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Theranostics Study of Neuroendocrine Tumors

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Abstract:
Theranostics is the association of a diagnostic imaging technique plus a treatment, having in common a single agent. Regarding neuroendocrine tumors, Ga-DOTATE PET/CT, treatment with LuOctreotate make up the theranostic set and all of them have in common the somatostatin analogues labeled with radioactive isotopes. We reported a series of 43 consecutive patients with advanced neuroendocrine tumors who underwent treatment with LuOctreotate after selection by Ga-DOTATE PET/CT or Octreoscan. The theranostic allowed good oncological results and low toxicity.

Key words:
Introduction,Objectives,Methods,Results,Discussion,Conclusion,Reference.

I. Introduction:

The term “theranostic” is the combination of the words “therapy” and “diagnosis”. It has been used to refer to agents or techniques that integrate diagnostic imaging and targeted therapy. This integration is in line with the concept of precision medicine, which assumes better oncological outcomes by offering a specific treatment for each subtype of cancer [1].Neuroendocrine tumors overexpress somatostatin receptors in their cell membranes, especially the subtype 2. This characteristic allows the use of somatostatin analogues labeled with radioisotopes for diagnostic or therapeutic purposes.In the field of imaging diagnosis, Octreotide labeled with the radioisotope 111-Indium has been used for a long time for the diagnosis of neuroendocrine tumors by means of scintigraphy. This technique became popular under the trade name Octreoscan.

Recently, radiopharmaceuticals labeled with -Gallium have been developed, which allow images using the positron emission tomography (PET) technique. In Brazil, Ga-DOTATE has been the most used marker for PET/CT studies with the purpose of diagnosing and staging neuroendocrine tumors. DOTATE, also known as octreotate, is a peptide with high affinity for somatostatin receptors [1].This same molecule can be labeled with beta radiation emitting radioisotopes, which have short range and high energy, with the aim of bringing ionizing radiation into close contact with the neoplastic cell. As a result, a highly specific “radiotherapy” directed to the tumor cell is obtained, preventing radiation from passing through other organs and tissues to reach the target, minimizing unwanted toxic effects and optimizing cytotoxic effects.

Currently, DOTATE labeled with Lutetium is the most studied radiopharmaceutical with better results in the treatment of well-differentiated neuroendocrine carcinomas. The NETTER-1 study was a prospective randomized controlled trial in a population with advanced midgut neuroendocrine tumors. It showed an objective response rate of 18% in the group of patients treated with Luoctreotate against 3% in the control group (octreotide-LAR only). Progression-free survival was higher in patients who were treated with Luoctreotate [2], but there was no difference in overall survival [3]. Luoctreotate treatment alsob provides a better quality of life [4].Despite the pivotal study mentioned above being exclusive to patients with midgut neuroendocrine tumors, other studies have evaluated the efficacy and safety of this treatment in pulmonary and pancreatic neuroendocrine tumors, and even in populations with WHO histological grade 3 tumors [5-8]. To date, we are not aware of publications with real-life data on the Brazilian population undergoing this treatment.

In summary, Octreoscan or Ga-DOTATE PET/CT in conjunction with Luoctreotate treatment make up the theranostic of neuroendocrine tumors. These imaging diagnostic and treatment techniques have in

