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Review Article

Prophylaxis, clinical management, and monitoring of datopotamab deruxtecan-associated oral mucositis/stomatitis

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Abstract

Oral mucositis/stomatitis (hereafter stomatitis) is a common dose-limiting toxicity seen with various classes of cancer treatment. Symptoms associated with stomatitis, primarily oral pain, may impact patient quality of life and may lead to dose delay and reduction or treatment discontinuation. Datopotamab deruxtecan (Dato-DXd) is a novel trophoblast cell surface antigen 2-directed antibody-drug conjugate undergoing clinical investigation in multiple solid tumor types. Stomatitis is among the most reported adverse events associated with Dato-DXd, with most cases being grades 1-2. This article reviews the incidence of stomatitis seen with Dato-DXd, including in the phase III pivotal studies TROPION-Lung01 and TROPION-Breast01 (in patients with non-small cell lung cancer and hormone receptor-positive/human epidermal growth factor receptor 2-negative breast cancer, respectively), both studies met a dual primary endpoint of statistically significant improvement in progression-free survival compared to standard-of-care chemotherapies. Developing new cancer therapies requires evidence-based strategies to successfully prevent, monitor, and manage adverse events. Accordingly, a thorough evaluation of potential underlying mechanisms, risk factors, available clinical data, and adequacy of preventive and management recommendations for stomatitis is presented here. Prophylaxis recommendations for a daily oral care plan include oral hygiene education and the use of a prophylactic steroid-containing mouthwash. Ongoing studies continue to collect data on Dato-DXd-associated stomatitis to further characterize clinical features and possible mechanisms of this toxicity. Appropriate management may reduce the incidence, duration, and severity of events, improve quality of life, and support patient adherence to treatment.

Key words: stomatitis; oral mucositis; antibody-drug conjugate; prophylaxis; management.

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Implications for practice

This review presents insights and recommendations on stomatitis management that arose from multiple clinical studies evaluating the antibody-drug conjugate datopotamab deruxtecan (Dato-DXd). High rates of stomatitis were reported in the first cohort of the first-in-human TROPION-PanTumor01 study. This observation led to the development of clinical practice recommendations for both prophylaxis and management. Prophylactic recommendations include a daily oral care plan with education for oral hygiene and hydration, and utilization of a steroid-containing mouthwash. Clinical findings from patients with breast or lung cancer enrolled in the TROPION-PanTumor01, TROPION-Breast01, TROPION-Lung01, and TROPION-Lung05 studies underpin the recommendations presented in this expert review.

Introduction

Stomatitis pathophysiology

Oral mucositis/stomatitis (hereafter stomatitis) is inflammation of the mucosal lining of any of the structures in the mouth, manifesting as erythema, ulceration, bleeding, and pain which may interfere with oral intake.[1,2] Stomatitis is commonly associated with anticancer agents; for example, in patients receiving chemotherapy for solid tumors, up to half may experience stomatitis adverse events (AEs; range: 6%-52%).[3-6] Stomatitis is also a common AE in patients with head and neck cancer treated with radiotherapy (range: 33%-99%), with generally higher incidences seen among patients treated with concomitant chemotherapy and radiotherapy.[7-10]

Several potential mechanisms leading to stomatitis development have been identified. A 5-stage model of stomatitis has been proposed for radiotherapy/chemotherapy and is characterized by initiation, activation, amplification, ulceration, and healing over a 15-21-day period (**Figure 1**).[2,11] The first stage—initiation—involves cellular damage in the form of DNA double-strand breaks induced by radiation and/or chemotherapy, which promotes the formation of reactive oxygen species and upregulates damage-associated pattern molecules. In the second stage, cellular damage results in the activation of damage response signaling molecules, p53 and nuclear factor kappa B (NF-κB). In the third stage, NF-κB activation results in damage signal amplification through the

