Turkish Journal of Medical Sciences

Volume 46 | Number 2 Article 26

1-1-2016

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Turkish Journal of Medical Sciences

http://journals.tubitak.gov.tr/medical/

Research Article

Turk J Med Sci
(2016) 46: 409-413
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doi:10.3906/sag-1412-11

The role of baseline Ga-68 DOTATATE positron emission tomography/computed tomography in the prediction of response to fixed-dose peptide receptor radionuclide therapy with Lu-177 DOTATATE*

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Received: 02.12.2014 • **Accepted/Published Online:** 27.04.2015 • **Final Version:** 17.02.2016

Background/aim: To describe the role of baseline gallium (Ga)-68 DOTATATE positron emission tomography (PET)/computed tomography (CT) in the prediction of the response to peptide receptor radionuclide therapy (PRRT) using lutetium (Lu)-177 DOTATATE.

Materials and methods: Analysis was made of baseline Ga-68 DOTATATE PET/CT images of 29 patients (17 females and 12 males; mean age: 50.7 ± 14.6 years) with metastatic neuroendocrine tumors who received PRRT with Lu-177 DOTATATE. Maximum standardized uptake values (SUVmax) of reference lesions and their ratios to physiological uptake organs were calculated. The relationship between these values and the radiological response was analyzed.

Results: Partial response was observed in 8 (28%) patients, stable disease in 18 (62%) patients, and progressive disease in 3 (10%) patients. Mean SUVmax of reference lesions was calculated as 23.8 ± 20.5 (min–max: 5.1–87.3). There was no significant correlation between radiological responses and SUVmax of reference lesions and their ratios to other organs.

Conclusion: Baseline Ga-68 DOTATATE PET/CT helps to show somatostatin receptor expression status and disease stage in patients who are candidates for PRRT. However, SUVs do not have a role in the prediction of treatment response.

Key words: Peptide receptor radionuclide therapy, Ga-68 DOTATATE positron emission tomography/computed tomography, treatment response

1. Introduction

Neuroendocrine tumors (NETs) are a heterogeneous group of neoplasms, mostly originating from the gastrointestinal system. At the time of diagnosis, they are generally in the advanced stage (1–3). At this stage, most cases are inoperable and therapeutic options are limited. Assessment of the disease stage is crucial in the selection of optimal treatment. Ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI) are commonly utilized imaging methods to evaluate the extent of the disease. Because NETs commonly overexpress somatostatin receptors, functional imaging techniques such as indium-111 octreotide, technetium-99m HYNIC scintigraphy, and positron emission tomography (PET) with Ga-68 labeled somatostatin analogs can be performed for assessment of the disease. Another advantage of functional imaging is the evaluation of appropriateness to peptide receptor radionuclide therapy (PRRT) as a treatment option (4–7).

PRRT with yttrium-90 (Y-90) or lutetium-177 (Lu-177) labeled somatostatin analogs is a promising treatment option in metastatic or inoperable NETs (8,9). As both Ga-68 and Lu-177 bind to similar synthetic somatostatin analogs, the relationship between tumor uptake in both methods has been the subject of interest. In the present study, analysis was applied to evaluate whether there was any relationship between standardized uptake values (SUVs) in baseline Ga-68 DOTATATE PET/CT and treatment response rates of NET patients who received fixed doses of PRRT with Lu-177 DOTATATE.

* This manuscript was accepted for oral presentation at the 2014 Annual Congress of the European Association of Nuclear Medicine.

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2. Materials and methods

2.1. Patients

This retrospective study comprised patients who received PRRT with Lu-177 DOTATATE for metastatic NETs in the Nuclear Medicine Department of the Ankara University Medical Faculty. The presence of metastatic or inoperable disease was confirmed by histopathological examinations as well as by morphological imaging methods in all patients. All the patients underwent routine physical examinations, hematological-biochemical tests, CT or MRI, and Ga-68 DOTATATE PET/CT before the treatment.

