Metastatic Merkel Cell Carcinoma responding favourably to targeted therapy with $^{177}$Lu-DOTATATE: will PRRT evolve as an important treatment approach in Receptor positive cases?

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Abstract

Excellent partial response with a single cycle of peptide receptor radionuclide therapy (PRRT) with $^{177}$Lu-DOTATATE in Merkel cell carcinoma with multiple bilobar hepatic metastases is illustrated in this report. Documentation of such response coupled with minimal side effects would warrant consideration of this therapy early in the disease course, if the metastatic lesions demonstrate adequate tracer avidity on Somatostatin receptor (SSTR) based imaging (rather than in an advanced state following failure of other therapies). Our patient demonstrated systemic disease progression following the second surgery and adjuvant radiotherapy to head and neck and chemotherapy and hence was considered for PRRT. The metastatic lesions demonstrated both SSTR and FDG avidity in the pre-treatment diagnostic study. Scan evidence of partial response in both scan parameters at 3 months before being worked up for the 2nd cycle of PRRT including two lesions demonstrated near-complete resolution. In view of the relative well tolerability, minimal side-effects and targeted nature of the treatment, PRRT can evolve as the first line therapy in patients of metastatic Merkel Cell carcinoma and needs further examination in more patients in the future.

Introduction

Merkel cell carcinoma (MCC) is an aggressive dermatological malignancy of the Merkel cells situated just below the epidermis and very close to the nerve endings that receive the touch sensation. Sun exposure, weak immune system, and psoralen and ultraviolet A (PUVA) therapy for psoriasis, are known risk factors [1]. Their association with neuroendocrine origin and function is postulated and hence various terminologies that have been used synonymously to denote this as primary neuroendocrine carcinoma of the skin, cutaneous APUDOMA, primary small cell carcinoma of the skin, and trabecular carcinoma of the skin [1]. While patients with small tumors without any regional spread have good prognosis (estimated 5-year survival of
around 80%), those with regional spread have an approximate 5 year survival of 50% and that of all stages combined being 60% [2, 3] with conventional treatment with radiation and chemotherapy. Thus, there is a need to explore newer therapeutic options in patients with metastatic MCC with an aim to improve survival.

Microscopic examination (both light and electron microscopy) and immunohistochemistry are the primary procedures for the definitive diagnosis. While wide local excision with adjuvant irradiation is the usual current treatment approach, neck dissection is employed for clinically positive nodes. Contrast enhanced CT scan had been the standard imaging modality for disease staging. In recent years, the potential of FDG-PET and somatostatin receptor based 68Ga-DOTA NOC/TATE PET-CT have been emphasized in the literature [4, 5]. In one of the early reports, metastatic disease in subcentimeter lymph nodes on pretreatment FDG-PET/CT was detected that were not appreciated on initial CT images. The post-treatment FDG PET scans were found to correctly depict response to therapy through the level of FDG uptake in the same report [4]. In a recently reported study of 24 patients of MCC with 68Ga-DOTATOC/TATE PET, the sensitivity of SSTR-PET was 73% for nodal disease, 100% for bone, and 67% for soft-tissue metastases respectively while the brain metastases were first detected by SSTR-PET in 2 patients [5]. These findings suggest the potential of PET imaging (with both FDG and somatostatin receptor based imaging) in MCC.

**Case Report:**

A 54 year old male, diagnosed patient of Merkel Cell carcinoma had earlier undergone surgery two times; the first surgery was wide local excision 3 years previously for right malar skin nodule. The second surgery was for recurrence in the same area with involvement of cervical lymph nodes for which he had undergone excision of recurrent right infraorbital skin nodule, right parotidectomy and right neck dissection for right infraparotid and right submandibular lymphadenopathy. Following the second surgery for the disease recurrence, the patient received external radiotherapy to right head and neck region and chemotherapy with capecitabine and temozolamide in an adjuvant setting. He presented with recent onset abdominal pain. An ultrasonography of abdomen revealed two hypoechoic lesions (2.5x 2 cm and 2.4 x1.7 cm) in right lobe of the liver. The contrast enhanced CT scan of the abdomen showed multiple
liver lesions with largest 2x1.8 cm. In view of systemic disease progression despite radiochemotherapy, he was considered for PRRT, for which formal consent was taken following Institutional norms.

He was administered 5735 Megabecquerel (Mbq) of 177Lu-DOTA-octreotate intravenously alongwith amino acids (for nephroprotection) following the standardized treatment protocol. PRRT with 177Lu-DOTATATE was considered in view of bilobar hepatic metastases positive on 68Ga-DOTATATE PET/CT (Krenning score of 3), the administered dose was decided, as per the approach followed for the fixed dose regimen mentioned in the joint IAEA, EANM, and SNMMI practical guidance on peptide receptor radionuclide therapy (PRRNT) and our Institutional protocol followed for the NETs (5550-7400 MBq).

