

Metastatic Neuroendocrine Tumor with Extensive Bone Marrow Involvement at Diagnosis: Evaluation of Response and Hematological Toxicity Profile of PRRT with ^{177}Lu -DOTATATE

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Abstract

The aim of this study was to evaluate the response and hematological toxicity in peptide receptor radionuclide therapy (PRRT) with lutetium (^{177}Lu)-DOTA-octreotate (DOTATATE) in metastatic neuroendocrine tumor (NET) with extensive bone marrow metastasis at the initial diagnosis. A retrospective evaluation was undertaken for this purpose: Patients with NET with extensive diffuse bone marrow involvement at diagnosis who had received at least three cycles of PRRT with ^{177}Lu -DOTATATE were considered for the analysis. The selected patients were analyzed for the following: (i) Patient and lesional characteristics, (ii) associated metastatic burden, (iii) hematological parameters at diagnosis and during the course of therapy, (iv) response to PRRT (using a 3-parameter assessment: Symptomatic including Karnofsky/Lansky performance score, biochemical finding, and scan finding), (v) dual tracer imaging features [with somatostatin receptor imaging (SRI) and fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT)]. Based on the visual grading, tracer uptake in somatostatin receptor (SSTR)-positive bone marrow lesions were graded by a 4-point scale into four categories (0-III) in comparison with the hepatic uptake on the scan: 0 - no uptake; I - clear focus but less than liver uptake; II - equal to liver uptake; and III - higher than liver uptake]. Hematological toxicity was evaluated using National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 score. A total of five patients (age range: 26-62 years; three males and two females) with diffuse bone marrow involvement at the diagnosis was encountered following analysis of the entire patient population of 250 patients. Based on the site of the primary, three had thoracic NET (two patients bronchial carcinoid and one pulmonary NET) and two gastroenteropancreatic NET (one in the duodenum and one patient of unknown primary with liver metastasis). Associated sites of metastases included the liver ($n = 5$), breast ($n = 1$), and aortocaval nodes ($n = 1$). On baseline diagnostic study [^{68}Ga -DOTANOC/TATE or the technetium ($^{99\text{m}}\text{Tc}$)-hydrazinonicotinamide (HYNIC)-tektrotyd (TOC)], tracer uptake in the bone marrow in all patients was Grade III. At the time of analysis, the patients received three to four cycles of PRRT and a cumulative dose of 16.1-25.6 GBq, with a follow-up duration ranging 10-27 months. The response as assessed by three parameters: (i) Symptomatic: All patients (except for one) reported excellent symptomatic palliation and better quality of life with improvement of Karnofsky/Lansky scores; the single case with nonresponse had shown symptomatic response in the initial 6 months following which he had a progressive disease and death at 18 months (ii) biochemical: Three patients had shown more than 50% reduction in the serum chromogranin level, one had shown increase but had demonstrated clinical evidence of response with radiologically stable disease while the other who had shown slight increase of chromogranin A (CgA) level had shown progressive disease thereafter (iii) radiological: Three patients demonstrated partial response (on FDG-PET/CT), one patient had stable disease and one patient had progressive disease following initial clinical response. As per the NCI-CTCAE score, only one patient had persistent Grade I anemia without any deterioration with the administered dose at the time of analysis. FDG uptake in the bone marrow metastatic lesions showed no obvious FDG avidity on visual

assessment except for two patients (low-grade FDG uptake). Interestingly, the associated metastatic lesions [except for patient I with Mib1 labeling index (LI): 1-2%], demonstrated high FDG avidity. Thus, we observed that the majority (in our series four out of five patients, i.e. 80%) of the patients had excellent symptomatic response with at least stabilization of the disease at a follow-up period of 10-27 months. The single patient who had a progressive disease also had a good symptomatic response in the initial 6 months from the first

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dose of PRRT. Despite the extensive bone marrow involvement, no hematological toxicity was observed (only one patient showed Grade I anemia), suggesting that PRRT is well-tolerated by this particular subgroup.

