Association of interleukin-6 and tumor necrosis factor-α with mortality in hospitalized patients with cancer

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Background: Severe cutaneous adverse reactions (SCARs) are associated with high morbidity and mortality in patients with cancer. Early identification and treatment of SCARs may improve outcomes.

Objective: To identify biomarkers to predict outcomes in hospitalized patients with cancer who developed SCARs.

Methods: Retrospective review of 144 hospitalized patients with cancer with a morbilliform rash, recorded testing for serum cytokines (interleukin [IL]-6, IL-10, and tumor necrosis factor [TNF]-α) or elafin, and a dermatology consultation. Rashes were categorized as simple morbilliform rash without systemic involvement or complex morbilliform rash with systemic involvement.

Results: Fifty-four of 144 (37.5%) patients died during follow-up. Elevated levels of IL-6, IL-10, and TNF-α were associated with decreased survival. Overall survivals in patients with elevated levels of IL-6, IL-10, and TNF-α were 53.7%, 56.6%, 53.6%, respectively, compared with 85.7%, 82.5% and 83.6%, respectively, in those with lower levels. Patients with increased levels of both IL-6 and TNF-α had a nearly 6-fold increase in mortality (hazard ratio, 5.82) compared with patients with lower levels.

Limitations: Retrospective design, limited sample size, and high-risk population.

Conclusions: Hospitalized patients with cancer with rash and elevated IL-6 and TNF-α were nearly 6 times more likely to die over the course of follow-up. These biomarkers may serve as prognostic biomarkers and therapeutic targets for this high-risk population. (J Am Acad Dermatol 2021;84:273-82.)

Key words: biomarker; cytokine; drug-induced hypersensitivity syndrome; drug rash; drug reaction; drug reaction with eosinophilia and systemic symptoms; graft-versus-host disease; interleukin-6 (IL-6); mortality; severe cutaneous adverse reaction; survival; tumor necrosis factor alpha (TNF-α).

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Funding sources: Dr Markova is supported by a Dermatology Foundation Career Development Award. This study was also funded in part by a grant from the National Cancer Institute/National Institutes of Health (P30-CA008748) made to the Memorial Sloan-Kettering Cancer Center.

Disclosure: Dr Lacouture has served in consultant/speaking roles with Legacy Healthcare Services, ADC Therapeutics America Inc, Adgero Biopharmaceuticals, Amryt Pharmaceuticals, Apricity Health LLC, Azitra Inc, Celldex Therapeutics, Deciphera, Debiopharm, Galderma Research and Development, Johnson and Johnson, NCODA, Novocure Inc, Kyowa Kirin Inc, Lindi, Loxo, Merck Sharp and Dohme Corporation, Helsinn Healthcare SA, Janssen Research & Development LLC, Menlo Therapeutics, Novartis Pharmaceuticals Corporation, F. Hoffmann-La Roche AG, QED Therapeutics, AbbVie Inc, Boehringer Ingelheim Pharma Gmbh & Co KG, Allergan Inc, Amgen Inc, E.R. Squibb & Sons LLC, EMD Serono Inc, AstraZeneca Pharmaceuticals LP, Genentech Inc, Leo Pharma Inc, Seattle Genetics, Bayer, Manner SAS, Lutris, Pierre Fabre, Paxman Coolers, Adjucare, Dignitana, Biotechspert, Teva Mexico, Parexel, OnQuality Pharmaceuticals Ltd, Takeda Millennium, and Our Brain Bank; he also receives also receives research funding from Bristol-Myers Squibb, Lutris, Paxman, Novocure, US Biotest, and Veloce. Dr Markova has served on the advisory board of AstraZeneca and receives research funding from Incyte. Mr Stoll, Mr Vaidya, and Drs Mori and Dusza have no conflicts of interest to disclose.

IRB approval status: Reviewed and approved by the IRB of Memorial Sloan Kettering Cancer Center.
Accepted for publication March 5, 2020.
Reprints are not available from the authors.

