

Original Article

Initial clinical evaluation of indigenous ^{90}Y -DOTATATE in sequential duo-PRRT approach (^{177}Lu -DOTATATE and ^{90}Y -DOTATATE) in neuroendocrine tumors with large bulky disease: Observation on tolerability, ^{90}Y -DOTATATE post-PRRT imaging characteristics (bremsstrahlung and PET-CT) and early adverse effects

ABSTRACT

^{177}Lu -DOTATATE peptide receptor radionuclide therapy (PRRT) alone has lesser potential in the clinical setting of neuroendocrine tumor (NET) with large bulky disease and nonhomogeneous somatostatin receptors (SSTR) distribution, owing to lower energy ($E_{\beta\text{max}}$ 0.497 MeV) and a shorter particle penetration range (maximum 2–4 mm) of ^{177}Lu . In large bulky NETs, ^{90}Y has the theoretical advantages because of a longer beta particle penetration range (a maximum soft tissue penetration of 11 mm). Therefore, a combination of ^{177}Lu and ^{90}Y is a theoretically sound concept that can result in better response in metastatic NET with large-bulky lesion and non-homogeneous SSTR distribution. The aim of the study was to determine the feasibility of combining ^{90}Y -DOTATATE with ^{177}Lu -DOTATATE PRRT as sequential duo-PRRT in metastatic NET with (5 cm) including the post ^{90}Y -DOTATATE-PRRT imaging and also to determine early toxicity of the duo-PRRT approach. A total of 9 patients received combination of ^{177}Lu -DOTATATE with ^{90}Y -DOTATATE (indigenously prepared and approved) through sequential duo-PRRT approach. These 9 NET patients were included and analyzed in this study. All 9 patients had undergone post-PRRT ^{90}Y -DOTATATE imaging, including a whole-body planar bremsstrahlung imaging followed by regional single-photon emission computed tomography (SPECT)-computed tomography (CT) imaging and also a regional positron emission tomography-computed tomography imaging. Grading of ^{90}Y -DOTATATE and ^{177}Lu -DOTATATE uptake was done on post-PRRT imaging by both modalities. The size of the lesions ranged from 5.5 cm to 16 cm with average size of 10 cm before sequential duo-PRRT was decided. Sequential duo-PRRT was administered because of stable, unresponsive disease following ^{177}Lu -DOTATATE in 5 patients (55.6%), progressive disease after ^{177}Lu -DOTATATE in 2 patients (22.2%), and with neoadjuvant intent in 2 patients (22.2%). The total cumulative dose of ^{177}Lu -DOTATATE before duo-PRRT ranged from 11.84 GBq to 37 GBq per patient and average administered dose of 27.21 GBq per patient in this study. Out of 9 patients, 8 patients received single cycle of ^{90}Y -DOTATATE (ranging from 2.66 GBq to 3.4 GBq per patient with average administered dose of 3.12 GBq per patient). One patient received two cycles of ^{90}Y -DOTATATE (total dose of 6.2 GBq). Out of 9 patients, 8 patients showed excellent tracer concentration in lesions on post-PRRT ^{90}Y -DOTATATE imaging and the remaining 1 patient showed fairly adequate ^{90}Y -DOTATATE tracer uptake in lesion on visual analysis. There was matched ^{90}Y -DOTATATE uptake with ^{68}Ga -DOTATATE and also with ^{177}Lu -DOTATATE in all 9 patients. The sequential duo-PRRT was well tolerated by all patients. Two patients (22.2%) developed mild nausea, one patient (11.1%) developed transient mild-grade hemoglobin toxicity, and one patient (11.1%) developed mild-grade

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Submitted: 27-May-2019, **Revised:** 29-May-2020

Accepted: 13-Jun-2020, **Published:** 02-Oct-2020

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How to cite this article: Parghane RV, Mitra A, Bannore TU, Rakshit S, Banerjee S, Basu S. Initial clinical evaluation of indigenous ^{90}Y -DOTATATE in sequential duo-PRRT approach (^{177}Lu -DOTATATE and ^{90}Y -DOTATATE) in neuroendocrine tumors with large bulky disease: Observation on tolerability, ^{90}Y -DOTATATE post-PRRT imaging characteristics (bremsstrahlung and PET-CT) and early adverse effects. World J Nucl Med 2021;20:73-81.

Access this article online

Website:

www.wjnm.org

DOI:

10.4103/wjnm.WJNM_52_20

Quick Response Code



gastrointestinal symptoms (loose motion and abdominal pain). No nephrotoxicity, hepatotoxicity, and other hematological toxicity was observed. The combination of the indigenous ⁹⁰Y-DOTATATE with ¹⁷⁷Lu-DOTATATE PRRT in NET as sequential duo-PRRT was well tolerated, feasible and safe in stable, unresponsive/progressive disease following single isotope ¹⁷⁷Lu-DOTATATE therapy and also in neoadjuvant PRRT setting with large bulky lesion (≥ 5 cm). Post-PRRT ⁹⁰Y-DOTATATE imaging showed excellent ⁹⁰Y-DOTATATE uptake in nearly all NET patients. Mild-grade early adverse effects were easily manageable and controllable in this sequential duo-PRRT approach.

