Current Trends in Clinical Trials for Merkel Cell Carcinoma (MCC)

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Background: Merkel cell carcinoma (MCC) is a rare neuroendocrine cutaneous malignancy. It is aggressive due to high rates of recurrence and metastasis. Additionally, its incidence is increasing due to an aging population and increased UV sun exposure. This dangerous cancer has historically been treated with surgery, radiation, and chemotherapy. However, the disease-related mortality rate remains at 25-50%, exceeding that of melanoma. Our focus in this review was to explore advancements in management of this complex malignancy as published by recent and ongoing clinical trials. These include the latest discoveries in efficacy of immunotherapy, direct tumor injections, alternative radiation dosing, and combination treatments. Information such as this may be tremendously beneficial in improving patient outcomes and decreasing the disease-related mortality rate in MCC.

Methods: A review of published clinical trials within the past 10 years was completed. These included the JAVELIN Merkel 200, KEYNOTE-017, CheckMate 358, PODIUM-201, ADMEC, ADMEC-O, STAMP, ADAM trials, and more. Improvements in patient outcomes after various methods of therapy were described based on patient objective response rate (ORR). The main therapy investigated was the efficacy of immune checkpoint blockade with anti-PD-1 and anti-PD-L1 antibodies, which was additionally assessed based on patient Merkel cell polyomavirus status. Adjuvant therapies such as radiation, surgery, and intra-tumoral injections were also studied in comparison to observation alone. Finally, new discoveries of the pathophysiology of the disease were included to discuss possible future directions of therapy.

Results: Immune checkpoint blockade is now considered standard first-line therapy for unresectable and metastatic MCC, as significant improvements in ORR have been seen by anti-PD-1 and anti-PD-L1 antibodies such as Avelumab (ORR 33%), Pembrolizumab (ORR 56%), and Nivolumab (ORR 60%). Combination immunotherapies have also shown significant benefit. For example, adding a CTLA-4 inhibitor (Ipilimumab) to Nivolumab without adjuvant radiation has displayed an ORR of 100% in naïve patients and 31% in patients previously treated with PD-1/PD-L1 immunotherapy. These immunotherapies are effective regardless of patient viral status. Across trials, PD-1/PD-L1 immunotherapy showed long-term remission, with 2-year survival of 60-70%. Studies exploring the efficacy of immunotherapy plus adjuvant treatments of radiation, surgery, and intra-tumoral injections are ongoing. Recent discoveries of potential molecular targets include inosine monophosphate dehydrogenase 2 (IMPDH2), an essential enzyme for guanosine biosynthesis and therefore MCC cell survival, as well as nicotinamide N-methyltransferase (NNMT), an overexpressed metabolic enzyme that promotes MCC cell proliferation and chemoresistance. Finally, immunotherapeutic approaches such as innate immune activators and multi-checkpoint inhibitor combinations are currently being tested.

Conclusions: Although MCC incidence is increasing, advancements are being made in the treatment of advanced and metastatic MCC. This is due to both increased understanding of the disease and discoveries made by innovative clinical trials. The utilization of immunotherapies, specifically PD1/PD-L1 and CTLA-4 inhibition, has shown promising results for improving patient outcomes. Further investigations are currently ongoing to evaluate the roles of adjuvant therapies, including alternative radiation dosing, intra-tumoral injections, IMPDH2 inhibitors, NNMT inhibitors, IFx-Hu2.0 innate immune activators, and triple immune checkpoint blockade. These methods may be useful in patients whose cancer is refractory to immunotherapy or have contraindications to receiving immunotherapy.