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Published online March 12, 2020.
0190-9622/$36.00

https://doi.org/10.1016/j.jaad.2020.03.010

Patients with cancer are at risk of developing therapy-related morbilliform eruptions, graft-versus-host disease (GVHD), and severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug-induced hypersensitivity/drug reaction with eosinophilia and systemic symptoms. SCARs are 28 to 57 times more common in patients with cancer, with 5.7 to 14.9 cases per 100,000 patients, and are more fatal (mortality of 32% with vs 8.5% without cancer in SJS/TEN), with the greatest risk among patients with hematologic cancer.[1-3] The increased mortality in this population is thought to be multifactorial due to malnutrition, cancer type, immunocompromised status, and chemotherapy type.[4]

Early recognition and treatment of SCARs is vital for improving survival.[4] Earlier withdrawal of the causative drug is associated with better SCAR prognosis (odds ratio, 0.69 for each day; 95% confidence interval [CI], 0.53-0.89).[5] Given the increased incidence and mortality of SCARs in patients with cancer and the difficulty in clinically diagnosing SCARs, reliable, objective markers are needed. Our previous study found an association of elafin, interleukin (IL)-6, and tumor necrosis factor (TNF)-α with all-cause mortality in patients with cancer who develop SCARs and IL-10 and IL-6 with a drug-related complex rash.[6] Elafin is overexpressed in wound healing and inflammatory skin disorders and is a diagnostic and prognostic plasma biomarker in GVHD. Elevated IL-6 and IL-10 levels have been found in patients with acute GVHD, SJS, and TEN.[7,8]

Biomarkers have potential prognostic and diagnostic utility in a hospitalized population of patients with cancer who develop SCARs. The objective of this study was to identify serologic markers or combinations of markers that may be used to predict outcomes in hospitalized patients with cancer who developed SCARs.

CAPSULE SUMMARY

- Reliable prognostic biomarkers are needed to predict outcomes in hospitalized patients with cancer with rash.
- Hospitalized patients with cancer with rash and elevated interleukin-6 and tumor necrosis factor-α levels have a nearly 6 times decreased overall survival. Given the availability of tumor necrosis factor α and interleukin 6 inhibitors, these biomarkers may serve as potential therapeutic targets.

METHODS

This was a retrospective cohort study approved by the institutional review board of Memorial Sloan Kettering Cancer Center. A database query of adult patients with cancer who were hospitalized between August 2016 and February 2019 and had International Classification of Diseases, 9th or 10th Revision, codes for rash (R23, R21, 693, 692, 695, 690-698, L20-L30, L51, L43.2, T88.7, L55-59); recorded testing for serum biomarkers IL-1β, IL-6, IL-10, TNF-α, or plasma elafin; and prior dermatology consultation revealed 151 eligible patients (Fig 1). These biomarkers are obtained at our institution as the standard of care for all patients who present with possible drug eruption to complement the clinical picture and serve as a potential therapeutic target. Seven patients were excluded because biomarkers were checked for a reason other than a morbilliform rash (ie, cytokine release syndrome, study protocol, sepsis, or cellulitis/panniculitis).

A total of 144 patients were evaluated through the inpatient service or in the urgent care center at Memorial Sloan Kettering Cancer Center with a diagnosis of morbilliform rash and were tested for cytokines or elafin. Chart review was performed for all patients to assign simple and complex morbilliform rash groups. Simple morbilliform rash was defined as a rash with no systemic involvement, or spontaneous resolution of rash with remote systemic involvement, or limited course of rash that did not require systemic therapy. Complex morbilliform rash was defined as a SCAR with systemic organ involvement requiring systemic therapy with a prolonged course.