common the somatostatin analogue peptide and are mainly aimed to well-differentiated neuroendocrine tumors with Ki-67 ≤ 20% [9].Neuroendocrine tumors (NETs) are a diverse group of neoplasms arising from cells of the neuroendocrine system, which combines features of nerve cells and hormone-producing endocrine cells. These tumors can occur throughout the body, most commonly in the gastrointestinal tract, pancreas, and lungs. The understanding of neuroendocrine tumors has evolved, and the prevailing theories provide insight into their origin, development, and clinical manifestations.[4]One theory regarding the pathogenesis of neuroendocrine tumors suggests that they arise from neuroendocrine cells that undergo neoplastic transformation. Neuroendocrine cells play a crucial role in the regulation of various physiological processes, including hormone secretion and neurotransmitter release. Genetic mutations or alterations in these cells can lead to uncontrolled growth, giving rise to tumors. Studies have identified specific genetic mutations, such as in the MEN1, RET, and VHL genes, which are associated with the development of neuroendocrine tumors. These mutations can disrupt normal cellular processes, leading to uncontrolled cell division and tumor formation.[12]Another theory explores the role of environmental factors in the development of neuroendocrine tumors. Exposure to certain carcinogens or toxins may contribute to the initiation and progression of these tumors. For example, in the case of lung neuroendocrine tumors, tobacco smoke has been identified as a significant risk factor. Additionally, chronic inflammation and other environmental stressors may create a microenvironment conducive to the development of these tumors.[23]The concept of neuroendocrine differentiation in other, non-neuroendocrine tumors has also been proposed as a theory. Some tumors that do not originate from classic neuroendocrine cells may exhibit neuroendocrine features. This phenomenon, known as neuroendocrine differentiation, suggests that tumors can acquire neuroendocrine characteristics during their development. The presence of neuroendocrine markers in these tumors may influence their behavior and response to treatment, adding complexity to their classification and management.[19]Clinically, neuroendocrine tumors are characterized by their ability to produce hormones, leading to distinct syndromes with hormonal hypersecretion. However, not all neuroendocrine tumors exhibit hormonal activity, and some may remain asymptomatic until they reach an advanced stage. The clinical manifestations and prognosis of neuroendocrine tumors vary widely, emphasizing the need for a comprehensive understanding of their underlying biology.[18]

4.Objectives:

To evaluate clinical and epidemiological data, as well as data on the effectiveness and safety of the treatment with Luoctreotate in patients with neuroendocrine tumors who were treated at the Instituto de Oncologia do Hospital Santa Paula – DASA (IOSP-DASA), from November 2016 to February 2022.

Theranostics refers to a medical approach that combines diagnostics and therapeutics. In the context of neuroendocrine tumors (NETs), theranostics involves using diagnostic techniques to identify specific biomarkers or receptors on the tumor cells and then delivering targeted therapeutic agents to those cells. This approach allows for a more personalized and effective treatment strategy.[All Article Including]

Here are some key aspects of theranostics in neuroendocrine tumors:

4.1.Diagnostic Imaging:

4.1.1.Somatostatin Receptor Imaging (SRI): Many neuroendocrine tumors express somatostatin receptors on their cell surfaces. Somatostatin analogs labeled with radioisotopes (e.g., Gallium-68 or Indium-111) can be used for imaging through positron emission tomography (PET) or single-photon emission computed tomography (SPECT). This helps locate and visualize the tumors.

4.2.Targeted Radioisotope Therapy:

4.2.1.Peptide Receptor Radionuclide Therapy (PRRT): Once the tumors are identified using somatostatin receptor imaging, therapeutic agents like radioisotopes (e.g., Lutetium-177 or Yttrium-90) can be attached to somatostatin analogs. These radiolabeled compounds specifically target and deliver radiation to the neuroendocrine tumor cells, causing localized damage and cell death.

4.3.Therapeutic Agents:

4.3.1.Somatostatin Analogues: Drugs like octreotide and lanreotide, which mimic the action of somatostatin, are often used for symptom control in NETs.

4.3.2Targeted Therapies: Molecularly targeted drugs, such as everolimus and sunitinib, may be employed to inhibit specific pathways involved in tumor growth.

4.5.Patient Selection:

Not all neuroendocrine tumors express the same receptors or respond equally to theranostic

approaches. Patient selection is crucial, and molecular profiling of tumors helps determine the most suitable treatment strategy.

4.6.Benefits:

Theranostics in NETs offers a more personalized treatment approach, potentially minimizing side effects and improving treatment outcomes.It allows for real-time monitoring of treatment response, enabling adjustments to the therapeutic plan based on individual patient responses.

4.7.Challenges:

Limited availability of radiolabeled compounds and specialized imaging facilities.

Not all patients may be eligible for or benefit from theranostic approaches.

