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Altered Biodistribution of Somatostatin Analogues After First Cycle of Peptide Receptor Radionuclide Therapy

Introduction

Peptide receptor radionuclide therapy (PRRT) targeting the somatostatin receptor has emerged as a powerful palliative therapy in metastasized neuroendocrine tumors.[1-4] A treatment schedule consisting of several administrations of ^{90}Y-[DOTA^{0}]-Tyr^{3}-octreotide (^{90}Y-DOTATOC) is the standard approach. Because long-term renal toxicity is the dose-limiting factor, dosimetry with ^{111}In-octreotide is performed in all patients. Sequential images are acquired at five different time points, allowing calculation of the biologic effective dose (BED) on the dose-limiting organs, the kidneys, after several cycles of ^{90}Y-DOTATOC treatment (1 GBq/m^2 per cycle). On the basis of published data, the maximum-tolerated BED after four cycles is fixed at 37 Gy.[5] In our protocol, ^{68}Ga-DOTATOC positron emission tomography (PET)/computed tomography (CT) and functional magnetic resonance imaging (perfusion and diffusion weighted) performed before and at weeks 7 and 40 are included.

Case Report

A 38-year-old woman with a neuroendocrine tumor of the small intestine with lymph nodes and liver metastases initially treated with resection of the primary tumor and radiofrequency ablation of the liver metastases (February 2008) followed by systemic therapy with somatostatin analogs was referred for PRRT because of clinical and radiologic progression. Dosimetry estimated a BED of 17 Gy to the kidneys after four cycles of PRRT; uptake on ^{68}Ga-DOTATOC PET/CT (April 2009) was sufficiently high in the metastases.

The early-response (August 2009) ^{68}Ga-DOTATOC PET/CT (at week 7 after PRRT) showed a striking increase in the bloodpool retention of the tracer (Fig 1) and a decrease in spleen uptake. After one therapy cycle, the patient's symptoms were already reduced, and routine blood evaluation was within normal limits. There was only faint uptake in the liver metastases compared with the physiologic liver uptake. A repeat scan, performed 3 days later, showed identical results. A careful comparison of all available ^{68}Ga-DOTATOC images (Figs 1A to 1D) revealed a slightly increased bloodpool on the pretherapeutic image (Fig 1B). Figure 2 (SUV, standardized uptake value) illustrates that the visual findings were confirmed by semi-quantitative analysis, knowing that at 0 weeks, ^{90}Y-DOTATOC was administrated.

Sequential scintigraphic images over 3 days after administration of ^{111}In-ocreotide was performed 9 weeks after therapy to evaluate if this change in biodistribution had also resulted in an altered dosimetry. Compared with the first dosimetry, we saw increased bloodpool retention and only minimal uptake of the metastases, particularly in the first 24 hours, consistent with the ^{68}Ga-DOTATOC findings. Western blotting was also used to investigate if a possible immunization reaction could have occurred to the radioactive peptide or somatostatin analog. At last, high-pressure liquid chromatography (HPLC) of the patient's blood and serum was compared with the HPLC of two control patients.

The dosimetry results showed some remarkable differences in the plasma half-life of ^{111}In-octreotide after the first radionuclide therapy administration, with an increase of 27.2%. The plasma half-life during the first dosimetry matches the mean plasma half-life of seven other patients (Fig 3). The estimated residence time in

