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Increased risk of cutaneous immune-related adverse events in patients treated with talimogene laherparepvec and immune checkpoint inhibitors: A multi-hospital cohort study

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Abstract

Background: Previous studies have shown that combining immune checkpoint inhibitors (ICIs) with talimogene laherparepvec (TVEC) may improve antitumor responses. However, the risk of developing cutaneous immune-related adverse events (cirAEs) in patients treated with ICI and TVEC has not been studied.

Objective: To evaluate the differences in cirAE development between patients treated with ICI alone and both ICI and TVEC (ICI + TVEC).

Methods: Patients with cutaneous malignancy receiving ICI with or without TVEC therapy at the Massachusetts General Brigham healthcare system were included. CirAE development, time from ICI initiation to cirAE, cirAE grade, cirAE morphology, and survival were analyzed. Pearson's x^2 test or Fisher's exact test for categorical variables and *t* test or Kruskal-Wallis test for continuous variables were used. To account for immortal time bias, we performed adjusted time-varying Cox proportional hazards modeling.

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Conflicts of interest

Dr Semenov is an advisory board member/consultant and has received honoraria from Incyte Corporation, Castle Biosciences, Galderma, and Sanofi outside of the submitted work. Dr LeBoeuf is a consultant and has received honoraria from Bayer, Seattle Genetics, 45 Sanofi, Silverback, and Synox Therapeutics outside the submitted work. Author Leung; Drs Wan and Nguyen; Authors Rashdan, Zhang, and Chen; Drs Cohen, Boland, and Sullivan; Author Fadden; and Drs Kaufman and Kwatra have no conflicts of interest to declare.

Results: The rate of cirAE development was 32.3% and 38.7% for ICI only and ICI + TVEC, respectively. After adjusting for covariates, ICI + TVEC was associated with a 2-fold increased risk of cirAE development (hazard ratio: 2.03, $P = .006$) compared to patients receiving ICI therapy alone.

Limitations: The retrospective nature and limited sample size from a tertiary-level academic center.

Conclusion: These findings underscore potential opportunities for dermatologists and oncologists in counseling and monitoring patients.

Keywords

cutaneous immune-related adverse events; cutaneous toxicities; immune checkpoint inhibitors; immunotherapy; melanoma; skin cancer; talimogene laherparepvec

INTRODUCTION

Immune checkpoint inhibitors (ICIs) have emerged at the forefront of cancer therapy, with increasing use and indications. Likewise, talimogene laherparepvec (TVEC), an intralesional oncolytic viral immunotherapy, has been approved for the management of locally advanced invasive melanoma by enhancing both local and systemic antitumor immune responses.[1] Its introduction has sparked interest in understanding its synergies as a complementary or alternative option to systemic immunotherapies. Prior studies suggest that combining TVEC and ICI therapy may be more effective than each drug alone.[2] However, stimulation of the immune system can lead to immune-related adverse events, of which cutaneous immune-related adverse events (cirAEs) are the most frequent and earliest.[3,4] The aim of this study is to investigate the influence of TVEC therapy on the development of cirAEs among ICI recipients.

METHODS

Patients with cutaneous malignancy receiving ICI with or without TVEC therapy at the Mass General Brigham healthcare system between September 12, 2014, and May 31, 2022, were included in this study (Fig 1). The Research Patient Data Registry[5] and the Enterprise Data Warehouse[6] are 2 institutional clinical databases within the Mass General Brigham healthcare system. We extracted the following variables from Research Patient Data Registry: patient age, sex, race, cancer type, International Classification of Diseases codes, date of death, or last follow-up. International Classification of Diseases codes from before ICI initiation were extracted to calculate Charlson Comorbidity Index.[7] The Enterprise Data Warehouse was used to ascertain the date of ICI and/or TVEC administration. ICIs include anti-programmed cell death 1 (PD-1; pembrolizumab, nivolumab, cemiplimab), anti-programmed cell death ligand 1 (PD-L1; atezolizumab, avelumab, durvalumab), anti-cytotoxic T-lymphocyte antigen 4 (CTLA4; ipilimumab), and combination therapy (anti-CTLA4 and either anti-PD-1 or anti-PD-L1 therapy). For patients without mortality status, their last encounters were considered their censoring dates.

