Clinical Characteristics and Outcomes of Oral Mucositis Associated With Immune Checkpoint Inhibitors in Patients With Cancer

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ABSTRACT

Background: Immune checkpoint inhibitor (ICI) therapy predisposes patients to immune-related adverse events (irAEs). Data are limited regarding the incidence, management, and outcomes of one such irAE: mucositis. In this study, we evaluated the clinical characteristics, disease course, treatment, and outcomes of ICI-mediated mucositis.

Methods: This was a retrospective, single-center study of patients who received ICI therapy and developed oral mucositis at The University of Texas MD Anderson Cancer Center from January 2009 to September 2019. Inclusion criteria included age ≥ 18 years, a diagnosis of oral mucositis and/or stomatitis based on ICD-9 and ICD-10 codes, and therapy using CTLA-4 or PD-1/L1 inhibitors alone or combined with other agents. **Results:** We identified 152 patients with a mean age of 60 years, 51% of whom were men. Of the sample patients, 73% had stage IV cancer, with melanoma the most common (28%). Median time from ICI initiation to mucositis was 91 days. The most common clinical presentation of mucositis was odynophagia and/or oral pain (89%), 91% developed CTCAE grade 1–2 mucositis, and 78% received anti-PD-1/L1 monotherapy. Compared with anti-PD-1/L1–based therapy, anti-CTLA-4–based therapy was more frequently associated with earlier onset of mucositis (73 vs 96 days; $P=.077$) and a lower rate of symptom resolution (76% vs 92%; $P=.029$); 24% of patients required immunosuppressive therapy, which was associated with longer symptom duration (84 vs 34 days; $P=.002$) and higher mucositis recurrence rate (61% vs 32%; $P=.006$). ICI interruption was associated with worse survival ($P=.037$). Mucositis recurrence, immunosuppressant use, and presence of other irAEs did not affect survival. **Conclusions:** For ICI-mediated mucositis, a diagnosis of exclusion has not been well recognized and is understudied. Although the clinical symptoms of mucositis are mostly mild, approximately 25% of patients require immunosuppression. Mucositis recurrence can occur in approximately 39% patients. Our results showed that ICI interruption compromises overall survival.

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Background

Immune checkpoint inhibitors (ICIs) are immunotherapeutic agents that inhibit checkpoint ligands and receptors that serve as downregulators of the adaptive and innate immune system, stimulating an immune response against cancer cells. Since their development, such as inhibitors of CTLA-4, PD-1, and PD-L1, ICIs have been found to be effective treatment options for various solid tumors, including melanoma; lung, genitourinary, colorectal, and head and neck malignancies; and leukemias.^{1–5}

Although ICIs have changed the landscape of cancer therapy, their enhancement of nonspecific immune responses can lead to immune-related adverse events (irAEs) of any organ system. These irAEs are observed in the skin, gastrointestinal tract, liver, lungs, and other systems.^{4,5–8} irAEs occur at any time during ICI treatment, range from mild symptoms to severe life-threatening or fatal events, and may require management using immunomodulatory agents and discontinuation of ICI therapy.^{5,6,9}

Gastrointestinal irAEs frequently involve the colon, liver, and stomach and present with nausea, vomiting, diarrhea, rectal bleeding, or abdominal pain.^{9–14} Rare gastrointestinal irAEs have been reported, such as

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esophagitis, pancreatitis, and cholecystitis.^{15–17} Furthermore, investigators have described adverse events in the oral cavity, including xerostomia, dysgeusia, lichenoid reactions, mucositis, and stomatitis.^{18–28}

The clinical presentation of ICI-mediated mucositis (IMM) can range from mild to severe, with onset ranging from several weeks to months after treatment initiation.^{18–23} The literature contains several reports of severe mucositis induced by pembrolizumab, an anti-PD-1 agent,^{24–27} with symptom onset occurring up to 1 year after initiation and mucositis lasting several months after discontinuation. Physical and endoscopic findings showed mucosal erythema, edema, and ulceration with odynophagia and dysphagia symptoms, resulting in limited food intake, weight loss, and hospitalization. Successful management was accomplished via discontinuation of ICI and immunosuppression using steroids.

The pathogenesis of irAEs has yet to be fully elucidated, and their occurrence can impact quality of life and the ICI therapy course and lead to morbidity and mortality. Given the limited data on IMM, we evaluated the clinical characteristics, disease course, treatment, and outcome of IMM in patients at a tertiary cancer center.

