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CASE REPORT

Significant impact of transient deterioration of renal function on dosimetry in PRRT

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Abstract Peptide receptor radionuclide therapy (PRRT), with ^{90}Y-DOTATOC and ^{177}Lu-DOTATATE as most clinically used radiopeptides, is widely used in the management of metastatic neuroendocrine tumors. With respect to radiation dosimetry, the kidneys are the critical organ for ^{90}Y-DOTATOC. Renal irradiation is significant because of reabsorption of the radiopeptide from the proximal tubuli and the resulting retention in the interstitium, mainly in the inner cortical zone. The high energy and consequently wide range in tissue of the yttrium-90 beta particle result in high absorbed doses to the kidney cortex and medulla. Accurate renal dosimetry can help minimizing radiation nephropathy. We report a case of a 69-year-old candidate for PRRT with an acceptable kidney function at the time of screening. When performing ^{111}In-octreotide pretreatment dosimetry 3 weeks later, we observed a drastic deterioration in kidney function, caused by undisclosed non-steroidal anti-inflammatory drug intake. The calculated kidney biological effective dose (BED) was 153 Gy after four projected cycles. PRRT was canceled as our full-course BED limit is 37 Gy and the patient was switched to morphine analgesics. Renal function normalized after 3 months and repeated dosimetry yielded an acceptable kidney BED of 28 Gy after four projected cycles (7 Gy/cycle). This case emphasizes that acute kidney insufficiency can yield toxic kidney doses in a single therapy cycle, with an inherent risk of persistent renal insufficiency. All clinical factors which might influence kidney function should be verified at screening and before PRRT administration.

Keywords Dosimetry · Peptide receptor radionuclide therapy · Yttrium-90 · Kidney function

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Introduction

Peptide receptor radionuclide therapy (PRRT) consists in a systemic administration of a synthetic peptide, labeled with a suitable radionuclide, able to irradiate tumors and their metastases by binding to a specific peptide receptor overexpressed on the cell surface [1]. The most intensely investigated (phase I–II trials) and clinically used radiopeptides are ^{90}Y-DOTATOC and ^{177}Lu-DOTATATE.

Complete (CR) and partial (PR) remissions are registered in 10–30 % of patients in most protocols and the median progression-free survival is more than 2 years [2]. The main side effects are short-term hematological effects and long-term renal toxicity [2, 3]. The renal irradiation arises from the proximal tubular reabsorption of the

radiopeptide and retention in the interstitium (mainly in the inner cortical zone [4]) and is the major dose-limiting factor for PRRT with ^{90}Y-DOTATOC. The electrons resulting from yttrium-90 decay have a higher maximal energy (E_{max} = 2.27 MeV; mean range in soft tissue = 2.5 mm, maximum range = 11 mm) and hence deeper tissue penetration than the electrons resulting from lutetium-177 decay (E_{max} = 0,497 MeV; mean range in soft tissue = 0.67 mm), resulting in a higher kidney marrow dose with yttrium-90 [1].

Because of the large variability in individual renal uptake of ^{90}Y-DOTATOC, some patients could potentially receive critical kidney radiation doses, particularly if high activities are administered to deliver the most effective tumor doses. We applied a patient-specific therapeutic regimen in a monocentric, phase II trial with ^{90}Y-DOTATOC in our institution. This trial was approved by the ethical commission of the University Hospitals Leuven. The biological effective dose (BED) on both kidneys after four cycles of a fixed activity of ^{90}Y-DOTATOC (1.85 GBq/m^2/cycle) was estimated using ^{111}In-octreotide scintigraphy. Quantitative kidney images were acquired by means of planar imaging at four different time points and applying the MIRD methodology. Based on Barone et al. [5], our maximal threshold projected BED was fixed at 37 Gy after four ^{90}Y-DOTATOC cycles.

During PRRT, as well as during pre-therapy dosimetry, a mixture of positively charged amino acids (lysine and arginine) was administered over 4 h. Co-administration of amino acids has been tested by several groups and leads to a 9–53 % reduction of the renal effective dose due to competitive inhibition of the reabsorption of the radiopeptide in the proximal tubulus [6, 7].