Keywords: ¹⁷⁷Lu-DOTATATE, ⁶⁸Ga-DOTATATE PET-CT, ⁹⁰Y-DOTATATE, duo-PRRT, peptide receptor radionuclide therapy (PRRT), Tandem PRRT

INTRODUCTION

Neuroendocrine tumors (NET) are a heterogeneous group of neoplasms, arising from the endocrine cells which are present throughout body most commonly in the gastrointestinal and bronchopulmonary tracts. The unique feature of NET is overexpression of somatostatin receptors (SSTR) in primary as well as metastatic lesions. There are five subtypes of SSTR. Out of five subtypes, type 2 is commonly expressed in most of NET cases and this is a key target molecule for peptide receptor radionuclide therapy (PRRT).^[1]

The treatment management of localized NET is surgery, which is possible in limited number of cases. More than 40% of NET patients present with metastatic disease at time of diagnosis and these patients require systemic therapies. The therapeutic landscape of advanced/metastatic NET has undergone a remarkable expansion in this decade specially within recent years, which includes long acting somatostatin analogs (SSAs), chemotherapy, molecular targeted treatments (everolimus and sunitinib), alpha-interferon, and PRRT.^[2-4]

The recently published randomized phase III NETTER-1 trial^[5] provided high-level evidence of efficacy and safety of ¹⁷⁷Lu-DOTATATE PRRT in mid-gut NET. However, the result of NETTER-1 trial generated a multitude of new questions regarding timing, sequencing, and matching of patients with the most appropriate treatment protocols available for the management of metastatic/advanced NET.

The role of ¹⁷⁷Lu-DOTATATE PRRT in NET may be doubtful in large bulky lesions (≥ 5 cm) with nonhomogeneous SSTR distribution and this is because of lower energy ($E_{\beta\text{max}}$ 0.497 MeV) and a shorter particle penetration range (maximum 2–4 mm) of ¹⁷⁷Lu-DOTATATE. In such conditions, ⁹⁰Yttrium (⁹⁰Y) has theoretical advantages because of a longer beta particle penetration range (a maximum soft tissue penetration of 11 mm).^[6,7]

A combination of ¹⁷⁷Lu and ⁹⁰Y therapy is a theoretically sound concept that can translate into better response in NETs with both small and large-bulky lesions. The aim of the present study was to determine the feasibility of combining ⁹⁰Y-DOTATATE with ¹⁷⁷Lu-DOTATATE PRRT as sequential duo-PRRT in NET with large bulky lesion (≥ 5 cm) and also to determine early toxicity of this duo-PRRT approach.

MATERIALS AND METHODS

In this study, we retrospectively reviewed the medical records of 9 patients who received combination of ¹⁷⁷Lu-DOTATATE with ⁹⁰Y-DOTATATE sequential duo-PRRT, within the period from September 2019 to February 2020 and these 9 NET patients were included and analyzed in this study (this corresponds to the time period during which the approved indigenous ⁹⁰Y was available to our Institute). The product was approved for the routine clinical use by the Radiopharmaceuticals Committee of the Department of Atomic Energy. The treatments were conducted after obtaining necessary approval from the Institutional Ethics Committee and were also approved by the Institutional Scientific Advisory Committee (IEC Ref: Project No P17/feb/2019).

The eligibility criteria for deciding for sequential duo-PRRT were as follows: patients with pathologically confirmed NET; unresectable and advanced large bulky (≥ 5 cm) disease; stable, unresponsive/progressive disease on ¹⁷⁷Lu-DOTATATE (≥ 2 cycles); and SSTR positive lesions on ⁶⁸Ga-DOTATATE positron emission tomography-computed tomography (PET-CT) (Krenning score ≥ 2 , compared on maximum intensity projection (MIP), coronal and transaxial images).

The exclusion criteria for sequential duo-PRRT included low or absent SSTR expression on ⁶⁸Ga-DOTATATE PET-CT, small sized disease (< 5 cm), glomerular filtration rate (GFR) of < 60 mL/min, hypoalbuminemia (< 20 g/L), platelet count $< 90 \times 10^9$ /L or pancytopenia, pregnancy, breast-feeding, severe concomitant illness including severe

psychiatric disorders, Eastern Cooperative Oncology Group (ECOG) performance score 4, Karnofsky Performance Status score of <60 , and expected life survival <3 months.

Treatment planning

All 9 NET patients had undergone the presequential duo-PRRT work up protocol, which included ^{68}Ga -DOTATATE PET-CT and ^{18}F -FDG PET-CT imaging, documentation of clinical symptoms, and measurement of serum chromogranin A (CgA) level before considering sequential duo-PRRT.

^{68}Ga -DOTATATE positron emission tomography-computed tomography and ^{18}F -FDG positron emission tomography-computed tomography imaging

^{68}Ga -DOTATATE PET-CT and ^{18}F -FDG PET-CT scans were obtained in all 9 NET patients before sequential duo-PRRT.

