UNIVERSIDADE FEDERAL DO RIO DE JANEIRO
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PEPTIDE RECEPTOR RADIONUCLIDE THERAPY (PRRT) FOR NEUROENDOCRINE NEOPLASMS: REAL-WORLD OUTCOMES AND SAFETY PROFILE ACROSS DIVERSE SITES IN BRAZIL

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Trabalho de Conclusão de Curso apresentado ao Serviço de Oncologia Clinica da Universidade Federal do Rio de Janeiro, como parte dos requisites para a obtenção do título de Oncologia Clinica.

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SUMMARY

1. ABSTRACT

OBJECTIVE:

Peptide receptor radionuclide therapy (PRRT) has established itself as a pivotal first-line treatment option for gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs). The first approval was based on the NETTER-1 trial focusing on midgut neuroendocrine tumors and, more recently, therapeutic indications have been expanded with the publication of NETTER-2 trial. Despite these limited approvals the clinical application extends to various neuroendocrine neoplasms (NEN) types. This study presents real-world outcomes and implementation data from four tertiary treatment centers in Brazil, highlighting the safety profile of PRRT across different NEN sites.

METHODS:

A retrospective analysis encompassing January 2007 to January 2021 was conducted across four Brazilian hospitals, involving 173 histologically confirmed NEN patients treated with 177Lu-dotatate PRRT. Clinician-evaluated data encompassed demographics, efficacy, and toxicity.

RESULTS:

Of the 171 patients (89 female- 52%), the median number of 177Lu-dotatate treatments was four (range 1-8). Tumor localization included 77% GEP-NENs, 42% midgut NENs, 7% lung and 10% other sites (breast, prostate, adrenal, ovary, cervix, paraganglioma, kidney, neuroblastoma, thymus, gallbladder, thyroid). Notably, most common significant toxicities (G3/G4) were renal- 5 patients- and

hematological - 6 patients. The majority of the treated patients (48%) had partial response.

CONCLUSIONS:

We observed an important utilization in non-midgut sites, such as pancreas and foregut. Despite this, PRRT exhibited a significantly low incidence of treatment-related toxicity in our cohort, establishing its safety with minimal hematological and renal effects. Real-world utilization of PRRT includes patients with varying disease stages, prior treatments, and a safety profile in response to therapy.

KEY WORDS**:** Peptide Receptor Radionuclide Therapy (PRRT)/ Neuroendocrine neoplasms (NENs) / Somatostatin receptor/ Treatment effectiveness/ Gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs)

INTRODUCTION

Neuroendocrine neoplasms (NENs) are rare group of neoplasms generally divided in two different subgroups and prognosis that can be distinguished as neuroendocrine neoplasms (NENs) and neuroendocrine carcinomas (NECs). They are currently classified according to the updated 2022 WHO Classification of Endocrine and Neuroendocrine Tumors (1) The prognostic is influenced by several factors such as proliferative index (Ki-67), TNM stage and secretory status – these neoplasms may secrete hormones and therefore can be functional or non-functional. NENs originate from the neuroendocrine system and may occur in different primary sites such as gastrointestinal (most common type), pancreas, lungs, prostate and biliary tract.

The majority of NENs (90%), particularly in well differentiated, have high density expression somatostatin receptors (SSTRs) on their cell surface- usually

SSTR2 and SSTR5. These receptors combined with radionuclides are the basis of theranostic therapy that allows both diagnosis and treatment of the pathology. (2) Advances such as 68Ga-DOTA PET-CT coupled with advances and greater access in endoscopy and peptide receptor radionuclide therapy (PRRT) have changed the diagnostic and therapeutic landscape for NENs. (3)

Surgery is the treatment of choice for local or locoregional disease in NENs. For unresectable/metastatic low-grade tumors, first-line treatment with somatostatin analogues (SSAs) are an established anti proliferative therapy based on two placebo-controlled phase 3 trials: PROMID and CLARINET. They use respectively Octreotide LAR and Lanreotide with modest activity in the first line scenario.(4,5)

