Merkel Cell Carcinoma: An Unusually Immunogenic Cancer Proves Ripe for Immune Therapy

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The article by Banks et al[1] summarizes the current understanding of Merkel cell carcinoma (MCC) immunobiology and treatment strategies. MCC is a rare but often lethal skin cancer that is associated with several risk factors, including immune suppression, advanced age (age > 50 years), and extensive prior sun exposure.[2] Within the past year, multiple independent sequencing studies have revealed that MCC can be caused either by the Merkel cell polyomavirus (MCPyV) or by heavy UV exposure.[3] In most cases of MCC (approximately 80%), MCPyV is clonally integrated in MCC tumor cells and viral oncoproteins drive oncogenesis.[2] The remaining approximately 20% of cases are not associated with MCPyV and seem to be mediated by UV damage, as whole-exome sequencing has revealed that these tumors harbor dramatically high mutational burdens with a distinct UV damage signature.[3] In Australia, with its heavy UV exposure and predominantly white population, this ratio is inverted: the majority of MCC tumors (approximately 75%) are UV induced and MCPyV negative.[1]

Why Is MCC Immunogenic Regardless of Viral Status?

Both virus-positive and virus-negative MCCs can be immunogenic, as reflected by the finding that robust intratumoral infiltration of CD8 T cells into MCC tumors can occur in virus-negative as well as in virus-positive tumors and is associated with 100% survival, independent of stage.[2] Among virus-positive MCCs, immunogenicity can be assessed with MCPyV oncoprotein–specific antibodies and T-cell responses, which are quite prevalent.[2] Whereas virus-negative MCCs do not express viral oncoproteins, these tumors often express extremely high numbers of tumor neoantigens—more, on average, than either non–small-cell lung cancer (NSCLC) or melanoma[4]—which may provide tumor-specific targets for immune recognition. A potential marker of immune recognition is programmed death-ligand 1 (PD-L1), which is geographically associated with infiltrating immune cells in melanoma, NSCLC, and renal cell carcinoma.[5] Of interest, PD-L1 expression was observed in a subset of virus-negative MCC tumors, and this subset harbored significantly higher mutational burdens than did virus-negative tumors that did not express PD-L1.[3] This suggests that increased neoantigen expression within these heavily mutated virus-negative tumors tends to elicit an immune response.[4]

Importantly, while immune recognition of MCCs can be detected, several mechanisms of immune evasion, including major histocompatibility complex-I and E-selectin downregulation, T regulatory cell recruitment, impaired natural killer cell function, and decreased Toll-like receptor-9 signaling, can dampen both innate and adaptive immune responses against MCC.[2] Therapies that target these evasion mechanisms are underway and several have shown dramatic clinical results as detailed below.

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DOI: 10.1200/JOP.2016.014498

Promising Responses to Immune-Based Therapies

Nearly all patients with MCC can initially be rendered free of detectable disease via standard surgical resection and radiotherapy; however, approximately one half of patients with MCC will experience disease recurrence, typically within 2 years of initial diagnosis.[2] Cytotoxic chemotherapy can mediate regression of distant metastatic disease in > 50% of cases; however, median time to progression is only 3 months, which indicates an urgent need for alternative approaches. Banks et al[1] summarize several immune-based and targeted therapies used for treating MCC, including pembrolizumab (anti–programmed death-1), which has shown clinical response in 56% of patients.[6] Notably, pembrolizumab has shown clinical activity in both virus-positive and virus-negative MCCs, which supports the notion that both subsets of MCC are immunogenic.[6] In addition, in a phase II trial, 88 patients with MCC who experienced disease relapse after chemotherapy were treated with avelumab (anti–PD-L1) with an objective response rate of 29.5%.[7] Fifteen (83%) of 18 responses were ongoing at 6 months.[7]

In addition to systemic immune therapy, two intralesional immune-based agents, glucopyranosyl lipid-A and plasmid interleukin-12 electroporation, have shown clinical efficacy in some patients, likely through induction of a Th1-type immune response.[2] Furthermore, single-fraction radiation has yielded a remarkable 94% objective response rate among targeted lesions for patients with limited MCC metastases who either developed chemotherapy-resistant disease or who were unable to receive fractionated radiation.[2] Of note, these responses are largely limited to local disease control and have typically not shown benefit at untreated lesions.

What Do We Do for Patients Who Do Not Experience Response?

While remarkable response rates have been observed with pembrolizumab treatment, no predictive biomarkers have been identified to delineate the approximately 50% of patients who will not experience response to treatment.[6] Tumoral CD8 T-cell infiltration and recruitment as well as tumoral PD-L1 expression are predictive of checkpoint response in melanoma; however, no association between these markers and response to pembrolizumab was observed in MCC.[6] In NSCLC, whole-exome sequencing has revealed that a higher mutational burden was associated with improved progression-free survival in response to programmed death-1 blockade.[8] In melanoma, a higher tumor mutation load also correlated with clinical benefit to ipilimumab (anti–cytotoxic T-cell lymphocyte-4) therapy.[9] Whereas predictive biomarkers remain elusive for MCC, combination therapies, such as nivolumab and ipilimumab, have shown higher response rates in treating melanoma. Therefore, these approaches may benefit patients whose disease proves refractory to immune checkpoint monotherapy.[10] JOP

Acknowledgement

Supported by National Institutes of Health Grants No. K24-CA139052 and T32-ES007032.

Authors' Disclosures of Potential Conflicts of Interest

Disclosures provided by the authors are available with this article at jop.ascopubs.org.

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Conception and design: All authors
Collection and assembly of data: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Natalie A. Vandeven
No relationship to disclose

Paul Nghiem
Consulting or Advisory Role: EMD Serono
Research Funding: Bristol-Myers Squibb (Inst)
Travel, Accommodations, Expenses: EMD Serono