Immunotherapy Infuses New Hope Into Merkel Cell Carcinoma Care

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Paul T. Nghiem, MD, PhD

Immunotherapy advances have infused new hope into the treatment landscape for patients with Merkel cell carcinoma (MCC), Paul T. Nghiem, MD, PhD, a professor at the University of Washington, said in a presentation at the 2017 World Congress of Melanoma.[1]

Historically, chemotherapy has been used to treat patients with MCC. Although chemotherapy can shrink Merkel cell tumors, “the cancer usually begins growing again within 6 months,” according to the National Cancer Institute.[2]

Nghiem said that chemotherapy has demonstrated an overall response rate (ORR) of 55% in the first-line setting and is included in the NCCN guidelines. However, the immunotherapy agents avelumab (Bavencio), pembrolizumab (Keytruda), and nivolumab (Opdivo) have shown response rates of 32%, 56%, and 73%, respectively, based on first- and/or second-line data.

“We didn't think that the response rates for any of these agents—avelumab, pembrolizumab, or nivolumab—would be significantly higher than chemotherapy, but we were hoping to see differences in terms of durability,” said Nghiem.

According to Nghiem, 19 in 20 patients with MCC treated with chemotherapy has their cancer progress. When chemotherapy was given in the first-line setting, there was a 6% progression-free survival (PFS) rate a year after starting systemic therapy, according to data published in *Cancer Medicine*. Patients who received pembrolizumab and nivolumab saw a PFS of 45% and 75%, respectively, a year after the start of systemic therapy.

“Broadly speaking, PD-1 axis blockade agents will generate a

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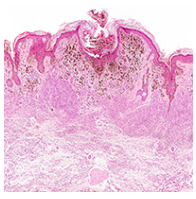
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durable response for a year or more in the first-line setting in more than half of patients," said Nghiem.

However, patients receiving a PD-1 inhibitor after prior chemotherapy saw durable responses drop from more than 50% to 30%, he added.

The auspicious outcomes with checkpoint inhibitors in MCC led to avelumab becoming the first FDA-approved treatment specifically for this disease. In March 2017, the FDA granted an accelerated approval to avelumab for the treatment of adults and pediatric patients 12 years and older with metastatic MCC, including those who have not received prior chemotherapy. Last month, the European Commission also approved avelumab for MCC.

The US and EU approvals of avelumab were both based on findings from the phase II JAVELIN Merkel 200 study. In Part A of the study, which enrolled 88 previously treated patients with metastatic MCC, the ORR with avelumab was 33% (95% CI, 23.3-43.8), which included an 11.4% (95% CI, 6.6-19.9) complete response (CR) rate and a 21.6% (95% CI, 13.5-31.7) partial response (PR) rate.[3,4] The duration of response (DOR) was at least 6 months in 93% of the responding patients, with 71% having a DOR of 12 months or more.[5] DOR ranged from 2.8 months to more than 24.9 months.[5]

Median PFS with avelumab was 2.7 months (95% CI, 1.4-6.9). The 6-month PFS rate was 40%. The median overall survival (OS) was 11.3 months (95% CI, 7.5-14.0) and the 6-month OS rate was 69%.

Part B of the JAVELIN Merkel 200 study included 39 patients with metastatic MCC who had not received prior systemic therapy in the metastatic setting.[5] The ORR was 62% in these patients, comprising a CR rate of 14% and PR rate of 48%. The 3-months PFS rate was 67%.

The FDA approval of avelumab paves the way for additional immunotherapy agents to gain regulatory approval for MCC, said Nghiem.

Immunotherapy has also made its way into the NCCN guidelines for patients with MCC. In the recent 2018 guidelines, immunotherapy regimens have displaced chemotherapy. Chemotherapy is now only being recommended for patients who show contraindications to immunotherapy.

The future of immunotherapy in the field of MCC could include combination regimens, such as pairing CTLA-4 and PD-1/PD-L1 inhibitors, which has been successful in patients with melanoma. However, according to Nghiem, adding an anti–CTLA-4 agent, such as ipilimumab (Yervoy), to a PD-1/PD-L1 inhibitor could lead to high toxicities, particularly for elderly patients, who represent the majority of MCC patients.

Immunotherapy in the adjuvant setting is also currently under investigation with the ADAM trial (NCT03271372), which is examining adjuvant avelumab in MCC. This study randomized 100 patients with node-positive MCC to avelumab or placebo. Patients will receive treatment for 2 years after surgery.

“Currently, there is a 70% chance of recurrence for patients with node-positive MCC. This study will be interesting to determine the adjuvant activity when patients receive an immunotherapy agent,” said Nghiem.

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