For each patient, a modified Registry of Severe Cutaneous Adverse Reaction (RegiSCAR) score[9] was calculated based on the following items: fever of 38.5°C or greater (0 points; -1 if absent); peripheral eosinophilia (≥700/mm^3 or ≥10%, 1 point; ≥1500/mm^3 or ≥20%, 2 points); presence of atypical lymphocytes (1 point); rash covering 50% or more of body surface area (1 point), with facial edema, purpura, infiltration, or desquamation (1 point); organ involvement (1 point for 1 organ; 2 points for 2 or more); disease duration of longer than 15 days (0 points; -1 if absent); and at least 3 biological investigations (eg, blood cultures, viral serology, biopsy) performed and with negative results, to rule out an alternative diagnosis (1 point). Comprehensive metabolic panel results, including glomerular filtration rate, blood urea nitrogen, creatinine, transaminases, total bilirubin, and urine

Abbreviations used:

CI: confidence interval
CRS: cytokine release syndrome
GVHD: graft versus host disease
HR: hazard ratio
IL: interleukin
OS: overall survival
SCAR: severe cutaneous adverse reaction
SJS: Stevens-Johnson syndrome
TEN: toxic epidermal necrolysis
Th: T helper
TNF: tumor necrosis factor alpha

eosinophils, were reviewed. For all laboratory values, only results within 7 days of biomarker testing were recorded to minimize the impact of nonrash events on biomarker levels. Reference values for cytokines (IL-10, ≤18 pg/mL; IL-6, ≤5 pg/mL; TNF-α, ≤22 pg/mL) are determined by our institution's laboratory, whereas that for elafin (≤23.8 ng/mL) is determined by Viracor, Inc (Summit, MO).

Descriptive statistics and graphical methods were used to assess the distributions of patient and medical test characteristics. Chi-square and Fisher's exact tests were used to assess the association between rash type (simple vs complex) and nominally scaled patient and medical test characteristics; *t* tests and Wilcoxon's rank-sum tests were used to assess differences in continuously scaled variables by rash type. Overall survival (OS) was calculated as the time elapsed between the initial assessment for SCARs to death from any cause. A patient was considered censored at the date of last follow-up if she or he was alive at that point of contact. Kaplan-Meier estimates with log rank tests were used to assess probabilities of survival. Cox proportional hazards regression models were used to explore prognostic factors associated with survival while controlling for patient characteristics. Proportionality assumptions for Cox models were evaluated by the visual assessment of Cox-Snell and standardized residuals. All *P* values are 2 sided. Analyses were performed with STATA, version 16.0, software (StataCorp LP, College Station, TX).

RESULTS

Patient characteristics

A total of 144 patients with cancer and morbilliform rash who were evaluated at a single institution for dermatology consultation were included in the study. Of these patients, 50.6% were men, and the average age was 55.5 years. Of the 144 patients, 81 (56.3%) had a simple rash, and 63 (43.7%) had a complex rash with systemic involvement. Among patients with complex rash, 46% (n = 29) had cutaneous GVHD, 6.3% (n = 4) had cutaneous GVHD-spectrum rash (engraftment syndrome), and the remaining 47.6% (n = 30) had a complex rash secondary to drug exposure (Table I). Most patients with complex rash had hematologic malignancy (69.8%), whereas most patients with a simple rash had solid malignancy (56.8%).

Biomarkers

The median values of cytokines (IL-10, IL-6, TNF-α) and elafin were higher in the patients with complex rash compared with those with simple rash, although only IL-10 reached statistical significance (P = .03) (Table II). Peripheral eosinophilia and white blood cell count did not differ between the simple and complex rash groups.

Biomarkers and organ involvement

The median IL-10 level was significantly higher in patients with elevated transaminases than in patients with transaminases in the normal range (24.5 pg/mL vs 14 pg/mL; P = .01). Median IL-6 levels were also elevated in patients with elevated transaminases; however, this difference did not reach statistical significance (41 pg/mL vs 19.5 pg/mL; P = .056). There was no significant association between IL-10, IL-6, TNF-α, or elafin and bilirubin or renal involvement, as measured by decreased glomerular filtration rate relative to baseline.

