JOURNAL OF ONCOLOGY PHARMACY PRACTICE

Commentary

J Oncol Pharm Practice
2019, Vol. 25(1) 214–216

DOI: 10.1177/1078155218785002
journals.sagepub.com/home/opp
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Inferior outcomes in immunocompromised Merkel cell carcinoma patients: Can they be overcome by the use of PD1/PDL1 inhibitors?

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Abstract

Cases of Merkel cell carcinoma have become increasingly more common in the last two decades, and its incidence has been predicted to climb further. Immunosenescence might explain in part the higher Merkel cell carcinoma prevalence in seniors aged 70 and older. This cancer might also be more aggressive in immunocompromised patients. In a subset of immunocompromised Merkel cell carcinoma patients, we identified significant lymphopenia and a more advanced disease stage compared with their immunocompetent counterparts. Time to death in this cohort was much shorter than in immunocompetent subjects, and their likelihood of death from Merkel cell carcinoma was five times higher. Avelumab approval in 2017 represents an important step forward in the therapy of Merkel cell carcinoma. Hopefully, PD1/PDL1 inhibitors will improve survival in immunocompromised Merkel cell carcinoma hosts, traditionally linked with inferior clinical outcomes.

Keywords

Avelumab, immunocompromised, lymphopenia, Merkel cell carcinoma, PD1/PDL1 inhibitors

Date received: 18 April 2018; revised: 3 June 2018; accepted: 4 June 2018

Merkel cell carcinoma (MCC) is a relatively rare, but aggressive skin malignancy with neuroendocrine features. It most commonly arises in sun-exposed areas of older subjects, and is associated with Merkel cell polyoma virus. Data from Surveillance, Epidemiology, and End Results (SEER) showed a sustained increase in its incidence over the last decades.[1] The incidence of MCC in the US has been predicted to climb to 2835 cases in 2020 and 3284 cases in 2025.[1] Recent research suggested that this skin neoplasm may be more aggressive in immunocompromised patients.[2]

To investigate this hypothesis, we performed a retrospective chart review of all consecutive MCC patients treated at our institution between the years of 2006 and 2017. Chi-square and Fisher's exact tests were used to assess the significance of associations in large and small populations, respectively. Survival analyses were performed using the Cox proportional hazards. Our study included 40 MCC patients; median age was 76.[3] Our population was entirely Caucasian and male predominant. All patients had primary tumors involving

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sun-exposed skin. Compared to the SEER data, our patients had more Tumor Node Metastasis stage I disease (50% vs. 39%; $p = 0.00003$) and a primary tumor size <2 cm (57.5% vs. 34%; $p < 0.01$).[3] They were also more frequently treated with lymph node dissection (70% vs. 63%, $p = 0.002$). Earlier stage at diagnosis in our cohort could be explained by the heightened suspicion for skin cancer in our geographic area due to extensive solar exposure. These factors also explain a more aggressive surgical oncology approach.

We identified a subset of immunocompromised patients ($n = 10$) including three subjects post-organ transplantation, two patients with chronic lymphocytic leukemia, one with metastatic skin cancer post-chemotherapy, one with rheumatoid arthritis on azathioprine, one with myasthenia gravis being treated with mycophenolate mofetil, one with follicular lymphoma post-chemotherapy and one with human immunodeficiency virus infection. The patients' age in this subset was not statistically different from the age in the immunocompetent cohort (Table 1).

The median absolute lymphocyte count in immunocompromised patients was 500×10^6/L (range, 100–900×10^6/L) as opposed to normal values accepted by the most laboratories ($1200–3100 \times 10^6$/L). T-cell counts were available for only a minority of patients. These immunocompromised subjects had more stage III disease (40% vs. 33%; $p = 0.021$) compared with the non-immunocompromised (Table 1).[4] Time to death averaged 290.1 days in this subset vs. 618.2 days ($p < 0.001$) in immunocompetent patients, and their likelihood of death was five times higher.[4]

Table 1. Demographic data of the study population and clinico-pathologic staging by immunocompetency status.

Characteristics	Immunocompromised, n (%)	Immunocompetent, n (%)	p
Age at diagnosis			
≥65 yrs	10 (100%)	26 (87%)	>0.05
<65 yrs	0 (0%)	4 (13%)	
Median age (range)	75 (66–82)	77 (61–93)	
Gender			
Female	0 (0%)	9 (30%)	<0.01
Male	10 (100%)	21 (70%)	
Disease stage at diagnosis			
Stage I	4 (40%)	15 (50%)	<0.05
Stage II	1 (10%)	0 (0%)	
Stage III	4 (40%)	10 (33%)	
Stage IV	1 (10%)	5 (17%)	
Lymphovascular involvement			
Yes	4 (40%)	19 (63%)	<0.01
No	3 (30%)	2 (7%)	
Unknown	3 (30%)	9 (30%)	

All deaths in the immunocompromised cohort were related to an aggressive MCC course. Of course, it is possible that these patients had worse outcomes for reasons other than being immunocompromised. Nonetheless, their Eastern Coopertaive Oncology Group performance status was similar to the one of the immunocompetent cohort, and they received similar treatments. These patients also had significantly decreased lymphocyte counts. It has been shown that low absolute lymphocyte counts and high neutrophil-to-lymphocyte ratios are associated with poor outcome in MCC.[5,6] Our analysis was performed before FDA approval of avelumab for MCC; therefore, none of the patients was treated with this agent or other immunotherapies.

Some degree of immune dysfunction such as decreased $CD4^+$ T-cell counts and CD4/CD8 T-cell ratio, along with diminished antibody production to various antigens, is expected in otherwise healthy elderly and is referred to as immunosenescence.[7] We believe that immunosenescence might explain at least in part the higher MCC prevalence in seniors aged 70 and older.

We also believe that immune dysfunction accounts, at least in part, for the rapid increase in MCC cases in the elderly in the last decade. Increased numbers of immunocompromised hosts are driven by more effective immunosuppressive agents, more hematopoietic and solid tumor transplants, more effective systemic therapies for cancer and other diseases in the recent years, some of which are associated with immunosuppression.[2] These facts warrant heightened awareness of MCC as a clinico-epidemiologic entity.

Approval of programmed death ligand 1 (PDL1) inhibitors for the therapy of advanced MCC represents a huge step forward in the treatment of this aggressive cancer. Avelumab is a human monoclonal antibody that reverses T-cell exhaustion and induces significant antitumor responses. Its safety has been proven across several tumor types. Avelumab showed a response rate (RR) of 62.1% in the first-line therapy setting in MCC patients, with a duration of responses in excess of six months in 83% responders.[8] In the second-line setting (after failure of platinum-based therapy), RR was 25% and overall survival was 12.9 months, which led to the avelumab approval in 2017.[9] Several other PD1/PDL1 inhibitors may soon join the anti-MCC armamentarium, as they have shown both safety and efficacy in this tumor type. Nonetheless, available clinical trials involving these agents are conducted in all comers with advanced MCC, and do not discriminate between immunocompromised and immunocompetent hosts.

We hope that PD1/PDL1 inhibitors will lead to superior outcomes in both advanced and early stage MCC patients. It is of great interest to see how immunocompromised MCC patients will respond to these agents, and whether or not these drugs will lead to improved survival in this traditionally poor prognosis MCC subset.

Authors' Contributions

Each author participated in the conception, design, analysis, interpretation, writing, revising, and approval of the manuscript.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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