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CASE REPORT

^{177}Lu-DOTA-Octreotate Therapy for Neuroendocrine Tumors: A Case Report and Review of the Literature

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Abbreviations
Ca_{19-9} = carbohydrate antigen
CT = computed tomography
EORTC = European Organisation for Research and Treatment of Cancer
FDG = fludeoxyglucose
GEP = gastroenteropancreatic tumors
NET = neuroendocrine tumors
PET = positron emission tomography
PRRT = peptide receptor radionuclide therapy
SUV = standardized uptake value

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ABSTRACT

Favorable outcomes of peptide receptor radiotherapy of neuroendocrine tumors (NET) have been reported during the recent years. A patient with a non-functional neuroendocrine pancreatic carcinoma with abdominal lymph nodes and metastatic involvement of the liver is presented. After initial chemotherapy failure, he received 4 cycles of fractionated treatment with 177Lu-DOTA-octreoate (29,6GBq), which induced an impressive improvement of patient´s symptoms. We conclude that ^{177}Lu-DOTA-octreotate fractionated therapy should be a therapeutic option for inoperable or metastasized NET patients promising symptomatic relief, and patients with large NETs expressing high somatostatin receptor density.

INTRODUCTION

Over the last decades, encouraging case reports of patients with neuroendocrine tumors (NET) undergoing peptide receptor radionuclide therapy (PRRT) have been increasingly published. PRRT, either with ^{90}Yttrium (^{90}Y)-DOTA-octreotide (DOTA-TOC) or ^{177}Lutetium (^{177}Lu)-DOTA-octreotate (DOTATATE), has been established as an efficient and effective therapeutic modality, relatively well tolerated with moderate toxicity, providing objective responses in NETs.[1-3] Previously published studies have shown that PRRT could achieve objective tumor responses post traditional biologic and cytotoxic chemotherapeutic usage failure.[4,5]

Regarding dosimetry and therapy planning, experience with chemotherapy and external beam radiotherapy have been the reference points.[6,7] However, there are important issues to be acknowledged. PRRT differs from chemotherapy and beam radiation due to the biological variables that influence radiation exposure. Dose radiation directed to tumor and normal surrounding tissues depends on tracer's availability to target volume, relying on tumor size, somatostatin receptor density, and tracer's pharmacokinetics. Therefore, a physician planning PRRT cannot precisely prescribe an absorbed tumor dose, but a certain amount or organ dose, considering patient's general condition and previous treatments benefits.

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Peptide receptor radionuclide therapy with somatostatin analogues is a treatment modality with new inherent rules which have to be explored.[8] ^{177}Lu-DOTATATE is a suitable tracer for both therapeutic and imaging needs, emitting a major beta particles therapeutic fraction, and a smaller gamma rays fraction of good characteristics facilitating imaging.[2,3] Continuous imaging and dosimetry of patients undergoing several cycles with ^{177}Lu-DOTATATE can provide important insights into the effects of previous cycles of therapy. In this manuscript, we will present a patient with metastatic pancreatic NET, treated with ^{177}Lu-DOTATATE and relevant PRRT literature will be reviewed.

CASE PRESENTATION

In August 2009, a 58-year-old man was referred to our Department complaining of abdominal discomfort and persisting 4 to 10 daily episodes of diarrhea. A subsequent computed tomography (CT) scan showed a malignant mass located at the narrow end of the pancreas, with disseminated liver infiltration and abdominal lymph node enlargement. The scheduled biopsy samples taken from several liver metastases confirmed a non-functional neuroendocrine carcinoma with Ki-67 rate up to 15%. Biochemistry evaluation of tumor markers recorded carbohydrate antigen (Ca_{19-9}) at 175.31 u/ml, and neuron-specific enolase at 21.55 ng/ml. The patient was started on cytotoxic cisplatin based plus etoposide chemotherapy regimen. He underwent various combinations of chemotherapy infusions from September 2009 until January 2012, including drugs such as oxaliplatine, irinotecan, capecitabine and bevacizumab monoclonal anti-VEGF antibody, completing a total of 28 cycles. No clinical or biochemical (Ca_{19-9} 173 u/ml and neuron specific enolase 31.8 ng/ml) response to treatment was documented although toxicity was acceptable and no chemotherapy discontinuation was noted.