Manual chart review was conducted by 2 independent trained research analysts to determine cirAE based on timing, morphology, competing risk factors, and histologic confirmation (Supplementary Methods, available via Mendeley at https://doi.org/10.17632/2sy8nfx9vp.1). Each cirAE was graded using Common Terminology Criteria for Adverse Events version 5.0.[8] In cases where concordance was not achieved, a third reviewer (Y.R.S.) arbitrated the cases. To compare groups, we used Pearson's x^2 test or Fisher's exact test for categorical variables and *t* test or Kruskal-Wallis test for continuous variables. To account for immortal time bias,[9] we performed time-varying Cox proportional hazard models, adjusting for sex, race/ethnicity, age at ICI initiation, ICI type, Charlson Comorbidity Index, and cancer type. All statistical analyses were conducted in R version 1.4.0.

RESULTS

A total of 892 patients treated with ICI were included in this study (Fig 1). Among them, 93 patients were treated with ICI and TVEC (ICI + TVEC) (cases), and 799 patients were treated with ICI alone (controls). Additionally, 52 patients were treated with TVEC alone, but this cohort was not used in our primary analyses.

The characteristics of the case and control groups are presented in Table I. Between the 2 groups, there were significant differences in median time from ICI initiation to cirAE (124 vs 55 days, $P = .014$), median age at ICI initiation (68.2 vs 65.1, $P = .002$), and median duration of follow-up (817 vs 1103, $P = .005$). ICI + TVEC recipients were more likely to have a non-melanoma skin malignancy ($P < .001$) and to be treated with ICI combination therapy ($P = .016$). In unadjusted analyses, there were no significant differences in cirAE development, grade, morphology, sex, and race between the study groups. In the ICI + TVEC group, 27 patients developed grade 1 cirAEs after receiving ICI therapy and before TVEC administration, of which 7 (25.9%) patients had cirAEs recur or flare after starting TVEC. The median time from TVEC initiation to cirAE onset was 72.8 [IQR: 20.3–304.3] days. Furthermore, of the 93 patients who received both ICI and TVEC, 72 (77%) patients started ICI followed by TVEC, while 12 (13%) patients started ICI after TVEC termination, and 6 (6%) patients started ICI during TVEC therapy. Lastly, 3 (3%) patients started TVEC and ICI on the same day. Details on each subgroup by timing are shown in Table II. For the TVEC only group, the baseline rate of cutaneous eruptions was 5.8%.

Multivariate modeling of cirAE development and subsequent mortality risk are presented in Table III. After adjusting for covariates, the time-varying Cox proportional hazard model demonstrated that the ICI + TVEC group was 2-fold more likely to develop cirAEs (hazard ratio = 2.03, $P = .006$). In addition, time-varying Cox proportional hazard model suggested increased mortality in the ICI + TVEC group (hazard ratio = 2.20, $P < .001$). We also conducted sensitivity analyses including only patients treated with ICI followed by TVEC (Table IV), including only patients with melanoma (Supplementary Tables I and II, available via Mendeley at https://doi.org/10.17632/2sy8nfx9vp.1), only melanoma patients receiving ICI followed by TVEC (Supplementary Table III, available via Mendeley at https://doi.org/10.17632/2sy8nfx9vp.1), and conducting experiments without adjusting Charlson Comorbidity Index (Supplementary Table IV, available via Mendeley at https://doi.org/10.17632/2sy8nfx9vp.1), which yielded similar results.

DISCUSSION

While more than half of the patients in both groups did not develop cirAEs, our data demonstrate that ICI+TVEC increases the likelihood of cirAE development by 2-fold. While TVEC enhances the production of granulocyte-macrophage colony stimulating factor and cross-primes cluster of differentiation 8 positive ($CD8^+$) T-cell responses, ICI induces the activation of T cells.[2] The combination of these 2 mechanisms may mediate the increased incidence of cirAEs. It is reassuring that most cirAEs in both cohorts are mild (grade 1 and 2).[1] Of the 294 patients with cirAEs, 105 (36%) patients were evaluated by dermatology for cutaneous eruptions. One hundred fifty-six (53%) received topical treatment. Seventy-nine (27%) received antihistamines, and 45 (15%) received systemic treatment (excluding antihistamines). ICI therapy interruption or dose reduction occurred for 11 (4%) patients, and therapy was permanently discontinued for 12 (4%) patients due to cirAEs.

