Theranostic in nuclear medicine: what is it and what experience do we have in Colombia?

Teranóstico en medicina nuclear: ¿qué es y qué experiencia tenemos en Colombia?

Vanessa Murad Gutiérrez[1]
Patricia Bernal Trujillo[2]
Gonzalo Ucrós Rodríguez[2]

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Summary

In the era of personalized and precision medicine, focused on improving health care by making the most of the opportunities offered by current biomedical, technological, social and economic developments, new terms such as theranostic have appeared. This term was born from the fusion of the concepts of therapy and diagnosis and, although it was proposed in recent years, it refers to an approach that has been used for a long time (1). Theranostic consists of a methodology where the diagnostic approach is focused on individualized therapeutic intervention, seeking to provide the best outcomes for the patient. The area of nuclear medicine has been a pioneer in theranostic, since the first treatment based on this concept was performed with radioactive iodine (^{131}I) in patients with thyroid disease. Currently, with advances in molecular imaging and reporter gene imaging (2), more and more theranostic agents are available to provide individualized or "lesionalized" therapies, as they more recently have come to be called (3). In this review, the theranostic approach in nuclear medicine is exposed, emphasizing how it works, what are the most frequent applications and what experience we have in Colombia.

Resumen

En la era de la medicina personalizada y de precisión, enfocada en mejorar la atención en salud aprovechando al máximo las oportunidades que ofrecen los desarrollos biomédicos, tecnológicos, sociales y económicos de la actualidad, han aparecido nuevos términos como el de *teranóstico*. Este término nace de la fusión de los conceptos de terapia y diagnóstico y, aunque fue propuesto en años recientes, hace referencia a un abordaje que se ha utilizado desde hace mucho tiempo (1). El teranóstico consiste en una metodología donde el abordaje diagnóstico se hace enfocado hacia la intervención terapéutica individualizada, buscando proporcionar los mejores desenlaces para el paciente. El área de la medicina nuclear ha sido pionera en el teranóstico, pues el primer tratamiento basado en este concepto se realizó con yodo radiactivo (^{131}I) en pacientes con patología tiroidea. Actualmente, con los avances en imagen molecular e imágenes con genes reporteros (2), cada vez se encuentran disponibles más agentes teranósticos para proporcionar terapias individualizadas o "lesionalizadas", como se han empezado a llamar más recientemente (3). En la presente revisión se expone el abordaje teranóstico en medicina nuclear, enfatizando en el funcionamiento, las aplicaciones más frecuentes y la experiencia que se tiene en Colombia.

Introduction

Theranostics is a term derived from combining the words therapy and diagnosis, which has been used in many fields of medicine to individualize therapies (4). It consists of a diagnostic approach focused on therapeutic intervention, seeking to provide the best outcome for the patient. A recognized example used for many years is the detection of HER2 oncogene overexpression in patients with breast cancer, to determine whether they are candidates for treatment with anti-HER2 therapies (lapatibnib or trastuzumab, for example), which, in the neoadjuvant setting, results in a better therapeutic outcome with a higher rate of complete pathological response and greater disease-free survival (5).

Nuclear medicine therapy

In nuclear medicine, theranostics refers to the use of specific molecules (peptides, agonists, antagonists, amino acids, analogues, etc.) which, when labeled with a specific radionuclide, allow diagnosis and treatment of a disease. These molecules labeled with radiation-emitting radionuclides γ are used to perform imaging studies to diagnose, localize and/or stage a disease; the same molecules labeled with a radiation-emitting radionuclide α or β are used to treat the disease, i.e., the lesions detected in the diagnostic study (4, 6). In this way, you see what you treat and you treat what you see, which is the principle of theranostics in nuclear medicine (Figure 1).

[1]Interventional Radiological physician. Fellow of Nuclear Medicine. Department of Nuclear Medicine, Seul National University Hospital, South Korea.

[2]Nuclear Physician. Department of Diagnostic Imaging, Hospital Universitario Fundación Santa Fe de Bogota, Colombia.