The patient was firstly evaluated with somatostatin receptor scintigraphy of 111In-DTPA-octreotide (octreoscan) on March 2012. Octreoscan revealed somatostatin receptors expression of high tracer uptake in all known tumor lesions (five–point scale, grade 4),[9] and the patient was considered for ^{177}Lu-DOTATATE therapy. All other inclusion PRRT criteria were fulfilled, including age >18 years, histological NET confirmation of inoperable metastatic disease, adequate hematologic laboratory measurements (hemoglobin >6 mmol/l, white blood cell count >$2x10^9$/l, platelet count >$80x10^9$/l, creatinine <150 μmol/l), Karnofsky performance score >50, satisfactory liver and renal function values (bilirubin levels <2.5 mg/dL, creatinine levels <2 mg/dL), discontinuation of any previous treatment with somatostatin analogues 28 days prior to scheduled PRRT, and life expectancy of at least 6 months.[10,11]

Premedication given prior to ^{177}Lu-DOTATATE included anti-emetic therapy with 3 mg of intravenous metoclopramide hydrochloride, and infusion of aminoacids (lysine 2.5%, arginine 2.5% in 1 liter of 0.9% NaCl at 250 ml/h) for kidney protection. ^{177}Lu-DOTA-octreotate was co-administered at a slow rate started 30 minutes after initiation of the aminoacid infusion and delivered for a 3.5-hour duration.[11] Treatment dose of 7400 MBq was injected in 15 minutes; total administered dose was 29.6 GBq delivered in 4 equal sessions with a break mean time up to 6-8 weeks. Routine hematology, biochemistry, liver and kidney function tests, hormone measurements and serum tumor markers were checked 1 week prior to each scheduled therapy. European Organisation for Research and Treatment of Cancer (EORTC) quality of life forms (QLQ-C30)[12] were filled out by the patient at each visit. Computed tomography scan was performed at the first infusion, on the fourth month and 1 year after the last treatment course. Octreoscan scintigraphy was also done at baseline prior to starting therapy, simultaneously with 1 to 4 cycles, and 2, 4 months and 1 year post last infusion. All suspected lesions on the CT scan imaging were measured and scored according to World Health Organization (WHO) solid tumor response criteria. The uptake on the pre-treatment octreoscan was scored visually on planar images on a 5-point scale.[9] Nausea and vomiting, not associated with administered dose, were the only recorded side-effects, occurring 3 hours post first delivery. A mild abdominal pain was also claimed during each therapy administration. Concerning laboratory tests, mild adverse hematological deterioration, as grade 1 toxicity, was recorded achieving normal values rapidly at follow up. Serum creatinine and creatinine clearance were closely monitored but no severe deterioration was documented. CT and octreoscan imaging, one year after completion of treatment, revealed tumor size diminution reflecting treatment effectiveness. In particular, CT scan showed stable disease with no significant decrease or increase in lesion diameters. Hence, octreoscan imaging documented partial response associated with infused treatment (5-point scale, grade 3)[9] (Fig. 1) with a prolonged duration of one year. Neuron specific enolase values were 17.5 ng/ml and 8.48 ng/ml at 4 months and 1 year after delivery of

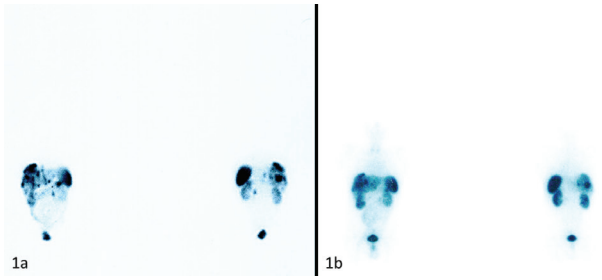

FIGURE 1: Octreoscan imaging. (1a) Octreoscan before treatment with ^{177}Lu-DOTATATE, (1b) Octreoscan one year after the end of ^{177}Lu-DOTATATE therapy.