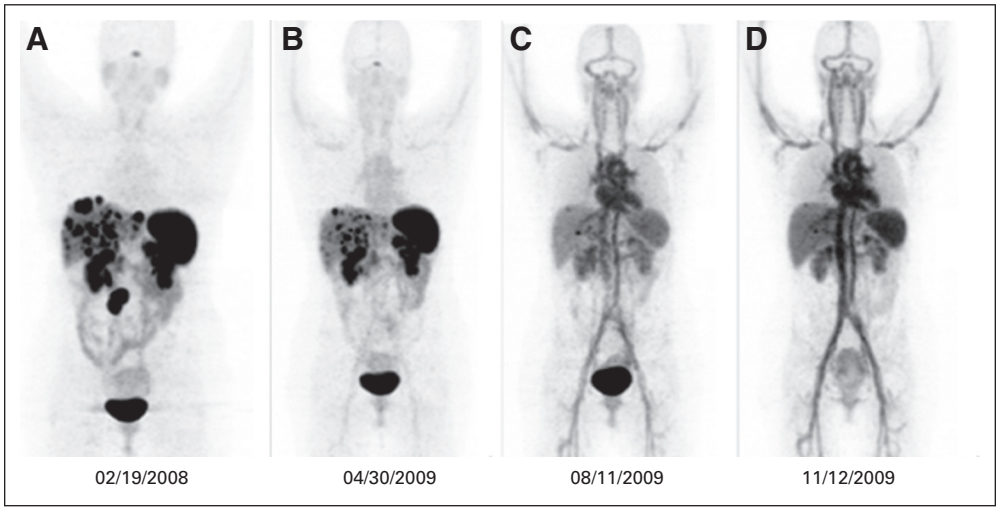

Fig 1.

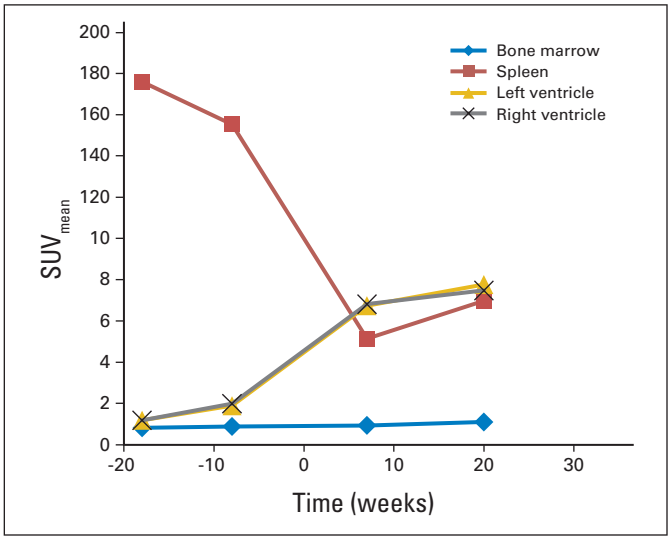

Fig 2.

the kidneys, spleen, and liver doubled, and in the red marrow, the increase was even more pronounced (approximately 3.5 times higher; Table 1). This resulted in an increase of BED to the kidneys and effective dose to the red marrow of 85% and 155%, respectively. Because the dose to the red marrow was higher than 2 Gy, no additional radionuclide therapy was administered. The somatostatin analogs were interrupted, and 3 months later, a new ^{68}Ga-DOTATOC PET/CT was performed, which showed a similar image with an even more pronounced bloodpool retention and slight increase in uptake at the liver metastases and spleen. Meanwhile, the clinical condition of the patient remained unchanged.

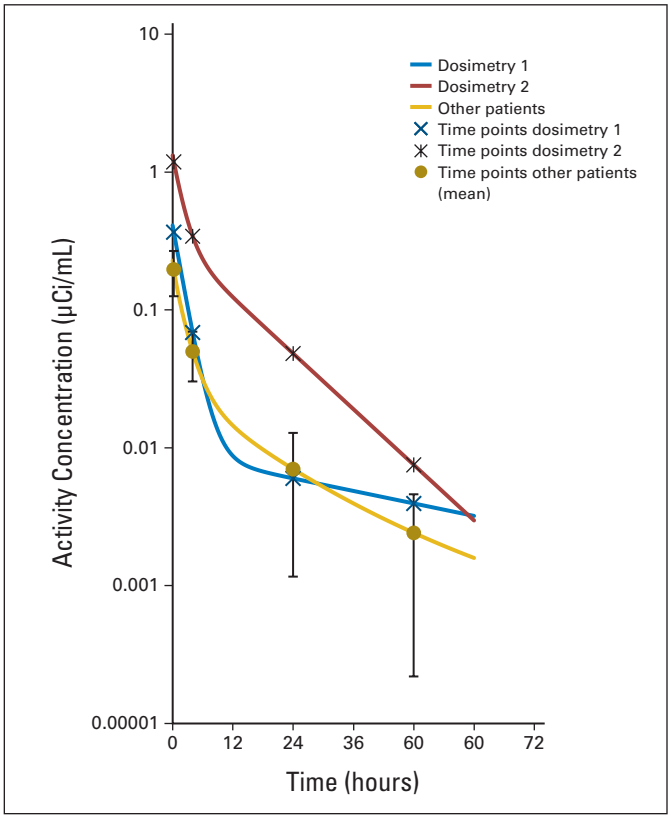

Fig 3.

