tumor and histological grade. In Europe, the Ki-67 proliferative index is used to differentiate tumors of low (<2%), intermediate (2–20%) and high (>20%) grade, whereas in the USA, tumors are graded as "well-" and "poorly-" differentiated where "well" equates to low-intermediate grade and "poorly" equates to high-grade tumors [3, 4].

Up to 80% of GEP NETs express somatostatin receptors

analogues have been used for both diagnosis and treatment of NETs. ^{111}In-labeled SST-analogues SPECT and ^{68}Ga SST-analogues PET/CT represent an accurate methods for NETs diagnosis peptide radioreceptor therapy (PRRT) indication and patients management [5–8].

When beta-emitters isotopes as ^{90}Y ($T_{1/2}$ of 2.67 days, maximum range of tissue irradiation of 12 mm) or ^{177}Lu ($T_{1/2}$ of 6.73 days, maximum range of irradiation of 1.5 mm) are used to label SST-analogues linked to a chelator, PRRT may be performed. After the i.v. injection, the radiopharmaceutical will distribute in the body, selectively bind to SSTRs, and actively be taken up by the cells through a process called receptor-ligand internalization [9, 10]. The internalization will ultimately lead to a selective accumulation of radioactivity in the tumor, thus determining cell death. The majority of clinical trials data available is from non-randomized retrospective case series. Due to variation in patients selection, dosing, scheduling, and total number of treatments it can be challenging to draw firm conclusions from the literature. However, it seems to be a benefit for selected patients with response rates in the range of 40% [11–14].

Here we present the results of a phase II study designed to treat disseminated or nonoperable NETs patients with PRRT. Patients demonstrated enhanced SSTR expression at PET/CT with ^{68}Ga-peptide (DOTATOC/DOTATATE).

2. Materials and Methods

2.1. Study Design. This was a prospective nonrandomized single-arm clinical trial performed at the Department of Nuclear Medicine, Santa Maria Nuova Hospital, Reggio Emilia (Italy). All patients with advanced, progressive NET fulfilling the study inclusion criteria were first evaluated with ^{68}Ga-peptide PET/CT followed by ^{111}In-peptide dosimetric evaluation to determine both the presence of SSTR expression as a target for the following treatment and eligibility to PRRT, that is in presence of provisional adsorbed doses: (a) >10 Gy to tumor, (b) <10 Gy to the kidneys, (c) <6 Gy for the liver, (d) <1.5 Gy for red marrow, (e) <3 Gy for lung, and (f) <8 Gy for whole body. In case of ^{177}Lu-PRRT (^{177}Lu-DOTATOC/DOTATATE), dosimetric evaluation was performed acquiring images during the first cycle of therapy. A fractionated treatment protocol was followed with the intravenous administration of an average activity of 2.6 GBq/cycle for ^{90}Y-PRRT and 6.0 GBq/cycle for ^{177}Lu-PRRT, respectively, with an interval of about 2 months.

Toxicity and tolerability were recorded through all the study and for additionally 6 months after the study completion. Serial follow-up ^{68}Ga-peptide PET/CT imaging was repeated after each PRRT cycle during the first part of the study as required by our ethic committee. The clinical trial was subsequently amended and the number of PET/CT examinations reduced to baseline, intermediate (after 2-3 PRRT cycles), and end-treatment (3–6 months after the last PRRT) scans. In order to homogenize data analysis, treatment response was assessed comparing PET/CT studies as patient's clinical response. The intermediate PET/CT evaluation was used only to assess the early progressive disease (PD).

The study was conducted in accordance with International Conference on Harmonization Good Clinical Practice guidelines, the Declaration of Helsinki and it was approved by local and national authorities (EudraCT numbers 2006-000897-65 and 2008-000983-17).

2.2. Patients. From January 2007 to August 2011, we enrolled 65 patients (38 men and 27 females; mean age = 65 years, range 33–83). All patients presented progressive disease and fulfilled the following inclusion/exclusion criteria.

2.2.1. Inclusion Criteria. The inclusion criteria were as follows:

(i) Age > 18 years;

(ii) histological confirmation of NET; inoperable or metastatic disease;

(iii) presence of at least one measurable lesion;

(iv) positive 68Ga-peptide PET/CT defined as radiopharmaceutical uptake in tumor and/or metastasis higher than liver, evaluated within 3 months before PRRT (qualitative analysis);

(v) adequate hematological parameter: hemoglobin level (Hb) $\geq$ 10 g/dL; leucocytes (WBC) $\geq 2.5 \times 10^3$/mL; platelets (PLT) $\geq 100 \times 10^3$/mL;

(vi) adequate liver and renal function: bilirubin levels <2.5 mg/dL; creatinine levels <2 mg/dL;

(vii) ECOG performance status <2;

(viii) Signed informed consent;

(ix) discontinuation of cold SST-analogues treatment at least 4 weeks before PRRT;

(x) Life expectancy of at least 6 months.

