Cutaneous and Noncutaneous Adverse Effects in Patients with Advanced Melanoma Receiving Immunotherapy

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Relationships between cutaneous adverse effects (CAEs) and noncutaneous adverse effects (NCAEs) of melanoma immunotherapy may help identify patterns tied to distinct immunologic pathways. The objective of this study was to determine the associations between CAEs and NCAEs among patients with stages III–IV melanoma receiving immunotherapy and who were enrolled in a prospective cohort. Electronic medical record data were abstracted from the first immunotherapy infusion until 1 year later. CAEs were rash or itch. NCAEs were symptoms and/or laboratory abnormalities documented as immunotherapy related. NCAE onset and time to NCAE were compared between participants with and without CAEs using ORs and Wilcoxon rank sum tests. Of 34 participants, 11 (32.4%) developed no adverse effects, 7 (20.1%) developed CAEs only, 3 (8.8%) developed NCAEs only, and 13 (38.2%) developed both CAEs and NCAEs. After adjustment for age, sex, and immunotherapy regimen, CAE was associated with higher odds of NCAE development (OR = 9.72; 95% confidence interval = 1.2–76.8). Median NCAE onset was 63 days in those with CAEs and 168 days in those without CAEs ($P = 0.41$). Limitations included a small sample size, and larger prospective studies should be performed to confirm findings. CAE was associated with NCAE development. Early identification and treatment of NCAEs may reduce symptom burden and hospitalizations associated with NCAEs.

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INTRODUCTION

Immune checkpoint inhibitors are increasingly prescribed for advanced melanoma because they have been shown to improve survival rates (Srivastava and McDermott, 2014). Although there are many benefits to immunotherapy, adverse effects are common and may lead to severe symptoms that require hospitalization (Redman et al., 2016). Early identification and mitigation of adverse effects among patients receiving immunotherapy may improve QOL and reduce required treatment of adverse effects (Andrews and Holden, 2012; Weber et al., 2015, 2012).

A potential avenue for reducing the burden of immunotherapy-related adverse effects is early detection of symptoms and identification of distinct immunologic pathways that could be targeted in treatment of adverse effects; prior research has shown that certain morphologies of cutaneous adverse effects (CAEs) may predict certain types of noncutaneous adverse effects (NCAEs) (Thompson et al., 2021). However, it is not known whether NCAEs are different between those who develop CAEs and those who do not develop CAEs. Characterizing differences in NCAEs on the basis of development of CAE may promote early identification and prevention of severe NCAEs.

In this study, data were abstracted from electronic medical records of patients with stage III or IV melanoma receiving immunotherapy. We hypothesize that those patients who develop immunotherapy-related CAEs will be more likely to develop NCAEs. Furthermore, among participants who developed CAEs, the onset of NCAEs will be earlier than the onset among those who did not develop CAEs.

RESULTS

Thirty-four participants (32 [94.1%] White; 17 [50.0%] female) were included (one was excluded for not receiving any immunotherapy). A total of 18 (52.9%) patients had stage III melanoma, and 16 (47.1%) patients had stage IV (Table 1). No differences in odds of CAE and NCAE development based on melanoma stage or immunotherapy goal were found. CAEs were observed among 20 (58.8%) participants and

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Abbreviations: CAE, cutaneous adverse effect; NCAE, noncutaneous adverse effect

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Table 1. Demographic Characteristics, Melanoma Stage, and Immunotherapy Details for 34 Patients with Advanced Melanoma Receiving Immunotherapy

Variable	n	%
Age (y)		
35–49	4	11.8
50–59	12	35.3
60–69	14	41.1
≥70	4	11.8
Sex		
Male	17	50.0
Female	17	50.0
Race		
White	32	94.1
Black	2	5.9
Education		
High school or less	19	55.9
Associates, Bachelors, or higher degrees	15	44.1
Missing	1	2.9
Household income ($)		
<75,000	11	32.4
75,000–99,999	4	11.8
≥100,000	16	47.1
Missing	3	8.8
Melanoma stage		
III (IIIA, IIIB, IIIC)	18	52.9
IV	16	47.1
Immunotherapy goal		
Adjuvant	16	47.1
Treatment of clinically evident disease	17	50.0
Missing	1	2.9
Immunotherapy regimen		
PD1 inhibitor only	21	61.7
CTLA4 inhibitor only	1	2.9
Combination therapy	12	35.2
Immunotherapy name (some participants received combinations)		
Ipilimumab	9	26.5
Nivolumab	26	76.5
Pembrolizumab	3	8.8
Received prior immunotherapy		
Yes	4	11.8
No	30	88.2

