Peptide Receptor Radionuclide Therapy in Merkel Cell Carcinoma: A Comprehensive Review

Emran Askari*[1], Soroush Zarehparvar Moghadam*[1], Damian Wild[2], Ebrahim Delpassand[3], Sergio Baldari[4], Bernhard Nilica[5], Philipp E. Hartrampf[6], Grace Kong[7], Chiara Maria Grana[8], Martin Alexander Walter[9], Francesca Capoccetti[10], Pashtoon Murtaza Kasi[11], and Jonathan Strosberg[12]

[1]Nuclear Medicine Research Center, Mashhad University of Medical Sciences, Mashhad, Iran; [2]ENETS Center of Excellence, Radiology and Nuclear Medicine, University Hospital Basel, Basel, Switzerland; [3]Department of Clinical Nuclear Medicine, Excel Diagnostics Imaging Clinic, Houston, Texas; [4]Nuclear Medicine Unit, Department of Biomedical and Dental Sciences and of Morpho-Functional Imaging, University of Messina, Messina, Italy; [5]Department of Nuclear Medicine, Medical University Innsbruck, Innsbruck, Austria; [6]Department of Nuclear Medicine, University Hospital Würzburg, Würzburg, Germany; [7]Sir Peter MacCallum Department of Oncology and Molecular Imaging and Therapeutic Nuclear Medicine, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia; [8]Division of Nuclear Medicine, European Institute of Oncology, IRCCS, Milan, Italy; [9]Nuclear Medicine and Molecular Division, Geneva Medical Hospital, Geneva, Switzerland; [10]UOC Nuclear Medicine–PET Center–Single Regional Center for Radiometabolic Therapy, Department of Radiological Diagnosis and Services, ASUR Marche Area Vasta 3, Macerata, Italy; [11]Meyer Cancer Center and Englander Institute of Precision Medicine, Weill Cornell Medicine, New York Presbyterian Hospital, New York, New York; and [12]Neuroendocrine Tumor Division, Gastrointestinal Department, Moffitt Cancer Center, Tampa, Florida

Merkel cell carcinoma is a rare, aggressive skin malignancy, also known as neuroendocrine carcinoma of the skin, with high rates of recurrence and distant metastasis. In refractory metastatic Merkel cell carcinoma (mMCC), besides immunotherapy, chemotherapy, and radiation, peptide receptor radionuclide therapy (PRRT) may be a viable option since this type of tumor can express somatostatin receptors. **Methods:** We performed a comprehensive review of the literature to evaluate the efficacy of PRRT in mMCC patients. **Results:** Thirty-seven patients with mMCC received PRRT (1–5 cycles) with ^{177}Lu- or ^{90}Y-labeled somatostatin analogs (cumulative activity, 1.5–30 GBq). Radiographic response was available for 19 of 28 patients who received PRRT alone. Six (31.6%) of 19 patients showed objective responses, from partial to complete, and no severe adverse events were reported. **Conclusion:** Our analysis supports the use of PRRT in mMCC with sufficient somatostatin receptor uptake, although the quality of the available evidence is low. Prospective clinical trials are already in development and have started accruing in some parts of the world.

Key Words: PRRT; SSTR; Merkel cell carcinoma; theranostics; Lu-177

J Nucl Med Technol 2023; 51:22–25
DOI: 10.2967/jnmt.122.264904

Merkel cell carcinoma (MCC) is a rare, aggressive skin malignancy. The known risk factors for MCC are immunosuppression and extensive exposure to ultraviolet light. It usually occurs in elderly patients (median age, 70 y); typically arises in the head, neck, or extremities; and is slightly more common in men. Treatments for MCC vary depending on the stage of the disease, from complete surgical resection with or without radiation therapy for localized disease to systemic therapies (immunotherapy or chemotherapy) for metastatic disease. The 5-y survival rates for patients with metastatic disease have been approximately 18% (*1,2*). Although the introduction of immune checkpoint inhibitors has shown promising results, with an approximately 50% objective response, about half of patients with metastatic MCC (mMCC) experience disease progression or resistance.

At least one third of MCC cases express high levels of somatostatin receptors (SSTRs) (*3,4*). In some studies, SSTR expression has been reported in as many as 80%–100% of MCC cases (*5*). There have even been reports of using SSAs for the treatment of MCC (*4*). A recent trial of a novel second-generation SSA (pasireotide) allowed MCC patients to participate given the SSTR expression (NCT01652547). All this sets the stage for a new therapeutic option of theranostics/peptide receptor radionuclide therapy (PRRT) in MCC.