^{68}Ga -DOTATATE PET-CT scan was performed approximately 60 min after intravenous injection of 74–111 MBq (2–3 mCi) of ^{68}Ga -DOTATATE dose. The scans were performed using a time of flight PET-CT scanner (Philips Gemini TF TOF 16 PET/CT scanner) with LYSO-based PET crystal. After obtaining a scout image whole-body CT scanning was performed first in craniocaudal direction (voltage 120 kVp, slice thickness 5 mm, pitch-0.83, FOV 600 mm, rotation time -0.5 s, 250 mA, image matrix- 512×512) without any breath hold instructions. Contrast or noncontrast CT was used for diagnostic and attenuation correction of the PET data. PET scanning was performed immediately after the CT acquisition in the three-dimensional (3D) emission mode with 3 min per bed position. Images were reconstructed iteratively using RAMLA algorithm (2 iterations, 21 subsets). The acquired studies were viewed (transaxial, coronal, and sagittal views) in multimodality workstation of Philips Gemini TF processing system. Similar imaging protocol was applied for ^{18}F -FDG PET-CT scan, which was done 1 day after ^{68}Ga -DOTATATE PET-CT scan. For ^{18}F -FDG PET-CT scan, all patients were fasted for at least 6 h prior to the intravenous injection of 5MBq/kg body weight of ^{18}F -FDG and whole-body full-ring dedicated 3D PET-CT scanning was done (50 mA, 120 kVp, noncontrast/contrast CT scan for attenuation correction and anatomical co-localization).

If PET-CT scans revealed SSTR avid large bulky lesions (≥ 5 cm) on ^{68}Ga -DOTATATE imaging as shown in Figure 1a, which were stable, unresponsive/progressive disease on ^{177}Lu -DOTATATE (≥ 2 cycles) then sequential duo-PRRT was planned in these patients.

Investigations and Health Related Quality of Life Scales

The various investigations such as hematological parameters, renal function test, GFR, liver function test, and serum CgA levels were measured and documented in all NET patients

before sequential duo-PRRT. The patients were examined for health related quality of life (HRQoL) scales which included ECOG Performance Status and Karnofsky score before and following sequential duo-PRRT.

^{177}Lu -DOTATATE therapy

Long and short-acting somatostatin was stopped for 4 weeks and 24 h respectively before ^{177}Lu -DOTATATE PRRT.

The Bhabha Atomic Research Centre (BARC), Mumbai, India, supplied a sterile solution of $^{177}\text{LuCl}_3$ in 0.01M HCl with a specific activity of >999 MBq/ μg . In house labeling was carried out with a radiochemical purity of $>99\%$ for ^{177}Lu -DOTATATE product.

The standard mixed amino acid preparation containing lysine and arginine was infused 30 min before PRRT and maintained over 7 h. To prevent nausea and vomiting, 4 mg of ondansetron and 4 mg of dexamethasone was administered before amino acid infusion.

^{177}Lu -DOTATATE with dose activity of 5.5–7.4 GBq per cycle in 100 ml of normal saline was administered intravenously over 30 min. For ^{177}Lu -DOTATATE PRRT, all NET patients were admitted in radionuclide therapy ward and monitored for 24 h after PRRT for any acute adverse effects. The ^{177}Lu -DOTATATE PRRT was divided into cycles and cycles were repeated at intervals of 10–12 weeks.

Post-peptide receptor radionuclide therapy ^{177}Lu -DOTATATE whole-body planar imaging

Whole-body planar imaging and single photon emission CT (SPECT) imaging were conducted 24 h after ^{177}Lu -DOTATATE using a large field of view gamma camera with a medium-energy collimator as shown in Figure 1b.

^{90}Y -DOTATATE therapy

Long- and short-acting somatostatins were stopped for 4 weeks and 24 h respectively before ^{90}Y -DOTATATE PRRT therapy.

^{90}Y -Acetate was indigenously sourced from high-level liquid waste, using separation method based on a two-stage $^{90}\text{Sr}/^{90}\text{Y}$ generator system based on supported liquid membrane technology, developed at Nuclear Recycle Group, BARC, and Mumbai, India. The quality control parameters of ^{90}Y -acetate were validated and compared to the pharmacopeia standard. This ^{90}Y -acetate was supplied as a sterile solution to Radiation Medicine Centre, Mumbai, India, and in-house labeling was carried with a radiochemical purity of $>99\%$ for ^{90}Y -DOTATATE final product. The product was approved by the regulatory body of DAE (Department of

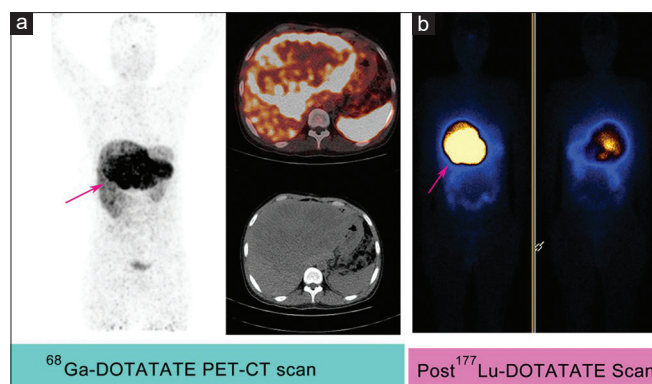


Figure 1: A 29 years old male patient, known case of duodenal neuroendocrine tumor (MIB Index = 8%) with bulky metastatic liver disease. Patient initially underwent surgical resection of duodenal lesion followed by 2 cycles of ^{177}Lu -DOTATATE peptide receptor radionuclide therapy then ^{90}Y -DOTATATE peptide receptor radionuclide therapy. ^{68}Ga -DOTATATE PET-CT scan (a) showed somatostatin receptors avid (Krenning score = 4) large sized (16 cm \times 13 cm) liver lesion (arrow) and post ^{177}Lu -DOTATATE therapy scan (b) showed good tracer uptake (grade = 3) in liver lesion

Atomic Energy) India, the Radiopharmaceutical Committee, for routine clinical use.