Patients who have had disease progression during first-line SSA therapy had limited therapeutic options for control of both hormonal secretion and tumor growth. There is limited data on higher dose or more frequent administration of SSAs and the slow growth of most of these tumors leads to very low response rates using conventional cancer therapies including cytotoxic chemotherapy and radiotherapy that rely on actively proliferating cells. Therapies with mTOR Everolimus and Tyrosine kinase inhibitors such as sunitinib were studied in phase 3 trials as second line treatment with similar median progression free survival (PFS) but different toxicity profiles.(6)

In this scenario, it stands out PRRT, a target therapeutic strategy that provides a means of delivering cytotoxic levels of radiation with a high therapeutic index to tumors that express specific receptors. This targeted form of systemic radiotherapy allows the delivery of radionuclides directly to tumor cells.(7) PRRT with radiolabeled somatostatin analogs has proven to be an option that resulted in longer progression-free survival and a higher response rate than previously established second line treatment therapies. (8)

The first-line treatment options with PRRT for patients with NENs was the subject of Neuroendocrine Tumors Therapy (NETTER) trials, with unprecedented response rates. Both NETTER 1(9) and NETTER 2(10) were randomized controlled trials conducted in developed countries, mostly in the United States and Europe. NETTER 1 included progressive G1 and G2 midgut NENs that expresses SSTR on

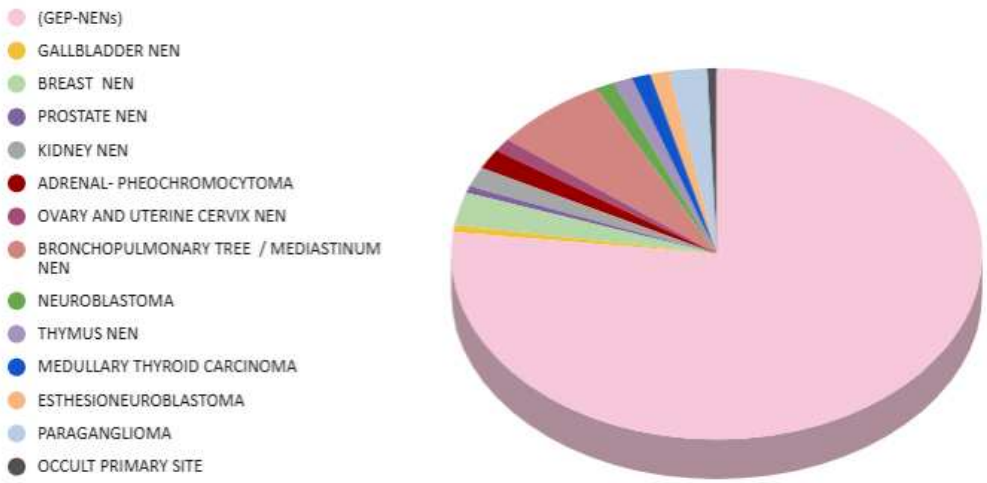
the cell surface, and it has reported superior PFS of 177 Lu-Dotatate plus octreotide 30mg LAR compared to high dose octreotide 60mg LAR- 28.4months vs 8.5 months- HR 0.21(0.14-A.33), becoming the new standard treatment in this scenario. NETTER 2 evaluated radioligand therapy (RLT) as first line treatment in G2 or G3 advanced tumors SSTR positive gastroenteropancreatic neuroendocrine tumors (GEP-NENs). The primary endpoint was PFS, that increased from 8.5 months in the high dose octreotide arm to 22.8 months in the 177Lu-DOTATATE arm.

Although these clinical trials provided essential information, they have strict inclusion criteria and may not fully represent the diverse patient population encountered in real-world settings. In everyday clinical practice patients with varying characteristics, comorbidities, and treatment histories are encountered, and they offer a more comprehensive understanding of PRRT's effectiveness and safety. The use of 177 Lu PRRT in non-GEP NEN scenarios is less robust. (11) Our aim is to present real-world outcomes and implementation data from four tertiary treatment centers in Brazil, highlighting the safety profile of PRRT across different NEN sites.