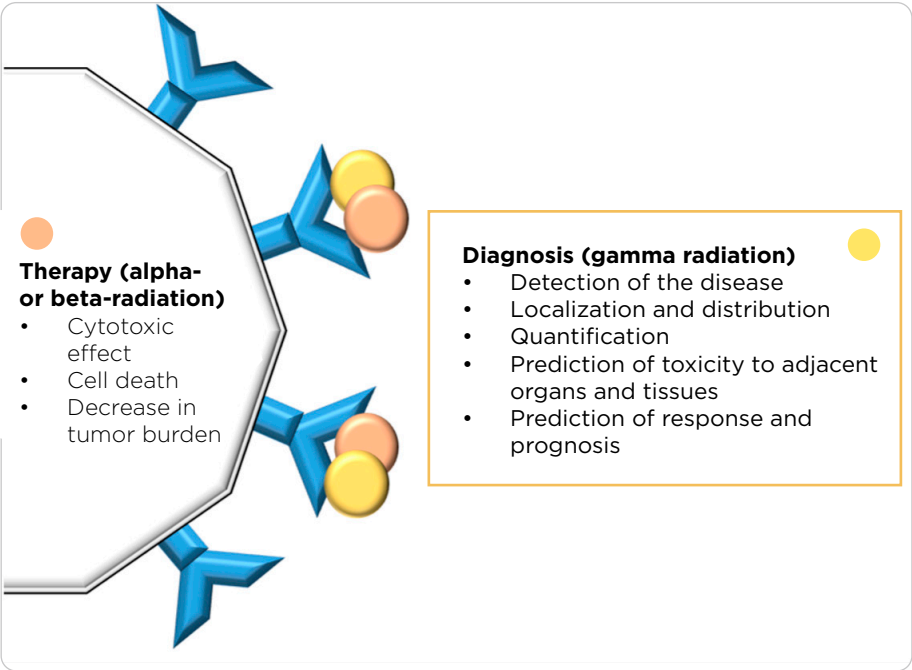

Figure 1. Principles of theranostics in nuclear medicine. The same molecule is used for diagnosis (labeled with a radionuclide emitting γ-radiation), and for specific treatment of the disease (labeled with radionuclide emitting β or α radiation).

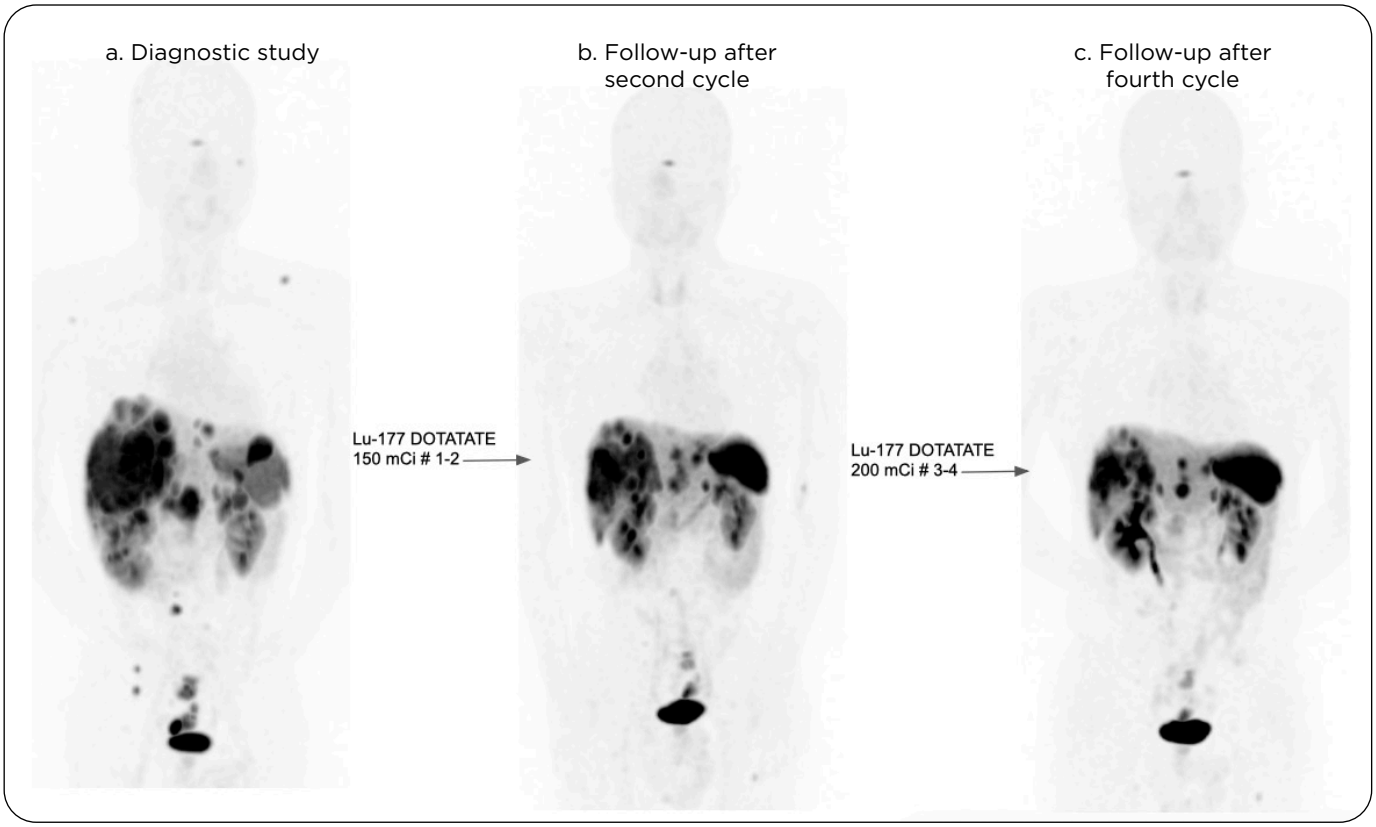

Figure 2. 54-year-old male patient with a diagnosis of rectal neuroendocrine tumor with hepatic metastases and seas. a) Diagnostic study: lesions were confirmed with somatostatin receptors. Two cycles of 177Lu were administered, each one with a dose of 150 mCi. b) Control after the second cycle: shows resolution of the lesions and decrease of the enhancement and size of the hepatic lesions. Two more 177Lu cycles were administered, each with a dose of 200 mCi. c) Control after the fourth cycle: shows a decrease in enhancement and size of most of the lesions in the right hepatic lobe, with an increase of two lesions in the left hepatic lobe.