2.2. Ga-68 DOTATATE positron emission tomography/computed tomography

PET/CT images were acquired with a Discovery ST PET/CT scanner (General Electric, Milwaukee, WI, USA). Long-lasting somatostatin analogs were discontinued for at least 4 weeks before imaging. Preparation of Ga-68 DOTATATE doses was made with an automated synthesis unit (Scintomics GmbH, Fürstenfeldbruck, Germany). Images were obtained approximately 1 h after an intravenous injection of a dose of 100 MBq of Ga-68 DOTATATE. An oral contrast agent was given to patients with abdominal lesions in conventional imaging methods. Whole body PET/CT imaging from the vertex to the mid-thigh was performed while patients were in the supine position. CT images were obtained from the integrated PET/CT scanner with the use of a standardized protocol involving 140 kV, 70 mA, a tube-rotation time of 0.5 s per rotation, a pitch of 6, and a section thickness of 5 mm. Immediately after the CT imaging, PET images were obtained for 4 min per bed position. The PET images were reconstructed using nonintravenous contrast CT data for attenuation correction. PET/CT images were evaluated visually and semiquantitatively using maximum standardized uptake values (SUVmax). Focally increased uptake higher than liver uptake was accepted as malignant. A reference lesion that had the highest uptake and was easy to define was selected in all patients. The SUV of the reference lesion (RefSUV) was defined by drawing irregular regions of interest. In patients with more than one organ involvement, arithmetic mean SUVmax was calculated by selecting reference lesions from each organ. Irregular regions of interest were drawn from the normal liver (SUVL), spleen (SUVS), pancreas (SUVP), and adrenal glands (SUVA) with the same threshold. The ratios of RefSUV to SUVL, SUVS, SUVP, and SUVA were calculated.

2.3. Peptide receptor radionuclide treatment

Synthesis of Lu-177 DOTATATE doses was performed by the same automated synthesis system. A fixed dose of 7400 MBq was given to all patients in each cycle. While one patient received 8 cycles of treatment, the rest of them had 4 cycles. Before treatment, all the patients received a solution containing a 50-g cocktail of lysine and arginine (25 g of lysine and 25 g of arginine) diluted in 2 L of normal saline infused over 4 h, starting 30–60 min before treatment, and they were checked for renal functions over a 24-h period. Lu-177 DOTATATE planar and SPECT images were obtained at hour 24 of treatment.

2.4. Evaluation of treatment response

The response to treatment was evaluated with Ga-68 DOTATATE PET/CT. Baseline scans were performed within 2–4 weeks before the first cycle of PRRT, and scans were repeated 6 weeks after the last cycle. Radiological response was evaluated by RECIST criteria from the corresponding CT slices of the PET/CT images.

2.5. Statistical analysis

SPSS 16.0 (Chicago, IL, USA) was used for statistical analyses. Logistic regression model was used to analyze the relationship between Ga-68 DOTATATE PET/CT parameters and treatment response rates. $P < 0.05$ was accepted as statistically significant.

3. Results

3.1. Patients

A total of 29 patients (17 females and 12 males; mean age 50.7 ± 14.6 years) received 7400 MBq Lu-177 DOTATATE treatment for 4 or 8 cycles. Diagnoses were metastatic gastroenteropancreatic NETs in 25 (86%) patients, carcinoid tumor of the lung in 2 (7%), and medullary thyroid cancer in 2 (7%). In the evaluation of histopathological differentiation, NETs of 3 (12%) patients were moderately differentiated, and the rest of them were well differentiated. While primary tumor localizations were the pancreas, ileum, ovary, stomach, thyroid, lung, retroperitoneum, colon, and appendix in 9 (31%), 3 (8%), 2 (7%), 2 (7%), 2 (7%), 2 (7%), 2 (7%), 1 (4%), and 1 (4%) patients, respectively, it was undefined in 5 (18%) patients. Cycles of given treatments were 8 and 4 in 1 (3%) and 28 (97%) patients, respectively. More details of the descriptive features are presented in Table 1.