MATERIALS AND METHODS

Data on PRRT in MCC exist only in the form of case reports or series. A search for articles or abstracts pertaining to "PRRT" and "MCC" on PubMed, Scopus, and Google Scholar was systematically performed. Articles or abstracts published up to January 2022 were retrieved. The references of all relevant studies were evaluated as well. We also contacted centers that had previously reported experience with SSTR imaging or therapy in mMCC patients (the search strategy and PRISMA flow diagram can be found in Supplemental Figs. 1 and 2; supplemental materials are available at http://jnmt.snmjournals.org) (*6–26*). Overall, 37 patients with mMCC have received PRRT with ^{177}Lu- or ^{90}Y-labeled somatostatin analogs

Received Sep. 10, 2022; revision accepted Sep. 14, 2022.
For correspondence or reprints, contact Jonathan Strosberg (jonathan.strosberg@moffitt.org).
*Contributed equally to this work.
Published online Oct. 4, 2022.

TABLE 1
Review of Studies Evaluating Treatment Response to PRRT Monotherapy in mMCC (n = 10)

Study	Age (y)	Sex	Primary location	Other sites of involvement	Type of radiotracer, cumulative dose, and no. of cycles	Treatments before PRRT					Survival from start of PRRT (mo)	Response to PRRT
						Surgery	EBRT	Chemo.	SSA	ICI		
Meier (*7*)	83	F	Facial (left cheek) (3 cm)	Cervical LNs	^{90}Y-DOTATOC, 15.72 GBq, 4 cycles	Yes	Yes	Yes	No	No	27	CR
Bodei (*8*)	78*	F*	Leg (left)*	Pelvic LNs*	^{90}Y-DOTATOC, 9.6 GBq, 3 cycles*	Yes*	Yes*	No*	No*	No*	7*	PD*
Maecke (*9*)	43	F	Head	NA	^{90}Y-DOTATOC, 5.4 GBq/m^2, 4 cycles	NA	NA	NA	NA	NA	>19*	CR
Imhof (*10*)	70*	M*	NA*	NA*	^{90}Y-DOTATOC, 8.14 GBq, 1 cycle*	Yes*	No*	Yes*	No*	No*	6.1*	PD*
	77*	M*	NA*	Liver, bone*	^{90}Y-DOTATOC, 6.66 GBq, 1 cycle*	Yes*	Yes*	No*	No*	No*	1*	PD*
	69*	F*	NA*	NA*	^{90}Y-DOTATOC, 5.37 GBq, 1 cycle*	No*	Yes*	Yes*	No*	No*	1.2*	PD*
	55*	M*	NA*	Liver*	^{90}Y-DOTATOC, 8.14 GBq, 1 cycle*	Yes*	No*	Yes*	No*	No*	1.7*	PD*
	54*	F*	NA*	NA*	^{90}Y-DOTATOC, 12.96 GBq, 2 cycles*	Yes*	No*	No*	No*	No*	13.9*	PR*
	66*	M*	NA*	Liver*	^{90}Y-DOTATOC, 14.06 GBq, 2 cycles*	Yes*	Yes*	Yes*	No*	No*	4.5*	SD*
	83*	F*	NA*	NA*	^{90}Y-DOTATOC, 15.73 GBq, 4 cycles*	Yes*	Yes*	No*	No*	No*	9.1*	SD*
	69*	F*	NA*	Liver*	^{90}Y-DOTATOC, 11.1 GBq, 2 cycles*	Yes*	No*	No*	No*	No*	9.7*	PR*
Villard (*11*)	76*	F*	NA*	NA*	^{177}Lu-DOTATOC, 12.95 GBq, 2 cycles; ^{90}Y-DOTATOC, 13.88 GBq, 2 cycles*	Yes*	No*	No*	No*	No*	15.1*	SD*
	73*	F*	NA*	NA*	^{177}Lu-DOTATOC, 14.43 GBq, 2 cycles; ^{90}Y-DOTATOC, 14.43 GBq, 2 cycles*	Yes*	Yes*	Yes*	No*	No*	9.8*	SD*
Romer (*12*)	76*	F*	NA*	Bone*	^{177}Lu-DOTATOC, 7.4 GBq, 1 cycle*	No*	Yes*	Yes*	No*	No*	0.7*	PD*
	53*	M*	NA*	NA*	^{177}Lu-DOTATOC, 7.4 GBq, 1 cycle*	No*	No*	Yes*	No*	No*	1.3*	PD*
Basu (*2*)	54	M	Facial (right malar)	Cervical LNs, liver	^{177}Lu-DOTATATE, 13.14 GBq, 2 cycles	Yes	No	Yes	Yes	Yes*	>3	PR
Nilica (*13*)	65*	M*	Arm (right forearm)*	Widespread (LNs, liver, bone, peritoneum, heart)*	^{177}Lu-DOTATATE, 14.2 GBq, 2 cycles; ^{90}Y-DOTATOC, 2.4 GBq, 1 cycle*	Yes*	Yes*	Yes*†	No*	No*	5*	PD*
Noorelahi (*14*)	59	M	Axilla (right) (9 cm)	Subpectoral and axillary LNs	^{177}Lu-DOTATOC, 10.62 GBq, 2 cycles	Yes	Yes	Yes	NA	NA	NA	PD
Moghadam (*3*)	77	M	Facial (right malar)	Extensive LNs (cervical, supraclavicular, mediastinal, axillary, abdominal)	^{177}Lu-DOTATATE, 5.5 GBq, 1 cycle	Yes	Yes	Yes	Yes	No	2*‡	PR