At follow-up, two lesions in segment VIII showed complete resolution on both 68Ga-DOTATATE and FDG-PET/CT studies whereas lesions in segment IVA, VI and V (2 lesions) demonstrated reduction in tracer avidity (Fig 1A and 1B). The SUVmax on FDG-PET/CT showed reduction in segment VI lesion from 11.28 to 6.7; 2 segment IVA lesions from 9.96 to 7.35 and from 16.73 to 13.65 respectively; 2 segment V lesions from 14.91 to 11.89 and 11.12 to 9.8. In view of excellent partial response obtained and the patient becoming asymptomatic at 3 months assessment, he was recently administered the 2nd cycle of PRRT with 7400 MBq 177Lu-DOTATATE and is being followed up for further disease outcome.

Discussion

Targeted somatostatin receptor (SSTR) based PRRT has emerged as a promising new therapeutic approach in neuroendocrine tumors (NETs), specifically the metastatic gastroenteropancreatic NETs (GEP-NETs). This molecular receptor targeted radionuclide therapeutic approach also holds promise in other malignancies that have neuroendocrine component such as metastatic medullary carcinoma of thyroid (MCT), pulmonary NET and hence is being increasingly explored in these clinical settings. Because of the relative rarity of MCC, there have not been any clearcut consensus about the therapeutic regimen in the presence of metastatic disease in MCC and there is a clear need of examining newer therapeutic regimens. There have been 2 published reports of employing PRRT in the setting of Merkel Cell
carcinoma, both of which used synchronous PRRT and radiosensitizing chemotherapy [6, 7]. In the report by Schmidt et al, two patients with progressive disease with chemotherapy were treated with PRRT with documentation of temporary partial response in both patients though the patients expired 10 and 14 months after first clinical symptoms [6]. Salavati et al reported a case of stage IV MCC with an impressive improvement of the clinical symptoms with synchronous PRRNT and radiosensitizing chemotherapy [7]. Mixed response was documented on follow-up (18)F-FDG and (68)Ga-somatostatin-receptor PET/CT [7].

In the present case, in view of the recent history of disease progression following adjuvant radio-chemotherapy, administration of only PRRT was decided with which objective evidence of partial response was documented. The response evaluation following PRRT is done through 3 parameters: (a) symptomatic response, (b) scan response and (c) tumor marker response. The toxicity profile is assessed by renal function, haematological profile and hepatic function. They were undertaken in this particular case as mentioned in Table 1A and 1B.

Conclusion

In view of the relative well tolerability, minimal side-effects and good disease control, PRRT can evolve as the first line targeted therapy in patients of metastatic Merkel Cell carcinoma and needs to be examined further in high power prospective studies in the future.
References


Fig 1A and 1B. MIP and transaxial slices of the whole body 68-Gallium DOTATATE PET-CT (Fig 1A) and 18-F-FDG PET/CT scan (Fig 1B) demonstrating near-complete resolution of 2 lesions in segment VIII whereas lesions in segment IVA, VI and V (2 lesions) demonstrated reduction in tracer avidity.
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<th>RFT</th>
<th>Blood Parameters</th>
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<td></td>
<td></td>
<td>Urea</td>
<td>Creatinine</td>
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<tr>
<td><strong>Baseline</strong></td>
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<tr>
<td><strong>Post 1st cycle PRRT</strong></td>
<td>14.2</td>
<td>0.5</td>
<td>13.1</td>
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**Table 1A.** The RFT, hematologicy and the LFT parameters at baseline and at 3 months following first cycle of PRRT

(Abb: RFT=Renal function test; LFT=Liver function test; Hb=Hemoglobin; Plt=Platelet);

[Normal Values : Hb – 13 -15 gm% ; TLC – 4000-11000/mm³ Platelets 150000-450000/mm³

Urea – 13 -45 mg/dl ; Creatinine – 0.5-1.5 mg/dl ; SGOT – 15 – 37 U/L ; SGPT 30 – 65 U/L ; ALP 50- 136 U/L; Tot. Bilirubin 0.3 – 1.2 mg/dl]
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<tr>
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<th>Renal scan parameters</th>
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<td></td>
<td>GFR</td>
<td>ERPF</td>
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<tr>
<td><strong>Baseline</strong></td>
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<td>544.46</td>
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<tr>
<td><strong>Post 1st cycle PRRT</strong></td>
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<td>576.3</td>
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**Table 1B.** The baseline and 3-month 1st cycle post PRRT renal scintigraphy parameters and the serum chromogranin A values.

[Normal Values : GFR : 80 -120 ml/min; ERPF : 450 – 600 ml/min; Serum Chromogranin A: <98 ng/ml]