2. PATIENTS AND METHODS

A retrospective analysis encompassing January 2007 to January 2021 was conducted across four reference institutions in Brazil for PRRT, involving 181 patients, 173 with histologically confirmed advanced NENs (from this group, we excluded two children aged 5 and 9 who were diagnosed with ne uroblastoma) and other 8 with different histologies(4 papillary thyroid tumor, 1 follicular thyroid tumor, 1 pituitary adenoma, 1 prostatic adenocarcinoma and1 clear cell renal carcinoma) also excluded from the analysis. (Figure 1).

Figure 1. Distribution of patients included in the study by primary site of disease



Source: Authorship.

The inclusion criteria were inoperable, advanced, progressive and somatostatin-receptor-positive neuroendocrine neoplasms with ^{99m}Tc -Octretate or ^{68}Ga-DOTATATE PET-generated Krenning score (12) that progressed first line treatment. Characteristics such as prevalence between gender, age, histological type, primary site, presence of metastases and main sites of involvement, number of cycles required, response to treatment and main toxicities were evaluated. Unfortunately, follow-up was lost for several patients, making it impossible to analyze outcomes and death.

The exclusion criteria were contraindications for the procedure such as: pregnancy and breastfeeding, renal insufficiency (creatinine clearance < 40-50 ml/min), affected hematological function (Hg <8g/dl; platelets < 75,000; Leucocytes < 2,000), severe hepatic impairment (total bilirubin > 3X over the upper limit of normal or alb. <30 g/l and increased prothrombin time and severe heart failure.

It was infused intravenously 7.4 GBq (200 mCi) of 177Lu-Dotatate over a period of 30 minutes. Patients received one to eight infusions every 8 weeks unless unacceptable toxic effects occurred, confirmed disease progression was present on imaging, the patient was unable or unwilling to adhere to trial procedures or the patient died. For renal protection, an intravenous amino acid solution (21.0 g of lysine and 20.4 g of arginine in 1 liter of solution) was administered concomitantly for at

least 4 hours, starting 30 minutes before infusion of the radiopharmaceutical. Patients continued to receive supportive care with octreotide LAR accordingly to symptoms or physician choice. Preparation for the procedure included discontinuation of subcutaneous octreotide 24 hours before admission or discontinue long-acting octreotide (LAR) 6 weeks prior to admission.

Response was evaluated according to Response Evaluation Criteria in Solid Tumors [RECIST], version 1.1 on either computed tomography (CT) or magnetic resonance imaging (MRI). Original research was evaluated and approved by Ethical Research Committee of Hospital Pró-Cardiaco on October 05, 2017, and approved under number 2.315.864. The ethics research committee of the other institutions also approved the research protocol.

3. RESULTS

A total of 171 patients were included in analysis, with a mean age of 56 years in general. Of these, 52% were female, and the majority (n=133; 77%) had GEP-NENs while 46% had midgut tumors (Figure 1). Among the 148 patients with a confirmed grade, 18% were classified as G1, 56% as G2, and 12% as G3. The PRRT treatment consisted of 1-8 doses (median of 4 doses) of 200 mCi of 177Lu-dotatate, with an average hospitalization duration of 24 hours per cycle and intervals ranging from eight to twelve weeks between each cycle.

The liver was the most common site of distant metastasis (71%), followed by lymph nodes (55%) and bone (18%). Regarding treatment response, 3% of patients had a complete response, 48% had a partial response, 28% had stable disease, and 13% experienced disease progression. Additionally, 8% of patients were lost to follow-up. Table 1 depicts the PRRT treatment response according to the different institutions.

Table 1: Response to PRRT treatment in each institution: A, B, C and D. PRRT: Peptide receptor radionuclide therapy.

