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Peptide receptor radionuclide therapy implementation and results in a predominantly gastrointestinal neuroendocrine tumor population

A two-year experience in a nonuniversity setting

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Abstract

Neuroendocrine tumors (NETs) are rare, but the incidence and prevalence of NETs are increasing in the United States. While surgery is the preferred treatment for NETs, it is not a viable option for metastatic disease. Lutathera (^{177}Lu-DOTATATE) is approved by the United States Food and Drug Administration and the European Medicines Agency for the treatment of gastroenteropancreatic (GEP)-NETs in adults. There is limited information on GEP-NET treatment responses to Lutathera.

Our institution launched a peptide receptor radionuclide therapy (PRRT) service line using Lutathera with involvement from a multidisciplinary team and complete collaboration between hospital administration and clinical providers. A prospective registry study was also established in order to collect patient demographics and clinical data regarding the treatment of GEP primary NETs with Lutathera.

Between August 2018 and July 2020, 35 GEP-NET patients were treated with Lutathera, of which 65.71% received 4 complete cycles and 25.71% received 3 cycles; 5.71% and 2.86% received 2 and 1 cycles of PRRT, respectively. Most adverse events during the course of our study were low grade using the common terminology criteria for adverse events system. Of the patients who completed all 4 cycles: 22% showed partial response to Lutathera, 44% showed stable disease, and 13% showed disease progression based on a qualitative assessment of positron emission tomography/computed tomography imaging.

From our experience, Lutathera was well tolerated in patients with GEP-NET. Additional studies are needed to examine long-term clinical and patient-reported outcomes associated with GEP-NET treatment as well as financial considerations for hospitals embarking on a PRRT program.

Abbreviations: AE = adverse events, CgA = chromogranin A, Cr = creatinine, FDA = Food and Drug Administration, G1 = grade 1, G2 = grade 2, G3 = grade 3, GEP = gastroenteropancreatic, HgB = hemoglobin, LAR = long-acting repeatable, NET = neuroendocrine tumors, OS = overall survival, PET/CT = positron emission tomography/computed tomography, PFS = progression free survival, PI = proliferation index, PRRT = peptide receptor radionuclide therapy, RECIST = response evaluation criteria in solid tumors, SPECT = single-photon emission computerized tomography, SSA = somatostatin analog, SSTR = somatostatin receptor, WBC = white blood cell.

Keywords: ^{177}Lu-DOTATATE, gastrointestinal neuroendocrine tumors, Lutathera, peptide receptor radionuclide therapy

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1. Introduction

Neuroendocrine tumors (NETs) are rare, but the incidence and prevalence of NETs are increasing in the United States.[1] NETs originate from cells in the diffuse neuroendocrine system, and can occur throughout the body, including the gastrointestinal tract, pancreas, and lung. The most common NETs develop in the gastroenteropancreatic (GEP) system.[2–4] GEP-NETs are associated with a 5-year survival rate less than 50%, and treatment is provided with palliative intent.[2] The clinical presentation of NET patients is varied, and is dependent on the type of hormones secreted by the NETs (eg, serotonin, gastrin, insulin, glucagon, vasoactive intestinal peptide, and others),[1,5] but many tumors can also be nonfunctional.

While surgery is the preferred treatment for NETs, it is not a viable option for metastatic disease. However, somatostatin analog (SSA) therapy, chemotherapy, selective internal radiation therapy, targeted biologics, and peptide receptor radionuclide therapy (PRRT) are treatment options for NETs that have metastasized. Response rates to these therapies range from 6% to 70%.[6]

Most NETs express somatostatin receptors (SSTRs) on their cell surface.[7] GEP-NETs express SSTR1, SSTR2, SSTR3, SSTR4, and SSTR5, with expression of these receptors varying based on the location of the tumor.[8] PRRT targets the SSTRs using radiolabeled SSAs such as ^{177}Lu-DOTA-DPhe-[Tyr^3] octreotate (^{177}Lu-DOTATATE, alternatively, Lutathera) to facilitate direct delivery of radiation to tumor cells.[9–11] In contrast to the ^{90}Y radionuclide that has a range of ~12 mm in tissues and is better suited for larger tumors, Lutathera has a maximum particle range of 2 mm and is preferentially used for smaller tumors.[12–14] Lutathera is approved by the United States Food and Drug Administration (FDA) and the European Medicines Agency for the treatment of GEP-NETs in adults.

Publications from single centers mostly in Europe and Australia have shown partial response rates and quality of life improvements in small populations of NET patients treated with Lutathera. However, there is limited information on the treatment responses and survival outcomes related to Lutathera treatment of GEP-NETs.[15] Understanding the efficacy and safety of Lutathera in GEP-NET patients is essential. This paper describes the administrative process that went into initiating PRRT with Lutathera at a major Southwest United State quaternary hospital, and the preliminary descriptive clinical investigation of the population treated.

