Lutetium DOTATATE whole body scans: A novel approach for evaluation of neuroendocrine tumors

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ABSTRACT

Aim: We undertook a study to evaluate whether Lutetium (Lu) DOTATATE whole body scan is well comparable to Gallium positron emission tomography (PET) / Indium Octreotide, and hence with dosimetric advantage can replace it in the pre-therapy setting. Materials and Methods: We undertook a prospective study of a total of 39 patients with metastatic neuroendocrine tumor (age 11–70 years), who underwent Lu-DOTATATE scans within the period August 2009–November 2010. This included 28 males and 11 females. Dose of Lu-DOTATATE injected for diagnostic scanning purpose was 10 mCi i.v. Whole body planar images and single-photon emission computed tomography (SPECT)-CT images were obtained at 4, 24 and 48 hours. The Lu-DOTATATE whole body and SPECT-CT images were compared to contrast CT scans in all patients, and Indium Octreotide and Gallium DOTATATE PET images in nine patients, with reference to detection sensitivity of number of lesions. The pre-therapy scans were also used for dosimetric calculations. Fourteen of these 39 patients further went ahead with Lu-DOTATATE therapy. Results: All 39 patients demonstrated Lu-DOTATATE uptake in the disease sites seen on the contrast CT images. The uptake intensity was well comparable to Indium Octreotide and Gallium DOTATATE PET scans of all nine patients, with equally well-defined lesions. The post-therapy Lu-DOTATATE scans of the 14 patients who underwent therapy demonstrated higher intensity uptake pattern in the same disease sites, suggesting favorable therapeutic effect. The scans were useful in determining dosimetric details for therapeutic purpose and adequate exposure rates to suggest good ablative effect. Conclusion: Our preliminary data suggest that Lu-DOTATATE whole body scanning procedure is cost effective and equally sensitive as Gallium DOTATOC/NOC PET scan in pre-therapy setting of neuroendocrine tumors. The additional advantage of dosimetry calculations on this scanning procedure makes it more ideal to tailor therapies with more accuracy.

Keywords: Lutetium DOTATATE, neuroendocrine tumors, pre-therapy, whole body scan

INTRODUCTION

Treatment with radiolabeled somatostatin analogs (peptide receptor radionuclide therapy) for metastatic neuroendocrine tumors is an established, relatively new development for objective cytoreductive therapy where surgery is not feasible. Other medical treatment modalities like chemotherapy, interferon x, etc. are seldom successful for adequate tumor reduction. In this context, the most vital criterion in management of patients with neuroendocrine tumors is demonstrating somatostatin receptor positivity of the tumor cell.

The conventional imaging modalities like sonography, endoscopic ultrasonography, contrast computed tomography (CT) scans, and magnetic resonance imaging (MRI) show only morphology. Functional imaging techniques such as somatostatin receptor scintigraphy (SRS) help in visualization of occult tumor primary, demonstration of small metastatic lesions and eligibility of the patient for somatostatin analog therapy. SRS has a diagnostic sensitivity superior to conventional radiological imaging, especially in gastro-entero-pancreatic neuroendocrine tumors.[¹] A host of neuroendocrine tumors demonstrate somatostatin receptors to a varying degree, and hence the sensitivity of SRS varies from almost 89 to 100% in most of them and to about 60–75% in others. Another factor is the various types of somatostatin receptors (SSTR2–5), and the affinity of the particular radiolabeled somatostatin analog to the particular SSTR.
Until very recently, the established radiopharmaceutical labeled for SRS had been \(^{111}\text{In}\)-DTPA-octreotide \(^{111}\text{In}\)-diethylenetriaminepentaacetic acid (DTPA)-[octreotide]. However, it had certain drawbacks. The physical characteristics of \(^{111}\text{In}\) made the imaging procedure inconvenient by requiring scanning even up to 96 hours for accurate results. The single-photon emission computed tomography (SPECT)-CT improved the resolution of the planar images to just less than a centimeter. However, lesions less than 8 mm could not be well identified, and primary neuroendocrine are usually very small in size.\(^{1,2}\)

The introduction of \(^{68}\text{Ga}\)-DOTATOC PET/CT scan labeled to newer somatostatin analogs – \(^{68}\text{Ga}\)-DOTATOC \(1,4,7,10\)-tetraazacyclododecane-N\(^{3}\), N\(^{5}\), N\(^{11}\), N\(^{13}\)-tetraacetic acid (D)-Phe\(^{1}\)-thy\(^{1}\)-octreotide], \(^{68}\text{Ga}\)-DOTA-NOC \(1,4,7,10\)-tetraazacyclododecane-1,4,7,10-tetraacetic acid]-1-Na\(^{3}\)-octreotide) improved lesion detection due to superior spatial resolution of PET. It localized neuroendocrine tumors in patients with clinical and hormonal evidence but no localization of the tumor on CT or MRI, and demonstrated uptake in ambiguous lesions verifying them as neuroendocrine tumors.\(^{5,8}\) In addition, the short imaging time of about 1–2 hours was patient friendly. This was also a good surrogate tool for monitoring response to therapy by virtue of its semiquantitative standardized uptake value (SUV), which could be obtained prior to and post therapy, and this SUV decrease on subsequent scans signified favorable response. However, these advantages came at an important factor of higher cost and relatively higher radiation exposure in \(^{68}\text{Ga}\)-DOTATOC PET/CT scans than SPECT/CT scans, which caused concern.