2.2.2. Exclusion Criteria. The exclusion criteria were as follows:

(i) other treatment (such as chemotherapy or radiotherapy) or participation in any investigational drug trial within 1 month of PRRT and for the following 2 months;

(ii) Pregnancy or lactation;

(iii) Bone marrow involvement >25%;

(iv) other concomitant tumors, except "in situ" basal cell carcinoma and tumors of the uterine cervix treated with radical surgery.

Additionally, before each PRRT cycle the following parameters should be maintained: Hb $\geq$ 10 g/dL, WBC $\geq 2.5 \times 10^3$/mL; PLT $\geq 100 \times 10^3$/mL, creatinine levels <2 mg/dL; bilirubin levels <2.5 mg/dL.

The final analysis was based on a total of 59 patients

carcinoid tumor of the lung, and 3 with pancreatic tumor) voluntarily interrupted the treatment. Tumor was localized in the gastrointestinal tract in 19/59 cases (32%), followed by pancreas in 16/59 cases (27%) and lung in 13/59 cases (22%). In 11/59 patients (19%), the origin was unknown.

All patients at enrollment had metastatic (stage IV) PD (Table 1). Histopathological findings including grading were not reported for patients since histological diagnosis was performed in different centers thus features were reported in different not comparable modalities. Previous treatments are reported in Table 2. Diabetes was present in 11/59 cases and 16/59 patients suffered from blood hypertension. Additionally, 9/59 had previous tumors (3/9 prostate cancers, 3/9 breast cancers, 2/9 large-bowel cancers and 1/59 stomach cancer) with a minimal time of free disease of 5 years. Main baseline clinical signs and symptoms were diarrhea (18/59), pain (12/59), weight loss (7/59), flush (5/59), cough (4/59), constipation (3/59), nausea (2/59), and carcinoid syndrome (1/59). Additionally, 32/59 patients presented at enrolment a variable grade of asthenia. Twenty-seven patients were asymptomatic at baseline. Serum baseline CgA levels were normal in 19/59 patients.

Table 1: Site and number of metastasis in the 59 evaluated patients at the enrollment in the clinical trial.

Site of metastasis	Number of metastasis	
	≤5	>5
Bone (21/59)	0/21	21/21
Liver (42/59)	2/42	40/42
Lung (4/59)	0/4	4/4
Lymph nodes (34/59)	3/34	31/34
Other (6/59)	1/6	5/6

Table 2: List of previous treatments in the 59 evaluated patients order on the basis of their frequency.

Previous treatment	Number of patients
Surgery	39/59
"Cold" SST analogues	25/59
Chemotherapy	13/59
TACE or RFTA	7/59
External beam radiotherapy	5/59

TACE: intra-arterial hepatic chemoembolization; RFTA: radiofrequency thermoablation.

2.3. Radiopharmaceuticals Preparation. ^{111}In-, ^{90}Y-, and ^{177}Lu-peptide (DOTATOC or DOTATATE) were synthesized by following internal protocol [15]. Every preparation was obtained by carrying out the following steps: (a) a 3 mL syringe was filled with a 1 mL solution containing 30 μg of sodium ascorbate and an amount of a 4 mg/mL peptide solution proportional to the ^{90}Y-, and ^{177}Lu- or ^{111}In- activity in order to achieve a radiolabeling specific activity of 106 MBq/nmol, 48 MBq/nmol, and 6 MBq/nmol, respectively (b) this solution was added to a 3 mL Schott vial containing an activity ranging between 7.4 to 30 GBq of ^{90}Y chloride solution, between 15 to 60 GBq of ^{177}Lu chloride solution or between 222 to 444 MBq of ^{111}In- chloride solution (Perkin Elmer, Boston, MA, United States) in 0.05 M hydrochloric acid obtaining a 4.6 pH solution; (c) the Schott vial was heated for 30 minutes at 90°C in a heating block; (d) a 5 μL aliquot of the solution was withdrawn for carrying out the quality controls by using solid phase extraction or chromatographic methods [16]; (e) only for ^{90}Y and ^{177}Lu-peptide: the preparation was transferred to a bigger vial containing 0.5 mL of 1 mM DTPA solution and diluted with 20 mL of 0.9% sodium chloride solution [17]; (f) single doses for the patients were obtained by fractioning the mother solution in vials containing 2 mL of an ascorbic acid/sodium ascorbate buffer solution in order to decrease the effects of radiolysis. The radiochemical purity of the ^{111}In-, ^{177}Lu-, and ^{90}Y-peptide preparations was always >99.8%.