2. Materials and methods

2.1. Establishment of PRRT treatment services

Considerable administrative and clinical collaborations and planning took place prior to being able to offer PRRT to our patient population post-FDA approval of Lutathera. This involved establishing the necessary administrative relationships; ensuring staffing, training, and education took place; instituting the required clinical processes; and developing tailored patient pathways and education materials.

Supportive administrative collaborations began by first forming a multidisciplinary committee, which included nuclear radiologists, medical oncologists, radiation oncologists, and hepatobiliary surgeons; staff from the nuclear medicine and radiation departments; a dedicated PRRT nurse navigator; and select administrative leaders. The committee's role was to oversee and inform the entire process of establishing PRRT at our institution. The committee collaborated with the institution's finance team to discuss reimbursement and also to develop pathways for alternative therapies to support unfunded patients. There were also work groups established within the institution's medical records and coding departments to work through documentation and billing considerations.

The multidisciplinary clinical team includes interventional radiologists, nuclear radiologists, radiation oncologists, nuclear medicine and radiation department staff/technicians, a dedicated PRRT nurse navigator, and nursing staff on our oncology fusion unit. The nurse navigator is primarily responsible for coordinating and managing the patient's care over the entire course of treatment. The nuclear medicine technologists complete calibrations, order appropriate doses and arrange shipping, complete tasks related to documentation, and establish intravenous access in preparation for the dose to be delivered. Lutathera is initiated by the nuclear radiologist assisted by the nuclear medicine technologists. The nurse navigator and nursing staff are trained to monitor patients for delayed reactions. Education materials were provided to the nuclear medicine and radiation staff, nurse navigator, and nursing staff on the oncology infusion units. This education included information about GEP-NETs; as low as reasonably achievable principles (ie, keeping radiation exposure "As Low As Reasonably Achievable"); radiation exposure from Lutathera; managing spills or other concerns; safety information; infusion set-up; potential adverse effects and drug interactions; treatment schedules; and roles and responsibilities.[16] Ongoing physician and staff education events are provided.

A literature search was conducted to identify published Lutathera treatment pathways as a starting point for developing pathways tailored for our institution.[17] The established multidisciplinary committee reviewed this literature and together developed a detailed patient flow chart across the continuum of care. Figure 1 outlines our center's patient pathway.

A PRRT patient resource guide was developed and included educational information about NETs; common imaging studies and laboratory tests; options for treatment (ie, surgery, chemotherapy, and radiation); education about PRRT; nutritional considerations; and additional resources, support groups, and contact information that patients may find helpful.

Overall, the process to establish the PRRT service line at our institution took approximately 6 to 8 months.

2.2. Lutathera treatment regimen

Our hospital follows the FDA recommended dose of Lutathera (ie, 7.4 Gbq (200mCi) given as 4 separate infusions every 8 weeks).[18] Patients are scheduled for an outpatient procedure and discharged at the end of the therapy. Patients receive a long-acting supportive octreotide (30 mg) intramuscularly between 4 and 24 hours after each Lutathera dose. A second dose of octreotide is administered 28 days after each Lutathera infusion. Octreotide is also administered by the medical oncologist or radiation oncologist midpoint between 2 Lutathera infusions.

2.3. Study methodology

A prospective registry study was established in order to collect clinical data regarding the treatment of primary GEP-NETs with Lutathera. Institutional review board approval was obtained (Aspire IRB, Inc., Santee, CA), and the need to obtain informed

