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Prognostic significance of cutaneous adverse events associated with pembrolizumab therapy

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The goal of cancer immunotherapy is to harness the immune system to recognize and destroy tumor cells, with the potential to produce durable responses that may translate into curative outcomes in patients with metastatic cancers. Results from multiple randomized clinical trials have established immune checkpoint inhibitors as the most successful class of immunotherapies to date. These include monoclonal antibodies that reinvigorate T cell responses by blocking cytotoxic T lymphocyte antigen-4 (CTLA-4) and programmed cell death-1 (PD-1), two coinhibitory receptors that regulate T cell activation.

The anti-CTLA-4 antibody ipilimumab was the first therapy to improve overall survival in patients with metastatic melanoma in a phase 3 trial, with an objective response rate of 11% and striking durable responses in a subset of patients[1]. Ipilimumab was approved for the treatment of advanced melanoma by the Food and Drug Administration (FDA) in 2011 and has been studied for the treatment of other cancers, with less clear benefit. In phase 3 studies, the anti-PD-1 drugs pembrolizumab and nivolumab delivered unprecedented objective response rates of approximately 30–40% in metastatic melanoma patients[2,3], and in the past year both antibodies were approved by the FDA for the treatment of advanced melanoma. Recently nivolumab was also approved for patients with squamous non-small cell lung cancer (NSCLC) following platinum-based chemotherapy, and in early clinical trials PD-1 inhibitors have demonstrated activity against other cancers including Hodgkin's lymphoma and renal cell carcinoma.

Ipilimumab therapy is associated with adverse events (AEs) that are tissue-specific inflammatory responses and likely result from potentiation of T cell activity against self antigens. These immune-related adverse events (irAEs) include colitis, dermatitis, hepatitis, and hypophysitis. Although nivolumab and pembrolizumab have milder irAE profiles than ipilimumab, common irAEs attributed to PD-1 inhibitors include several skin disorders. For example, rash, pruritis, and vitiligo occurred in 21%, 21%, and 9% of melanoma patients treated with pembrolizumab[3].

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Interestingly, induction of certain irAEs has historically been suggested as a positive prognostic factor in patients treated with earlier immunotherapies such as interferon and IL-2. Among cancer patients receiving IL-2, tumor regressions were reported in 71% of patients who developed hypothyroidism but only 19% of euthyroid patients[4]. Clinical responses were observed in 33% of 374 metastatic melanoma patients who developed vitiligo following IL-2 therapy compared to 10% of patients without vitiligo[5]. A large meta-analysis of multiple melanoma immunotherapy modalities found that vitiligo is significantly associated with progression free survival (PFS) and overall survival, with a two- to four-fold reduction in risk of disease progression and death in patients that develop vitiligo[6]. These associations may be related to lead time bias, as patients who progress either switch to other therapies or succumb to their disease while those who respond to immunotherapies have longer treatment duration and more time to develop autoimmune toxicities. Still, the correlation of some irAEs with anti-tumor responses in multiple studies is intriguing and highly suggestive of a true association.

In a recent retrospective cohort study published in *JAMA Dermatology*, Sanlorenzo et al report that cutaneous AEs are associated with better outcomes among cancer patients on pembrolizumab therapy[7]. In this study, which included 83 patients treated for melanoma, lung cancer, prostate cancer, and Merkel cell carcinoma enrolled in two pembrolizumab trials, 42% of patients developed cutaneous AEs (macular papular eruption, pruritis, or hypopigmentation). The cutaneous safety profile appeared favorable in the two trials, with no patients developing grade 4 cutaneous AEs and only two patients developing grade 3 cutaneous AEs. Most cutaneous AEs were self-limited or resolved with steroids or antihistamines. Patients who received more pembrolizumab cycles tended to have longer PFS and more cutaneous AEs. The major finding was that cancer patients who received 2 mg/kg of pembrolizumab every three weeks and developed cutaneous AEs had significantly longer PFS than patients without cutaneous AEs (hazard ratio 0.12, 95% CI 0.02–0.74, p=0.022, corrected for number of pembrolizumab cycles received). Longer PFS was also associated with cutaneous AEs in patients receiving other dosing regimens but did not reach statistical significance after correction for number of pembrolizumab cycles.