5.Methods:

This is a retrospective study and it was approved by our local research ethics committee. We report here 43 patients with advanced neuroendocrine tumors who were treated consecutively with Luoctreotate. The selection of patients for this treatment, was done through a Ga-DOTATE PET/CT or Octreoscan. The patients clinical and epidemiological characteristics are presented through descriptive statistics. Continuous variables were expressed as means, medians, standard deviations and minimum and maximum values. Categorical variables were expressed as absolute and relative frequencies.Response assessment was performed using RECIST criteria (stable disease, partial response, complete response, or disease progression), when conventional imaging methods were used or by metabolic response, when nuclear medicine methods were used to assess response (Octreoscan or Ga-DOTATE PET/CT). Statistical analyzes were performed using MedCalc software version 11.3.1.0.[Methods Testing software]

6.Results:

From November 2016 to February 2022, 43 patients with advanced neuroendocrine tumors were treated with Luoctreotate at IOSP-DASA of whom 23 were women (53%) and 20 were men (47%). The mean age was 57.4 years, ranging from 25-81 years-old.The most common primary sites of neoplasia were pancreas (60%), small intestine (16%) and liver (9%).[New]

Regarding the Ki-67 index, it was possible to evaluate it in 62% of the group (27/43 patients), most of them being between 3-20% (49%).Regarding the previous systemic treatments, information was obtained in 38 out of 43 patients and, in 36% of these (14 out of 38 patients), other therapies beyond somatostatin analogue were used. The most common previous treatment were everolimus (50%), cisplatin/etoposide (35%), capecitabine/temozolamide(21%) and capecitabine/oxaliplatin (21%).

The table 1 below summarizes the main clinical and demographic characteristics of the treated patients.The mean time from disease diagnosis to treatment with Luoctreotate was 4.5 years, ranging from 1-22 years.We could assess treatment response in 27 out of 43 patients treated, and 85% of these (23/27 patients) had disease control (stable disease, partial response or complete response).Below, the figure 1 shows an example of excellent treatment response.

Table1Clinicalanddemographiccharacteristics(n= 43).

Characteristics	N	Proportion
Gender		
Female	23	53%
Male	20	47%
Meanage57.4years(25-81years)		
Primarytumorsite		
Pancreas	26	60%
Smallintestine	7	16%
Liver	4	9%
Lung	2	5%
Unknown	2	5%
Ovary	1	2.5%

Rectum	1	2.5%
Ki-67index		
<3%	3	7 %
3-20%	21	49%
>20%	3	7%
Not available	16	37%
Previoussystemictreatment(beyondSSA)		
Yes	14	32%
No	24	56%
Not available	5	12%
Previoussystemictreatments(beyondSSA)		
Everolimus	7	50%
Cisplatin/Etoposide	5	35%
Capecitabine/Oxaliplatin	3	21%
Capecitabine/Temozolamide	3	21%
Cisplatin/Irinotecan	2	14%
Sunitinib	1	7%

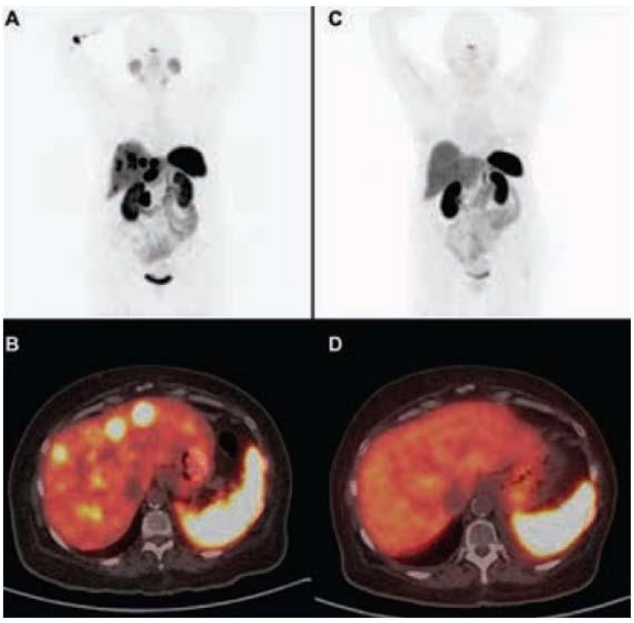

Fig. 1 Example of a patient with complete metabolic response. Whole-body PET image performed before Luoctreotate treatment