Dosimetry

In PRRT with ^{90}Y-labeled peptides the organ uptake of the radiopeptide cannot be readily quantified due to the lack of a gamma emission and the difficulty of quantifying bremsstrahlung imaging. Therefore, ^{111}In-octreotide was used as a proxy to assess the kinetic behavior of ^{90}Y-DOTATOC. For each patient, four whole-body (WB) images were acquired at 15 min, 4 h, 24 h, and 48 h with a standard source with known activity positioned at the feet. Preceding each WB scan, blood samples were drawn to assess the red marrow dose. Since the radiopeptide is eliminated through renal excretion, urine was collected to assess the dose to the urinary bladder wall. Indium-111 samples were used to perform cross-calibration of the gamma camera, dose calibrator, and well-counter. On each WB scan, regions-of-interest (ROI) were drawn around the total body, spleen, liver, and kidneys. Geometric mean counts within each organ ROI were converted to the fraction of injected ^{90}Y-DOTATOC activity (FIA) at the observed time points, assuming a similar kinetic profile of ^{111}In-octreotide and ^{90}Y-DOTATOC. Non-linear regression analysis was used to assess the radiopeptide clearance based on a bi-exponential model. These regressions were used to estimate the residence time for each organ that was entered in the internal dosimetry software program OLINDA/EXM for a phantom model-based computation of the absorbed radiation doses for each organ. The kidneys are the dose-limiting organ in ^{90}Y-DOTATOC therapy, hence, we estimated the BED to the kidneys using the absorbed dose, the kidney mass based on MRI measurements and the therapy fractionation scheme [8].

Case report

A 69-year-old male patient was diagnosed with a neuroendocrine tumor of the small intestine which was surgically removed. Three years later, liver and peritoneal metastases were detected and the patient was hormonally treated with somatostatin analogs (sandostatin LAR and somatulin) for 5 years. Abdominal pains, diarrhea and flushes became more frequent after this period and CT showed an increase in the lesions size. Because of this clinical and radiological progression the patient was referred for PRRT. His glomerular filtration rate (GFR) was calculated using ^{51}Cr-EDTA (60 ml/min/1.73 m^2) and was sufficient for inclusion in our treatment protocol (lower limit: 50 ml/min/1.73 m^2). His serum creatinine level was 0.97 mg/dl (estimated GFR (eGFR) based on the Modification of Diet in Renal Disease (MDRD) study formula: 77 ml/min/1.73 m^2).

The dosimetry procedure was performed 3 weeks after the ^{51}Cr-EDTA assay. At that moment, an episode of acute renal insufficiency was biochemically documented (serum creatinine 2.16 mg/dl; eGFR 30 ml/min/1.73 m^2). The etiology remained unclear at first, but a repeated history of the patient revealed a systematic intake of NSAIDs for back pain during the last month.

Results of ^{111}In-octreotide pretreatment dosimetry during this episode of acute kidney insufficiency were extrapolated in a kidney BED of 153 Gy after four projected therapy cycles with ^{90}Y-DOTATOC. Because of this high dose, PRRT was canceled and the patient was switched to oral oxycodon (Oxycontin® 5 mg × 2/day) to control his back pain.

Three months later, the renal function of the patient had normalized (serum creatinine 0.96 mg/dl; eGFR 78 ml/min/1.73 m^2, similar to baseline renal function) and the entire dosimetry procedure was repeated. With the normalized renal function, the kidney BED after four