Overall survival

The median follow-up time for the cohort was 14.7 months. Fifty-four of 144 (37.5%) patients died during follow-up. The 6-month OS was not statistically significantly different between complex versus simple rash or between patients with a Common Terminology Criteria for Adverse Events, version 5.0, score of 0 to 2 versus 3 to 4. Patients with morbilliform rash and elevated IL-6 levels had a decreased OS that worsened in concordance with rising IL-6 levels. At 6 months, patients with IL-6 levels above the median (>24 pg/mL) had an OS of 53.7% (95% CI, 39.7-65.5), compared with 85.7% OS (95% CI, 73.5-92.6) in those with lower IL-6 levels (≤24 pg/mL) ($P < .001$). Patients with TNF-α levels above the median value (14 pg/mL) had a significantly shorter OS at 6 months than those with TNF-α levels in the bottom 2 quartiles (≤14 pg/mL): 56.6% versus 82.5% ($P < .001$). Elevated IL-10 levels were also associated with decreased 6-month OS, because patients with IL-10 levels greater than the median (≥18 pg/mL) had a 6-month survival of 53.6% (95% CI, 42.5-68.0) compared with 83.6% (95% CI, 70.9- 91.1) for those below the median (P = .006). Table III presents univariate and multivariate Cox models for OS. In

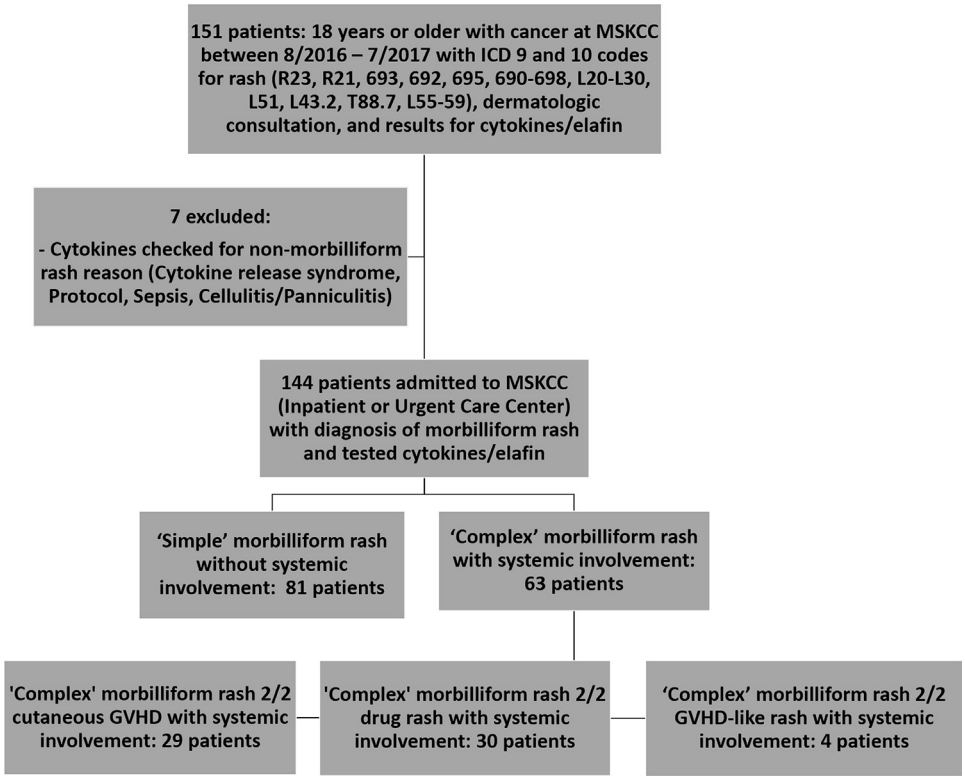

Fig 1. Flowchart of patient selection. *2/2*, Secondary to; *GVHD*, graft-versus-host disease; *ICD*, International Classification of Diseases; *MSKCC*, Memorial Sloan Kettering Cancer Center.

univariate analysis, higher levels of IL-6, IL-10, and TNF-α were all associated with worse prognosis. On multivariate analysis examining cytokines, rash type (simple vs complex), and patient age, patients with elevated levels of IL-6 were 3.2 times more likely to die (hazard ratio [HR], 3.21; 95% CI, 1.64-6.32) over the course of the follow-up compared with those with lower levels. Similarly, patients with higher levels of TNF-α were also more likely to die compared with those with lower levels (HR, 1.78; 95% CI, 0.94-3.35). Fig 2 depicts the multivariate survival experience of patients with the combination of increased levels of IL-6 and TNF-α. These patients had a 5-fold increase in mortality compared with those with lower levels of both measures (HR, 5.82; 95% CI, 1.53-17.43). No difference was observed in 6-month OS in patients with cancer with simple versus complex rash and elevated absolute eosinophils.