the last treatment course, while Ca_{19-9} was recorded at 56.42 u/ml and 40 u/ml, during the respective time intervals. Patient's quality of life, according to EORTC-QLQ30 questionnaire was assessed prior to treatment, after each 7400 MBq dose delivery, and 4 months and 1 year after completion of therapy. There were no significant differences for functional scales or single symptom scales. The global health scale, which patient was asked to assign marks reflecting his general health and quality of life, ranging from 0 to 100, was judged higher than 80 without any tumor related symptoms.

DISCUSSION

Somatostatin receptor imaging is widely used for diagnostic purposes, and staging and restaging NETs.[13] Octreotide, a long-acting somatostatin analogue radiolabelled mainly with indium 111 (^{111}In), has been in daily practice usage since 1989, and proved to be an important agent in nuclear medicine. ^{111}In-DTPA-octreotide used to be the first choice for the visualization of somatostatin receptors.[14] Somatostatin receptor imaging in NET patients has been proven of great value, providing important information and having a strong impact on further therapeutic management.[15-18] Both positive and negative results in somatostatin receptor ima ging are useful and may predict the effect of octreotide therapy for NETs.[16] However, gamma ray imaging using ^{111}In-DTPA-octreotide has several limiting factors which decrease image quality and the overall efficiency of this imaging method.

One of the main advantages of positron emission tomography (PET) over conventional scintigraphy is its inherent high spatial resolution. The most commonly used PET radiopharmaceutical is the cell's glucose metabolism measurement with fludeoxyglucose (^{18}F-FDG). ^{18}F-FDG is of limited value in NET cells because of its known low metabolic rate, although it may show variable uptake among patients, or even in different lesions of the same patient and/or within same different areas of the tumor, contributing to different tumor grading.[19] The detection of ^{18}F-FDG uptake in tumor lesions is clinically relevant since it depicts the presence of less differentiated tumor cells, conferring a worse prognosis and susceptible to different therapeutic approaches.

^{68}Ga-labeled somatostatin analogues are widely used for NETs PET imaging.[20-24] Three major ^{68}Ga-DOTA-peptides are currently available for imaging: ^{68}Ga-DOTA-Phe1-Tyr3-Octreotide (TOC), ^{68}Ga-DOTA-NaI3-Octreotide (NOC), and ^{68}Ga-DOTA-Tyr3-Octreotate (TATE).[19] The main difference among these three tracers is their variable affinity to somatostatin receptor subtypes but it seems that this difference has no clinical impact, and therefore no preferential use of one compound over the others can be advised.[20] Studies have shown that the diagnostic value of PET/CT with ^{68}Ga-DOTATATE and ^{68}Ga-DOTATOC in the same patients with NET is almost the same, but the maximum standardized uptake value (SUV-max) of ^{68}Ga-DOTATOC tends to be higher than that of ^{68}Ga-DOTATATE.[19] The comparison of the ^{111}In-DTPA-octreotide single-photon emission tomography and ^{68}Ga-DOTA-peptides PET shows that the latter has a significantly higher detection rate, especially for small lesions with low tracer uptake.[22,23] A case reported by Gabriel M et al concerns a patient who had synchronous colorectal cancer and pancreatic NET, whereby the ^{68}Ga-DOTATATE PET and ^{18}F-FDG PET imaging tests succeeded to detect the two different tumor origins within liver metastatic lesions. This case underlined that the combination of ^{68}Ga-DOTATATE PET and ^{18}F-FDG PET imaging modalities may have a potential use in understanding NET biology and guiding their management.[25]