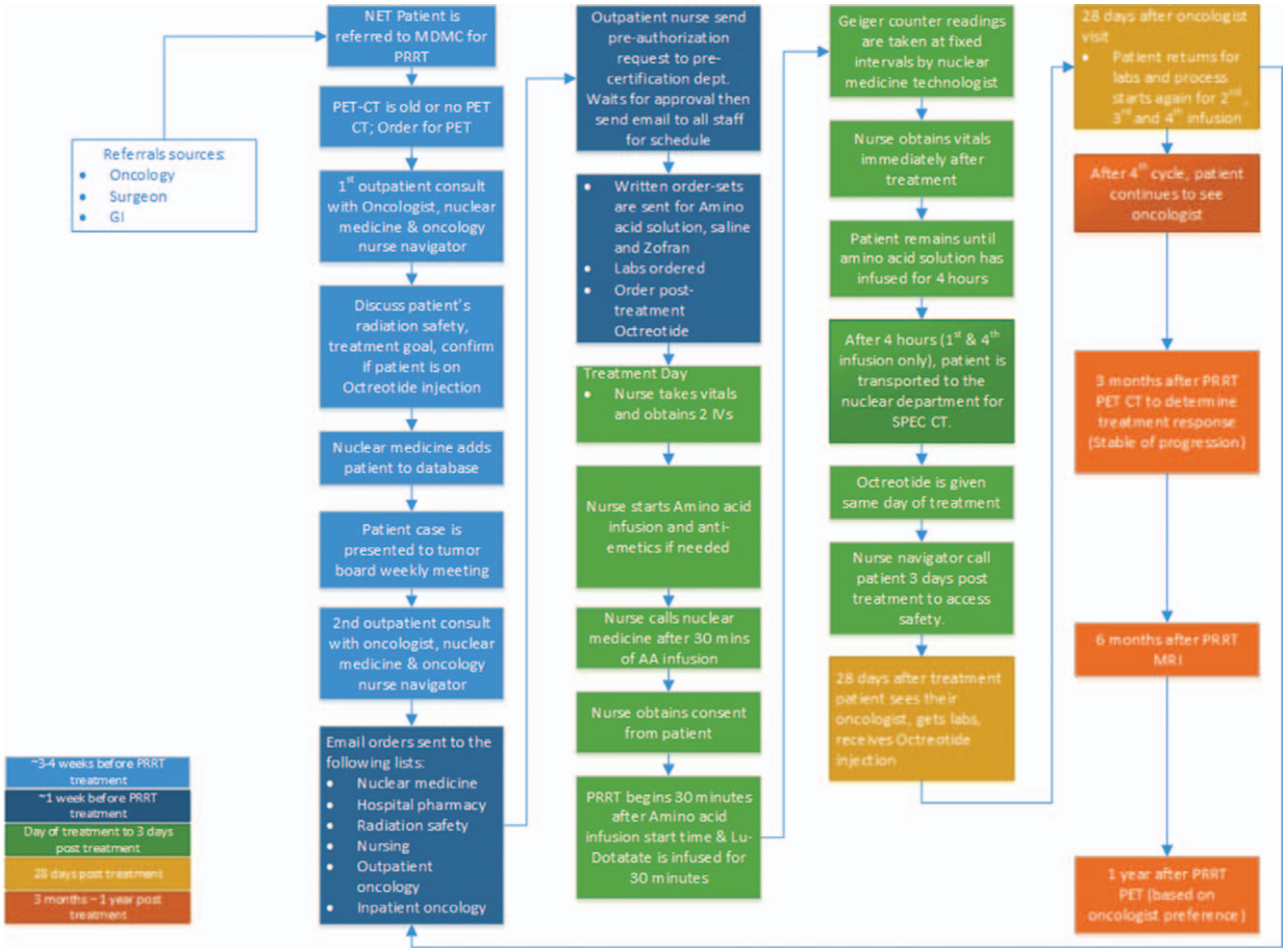

Figure 1. PRRT patient pathway. MRI = magnetic resonance imaging, PET/CT = positron emission tomography/computed tomography, PRRT = peptide receptor radionuclide therapy.

consents was waived. The waiver was approved because the research satisfied all 3 requirements for a waiver of authorization under 45 code of Federal Regulations 164.512. All data on patients who underwent treatment with Lutathera were collected from the electronic medical record and entered prospectively into a database. The clinical trial registration number is NCT04090034.

Basic patient demographics, history of prior treatment, primary tumor site, tumor characteristics, Ki-67 proliferation index (PI) before treatment, laboratory values [ie, creatinine (Cr), hemoglobin (HgB), white blood cell (WBC) count, platelet count, total bilirubin, estimated glomerular filtration rate] at each treatment interval, chromogranin A (CgA) pre- and post-treatment, Krenning score,[19] and adverse events (AEs) were collected and analyzed. GEP-NETs are graded according to Ki-67 PI: grade 1 (G1) <3%, grade 2 (G2) 3% to 20% and grade 3 (G3) >20%.[20] AEs were classified according to the common terminology criteria for adverse events version 5.0.[21] Briefly, AEs were classified as Grade 1 (mild), 2 (moderate), 3 (severe or medically significant but not immediately life threatening), 4 (life-threatening), or 5 (death related to AE). ^{68}Ga -DOTATATE positron emission tomography/computed tomography (PET/CT) imaging was performed according to the updated guidelines before the first cycle and 3 months after the fourth cycle of PRRT therapy.[22] Index lesion selection and measurement was based on response evaluation criteria in solid tumors (RECIST) 1.1 principles.[23] Treatment response (ie, partial, stable, progression, or unknown) was determined 3 months after the last cycle based on a qualitative assessment of PET/CT tumor characteristics of patients who tolerated 4 cycles.