The standard mixed amino acid preparation containing lysine and arginine was infused 30 min before PRRT and maintained over 7–8 h. To prevent nausea and vomiting, 4 mg of ondansetron and 4 mg of dexamethasone were administered before amino acid infusion.

^{90}Y -DOTATATE with dose activity of 2.6–3.4 GBq per cycle in 100 ml of normal saline was administered intravenously over 30 min. For ^{90}Y -DOTATATE PRRT, all NET patients were admitted in radionuclide therapy ward and monitored for 24 h after PRRT therapy for any acute adverse effects.

Post-peptide receptor radionuclide therapy ^{90}Y -DOTATATE imaging

Whole-body planar bremsstrahlung imaging [Figure 2a] and SPECT-CT imaging were acquired 24 h after ^{90}Y -DOTATATE PRRT using a large field of view gamma camera with a high-energy collimator and various windows setting with a range of 76–250 keV. A whole-body planar scan was performed at a speed of ~ 10 cm/min. The SPECT/SPECT-CT of regional part of body [Figure 2b] was performed after whole-body scan using a dual-head camera. The high-energy, parallel hole, general-purpose collimators were used. In the case of SPECT or SPECT/CT, acquisition parameters were: 128 \times 128 matrix, zoom 1.00, 1 min/frame for 12 frames.

Regional PET-CT scans were conducted 24–36 h after ^{90}Y -DOTATATE PRRT using a time of flight PET-CT scanner (Philips Gemini TF TOF 16 PET/CT scanner) with

LYSO-based PET crystal. After obtaining a scout image regional CT scanning was performed first in cranio-caudal direction (voltage 120 kVp, slice thickness 5 mm, pitch-0.83, FOV 600 mm, rotation time-0.5 sec, 50 mA, image matrix-512 \times 512) without any breath hold instructions. Non contrast low dose CT was used for attenuation correction of the PET data. PET scanning was performed immediately after the CT acquisition in the 3D emission mode with 20 mins per bed position for 2 beds. Images were reconstructed iteratively using RAMLA algorithm (2 iterations, 21 subsets). The acquired studies were viewed (transaxial, coronal and sagittal views) in multimodality-work-station of Philips Gemini TF processing system [Figure 2c].

Post-PRRT ^{177}Lu -DOTATATE uptake in the lesions (on gamma camera imaging) and the post-PRRT ^{90}Y -DOTATATE uptake in lesions on gamma camera imaging and on PET/CT scanner were divided into 1, 2 and 3 grade based on visual comparison of tracer uptake in the lesions with physiological liver/kidney uptake, where tracer uptake (^{177}Lu -DOTATATE or ^{90}Y -DOTATATE uptake) in lesion was less than liver/kidney uptake consider as grade 1, tracer uptake in lesion equal to liver/kidney uptake as grade 2, and tracer uptake in lesion more than liver/kidney uptake as grade 3.

Follow-up

Clinical examinations with vital signs were undertaken both before and after sequential duo-PRRT. The patients were evaluated for symptomatic, ECOG and Karnofsky scores, and biochemical parameters following sequential duo-PRRT. Blood biochemistry and hematological variables, including renal function tests, complete blood counts, serum hemoglobin levels, and liver function test, were measured at biweekly interval after sequential duo-PRRT. Any observed toxicity was recorded continuously. Adverse events were graded according to the Common Terminology Criteria for Adverse Events version 5.0 of the National Cancer Institute with special attention to nausea, vomiting, leukopenia, thrombocytopenia, anemia, and liver and renal adverse events.

RESULTS

A total of 9 patients (3 women, 6 men; median age 55 years, range 46–62 years) received sequential duo-PRRT were included and analyzed retrospectively in this study. The detail of patient characteristics in the study population is shown in Tables 1 and 2.

The Ki-67/MiB-1 index ranged from 1% to 30% with an average of 9% in this study population. The WHO grade 1 (Ki-67 index $< 3\%$) of tumor differentiation was noted

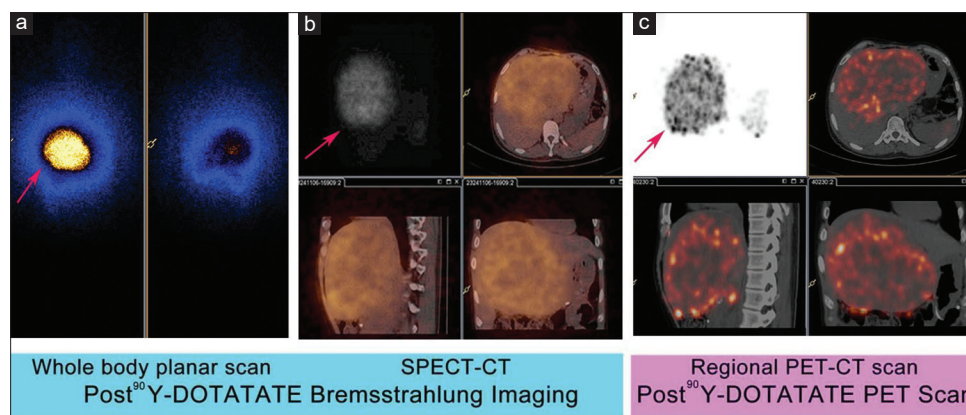


Figure 2: After 2 cycles of ¹⁷⁷Lu-DOTATATE peptide receptor radionuclide therapy, the patient received ⁹⁰Y-DOTATATE therapy (single cycle, dose = 3.4 GBq). Post ⁹⁰Y-DOTATATE Bremsstrahlung imaging with whole-body planar and single photon emission computed tomography-computed tomography scans (a and b) and post ⁹⁰Y-DOTATATE regional positron emission tomography-computed tomography scan (c) demonstrated good tracer uptake of ⁹⁰Y-DOTATATE (grade = 3) in liver lesions (arrows). No major adverse effect was seen after ⁹⁰Y-DOTATATE peptide receptor radionuclide therapy in this patient