After the established therapy of \(^{90}\text{Y}\)-DOTATOC for metastatic neuroendocrine tumors, treatment with \(^{177}\text{Lu}\)-DOTATATE has shown promising results. \(^{177}\text{Lu}\)-labeled somatostatin analogs demonstrated less nephrotoxicity than \(^{90}\text{Y}\), and have been the choice of therapy in recent times.\(^{50}\) The radionuclide \(^{177}\text{Lu}\) emits both beta and gamma radiations, allowing imaging and dosimetry after therapy.\(^{51}\) These characteristics of the isotope helped us to conceptualize pre-treatment scanning role using its gamma emissions, followed by therapy using beta component.

**MATERIALS AND METHODS**

**Patients**

Thirty-nine (28 males and 11 females) patients with neuroendocrine tumors, aged 11–70 years, were included in the prospective study of pre-treatment whole body diagnostic scanning with \(^{177}\text{Lu}\)-DOTATATE, during the period August 2009–November 2010. All patients had histopathologically proven metastatic neuroendocrine tumors, with or without known site of the primary, and all demonstrated raised serum chromogranin A levels. Symptomatology varied from mild complaints like fullness of stomach/occassional dyspepsia to significant diarrhea and/or pain. The types of neuroendocrine tumors within the study group were carcinoids (majority), glucagonoma, adrenocortical carcinoma, medullary carcinoma thyroid, and metastatic tumors with unknown primary. All patients had undergone a diagnostic contrast CT scan before being referred for the \(^{177}\text{Lu}\)-DOTATATE scan. 80% of these patients had undergone either an \(^{111}\text{In}\) Octreotide diagnostic scan or \(^{68}\text{Ga}\)-DOTATOC PET/CT scan.

Patient preparation included only withdrawal of somatostatin analog/Sandostatin injections prior to imaging. Long-acting Sandostatin was withdrawn for 6 weeks, and short-acting form for about 72 hours.

Ten millicuries of \(^{177}\text{Lu}\)-DOTATATE was administered as a slow intravenous injection. Whole body planar and SPECT/CT imaging was done at three time intervals post injection, i.e. at 4, 24 and 48 hours, on the Infinia Hawkeye 4 gamma camera (GE system). Acquisition parameters were with dual window of 113 KeV and 208 KeV (20%), and medium energy collimator. Few of the scans were also acquired with low-energy all purpose collimator. Whole body image was taken with exposure time per pixel of 180 sec, 10–13 cm/minute speed of the table, and matrix of 256 × 256. SPECT acquisition parameters included matrix of 128 × 128, zoom 1, scan mode 6 sec/projection, 3° view angle, total angular range 360°, and clockwise direction.

CT parameters of the SPECT/CT acquisition included 4-slice helical CT, with pitch of 1.9, interval of 4.42 mm, 140 kV, 2.5 mA, velocity of 2.6 rpm, slice thickness 5 mm, 512 × 512 matrix, and 1.10 mm pixel size, extended field of vision (FOV).

Comparison was done between images acquired with medium-energy collimator and low-energy all purpose collimator, and imaging time of 4, 24 and 48 hours. Factors considered for comparison of \(^{177}\text{Lu}\)-DOTATATE scans with \(^{68}\text{Ga}\)-DOTATOC PET/CT scan or \(^{111}\text{In}\) Octreotide scan were detection sensitivity and intensity of lesion uptake.

In the \(^{177}\text{Lu}\)-DOTATATE scans, the possibility of dosimetric calculation for the purpose of dose estimation for therapy was explored. For this, the injected dose activity was noted. The whole body scans acquired at three reference times (4, 24 and 48 hours) were taken. Retention of uptake in the whole body, lesions, and kidneys was obtained by drawing regions of interest over these respectively, and at all three time periods. The Medical Internal Radiation Dose (MIRD) formula for absorbed dose calculation \(\text{[} (\text{Ao} \times \text{fi} \times 1.44 \times T_{\text{eff}} \times K) / \text{mass} \text{]} \) was used to obtain the dose (Ao: initial activity in microcurie, fi: % fractional uptake, T\(_{\text{eff}}\) effective half-life in hours, K: constant = 0.2834, mass: in grams).

**RESULTS**

The whole body \(^{177}\text{Lu}\)-DOTATATE scan with SPECT/CT [Figure 1] demonstrated excellent normal physiological distribution, and abnormal increased uptakes in all the lesions demonstrated on the contrast CT scan of the patient. In addition, the SPECT/CT images not only demonstrated the heterogeneous
Figure 1: Whole body image shows physiological uptake in spleen, liver, kidneys and bladder. Abnormal increased uptakes are seen in multiple liver lesions (largest in right lobe), and left lung lesion, also defined on corresponding fused SPECT-CT images, with receptor distribution pattern.

