

A Case of Merkel Cell Carcinoma Treated with Anti-CTLA-4 Antibody (Ipilimumab)

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Abstract

Merkel Cell Carcinoma (MCC) is a rare but aggressive skin cancer. Similar to melanoma, infiltration of CD8+ T cells is associated with an improved prognosis, which provides rationale for immunotherapy in MCC. This manuscript reports the first application of ipilimumab in the treatment of a MCC patient. In this case, combination treatment of a stage IV MCC patient with ipilimumab, radiotherapy, and chemotherapy resulted in stable disease. Unfortunately, the patient passed away from an unrelated cardiac event prior to being able to be fully evaluated for the effects of ipilimumab. Immunotherapy represents a promising treatment option for advanced cancers. Ongoing clinical trials should provide information regarding the efficacy of immunotherapy in otherwise often-lethal metastatic MCC.

Keywords: Merkel cell carcinoma; Ipilimumab; Immunotherapy

Introduction

Merkel Cell Carcinoma (MCC) is a rare skin malignancy with a 5-year disease-associated mortality of 46% [1]. Management of localized MCC has traditionally entailed wide local excision with radiation. Pathological nodal evaluation provides valuable prognostic information; however, available treatment options for widespread disease have limited efficacy [2]. Current treatment options for distant metastasis include chemotherapy with platinum agents and etoposide. Since traditional chemotherapy agents have limited efficacy, significant interest has been placed on the development of targeted therapies and therapies to enhance immunity against the tumor. Application of interferon alpha-2a and 2b in MCC has not been as promising as it is in melanoma [3-5]. Ipilimumab, a fully human IgG1 monoclonal antibody blocking cytotoxic T-lymphocyte antigen (CTLA-4, CD152), causes activation/proliferation of T cells and improved overall survival in melanoma [6,7]. Nivolumab, a fully human IgG antibody blocking the programmed death 1 (PD-1) receptor, has also shown durable responses in melanoma, renal cell carcinoma and small cell lung cancer [8]. Similar to that in melanoma, it has been reported that intratumoral infiltration of CD8+ lymphocytes is associated with a good prognosis in MCC, which provides compelling rationale of immunotherapy in treating MCC with distant metastasis [9]. To our knowledge the use of ipilimumab immunotherapy in Merkel cell carcinoma has not been reported.

Case Report

A 77-year-old man presented with a three-month history of nodules and ulceration on the left leg (Figure 1). A biopsy revealed Merkel cell carcinoma with a positive cytokeratin 20 (CK20) and a negative thyroid transcription factor-1. There were scant tumor infiltrating cytotoxic lymphocytes. Positron emission tomography/computed tomography (PET/CT) showed external iliac and para-aortic nodal involvement. Further molecular testing in search of genetic alterations using a next generation sequencing assay including 315 genes by Foundation One™, uncovered no mutations with clinical significance. He was started on standard treatment with etoposide and carboplatin. He initially responded well to chemotherapy with decreasing in size of his nodules on the left lower leg and stable abdominal lymph node disease. Inspired by the recent success of immune checkpoint blockade therapy in multiple malignancies, ipilimumab was added to the regimen and he received the first dose of ipilimumab at 3 mg/kg during the third chemotherapy cycle, following a standard regimen as for melanoma with a total of 4 doses. Shortly after the third dose of ipilimumab he developed significant diarrhea. He was felt to have developed immune



Figure 1: Multiple red nodules of Merkel cell carcinoma along the left lower extremity demonstrating in-transit metastases.

mediated colitis related to ipilimumab. No rectal biopsy was performed as he was on clopidogrel from a recent stent placement. His diarrhea resolved with prednisone and sulfasalazine and the decision was made not to give the fourth dose of ipilimumab. Additional biopsies performed on the leg lesions 5 weeks after the last dose of ipilimumab did not reveal increased tumor infiltrating cytotoxic T lymphocytes.

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Received November 08, 2015; **Accepted** December 02, 2015; **Published** December 09, 2015

Citation: Williams BA, Hardee ME, Hutchins LF, Shalin S, Gao L (2015) A Case of Merkel Cell Carcinoma Treated with Anti-CTLA-4 Antibody (Ipilimumab). J Clin Case Rep 5: 659. doi:10.4172/2165-7920.1000659

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Clinically, there was a significant reduction of cutaneous lesions and no evidence of metastasis to the internal organs following the third dose of ipilimumab as demonstrated by a repeated PET/CT (Figure 2). To minimize the side effects from chemotherapy, he was continued on oral etoposide. Unexpectedly, the patient passed away 7 months after initial treatment from a cardiac death. An autopsy was not performed.