in 3 patients, grade 2 (Ki-67 index 3%–20%) in 5 patients, and grade 3 (Ki-67 index >20%) in 1 patient. Out of the 9 patients, 4 patients (44.4%) had pancreatic NET and the remaining 5 patients (55.6%) included mediastinal NET in 1 patient, rectal NET in 1 patient, duodenal NET in 2 patients, and metastases with unknown primary site in 1 patient. Three patients (33.3%) were symptomatic before sequential duo-PRRT with the most common complaints being abdominal pain, weakness, and weight loss. Out of the 9 patients, 3 patients underwent surgical resection of the primary disease (resection of pancreatic lesion in 1 patient, resection of mediastinal lesion in 1 patient, and resection of duodenal lesion in 1 patient), 5 patients received somatostatin analog therapy, and 1 patient received external beam radiation therapy before sequential duo-PRRT. Out of 9 NET patients, 8 patients (88.8%) had metastatic disease before sequential duo-PRRT and most common site for metastatic disease was liver ($n = 7$ patients), followed by lymph nodes ($n = 3$ patients), and bone ($n = 2$ patients). One patient had localized pancreatic disease in this study. The size of lesions ranged from 5.5 cm to 16 cm with an average size of 10 cm before sequential duo-PRRT was noted in this study. Out of 9 NET patients, 6 patients (66.6%) had FDG avid disease. The total cumulative dose of ¹⁷⁷Lu-DOTATATE before the adoption of duo-PRRT approach ranged from 11.84 GBq to 37 GBq with average administered dose of 27.21 GBq per patient and ¹⁷⁷Lu-DOTATATE cycles ranging from 2 to 6 cycles and an average of 4 cycles per patient was given in this study.

Out of the 9 patients, sequential duo-PRRT was considered because of stable, unresponsive disease following ¹⁷⁷Lu-DOTATATE in 5 patients (55.6%), progressive disease after ¹⁷⁷Lu-DOTATATE in 2 patients (22.2%) and in an neoadjuvant intent in 2 patients (22.2%). At the time of analysis, single cycle of ⁹⁰Y-DOTATATE was given in 8 patients,

Table 1: Patient characteristics

Patients characteristics	Number of patients
Total number of patients received sequential duo-PRRT	9
Sex (male:female)	6:3
Symptomatic patients before sequential duo-PRRT	3
Metastatic disease before sequential duo-PRRT	8
Stable, unresponsive disease following ¹⁷⁷ Lu-DOTATATE	5
Progressive disease after ¹⁷⁷ Lu-DOTATATE	2
Sequential duo-PRRT used as neoadjuvant intent	2
FDG positive disease before sequential duo-PRRT	6
Site of primary disease	
Pancreatic NET	4
Mediastinal NET	1
Rectal NET	1
Duodenal NET	2
Unknown primary site	1
WHO Grade	
Grade 1	3
Grade 2	5
Grade 3	1
Prior therapies	
Surgical resection of lesion	3
Somatostatin analog therapy	5
External beam radiotherapy	1

PRRT: Peptide receptor radionuclide therapy; NET: Neuroendocrine tumor; FDG: 2-deoxy-2-[fluorine-18]fluoro-D-glucose

administered dose ranging from 2.66 GBq to 3.4 GBq per patient and average administered dose of 3.12 GBq per patient. One patient was given two cycles of ⁹⁰Y-DOTATATE with total dose of 6.2 GBq.

All 9 patients were underwent post-PRRT ⁹⁰Y-DOTATATE imaging, a whole-body planar bremsstrahlung imaging followed by regional SPECT-CT and also a regional PET-CT imaging on PET/CT scanner. Out of 9 patients,