Keywords: Bone marrow metastasis, neuroendocrine tumor, peptide receptor radionuclide therapy, lutetium (^{177}Lu)-DOTA-octreotate (DOTATATE)

Introduction

Bone marrow metastases from neuroendocrine tumor (NET) have been primarily reported as individual case studies; a literature search on the topic yielded only four such reports since 2009 over the last 6 years, all as case reports.^[1-4] With increasing use of peptide receptor radionuclide therapy (PRRT) in patients with NET, it is imperative to assess the response of this particular subgroup to this novel somatostatin receptor (SSTR) targeted therapy. Thus, we evaluated the patient characteristics, response profile, and toxicity profile (focusing primarily on bone marrow toxicity) of this particular subset of patients selected from a population of 250 patients of NET who had undergone PRRT over last 5 years in a large tertiary care center. For an appropriate assessment of treatment response and associated toxicity, we selected those patients who had received at least three cycles of PRRT. In our analysis, however, there was no patient of this particular subgroup who received less than three cycles or in whom PRRT was terminated with fewer cycles.

Materials and Methods

This was a retrospective analysis of NET patients (a population of 250 patients treated over the last 5 years) who had undergone PRRT with lutetium (^{177}Lu)-DOTA-octreotate (DOTATATE) at a large tertiary care center. The patients selected for the study fulfilled the following criteria: These patients demonstrated diffuse bone marrow metastases on initial diagnostic study [^{68}Ga -DOTANOC/TATE or the technetium ($^{99\text{m}}\text{Tc}$)-hydrazinonicotinamide (HYNIC)-tektrotyd (TOC)] and had received at least three cycles of PRRT with ^{177}Lu -DOTATATE.

The selected patients were analyzed under the following parameters: (i) Patient characteristics, (ii) associated metastatic burden, (iii) hematological parameters at diagnosis and during the course of therapy, (iv) response (using a 3-parameter assessment: Symptomatic including Karnofsky/Lansky performance score and biochemical and scan features), and (v) dual tracer imaging features [with somatostatin receptor imaging (SRI) and fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT)] and correlation with response.

Based on the visual grading, tracer uptake in SSTR-positive bone marrow lesions were graded by a 4-point scale into four categories 0-III in comparison with the hepatic uptake on the scan: 0 - no uptake; I - clear focus but less than liver uptake; II: Equal to liver uptake; III: Higher than liver uptake). With respect to associated number of metastases at other sites, the patients were subdivided into two subgroups: Group A (those patients with less than five metastases) and Group B (those with more than five target lesions at other locations). Hematological toxicity was evaluated using National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 score.

A comparative assessment was undertaken using dual tracer imaging approach between SRI and FDG-PET/CT imaging with regard to the following: (a) At the bone marrow level and (b) at the associated metastatic sites. The overall response was correlated with the imaging features.

Observations and Results

On analyzing the entire patient population of 250 patients, it yielded a total of five patients with diffuse bone marrow involvement at diagnosis with age ranging from 26 years to 62 years; it included three males and two females. Based on the site of the primary, three patients had thoracic NET (two patients had bronchial carcinoid and one patient had pulmonary NET) and two patients had GEP-NET (one in the duodenum and one patient of unknown primary with liver metastasis) [Table 1a].

Table 1a: Patient and lesion characteristics

Characteristics	Values
Age distribution	26-62 years
Sex (male: female)	3:2
Site of primary	
Lung/bronchial carcinoid	3
Unknown primary	1
Duodenum	1
Number of metastases	
>5	5
<5	0
Grade of HYNIC/gallium uptake	
Grade 0 (no uptake)	0
Grade I (less than liver)	0
Grade II (equal to liver)	0
Grade III (more than liver)	5

HYNIC: Hydrazinonicotinamide

Associated sites of metastases included the liver (most predominant and involved in all five patients), breast (patient III), and aortocaval nodes (patient I), in addition to the primary sites as applicable in each patient.

Cumulative dose and hematological toxicity profile

On baseline diagnostic study (^{68}Ga -DOTANOC/TATE or $^{99\text{m}}\text{Tc}$ -HYNIC-TOC), tracer uptake in the bone marrow in all patients was Grade III [Table 1a]. With regard to the number of metastases at other sites, all patients belonged to Group B, that is, all had more than five target lesions at other sites [Table 1a]. The detailed patient- and lesion-specific histopathological characteristics have been depicted in Table 1b. At the time of analysis, the patients received PRRT with ^{177}Lu -DOTATATE of three to four cycles and a cumulative dose of 16.1-25.6 GBq [Table 2a]. The duration of follow-up ranged 10-27 months [Table 2a]. As per the NCI-CTCAE score, only one patient had persistent Grade I anemia without any deterioration with the administered dose at the time of analysis [Tables 2a and b].