While a prior study has suggested that combining ICI and TVEC may lead to improved response, its impact on progression free survival and overall survival remains unclear.[2] Moreover, prior studies have found that cirAE development is associated with ICI therapy response and improved survival.[10] Our data suggest that the ICI + TVEC population may have less favorable survival. This was largely due to overall sicker patients selected for TVEC in our cohort as 55/93 (59.1%) patients in our ICI + TVEC group transitioned to TVEC due to disease progression on ICI alone. When including only patients who received ICI followed by TVEC for our case group, the impact of TVEC on cirAE development was even more pronounced. Furthermore, given that the majority of patients who received both ICI and TVEC experienced disease progression while on ICI alone, they likely had more advanced and aggressive disease, less robust immune systems to keep their malignancy in control, and more extensive comorbidities, which may contribute to longer time from ICI initiation to cirAE development. Additionally, patients who started ICI after TVEC termination had the longest median time from ICI initiation to cirAE of 231 days, compared with 112 days for those who started ICI followed by TVEC and 130 days for those who started ICI during TVEC treatment. Patients who only received ICI had a relatively shorter median time from ICI initiation to cirAE of 55 days.

Our study highlights the importance of closer monitoring strategies and appropriate counseling for those who are considering or receiving ICI and TVEC. More individualized education and management can improve decision-making and quality of life for patients and caregivers. Limitations of this study include its retrospective nature and limited sample size from a tertiary-level academic healthcare system. Future trials will need to investigate outcomes with a larger cohort to understand the best standard of care.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations used:

cirAE	cutaneous immune-related adverse event
ICI	immune checkpoint inhibitors
TVEC	talimogene laherparepvec

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CAPSULE SUMMARY

- Immune checkpoint inhibitors and talimogene laherparepvec may be complementary treatments for locally advanced melanoma and cutaneous squamous cell carcinoma.
- Given that patients receiving both immune checkpoint inhibitors and talimogene laherparepvec are at higher risk of developing cutaneous toxicities, they should receive closer monitoring and counseling during their treatment.

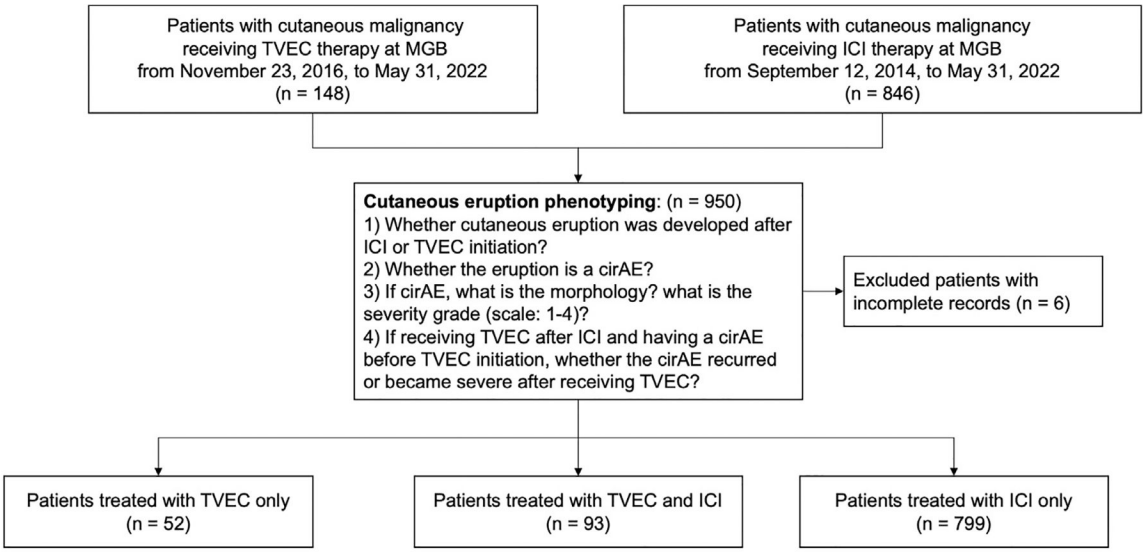

Fig 1.

Study design flowchart. *cirAE*, Cutaneous immune-related adverse event; *ICI*, immune checkpoint inhibitor; *MGB*, Mass General Brigham; *TVEC*, talimogene laherparepvec.

Table I.