Table 2: Patient details

Case number	Primary site, MIB-1 index	Prior therapies	Size of lesions (largest diameter)	Indication for sequential duo-PRRT	Cumulative dose and cycles of ¹⁷⁷ Lu-DOTATATE PRRT	Dose of ⁹⁰ Y-DOTATATE PRRT	Adverse effects	Follow-up period after sequential duo-PRRT
I	Mediastinal NET, 30%	Surgical resection of primary lesion, Somatostatin analog therapy and external beam radiotherapy	12 cm	Stable, unresponsive disease following ¹⁷⁷ Lu-DOTATATE	33.3 GBq, 5 cycles	2.7 GBq - First cycle	No	105 days
II	Pancreatic NET, 2%	Somatostatin analog therapy	8 cm	Progressive disease after ¹⁷⁷ Lu-DOTATATE	25.23 GBq, 4 cycles	2.8GBq-First cycle, 3.3 GBq-second cycle	No	135 days
III	Duodenal NET, 10%	No prior therapies	10 cm	Stable, unresponsive disease following ¹⁷⁷ Lu-DOTATATE	31.59 GBq, 5 cycles	2.66 GBq - First cycle	No	135 days
IV	Pancreatic NET, 10 %	Surgical resection of primary lesion, somatostatin analog therapy	5.5 cm	Stable, unresponsive disease following ¹⁷⁷ Lu-DOTATATE	37 GBq, 6 cycles	3.14 GBq - First cycle	Transient mild-grade hemoglobin toxicity	105 days
V	Rectal NET, 12%	Somatostatin analog therapy	13 cm	Progressive disease after ¹⁷⁷ Lu-DOTATATE	22.2 GBq, 4 cycles	3.4 GBq- First cycle	Mild-grade of nausea	75 days
VI	Pancreatic NET, 1%	No prior therapies	5.5cm	Neoadjuvant intent	14.8 GBq, 2 cycles	3.25 GBq - First cycle	Mild-grade of nausea and gastrointestinal symptoms	75 days
VII	Pancreatic NET, 1%	Somatostatin analog therapy	7 cm	Stable, unresponsive disease following ¹⁷⁷ Lu-DOTATATE	32 GBq, 5 cycles	3.4 GBq - First cycle	No	60 days
VIII	Unknown primary site, 8%	No	13 cm	Stable, unresponsive disease following ¹⁷⁷ Lu-DOTATATE	37 GBq, 6 cycles	3.4 GBq - First cycle	No	30 days
IX	Duodenal NET, 8%	Surgical resection of primary lesion	16 cm	Neoadjuvant intent	11.84 GBq, 2 cycles	3.4GBq- First cycle	No	15 days

PRRT: Peptide receptor radionuclide therapy; NET: Neuroendocrine tumor; MIB: antibody directed at the protein Ki-67

8 patients showed excellent (grade 3) ⁹⁰Y-DOTATATE tracer concentration in lesions on post-PRRT ⁹⁰Y-DOTATATE imaging and 1 patient (Grade 1) showed fairly adequate ⁹⁰Y-DOTATATE tracer uptake on visual analysis. In all 9 patients, the lesions visualized on ⁶⁸Ga-DOTATATE PET-CT, post-PRRT ¹⁷⁷Lu-DOTATATE and post-PRRT ⁹⁰Y-DOTATATE imaging (bremsstrahlung—planar, regional SPECT-CT and regional PET-CT) demonstrating congruent good tracer activity of ⁹⁰Y-DOTATATE as shown in the comparison in Table 3.

At the time of analysis, the follow-up period after ⁹⁰Y-DOTATATE therapy ranged from 15 to 135 days (average of 82 days). During this follow-up period, two patients (22.2%) developed mild nausea (controlled well by giving another dose of 4 mg of ondansetron), one patient (11.1%) developed transient mild-grade hemoglobin toxicity (recovered within 10 days) and one patient (11.1%) developed mild-grade gastrointestinal symptoms (loose motion and abdominal pain recovering within 7 days). No nephro-toxicity, hepato-toxicity and other hematological toxicity was observed after the ⁹⁰Y-DOTATATE therapy (as part of sequential duo-PRRT), as mentioned in Table 4.

DISCUSSION

For the metastatic/advanced NET, PRRT with radiolabelled somatostatin analogs has become an established method of treatment. Historically, ¹¹¹Indium labeled with (diethylenetriaminepentaacetic acid [DTPA]⁰) octreotide was used in some clinical trials, which had a short tissue penetration of the emitted Auger electrons (ranging between nanometers and micrometers) with best result observed in small sized and highly SSTR avid NETs.^[8] In one of study, amongst the 50 NET patients treated with ¹¹¹In-pentetreotide, 3 patients developed leukemia or myelodysplastic syndrome (MDS) who received >100 GBq therapeutic dose of ¹¹¹In-pentetreotide.^[9] Presently, ¹¹¹In-pentetreotide is not commonly used in the management of NET, because of limited therapeutic result, higher therapeutic doses requirement, and also availability of better β-emitter radionuclides for PRRT in NET.

Also subsequently a modified somatostatin analog (Tyr3) octreotide with a higher affinity for the SSTR subtype-2 was developed and new chelator,

Table 3: Tracers uptake in the lesions on visual analysis

Case number	⁶⁸ Ga-DOTATATE uptake in lesions on PET/CT scanner with Krenning score	Post-PRRT ¹⁷⁷ Lu-DOTATATE uptake in lesions on gamma camera imaging with grading*	Post-PRRT ⁹⁰ Y-DOTATATE uptake in lesions on gamma camera imaging with grading*	Post-PRRT ⁹⁰ Y-DOTATATE uptake in lesions on PET/CT scanner with grading*
I	4	3	3	3
II	4	3	3	3
III	4	3	3	3
IV	4	3	3	3
V	4	3	3	3
VI	2	2	2	2
VII	4	3	3	3
VIII	4	3	3	3
IX	4	3	3	3

*Grade 1: Tracer uptake in lesion less than physiological liver/kidney uptake, Grade 2: Tracer uptake in lesion equal to physiological liver/kidney uptake, Grade 3: Tracer uptake in lesion more than physiological liver/kidney uptake. PRRT: Peptide receptor radionuclide therapy; PET/CT: Positron emission tomography/computed tomography