3.2. Treatment response

While partial response to treatment was observed in 8 (28%) patients, the disease was stable in 18 (62%) patients. The disease had progressed in 3 (10%) patients in the radiological evaluation. Mean SUVmax of reference lesions was calculated as 23.8 ± 20.5 (min–max: 5.1–87.3). In logistic regression analysis, no significant relationship was found between the radiological response rate and RefSUV and its ratios to SUVL, SUVS, SUVP, and SUVA. The statistical relationship between the PET/CT parameters and the response rate is shown in Table 2.

Table 1. Details of demographic features and treatment responses of patients.

Patient no.	Age	Sex	Diagnosis	Differentiation degree	Primary site	Metastases	Previous treatments	Sandostatin usage	Treatment cycles	Radiological response
1	31	F	NET	Well	Pancreas	LNs, bone	None	Yes	4	PR
2	76	F	NET	Well	Pancreas	LNs	Op, Chtx, PRRT	Yes	4	SD
3	72	F	NET	Well	Pancreas	Liver	Chtx, TACE	Yes	4	PD
4	65	M	NET	Well	Unknown	Liver, bone	None	Yes	4	PD
5	63	M	NET	Well	Colon	LNs, liver	Op, Chtx	No	4	SD
6	60	M	NET	Well	Stomach	Liver	Op, RFA	Yes	4	PD
7	57	M	NET	Well	Lung	Bone	Op, Chtx	Yes	4	PR
8	57	F	NET	Moderately	Unknown	LNs, liver, bone	Chtx, Rtx	No	4	SD
9	56	M	NET	Well	Retroperitoneum	Liver, kidney	Op, Chtx	Yes	4	PR
10	50	F	NET	Well	Stomach	LNs, liver	Op	Yes	4	SD
11	49	K	NET	Well	Unknown	LNs, liver	Chtx	No	4	PR
12	48	M	NET	Well	Pancreas	LNs, liver	Op, Chtx	Yes	4	PR
13	46	F	NET	Moderately	Pancreas	LNs, liver, bone	Chtx, Rtx	No	4	PR
14	39	K	NET	Well	Pancreas	Liver, bone	None	No	4	SD
15	38	M	NET	Well	Unknown	Pericardium	None	Yes	4	SD
16	36	F	NET	Well	Retroperitoneum	LNs	Op	No	4	PR
17	35	F	NET	Well	Ovary	LNs, liver	Op	Yes	4	SD
18	33	F	NET	Well	Lung	None	Chtx	No	8	SD
19	47	M	TMC	-	Thyroid	LNs, liver	Rtx	No	4	SD
20	35	F	TMC	-	Thyroid	LNs, liver, lung	None	No	4	SD
21	59	M	NET	Well	Ileum	Liver	Op, Chtx	Yes	4	SD
22	65	M	NET	Well	Pancreas	Liver	Op, SIRT	Yes	4	SD
23	56	F	NET	Moderately	Ileum	Liver	Op	Yes	4	SD
24	32	M	NET	Well	Unknown	LNs, liver	Op	Yes	4	SD
25	68	F	NET	Well	Appendix	Liver, spleen	Op, TACE, SIRT, RFA	Yes	4	SD
26	68	M	NET	Well	Ileum	Liver	Op, IFN	Yes	4	SD
27	19	F	NET	Well	Ovary	LNs, liver	Op, Chtx	No	4	PR
28	56	F	NET	Well	Pancreas	None		Yes	4	SD
29	50	F	NET	Well	Pancreas	Liver	Chtx	Yes	4	SD

Table 2. Statistical relationship between PET/CT parameters and treatment response.

Parameter	P-value for radiological response
RefSUV	0.25
RefSUV/SUVL	0.37
RefSUV/SUVS	0.48
RefSUV/SUVP	0.17
RefSUV/SUVA	0.36

4. Discussion

At the time of diagnosis, well or moderately differentiated neuroendocrine tumors are generally at an advanced or inoperable stage due to the asymptomatic course of the disease. Therefore, treatment options and expected benefits are limited. Long-acting somatostatin analogs, chemotherapy, and interferon-α have been demonstrated to have low response rates (10,11).

