VIEWPOINT

Less Toxic, More Effective Treatment—A Win-Win for Patients With Merkel Cell Carcinoma

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Merkel cell carcinoma (MCC) is an aggressive skin cancer that recurs in more than one-third of cases, with reported mortality rates of 33% to 46%.[1] Given this high-risk situation, MCC is often managed with therapies that are aggressive and potentially toxic: extensive surgery, radiation therapy (RT), and systemic therapy. Fortunately, recent advances in multiple realms now allow MCC management to be more effective and less toxic. In this Viewpoint, we highlight 3 recent developments relating to progress in local management, early detection of recurrent disease, and systemic therapy. Although it is not practical for physicians who rarely see patients with MCC to remain up-to-date on the details of management, herein we provide resources and guidelines to help physicians ensure optimal initial care and participate in longitudinal treatment of patients with MCC.

Surgery: From Wide Margins to Wise Margins, Integrating Irradiation

Local treatment of MCC often includes wide excision of the primary site, which can lead to significant morbidity, such as delayed graft and/or wound healing during which radiation cannot be initiated. Because MCC has a high risk of local recurrence after excision in the absence of adjuvant radiation (up to 40%),[2] RT is often used to achieve better local control. Nationwide data indicate that 54% of patients with MCC received adjuvant RT,[3] and in our Seattle-based cohort, 738 (92%) of 803 MCC patients received local adjuvant RT (P.N., unpublished data, 2019).

The National Comprehensive Cancer Network (NCCN) guidelines for MCC suggest that surgical management should be planned so as not to delay initiation of adjuvant RT when indicated.[4] However, there is no consensus on the appropriate surgical margin size, with NCCN guidelines suggesting 1- to 2-cm margins with intent to obtain negative margins whenever possible.[4]

Limited prior reports[5] and unpublished data from our own cohort (P.N., unpublished data, 2019) strongly indicate that if no adjuvant RT is given to the local site, wider margins are important (surgical margins >1 cm are associated with better local control). In contrast, patients who received adjuvant RT had excellent local control, even if margins were narrow or in many cases pathologically positive.

Six factors that are associated with greater risk of recurrence include (1) chronic T-cell immune suppression, (2) larger tumor size (diameter >1 cm), (3) presence of lymphovascular invasion within the tumor, (4) positive sentinel lymph node biopsy (SLNB) results, (5) pathologically positive surgical margins, and (6) primary tumor on the head and/or neck. When 1 or more of these risk factors are positive, it is appropriate to consider adjuvant RT.[1,4] Unfortunately, at the time of initial surgery, the clinical team is missing key information needed to decide whether RT should be performed. These missing data include SLNB status and pathologic margin status.

For management of MCC, a practical approach is to select surgical margins that are as wide as possible, while allowing primary closure. This approach lowers the morbidity of extensive surgery (wide margins are not needed if RT will be used) and ensures that adjuvant RT can proceed promptly (MCC progresses quickly) should it later become apparent that RT is indicated.

Surveillance: A New Blood Test and Risk-Appropriate Follow-up

Depending on stage, MCC has a 20% to 75% chance of recurrence,[6] which necessitates careful surveillance. Herein we describe 2 new approaches that improve clinicians' ability to efficiently and appropriately screen for MCC recurrence.

Merkel Cell Polyomavirus Oncoprotein Antibody Serology

Most MCC tumors (about 80% in the United States) are driven by Merkel cell polyomavirus (MCPyV).[7] Determining the baseline titer of MCPyV oncoprotein antibodies is useful for initial workup as well as surveillance,[1] and is thus indicated in the NCCN guidelines.[4] Carrying out this blood test at the time of diagnosis benefits patients with MCC regardless of whether they produce these antibodies.