Response assessment

The response to PRRT was assessed by three parameters: (i) Symptomatic: All patients, except for one patient (Case IV), reported excellent symptomatic palliation and better quality of life including better Karnofsky/Lansky performance score (detailed symptomatic response, along with subjective description stated in Tables 3a and b); the single case with nonresponse had shown response in the initial 6 months following which

he had progressive disease and death at 18 months. Scan-wise, however, he had a stable disease and the death was primarily due to massive effusion and ascites consistent with extensive hepatic involvement and hypoalbuminemia; (ii) biochemical: Three patients had shown more than 50% reduction in the serum chromogranin level, one had shown an increase (patient I) but had demonstrated clinical evidence of response while the other (patient IV) who had shown a slight increase of chromogranin A (CgA) level had shown progressive disease thereafter; (iii) radiological: Three patients demonstrated partial response (on FDG-PET/CT [Figure 1], whereas SRI showed stable disease in these cases), one had stable disease [Figure 2] and one patient had progressive disease following initial clinical response.

SRI and FDG-PET/CT correlation

Comparison between SRI and FDG-PET/CT between the bone marrow lesions and the associated lesions at other organ sites revealed the following [Table 4]:

- Bone marrow lesions: FDG uptake in the bone marrow metastatic lesions showed no obvious lesion on visual assessment except for patient II and patient V, who showed low-grade FDG uptake
- Associated metastatic lesions: Interestingly, the associated metastatic lesions, except in the case of patient I, demonstrated FDG avidity and hence, in terms of overall assessment showed partial concordance (where the associated metastatic lesions showed concordance and the bone marrow lesions were discordant with respect to tracer uptake among the two diagnostic studies). The solitary case that had a progressive disease had partial concordance.

Table 1b: Patient- and lesion-specific histopathological characteristics

Patient	Site	Histopathological characteristics
Case I	Lung	Well-differentiated NET Lung; Mib1 LI: 1-2%
Case II	Unknown primary with metastases to the liver	Liver lesion Bx: NET; Mib1 LI: 12%
Case III	Duodenal NEC	Mib1 LI: 20%
Case IV	Bronchial carcinoid	Well-differentiated NET (Mib1 LI not available)
Case V	Bronchial carcinoid	Well-differentiated NET (Mib1 LI not available)

NET: Neuroendocrine tumor; NEC: Neuroendocrine carcinoma

Table 2a: Individual patient specific treatment details and hematological toxicity profile

Patient	Number of cycles of PRRT given (cumulative activity in GBq)	Duration of follow-up (months)	Hematological toxicity		
			Anemia	WBC* count	Platelet count
Case I	3 (17.2 GBq)	12	-	-	-
Case II	3 (14.9 GBq)	10	+ (grade I persistent)	-	-
Case III	4 (25.6 GBq)	27	-	-	-
Case IV	3 (20.9 GBq)	18	-	-	-
Case V	3 (16.1 GBq)	16	-	-	-

*WBC: White blood cell; PRRT: Peptide receptor radionuclide therapy

Discussion

PRRT with ^{177}Lu -DOTATOC/TATE has been a promising novel receptor targeted therapy in advanced neuroendocrine tumors that has gained substantial popularity over recent times.^[5,6] The standard guideline recommendation for PRRT includes well-differentiated Grade 1 and Grade 2 NETs [Mib1 (Ki-67) LI of up to 20 %] that express SSTR positivity, as evaluated by SRI with ^{68}Ga -DOTA-TOC/

Table 2b: Individual patient and PRRT cycle-wise details of hematological toxicity profile

	PRRT Cycle	Number of months of follow-up	Toxicity		
			Anemia	Hb*	Platelet
Case I	Baseline		-	-	-
	1 st cycle of PRRT	3	-	-	-
	2 nd cycle of PRRT	6	-	-	-
	3 rd cycle of PRRT	12	-	-	-
Case II	Baseline		+	-	-
	1 st cycle of PRRT	3	+	-	-
	2 nd cycle of PRRT	6	+	-	-
	3 rd cycle of PRRT	10	+	-	-
Case III	Baseline		+	-	-
	1 st cycle of PRRT	3	-	-	-
	2 nd cycle of PRRT	8	-	-	-
	3 rd cycle of PRRT	12	-	-	-
Case IV	Baseline		-	-	-
	1 st cycle of PRRT	6	-	-	-
	2 nd cycle of PRRT	11	-	-	-
	3 rd cycle of PRRT	16	-	-	-
Case V	Baseline		-	-	-
	1 st cycle of PRRT	4	-	-	-
	2 nd cycle of PRRT	11	-	-	-
	3 rd cycle of PRRT	16	-	-	-