PRRT with Y-90 or Lu-177 labeled somatostatin analogs is a promising method at that stage of disease. However, in the literature, reported response rates to PRRT vary depending on the variation of selected patient populations and treatment protocols (12–15). In the present study, the response to PRRT was evaluated from radiological aspects. We have not performed functional evaluations due to the lack of standardized functional response evaluation criteria. A strong relationship between a decrease in tumor load and a decrease in Ga-68 DOTATATE uptake has not been proven. In addition, Ga-68 DOTATATE uptake difference might be related to loss of tumor differentiation. Therefore, objective and quantitative usage of Ga-68 DOTATATE PET/CT such as adaptation of PERCIST criteria was not possible. However, in consideration of the slow-growing nature of NETs and necrosis in the center of the tumor without a change in size, RECIST criteria might be insufficient in the evaluation of response to PRRT. A definition of new combined treatment response criteria for this group of malignancies would be helpful to standardize the data in the literature.

There is no doubt of the performance of Ga-68 DOTATATE PET/CT in the evaluation of appropriate candidates for PRRT. The present study was designed to research whether or not there is a direct relationship between SUVs in baseline Ga-68 DOTATATE PET/CT and treatment response rates in individual assessment. At first sight, it is reasonable to assume a relationship because both Ga-68 and Lu-177 bind to similar/the same synthetic somatostatin analogs. However, no significant correlation could be demonstrated between response rates and RefSUVmax or the ratio to SUVL, SUVS, SUVP, and SUVA. From a similar standpoint, Ezziddin et al. (16) researched the correlation of pretherapeutic SUV in Ga-68 DOTATOC PET with absorbed dose of Lu-177 DOTATATE and reported a significant correlation between these parameters. In the current study, as fixed doses were routinely administered without performing dosimetry, absorbed doses could not be interpreted. However, it would not be surprising to find a strong correlation between Ga-68 DOTATATE uptake and absorbed doses. Despite that relationship, there might be some other explanations for these results. First of all, NETs are a very large malignancy group with biological heterogeneity and different responsiveness levels to radiation therapy. The patient population was also heterogeneous with different treatment histories, which could affect somatostatin receptor expression levels. Another explanation might be the fixed dose protocol. In a recent study by Sabet et al. (17), somatostatin receptor saturation levels with fixed-dose PRRT were assessed. It was demonstrated that in some patients with bulky tumors, somatostatin receptor saturation could not achieve relevant levels with fixed doses. Therefore, in some patients with a bulky tumors, maximum doses might not have been delivered to the tumor for treatment response despite high Ga-68 DOTATATE uptake. Similar to the current study's data, Gabriel et al. (18) did not find any relationship between tumor response and SUVs of Ga-68 DOTATATE PET/CT. However, recently Oksüz et al. (19) showed a correlation in SUVs of reference lesions and treatment response with a cutoff value of 17.9. Differing from the current study, a mixed response classification and different time period were used for Ga-68 DOTATOC imaging.

In consideration of the different data in the literature, a new prospective, randomized study with a patient population as homogeneous as possible should be designed to demonstrate the real relationship between tumor uptake in Ga-68 DOTATATE PET/CT and the response to PRRT. In addition, because of the above-mentioned limitations of the assessment of the response with functional or radiological methods only, the relationship between tumor uptake and progression-free survival times might be evaluated. Until the literature becomes more clear, during evaluation of baseline Ga-68 DOTATATE PET/CT images, it is beneficial to assume that there is no relationship between tumor Ga-68 DOTATATE uptake and treatment response.

In conclusion, baseline Ga-68 DOTATATE PET/CT helps to demonstrate somatostatin receptor expression status and disease stage in patients who are candidates for PRRT. However, treatment response is independent from tumor Ga-68 DOTATATE uptake.

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