The radiolabeling of ^{68}Ga-peptide was performed by means of a modular lab synthesizer (Eckert & Ziegler, Berlin, Germany) as already described [18]. Briefly, the fraction of about 2 mL of the ^{68}Ge/^{68}Ga-generator eluate containing about 80% of the ^{68}Ga activity in 0.1 M hydrochloric acid was selected and directed to a reactor vial containing a 20 μL of peptide solution (1 mg/mL) and 200 μL of a 1.5 M sodium formate solution or 140 μL of a 1.5 M sodium acetate

3.5. The mixture was heated at 100°C for 5 minutes and, then, passed through a light C-18 cartridge. ^{68}Ga-peptide was eluted with 0.5–1 mL of a 50% ethanol solution and diluted with 8 mL of 0.9% sodium chloride solution. The synthesis was carried out in 14 minutes with a mean yield of 63 ± 3% (not corrected for decay). Quality controls were performed by chromatographic methods as already described, obtaining a radiochemical purity always >95% [19].

2.3.1. Pretherapeutic Somatostatin Receptor Imaging. Pretherapeutic imaging was performed by ^{68}Ga-peptide PET/CT. For this study, PET/CT scans were acquired on a GE Discovery at 60 min after injection of about 120 MBq of ^{68}Ga-peptide. Seven or eight bed positions with 5 slices overlap were acquired for 4 min emission time in 3D. The CT-exposure factors for all examinations were 120 kVp and 80 mA in 0.8 seconds. PET images were reconstructed using CT-attenuation correction (OSEM). All studies were visually and semiquantitatively assessed. SUV calculations were performed on a Xeleris workstation. Mean and maximum SUV (activity concentration corrected for patient weight and total injected dose) was determined in all lesions and recorded.

2.3.2. Selection of Patients Eligible for PRRT. ^{68}Ga-peptide PET/CT was considered positive in patients who showed uptake in the tumor lesions at least two-times higher than the liver; thus they were considered eligible for PRRT and, therefore, admitted to dosimetric evaluation.

2.4. Dosimetry. Planar imaging was initially performed after the i.v. injection of 185 MBq of ^{111}In-peptide with a dual-

using parallel-hole, medium-energy, general-purpose collimators. The windows were centered over both ^{111}In- photon peaks (247 and 172 keV with a window width of 20%), whereas scatter fraction was evaluated at 140 keV (width 20%).

In all the patients, whole-body scan and, in selected cases, spot images of the abdomen were obtained after 1, 4, 20, 48, and 72 hours for control of biodistribution. To determine blood clearance, we drew blood samples at 30 and 60 minutes and at 4, 20, and 48 hours after injection. Radioactivity in blood was measured with a HPGe spectrometer (DSPEC jr 2.0—Ortec). For dosimetric calculations, regions of interest were drawn manually on the whole-body scans from anterior and posterior projections and ULMDOS software (University of Ulm, Germany) was used. Background regions were placed on the abdomen or on the thigh for background correction. Scans were corrected for background, self-absorption, patient thickness attenuation, and organ overlapping. Whole-body activity acquired immediately after injection was defined as 100% of the injected activity. Data were expressed as percentage injected activity as a function of time. The resulting time-activity points were fitted to a monoexponential or multiexponential curve for whole-body, kidneys, liver, spleen, and red marrow to calculate residence time. Patient-specific organ masses were also considered. The estimated doses delivered to critical organs and to the tumor were obtained by the software OLINDA/EXM [20]. The activity in blood was fitted to a biexponential curve to determine the residence time in blood. The dose to the red marrow was calculated from the residence time in blood, assuming no specific uptake, a uniform distribution of activity, and clearance from red marrow equal to that from blood. A correction factor of 1 was used as described by Cremonesi et al. [21].

In case of ^{177}Lu-PRRT the dosimetric evaluation was performed acquiring images during the first cycle of therapy, thanks to the low gamma emission of this isotope.