*Hb: Hemoglobin; PRRT: Peptide receptor radionuclide therapy

TATE/NOC PET-CT or ^{99m}Tc-HYNIC-TOC scintigraphy or ¹¹¹In-octreoscan. The recently published European Society for Medical Oncology (ESMO) Clinical Practice Guidelines^[5] have recommended PRRT up to the upper limit of Ki-67 LI to 30%. There has been an increasing emphasis on critically exploring the various subsets of patients with NET with regard to evaluation of clinical response and the adverse effects of this therapy. Also, based on histopathological subtypes, sites of disease involvement, molecular imaging parameters, there have been endeavors toward the development of personalized model and decision-making.^[7-9]

Diffuse bone marrow involvement in NET on pretreatment diagnostic study is a relatively uncommon but definitive entity that could be encountered in clinical PRRT practice. In our study, we focused to this particular subgroup with respect to the efficacy and safety of PRRT. All recruited patients received at least three cycles of therapy with ¹⁷⁷Lu-DOTATATE. We observed that the majority (in our series, four out of five patients, i.e. 80%) had excellent symptomatic response with at least stabilization of the disease at a follow-up period of 10-27 months. The single patient who had a progressive disease also had a good symptomatic

Table 3a: Individual patient-specific response in three parameters at the time of analysis

	Clinical response	Radiological response	Biochemical response (serum CgA level) µg/L	Progression-free survival (months)
Case I	+++	SD*	575→2800	12
Case II	+++	PR (by FDG-PET/CT)	3520→46.1	10
Case III	+++	PR (by FDG-PET/CT)	1135→462	27
Case IV	Initial response followed by progression	PD** and death (scan-wise SD)	716→797	Initial 6 months. Subsequently disease progression and death at 18 months following the 1 st dose
Case V	+++	PR (by FDG-PET/CT)	75,935→17,982	16

*SD: Standard deviation; **PD: Progressive disease; FDG-PET/CT: Fluorodeoxyglucose-positron emission tomography/computed tomography; CgA: Chromogranin A; PR: Partial response

Table 3b: Detailed clinical response, along with subjective description

	Clinical response	
	Symptom-specific response	Karnofsky/Lansky performance score
Case I	Baseline: severe skeletal pain; the patient was wheelchair-bound	Baseline: 50
	After treatment: At 3 months after 1 st cycle, totally symptom-free; complete resolution of skeletal pain. Still asymptomatic	Post 1 st cycle: 100 Subsequent cycles: 100
Case II	Baseline: severe skeletal and abdominal pain; weight loss and diarrhea	Baseline: 70
	After treatment: Gradual decrease in all symptoms with about 70% relief in all symptoms at the end of 3 cycles	Post 1 st cycle: 80 Subsequent cycles: 90
Case III	Baseline: Weight loss and abdominal pain	Baseline: 80
	After treatment: Complete resolution of abdominal pain after 1 st cycle with weight gain over the subsequent cycles (40 kg over 24 months)	Post 1 st cycle: 90 Subsequent cycles: 100
Case IV	Baseline: Dry cough, dyspnea, and weight loss.	Baseline: 80
	After treatment: Initially relief of dry cough and dyspnea but weight loss persists. Gradually cough and dyspnea present again at the time of the 2 nd cycle, along with massive ascites and pleural effusion	Post 1 st cycle: 80 Post 2 nd cycle and 3 rd cycle: 50
Case V	Baseline: Uncontrolled episodes of sweating, flushing, and diarrhea. The patient was on daily short acting octreotide injections.	Baseline: 80
	After treatment: Gradual reduction in the symptoms in the reduction of symptoms and frequency of octreotide injections. Post 3 rd cycle PRRT complete resolution of all symptoms with complete cessation of octreotide injections	Post 1 st cycle and 2 nd cycle: 90 Post 3 rd cycle: 100