DISCUSSION

This study examined patients with cancer who presented with morbilliform rash and found the combination of elevated TNF-α and IL-6 to be significantly associated with a nearly 6-times increased all-cause mortality after rash onset ($P < .001$). Although past studies have shown an increased mortality associated with elevated IL-10, IL-6, and elafin, the prognostic value of combinations of cytokines have not been elucidated.[6,10] Using multiple biomarkers as opposed to single cytokines can strengthen the overall prognostic value and serve as a reliable tool for SCAR diagnosis and prognostication.[11] Our study did not find a statistically significant difference in OS at 6 months between patients with complex and simple rashes (69.5% compared with 75.8%, respectively; $P = .23$), highlighting the need for objective tools to guide patients who require therapy. The availability of TNF-α and IL-6 inhibitors make these biomarkers attractive therapeutic targets for intervention. The US Food and Drug Administration's approval of the IL-6 receptor antibody tocilizumab for the treatment of cytokine release syndrome (CRS) further underscores the therapeutic potential of identifying inflammatory markers in supportive oncodermatology.[12] The severity of symptoms in CRS may correlate with the duration of exposure to the inflammatory cytokines, emphasizing the importance of prompt recognition of these markers for both diagnostic and treatment purposes.[13]

Our study found that levels of IL-6 in patients with cancer with morbilliform rash are inversely related to OS, confirming in a larger cohort the previous report

Table I. Characteristics of hospitalized patients with cancer and simple morbilliform rash versus complex morbilliform rash

Category	Rash type		Total, n (%)	*P* value
	Simple morbilliform rash (n = 81), n (%)	Complex morbilliform rash (n = 63), n (%)		
Patient sex				
Female	40 (49.4)	31 (49.2)	71 (49.3)	.983
Male	41 (50.6)	32 (50.8)	73 (50.7)	
Location				
Inpatient	49 (60.5)	53 (84.1)	102 (70.8)	.002
Urgent care center	32 (39.5)	10 (15.9)	42 (29.2)	
Cancer type				
Solid	46 (56.8)	18 (28.6)	64 (44.4)	.001
Hematologic	32 (39.5)	44 (69.8)	76 (52.8)	
Both	3 (3.7)	1 (1.6)	4 (2.8)	
Diagnosis				
Complex drug	1 (1.2)	30 (47.6)	31 (21.5)	<.001
GVHD	0 (0)	29 (46)	29 (20.1)	
Simple drug	77 (95.1)	0 (0)	77 (53.5)	
GVHD-like	0 (0)	4 (6.4)	4 (2.8)	
Viral exanthem	3 (3.7)	0 (0)	3 (2.1)	
CTCAE grade				
0	0 (0)	1 (1.6)	1 (0.7)	.002
1	9 (11.1)	0 (0)	9 (6.3)	
2	28 (34.6)	13 (20.6)	41 (28.5)	
3	44 (54.3)	46 (73)	90 (62.5)	
4	0 (0)	3 (4.8)	3 (2.1)	
RegiSCAR score				
0	33 (40.7)	3 (4.8)	36 (25)	<.001
1	28 (34.6)	14 (22.2)	42 (29.2)	
2	16 (19.8)	14 (22.2)	30 (20.8)	
3	3 (3.7)	24 (38.1)	27 (18.8)	
4	1 (1.2)	7 (11.1)	8 (5.6)	
5	0 (0)	1 (1.6)	1 (0.7)	
Atypical lymphocytes				
No	78 (96.3)	54 (87.1)	132 (92.3)	.041
Yes	3 (3.7)	8 (12.9)	11 (7.7)	
Rash (50% BSA + purpura, edema, scale)				
0	37 (46.3)	3 (4.8)	40 (28)	<.001
1	30 (37.5)	29 (46)	59 (41.3)	
2	13 (16.3)	31 (49.2)	44 (30.8)	
Fever, >38°C				
No	5 (6.2)	8 (12.7)	13 (9)	.175
Yes	76 (93.8)	55 (87.3)	131 (91)	
Decreased GFR relative to baseline				
No	72 (90)	47 (74.6)	119 (83.2)	.04
Yes	8 (10)	16 (25.4)	24 (16.8)	
Elevated transaminases relative to baseline				
No	68 (84)	28 (44.4)	96 (66.7)	<.001
Yes	13 (16.1)	35 (55.6)	48 (33.3)	
Elevated total bilirubin relative to baseline				
No	76 (93.8)	55 (87.3)	131 (91)	.175
Yes	5 (6.2)	8 (12.7)	13 (9)	
Internal organs involved				
0	59 (72.8)	12 (19.1)	71 (49.3)	<.001
1	22 (27.2)	43 (68.3)	65 (45.1)	
2	0 (0)	8 (12.7)	8 (5.6)	

