Checkpoint inhibitors: a new standard of care for advanced Merkel cell carcinoma?

Merkel cell carcinoma represents a rare group of cutaneous malignancies, which typically develop in the sun-damaged skin of elderly individuals and often in immunosuppressed patients. Locally advanced and metastatic Merkel cell carcinoma have a grave prognosis, and until recently, the European inter-disciplinary consensus-based guidelines recommended clinical trials as a standard of care. However, in reality, patients with advanced Merkel cell carcinoma receive platinum-based chemotherapies, which have a limited and short-lived clinical efficacy. Chemotherapy achieves response rates of up to 50–60% without showing a clear survival benefit. The median overall survival noted for treatment with chemotherapy is around 9 months. Complete responses and long-term survivors are rare.

In The Lancet Oncology, Howard Kaufman and colleagues report results from a phase 2 study in which 88 patients with advanced Merkel cell carcinoma were treated with the PD-L1-blocking antibody avelumab. Eight (9%) patients achieved a complete response and 20 (23%) patients achieved a partial response. All patients had histologically confirmed stage IV (advanced) disease and had documented progression following at least one previous line of chemotherapy in the metastatic setting. The median duration of response was not reached after a median follow-up time of 10 months. Clinical responses were observed independently of PD-L1 expression on tumour cells or presence of Merkel cell polyomavirus. Tolerability of avelumab was excellent, with only one permanent treatment discontinuation. Two patients discontinued treatment because of adverse effects.

These results in patients heavily pre-treated with chemotherapy indicate that avelumab has a high potential to change clinical practice in this aggressive cutaneous malignancy and led the US Food and Drug Administration to award avelumab a breakthrough therapy designation for the treatment of metastatic Merkel cell carcinoma in November, 2015. There are multiple reasons to treat patients with advanced Merkel cell carcinoma with checkpoint inhibitors, such as avelumab, which include strong interactions between this disease and the immune system and its high mutational burden and prominent ultraviolet-light mutation signature. PD-L1 expression is high in roughly 60% of the Merkel cell carcinomas: an additional indicator that it might be classified as a highly immune responsive tumour.

The results of Kaufman and colleagues’ study are strongly supported by results from other clinical trial data, including a phase 2 trial using the PD-1-blocking antibody pembrolizumab in patients with advanced Merkel cell carcinoma. In this study, 26 treatment-naive patients received pembrolizumab at a dose level currently approved for patients with metastatic melanoma (2 mg/kg bodyweight every 3 weeks). The difference in the proportion of patients who achieved an objective response with pembrolizumab (56%; four patients with a complete response and ten patients with a partial response) versus with avelumab (32%) might be explained by different patient characteristics, including pre-treatment status. Clinical data for first-line application of avelumab in Merkel cell carcinoma are therefore eagerly awaited. In the pembrolizumab trial, relapses were only observed in two of 14 responding patients after a median follow-up of 33 weeks. Similarly to the avelumab trial, responses to pembrolizumab were observed irrespective of Merkel cell polyomavirus status. In 15% of patients, grade 3–4 toxicities were associated with pembrolizumab treatment.

Taken together, these reports strongly suggest that checkpoint blockade is the best option to treat patients with advanced Merkel cell carcinoma, establishing a new standard of care, especially in view of the excellent tolerability of pembrolizumab and avelumab and the substantial comorbidities in this elderly patient cohort. Results of these two independent phase 2 trials have increased clinical expectations by their high proportion of responses and long response duration and are increasing hopes of achieving a long-term clinical benefit in a larger subset of patients. In view of these fascinating clinical results, running definitive phase 3 trials with chemotherapy as the comparator will be almost impossible for ethical reasons and because Merkel cell carcinoma is an orphan disease. Only in patients who have had organ and bone marrow transplantation and are at an extreme risk of...
developing Merkel cell carcinoma might checkpoint blockade be more difficult because of an increased risk of organ rejection. Besides Merkel cell carcinoma, other cutaneous skin cancers (mostly of epithelial origin) develop in this patient population with increased incidence.

However, early evidence from case reports suggests that checkpoint inhibition with PD-1/PD-L1 antibodies might also be useful for other non-melanoma skin cancers. In pre-treated advanced basal cell carcinomas and cutaneous squamous cell carcinomas, clinical responses with checkpoint blockade have also been described. These encouraging results will hopefully stimulate the field to investigate Merkel cell carcinoma as a new immunosensitive tumour model and generate growing interest in checkpoint blockade in so far neglected rare tumors, such as cutaneous squamous cell carcinomas and advanced basal cell carcinomas. In parallel, research to establish an (immune) biomarker should be further intensified to select the right patients for an effective checkpoint blockade. Furthermore, clinical trials to maximise synergistic benefits from combinations of checkpoint inhibitors such as CTLA-4 antibodies, PD-1 antibodies, or PD-L1 antibodies, with or without radiotherapy, should now be designed and executed. For the first time, there is some optimism on the horizon for treating patients with Merkel cell carcinoma and hopefully this will also expand to other non-melanoma skin cancers.

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