Characteristics of the study cohort

	ICI and TVEC (*N* = 93)	ICI alone (*N* = 799)	*P* value
CirAE			
No	57 (61.3%)	541 (67.7%)	.259
Yes	36 (38.7%)	258 (32.3%)	
Sequence			
Started ICI and then TVEC	72 (77.4%)	Not applicable	
Started ICI after TVEC termination	12 (12.9%)	Not applicable	
Started ICI during TVEC	6 (6.5%)	Not applicable	
ICI and TVEC started on same day	3 (3.2%)	Not applicable	
ICI initiation to CirAE (days)			
Median [IQR]	124 [38, 373]	55 [21, 160]	.014
CirAE severity grade			
Median [IQR]	1 [1, 2]	1.5 [1, 2]	.081
CirAE morphology			
Acne	0 (0%)	7 (0.9%)	.124
Bullous dermatitis	1 (1.1%)	7 (0.9%)	
Drug hypersensitivity	0 (0%)	12 (1.5%)	
Eczematous dermatitis	3 (3.2%)	9 (1.1%)	
Lichen planus	5 (5.4%)	17 (2.1%)	
Maculopapular eruption	7 (7.5%)	57 (7.1%)	
Pruritus	8 (8.6%)	31 (3.9%)	
Morbilliform eruption	0 (0%)	4 (0.5%)	
Psoriasis	0 (0%)	12 (1.5%)	
Non-specified rash	12 (12.9%)	77 (9.6%)	
Vitiligo	0 (0%)	17 (2.1%)	
Other	0 (0%)	8 (1.0%)	
Age at ICI initiation			
Median [IQR]	68.2 [61.7, 77.4]	65.1 [56.4, 74.3]	.002
Cancer type			

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	ICI and TVEC (*N* = 93)	ICI alone (*N* = 799)	*P* value
Melanoma	78 (83.9%)	765 (95.7%)	<.001
Other skin malignancy	15 (16.1%)	34 (4.3%)	
ICI type			
CTLA4	2 (2.2%)	46 (5.8%)	.016
PD-1	57 (61.3%)	574 (71.8%)	
PD-L1	3 (3.2%)	18 (2.3%)	
Combination	31 (33.3%)	161 (20.2%)	
Charlson comorbidity index			
0	1 (1.1%)	3 (0.4%)	.336
1–2	72 (77.4%)	568 (71.1%)	
3–4	16 (17.2%)	163 (20.4%)	
≥5	4 (4.3%)	65 (8.1%)	
Sex			
Female	44 (47.3%)	307 (38.4%)	.121
Male	49 (52.7%)	492 (61.6%)	
Race			
White	90 (96.8%)	778 (97.4%)	.225
Other	0 (0%)	10 (1.3%)	
Unknown	3 (3.2%)	11 (1.4%)	
Mortality status			
Alive	49 (52.7%)	462 (57.8%)	.403
Dead	44 (47.3%)	337 (42.2%)	
Duration of follow-up			
Median [IQR]	817 [479, 1287]	1103 [396, 1648]	.005

cirAE, Cutaneous immune-related adverse event; *ICI*, immune checkpoint inhibitor; *TVEC*, talimogene laherparepvec.

Table II.

Subgroups of patients who received both immune checkpoint inhibitor and talimogene laherparepvec (TVEC)

	Number of patients	Number of patients who developed a cirAE	Number of patients who developed a cirAE after TVEC initiation	Median time from [IQR] ICI initiation to cirAE in days
ICI and TVEC* (*N* = 93)				
Started ICI first and then started TVEC	72	28 (38.9%)	9 (32.1%)	112 [32, 384]
Started ICI after TVEC termination	12	4 (33%)	4 (100%)	231 [148, 371]
Started ICI during TVEC treatment	6	2 (33%)	2 (100%)	130 [89, 170]
Started TVEC and ICI on the same day	3	2 (67%)	2 (100%)	43 [26, 60]
ICI alone	799	258 (32.3%)	Not applicable	55 [21, 160]

cirAE, Cutaneous immune-related adverse event; *ICI*, immune checkpoint inhibitor; *TVEC*, talimogene laherparepvec.

*In the ICI and TVEC group, 55/93 (59.1%) patients transitioned to TVEC due to disease progression on ICI alone.

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Table III.

Multivariate modeling of associations between talimogene laherparepvec use, cutaneous immune-related adverse event development, and mortality