Methods

Study Design and Population

This was a retrospective, descriptive, single-center study of adult patients at The University of Texas MD Anderson Cancer Center who received ICI therapy and experienced oral mucositis from January 2009 through September 2019. Inclusion criteria included age ≥ 18 years, a diagnosis of oral mucositis and/or stomatitis based on ICD-9 and ICD-10 codes, and therapy using CTLA-4 or PD-1/L1 inhibitors alone or combined with other agents. Patients who received a combination of ICI and non-ICI chemotherapy were included. The event time window for mucositis/stomatitis was from administration of the first ICI dose to 6 months after the last ICI dose. Exclusion criteria included (1) radiation therapy to the head, neck, or chest within 3 months of mucositis/stomatitis onset; (2) stem cell or bone marrow transplantation with gastrointestinal graft-versus-host disease; (3) confirmed upper gastrointestinal viral, fungal, or bacterial infection; (4) cancer in the oral cavity; and (5) mucositis resulting from other non-ICI cancer treatment. In patients in whom the etiology of mucositis was ambiguous, attribution to ICI therapy was made based on typical timing of disease onset from initiation of ICI therapy.

Clinical Data

Patient demographics, medical and oncologic history, cancer treatment regimens, and irAEs were collected. Demographics included age, sex, and ethnicity. Comorbidities

evaluated included hypertension, coronary artery disease, congestive heart failure, atrial fibrillation, cerebral vascular disease, diabetes mellitus, chronic obstructive pulmonary disease, asthma, HIV infection, and thyroid disease. Information collected regarding presumed risk factors for mucositis included smoking history, use of nonsteroidal anti-inflammatory agents, other concurrent chemotherapy using ICIs, and premucositis use of immunosuppressants. Oncologic data analyzed included cancer type and stage, cancer treatment agents (ICI and non-ICI chemotherapy), and irAEs. ICIs administered included ipilimumab, nivolumab, pembrolizumab, atezolizumab, durvalumab, avelumab, cemiplimab, and tremelimumab. ICI regimens were categorized as single-agent or combined regimens. The duration of each ICI regimen before onset of mucositis was recorded. Information regarding mucositis and other irAEs within the same study window and their medical treatments was also documented.

Mucositis Data

Mucositis events were screened for time of onset, duration, severity, treatment, complications, recurrence, and need to hold or discontinue the ICI regimen. Mucositis severity was graded based on version 5 of the NCI's CTCAE.²⁸ Signs of mucositis identified in history and physical examination were recorded as ulcers/aphthae or nonulcer inflammation. Symptoms included oral pain, odynophagia, dysphagia, nausea or vomiting, and bleeding. Treatment of mucositis was categorized as nonimmunosuppressive (proton pump inhibitors [PPIs], H₂ blockers, sucralfate, or topical anesthetics) or immunosuppressive, including topical agents (eg, liquid dexamethasone, fluocinonide ointment) and systemic agents (intravenous methylprednisolone, oral dexamethasone, and oral prednisone). Duration of systemic steroid use was defined as the time from initiation to either cessation of treatment or return to the baseline maintenance dose. Clinical outcomes included requirement of hospitalization, duration of hospital stay, requirement of additional nutrition support, clinical resolution and recurrence of mucositis, and overall survival (OS) after mucositis onset.

Statistical Analysis

Statistical analysis was performed using RStudio version 1.0.136 (R Foundation for Statistical Computing) and SPSS Statistics, version 24.0 (IBM Corp). Categorical variables were summarized using frequencies and percentages. Continuous variables were summarized using means and standard deviations or medians and interquartile ranges (IQRs). A chi-square test was used to determine associations between categorical variables. The Mann-Whitney *U* test was used to compare differences between continuous variables. Differences in OS durations between groups were analyzed using

Table 1. Baseline Clinical Characteristics

Characteristic	n (%)
Total, N	152
Mean age [SD], y	60.0 [13.6]
Male sex	77 (51)
Race	
White	109 (72)
Black	5 (3)
Hispanic	20 (13)
Other	18 (12)
Comorbidities	117 (77)
Baseline risk factors	
NSAID use	28 (18)
History of smoking	72 (47)
Premucositis immunosuppressant use	36 (24)
Other concurrent chemotherapy ^a with ICIs	87 (57)
Antacid medication	
PPI	48 (32)
H2 blocker	20 (13)
Cancer type	
Melanoma	42 (28)
Lung or head and neck	27 (18)
Genitourinary	26 (17)
GI	16 (11)
Endocrine	6 (4)
Other solid tumors	13 (9)
Hematologic malignancies	25 (16)
Cancer stage ^b	
III	13 (9)
IV	111 (73)

(continued)

the Kaplan-Meier method and a log-rank test. *P* values up to .05 were considered significant.

