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Original Article

^{177}Lu-DOTATATE treatment in neuroendocrine tumors. A preliminary study☆

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ABSTRACT

Therapy with radiolabelled somatostatin analog peptides is a promising new therapy to treat neuroendocrine tumors. The aim of this preliminary study is to present our experience with ^{177}Lu-DOTATATE therapy, and evaluate tolerability and short-term efficacy in patients with tumors expressing somatostatin receptors. A total of 7 patients with metastatic neuroendocrine tumors were treated, each with 4 doses of ^{177}Lu-DOTATATE. The treatment response was evaluated in the form of biochemical response (tumor markers), imaging methods (somatostatin receptor scintigraphy, computed tomography, and magnetic resonance), and functional and quality of life responses using the Karnofsky performance status scale. Treatment toxicity was also evaluated. The results obtained were as follows: Biochemical response: 60% of patients showed tumor marker levels returning to normal, while they decreased significantly in the remaining 40%. Imaging response: 85.7% had a partial response, while 14.3% showed stable disease. All (100%) patients showed a significant improvement in quality of life, with increased Karnofsky scale scores. No patient had acute or chronic toxicity, and subacute transient hematological toxicity was observed in 42.8% of patients. Despite being a preliminary study, it was found that treatment with ^{177}Lu-DOTATATE is a safe treatment with few side effects, and an objective response was achieved in most patients.

Tratamiento con ^{177}LU-DOTATATE en tumores neuroendocrinos. Estudio preliminar

Palabras clave:
Tumores neuroendocrinos
Terapia con radionúclidos
^{177}Lu-DOTATATE

RESUMEN

La terapia con péptidos análogos de la somatostatina marcados con radionúclidos es un nuevo tratamiento prometedor para tratar tumores neuroendocrinos. El objetivo del presente estudio preliminar es presentar nuestra experiencia en la terapia con ^{177}Lu-DOTATATE y evaluar la tolerabilidad y la eficacia a corto plazo en pacientes con tumores que expresan receptores para la somatostatina. Se han tratado 7 pacientes con tumores neuroendocrinos metastásicos, cada uno con 4 dosis de ^{177}Lu-DOTATATE y se ha evaluado su respuesta al tratamiento en forma de respuesta bioquímica (marcadores tumorales y analítica), según métodos de imagen (gammagrafía de receptores de somatostatina, tomografía computarizada y resonancia magnética) y respuesta funcional y de calidad de vida (mediante la Escala de actividad de Karnofsky). Se ha evaluado también la toxicidad del tratamiento. Los resultados obtenidos han sido los siguientes: respuesta bioquímica: el 60% de los pacientes mostraron una normalización de sus niveles de marcadores tumorales, mientras que en el 40% disminuyeron de manera significativa; respuesta en técnicas de imagen: el 85,7% presentaron una respuesta parcial, mientras que el 14,3% mostraron enfermedad estable; mejoría de la calidad de vida: el 100% de los pacientes mostraron una mejoría significativa en la calidad de vida con un incremento de la Escala de actividad de Karnofsky, y en cuanto a la toxicidad: ningún paciente presentó toxicidad aguda o crónica, y el 42,8% de los pacientes presentaron toxicidad subaguda hematológica transitoria. A pesar de tratarse de un estudio preliminar podemos afirmar que el tratamiento con ^{177}Lu-DOTATATE es un tratamiento seguro, con pocos efectos adversos y que consigue una respuesta objetiva en la mayoría de los pacientes.

Introduction

Neuroendocrine tumors (NET) make up a group of infrequent, heterogeneous neoplasms originating in the diffuse neuroendocrine system and the gastrointestinal and bronchial tracts.[1–5] The most frequent types of NET are carcinoid and pancreatic NET. Although the incidence is relatively low the prevalence is much

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greater since the 5-year survival rates of patients with NET are of around 60%, regardless of the stage at diagnosis.[1]

The discovery of the expression of somatostatin receptors in these tumors two decades ago has led to great advances in the diagnosis and follow up of these tumors.[1–6]

The treatment of choice in NET is surgical resection when the disease is localized. However, a high percentage of patients are diagnosed with advanced disseminated disease.[5]

When surgery is not possible or patients are in advanced stages with metastasis, the options of chemotherapy and external radiotherapy are limited and thus, peptide receptor radionuclide therapy with somatostatin analogs is promising in these cases.[1–13]

The first radiotracer used in this type of therapy was [^{111}In-DTPA^{0}]-octreotide, showing good symptomatic results but with scarce partial remissions and possible severe secondary hematological, renal, and hepatic toxicity in patients receiving high doses of this radionuclide-labeled somatostatin analog.[4,14]

The next transporting molecule used in this type of therapy was a modified somatostatin analog, [Tyr^{3}] octreotide, which presented greater affinity for the subtype 2 somatostatin receptor. The chelanting agent DOTA was also used instead of DTPA to ensure a more stable chelate for the beta emitter radionuclide. ^{90}Y (β_{max} 2.27 MeV) was the first beta emitting radionuclide used, having a maximum tissue penetration of 12 mm and a half life of 64 h. Later, ^{177}Lu (β_{max} 0.5 MeV) was used, which had a maximum tissue penetration of 2 mm, a half life of 6.7 days and is also an emitter of 113 and 208 keV of gamma radiation, providing an advantage for performing imaging studies and calculating the dosimetry received.[3]

In the last years the octreotide somatostatin analog has been replaced by octreotate,[3,4] in which the threoninol c-terminal is replaced by threonine, thereby conferring octreotate with greater affinity for the subtype 2 somatostatin receptor.