Patients who have undetectable antibody levels at the time of MCC diagnosis (seronegative) are 42% more likely to have a recurrence than those with seropositive levels.[1] It is thus appropriate to monitor seronegative patients carefully with imaging studies. In seropositive patients, the MCPyV antibody level decreases if disease does not recur, and rapidly rises if disease recurs. Recent data from our cohort of 254 patients, with an overall recurrence rate of 33%, indicate that an increasing level of MCPyV antibodies has a positive predictive value for disease recurrence of 99% (95% CI, 94%-100%).[8] Among patients with increasing titers of these antibodies, 90% (76 of 83) of recurrences occurred within 45 days of an increase in MCPyV antibody level. In contrast, a level that has significantly decreased (or has fallen below the limit of detection) has a 99% negative predictive value (95% CI, 96%-100%; no MCC recurrence was detected within 45 days after the decreased level observed on the titer; https://merkelcell.org/testing-and-diagnosis/sero/).[8] The corresponding sensitivity and specificity estimates were

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98% (95% CI, 92%-100%) and 99% (95% CI, 97%-100%), respectively.

Stage-Specific Recurrence-Free Survival Data

Regarding surveillance imaging studies, NCCN guidelines recommend that these studies be obtained "as clinically indicated."[4] The NCCN does not provide detail on how imaging frequency should be diminished as recurrence risk decreases over the years after diagnosis. Stage-specific recurrence-free survival data can assist in determining a patient's risk of recurrence in the subsequent years and the appropriate frequency of imaging studies. Although there are no published studies detailing recurrence-free survival in a stage-specific manner from a large cohort of patients with MCC, we have now made such data available (http://www.merkelcell.org/prognosis).

Systemic Therapy: From Cytotoxic Chemotherapy to Immunotherapy

Several lines of evidence suggest that T-cell immunity is particularly important in controlling MCC, and that MCC-specific T cells appear exhausted (their capacity to recognize and eliminate tumor cells is decreased).[1,7] For these reasons, anti–programmed cell death-1 (PD-1) pathway inhibitors were studied in several clinical trials of patients with MCC who had or had not previously received chemotherapy.[1,7]

Inhibition of the PD-1 pathway resulted in a 50% to 70% response rate for first-line therapy, and a response rate of about 30% for patients who previously received chemotherapy.[1,7] Although these initial response rates to immunotherapy were not very different from chemotherapy, the striking difference was in the improved durability of responses to PD-1 pathway inhibitors.[9] Indeed, overall survival was several-fold better for immunotherapy than for chemotherapy at 3 years from onset of treatment (64% for anti–PD-1 therapy vs about 10% for historical chemotherapy-treated cohorts).[9]

These data have led to rapid changes in the NCCN guidelines for MCC and US Food and Drug Administration approvals of both avelumab (anti–PD-L1) and pembrolizumab (anti–PD-1). Treatment with a PD-1 pathway blocking agent has become the preferred first-line therapy for advanced MCC in appropriate patients.[1,4,7]

Role of the Dermatologist: Advocate for Multidisciplinary and Longitudinal Care

Although initial management of MCC often requires care that is beyond the usual scope of dermatology (SLNB, imaging studies, RT, and/or systemic therapies), patients with MCC can benefit from the involvement of a dermatologist in many ways. Although MCC is rare, because it is a skin cancer, dermatologists will often be more familiar with this cancer than other specialists who may be involved in the care of a patient with this disease. Also, MCC is often diagnosed by a dermatologist who is needed for ongoing skin cancer surveillance in the long-term follow-up of patients with MCC. The dermatologist is in a unique position to ensure multidisciplinary care among appropriate specialties, to integrate multiple aspects of patients' medical and social status, and to assist with longitudinal surveillance. Dermatologists can greatly facilitate care at diagnosis by referring patients to a regional and/or expert center where optimal multidisciplinary care can be delivered. Several dozen such centers exist around the world.[10]

Conclusion

There has been great progress in the management of MCC, and developments are continuing at a rapid pace. We believe that a patient's dermatologist should play an important role in optimizing the multidisciplinary management of this challenging disease.

ARTICLE INFORMATION

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