Results

Baseline Characteristics

Of the 10,275 patients who received ICI therapy during the study period, 652 (6.3%) developed mucositis, 500 of whom were excluded (supplemental eFigure 1, available with this article at JNCCN.org); 152 patients were included in the final analysis. Mean age at ICI initiation was 60 years, 51% were men, and 72% were White (Table 1). Concurrent chemotherapy in addition to ICIs (57%) and history of smoking (47%) were the most prevalent baseline risk factors, and the most common malignancies were melanoma (28%), lung (10%), head and neck (8%), and hematologic (16%). Most patients (73%) had stage IV disease.

Table 1. Baseline Clinical Characteristics (cont.)

Characteristic	n (%)
Median number of ICI therapy cycles before mucositis diagnosis (IQR)	3 (1–6)
ICI type	
CTLA-4 inhibitor ^c	33 (22)
PD-1/L1 inhibitor	119 (78)
Other irAEs	
GI toxicity	
Upper GI tract (esophagus-jejunum)	7 (5)
Lower GI tract (ileum and colon)	18 (12)
Liver	13 (9)
Endocrine	9 (6)
Lung	12 (8)
Skin	41 (27)
Hematologic	34 (22)
Other	18 (12)

Abbreviations: GI, gastrointestinal; ICI, immune checkpoint inhibitor; IQR, interquartile range; irAE, immune-related adverse event; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor.

^aClasses of chemotherapy included antimetabolites, kinase inhibitors, alkylating agents, anthracyclines, MEK inhibitors, angiogenesis inhibitors, CCR4 inhibitors, and selective inhibitors of nuclear export.

^bFor solid tumors, cancer stage was recorded based on the TNM Staging System. Stage was not recorded for hematologic cancers. Comorbidities were myocardial infarction/angina, coronary artery disease with percutaneous coronary intervention or coronary artery bypass graft, congestive heart failure, chronic obstructive pulmonary disease, HIV infection, hypocortisolism, atrial fibrillation, graft-versus-host disease, asthma, hypertension, diabetes mellitus, cerebral vascular disease, and thyroid disease.

^cAnti-CTLA-4 therapy included monotherapy and combination with anti-PD-1/L1 agents.

Mucositis-Related Characteristics

Among different ICI regimens, 119 patients (78%) received PD-1/L1 monotherapy and 33 (22%) received CTLA-4-based therapy. In the latter group, 16 received monotherapy and 17 received combination therapy (Table 2). Clinically, patients presented most commonly with odynophagia and/or oral pain (89%) followed by nausea or vomiting (20%). Most patients (91%) had mild disease, with a peak CTCAE grade of 1 or 2. Median time of mucositis onset after ICI initiation was 91 days (IQR, 27–174 days), with a shorter duration in the anti-CTLA-4 versus the anti-PD-1/L1 group (73 vs 96 days, respectively; *P* = .077). Nearly all patients (97%) presented with oral ulcers or aphthae (Figure 1), with a median duration of symptoms of 48 days (IQR, 19–99 days). Although most patients received supportive therapy, 36 (24%) needed immunosuppressants (systemic or topical steroids), with a median duration of 51 days (IQR, 26–81 days). Of these patients, 22 received systemic steroids alone, 7 received topical steroids alone, and the remaining 7