Continued

Table I. Cont'd

Category	Rash type: Simple morbilliform rash (n = 81), n (%)	Rash type: Complex morbilliform rash (n = 63), n (%)	Total, n (%)	*P* value
Respiratory virus panel positive				
No	43 (86)	46 (93.9)	89 (89.9)	.193
Yes	7 (14)	3 (6.1)	10 (10.1)	
Human herpesvirus positive				
No	36 (87.8)	41 (82)	77 (84.6)	.445
Yes	5 (12.2)	9 (18)	14 (15.4)	
Cytomegalovirus positive				
No	42 (93.3)	48 (90.6)	90 (91.8)	.618
Yes	3 (6.7)	5 (9.4)	8 (8.2)	
Epstein-Barr virus positive				
No	41 (93.2)	52 (92.9)	93 (93)	.950
Yes	3 (6.8)	4 (7.1)	7 (7)	
Adenovirus positive				
No	40 (100)	48 (98)	88 (98.9)	.364
Yes	0 (0)	1 (2)	1 (1.1)	
Skin biopsy supportive of drug reaction				
No	56 (69.1)	32 (50.8)	88 (61.1)	.025
Yes	25 (30.9)	31 (49.2)	56 (38.9)	
Status				
Living	53 (65.4)	35 (55.6)	88 (61.1)	.228
Deceased	28 (34.6)	28 (44.4)	56 (38.9)	

BSA, Body surface area; *CTCAE*, Common Terminology Criteria for Adverse Events; *GFR*, glomerular filtration rate; *GVHD*, graft-versus-host disease; *SCAR*, severe cutaneous adverse reaction.

Table II. Comparison of median values of patient characteristics by simple morbilliform rash versus complex morbilliform rash

Characteristic	Overall median	Rash type	Median	Binomial interpolation of 95% CI: Lower	Binomial interpolation of 95% CI: Upper	*P* value
Age, years	60.5	Simple	62	56.2	66.8	.17
		Complex	56	53.0	63.0	
IL-1β, pg/mL	0	Simple	0	0	0	.38
		Complex	0	0	0	
IL-10, pg/mL	17.5	Simple	14	10.0	19.5	.03
		Complex	26.5	16.0	31.6	
IL-6, pg/mL	24.5	Simple	17.5	10.5	30.0	.14
		Complex	31.5	22.8	50.8	
TNF-α, pg/mL	14	Simple	12.5	10.0	16.5	.27
		Complex	16	13.4	19.0	
Elafin, ng/mL	18.35	Simple	17	13.3	23.3	.43
		Complex	20.2	17.2	28.0	
% Eosinophils	1.95	Simple	2.1	1.0	2.8	.80
		Complex	1.8	0.2	4.7	
Absolute eosinophils, K/mcL	0.1	Simple	0.1	0.1	0.2	.96
		Complex	0.15	0	0.3	
White blood cells, K/mcL	5.65	Simple	5.5	4.6	6.7	.72
		Complex	5.7	4.3	7.8	