2.5. Therapy (Administration Protocol). A fractionated treatment protocol was followed with the intravenous administration of an average activity of 2.6 GBq and 6.0 GBq per cycle for ^{90}Y-PRRT and for ^{177}Lu-PRRT, respectively, with an interval of about 2 months. For each cycle, patients were hospitalized for 3 days in accordance with local requirements. Thirty minutes before administration of the radiopeptide 2 L of amino acid solution of Hartmann-Hepa 8 (Ringer's Lactate Hartmann, Proteinsteril Hepa 8%, Mg 5-sulfat) were infused, which were continued up to 3 hours after injection to inhibit tubular reabsorption of the radioactive tracer. Repeated treatments were performed in case of response and significant improvement in symptoms and quality of life, except in cases of renal toxicity and rejection by the patient for further treatment within 3 months. Additional cycles were suspended in case of PD.

2.6. Biodistribution of the Radiotracer. In order to evaluate the biodistribution of therapeutic activity, after each

SPECT gamma camera (Genesys, Philips, The Netherlands) or with a dual-head SPECT/CT gamma camera (Symbia-T, Siemens, Germany) using parallel-hole, medium-energy, general-purpose collimators. The windows were centered over ^{177}Lu-PRRT photon peaks (208 keV and 110 keV width 20% in both cases; scatter window at 160 keV) in case of treatment with ^{177}Lu-PRRT; while at 170 keV (20%) and 80 keV (55%) in case of treatment with ^{90}Y-PRRT, as Bremsstrahlung planar scan. Whole-body scans (acquisition time: 25 minutes) and spot images (acquisition time: 10 minutes) were obtained.

2.7. Assessment of Clinical Benefit and Evaluation of PRRT Response. Clinical benefit was assessed comparing baseline clinical conditions with end-treatment parameters. In the clinical benefit evaluation the worsening of clinical conditions (i.e., appearance of new sign(s)/symptom(s)) were considered as PD. Indeed any significant variations in baseline clinical conditions was defined as stable disease (SD). Clinical benefit was defined as non-PD/SD. For the follow-up blood tests were evaluated, as described in the clinical protocol, repeated before and after each treatment cycle and every two weeks. Blood tests included hematological parameters, liver and renal function. Baseline and end-treatment serum CgA values were compared and the trend was defined as increased, stable (variation over time $\leq$10%) or decreased. All patients were followed for an additional 6 months after the last radiopharmaceutical administration. Acute and long-term adverse events were graded according to the Common Terminology Criteria for Adverse Events, version 3.0 of the National Cancer Institute [22]. To assess response to treatment PET/CT studies performed at baseline and at the end of treatment were considered.

Treatment responses assessed by PET/CT scan were defined as follows:

(i) complete response (CR): disappearance of radiopharmaceutical uptake in all detectable lesions;

(ii) partial response (PR): reduction of radiopharmaceutical uptake (>50%) in all detectable lesions in absence of appearance of new lesion(s);

(iii) stable disease (SD): no variation or reduction of radiopharmaceutical uptake (<50%) in some detectable lesions in absence of appearance of new lesion(s);

(iv) progressive disease (PD): increase >25% of radiopharmaceutical uptake in one or more lesions or appearance of new lesions and/or >10% increasing of tumor marker.

In this series of patients, we did not assess treatment response based on the size of lesions using the CT component of PET/CT images or CT scan, but as described above we evaluate only the functional response.

2.8. Statistical Analysis. All values are expressed as median and range, as customary for nonparametric data.Correlation

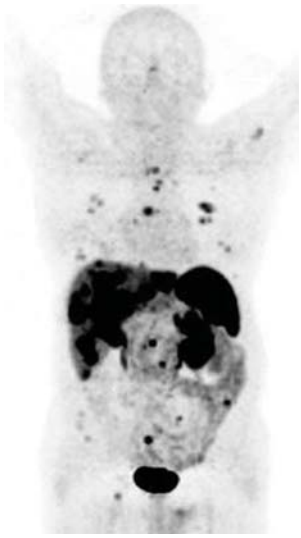

Figure 1: ^{68}Ga-DOTATOC PET/CT: liver, lung, lymph node, and bone metastases from NET of unknown origin.

3. Results

^{68}Ga-DOTATOC/DOTATATE PET/CT was performed in all the patients to evaluate the eligibility. Baseline ^{68}Ga-DOTATOC/DOTATATE PET/CT demonstrated at least one site of radiopharmaceutical uptake.

Figure 1 shows an example of ^{68}Ga-DOTATOC accumulation in tumor lesions. ^{68}Ga-DOTATOC positive lesions were preferentially localized at liver, lymph nodes, lung, and skeleton.