Table 2. Clinical Characteristics of Mucositis by Type of ICI Therapy

Characteristic	Overall n (%)	Anti-CTLA-4 ^a n (%)	Anti-PD-1/L1 n (%)	P Value
Total, n	152	33	119	
Median duration from ICI therapy to mucositis onset (IQR), d	91 (27–174)	73 (22–119)	96 (35–199)	.077
Clinical presentation				
Odynophagia/Oral pain	136 (89)	28 (85)	108 (91)	.511
Nausea or vomiting	31 (20)	7 (21)	24 (20)	1.000
Dysphagia	15 (10)	1 (3)	14 (12)	.247
Bleeding	6 (4)	3 (9)	3 (3)	.226
Peak CTCAE grade of mucositis				.630
1–2	139 (91)	29 (88)	110 (92)	
3–4	13 (9)	4 (12)	9 (8)	
Physical examination finding				1.000
Ulcers/Aphthae	148 (97)	32 (97)	116 (97)	
Nonulcer inflammation	4 (3)	1 (3)	3 (3)	
Median duration of symptoms (IQR), d; n=133	48 (19–99)	35 (21–77)	56 (18–112)	.400
Presence of other irAEs	98 (64)	27 (82)	71 (60)	.032
ICI therapy interrupted	117 (77)	29 (88)	88 (74)	.148
Mucositis treatment				
Immunosuppressants ^b				
Systemic ± topical	29 (19)	6 (18)	23 (19)	.690
Topical alone	7 (5)	2 (6)	5 (4)	1.000
Supportive medication only ^c	99 (65)	21 (64)	78 (66)	1.000
No medical treatment	17 (11)	5 (15)	12 (10)	.610
Median duration of immunosuppressant use (IQR), d; n=24	51 (26–81)	39 (30–57)	60 (21–85)	.830
Outcome				
Hospitalization	17 (11)	3 (9)	14 (12)	.905
Median duration of hospitalization (IQR), d; n=29	10 (6–20)	18 (7–24)	9 (6–15)	.240
Malnutrition requiring additional nutrition support (tube feeding or TPN)	6 (4)	2 (6)	4 (3)	.840
Clinical improvement/resolution	134 (88)	25 (76)	109 (92)	.029
Recurrence of mucositis	52 (34)	11 (33)	41 (34)	.716
Rehospitalization for recurrent mucositis	2 (1)	0	2 (2)	1.000
Resumed ICI therapy; n=117	25 (21)	5 (17)	20 (23)	.716
All-cause mortality	76 (50)	19 (58)	57 (48)	.430

Abbreviations: ICI, immune checkpoint inhibitor; IQR, interquartile range; irAE, immune-related adverse event; PPI, proton pump inhibitor; TPN, total parenteral nutrition.

^aAnti-CTLA-4 therapy included monotherapy (n=16) and combination with anti-PD-1/L1 agents (n=17).

^b22 patients used systemic immunosuppressants only, 7 used topical immunosuppressants only, and 7 used both topical and systemic immunosuppressants. These agents included intravenous methylprednisolone, oral dexamethasone, oral prednisone, topical dexamethasone, and topical fluocinonide.

^cSupportive medications included PPIs, H2 blockers, sucralfate, and viscous lidocaine.

received a combination. No patient received biologic therapy for mucositis.

Overall, 88% of patients had clinical improvement or resolution of mucositis: 92% in the anti-PD-1/L1 group versus 76% in the anti-CTLA-4 group ($P=.029$). Seventeen patients (11%) were hospitalized for a median stay of 10 days (IQR, 6–20 days). Of those hospitalized, 4 (24%) had central line placement due to

mucositis and 1 (6%) had line-related bloodstream infection. Six patients (4%) had mucositis compromising nutrition, necessitating support via tube feeding (2 using nasogastric feeding, 4 using percutaneous endoscopic gastrostomy tube) or total parenteral nutrition. Thirty-four percent of patients had recurrence of mucositis, leading to 1.3% of patients requiring rehospitalization. Among all patients, 64% had irAEs in

Figure 1. Oral mucositis.

(Courtesy of Andrea M. Perdue and John A. Thompson at the University of Washington, Seattle, Washington).

addition to mucositis, with a higher incidence in patients given CTLA-4–based regimens than in those with anti-PD-1/L1–based regimens (82% vs 60%; $P=.032$). Of these irAEs, 25% involved the gastrointestinal system, including gastritis and enterocolitis. ICI therapy was interrupted in 77% of patients because of irAEs. The all-cause mortality rate at the end of the study period was 50% (Table 2).

Immunosuppressive therapy was associated with a longer duration of mucositis-related symptoms compared with nonimmunosuppressive therapy (84 vs 34 days; $P=.002$) (Table 3). The other parameters were comparable in these 2 groups. In the immunosuppressive therapy group, patients who received topical therapy generally had milder symptoms compared with those who received systemic therapy, and all patients had resolution of their symptoms ($P>.05$; supplemental eTable 1).

We found that patients receiving anti-CTLA-4 therapy were more likely to have mucositis and other irAEs than were those receiving anti-PD-1/L1 therapy ($P=.032$; supplemental eTable 2). Basic risk factors at the time of mucositis diagnosis did not affect the severity or outcomes of mucositis.