Table 4: Adverse events documentation

Adverse events↓/Grade*→	Grade 1 (%)	Grade 2	Grade 3	Grade 4
During/related to PRRT in number of NET patients				
Nausea	2 (22.2%)	0	0	0
Vomiting	0	0	0	0
Gastrointestinal symptoms	1 (11.1%)	0	0	0
Anemia	1 (11.1%)	0	0	0
Thrombocytopenia	0	0	0	0
Neutropenia	0	0	0	0
Nephrotoxicity	0	0	0	0
Hepatotoxicity	0	0	0	0

*Grade: Signifies grade of toxicity. PRRT: Peptide receptor radionuclide therapy; NET: Neuroendocrine tumor

1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) instead of DTPA was used to enable a more stable binding of the intended β -emitter (⁹⁰Y and ¹⁷⁷Lutetium) radionuclide. The beta-emitter radionuclides such as ⁹⁰Y (pure β -emitter) emits beta particles with a high maximum energy (E_{max} 2.27 MeV) and longer maximum particle range in tissues (11 mm) with physical half-life of 64 h. The use of ⁹⁰Y labeled with DOTA-Tyr3-octreotide (⁹⁰Y-DOTATOC) in NET had showed objective response rates of 6%–37% and occurrence of high renal toxicity in initial studies.^[10,11] This higher renal toxicity of ⁹⁰Y-DOTATOC therapy may be related to longer penetration particle range of ⁹⁰Y that results in “cross-fire” effect to irradiate not only the targeted cell but also the surrounding cells and also higher affinity of DOTATOC to SSTR 3 and SSTR5 as compared to SSTR2. The ¹⁷⁷Lu emits both beta particles (E_{max} 0.497 MeV and a shorter particle range in tissues [maximum 2–4 mm]) and gamma rays (113 keV [6.4%]; 208 keV [11%]). Because of the γ -emission, posttherapeutic gamma camera scintigraphic imaging is possible with ¹⁷⁷Lu. This posttherapeutic imaging provided an accurate representation of the distribution of the radionuclide therapy in all the lesions, and used to monitor SSTR uptake following PRRT treatments. The ¹⁷⁷Lu-DOTA-Tyr3-octreotate (¹⁷⁷Lu-DOTATATE)

has shorter tissue penetration range and 9-fold higher peptide receptor affinity for SSTR2 compared to DOTATOC^[12] and this resulted in higher tolerability of ¹⁷⁷Lu-DOTATATE therapy, especially with regard to the kidneys. A lower whole-body dose, especially lower bone marrow and renal toxicity following ¹⁷⁷Lu-DOTATATE therapy was reported in various studies.

However, ¹⁷⁷Lu-based PRRT is less effective in large sized tumors with heterogeneous distribution of SSTR over larger areas in tumor and this is because of a lower energy and smaller particle range of ¹⁷⁷Lu. As such the energy deposition of ¹⁷⁷Lu is 67% inside a 2-mm lesion, whereas ⁹⁰Y deposited 87% of energy in large tumors (diameter up to 5 cm).^[13,14] Therefore, in patients with both small sized and large bulky NET with heterogeneous distribution of SSTR, a combination of radionuclide (¹⁷⁷Lu and ⁹⁰Y) therapy might be the useful, which potentially leads to a better effectiveness than one isotope alone. This combination of radionuclide treatment was first described by De Jong *et al.* in their animal studies which consisted of 50% ¹⁷⁷Lu-DOTATATE and 50% ⁹⁰Y-DOTATOC. They found extended duration of survival time by 3 times in rats after use of this combination and they concluded in their studies that complementary characteristics of both isotopes allow irradiation of both large and small metastases.^[14,15]

The combination of radionuclide treatment in humans was first time reported by Kunikowska *et al.* in their clinical trial and this trial was conducted in total 50 NET patients with multiple metastatic lesions of varying sizes. Out of 50 patients, 25 patients were given ⁹⁰Y-DOTATATE alone and 25 patients were given combination of ¹⁷⁷Lu-DOTATATE and ⁹⁰Y-DOTATATE with 3.7 GBq/m² body surface area activity dose in three to five cycles along with amino acid infusion for renal protection. They found a longer overall survival (OS) time after treatment with ⁹⁰Y/¹⁷⁷Lu-DOTATATE than in the group treated

with ^{90}Y -DOTATATE alone (OS not reached vs. 26.3 months, $P < 0.01$). No severe adverse events occurred in ^{90}Y -DOTATATE alone and combined $^{90}\text{Y}/^{177}\text{Lu}$ -DOTATATE treated groups. They found WHO hematological toxicity of grades 1 and 2 with nearly the same frequency in both groups without clinical symptoms and deterioration in kidney function was observed in three patients in each group. They concluded that PRRT with tandem approach ($^{90}\text{Y}/^{177}\text{Lu}$ -DOTATATE) provides longer OS than with a single radioisotope (^{90}Y -DOTATATE) with comparable safety profile in both groups.^[16]

A similar study was conducted by Villard *et al.*^[17] on a larger cohort of 486 NET patients and these patients were divided into two groups, one group ($n = 237$ patients) received ^{90}Y -tetraazacyclododecane-tetraacetic acid modified Tyr-octreotide (DOTATOC) alone and another group ($n = 249$ patients) received ^{90}Y -DOTATOC plus ^{177}Lu -DOTATOC PRRT. The patients received combined radionuclide therapy (OS = 5.51 years) had a significantly longer OS than patients who received ^{90}Y -DOTATOC (OS 3.96 years) PRRT alone. The rates of adverse effects (severe hematologic and renal toxicity) were comparable in both groups. They concluded that combined radionuclide therapy associated with improved OS compared with single isotope ^{90}Y alone PRRT in NET patients with comparable adverse effect profiles in both groups. Villard *et al.*^[17] used DOTATOC instead of DOTATATE for PRRT in their study and found similar result as reported by Kunikowska *et al.*^[16]