An end-treatment ^{68}Ga-peptide PET/CT was performed in all treated patients about 3–6 months after the last PRRT administration except for 6 patients in which PD was determined on the basis of worsening of clinical conditions.

Figures 2 and 3 represent examples of pre- and posttherapeutic ^{68}Ga-DOTATOC PET/CT.

Dosimetric estimates for kidney and bone marrow are summarized in Table 3. No toxicities were recorded after radiopharmaceutical injection administered for dosimetric purpose.

PRRT cycles were administered at 70 ± 24.6 days apart (range 35–140) with a median cumulative activity of 5.5 GBq (range 3.6–7.4 GBq). Thirty-five patients received 4 or 5 PRRT cycles, 10/59 more than 5 cycles while 14/59 patients had <4 PRRT cycles. ^{90}Y-PRRT was administered in 33/59 patients (56%), ^{177}Lu-PRRT in 9/59 patients (15%) while 17/59 patients (29%) received both ^{90}Y-PRRT and ^{177}Lu-PRRT in different cycles. Posttherapeutic scintigraphy confirmed a correct distribution of the radiopharmaceutical in all patients.

In 18/59 (30%) patients no adverse effects after administration of the radiopharmaceuticals were observed. Hematological toxicity including grade 2-3 anemia, thrombocytopenia and leukopenia occur in 12/59 patients (20%). Two of the 12 patients who had hematological toxicity presented from previous chemotherapies. Asthenia (grade 2-3, 28/59) nausea (grade 1-2, 14/59), vomiting (grade 2-3, 5/59), were frequently observed. Stomatitis (grade 2) and gastritis (grade 1) were also reported in 1 case each. Long-term nephrotoxicity was observed in 3 patients (2 moderate; 1 severe requiring dialysis). Patients who developed nephrotoxicity were treated with ^{90}Y-PRRT receiving 5 (2/3) and 6 (1/3) cycles. One of them suffered from both diabetes and blood hypertension. Patient who required dialysis had only one kidney. Clinical benefit was recorded in 21/59 patients while a worsening of clinical conditions was observed in 9/59 patients. All patients which were asymptomatic at baseline and not present modifications of their clinical conditions.

Best objective response was CR in 1/59 patient (2%), PR in 24/59 (40.5%), SD in 24/59 patients (40.5%) while PD was demonstrated in 10/59 (17%) of patients. The overall tumor response rate considering both CR and PR was 42.5%. SUVmax values in the main lesion for both baseline and end-treatment ^{68}Ga-peptide PET/CT scans were reported in Table 4 based on functional response. A significant difference in cumulated administered activity between PD and non-PD patients was found as shown by Figure 4.

Table 5 shows treatment responses based on primary tumor site. Table 6 shows results of treatment responses based on the type of treatment (^{90}Y-PRRT, ^{177}Lu-PRRT, or combined ^{90}Y-PRRT and ^{177}Lu-PRRT) while treatment responses based on the numbers of PRRT cycles are reported in Table 7. In Table 8 functional response was tabulated on the basis of clinical benefit assessment. In the eleven patients with both normal baseline and end-treatment serum CgA levels functional response assessed by ^{68}Ga-peptide PET/CT resulted in 1/11 CR, 5/11 PR, 4/11 SD, and 1/11 PD. Discordant results between serum CgA levels trend over time and ^{68}Ga-peptide results were found in 23/59 patients. Despite the increase of CgA values ^{68}Ga-peptide PET/CT documented a PR in 7 patients and a SD in 6 cases, respectively (Table 9). In one patient classified as SD by ^{68}Ga-peptide PET/CT, serum CgA levels completely normalized after PRRT.

4. Discussion

The development of imaging agents specifically designed to target tumor metabolic pathways and associated antigens including membrane receptors opens new horizon both for the selection of patients candidate to target treatment by the *in vivo* detection of enhanced target expressions as well as for the development of new multimodality treatment strategies.

The expression of SSTRs by NETs made molecular imaging with specific SST-analogues for specific SSTR subtypes the method of choice for their diagnostic workup. In fact ^{111}In-labeled SST analogues scintigraphy and more recently ^{68}Ga-DOTA-peptides significantly change the diagnostic approach to neuroendocrine tumors. In our study, ^{68}Ga-peptide PET/CT as first-selection procedure to determine the presence of high SSTR expression and a tumor uptake at least two times higher than the liver were considered the criteria

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