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Cutaneous immune-related adverse event burden and effect on immunotherapy: A retrospective review of the experience at a tertiary care immunotherapy center

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To the Editor: Immune checkpoint inhibitors (ICIs) have revolutionized cancer care. Cutaneous immune-related adverse events (cirAEs) are frequent ICI side effects, often with a diverse presentation. However, cirAE duration and impact on ICI treatment are poorly characterized.[1–4] Here, we investigate the timeline of cirAE presentation and resolution in a real-world setting by both nondermatologist and dermatologist providers.

This is a retrospective chart review of patients with cirAEs seen by dermatologists from January 1, 2018 to June 30, 2020 within a health care system. Sociodemographic characteristics, medical history, cancer type, and treatment variables were evaluated. CirAEs were graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

The following 4 time metrics were documented: (1) time from initiation of ICI to appearance of cirAE, (2) time to dermatologist evaluation, (3) time to complete resolution, and (4) total time burden of cirAE (Supplementary Fig 1, available via Mendeley at https://data.mendeley.com/datasets/3tgyvwj7h4/1). Total time burden was only calculated

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Conflicts of interest

Dr Shawn G. Kwatra is on the consulting/advisory board for Incyte Corporation, Pfizer Inc., Castle Biosciences. The remaining authors have no conflicts to disclose.

for patients with documentation of cirAE management outcome (complete resolution or documented ongoing disease).

There were 44 patients included in this study and 51 separate ICI treatments (Table I). There were 50 separate cirAEs documented (Table II), and a wide range of distinct cirAEs (Supplementary Fig 2, available via Mendeley at https://data.mendeley.com/datasets/3tgyvwj7h4/1) and treatments given (Supplementary Fig 3, available via Mendeley at https://data.mendeley.com/datasets/3tgyvwj7h4/1). Only patients with new-onset disease were included. At the time of chart review, 42 treatments had been stopped by oncology (82.4%), of which 15 (35.7%) were stopped because of cirAE.

The median time from the initiation of ICI to the documentation of cirAE was 12.1 weeks (Table II). The median time from cirAE appearance to dermatology presentation was 5.3 weeks. For cirAEs with resolution, the median time of complete resolution after dermatologist presentation was 26.1 weeks. In total, the median time burden of cirAEs was 57.3 weeks (Table II).

Our data provides a perspective on the timeline of ICI initiation, including cirAE presentation, clinical evaluation, cirAE resolution, and patient outcomes. We demonstrate a large time burden, ie, a median time of 60 weeks from the first documentation of cirAE to the final outcome (complete resolution or documented ongoing disease). Early dermatologist input in ICI treatment may mitigate the progression of cirAE toxicities to higher-grade events, decrease reliance on systemic immunosuppression by treating early-stage toxicities, and minimize ICI discontinuation. According to CTCAE criteria, once a patient's dermatosis reaches 30% of the body surface area, they are considered to have grade 3 toxicity and, per guidelines, recommended to stop ICI treatment.[5] In these cases, dermatologist involvement becomes crucial, especially for cirAEs such as psoriasiform, lichenoid, and eczematous dermatitis; for these conditions, it would be rarely recommended to discontinue life-saving immunotherapy treatment. Treatment of these cirAEs can also be performed by any dermatologist and not necessitate a referral to a tertiary medical center. Limitations include lack of generalizability owing to the single-center study. In summary, cirAEs have a lengthy burden of disease and warrant early dermatologic referral to help minimize morbidity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table I.

