RESEARCH LETTER

Cutaneous immune-related adverse events in patients with metastatic melanoma on antiprogrammed cell death protein 1 and anticytotoxic T-lymphocyte–associated protein 4 therapy: A retrospective cohort study

To the Editor: While immune checkpoint inhibitors (ICIs) against cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1) have been at the forefront of metastatic melanoma treatment, they commonly induce immune-related adverse events, such as cutaneous adverse events (CAEs). Many studies on CAEs have been previously restricted to individual types of CAEs or classes of ICIs.[1-3] As the CTLA-4 and PD-1 molecules are implicated in different interactions, we comprehensively examined the characteristics of all CAEs and their associations with treatment outcome to shed light on potential mechanisms for CAEs irrespective of the ICI therapy. This retrospective study included metastatic melanoma patients ≥18 years old who received ICIs at Sunnybrook Health Sciences Centre from June 2012 to December 2018. The Kaplan-Meier statistical analysis and log-rank test were used to examine overall survival.

We identified 235 patients with metastatic melanoma, of which 151 (64.3%) were male. The median age at treatment initiation was 66 (range 18-95) years. CAEs were the most common immune-related adverse events and occurred in 45/235 patients. The morphologies and anatomical locations of CAEs varied between the anti-PD-1 and anti-CTLA-4 therapies and are recorded in Table I. There was a lower percentage of negative outcomes, such as death and disease progression, in patients with CAEs, 1/28 (3.6%) and 13/28 (46.4%), respectively, compared to patients with no CAEs, 13/128 (10.2%) and 86/128 (67.2%) respectively. There was a significant difference in the overall survival between those with and without CAEs ($P = .0025$ with the log-rank test; Fig 1). For patients who had documentation of the specific treatment for CAEs, 23/44 received topical steroid, 5/44 received systemic oral steroid, and 16/44 received no treatment.

Table I. Percent prevalence of CAE types in patients with anti-PD-1 therapy versus that of CAE types in patients with anti-CTLA-4 therapy

CAE morphology	Percent prevalence for anti-PD-1 therapy	Percent prevalence for anti-CTLA-4 therapy
Rash containing macules and papules	17.1	41.7
Vitiligo	14.3	16.7
Erythema	0	8.3
Peripheral edema	8.6	0
Bullous pemphigoid	5.7	8.3
Dermatitis	5.7	0
Pruritus	5.7	8.3
Cellulitis	2.9	8.3
Psoriasis	2.9	0
Combination CAEs	3.1	16.7
Total	100	100

Anti-CTLA-4, Anticytotoxic T-lymphocyte-associated protein 4; *anti-PD-1*, antiprogrammed cell death protein 1; *CAEs*, cutaneous adverse events.

A study of 285 patients with ICIs supports the CAE morphologies observed in our study, including pruritus, rash containing macules and papules, and psoriasis.[4] Unlike our results, systemic immunomodulators were used for corticosteroid-refractory disease, reducing CAEs in 75% of the cases.[4] Other studies have identified associations between CAEs and survival for anti-PD-1 therapy,[1] vitiligo and survival for anti-PD-1/anti-CTLA-4 therapy,[2] and CAEs and survival for anti-PD-1/antiprogrammed death ligand 1 therapy.[5] Yet our results add to these findings by demonstrating a survival benefit regardless of the ICI subtype or CAE morphology.

Our results suggest a common mechanism in both the ICI therapies, through which CAEs are linked to improved survival. This pathway can be explained by the interaction of PD-1 receptors on T cells with tumor cells and that of CTLA-4 receptors on T cells with antigen-presenting cells. Circulating proinflammatory markers, such as interleukin 1α, IL-1β, and interferon α2, have been correlated with immune-related adverse events in PD-1 therapy.[4] These proinflammatory markers provide a mechanistic explanation for the shared pathway between the ICI therapies. Furthermore, the pathophysiologic

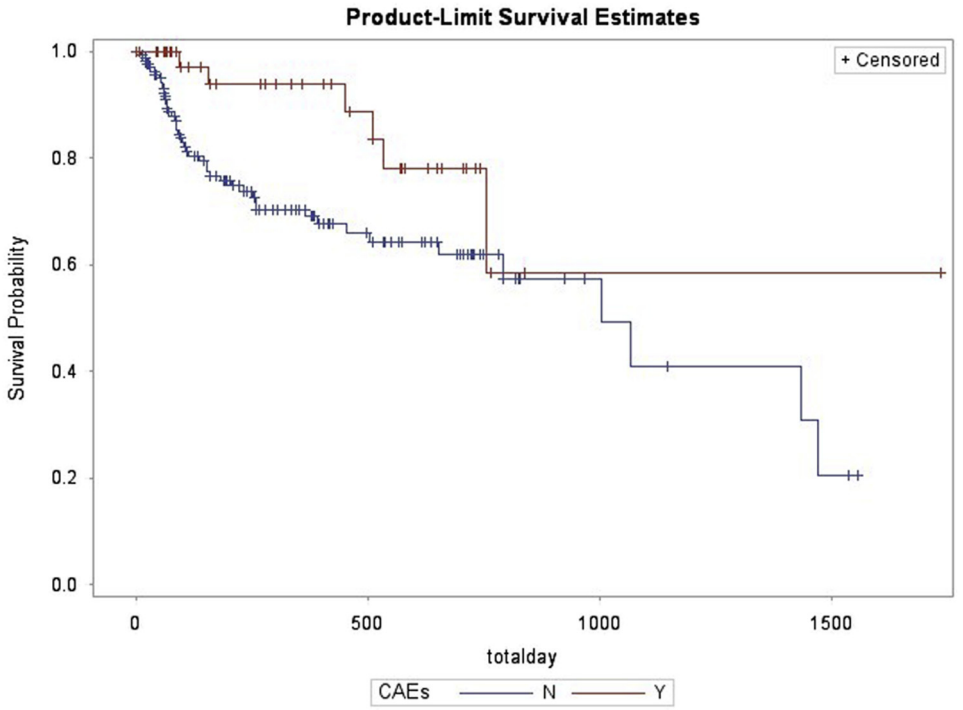

Fig 1. The Kaplan-Meier plot of survival rate based on the presence or absence of CAEs. *CAEs*, Cutaneous adverse events; *N*, no; *Y*, yes.

mechanism for vitiligo and bullous pemphigoid might be related to tumor cell interactions, given their higher prevalence in anti-CTLA-4 therapy (eg, via IgG and C3, as seen in anti-CTLA-4 therapy and bullous pemphigoid).[4] Similarly, the mechanism for peripheral edema and psoriasis might be related to antigen-presenting cell interactions, given their higher prevalence in anti-PD-1 therapy (eg, via IL-2, as seen in anti-PD-1 therapy[4] and psoriasis). These findings underscore the need for effective interventions that permit CAE treatment and dose maintenance.

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Funding sources: This work was supported by a Strategic Innovation Grant from the University of Toronto, Division of Medical Oncology to Dr Pezo.

Conflicts of interest: Dr Pezo reports receipt of honoraria from Pfizer, EMD Serono, and Novartis and research funding from Merck and serves on advisory boards for Astra Zeneca, Exact Sciences, Lilly, Myriad Genetics, Pfizer, and Novartis, all outside the submitted work. Author Naderi-Azad and Dr Sickandar have no conflicts of interest to declare.

IRB approval status: Approved by the Sunnybrook Health Sciences Centre Research Ethics Board.

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https://doi.org/10.1016/j.jdin.2020.10.005