Recurrence of Mucositis

Among 134 patients who achieved symptom improvement/resolution, 52 (39%) had recurrence of mucositis (Table 4). Recurrence was associated with the presence of coexisting irAEs ($P=.038$) and the requirement of immunosuppression for the initial mucositis event ($P=.006$). Median duration of symptoms was longer in patients with recurrence versus without (56 vs 36 days; $P=.058$). Univariate logistic regression analysis showed that the following factors were significantly associated

with mucositis recurrence: dysphagia symptoms (odds ratio [OR], 3.222; $P=.047$), longer duration of symptoms (OR, 1.003; $P=.051$), and immunosuppressant use for the initial mucositis event (OR, 3.317; $P=.004$) (Table 5).

Overall Survival

Patients in whom ICI therapy was continued or resumed after interruption had significantly favorable OS ($P=.037$; Figure 2). We observed a complete separation in the OS curves for patients with and without recurrent mucositis, although the difference was not significant (supplemental eFigure 2A). In addition, OS was not associated with immunosuppressant use or the presence of other irAEs along with mucositis ($P>.05$) (supplemental eFigure 2B, C).

Discussion

ICI therapy can have a dramatic positive impact on OS in patients with advanced cancers.^{1–4} However, decreased immune regulation can involve a breakdown of tolerance to self-antigens, leading to the development of irAEs.⁵ Oral mucositis has not been well studied given the variations in its diagnosis, determination of causality, and mild presentation when compared with other irAEs.²⁵ This study is the first focused analysis with the largest sample size to characterize the clinical presentations, response to therapy, and outcomes of ICI-related oral mucositis.

Our study showed that the median time to onset of mucositis was 3 months after ICI initiation, similar to ICI colitis.²⁹ Patients receiving anti-CTLA-4–based therapy had earlier onset of mucositis, lower mucositis treatment response rates, and more irAEs than did those receiving anti-PD-1/L1 therapy, although the

Table 3. Clinical Characteristics and Outcomes of Mucositis by Immunosuppressive and Nonimmunosuppressive Treatment

Characteristic	Immunosuppressive Treatment n (%)	Nonimmunosuppressive Treatment n (%)	P Value
Total, n	36 ^a	116	
Median duration from ICI therapy to mucositis onset (IQR), d	97 (44–206)	87 (23–170)	.230
Clinical presentation			
Odynophagia/Oral pain	35 (97)	101 (87)	.155
Nausea or vomiting	6 (17)	25 (22)	.690
Dysphagia	5 (14)	10 (9)	.545
Bleeding	0	6 (5)	.367
Peak grade of mucositis			.770
1–2	32 (89)	107 (92)	
3–4	4 (11)	9 (8)	
Physical examination finding			1.000
Ulcers/Aphthae	35 (97)	113 (97)	
Nonulcer inflammation	1 (3)	3 (3)	
Median duration of symptoms (IQR), d; n=133	84 (46–120)	34 (14–84)	.002
Other coexisting irAEs within study window	25 (69)	73 (63)	.607
Gastrointestinal irAEs	8 (22)	16 (14)	.342
Outcome			
Hospitalization	6 (17)	11 (9)	.370
Median hospital stay (IQR), d; n=29	8 (4–16)	11 (7–21)	.350
Malnutrition requiring additional nutrition support (tube feeding or TPN)	0	6 (5)	.370
Clinical improvement/resolution	33 (92)	101 (87)	.652
Recurrence of mucositis; n=134	20 (61)	32 (32)	.006
All-cause mortality	14 (39)	62 (53)	.180

Abbreviations: ICI, immune checkpoint inhibitor; IQR, interquartile range; irAE, immune-related adverse event; TPN, total parenteral nutrition.

^a22 patients used systemic immunosuppressants only, 7 used topical immunosuppressants only, and 7 used both topical and systemic immunosuppressants. These agents included intravenous methylprednisolone, oral dexamethasone, oral prednisone, topical dexamethasone, and topical fluocinonide.

peak CTCAE grade of symptoms was comparable. irAEs of greater toxicity are more frequently related to anti-CTLA-4 therapy,^{30–33} possibly because of the different mechanisms of action of these agents. Although PD-1/L1 inhibition restores immune function and decreases the regulation of specific T cells inactivated due to high levels of antigen exposure, CTLA-4 inhibition leads to the activation and proliferation of a large number of effector T cells and decreases their regulation regardless of T-cell specificity, potentially leading to greater autoreactivity.³⁴ Both mechanisms can lead to severe irAEs.