We tried to identify the causative agent of this altered biodistibution. Kidney function was normal (serum creatinine, 0.66 mg/dL; estimated glomerular filtration rate, > 90 mL/min/1.73 m^2). Hematology and biochemistry were unremarkable, with a normal protein electrophoresis. No circulating tumor cells were detected on microscopic examination. We performed immunoblots against human immunoglobulins (Igs) to detect antibodies against a common epitope in ^{68}Ga-DOTATOC and ^{111}In-octreotide. They showed a similar lack of IgM and IgG binding to cold DOTATOC peptide in the patient's serum, as in the serum of two healthy controls, despite testing varying levels of antigen and serum (data not shown). We performed HPLC with ^{68}Ga-DOTATOC and ^{111}In-octreotide incubated with serum from the patient and two healthy controls (data not shown) on two different columns: Superdex Peptide 10/300 GL (Amersham Biosciences, Uppsala, Sweden) to detect small antibodies (10^2 to 10^4 molecular mass) and Superdex 200 10/300 GL (Amersham Biosciences) to detect larger antibodies (10^4 to 10^6 molecular mass). No significant differences in retention times were observed. Finally, we incubated whole blood (patient and two healthy controls) with ^{68}Ga-DOTATOC and ^{111}In-octreotide and observed no difference in the cell-bound fraction between the patient and controls.

Discussion

We observed an impressive change in biodistribution of ^{68}Ga-DOTATOC and ^{111}In-octreotide after the first cycle of ^{90}Y-DOTATOC. This might represent an exacerbation of a pre-existing abnormality because the pretherapeutic ^{68}Ga-DOTATOC scan shows a clear, although slight, increase in bloodpool retention compared with a scan taken 1 year earlier. The cause of this changed biodistribution remains unclear, but we excluded poor kidney function, activated leukocytes, and circulating tumor cells and could find no evidence for DOTATOC/octreotide-binding antibodies (negative immunoblot and HPLC) or circulating shed receptors (negative HPLC).

Antibodies against octreotide have been documented, with a prolongation of the plasma half-life.[6-8] Characteristic abnormalities, such as high background radioactivity together with visualization of the injection sites because of circulating antibodies, have been described.[6] In two other patients treated with octreotide for acromegaly, a marked prolongation of the interval of maximal growth hormone inhibition was observed, due to the development of specific IgG antibodies against octreotide.[7]

This prolonged plasma residence time and altered biodistribution caused a change in dosimetry, which would have resulted in an almost four-fold increased dose to the red marrow after four cycles, exceeding the maximum-tolerated dose to the bone marrow of 2 Gy.[9-11]

Imaging the biodistribution of the therapeutic peptide in PRRT, either directly as with ^{177}Lu-DOTATATE or indirectly as with ^{68}Ga-DOTATOC, enables the uncovering of altered biodistribution and guides the reassessment of dosimetry, potentially sparing the patient additional therapy with an unacceptable risk/benefit ratio. Biodistribution of ^{68}Ga-DOTATOC and ^{111}In-octreotide can be profoundly altered in the course of PRRT with ^{90}Y-DOTATOC, resulting in significant changes in dosimetry. It can be detected by direct or indirect scintigraphy of the peptide.

Table 1. Dosimetry Results

Organ	Residence Time Before ^{90}Y-DOTATOC Therapy (hours)	Residence Time After ^{90}Y-DOTATOC Therapy (hours)	Change in Residence Time (%)	Estimated (BE)D Before ^{90}Y-DOTATOC Therapy (Gy)	Estimated (BE)D After ^{90}Y-DOTATOC Therapy (Gy)	Change in (BE)D (%)
Kidneys	0.66	1.19	80	13	24	85
Liver	0.74	1.30	76			
Spleen	0.34	0.77	126			
Red marrow	0.09	0.42	347	0.88	2.24	155
Remainder	6.66	11.73	76			

Abbreviations: ^{90}Y-DOTATOC, ^{90}Y-[DOTA^{0}]-Tyr^{3}-octreotide; (BE)D, (biologically effective) dose.

This needs to be acknowledged by the PRRT community, because it could cause important and unexpected adverse effects.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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