2.4. Patients

The inclusion criteria for this study was all patients 18 years of age or older diagnosed with GEP primary NET who consented to undergo PRRT per their treating physician between August 2018 and July 2020. Other primaries were considered on a case by case basis if DOTATATE scan (+) and patient meets all other criteria:

- Metastatic or Locally Advanced AND Inoperable
- Clear disease progression on Octreotide over less than 3 years (RECIST 1.1)
- Presence of disease within 24 weeks as identified by PET/CT scans with Ga-68 DOTATATE reporting the Krenning score for low-grade NET and/or PET/CT scans with FDG for transformation to high-grade NET
- Ki-67 PI < 20%
- Octreotide positive on pathology (if not documented, acceptable if PET/CT imaging shows lesions with Ga-68 DOTATATE uptake Labs:

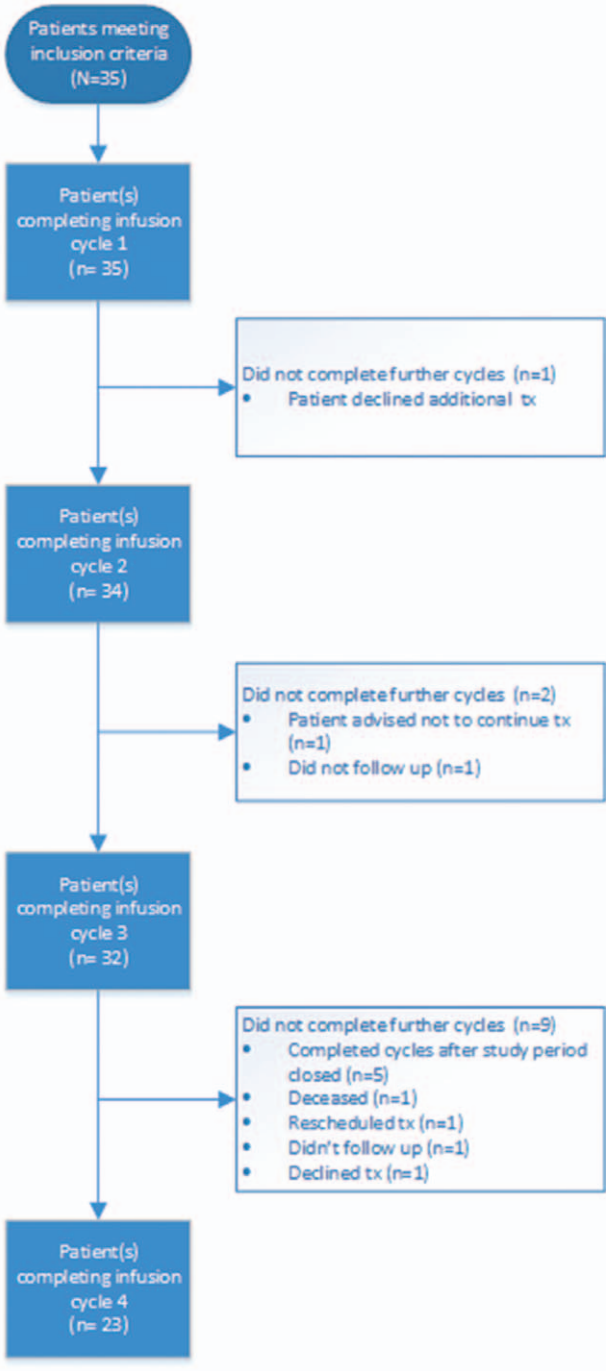

Figure 2. Patient flow diagram showing patients included/excluded at each stage of treatment.

- ^ Cr < 1.7
- ^ HgB > 8
- ^ WBC > 2K
- ^ Platelets > 75K
- ^ Bilirubin < 3× normal limit

• No Octreotide within 30 days of administration.

See Figure 2 for patient flow diagram of patients included/excluded at each stage of treatment. A total of 35 patients were included during this time period. The primary site tumors in the patients were gastrointestinal (42.9%), pancreas (25.7%), liver metastases from NET with unknown primary (11.4%), other metastases from NET with unknown primary (11.4%), and lung (8.57%).

2.5. Statistical analysis

All analyses were conducted using SAS v. 9.4 (SAS Institute Inc., Cary, NC). Descriptive statistics are reported as mean (standard deviation [range] for all continuous variables and as absolute (n) and relative frequencies (%) for categorical variables. A paired *t* test was used to evaluate differences in patients' laboratory values prior to treatment (baseline) and after the fourth cycle of treatment. Statistical significance was considered at $P < .05$.