Time-varying CoxPH model on cirAE status				Time-varying CoxPH model on mortality status			
Characteristic	**HR**	**95% CI**	***P* value**	**Characteristic**	**HR**	**95% CI**	***P* value**
TVEC	2.03	1.22, 3.36	.006	TVEC	2.20	1.60, 3.05	<.001
ICI Type				ICI Type			
CTLA4	Ref	Ref		CTLA4	Ref	Ref	
Combination	1.55	0.89, 2.70	.12	Combination	1.59	0.98, 2.58	.062
PD-1	0.88	0.51, 1.49	.6	PD-1	0.73	0.46, 1.17	.2
PD-L1	0.67	0.24, 1.87	.4	PD-L1	0.76	0.34, 1.67	.5
Age at ICI initiation	1.00	0.99, 1.01	.7	Age at ICI initiation	1.03	1.02, 1.04	<.001
Cancer type				Cancer type			
Melanoma	Ref	Ref		Melanoma	Ref	Ref	
Other skin malignancy	1.17	0.71, 1.94	.5	Other skin malignancy	2.09	1.43, 3.06	<.001
CCI				CCI			
≥5	Ref	Ref		≥5	Ref	Ref	
3–4	0.73	0.42, 1.26	.3	3–4	0.51	0.35, 0.74	<.001
1–2	1.02	0.63, 1.67	>.9	1–2	0.41	0.29, 0.58	<.001
0	4.35	1.43, 13.2	.009	0	0.21	0.03, 1.52	0.12
Race				Race			
White	Ref	Ref		White	Ref	Ref	
Other	0.59	0.14, 2.39	.5	Other	1.29	0.48, 3.50	.6
Unknown	0.34	0.08, 1.36	.13	Unknown	0.48	0.15, 1.51	.2
Sex				Sex			
Female	Ref	Ref		Female	Ref	Ref	
Male	1.08	0.85, 1.37	.5	Male	0.80	0.65, 0.98	.034

Multivariate time-varying Cox proportional hazards model.

CCI, Charlson Comorbidity Index; *CI*, confidence interval; *cirAE*, cutaneous immune-related adverse event; *CoxPH*, Cox proportional hazard; *HR*, hazard ratio; *ICI*, immune checkpoint inhibitor; *PD-1*, programmed cell death 1; *PD-L1*, programmed cell death ligand 1; *Ref*, reference; *TVEC*, talimogene laherparepvec.

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Table IV.

Multivariate modeling of the influence of TVEC on cutaneous immune-related adverse event development and mortality restricting the study population to patients receiving TVEC after immune checkpoint inhibitor

Time-varying CoxPH model on cirAE status				Time-varying CoxPH model on mortality status			
Characteristic	**HR**	**95% CI**	***P* value**	**Characteristic**	**HR**	**95% CI**	***P* value**
TVEC	4.35	2.13, 8.90	<.001	TVEC	2.82	1.98, 4.02	<.001
ICI Type				ICI Type			
CTLA4	Ref	Ref		CTLA4	Ref	Ref	
Combination	1.55	0.89, 2.70	.12	Combination	1.55	0.95, 2.52	.077
PD-1	0.87	0.51, 1.48	.6	PD-1	0.74	0.46, 1.18	.2
PD-L1	0.76	0.27, 2.16	.6	PD-L1	0.68	0.30, 1.54	.4
Age at ICI initiation	1.00	0.99, 1.01	.7	Age at ICI initiation	1.03	1.02, 1.04	<.001
Cancer type				Cancer type			
Melanoma	Ref	Ref		Melanoma	Ref	Ref	
Other skin malignancy	1.06	0.61, 1.84	.8	Other skin malignancy	2.03	1.37, 3.02	<.001
CCI				CCI			
≥5	Ref	Ref		≥5	Ref	Ref	
3–4	0.74	0.43, 1.29	.3	3–4	0.54	0.37, 0.78	.001
1–2	1.02	0.62, 1.67	>.9	1–2	0.43	0.30, 0.60	<.001
0	4.49	1.48, 13.6	.008	0	0.21	0.03, 1.55	.13
Race				Race			
White	Ref	Ref		White	Ref	Ref	
Other	0.58	0.14, 2.36	.4	Other	1.29	0.48, 3.50	.6
Unknown	0.33	0.08, 1.33	.12	Unknown	0.45	0.14, 1.42	.2
Sex				Sex			
Female	Ref	Ref		Female	Ref	Ref	
Male	1.06	0.83, 1.34	.7	Male	0.81	0.66, 1.01	.056

Multivariate time-varying CoxPH models on cirAE and mortality when the study group includes only patients who received ICI first and then TVEC ($n = 72$ cases vs $n = 799$ controls).

CCI, Charlson Comorbidity Index; *CI*, confidence interval; *cirAE*, cutaneous immune-related adverse event; *CoxPH*, Cox proportional hazard; *HR*, hazard ratio; *ICI*, immune checkpoint inhibitor; *PD-1*, programmed cell death 1; *PD-L1*, programmed cell death ligand 1; *Ref*, reference; *TVEC*, talimogene laherparepvec.