In our sample, most patients with mucositis had mild symptoms (CTCAE grade 1 or 2). Although 11% of patients did not receive treatment, the remainder needed supportive care (65%) or immunosuppressive therapy (24%). Management of mucositis was highly variable due to a lack of available guidelines. Most management

strategies are extrapolated from guidelines for mucositis secondary to irradiation or treatment using other anti-neoplastic agents,^{35,36} although the pathophysiology differs starkly. Notably, regardless of the use of immunosuppressive therapy in patients with long symptom durations, we found negligible improvement in their clinical outcomes (eg, hospitalization, length of hospital stay, mucositis response rate) and a dramatically higher recurrence rate. These findings question the benefit of corticosteroids in the management and outcomes of mucositis and highlight potential complications.³⁷ However, disease severity, timing of immunosuppressive therapy initiation, treatment duration, and concomitant medications and comorbidities can also confound the outcomes.

In our cohort, mucositis improved with supportive care in most patients. Sucralfate, an agent that creates a protective mucosal barrier, had mixed outcomes in

Table 4. Clinical Characteristics of Patients With Responses or Resolution of Initial Mucositis Episodes

Characteristic	Recurrence n (%)	No Recurrence n (%)	P Value
Total, n	52	82	
ICI type			.716
Anti-CTLA-4 therapy	11 (21)	14 (17)	
Anti-PD-1/L1 monotherapy	41 (79)	68 (83)	
Clinical presentation			
Odynophagia/Oral pain	48 (92)	73 (89)	.744
Nausea or vomiting	5 (10)	23 (28)	.075
Dysphagia	9 (17)	5 (6)	.019
Bleeding	1 (2)	4 (5)	.681
Peak grade of mucositis			1.000
1–2	48 (92)	75 (91)	
3–4	4 (8)	7 (9)	
Other coexisting irAEs	38 (73)	44 (54)	.038
Gastrointestinal irAEs	11 (21)	10 (12)	.252
Median duration of symptoms (IQR), d; n=51 and n=75	56 (21–181)	36 (15–93)	.058
Hospitalization	3 (6)	8 (10)	.620
Mucositis treatment			
Immunosuppressants	20 (38)	13 (16)	.006
Duration from onset of symptoms to immunosuppressant use (IQR), d; n=36	10 (0–43)	7.5 (0–29)	.728
Duration of immunosuppressant use (IQR), d; n=36	38 (23–63)	67 (34–88)	.290
ICI therapy resumption	13 (25)	12 (15)	.203

Abbreviations: ICI, immune checkpoint inhibitor; IQR, interquartile range; irAE, immune-related adverse event.

mucositis treatment,³⁸ although a few trials have shown improvement of radiation- and 5-FU-induced oral mucositis.^{39,40} Small case series have shown improvement of radiation-induced mucositis using PPIs, although they seem to be helpful only in patients with severe reflux symptoms.⁴¹ Although authors have cautioned against the use of PPIs without clear indication,⁴² largely due to the risk of hypersensitivity and cutaneous reactions,^{43–46} our findings illustrate the benefit of their use as first-line therapy for mild mucositis.

Topical immunosuppressive agents can serve as alternatives to systemic corticosteroids given their highly favorable adverse effect profiles. In our cohort, we observed that patients who received topical steroid therapy alone had lower mucositis grades, complete symptom improvement, fewer hospitalizations, and shorter hospital stays than did those undergoing systemic immunosuppression. In previous case studies, the use of topical corticosteroids in the management of inflammatory mucositis in patients with graft-versus-host disease was promising.^{47–49} Bertelli et al⁴⁹ described a patient with severe oral mucositis limiting nutritional intake whose

condition was completely resolved using systemic methylprednisolone followed by oral viscous budesonide. Our findings suggest that topical immunosuppressants can be beneficial in the management of IMM, which should be further explored.

