The Role of Immunotherapy in Merkel Cell Carcinoma

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Merkel cell carcinoma (MCC) is a highly aggressive skin cancer, which frequently exhibits resistance to treatment, recurrence of disease, spread to distant sites, and has a mortality rate higher than that of melanoma. Though rare, the global incidence of MCC is predicted to increase considerably in 2025. Risk factors include age, a weakened immune system, sun exposure, and infection by Merkel cell polyomavirus (MCPyV), a virus found to be present in about 80% of tumors. In patients with local disease, the 5-year overall survival rate is 55.6%, while in those with distant spread of disease, the 5-year overall survival rate is 13.5%. These statistics highlight the persistent absence of effective treatment options for patients with MCC.

Currently, treatment for local disease includes removal of the tumor via surgery, with or without radiation therapy. However, despite definitive treatment of local disease, there remains a high rate of recurrence. Patients found to have disease that has spread to the lymph nodes should undergo a complete lymph node dissection, radiation therapy, or both.

For patients with advanced MCC, chemotherapy has historically been the preferred treatment option, including platinum-based regimens, etoposide, taxanes, and anthracyclines, either alone or in combination. Though MCC has a relatively high response rate to first-line chemotherapy, responses are rarely maintained, and resistance quickly develops.

Immune checkpoint inhibitors are a promising new therapy for advanced MCC. The programmed cell death-1/programmed cell death ligand-1 (PD-1/PD-L1) pathway is a key target in activating the immune system to respond to cancer cells. Blocking this pathway has been associated with an improvement in the overall survival in patients with advanced MCC.

Pembrolizumab, a therapy targeting PD-1, was the first immune checkpoint inhibitor to demonstrate tumor shrinkage in patients with MCC. In one study, patients with advanced MCC who had not previously received systemic therapy were treated with pembrolizumab 2mg/kg every 3 weeks for a maximum of 2 years or until disease progression. Out of 26 patients, 4 experienced a complete response and 10 experienced a partial response. These results led to the inclusion of pembrolizumab as a treatment option for disseminated MCC in the National Comprehensive Cancer Network (NCCN) guidelines.

In 2017, avelumab, a therapy targeting PD-L1, became the first FDA-approved agent for the treatment of advanced MCC. Approval was based on data from a study in which 88 patients with advanced MCC who had progressed after chemotherapy received avelumab 10mg/kg every 2 weeks. At a median follow-up duration of 16.4 months, 10 patients experienced a complete response and 19 experienced a partial response. Compared to trials of patients with advanced MCC receiving chemotherapy, the responses to avelumab were significantly superior.

Nivolumab, another therapy targeting PD-1, has also demonstrated clinical activity in advanced MCC. As part of one study, 25 patients with advanced MCC were treated with nivolumab 240mg every 2 weeks. At a median follow-up of 51 weeks, there was a 73% objective response rate in patients who had never before received treatment for MCC, compared to a 50% objective

response rate in previously-treated patients. Because of these results, nivolumab was also included in the NCCN guidelines as a preferred treatment option for patients with disseminated disease.

Currently, additional studies are investigating the activity and safety of nivolumab in combination with ipilimumab, a therapy targeting cytotoxic T-lymphocyte associated protein 4 (CTLA-4), or relatlimab, a therapy targeting the lymphocyte activation gene-3 (LAG-3) protein, in patients with advanced MCC. Additionally, treatment with ipilimumab alone has demonstrated anti-tumor activity in a small study of 5 patients who metastatic MCC who had not previously underwent chemotherapy.

The side effects of therapies targeting PD-1/PD-L1 in patients with MCC include issues with functioning of the adrenal glands, inflammation of the intestines, heart, lungs, liver, kidneys, or thyroid, and elevation of liver enzymes. Additionally, infusion-related reactions were observed with the administration of avelumab, so receiving treatment with an antihistamine and acetaminophen prior to the first four infusions is now recommended.

Though the data is still preliminary, it appears that the rates of MCC shrinkage with immune checkpoint inhibitors in patients who have previously not undergone treatment for MCC may exceed those who have previously undergone treatment. While these findings still require evaluation in larger groups of patients, they suggest that immune checkpoint inhibitors may be most effective in patients with MCC when used as a first-line therapy. Additionally, because responses appear to last longer than those seen with chemotherapy, immune checkpoint inhibitors are becoming the new standard-of-care for metastatic or unresectable MCC.

References

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