Seregini M *et al.* evaluated tandem ^{90}Y -DOTATATE and ^{177}Lu -DOTATATE PRRT in 26 metastatic NET patients in their study. These 26 patients were given four therapeutic cycles of alternating ^{177}Lu -DOTATATE (5.55 GBq) and ^{90}Y -DOTATATE (2.6 GBq). They calculated the absorbed doses in healthy organs using a dosimetric method after administration of ^{177}Lu -DOTATATE. They found objective responses of 42.3% with a median progression-free survival longer than 24 months and the cumulative biologically effective doses were below the toxicity limit in the majority of patients in their study. They concluded that tandem ^{90}Y -DOTATATE and ^{177}Lu -DOTATATE PRRT is an effective therapeutic option in NET cases refractory to conventional therapy with absence of renal damage.^[18]

Dumont *et al.* explored the effects of ^{90}Y -DOTATOC ($n = 30$ patients) and ^{90}Y -DOTATOC plus ^{177}Lu -DOTATOC ($n = 6$ patients) on survival of metastatic gastrinoma patients. They found that longer median survival in patients who received ^{90}Y -DOTATOC plus ^{177}Lu -DOTATOC (median OS = 60.2 months) as compared to ^{90}Y -DOTATOC (median OS = 27.0 months) alone received PRRT and concluded that

combination of radionuclide therapy was promising tool for management of metastatic progressive gastrinoma.^[19]

The size of lesions was not clearly mentioned for treatment of combined radionuclide therapy in most of the studies available in literature. Kong *et al.* evaluated sequential PRRT therapy (^{90}Y -DOTATATE followed by ^{177}Lu -DOTATATE) along radiosensitising chemotherapy in NET patients with >4 cm size lesion. They found that 42% of partial response and 21% of minor response on anatomical response evaluation after use of sequential peptide receptor chemoradionuclide therapy (PRCRT). Out of 26 patients, 8 patients and 2 patients developed grade 3/4 lymphopenia and grade 3/4 thrombocytopenia in their study respectively without significant hepatic or renal toxicity. They concluded that, PRCRT with ^{90}Y -DOTATATE followed by ^{177}Lu -DOTATATE achieved high clinical and morphological response in NET patients with bulky tumors.^[20]

The long-term (10-year follow-up period) side effects of tandem $^{90}\text{Y}/^{177}\text{Lu}$ -DOTATATE therapy in 59 NET patients were evaluated by Kunikowska *et al.* in one of their studies. One patient (2%) developed MDS and one patient (2%) grade 3 nephrotoxicity in their study. No other grade 3 and 4 hematological or renal toxicity was observed during their 10-year follow-up period. They concluded that, tandem $^{90}\text{Y}/^{177}\text{Lu}$ -DOTATATE therapy was highly effective and safe considering long-term side effects of PRRT.^[21]

In our study, we evaluated sequential duo-PRRT (^{177}Lu -DOTATATE followed by ^{90}Y -DOTATATE) in total 9 NET patients with bulky large sized lesion (≥ 5 cm) which was unique in the sense that, as we have started using the combined radionuclide therapy with a size criterion. In our initial observational study with the indigenous ^{90}Y , 8 patients showed excellent (grade 3) ^{90}Y -DOTATATE uptake in lesions on visual analysis, which were matched with ^{68}Ga -DOTATATE uptake and ^{177}Lu -DOTATATE uptake in both PET/CT scanner and bremsstrahlung imaging respectively as shown in Figures 1 and 2.

In our study, the follow-up period after ^{90}Y -DOTATATE therapy ranged from 15 to 135 days with average of 82 days and during this follow-up period, two patients (22.2%) developed mild nausea, one patient (11.1%) developed transient mild-grade hemoglobin toxicity and one patient (11.1%) developed mild-grade gastrointestinal symptoms, which were easily manageable and controllable. In our study, no nephro-toxicity, hepato-toxicity and other major hematological toxicity was noted and these finding were similar to various studies available in literature that used tandem/duo-PRRT for treatment of metastatic/advanced NET. Small population

size, short follow-up period, lack of dosimetry and control group, were the major limitations, though we felt it would be worthwhile to report the initial observations.

CONCLUSION

The combination of the indigenous ⁹⁰Y-DOTATATE with ¹⁷⁷Lu-DOTATATE PRRT in NET as sequential duoPRRT was well tolerated, feasible and safe in stable, unresponsive/progressive disease following single isotope ¹⁷⁷Lu-DOTATATE therapy and also in neoadjuvant PRRT setting with large bulky lesion (≥ 5 cm). Post-PRRT ⁹⁰Y-DOTATATE imaging showed excellent ⁹⁰Y-DOTATATE uptake in nearly all NET patients. Mild-grade early adverse effects were easily manageable and controllable in this sequential duo-PRRT approach.

Acknowledgements

The authors acknowledge the contribution of the Fuel Reprocessing Division, Nuclear Recycle Group, BARC for providing the indigenously sourced ⁹⁰Y-Acetate as a Clinical Grade Radiochemical for use in Radiopharmaceutical Formulations.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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