Our findings illustrate the critical need for a standardized approach to managing IMM. Topical agents should be considered before systemic therapy. Elad et al⁵⁰ reported the efficacy of topical immunomodulators (azathioprine, benzydamine, and tetracyclines) in managing IMM refractory to topical corticosteroids. In addition, high-risk patients who would benefit from maintenance therapy to prevent recurrence of IMM should be identified. If patients are refractory to steroid treatment, then biologics may be considered as a potential salvage option. For instance, Horisberger et al⁵¹ reported success in treating refractory mucositis and esophageal stenosis using anti-PD-1 therapy and tocilizumab, an IL-6 blocker. Other studies have shown promising outcomes in patients with immune-mediated colitis treated using infliximab or vedolizumab as adjunct or salvage therapy, with 70% to 85% clinical improvement, and a much lower recurrence rate with

Table 5. Univariate Logistic Regression Analysis for Recurrence of Mucositis

Characteristic	OR (95% CI)	P Value
Age	0.997 (0.971–1.023)	.804
Male sex	0.952 (0.474–1.912)	.891
Basic risk factors	0.746 (0.318–1.778)	.502
NSAID use	1.198 (0.492–2.848)	.683
History of smoking	0.645 (0.317–1.298)	.222
Concurrent chemotherapy	0.765 (0.379–1.541)	.453
Concurrent GI toxic effects	1.931 (0.753–5.018)	.169
Anti-CTLA-4 regimen ^a	1.303 (0.532–3.136)	.555
Odynophagia/Oral pain	1.480 (0.454–5.708)	.533
Nausea or vomiting	0.273 (0.086–0.721)	.014
Dysphagia	3.222 (1.045–11.065)	.047
Duration of symptoms	1.003 (1.000–1.006)	.051
Continued ICI therapy	1.944 (0.806–4.731)	.137
Duration from ICI therapy to mucositis onset	1.000 (0.999–1.002)	.736
Required immunosuppressive therapy	3.317 (1.485–7.645)	.004
Duration of immunosuppressive therapy	1.000 (0.981–1.024)	.530
Hospitalization	0.566 (0.120–2.066)	.418

Abbreviations: GI, gastrointestinal; ICI, immune checkpoint inhibitor; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio.

^aAnti-CTLA-4 therapy included monotherapy and combination with anti-PD-1/L1 agents.

vedolizumab maintenance therapy among patients at high risk for recurrence of immune-mediated colitis.^{52–55} Unfortunately, evidence regarding the efficacy of biologic therapy for upper gastrointestinal toxicities is limited.

In addition to medical options, oral microbial derangements were recently found to be associated with recurrent aphthous stomatitis and ulceration.^{56–58} Wang et al⁵⁹ showed that the reconstitution of the gut microbiome via fecal microbiota transplantation in patients with immune-mediated colitis led to the resolution of inflammation and the upregulation of colonic regulatory T lymphocytes. We speculated that oral microbiome modification may provide a similar benefit to mucositis and could be explored further as a novel therapeutic avenue.

As shown previously, irAEs are generally associated with improved OS, progression-free survival, and ICI efficacy in patients with advanced cancer.^{11,60–65} Severe forms of irAEs—higher CTCAE grade, more organ involvement, and irAE-related complications—have been associated with longer OS.^{17,37,65} An irAE may recur despite resolution of the initial event and ICI discontinuation, as reported previously.^{51,66–68} A severe, refractory irAE prompts cessation of ICI therapy for the underlying malignancy in view of poor quality of life, which is likely

Figure 2. Overall survival based on ICI treatment status. Abbreviation: ICI, immune checkpoint inhibitor.

reflective of the long-lasting systemic effect of ICIs and lingering toxicities that may be associated with favorable oncologic outcomes. This is supported by previous studies of other irAEs^{16,17} and suggested by the superior OS in patients with ICI continuation in this study. An OS benefit was not manifested in our patients with recurrent mucositis, perhaps because of the small sample size and other confounders. Overall, these findings raise the question of how to optimize ICI treatment duration while effectively managing irAEs.

Our study has some limitations. First, data collection and analysis were limited by the retrospective, single-center design and small sample size. Second, the true incidence and severity of mucositis may have been underrepresented with mild or subclinical cases. The CTCAE grading system, although standardized, relies purely on self-reported documentation, with wide variation. Third, diagnosis, monitoring, and management of mucositis were performed at the discretion of the provider and bore no standardized management approach. Patients who received treatment for coexisting irAEs may have confounded outcomes of mucositis. Finally, we did not perform landmark analysis given neglectable immortal time and did not conduct subgroup OS analysis for different types of malignancy because of the small sample size. However, despite these limitations, we present new, important data that generate hypotheses in a clinically relevant setting and that support further investigation of this topic.