CI, Confidence interval; *IL*, interleukin; *TNF-α*, tumor necrosis factor α.

by Mori et al.[6] IL-6 is a pleiotropic cytokine with proinflammatory effects that inhibit the induction of regulatory T cells by transforming growth factor β and shifts naive T-cell differentiation toward T helper (Th) type 17 cells.[14,15] Th17 cells release large quantities of IL-17, IL-22, and IL-21, and are a major

Table III. Univariate and multivariate analyses of overall survival using Cox proportional hazards models

	Univariate		Multivariate*	
Category	**HR for death (95% CI)**	***P* value**	**HR for death (95% CI)**	***P* value**
Rash type				
Simple	referent	.165	referent	.666
Complex	1.46 (0.85-2.51)		0.88 (0.48-1.59)	
IL-6, pg/mL				
0-24	referent	<.001	referent	.001
25/max	3.77 (2.02-7.04)		3.21 (1.64-6.32)	
IL-10, pg/mL				
min/17	referent	.008	referent	.386
18/max	2.22 (1.23-4.02)		1.35 (0.68-2.70)	
TNF-α, pg/mL				
min/14	referent	.001	referent	.076
15/max	2.66 (1.46-4.84)		1.78 (0.94-3.35)	

CI, Confidence interval; *HR*, hazard ratio; *IL*, interleukin; *max*, maximum; *min*, minimum; *TNF-α*, tumor necrosis factor α.
*Variables included in the multivariate column are the ones listed in the table, along with age.

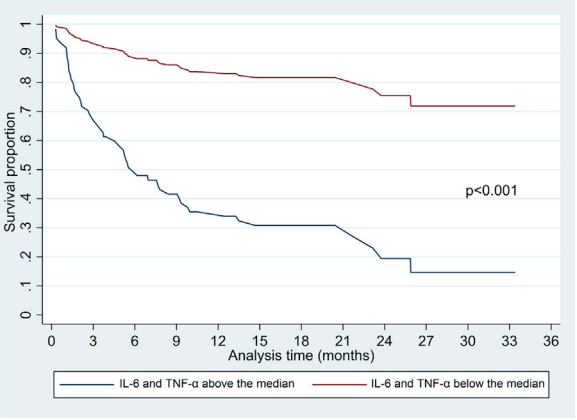

Fig 2. Survival functions for patients with IL-6 and TNF-α levels above versus below the median. In both groups, the model predictions are based on patients with a mean age of 55.5 years. Variables included in the multivariate analyses are IL-6, TNF-α, IL-10, rash type (simple morbilliform vs complex morbilliform), and age. *IL*, Interleukin; *TNF-α*, tumor necrosis factor α.

inducer of tissue inflammation.[16] Significant elevations in serum IL-6 have previously been reported in patients with SCARs and have also been associated with increased incidence and severity of GVHD.[6,11,17] IL-6 is implicated in the development of rashes, and elevated lesional IL-6 levels have been found in numerous other inflammatory skin disorders.[18-20] The administration of recombinant IL-6 to a patient resulted in an inflammatory skin eruption with recurrence after rechallenge.[21] Although the exact mechanism is not well understood, the rapid resolution of rash in CRS with the use of IL-6 inhibitors implies the pathophysiologic importance of IL-6.[12] Moreover, IL-6 mediates tumor progression and therapeutic resistance.[22-24] Elevated levels of IL-6 in patients with cancer have been associated with poor outcomes, and addition of an IL-6 blockade to immune checkpoint inhibitor therapy and messenger RNA–based immunotherapy has resulted in a significant reduction in tumor volume and led to prolonged survival in mice.[22,25] IL-6 blockade reversed anti–programmed death-ligand 1 (anti–PD-L1) resistance and prolonged tumor-bearing mouse survival in a preclinical colorectal cancer model.[26] IL-6 blockade also augments regulatory T-cell reconstitution.[17] IL-6 inhibitors have been effectively used in GVHD prophylaxis and treatment of steroid-refractory acute and chronic GVHD.[27-29] IL-6 blockade receptors in murine models of GVHD significantly reduced GVHD-associated mortality.[30] Given our findings of decreased OS in patients with cancer with rash and high IL-6 level, IL-6 may represent an actionable therapeutic target to improve OS in this patient population.