were predominantly Common Terminology Criteria for Adverse Events grade 1 or 2 (Table 2). The most common rash morphology observed was eczematous (n = 13, 65.0%), followed by psoriasiform (n = 2, 10.0%) (Table 2). NCAEs were observed among 16 (47.1%) participants and commonly involved the endocrine (n = 9, 56.3%) and gastrointestinal (n = 7, 43.8%) organ systems (Table 3).

Stratifying the sample for analysis demonstrated that 11 (32.4%) developed no adverse effects, 7 (20.1%) developed only CAEs, 3 (8.8%) developed only NCAEs, and 13 (38.2%) developed both CAEs and NCAEs. Those who developed CAEs were significantly more likely to develop any NCAEs than those who did not develop CAEs after adjustment for age, sex, and immunotherapy regimen (adjusted OR = 9.72; 95% confidence interval = 1.2–76.8). Median time to NCAE onset was shorter in those who developed CAEs than in those who did not, but differences were not significant (63 vs. 168 days, $P = 0.41$).

Table 2. Cutaneous Adverse Effect Morphology and Severity among 20 Patients with Advanced Melanoma Receiving Immunotherapy Captured by Study Dermatologists during In-Person Visits

Variable	n	%
Rash morphology		
Eczematous	13	65.0
Psoriasiform	2	10.0
Lichenoid	0	0.0
Morbilliform	1	5.0
Vesiculobullous	1	5.0
No rash (itch only)	3	15.0
Missing	0	0.0
Common Terminology Criteria for Adverse Events for Rash		
4	0	0.0
3	0	0.0
2	6	30.0
1	10	45.0
Not applicable/missing	4	25.0
Common Terminology Criteria for Adverse Events for Itch		
3	0	0.0
2	7	35.0
1	9	45.0
Not applicable/missing	4	20.0

Prevalence of secondary study outcomes based on development of CAEs and NCAEs is shown in Table 4. Those who developed CAEs, when compared with those who did not develop CAEs, had increased odds of improved tumor burden or continued suppression of melanoma (unadjusted OR = 6.61, 95% confidence interval = 1.28–34.14). Those who

Table 3. Characteristics of Noncutaneous Adverse Effects among 16 Patients with Advanced Melanoma Receiving Immunotherapy Captured from Retrospective Medical Record Review

Variable[1]	n	%
Ear, nose, and throat (1 of 16, 6.3%)		
Xerostomia	1	100.0
Endocrine (9 of 16, 56.3%)		
Asymptomatic thyroiditis	4	44.4
Symptomatic thyroiditis	3	33.3
Adrenal insufficiency	2	22.2
Pan hypopituitarism	1	11.1
Hepatic (2 of 16, 12.5%)		
Asymptomatic transaminitis	2	100.0
Gastrointestinal (7 of 16, 43.8%)		
Diarrhea and abdominal pain secondary to colitis	7	100.0
Pulmonary (2 of 16, 12.5%)		
Shortness of breath and cough secondary to pneumonitis	2	100.0
Renal (2 of 16, 12.5%)		
Asymptomatic creatinine elevation	2	100.0
Rheumatology (1 of 16, 6.3%)		
Inflammatory arthritis	1	100.0

[1]Participants may have had multiple noncutaneous adverse effects.