*Data were obtained after personal communication with corresponding authors of that article/unpublished data.
†Intracardiac instillation of chemotherapeutic drugs due to cardiac involvement.
‡Death due to other cause (acute respiratory distress syndrome).
EBRT = external-beam radiation therapy; chemo. = chemotherapy; SSA = somatostatin analogue; ICI = immune checkpoint inhibitor; LN = lymph node; CR = complete response; PD = progressive disease; NA = not available; PR = partial response; SD = stable disease.

(DOTATATE/DOTATOC) (Table 1; Supplemental Tables 1 and 2). Fifteen and 18 patients received ^{177}Lu-DOTATATE and ^{90}Y-DOTATOC, respectively. Four patients underwent tandem PRRT with ^{177}Lu and ^{90}Y. The number of PRRT cycles ranged from 1 to 5, with the cumulative activity ranging from 1.5 to 30 GBq. Three patients received PRRT in combination with chemotherapy, and 4 patients received PRRT with immune checkpoint inhibitors.

RESULTS

Of the 37 patients who received PRRT, 18 were excluded because response data were unavailable (Supplemental Tables 1 and 2) or because PRRT had been used in combination with other active treatments (Supplemental Table 1). Consequently, radiographic response was available for 19 of 28 patients who received PRRT alone (not in combination with immunotherapy or chemotherapy). Six (31.6%) of 19 patients showed objective responses, from partial to complete, and no severe adverse events were reported (Table 1).

The median overall survival from the start of PRRT was 5 and 8 mo in patients receiving PRRT alone and in combination with other active treatments, respectively (Table 1; Supplemental Table 1). Median overall survival from diagnosis was 22 mo (Supplemental Table 3; methods for statistical analyses are described in the supplemental materials). Few studies addressed the Merkel cell polyomavirus status or ^{18}F-FDG PET findings, whereas most reported the Krenning score (Supplemental Table 4). No significant difference was noted between Krenning scores in terms of objective response to PRRT ($P = 0.86$).

DISCUSSION

Because of the small sample size, retrospective nature of the studies, selection bias, and low quality of the evidence, we cannot recommend PRRT for mMCC patients. However, the promising results from the available data lay the foundation for clinical trials in this space. Despite approval of immune checkpoint inhibitors, treatment resistance can occur and a fair proportion do not respond. Five of 7 patients who received PRRT in combination with immune checkpoint inhibitors or chemotherapy showed partial to complete responses, indicating better objective responses in this category than in the PRRT-alone group. Novel therapies or combinations are needed to further improve patient outcome. The ongoing GoTHAM trial (NCT04261855) is one example of a clinical trial evaluating the immunotherapy avelumab with ^{177}Lu-DOTATATE in patients with mMCC. The results of this and other ongoing trials using theranostics might change the management of mMCC patients soon.

CONCLUSION

Our analysis supports the use of PRRT in mMCC with sufficient SSTR uptake, although the quality of the available evidence is low. Prospective studies in terms of clinical trials are already in development and have started accruing in some parts of the world.

DISCLOSURE

Jonathan Strosberg has consulted for Novartis and is on the speakers' bureau for Ipsen. Damian Wild reports personal fees from Ipsen. Pashtoon Murtaza Kasi reports having a consultancy or advisory board role with Natera, Foundation Medicine, Merck/MSD Oncology, Tempus, Bayer, Lilly, Delcath Systems, QED Therapeutics, Servier, Taiho Oncology, Exact Sciences, and Ipsen and has received grant or research funding from Advanced Accelerator Applications, Boston Scientific, and Tersera. No other potential conflict of interest relevant to this article was reported.

ACKNOWLEDGMENTS

We thank Soheil Yazdani for the patient data of Hamiditabar et al. (*17*), Sandip Basu for the patient data of Basu et al. (*2*), and Riccardo Laudicella and Ludovica Crocè for the patient data of Herberg et al. (*15*). We also thank Paul Nghiem for useful links for collaboration between centers, Tomoko Akaike for thoughtful comments on the manuscript, Lindsay Gunnell for an MCC skin lesion, and Owen Prall for SSTR-staining slides.

KEY POINTS

QUESTION: Is radioligand therapy with ^{177}Lu-DOTATATE effective and safe in mMCC patients?

PERTINENT FINDINGS: Because of the small sample size and low-quality evidence, we cannot recommend PRRT for mMCC patients; however, the available data show promising results, laying the foundation for clinical trials in this space.

IMPLICATIONS FOR PATIENT CARE: ^{177}Lu-DOTATATE may be effective in some mMCC patients with high SSTR expression.

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