3. Results

3.1. Patient demographics and tumor characteristics

Demographics, tumor characteristics, AEs, and preliminary treatment responses were collected on all patients (Tables 1–3). Twenty-one patients (60.0%) were female. The mean age was 68.69 (± 11.03) years (range 37–90 years) and the mean body mass index was 27.97 (± 6.44) kg/m^2 (range 18.20–53.50 kg/m^2) at initiation of treatment. Twenty-three patients (65.7%) received 4 complete cycles, 9 (25.7%) received 3 cycles, 2 (5.7%) received 2 cycles, and 1 (2.9%) received 1 cycle of PRRT (Fig. 2). At initiation of treatment, 13 patients (37.1%) had a Ki-67 PI < 3%,

Table 1

Patient demographics.

Parameter	Total (N = 35)
Gender, *n (%)*	
Female	21 (60.0)
Male	14 (40.0)
Race, *n (%)*	
Black	7 (20.0)
White	27 (77.1)
Other	1 (2.86)
Ethnicity, *n (%)*	
Hispanic	2 (5.7)
Not Hispanic	33 (94.3)
Insurance, *n (%)*	
Commercial	15 (42.9)
Medicare	19 (54.3)
Medicaid	1 (2.9)
Age at diagnosis (yr), *mean ± SD [min–max]*	61.94 ± 11.58 [25–86]
Age at initiation of treatment (yr), *mean ± SD [min–max]*	68.69 ± 11.03 [37–90]
BMI at initiation of treatment (kg/m^2), *mean ± SD [min–max]*	27.97 ± 6.44 [18.2–53.5]
Prior treatment (N = 34), *n (%)*	
Radioembolization	3 (8.8)
Resection	21 (61.8)
Somatostatin analogs	8 (23.5)
Chemotherapy	2 (5.88)
Primary tumor site, *n (%)*	
Gastrointestinal	15 (42.9)
Liver	4 (11.4)
Lung	3 (8.57)
Pancreas	9 (25.7)
Undefined	4 (11.4)

BMI = body mass index, max = maximum, min = minimum, SD = standard deviation.

Table 2

Tumor and treatment characteristics.

Ki-67 proliferation index (N = 26), *n (%)*	
<3%	13 (37.1)
3%–20%	13 (37.1)
Unknown	9 (25.7)
Ki-67 primary site or metastasis (N = 26), *n (%)*	
Primary biopsy site	10 (38.5)
Primary resection site	7 (26.9)
Metastatic biopsy site	5 (19.2)
Metastatic resection site	4 (15.4)
Site of specimen that generated Ki-67 (N = 26), *n (%)*	
Liver	10 (38.5)
Lung	1 (3.8)
Pancreas	7 (26.9)
Small intestine	6 (23.1)
Retroperitoneal lymph node	1 (3.8)
Breast	1 (3.8)
Number of cycles started/tolerated, *n (%)*	
1	1 (2.9)
2	2 (5.7)
3	9 (25.7)
4	23 (65.7)
Chromogranin A pretreatment (N = 25), *n (%)*	
<95	6 (24.0)
95–1000	13 (52.0)
>1000	6 (24.0)
Chromogranin A post-treatment (N = 3), *n (%)*	
<95	0
95–1000	2 (66.7)
>1000	1 (33.3)
Krenning score, *mean ± SD [min–max]*	4.09 ± 0.31 [4.00–5.00]

max = maximum, min = minimum, SD = standard deviation.

while 13 (37.1%) had a Ki-67 PI between 3% and 20%. Ki-67 PI data was not available for 9 (25.7%) patients. For the 26 patients that had Ki-67 assessed the primary sites that generated Ki-67-positive specimens were liver (38.5%), pancreas (26.9%), small intestine (23.1%), lung (3.8%), breast (3.8%), and retroperitoneal lymph node (3.8%). Most (97.1%) of our PRRT patients had prior treatments, including prior resection (61.8%), SSAs (23.5%), radioembolization (8.8%), and chemotherapy (5.9%). Prior treatment data was not available for 1 patient.

3.2. Treatment responses to PRRT

PET/CT imaging were done to determine treatment responses 3 months post-PRRT treatment. Only patients who completed 4 cycles (n = 23) were included. Five patients (21.7%) showed partial response, 10 patients (43.5 5%) showed stable disease, and 3 patients (13.0%) showed disease progression; the responses from 5 patients (21.7%) were unknown because no PET/CT scan was done.

Table 3

Tumor response and adverse events and initial treatment response.

