Talimogene laherparepvec for regionally advanced Merkel cell carcinoma: A report of 2 cases

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INTRODUCTION

Merkel cell carcinoma (MCC) is a rare, aggressive cutaneous malignancy with a propensity for locoregional recurrence and hematogenous spread.[1,2] MCC typically presents in elderly patients with fair complexion as a rapidly growing, firm, flesh-colored or bluish-red cutaneous nodule on sun-exposed areas, most commonly of the head and neck.[3] It is traditionally thought to arise from Merkel cells, receptor cells located in the basal layer of the epidermis involved in the sense of light touch.[4] Alternatively, these tumors may originate from an immature, totipotent stem cell.[5] Merkel cell polyomavirus (MCPyV), a ubiquitous virus in the human skin microbiome, is a nonenveloped, double-stranded DNA virus directly involved in the pathogenesis of approximately 80% of MCCs.[6-9] Steps involved in the development of $MCPyV^+$ tumors include clonal integration into the host cell genome, mutational loss of viral replication competence, expression of 2 key oncoproteins designated small tumor antigen and large tumor antigen, retinoblastoma gene suppression by large tumor antigen, and evasion of a destructive immune response.[10,11] $MCPyV^-$ tumors have the highest somatic mutation burden of any characterized malignancy with ultraviolet (UV) signature mutations predominating and exhibit high levels of T-cell–infiltrating lymphocytes and programmed death (PD)-L1 expression.[12-14] Thus, MCC is an attractive target for immunotherapy because $MCPyV^+$ tumors contain integrated viral genes expressing oncoproteins, and virus-negative tumors carry a large burden of UV signature mutations providing non–self-epitopes for immune recognition. MCC commonly presents in the context of immunosuppression from organ transplant, HIV, B-cell malignancy, or immune senescence with a median age at diagnosis of 75 years.[3,15-17]

Abbreviations used:

MCC:	Merkel cell carcinoma
MCPyV:	Merkel cell polyomavirus
PET/CT:	position emission tomography/computed tomography
PD:	programmed death
TVEC:	talimogene laherparepvec
UV:	ultraviolet

There are no randomized or prospective trials of chemotherapy in patients with distant metastasis of MCC. Retrospective series have reported median durations for complete and partial responses of 6 and 3 months, respectively, with no clear prolongation of survival.[18]

Talimogene laherparepvec (TVEC) is the first oncolytic viral immunotherapy approved by the US Food and Drug Administration, receiving an indication for advanced melanoma in October 2015. It consists of a herpes simplex type 1 virus genetically modified to selectively replicate in tumor cells and express human granulocyte-macrophage colony-stimulating factor to activate dendritic cells for

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Fig 1. Photographs of patient 1 show multiple dermal metastases (*arrows*) up to 1.4 cm in diameter along the infraorbital rim before TVEC (**A**) and complete clinical response after 4 doses of TVEC (**B**).

antigen presentation.[19] Viral infection causes release of pro-inflammatory and danger-associated molecules including viral and cellular DNA which, induce innate immunity, host interferon response, and T-cell infiltration of the tumor microenvironment.[20] Dying tumor cells may release soluble antigens or be engulfed by antigen-presenting cells to prime tumor-specific T cells, which can destroy uninfected tumors at distant sites. This may by particularly true for MCC harboring antigenic MCPyV oncoproteins or neo-epitopes produced by UV signature mutations. Thus, intratumoral injection of TVEC exerts antitumor effects through both a direct oncolytic effect in injected lesions and induction of systemic antitumor immunity.[19,21] TVEC has a favorable toxicity profile consisting primarily of mild-to-moderate transient flulike symptoms and injection-site pain. Here we report the cases of 2 elderly, frail patients with locoregionally advanced, surgically incurable MCC who refused cytotoxic chemotherapy and consented to receive intratumoral TVEC off label as first-line drug therapy.

CASE 1

An 87-year-old white man with coronary artery disease underwent margin-negative resection of an MCC from the right cheek extending into subcutaneous fat in August 2015 followed by adjuvant radiotherapy. In March 2016, he had biopsy confirmation of locoregional recurrence with 3 firm red nodules distributed both anterior and posterior to the surgical scar as well as angiolymphatic and perineural invasion. Position emission tomography/computed tomography (PET/CT) in June found a 9-mm cutaneous nodule in the right cheek with standardized uptake value (SUV) of 2.5 but no evidence of metastases to regional lymph nodes or distant sites. Three weeks later, he had 8 palpable reddish dermal metastases up to 1.4 cm in diameter widely distributed over the right side of the face from the inferior orbital rim to the angle of the jaw (Fig 1, *A*). Serology testing performed at the University of Washington was negative for antibody against MCPyV oncoprotein, indicating no evidence of virus exposure, although the negative prediction value of the test is low. With the patient's consent, TVEC was administered intratumorally into all detectable metastases across the right side of the face using standard dosing according to the product insert. He received an initial dose of 2 mL of 10^6 PFU (plaque-forming unit)/mL TVEC on July 1, 2016 followed by maintenance doses of 1 to 2 mL of 10^8 PFU/mL at 2-week intervals on 3 occasions from July 25 to August 19, 2016. Toxicity was limited to mild fatigue. Two weeks after the fourth dose and 9 weeks after treatment initiation, he had a complete clinical response with no residual detectable tumor to inject (Fig 1, *B*). PET/CT and physical examination in January 2017 found continued complete response 5 months after the last dose.

CASE 2

A 77-year-old white man with coronary artery disease and history of localized prostatic adenocarcinoma underwent margin-negative resection of an apical scalp MCC in January 2016. PET/CT showed no detectable metastases. Within 2 weeks, palpable left postauricular and posterior cervical