IMMUNOTHERAPY

Overcoming checkpoints in Merkel-cell carcinoma

Immune-checkpoint inhibition has initiated a new era of melanoma therapy. Now, results from a phase II trial suggest that this approach to therapy could improve outcomes of patients with another form of skin cancer: Merkel-cell carcinoma (MCC).

MCC is rare, with <2,000 new cases annually in the USA, but has an aggressive clinical course and limited treatment options. Around 55% of patients with advanced-stage MCC respond to standard-of-care chemotherapy, although the median progression-free survival (PFS) is only ~3 months. Thus, the disease has 'orphan' status, owing to its rarity and the dire need for novel therapies.

Merkel-cell polyomavirus (MCPyV) infection, or exposure to UV light underlies the development of MCC; therefore, the tumours are hypothesized to be highly immunogenic. Indeed, as author Paul Nghiem states, "that MCC is closely linked to immune function, both in terms of the incidence of disease and survival, has long been clear: patients with HIV or lymphoid malignancies, and solid-organ-transplant recipients are all at higher risk of MCC; conversely, patients who have MCC with CD8⁺ T-cell infiltration are at lower risk of recurrence and death." Moreover, ~50% of MCCs harbour the immune-checkpoint protein programmed cell death 1 ligand 1 (PD-L1), while infiltrating T cells express the cognate inhibitory receptor, programmed cell-death protein 1 (PD-1). These findings suggest that drugs blocking this immunosuppressive pathway could unleash the T-cell response for effective MCC therapy.

In the phase II trial, this possibility was tested by treating 26 patients with advanced-stage MCC with the anti-PD-1 antibody pembrolizumab as their first systemic therapy. "The use of pembrolizumab in the first-line setting, without precedent in later-line settings, was based on experience showing the very limited efficacy of standard chemotherapy," explains Suzanne Topalian, co-corresponding author of the study.

The response rate was similar to that observed with chemotherapy, 56% among 25 evaluable patients, but included four complete responses. Furthermore, "responses appeared to be durable: within a median follow-up period of 33 weeks, the estimated PFS was 9 months, approximately three times longer than would be expected after chemotherapy," Topalian adds. Of note, PD-L1 expression in the tumour was not correlated with response. Moreover, responses were seen in 62% of patients with MCPyV-positive MCC and 44% of those with MCPyV-negative disease, "suggesting that viral antigens might represent strong immunogens in the former group, and abundant UV-light-associated mutations might generate neoantigens that are immunological targets in the latter," says Topalian.

"We believe that, going forward, PD-1 blockade is likely to be a backbone of therapy for this highly immunogenic cancer," Nghiem opines. "The strategic addition of radiation and other immune-stimulating agents is likely to further improve these encouraging responses".

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