Table 4. Clinical Outcomes among 34 Patients with Advanced Melanoma Receiving Immunotherapy on the Basis of Adverse Effect Status

Variable	Total (n = 34)		Any CAE[1] (n = 20)		Any NCAE[1] (n = 16)	
	n	%	n	%	n	%
Hospitalization for CAEs or NCAEs	4	11.8	4	20.0	4	25.0
Melanoma progression despite immunotherapy	10	29.4	3	15.0	3	18.8
Hospitalization for progression of melanoma	5	14.7	1	5.0	2	12.5
Hospice or death	5	14.7	2	10.0	2	10.0

Abbreviations: CAE, cutaneous adverse effect; NCAE, noncutaneous adverse effect.
[1]Groups are not mutually exclusive. Any CAEs and NCAEs were compared with no cutaneous and no noncutaneous adverse effects, respectively.

developed NCAEs, when compared with those who did not develop NCAEs, did not demonstrate a statistically significant improvement in treatment response (3.03, 95% confidence interval = 0.62−14.79). The odds of being hospitalized, being placed on hospice, or dying from melanoma progression did not differ on the basis of CAE or NCAE development. Delay or cessation of immunotherapy occurred in nine (26.5%) participants—eight (88.9%) for NCAE and one (11.1%) for CAE—and was not associated with treatment efficacy or adverse outcomes secondary to melanoma.

DISCUSSION

In this cohort of patients with stage III and IV melanoma receiving immunotherapy, CAE was associated with NCAE development and increased treatment efficacy. NCAE development occurred earlier among those who developed CAE, but differences were not statistically significant. Similar to prior investigations, the most commonly observed NCAEs were endocrine such as autoimmune thyroiditis and immune hypophysitis and gastrointestinal toxicities such as colitis (Topalian et al., 2012). Less common NCAEs observed in this study included transaminitis, acute kidney injury, and pneumonitis, all of which have been previously reported (Baxi et al., 2018; Hofmann et al., 2016; Moreira et al., 2020).

This study compared NCAEs between those who developed CAEs and those who did not develop CAEs. Observed associations between CAEs and NCAEs reinforce prior research suggesting that immunotherapy-related adverse effects are caused by immune system overactivation and emphasize the importance of identifying specific pathways shared between certain CAEs and NCAEs (Boutros et al., 2016). A strong association between CAEs and NCAEs emphasizes the importance of carefully monitoring for adverse events once patients are diagnosed with a CAE because CAE onset often precedes NCAE onset (Haanen et al., 2017). In cases where CAEs develop, appropriate anticipatory guidance and increased clinicovigilance for NCAE symptoms can be provided to patients, which in turn may prevent the development and progression to severe adverse events that can result in hospitalization and escalation of care.

Although CAEs and NCAEs may significantly disrupt QOL and require hospitalization among patients receiving immunotherapy, the presence of CAEs may be a strong indicator of treatment efficacy and predict improved melanoma-related outcomes (Das and Johnson, 2019). Large but nonsignificant associations between NCAEs and treatment efficacy suggest that this study was underpowered to detect true effects. Positive associations between adverse effects and treatment efficacy are reflected in prior research, and a growing body of evidence suggests that there are no differences in outcomes for patients even when immunotherapy is delayed or stopped (Das and Johnson, 2019; Johnson et al., 2020; Tang et al., 2022).

Study limitations included a small sample size, which prevented disaggregated analyses of specific NCAEs and may have underpowered the study to detect true effects between adverse effects and immunotherapy-related outcomes. Study outcomes, particularly NCAEs, were elucidated using clinician notes rather than using uniform raters to apply previously validated criteria such as the Response Evaluation Criteria in Solid Tumors for treatment efficacy (Eisenhauer et al., 2009; Trotti et al., 2003). Although participants were recruited for a prospective cohort study, present analyses were retrospective and prone to information bias. Future studies among a larger prospective cohort of patients are needed to determine whether certain NCAEs are more common among those who develop CAEs so that specific immunologic pathways activated by checkpoint inhibitors can be elucidated. Knowledge of pathways activated in immunotherapy-related adverse effects would enable the use of more targeted therapies rather than broad immunosuppressants such as oral corticosteroids (Friedman et al., 2016).