Although these results suggest that cutaneous toxicities may reflect more potent immune activation in the setting of pembrolizumab therapy, they do not discriminate between vitiligo and other cutaneous AEs as potential prognostic factors. Individuals with vitiligo are known to have a lower risk of developing melanoma, and vitiligo following immunotherapy has already been described as a predictor of survival in melanoma patients[6]. Notably, vitiligo has not been reported as a toxicity following immune checkpoint inhibitor therapy in patients with non-melanoma cancers, including NSCLC, prostate, renal cell, and colorectal cancer. Although only 17 out of 83 patients were treated for other cancers, all vitiligo cases in the current pembrolizumab study also occurred in melanoma patients[7]. These observations suggest that vitiligo in the context of cancer immunotherapy is a lineage-specific irAE. Given that emerging data have established the importance of neoantigens produced by somatic mutations as targets of anti-tumor immunity, an intriguing mechanistic question is how a putatively neoantigen-driven immune response against melanoma can trigger autoimmune attack of nonmalignant melanocytes in which the precise neoantigens

are absent. One potential explanation is epitope spreading, in which initial immune activity against one or a few tumor-specific epitopes extends to antigens shared by melanoma cells and melanocytes. Such epitope spreading would be predicted to enhance anti-melanoma immunity, consistent with vitiligo being a positive prognostic factor in patients receiving immune checkpoint inhibitor therapy.

Further analysis is required to determine whether non-vitiligo cutaneous AEs such as rash and pruritis are additional manifestations of disrupted immune tolerance that contribute to the observed outcome association in the study by Sanlorenzo et al. Though some analyses of skin biopsies have been reported elsewhere and identified immune infiltrates, little insight has been gained regarding the specific antigens being recognized in the skin. It will also be important to determine whether cutaneous AEs have prognostic significance in non-melanoma cancers. This may provide insight into tissue site selectivity of immune responses following immune checkpoint blockade. Better understanding the significance of irAEs as potential indicators of immunotherapy responses and outcome, as well as more detailed mechanistic explanations, will be important as ipilimumab, pembrolizumab, nivolumab, and other checkpoint inhibitors in development become increasingly used for cancer treatment in the clinic.

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References

1. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med. 2010; 363(8):711–723.10.1056/NEJMoa1003466 [PubMed: 20525992]
2. Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med. 2012; 366(26):2443–2454.10.1056/NEJMoa1200690 [PubMed: 22658127]
3. Hamid O, Robert C, Daud A, et al. Safety and Tumor Responses with Lambrolizumab (Anti-PD-1) in Melanoma. N Engl J Med. 201310.1056/NEJMoa1305133
4. Atkins MB, Mier JW, Parkinson DR, Gould JA, Berkman EM, Kaplan MM. Hypothyroidism after Treatment with Interleukin-2 and Lymphokine-Activated Killer Cells. N Engl J Med. 1988; 318(24):1557–1563.10.1056/NEJM198806163182401 [PubMed: 3259674]
5. Phan GQ, Attia P, Steinberg SM, White DE, Rosenberg SA. Factors Associated With Response to High-Dose Interleukin-2 in Patients With Metastatic Melanoma. J Clin Oncol. 2001; 19(15):3477–3482. [PubMed: 11481353]
6. Teulings HE, Limpens J, Jansen SN, et al. Vitiligo-Like Depigmentation in Patients With Stage III–IV Melanoma Receiving Immunotherapy and Its Association With Survival: A Systematic Review and Meta-Analysis. J Clin Oncol. 2015; 33(7):773–781.10.1200/JCO.2014.57.4756 [PubMed: 25605840]
7. Sanlorenzo M, et al. Pembrolizumab treatment: cutaneous adverse events and correlation with disease progression. JAMA Dermatol. 2015