PET tumor characteristics 3 mo post-PRRT of patients who tolerated 4 cycles (N = 23), *n (%)*	
Partial response	5 (21.7)
Stable disease	10 (43.5)
Progression	3 (13.0)
Unknown	5 (21.7)
Adverse events (N = 13), *n (%)*	
Grade 1	5 (38.5)
Grade 2	1 (7.7)
Grade 3	5 (38.5)
Grade 4	0 (0.0)
Grade 5	2 (15.4)

PET = positron emission tomograph, PRRT = peptide receptor radionuclide therapy.

CgA is a marker used in the diagnosis of NETs. Pre-treatment CgA levels were measured in 25 patients. Of the 25 patients, 6 (24.0%), 13 (52.0%), and 6 (24.0%) patients had pretreatment CgA blood level less than 95 ng/mL, between 95 and 1000 ng/mL, and greater than 1000 ng/mL, respectively. After all 4 PRRT cycles were completed; CgA levels were measured in 3 patients. Two (66.7%) patients had post-treatment CgA between 95 and 1000 ng/mL while 1 (33.3%) patient had levels above 1000 ng/mL.

A Krenning score is used to grade the uptake intensity of NETs, with a higher Krenning score indicating a higher predicted uptake of the targeted therapy. Krenning scores were available for 12 patients (34.3%) prior to treatment. Of those, 11 patients (91.7%) had a Krenning score of 4 and 1 patient (8.3%) had a score of 3.

A qualitative assessment of PET tumor characteristics at 3 months post-PRRT showed that 65% of the 23 patients that completed 4 cycles of treatment had either partial response (21.7%) or stable disease (43.5%), and that there was no evidence of disease progression 1 year after PRRT treatment in 1 patient.

AEs were graded using the common terminology criteria for adverse events system. AE was recorded for all patients PRRT regardless of the number of cycles completed. AE was recorded in 13 patients out of the entire 35 patients treated with PRRT. A grade 5 AE was reported in 2 patients (15.4%) and grade 3 AEs were reported in 5 patients (38.5%). Of the 5 grade 3 AE patients, 1 patient developed ascites, pleural effusion, and acute kidney injury; the second patient developed hematoma at the injection site and pain in the lower extremities; the third patient had shortness of breath, cough, and hemoptysis; the fourth patient had nausea, vomiting, and deep vein thrombosis; and the fifth patient developed obstructive jaundice. All 5 grade 3 AE patients were hospitalized and treated. One patient (7.7%) with a grade 2 AE developed an upper respiratory infection and required antibiotics. Five patients (38.5%) with grade 1 AEs had nausea, vomiting, abdominal pain, and/or diarrhea. No patients developed a grade 4 AE.

Laboratory values were collected prior to initiation of PRRT treatment and monitored after each treatment cycle (Table 4). Also, laboratory values in patients that completed all 4 PRRT cycles were compared to values before initiation of treatment and after the fourth PRRT cycle using the paired *t* test (Table 5). Only platelet counts showed a statistical significant decrease in the patients that completed all 4 PRRT cycles (269.44 ± 109.10 vs 167.00 ± 82.68, $P = .0292$), but there was no significant difference in Cr, WBC, HgB, total bilirubin, and estimated glomerular filtration rate levels.

4. Discussion

In August 2018, our institution administered the first Lutathera infusion. In 2 years, 35 GEP-NET patients were treated. Of those, 23 patients received all 4 cycles and of which, 65% either showed partial response or stable disease to Lutathera. Over the past 30 years, the incidence and prevalence of NETs have steadily increased and effective treatment methods are needed.[24] Various

Table 4

Laboratory values prior to treatment and after each PRRT cycle.

Laboratory test mean ± SD (min–max)	n	Prior to treatment (baseline)	n	Postcycle 1	n	Postcycle 2	n	Postcycle 3	n	Postcycle 4
Cr (mg/dL)	28	0.97±0.39 (0.33–1.94)	12	1.03±0.38 (0.40–1.80)	12	0.83±0.35 (0.31–1.50)	10	0.93±0.26 (0.56–1.30)	7	0.75±0.32 (0.20–1.20)
HgB (g/dL)	28	12.14±1.72 (6.10–15.00)	9	11.10±3.35 (3.5–14.90)	12	11.88±1.34 (9.60–13.70)	10	10.49±1.51 (8.50–13.50)	8	11.45±2.13 (8.90–15.30)
WBC ($\times 10^9$ cells/L)	27	6.11±1.81 (3.40–10.0)	12	6.21±2.12 (4.10–11.80)	12	5.45±3.61 (2.50–16.00)	10	4.27±1.64 (2.30–7.40)	8	5.31±1.86 (4.00–9.80)
Platelet count (cells/mL)	27	221.89±89.58 (93.00–449.00)	12	227.83±114.66 (125.00–521.00)	12	202.33±86.55 (92.00–346.00)	10	190.70±96.16 (51.00–334.00)	8	167.00±82.68 (66.00–326.00)
Total bilirubin (mg/dL)	27	0.60±0.42 (0.10–1.90)	11	0.41±0.12 (0.20–0.60)	12	0.59±0.43 (0.30–1.90)	11	0.59±0.44 (0.30–1.80)	8	0.69±0.41 (0.20–1.40)
eGFR (mL/min/1.73 m^2)	23	64.31±17.67 (35.0–105.0)	10	67.85±22.16 (33.90–112.00)	11	73.87±22.12 (55.00–114.00)	10	74.00±20.56 (60.00–111.00)	8	61.14±14.00 (49.20–94.00)