Demographics of patients and ICI treatment characteristics, including status of treatment as a result of cirAE

Demographics of patients	No. of patients (%, *N* = 44)*	ICI treatment characteristics	No. of treatments (%, *N* = 51)†
Sex		Treatment	
Male	28 (63.6)	Nivolumab	20 (39.2)
Female	16 (36.4)	Pembrolizumab	16 (31.4)
Age (y), median (IQR)	70 (73–77)	Nivolumab + ipilimumab	6 (11.8)
Race/ethnicity		Cemiplimab	2 (3.9)
White or Caucasian	30 (68.2)	Durvalumab	2 (3.9)
Black or African American	9 (20.5)	Atezolizumab	2 (3.9)
Asian	3 (6.8)	Other‡	3 (5.9)
Hispanic or Latino	1 (2.3)	Concurrent treatment	
Other	1 (2.3)	Targeted therapy	10 (19.6)
History of an autoimmune disease, n (%)	14 (31.8)	Radiation	11 (21.6)
Cancer type		Chemotherapy	9 (17.6)
Lung	17 (38.6)	SOC or trial	
Skin	8 (18.2)	SOC	26 (51)
Head and neck	5 (11.4)	Trial	25 (49)
Liver/bile duct	3 (6.8)	ICI therapy stopped	
Pancreatic	2 (4.5)	Yes	42 (82.4)
Prostate	2 (4.5)	No	9 (17.6)
Bladder	2 (4.5)	Reasons why therapy was stopped (*N* = 42)	
Colon	1 (2.3)	Primarily because of cirAE	15 (35.7)
Renal	1 (2.3)	Primarily because of other irAEs	8 (19.0)
Endometrial	1 (2.3)	Other§	19 (45.2)
Ovarian	1 (2.3)	If ICI therapy was stopped because of cirAE, was it resumed? (*N* = 15)	
Lymphoma	1 (2.3)	Yes, and treatment was changed	1 (6.7)
Stage		Yes, and treatment was not changed	2 (13.3)
I	2 (4.5)	No, pending resolution of cirAE	0 (0)
II	3 (6.8)	No, pending disease progression	2 (13.3)
III	8 (18.2)	No, with no plans to restart because of cirAE	10 (66.7)

Demographics of patients	No. of patients (%, *N* = 44)*	ICI treatment characteristics	No. of treatments (%, *N* = 51)†
IV	25 (56.8)		
Unknown	6 (13.6)		

cirAEs, Cutaneous immune-related adverse events; *ICI*, immune checkpoint inhibitors; *SOC*, standard of care.

*Denominator is the total number of patients in the study.

†Denominator is the total number of individual ICI treatments.

‡Includes monotherapy with ipilimumab, M7824, and zimberelimab.

§Because of ineffectiveness of treatment, palliative care transition, disease progression, unclear reason (but treatment cessation clearly documented), or other reason.

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Table II.

Characteristics and time metrics for cirAEs

Characteristics	No. of patients (%, $N = 50$)*		
CTCAE grade			
1	5 (10.0)		
2	33 (66.0)		
3	11 (22.0)		
4	1 (2.0)		
Did cirAE appear during or after treatment?			
During	40 (80.0)		
After	10 (20.0)		
Hospitalization because of any irAE ($N = 44$ patients)?			
Yes	7 (15.9)		
Attributable to cirAE ($N = 7$)	4 (57.1)		
Attributable to other irAEs ($N = 7$)	3 (42.9)		
AE management outcome, n (%)			
Completely resolved	23 (46.0)		
Improved	12 (24.0)		
Stable/unchanged	8 (16.0)		
Worsened	0 (0)		
Death	1 (2.0)		
Unknown	6 (12.0)		
Time metrics for cirAEs (wk)	**Median**	**Mean**	**IQR**
Initiation of ICI to first documentation of cirAE ($N = 49$)	12.1	26.2	4.0–33.9
First documentation of cirAE to dermatology presentation ($N = 50$)	5.3	14.8	1.3–14.0
Time from dermatology presentation to complete resolution ($N = 23$)†	26.1	41.0	13.4–63.2
Total burden of cirAE ($N = 45$)‡	57.3	56.7	18.1–70.9

AE, Adverse effect; *CTCAE*, Common Terminology Criteria for Adverse Events; *cirAEs*, cutaneous immune-related adverse events; *ICI*, immune checkpoint inhibitors.

*Denominator is the total number of cutaneous immune-related adverse events.

†Time metric was only calculated for cirAEs that were documented as completely resolved on review.

‡Time metric was not calculated for those with an undocumented management outcome.