Although the term theranostic is relatively recent, the technique as such began in nuclear medicine in 1941, when Saul Hertz administered the first dose of 131I for treatment of hyperthyroidism. For many years 131I was the only example of a theranostic agent, i.e. a radiotracer capable of both diagnostic and therapeutic effects (7, 8). This therapeutic approach is currently indicated in patients with differentiated thyroid cancer in the post-surgical setting, for: ablation of remnant normal thyroid tissue, adjuvant treatment in patients with suspected or high risk of occult disease, and treatment of confirmed metastatic disease both locoregionally and systemically (9).

Subsequently, in 1983, 131I-MIBG (131I-labeled metaiodobenzylguanidine) was developed for diagnosis (using radiation ɣ) and therapy (using radiation β at much higher doses) of pheochromocytoma and neuroblastoma. Currently, their use can be considered part of palliative symptomatic management in patients with disseminated, inoperable or progressive disease (10).

The next important development in this field was in the diagnosis and treatment of neuroendocrine tumors, especially gastroenteropancreatic tumors, most of which express large amounts of somatostatin receptors. The diagnostic approach began with the use of 111In-pentetreotide, a radiolabeled somatostatin analog used for gammagraphic diagnosis (OcreoScan), later labeled with 99mTc (11). However, in 2000 new radiopharmaceuticals emerged for use in PET and PET/CT (68Ga-DOTATOC, 68Ga-DOTATATE, 68Ga-DOTANOC), with better resolution and image quality and greater sensitivity and specificity, which is why they are currently considered the diagnostic method of choice (12-14). The therapeutic approach in these patients is indicated and approved as a second line in case of metastatic or inoperable somatostatin receptor positive (demonstrated by hybrid imaging), well differentiated and moderately differentiated tumors (grade 1 and grade 2, according to the WHO classification) (15). Therapy has been shown to be effective with both 90Y-octreotate and 177Lu-octreotate, the latter being more widely available and recognized by the results of the NETTER-1 study, where the benefits of its use were shown to be a sustained improvement in the overall health status of patients, greater symptom-free survival and longer functional time (16). Some authors recommend combined therapy with 90Y and 177Lu, but there are still no studies that support this recommendation as definitive (17) (Figure 2).

The most recent therapeutic procedure in nuclear medicine is the prostate-specific membrane antigen (PSMA)-based radiopharmaceuticals labeled with 68Ga-PSMA or 18F-PSMA for PET/CT diagnosis, which has revolutionized the diagnosis of prostate cancer. PSMA is a transmembrane glycoprotein that is expressed in normal prostate cells, but is overexpressed in neoplastic cells, in direct relation to tumor grade, disease aggressiveness and pathological stage (18). PSMA-PET/CT has proven to be the study with the highest sensitivity and specificity in these patients for detecting lymph node metastasis and biochemical recurrence (19, 20). Currently, it is positioning itself as a tool of great value in the statification of intermediate and high risk patients, leading to a change in treatment in up to 12.6% of cases (21). PSMA marked with β or α emitters allows therapy to be performed and is a treatment option that is gaining increasing attention. Multiple approaches have been studied, and 177-Lu-PSMA and 225Ac-PSMA are the ones that have shown the best response rates with less toxicity (22, 23), with a significant decrease in PSA levels, good tolerance and longer survival, in addition to symptom control (24).

Theranostics in Colombia

In Colombia, theranostic therapy began in the same way, with the use of radioactive iodine, which dates back to 1951, when the first therapies were applied at the National Cancer Institute (INC). It is currently a therapeutic procedure that is routinely performed in practically any nuclear medicine service in the country.

In the field of neuroendocrine tumors, diagnostic studies began with 111In and 99mTc-labeled somatostatin logos, and currently 68Ga-DOTA PET/CT is the study of choice for the diagnosis of these patients. The therapeutic use of 177Lu-DOTA started in 2009 and is increasingly performed in some institutions.

Recently, in 2019, work was initiated with 68Ga-PSMA and in 2020 with 18F-PSMA for prostate cancer diagnosis, now implemented more frequently by some institutions. Therapy with 177Lu-PSMA, as a treatment option for patients with metastatic prostate cancer, was initiated in late 2020.

Conclusion

The theranostic approach in nuclear medicine has multiple advantages. Making a precise diagnosis aimed at treatment allows for the appropriate selection of patients to receive such treatment, which also makes it possible to directly predict the response to treatment and to determine the prognosis (25). This means that theranostics has a definitive role in today's medicine, and it is essential that clinicians are aware of these therapeutic options and their availability in the country, so that they can be used more and more effectively.

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Correspondence

Vanessa Murad
158 Chang Gyung Gung-Ro, Jongno-gu,
Seoul, Corea
murad.vanessa@gmail.com

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