- shows intense uptake of Ga-DOTATE by liver metastases and by the primary pancreatic tumor.
- (A)After treatment, the liver metastases and the primary tumor disappeared.
- (B) disappeared after treatment.
- (C)PET-CT axial sections show that liver metastases present before treatment.
- (D).It was not possible to perform progression-free survival or overall survival analysis in our sample because many patients were lost to follow-up after treatment with Luoctreotate. Regarding treatment toxicities, no patient had grade 3 or 4 toxicities. No patient discontinued treatment due to toxicity. The most observed adverse effects were haematological, fatigue and gastrointestinal.

Table 2 summarizes the adverse events in order of frequency.

Table2 Treatment toxicities.

Adversereactionsduringtreatment	Percentage
Anemia	42%
Thrombocytopenia	33%
Fatigue	30%
Nausea/vomiting;Leukopenia	26%
Diarrhea	9%
Anorexia; Abdominal pain	7%
Alopecia	5%

II. Discussion:

This is a retrospective study that presents real-life data on a Brazilian population with advanced neuroendocrine tumors that were selected, through Octreoscan® or Ga-DOTATE PET/CT, for targeted therapy with Luoctreotate. As previously mentioned, we are not aware of a publication prior to ours with data on treatment in an exclusively Brazilian population.The profile of patients in our study is in line with that previously reported in the literature, which means no predominance of the disease by sex and most common primmary sites being pancreas and digestive tract, followed by bronchopulmonary tumors [10, 11].As this was a retrospective study, the Ki-67 index was not available in the medical records of 37% of the patients and this is one of the limitations of this study design. As expected, since patients were selected for treatment according to somatostatin receptor expression by imaging methods, there was a predominance of well-differentiated tumors, probably WHO grades 1 or 2.In our sample, there was a predominance of patients who were not heavily pretreated (beyond somatostatin analogues). This is probably justified by the adequate Indication and use of imaging methods in the selection of patients for treatment. Such therapy, as previously discussed, as it is directed to cells expressing somatostatin receptors (SSR), spares patients from more intense toxicities such as those experienced by individuals undergoing cytotoxic chemotherapy. According to NCCN guidelines, the Peptide Receptor Radionuclide Therapy (PRRT) with Luoctreotate is recommended in patients with advanced disease who have symptomatic disease, clinically significant tumor burden, or clinically significant progressive disease, and disease progression with positive SSR imaging [12].Regarding efficacy data, we observed that the disease control rate in our population was very similar to previous reports in the literature [2, 6, 8]. Unfortunately, we were unable to obtain progression-free survival and overall survival data due to the large amount of loss to follow-up in this group of patients, once again showing the fragility of our study design.Finally, the assessment of toxicities was not carried out systematically, which could be a bias. But even so, we found incidences similar to those described in previously published studies, with a predominance of mild toxicities, grades 1 or 2 [2, 7, 8, 13]. In our sample, only 1 patient developed congestive heart failure and chronic kidney dysfunction after the 4 doses of Luoctreotate.

III. Conclusions:

Although the methodological limitations of our study, it is important due to the dissemination of real data on Brazilian patients receiving Luoctreotate. We could confirm that the efficacy and toxicity characteristics of this treatment were similar to those described in the literature.Theranostics in neuroendocrine cancer represents a cutting-edge approach that integrates diagnostic and therapeutic modalities to provide personalized and precise treatment strategies. Neuroendocrine tumors (NETs) are a heterogeneous group of neoplasms that arise from neuroendocrine cells, and their theranostic management aims to improve patient outcomes by tailoring treatment plans to individual characteristics of the tumors.

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