With this in mind our center chose ^{177}Lu-[DOTA^{0},Tyr^{3}]octreotate (^{177}Lu-DOTATATE) to perform radionuclide therapy in tumors expressing somatostatin receptors since previous comparative studies between ^{177}Lu-DOTATATE and ^{177}Lu-DOTATOC have shown that greater doses are achieved with the first in tumors without increasing the dose to critical organs[15] or achieve at least comparable doses in the tumor but with a lower body retention of ^{177}Lu-DOTATATE.[16]

The aim of the present preliminary study was to evaluate the tolerability and short-term efficacy of ^{177}Lu-DOTATATE in patients treated in our center for tumors expressing somatostatin receptors.

Material and method

Patient selection. Inclusion criteria

The inclusion criteria to receive treatment with ^{177}Lu-DOTATATE in our center were as follows:

- Patients with metastatic or inoperable NET (histologically confirmed by immunohistochemistry).
- High somatostatin receptor expression: positive somatostatin receptor scintigraphy (SRS).
- Tumor proliferation rate with a Ki67 index <20%.
- Favorable analytical study:
- Creatinine <1.7 mg/dl, glomerular filtration >60%.
- Hemoglobin (Hb) >8 g/dl, erythrocyte count >3 × 10^{6}/μl.
- Leukocyte count >2 × 10^{3}/μl.
- Platelet count >75 × 10^{3}/μl.

Since 2014 a total of 10 patients from different autonomous communities in Spain have been referred to our center for treatment. Of these, 7 fulfilled the inclusion criteria.

Request for the medication and radiotracer

The treatment of NET with radionuclide-labeled somatostatin analogs is still under investigation and must fulfill the prevailing national legislation as well as the ethical principles for studies in humans.

The doses of ^{177}Lu-DOTATATE were requested according to the Royal Decree 1015/2009 which regulates the availability of medicines in special situations in Spain.

Sample description

From April 2014 to the present a total of 7 patients (5 women and 2 men from 19 to 73 years of age [mean age: 52 years; median 49 years]) have been treated in our center. Table 1 shows the demographic data of these patients as well as the types of tumors presented, the presence of bone and hepatic metastasis, the main symptomatology, Karnofsky performance scale (KPS) score, SRS and tumor markers prior to treatment with ^{177}Lu-DOTATATE.

All the patients were interviewed by a specialist in nuclear medicine who explained the treatment and signed informed consent was obtained by the patients. The study was approved by the Ethical Committee of our hospital.

Treatment protocol: patient preparation and administration of the radiotracer

Cold somatostatin analogs were withdrawn from patients receiving these agents prior to the treatment depending on the half life of the analog used: 4–6 weeks for long-acting formulations and at least 24 h for short-acting formulations.

The patients had fasted at least 6 h the day of ^{177}Lu-DOTATATE administration and were accompanied to a hospital room. ^{177}Lu-DOTATATE was generally administered in an antecubital vein with the patient in bed. The total duration of the treatment was 4 h and a half including the administration of the protective therapies and the administration of ^{177}Lu-DOTATATE, as shown in Fig. 1.

The patients remained in the nuclear medicine hospitalization wards of our hospital for 24 h. Prior to treatment the patients were informed of bathroom use and the norms of radiological protection to be followed. At discharge a SRS was carried out with a dual head SPECT/CT gamma camera.

The radioactivity of the doses of ^{177}Lu-DOTATATE administered in each of the treatment cycles varied between 7.366 GBq (199.1 mCi) and 8.417 GBq (227.5 mCi), with an average dose of 8.057 GBq (217.8 mCi) and median dose of 8.069 GBq (218.1 mCi). Each patient received a total of 4 cycles at intervals of approximately 6–8 weeks.

Imaging methods

Control images

Whole body images were made at 24 h after the administration of each of the therapeutic doses of ^{177}Lu-DOTATATE taking advantage of the gamma emission of 112 and 208 keV of ^{177}Lu. To do this we used a medium energy collimator with energy windows centered on the previously described photopeaks.

These images showed the distribution of the radioactivity of the therapeutic doses and the tumor uptake in the successive treatments.

Somatostatin receptor scintigraphy

An essential requisite of the inclusion criteria is the uptake of the somatostatin analogs by most of the lesions. This is demonstrated in a previous SRS performed in a dual-head SPECT/CT gamma camera after the administration of a dose of ^{111}In-DTPA-D-Phe1-octreotide