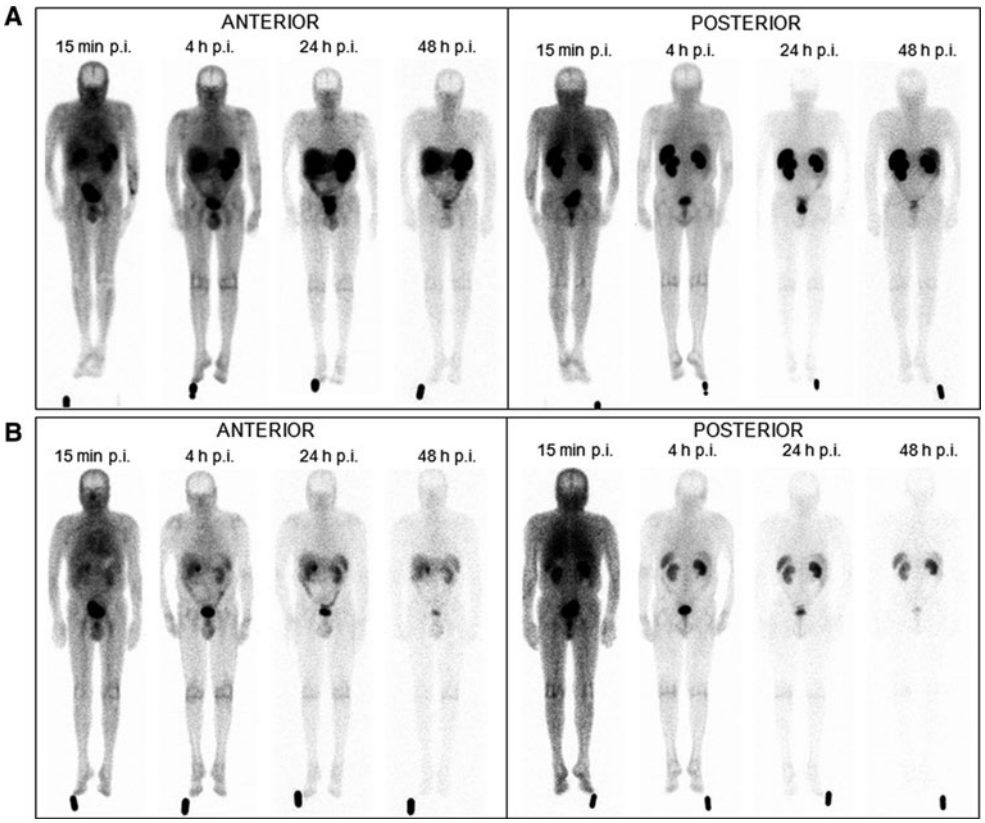

Fig. 1 Whole body ^{111}In-octreotide images of the patient (15 min, 4 h, 24 h and 48 h post injection). All images are scaled so that the standard at the feet is of similar intensity: **a** acute renal insufficiency with eGFR of 30 ml/min/1.73 m^2; **b** normalized renal function with eGFR of 78 ml/min/1.73 m^2. At every time point, the activity in the kidneys is higher during the acute kidney insufficiency than during normalized renal function

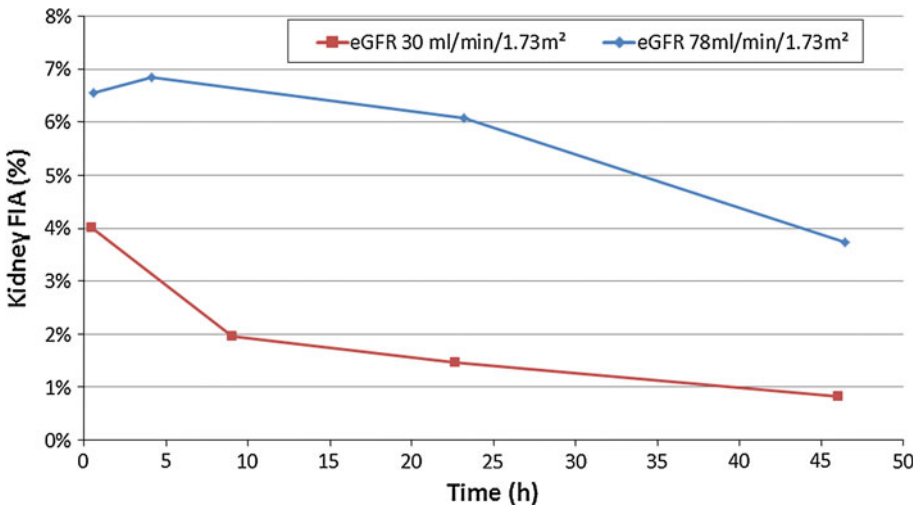

Fig. 2 Evolution of the fraction of injected ^{111}In-octreotide activity (FIA) in the kidneys over time, during acute renal insufficiency (eGFR 30 ml/min/1.73 m^2) and after normalization of renal function (eGFR 78 ml/min/1.73 m^2), measured with planar imaging at four time points (15 min, 4 h, 24 h and 48 h post injection). The area under the curve during renal insufficiency is markedly larger than during normal renal function

projected ^{90}Y-DOTATOC cycles was 28 Gy. PRRT with ^{90}Y-DOTATOC was planned and the patient was strongly advised to systematically take a morphine derivative as pain reliever and to avoid NSAIDs.

Discussion

PRRT with ^{90}Y-labeled peptides is efficient with an acceptable radiotoxicity profile. PRRT induces objective responses in ~30 % of patients. PRRT with ^{177}Lu-DOTATATE was proven to induce a significant improvement of the quality of life and of all the symptoms related to the disease in the majority of patients treated [9].

Dosimetry of the projected dose to normal organs and tumors resulting from ^{90}Y-DOTATOC administration is a preliminary step for patient selection and therapy planning, especially to prevent nephrotoxicity. Despite amino acid protection, renal function loss may become clinically evident 1–5 years after receptor radionuclide therapy. Not only cumulative high renal tracer uptake on the pretreatment whole-body scan, but also low baseline glomerular filtration rate, older age, hypertension, diabetes and pretreatment with nephrotoxic chemotherapy are considered risk factors for kidney function decline after PRRT [10, 11].

This case is an example of an acute decrease in kidney function which can lead to toxic kidney doses in a single therapy cycle, leading to an inherent risk of persistent kidney insufficiency. It is concluded that all factors which might influence kidney function must be checked during screening and at the time of PRRT administration. (Figs. 1, 2).

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