TNF-α, a proinflammatory cytokine, appears to be involved in the pathogenesis of severe cutaneous adverse reactions. TNF-α induces keratinocyte apoptosis through a Fas-mediated pathway, leading to the extensive epithelial cell death seen in SJS/TEN.[31] This mechanism of action may explain the elevated TNF-α frequently found in the plasma and blister fluids of patients with SJS/TEN and in the plasma of patients with GVHD and acute generalized exanthematous pustulosis.[7,32-35] Additionally, TNF-α has been linked to the promotion and progression of cancer.[36,37] Levels of IL-6 and TNF-α directly correlated with the extent of disease in patients with

prostate cancer.[38] TNF-α was also an independent predictor of poor survival in patients with cancer, highlighting the potential role of TNF-α antagonists in the treatment of these patients.[39,40] Furthermore, TNF-α inhibitors are an effective treatment for steroid-refractory acute GVHD and SCARs.[32,41-43] Moreover, a randomized controlled trial found that TNF-α antagonists decrease the predicted mortality rate and healing time in patients with cytotoxic T lymphocyte2mediated SCARs (including SJS/TEN).[44]

In our study, elevated IL-10 levels in patients with cancer with morbilliform rash were significantly associated with subsequent development of a complex rash (P = .03) and decreased OS at 6 months (P = .006). IL-10 is an anti-inflammatory cytokine produced by Th2 cells and keratinocytes in the skin that inhibits the production of IL-6 and TNF-α.[45,46] IL-10 may act as a defense mechanism against excessive tissue inflammation.[47] Patients with SJS/TEN may have elevated blister fluid concentrations of IL-10.[7] Past studies have similarly found that elevated IL-10 levels may be produced as a result of excessive tissue inflammation in toxic epidermal necrolysis and reflect a compensatory response.[46] Elevated levels of IL-10 have also been correlated with a poor response in numerous types of cancer; however, the role of IL-10 in tumorigenesis remains controversial.[48-50] Its immunosuppressive influence has been thought to reduce the antitumor immune response, yet murine tumor models have shown rapid tumor rejection with increased IL-10 secretion.[51] Given the significantly decreased 6-month OS (P = .006) in patients with elevated IL-10 levels in our cohort, our study supports prior literature regarding patients with cancer and suggests that this marker may also have prognostic value in patients with cancer at the time of rash development.[49,52]

Although eosinophilia is a criterion on the RegiSCAR scoring system for identifying patients with drug reaction with eosinophilia and systemic syndrome/drug-induced hypersensitivity syndrome, there was no difference in 6-month OS in patients with cancer with morbilliform rash and elevated absolute eosinophils. Past studies have similarly found that eosinophils are associated with immune-related adverse events but not OS.[53]

Limitations of this study include its retrospective design and limited sample size. All cases were recruited from a tertiary referral cancer center. A larger, prospective study examining the effect of IL-6 or TNF-α inhibitors on OS in patients with elevated IL-6 or TNF-α is needed. This exploratory analysis presents potential therapeutic targets to improve OS in a high-risk patient population.

CONCLUSION

This study highlights the prognostic significance of biomarker combinations for patients with cancer with a morbilliform rash. The combination of elevated IL-6 and TNF-α in this population is significantly associated with a nearly 6-times decreased OS ($P < .001$), whereas IL-10 may predict progression of a simple morbilliform rash to a SCAR. A growing number of studies suggest an increased survival associated with IL-6 and TNF-α inhibition in cancer or SCARs. Further studies evaluating the impact of TNF-α and IL-6 inhibitors on survival in this population are needed.

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