Cr = creatinine, eGFR = estimated glomerular filtration rate, HgB = hemoglobin, max = maximum, min = minimum, PRRT = peptide receptor radionuclide therapy, SD = standard deviation, WBC = white blood cell.

treatment options for patients with advanced GEP-NETs have been introduced in recent decades. In the 1980s, a short-acting SSA improved symptoms in 88% of NET patients. Supportive octreotide long-acting repeatable (LAR) SSAs were subsequently developed. Octreotide LARs are more convenient for patients as they are administered only once per month while maintaining efficacy.[25] A randomized study by Rinke et al[26] showed octreotide LARs significantly lengthened time to tumor progression compared with placebo in metastatic midgut NET patients. In the larger randomized controlled Lanreotide Antiproliferative Response in Neuroendocrine Tumors (CLARINET) study, Lanreotide was associated with significantly prolonged progression free survival (PFS) among metastatic GEP-NET patients with well-differentiated or moderately differentiated NET (Ki-67 PI < 10%).[27]

In 2017, results from the phase 3 Neuroendocrine Tumors Therapy (NETTER-1) trial were published.[28] Patients with well-differentiated metastatic midgut NETs received either Lutathera plus octreotide LAR (30 mg) or high-dose octreotide LAR (60 mg). At 20 months, 65% of patients in the Lutathera plus octreotide LAR (30 mg) group were living progression free and had a significant higher response rate than the high-dose octreotide LAR group. The researchers recently published their final results on overall survival (OS) between the 2 groups. Although treatment with Lutathera plus octreotide LAR (30 mg) did not significantly improve the median OS versus the controlled group, the median OS of 48 months in the treatment group institutes a new benchmark for survival in grade 1 or 2 GEP-NET.[29]

In this prospective study, data from 35 metastasized and previously treated NET patients was analyzed. A majority of our patients (65.7%) received all 4 infusions of Lutathera. Abou Jokh Casas et al[30] evaluated 36 patients with metastatic NETs treated with Lutathera, and the median age of their study's participants was 61 ± 12 years. In our study, the median age of the participants at the time of treatment was 69 ± 11 years and 5 patients (14.3%) were 80 years and above. Treatment patterns prior to PRRT and primary tumor sites in our study were similar to other studies[30,31] in that the majority of patients underwent prior resection and the most common primary tumor site was gastrointestinal.

Literature shows that the Ki-67 PI is an important tool for grading NETs and a strong predictor of OS.[32,33] A recent study demonstrated advanced metastasized NET patients treated with PRRT who had lower Ki-67 PIs had a prolonged PFS and OS.[34] Our analysis was a preliminary descriptive clinical investigation of the population treated and we did not evaluate PFS or OS. However, Baum et al[33] treated 1048 NET patients with Yttrium-90 or Lutathera and found longest OS and PFS in G1, followed by G2 and G3. Interestingly, shortest OS and PFS was observed in patients treated only with Yttrium-90. A multi-institutional registry study found similar results where G2 and G3 NETs had significantly worse OS than G1 NETs.[35] Patients with G2 NETs have also benefitted and responded well with Lutathera treatment. Ezziddin et al[11] treated 74 GEP-NET patients with Lutathera and found patients with Ki-67 PI > 10% had a long-term outcome with median PFS of 19 months. Another study learned a high Ki-67 PI was one of the risk factors to OS.[30] Ki-67

Table 5

Laboratory values prior to treatment and cycle 4 in patients that completed all 4 PRRT cycles.