Discussion

Merkel Cell Carcinoma (MCC) is less common than cutaneous melanoma, but it is far more deadly, especially if it is not detected at an early stage. The reported incidence has increased over the past 20 years to 1,600 cases/year in the US. Standard treatment regimens are surgery in conjunction with radiation. For disseminated disease, chemotherapy with etoposide with or without cisplatin or carboplatin is recommended. More durable remissions have become available for many malignancies with targeted therapies and immunotherapy. In MCC, imatinib has shown efficacy in case reports; however, a clinical trial with 23 patients was terminated due to progression of disease [10]. Similarly, early clinical trials blocking anti-apoptotic protein Bcl-2 expression (Oblimersen sodium, G3139, Genasense, Genta Incorporated) and immune therapy with interferon alpha-2a and 2b have not been successful [3]. The discovery of Merkel cell carcinoma polyomavirus has advanced our understanding of MCC pathogenesis and provides another rational approach to directed therapy. Another potential approach to targeted therapy includes blockade of the PI3K/Akt pathway, which is occasionally mutated in MCC. Recently, immune checkpoint blockade therapy has shown great success in inducing tumor regression as well as improved survival in human cancers including melanoma. Inhibition of CTLA-4 by ipilimumab has been shown to be effective in improving overall survival in patients with advanced melanoma in phase 3 clinical trials [6]. Recently, a study showed that MCC-infiltrating lymphocytes express PD-1 and Tim-3 inhibitory receptors at high levels, providing evidence of the recently opened clinical trials of anti-PD1 and anti-PDL1 in the treatment of MCC [11].

The development of immune checkpoint inhibitors has led to intensive research on the exact process or processes that lead to tumor control. In early trials of ipilimumab it was observed that patients with immune related adverse events had a higher likelihood of clinical response [12]. Examination of biopsy specimens from melanoma patients after ipilimumab treatment suggested that the ratio of infiltrating CD8+ cytotoxic T cells to FoxP3+ T regulatory cells was most indicative of tumor response, with a higher ratio corresponding to a better response [13]. In addition, an increase in the ratio of effector to regulatory T (T reg) cells and an increased frequency of CD4+ICOS (hi) T cells was found to correlate with the likelihood of clinical benefit in several human cancers [14]. A future goal of research will be to identify which patients are likely to respond to immune checkpoint blockade with ipilimumab, but at present there is no definitive marker(s) to predict the effectiveness of ipilimumab treatment.

Although ipilimumab can be effective as early as 6 weeks, responses can be observed 3-6 months after completion of treatment. We reason that failure of identifying increased intratumoral T lymphocytes one month after the last dose of ipilimumab is two-fold. One could be that our patient's immune system failed to respond to ipilimumab; however, clinically diagnosed immune mediated colitis would argue against that. The other was simply that it would take longer time to observe the response in tumor tissues. Unfortunately, we were not able to obtain more tissue samples upon his death to further assess the effect of ipilimumab. This report is the first to our knowledge utilizing immune checkpoint blockade therapy for MCC. Although the complete response to ipilimumab could not be assessed in our patient, this represents a pilot study of immune checkpoint blockade therapy in MCC patients. Mechanistic evidence supports a role of immunotherapy for MCC, in a fashion similar to that found to be effective in melanoma. The patient in our case demonstrates stable disease with an apparent immune response to ipilimumab but without evidence of an increase in tumor infiltrating CD8+ lymphocytes. Ongoing clinical trials including using monoclonal antibodies directed against PD-1 and PDL-1 should provide further evidence as to whether immunotherapy may improve survival in often-lethal advanced MCC. Additionally, results from an ongoing clinical trial regarding adoptive immunotherapy using viral oncoprotein targeted autologous T cell therapy is currently in clinical trial [3]. Recently, a patient was reported with a complete clinical response to idelalisib, a PI3K inhibitor [15]. Together, these results show promise for the future treatment of often deadly, MCC.

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Figure 2: Regression of lesions proximally and stabilization of distal lesions after ipilimumab and on oral etoposide.

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