In conclusion, participants who developed CAEs were more likely to develop any NCAEs than those who did not develop CAEs. CAE onset was also associated with increased immunotherapy efficacy. Dermatologists and oncologists should routinely screen for CAEs among patients receiving checkpoint inhibitor immunotherapies because that may predict NCAE onset and indicate treatment efficacy. Although prevention of severe adverse effects may not be associated with improved melanoma-related outcomes, early identification and treatment of NCAEs may reduce symptom burden and hospitalizations associated with NCAEs.

MATERIALS AND METHODS

Participants previously enrolled in a prospective cohort study at Emory University from October 2018 to June 2020 were eligible. Electronic medical record data were abstracted retrospectively from the first immunotherapy infusion to 1 year later. Covariates included

melanoma stage, immunotherapy details, and self-reported sociodemographic features.

Primary outcomes were CAE and NCAE development; CAEs were defined as rash or symptoms of itch, whereas NCAEs were collected by organ system and defined as symptoms and/or laboratory abnormalities documented as related to immunotherapy. Participants who developed rash and/or itch were scheduled for in-person evaluation with a study dermatologist, who documented rash morphology and obtained biopsies as appropriate; a combination of clinical data and pathologic findings were used to assess whether CAEs were related to immunotherapy. Secondary outcome was treatment efficacy; no evidence of disease for adjuvant therapy or mention of positive responses to immunotherapy for treatment of evident disease documented in the oncology clinical note were regarded as effective treatment. Tertiary outcomes included hospitalization, hospice, and death separated by cause (melanoma, adverse effect, other). The protocol was approved by the Emory University Institutional Review Board, and results were reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines (von Elm et al., 2008).

Participants were stratified by CAE development. NCAEs by organ system were grouped together as any NCAE for analysis owing to small sample sizes. ORs for developing any NCAE were calculated through multivariate logistic regression adjusted for age, sex, and immunotherapy regimen. Wilcoxon rank sum tests were used to compare time to NCAE onset between groups. Unadjusted ORs for treatment efficacy, hospitalization, hospice, or death due to melanoma were calculated on the basis of CAE and NCAE development separately. Unadjusted ORs of developing any melanoma-related adverse outcome (hospitalization, hospice, or death due to melanoma) were calculated on the basis of immunotherapy delay or cessation versus completed regimens. Missing data were excluded from analysis. Statistical analyses were performed on SAS, version 9.4; $P \leq 0.05$ on two-tailed *t*-tests was considered statistically significant.

Data availability statement

Deidentified data are available upon request to the corresponding author (HY). Data are not publicly available to protect participant privacy.

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CONFLICT OF INTEREST

SCC receives royalties from for-profit companies that license QOL instruments for which Emory holds copyright; no such instruments were used in this study. HY is supported in part by the American Skin Association, the American Cancer Society and Melanoma Research Alliance Pilot Award, the Department of Veterans Affairs, and the National Institute of Arthritis and Musculoskeletal and Skin Diseases under award numbers L30AR076081 and K23AR075888. RRK currently works for Daiichi Sankyo, a pharmaceutical company with a number of drugs in development throughout solid tumor oncology, including melanoma. AIS is a speaker and consultant for Merck and a consultant for Bristol Myer Squibb. The remaining authors state no conflict of interest.

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AUTHOR CONTRIBUTIONS

Conceptualization: HY, RRK, DHL, MLY, SCC; Data Curation: KJS, SF, CHA; Formal Analysis: HY, KJS, SF, CHA, RRK, DHL, MLY, AIS, SCC; Funding Acquisition: HY, RRK, DHL, SCC; Investigation: HY, KJS, SF, CHA, RRK, DHL, MLY, AIS, SCC; Methodology: HY, KJS, SF, CHA, RRK, DHL, MLY, AIS, SCC; Project Administration: KJS, SF, CHA; Supervision: HY, RRK, DHL, MLY, AIF, SCC; Validation: HY, KJS, SF, CHA, RRK, DHL, MLY, AIS, SCC; Visualization: HY, KJS, SF, CHA, RRK, DHL, MLY, AIS, SCC; Writing − Original Draft Preparation: HY, KJS; Writing − Review and Editing: HY, KJS, SF, CHA, RRK, DHL, MLY, AIS, SCC

Disclaimer

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