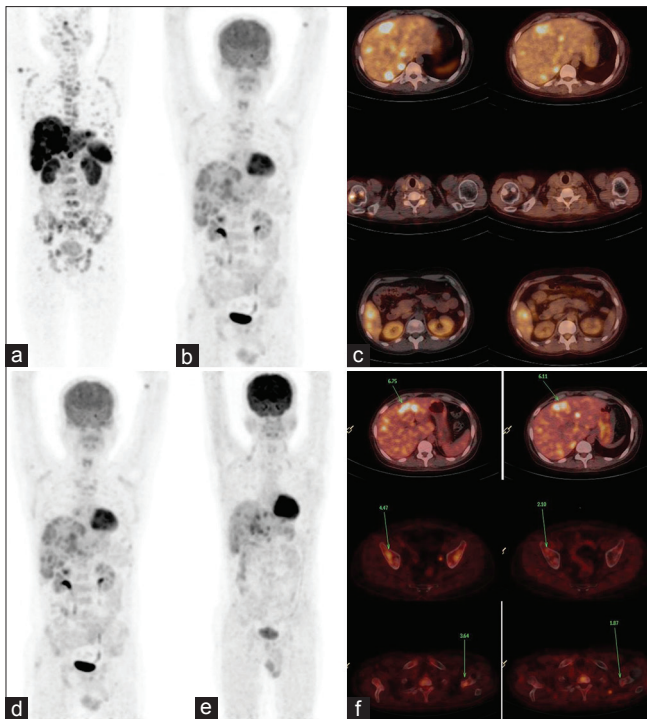


Figure 1: A 38 year-old male, a known case of well-differentiated bronchial carcinoid (operated primary) presented with multiple uncontrolled episodes of sweating, flushing, and diarrhea. The patient was on daily short acting octreotide injections. On ⁶⁸Ga-DOTANOC PET/CT (a), there was multiple and extensive metastatic liver and skeletal marrow involvement. FDG-PET/CT (b) demonstrated uptake in some of the hepatic metastatic foci and very low-grade uptake in the bone marrow. Figure 1c (depicting transaxial slices of both studies side by side) further substantiates this. Following three cycles of PRRT the patient demonstrated complete resolution of all symptoms with complete cessation of octreotide injections. The FDG-PET/CT comparison (d-f) showed a partial response of the FDG concentrating lesions

Table 4: Dual tracer imaging comparison with SRI and FDG-PET/CT for marrow and other associated metastatic lesions

	Pattern of FDG uptake		Relation between SSTR and GLUT* expression
	Marrow metastases	Associated metastatic lesions	
Case I	No FDG uptake	Low grade	Discordant
Case II	Low grade	Intense	Partial concordance
Case III	No FDG uptake	Intense	Partial concordance
Case IV	No FDG uptake	Intense	Partial concordance
Case V	Low-grade FDG uptake	Intense	Partial concordance

*GLUT: Glucose transporter; SRI: Somatostatin receptor imaging; FDG-PET/CT: Fluorodeoxyglucose-positron emission tomography/computed tomography; SSTR: Somatostatin receptor

response in the initial 6 months since the first dose of PRRT. Despite the extensive bone marrow involvement, no hematological toxicity was observed (only one patient showed persistent Grade I anemia present at the baseline), suggesting that PRRT was well-tolerated

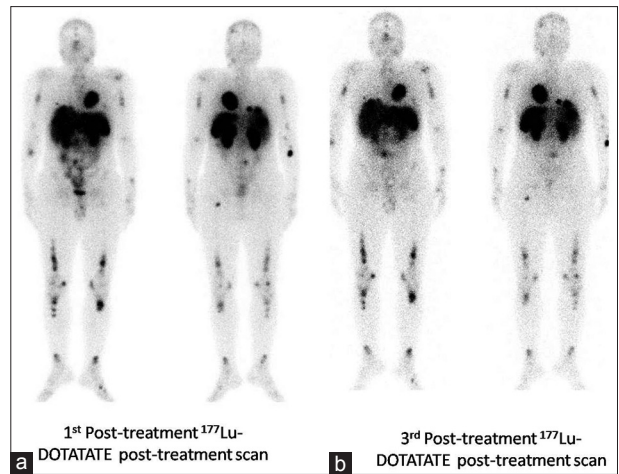


Figure 2: A 26-year-old male, a diagnosed case of NET lung (Mib1 LI: 1-2%), presented with severe skeletal pain (the patient was wheelchair-bound). At 3 months after the first cycle, he became totally symptom-free with complete resolution of skeletal pain. After three therapies and at 12 months since the first therapy, he continues to be asymptomatic. The first (a) and third (b) posttreatment ¹⁷⁷Lu-DOTATATE scans show stable disease

by this particular subgroup. Interestingly, a behavioral heterogeneity (by molecular imaging features) was observed between the bone marrow lesions and the associated metastatic sites that need to be further studied for its possible implications.

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