Conclusions

IMM is an underrecognized irAE in patients receiving ICI therapy, and is often mild and effectively managed using supportive medications. Rarely, patients with severe IMM require hospitalization, immunosuppression, nutrition support, and disruption of ICI treatment. Our findings

showed that up to 39% of patients may experience recurrence, which is associated with longer duration of symptoms and immunosuppressive therapy for the initial episode, and that ICI interruption due to irAEs shortens OS. Further studies are warranted to identify risk factors associated with refractory mucositis, clarify the role and logistics of immunosuppressive therapy, and develop standardized diagnostic and management strategies to optimize the clinical benefit of ICI therapy in patients with mucositis.

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Clinical Characteristics and Outcomes of Oral Mucositis Associated With Immune Checkpoint Inhibitors in Patients With Cancer

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eFigure 1: Patient Selection Criteria

eFigure 2: Overall Survival According to Mucositis Recurrence, Immunosuppressive Therapy, and Mucositis

eTable 1: Clinical Characteristics and Outcomes of Mucositis

eTable 2: Clinical Characteristics of Study Patients Based on Status of irAEs Other Than Mucositis

eFigure 1. Patient selection criteria.
Abbreviation: ICI, immune checkpoint inhibitor.
^aIncluding herpes simplex virus, cytomegalovirus, and *Candida*.
^bChemotherapeutic agents, including alkylating agents, antitumor antibiotics, antimetabolites, vinca alkaloids, anthracyclines, and taxanes.
^cIncluding oral/tongue dysplasia, allergic reaction, mechanical trauma, and pill-induced sores.

eFigure 2. Overall survival according to (A) mucositis recurrence, (B) immunosuppressive therapy, and (C) mucositis alone or with other irAEs. Abbreviation: irAE, immune-related adverse event.

eTable 1. Clinical Characteristics and Outcomes of Mucositis Stratified by Type of Immunosuppressive Treatment

Characteristic	Systemic Immunosuppressants n (%)	Topical Immunosuppressants n (%)	P Value
Total, n	29	7	
Clinical presentation			
Odynophagia/Oral pain	28 (97)	7 (100)	1.000
Nausea or vomiting	6 (21)	0 (0)	.451
Dysphagia	5 (17)	0 (0)	.565
Bleeding	0 (0)	0 (0)	
Peak grade of mucositis			.710
1–2	25 (86)	7 (100)	
3–4	4 (14)	0 (0)	
Physical examination finding			1.000
Ulcers/Aphthae	28 (97)	7 (100)	
Nonulcer inflammation	1 (3)	0 (0)	
Outcome			
Hospitalization	6 (21)	0 (0)	.451
Median duration of hospitalization, d (IQR); n=29	88 (45–126)	73 (52–106)	.981
Clinical improvement/resolution	26 (90)	7 (100)	.899
Recurrence of mucositis	15 (52)	5 (71)	.822
All-cause mortality	13 (45)	1 (14)	.291

Abbreviation: IQR, interquartile range.

eTable 2. Clinical Characteristics of Study Patients Based on Status of irAEs Other Than Mucositis

Characteristic	No Other irAEs n (%)	Other irAEs ^a n (%)	P Value
Total, n	54	98	
Median duration from ICI therapy to mucositis onset (IQR), d	91 (24–171)	85 (29–171)	.841
ICI treatment type			.032
Anti-CTLA-4 therapy	6 (11)	27 (28)	
Anti-PD-1/L1 monotherapy	48 (89)	71 (72)	
Peak grade of mucositis			.593
1–2	48 (89)	91 (93)	
3–4	6 (11)	7 (7)	
Clinical presentation			
Odynophagia/Oral pain	48 (89)	88 (90)	1.000
Nausea or vomiting	8 (15)	23 (23)	.291
Dysphagia	5 (9)	10 (10)	1.000
Bleeding	4 (7)	2 (2)	.234
Hospitalization	5 (9)	12 (12)	.772
Mucositis treatment			
Immunosuppressants	11 (20)	25 (26)	.607
Supportive treatment	34 (63)	65 (66)	.811
All-cause mortality	27 (50)	49 (50)	1.000

Abbreviations: ICI, immune checkpoint inhibitor; IQR, interquartile range; irAE, immune-related adverse event.

^aIncluded hepatic, endocrine, pulmonary, dermatologic, hematologic, neurologic, renal, musculoskeletal, and ophthalmic toxicities.