Figure 2: Metastatic lesions in the liver and abdominal node (as seen by focal increased uptakes) are better delineated with higher target to background ratio on medium-energy collimator and well-defined lesion uptake.

Figure 3a: The abnormal increased uptake in the metastatic lesion in right lobe of liver is demonstrated equally on both 111Indium Octreotide and 177Lu-DOTATATE scans, however, it is well defined in the latter (Planar whole body images).

Figure 3b: The abnormal increased uptake in the metastatic lesion in right lobe of liver is demonstrated equally on both 111Indium Octreotide and 177Lu-DOTATATE scans, however, it is well defined in the latter (SPECT-CT images).

Figure 4: The large metastatic lesion in right lobe of liver demonstrates equally increased intensity of uptake in its periphery with central photopenia, on both the 177Lu-DOTATATE scan and 68Ga-DOTATOC PET scan of the same patient.

Figure 5: Avidity of uptake on the post therapy scans in the lesions demonstrated on the pre-therapy 177Lu DOTATATE scan, were evident with high uptake on the post therapy scan.
versus homogeneous distribution of receptor uptake, but also aided in tumor volume estimation.

The comparison of $^{177}$Lu-DOTATATE images acquired with medium- and low-energy collimators clearly demonstrated the ideal collimator for acquisition to be of medium energy. Its images had higher resolution with more target to background ratio and sharp lesion demonstration [Figure 2].

The $^{177}$Lu-DOTATATE scans compared with $^{111}$Indium Octreotide scan of the same patients matched 100% lesion by lesion and did not reveal any additional lesion on the $^{177}$Lu-DOTATATE scan. However, the $^{177}$Lu-DOTATATE scan showed better resolution with higher target to background ratio [Figure 3].

Comparison of lesions between $^{177}$Lu-DOTATATE scan and $^{68}$Ga-DOTATOC PET scan of the same patient revealed promising results of identical lesion uptake, and with no additional lesions identified on $^{68}$Ga-DOTATOC [Figure 4].

A few scans were also compared along with the post-therapy scans of the same patients. The avidity of uptake on the post-therapy scans in the lesions demonstrated on the pre-treatment diagnostic scans was interpreted in the light of ablative effect favoring positive response. In addition, few of the equivocal uptake intensities on the pre-therapy $^{177}$Lu-DOTATATE scan were evident with high uptake on the post-therapy scan [Figure 5]. These results were promising and opened up the opportunity to decide the doses for the subsequent fractions.

DISCUSSION

The results of the pre-therapy whole body $^{177}$Lu-DOTATATE diagnostic scans have been encouraging by demonstrating sensitivities comparable with the $^{68}$Ga-DOTATOC PET and $^{111}$Indium Octreotide scan, opening a whole new approach toward the management of neuroendocrine tumors. The possibility of utilization of the same radiopharmaceutical both for therapy and pre-treatment diagnostic scanning makes it analogous to the whole body $^{131}$I scan in thyroid cancer, giving it similar advantages. The demonstration of receptor positivity on the $^{177}$Lu-DOTATATE diagnostic scan would be more accurate in terms of the same type of receptor distribution and the affinity for the particular receptor, as would be expected by the therapeutic dose. For example, DOTATATE, which is the currently used compound for therapy, has high affinity for SST2, whereas DOTATOC and DOTANOC have affinity for SST3 and SST5 too. Hence, the prediction of therapeutic response would be more accurate on the $^{177}$Lu-DOTATATE diagnostic scan. Since Ga-DOTATOC / DOTANOC PET could be positive targeting SST3 and 5 also, and not only SST2, the treatment with Lu-DOTATATE based only on $^{68}$Ga-DOTANOC would be erroneous without any therapeutic benefit. Hence, scanning with Lu-DOTATATE would be ideal before treatment. The monitoring of treatment response post therapy and prior to next fraction of the dose delivery would also be more accurate with $^{177}$Lu-DOTATATE scans rather than $^{68}$Ga-DOTATOC and DOTANOC PET scans for the same reasons. The pre- and post-therapy Lu-DOTATATE scans would give a much fairer estimate of the disease status in terms of intensity of lesion uptakes and its extent, also aiding in deciding the dose for subsequent fractions. Till the possibility of labeling Lutetium with DOTATOC or DOTANOC for therapy is not explored, or the possibility of labeling Gallium with DOTATATE, the more reasonable approach would be to perform pre-therapy diagnostic scans with Lutetium DOTATATE. Another factor which makes an immense difference is the much lower cost of Lu-DOTATATE as compared to Ga PET scans. Dosimetry is an added advantage with Lu-DOTATATE scans.

CONCLUSION

$^{177}$Lu-DOTATATE scan compares with $^{68}$Ga-DOTATOC/DOTANOC PET scan both in sensitivity and lesion characteristics. It demonstrated all the metastatic lesions seen on the contrast CT. Lu-DOTATATE is cost effective. Pre-treatment dosimetry is possible with Lu-DOTATATE whole body diagnostic scans, giving the opportunity to tailor therapies with more accuracy.

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