Laboratory test mean ± SD [min–max]	n	Prior to treatment (baseline)	Postcycle 4	*P*-value (paired *t* test)
Cr (mg/dL)	7	0.87±0.32 (0.53–1.39)	0.75±0.32 (0.20–1.20)	.6274
HgB (g/dL)	7	12.4±1.17 (10.10–14.00)	11.45±2.13 (8.90–15.30)	.6209
WBC ($\times 10^9$ cells/L)	7	6.04±1.09 (4.10–7.40)	5.31±1.86 (4.00–9.80)	.3572
Platelet count (cells/mL)	7	269.44±109.10 (93.00–449.00)	167.00±82.68 (66.00–326.00)	.0292
Total cbilirubin (mg/dL)	6	0.60±0.23 (0.20–.90)	0.69±0.41 (0.20–1.40)	.4987
eGFR (mL/min/1.73 m^2)	7	68.47±22.29 (39.2–105.0)	61.14±14.00 (49.20–94.00)	.1422

Cr = creatinine, eGFR = estimated glomerular filtration rate, HgB = hemoglobin, max = maximum, min = minimum, PRRT = peptide receptor radionuclide therapy, SD = standard deviation, WBC = white blood cell.

PI is being increasingly recognized as a prognostic factor in patients with GEP-NET. Future studies examining the long-term effects of Lutathera in our study participants can determine if Ki-67 PI correlates with differences in PFS and OS.

Elevated CgA is a significant predictor of shorter survival in patients with midgut and pancreatic NETs.[36] CgA is also a reliable and circulating marker for diagnosis of GEP-NET, and a CgA level ≥95 ng/mL results in significantly shorter survival compared with patients with CgA <95 ng/mL.[37] In our study, 19 of 25 patients with pretreatment CgA measurements available had a CgA level of ≥95 ng/mL. Further studies will determine if these CgA levels correlate with survival in our study cohort.

Complete blood counts as well as renal and liver function tests were done after each PRRT cycle to monitor hematologic toxicity and side effects of the treatment. A salvage PRRT study found that WBC, erythrocyte, and platelet count decreased significantly in patients with metastasized NET after 4 PRRT cycles and after salvage PRRT compared to baseline.[31] Löser et al[38] found similar results in which WBC and platelet levels decreased in neuroendocrine neoplasia patients after PRRT treatment. In our study, we also observed a significant decrease in platelet levels after the last PRRT cycle, but the differences in other laboratory values were not significant.

Hope and colleagues found that ^{68}Ga -DOTATATE PET/CT resulted in higher Krenning scores than ^{111}In-pentetreotide single-photon emission computerized tomography (SPECT) for smaller lesions of 2 cm or less.[39] Our study found that of the 12 patients with Krenning scores available, that most had a score of 4, indicating that uptake of Lutathera by the patients' lesions was greater than that of the spleen.

A systematic review and meta-analysis by Zhang et al[4] showed that NETs characterized by either RECIST or Southwest Oncology Group criteria showed similar disease responses and disease control rates after treatment and concluded PRRT therapy was effective in patients with inoperable or metastatic NETs. Huizing et al[40] recently showed that 90.5% of patients with NETs characterized by the RECIST criteria in their study showed partial response or stable disease to PRRT at 3 months post-treatment. Similarly, our study showed that most patients had either a partial response or stable disease to Lutathera, indicating treatment efficacy.

Studies have shown side effects such as hemotoxicity and renal toxicity after PRRT treatment.[15,28,35] Abou Jokh Casas et al[30] saw acute side effects in 33% of patients in less than 24 hours after the administration of the first dose of ^{177}Lu PRRT. In our study, 1 patient was admitted to the hospital within 24 hours because of nausea, vomiting, abdominal pain, and deep vein thrombosis immediately after the fourth cycle. Two mortalities were observed after completion of 4 cycles and both of those patients had developed extensive liver metastases. However, most AEs during the course of our study were low grade (eg, nausea, vomiting or abdominal pain), putatively related to amino acid infusion or radiopeptide side effects.

The present study outlines our initial experience developing and implementing a PRRT program and treating GEP-NET patients referred to a nonuniversity tertiary hospital. The study does have some limitations and opportunities for improvement. It should be noted that all patients were treated at our facility and their eligibility for inclusion was confirmed by the treating physician, however, Ki67 PI values for 9 patients were missing from our analysis. This was due to the fact that these patients were treated solely or initiated by a physician associated with an outside facility, which prevented our access to their pathology reports at the time of data abstraction. Only 2 years of data are reported and the number of patients is limited. Longer-term data related to side effects, PFS, and OS of PRRT therapy is being collected prospectively. Additionally, we will soon begin collecting patient-reported outcomes of patients at regular intervals throughout and after treatment.

5. Conclusion

From our initial experience, Lutathera has been well tolerated in patients with GEP-NET. Additional studies are needed to examine long-term clinical and patient-reported outcomes associated with treatment of GEP-NETs as well as financial considerations for hospitals embarking on a PRRT program. A multidisciplinary team and complete collaboration between hospital administration and clinical teams are required for successful implementation of a PRRT program.

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