^{68}Ga-DOTA-peptides PET/CT imaging has been published that affects both tumor staging and modifies therapeutic decisions in more than 40% of NET patients.[26] Aiming to predict earlier tumor's response is fundamental to guide therapy and avoid critical side-effects. This really leads to lower costs and prevents application of ineffective therapies.[27] On the other hand, it is established that conventional imaging techniques and applied therapeutic response criteria are most often too complicated and always prove insufficient. [28] The decreased ^{68}Ga-DOTATATE lesions uptake post PRRT first cycle seems to correlate with clinical symptom relief predicting time to progression in well-differentiated NET patients.[27]

Nowadays, there are a few treatment options for metastatic NETs. The use of radiolabelled somatostatin analogues for tumor regression is a promising landmark development. The side-effects of ^{177}Lu-DOTATATE treatment are few, well documented and mostly transient. All previous studies have reported side effects of a maximum injected activity of 7400 MBq per cycle of ^{177}Lu-DOTATATE which have been thoroughly analysed in 504 patients with gastroenteropancreatic (GEP) NETs.[29-31] Acute side effects occurring within 24 hours post radiopharmaceutical administration are nausea, vomiting and abdominal pain. Subacute hematological toxicity (WHO, toxicity grade 3 to 4) and renal failure occur 4-8 weeks later. In our patient, neither renal nor hematological toxicity or any hormone-related crisis were recorded.

PRRT is a new promising and challenging treatment option for metastatic or inoperable patients with NETs. Review of the literature reveals studies reporting on ^{177}Lu-DOTATATE treatment, as providing tumor regression up to more than 50% in 28% of NET patients.[32] The quality of life is also improved remarkably based on the reported scales prior to and after ^{177}Lu-DOTATATE treatment.[32,33] A large study conducted by Kwekkeboom DJ et al showed that tumor remission was positively correlated with a high uptake during octreoscan and limited liver metastases, whereas disease progression was significantly more frequent in patients of low performance status and high tumor load.[34] ^{177}Lu-DOTATATE seems to be more efficacious in small lesions compared to ^{90}Y-DOTATOC,

which seems more efficient in large lesions.[35,36] Other studies have reported that ^{177}Lu-DOTATATE may be equally effective in large tumors, hence patients with large tumors and high receptor density expression are distinctly included.[37-39] Quality of life measured in this subgroup of patients was remarkably improved post therapeutic infusion and the published median progression-free survival is longer than 40 months.[40,41]

Partial or complete response achieved by ^{90}Y-DOTATOC therapy ranges from 10%-25% in NET patients.[42-48] High dose ^{90}Y-DOTATOC targeted therapy is another well tolerated treatment for NETs promising good antitumor effects.[44,45] A review revealed that GEP-NET patients presented higher response rate, ranging from 28% to 36%, while the noted cumulative response rate was 24%.[46] Additionally, there is a significantly longer overall survival compared to historical controls.[47]

Furthermore, the combination of ^{90}Y and ^{177}Lu-labelled somatostatin analogues seems to have superior antitumor effects compared to separate ^{90}Y or ^{177}Lu-labelled somatostatin analogues, tested in a vast majority of variable size tumors.[49] A well designed study with 50 metastatic NET patients enrolled, compared combined use of ^{90}Y and ^{177}Lu-DOTATATE therapy to the single ^{90}Y-DOTATATE usage arm and showed that tandem radioisotopes give prolonged overall survival than the single use.[49]

CONCLUSION

Fractionated therapy with ^{177}Lu-DOTATATE should be considered as a promising treatment option either for symptomatic, inoperable or metastasized neuroendocrine tumors, or for special large tumors of high somatostatin receptor density expression. Literature review of cases similar to our own indicates that in such special subgroups of malignant diseases of unknown prediction and difficult therapeutic decisions, the selective option of newer radiopharmaceutical agents remains a promising, albeit challenging, possibility.

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