Response to PRRT	A (n=25)	B (n=69)	C (n=60)	D (n=17)	Total (n=171)
Complete Response	0	3	2	0	5 (3%)
Partial Response	13	29	30	11	83 (48%)
Stable Disease	2	19	24	3	48 (28%)
Disease Progression	2	13	4	3	22 (13%)
Loss to Follow-Up	8	5	0	0	13 (8%)

Source: Authorship.

During the treatment cycles, there were 23 cases (12%) of treatment-related adverse events. The most common were hematological issues, majority G1 toxicity (n=13) and renal toxicity (n=5), followed by bone and abdominal pain – those not always related to the treatment(n=4). Only 3 cases were reported as grade ≥ G3. Treatment plans were adapted to optimize efficacy while minimizing adverse effects

4. DISCUSSION

Our study demonstrated the experience in reference centers for the treatment of advanced, progressive somatostatin-receptor-positive neuroendocrine neoplasms patients with 177Lu-dotatate in Brazil within a real-world scenario. The patients presented a diversity of types of neoplasms, including non-neuroendocrine tumors- those were taken from our analysis due to the lack of studies supporting its use.

The baseline clinical characteristics of our patients were comparable to those observed in the NETTER 1 and NETTER 2 trials: a similar average age and gender ratio. Specifically, 52% were women and 48% were men, with an average age of 59 years for patients with GEPNENS and 61 years for Midgut NENs patients. The

majority of primary tumor sites were small intestine and prevalent sites of metastases were also quite similar, including the liver, lymph nodes, and bones.

Tumor grade was also evaluated: 56% had G2 tumors. Unfortunately, around 14% of our patients had an unknown grade. The nuclear antigen Ki-67 is a marker of the proliferation activity of these neoplasms and this classification is essential for treatment selection and prognostication(1).

The response in most patients was favorable – 51% presented with complete or partial response. This indicates a higher response rate compared to the pivotal studies: 43% in NETTER 2 and 18% in NETTER 1.(10)(9). In the non-GEPNEN tumors group, we observed a 6% complete response, 36% partial response, 40% stable disease, and 18% progression, inferior results compared to the overall group.

Another important parameter we evaluated was treatment toxicity, with special interest adverse event being renal (3%) and hematological (5%). It was observed that 8% rate of serious toxicities was observed related to the use of lutetium (vs 9% NETTER 1 and 5% in NETTER 2) with only two cases reported in the non-GEPNENS (kidney and bronchopulmonary tree)

Bone marrow involvement is generally the cause of dose limiting in all patients treated with 177Lu-dotatate PRRT. Patients with extensive skeletal metastases, reduced kidney function, large tumor volume and advanced age are at higher risk of grade 3/4 BM suppression.(13) On the other hand, deterioration in kidney function has been linked to the retention of radiopeptides in radiosensitive glomeruli as a result from cumulative high radiation exposure. The incidence of renal toxicity has reduced with the co-infusion amino acids which inhibit the reabsorption of radiopeptide, reducing renal radiation dose.(11) In general, the toxicity found was low and the treatment quite well tolerated.

By observing outcomes in patients with different tumor types, grades, and Ki-67 indices, treatment plans can be adapted to optimize efficacy while minimizing adverse effects, such as hematologic and renal toxicities. Understanding how PRRT

performs in other sites then guides personalized therapeutic choices and improves patient outcomes.

5. CONCLUSIONS

Clinical trials offer crucial information to the safety and effectiveness needed for the approval of new therapies, but they often impose strict inclusion criteria that may not fully reflect the diversity of the patient population seen in practical healthcare settings. Real-world data encompass a broader spectrum of patients, reflecting their diverse characteristics with varying disease stages, prior treatments, and individual responses to therapy.

In practice, this data highlights challenges, such as patient adherence and resource availability providing a more comprehensive understanding of PRRT's true effectiveness and safety allowing a personalized therapeutic choice and improving patient outcomes.

6. REFERENCES

1. Rindi G, Mete O, Uccella S, Basturk O, La Rosa S, Brosens LAA, et al. Overview of the **2022 WHO Classification of Neuroendocrine Neoplasms**. Vol. 33, Endocrine Pathology. Springer; 2022. p. 115–54

2. Burkett BJ, Bartlett DJ, McGarrah PW, Lewis AR, Johnson DR, Berberoğlu K, et al. **A Review of Theranostics: Perspectives on Emerging Approaches and Clinical Advancements**. Vol. 5, Radiology: Imaging Cancer. Radiological Society of North America Inc.; 2023

3. Panzuto F, Partelli S, Campana D, de Braud F, Spada F, Cives M, et al. **Epidemiology of gastroenteropancreatic neuroendocrine neoplasms: a review and protocol presentation for bridging tumor registry data with the Italian association for neuroendocrine tumors (Itanet) national database.** Vol. 84, Endocrine. Springer; 2024. p. 42–7

4. Rinke A, Müller HH, Schade-Brittinger C, Klose KJ, Barth P, Wied M, et al**. Placebo-Controlled, Double-Blind, Prospective, Randomized Study on the Effect of Octreotide LAR in the Control of Tumor Growth in Patients With Metastatic Neuroendocrine Midgut Tumors: A Report From the PROMID Study Group**. Journal of Clinical Oncology. 2009 Oct 1;27(28):4656–63

5. Caplin ME, Pavel M, Ćwikła JB, Phan AT, Raderer M, Sedláčková E, et al. **Lanreotide in Metastatic Enteropancreatic Neuroendocrine Tumors**. New England Journal of Medicine. 2014 Jul 17;371(3):224–33

6. Yao JC, Shah MH, Lombard Bohas C, Wolin EM, Cutsem V, Hobday TJ, et al. **Everolimus for Advanced Pancreatic Neuroendocrine Tumors**. Vol. 364, N Engl J Med. 2011

7. Merola E, Grana CM**. Peptide Receptor Radionuclide Therapy (PRRT): Innovations and Improvements**. Vol. 15, Cancers. MDPI; 2023

8. Riechelmann RP, Taboada RG, de Jesus VHF, Iglesia M, Trikalinos NA. **Therapy Sequencing in Patients With Advanced Neuroendocrine Neoplasms**. American Society of Clinical Oncology Educational Book. 2023 May;(43)

9. Strosberg J, El-Haddad G, Wolin E, Hendifar A, Yao J, Chasen B, et al. **Phase 3 Trial of 177 Lu-Dotatate for Midgut Neuroendocrine Tumors .** New England Journal of Medicine. 2017 Jan 12;376(2):125–35

10. Singh S, Halperin D, Myrehaug S, Herrmann K, Pavel M, Kunz PL, et al. **[177Lu]Lu-DOTA-TATE plus long-acting octreotide versus high-dose long-acting octreotide for the treatment of newly diagnosed, advanced grade 2–3, well-differentiated, gastroenteropancreatic neuroendocrine tumours (NETTER-2): an open-label, randomised, phase 3 study.** The Lancet [Internet]. 2024 Jun; Available from: https://linkinghub.elsevier.com/retrieve/pii/S0140673624007013

11. Navalkissoor S, Toumpanakis C, Caplin M, Gnanasegaran G. **Treatment of neuroendocrine tumours with 177Lu-peptide receptor radionuclide therapy: Challenging clinical scenarios and their management**. Vol. 34, Journal of Neuroendocrinology. John Wiley and Sons Inc; 2022

12. Metser U, Eshet Y, Ortega C, Veit-Haibach P, Liu A, K.s. Wong R. **The association between lesion tracer uptake on 68Ga-DOTATATE PET with morphological response to 177Lu-DOTATATE therapy in patients with progressive metastatic neuroendocrine tumors**. Nucl Med Commun. 2022 Jan 1;43(1):73–7

13. Bergsma H, Konijnenberg MW, Kam BLR, Teunissen JJM, Kooij PP, de Herder WW, et al. **Subacute haematotoxicity after PRRT with 177Lu-DOTA-octreotate: prognostic factors, incidence and course**. Eur J Nucl Med Mol Imaging. 2016 Mar 1;43(3):453–63