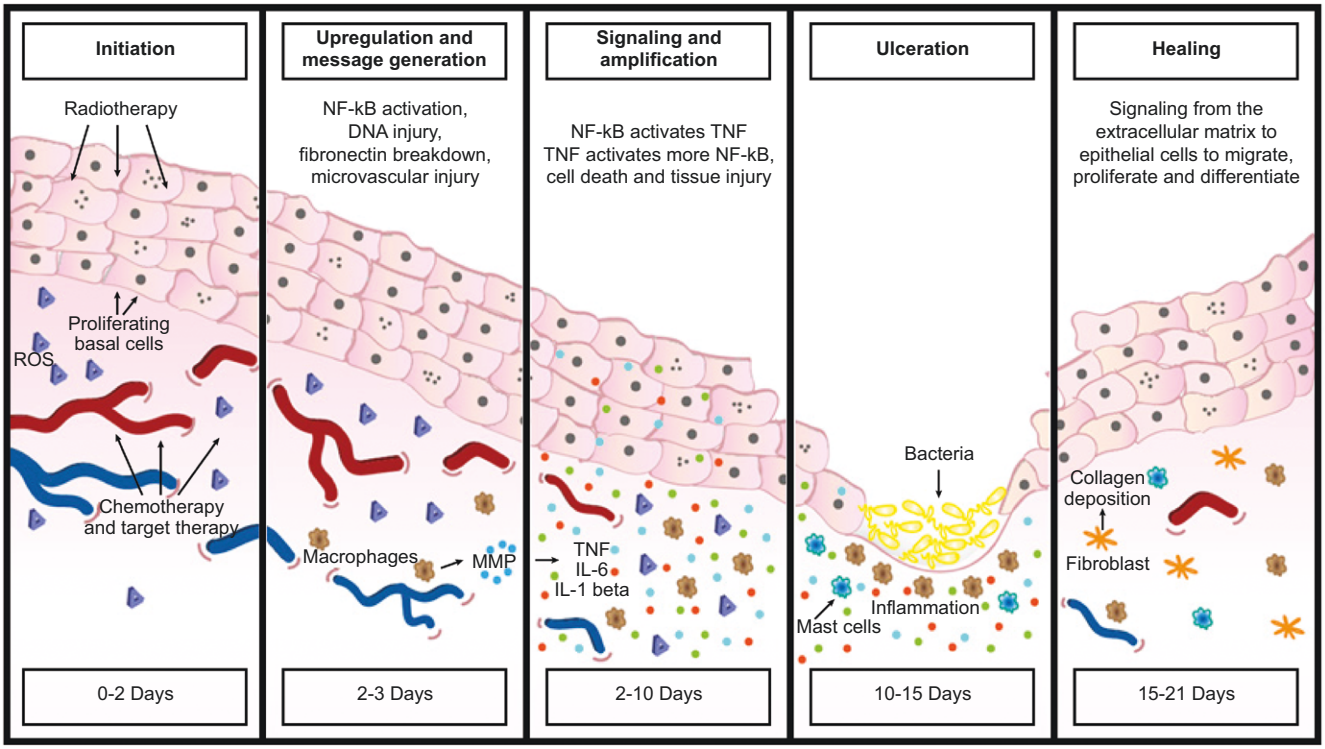

Figure 1. Five-stage model for mucositis in patients treated with chemotherapy and radiotherapy.This model represents the pathogenesis of stomatitis induced by chemotherapy and radiotherapy. 0-2 days: Initiation phase and primary injury response. Radio- and chemotherapy-induced damages lead to DNA double-strand breaks and oxidative stress and, consequently, generates ROS. The injury to epithelial, submucosal, and endothelial cells provokes the release of endogenous DAMPs. 2-3 days: ROS, innate immune response, and binding of endogenous DAMPs (CRAMPs) to receptors further propagates and activates several transcriptional pathways, including NF-κB. This leads to the production of inflammatory cytokines, such as TNF-α and IL-6. 2-10 days: Amplification of the injury signal. The effectors produced during the previous phase result in an amplification of the injury signal. The released TNF-α initiates the activation of MAPK that sustains NF-κB activity. During this stage, the primary damage signaling is amplified through positive-feedback loop mechanisms. 10-15 days: Ulceration. Breaks in the submucosa allow microorganisms to invade this tissue district leading to mononuclear-infiltrating cell-mediated inflammation response. 15-21 days: Tissue re-epithelialization. Stimuli from the submucosa extracellular matrix and mesenchyme promote the healing process. Abbreviations: CRAMP, chemoradiation-associated pattern molecule; DAMP, damage-associated pattern molecule; IL, interleukin; MAPK, mitogen-activated protein kinase; MMP, metalloproteinase; NF-κB, nuclear factor kappa B; ROS, reactive oxygen species; TNF, tumor necrosis factor. Reprinted from Cancers (Basel), Vol 11, Basile D, et al. Mucosal injury during anti-cancer treatment: from pathobiology to bedside, pg 857, 2019, with permission from MDPI. https://creativecommons.org/licenses/by/4.0/.

production of inflammatory cytokines such as interleukin (IL)-6, tumor necrosis factor alpha, and IL-1 beta, which subsequently activate more NF-κB in a positive feedback loop. The fourth stage involves tissue damage and cell death due to the inflammatory response, leading to ulcerations in the mucosa and increasing susceptibility to infections. The final stage—healing—occurs when the initiating cellular damage that drove the inflammatory response and consequent tissue damage stops (**Figure 1**).[2,11,12]

Newer targeted therapies, including mammalian target of rapamycin (mTOR) inhibitors and antibody-drug conjugates (ADCs), may have different underlying mechanisms for stomatitis which are not yet fully understood.[13-15] mTOR inhibitors have shown proinflammatory properties in experimental models, and immune dysregulation may be involved in the development of mTOR inhibitor-associated stomatitis (mIAS).[13] mIAS presents as single or multiple superficial grayish-white ulcers that are ovoid in shape and well demarcated, typically involving areas of non-keratinized mucosa. Clinically, mIAS resembles aphthous stomatitis more than oral mucositis, although its pathobiology is also not well understood.[13] Aphthous stomatitis is characterized by recurrent painful oral ulcers with inflammatory halos that are round or ovoid in shape.[16] Impaired wound healing has also been suggested in aphthous ulceration and may also be involved in the pathogenesis of mIAS. Angiogenesis and vascular cell proliferation are important for wound repair, and both processes may be impeded by mTOR inhibitors. The mechanisms of stomatitis that are induced by some newer therapies, including datopotamab deruxtecan (Dato-DXd), have not yet been fully elucidated.[13,17]

Risk Factors for Development of Stomatitis

Both intrinsic and extrinsic risk factors have been implicated in the development of stomatitis. Intrinsic factors include age, sex, ethnicity, and some genetic conditions.[2,18,19] The youngest and oldest patients with cancer are at increased risk of experiencing AEs and events of greater severity.[1,20] Additionally, patients with underlying systemic illnesses, such as autoimmune diseases, may be predisposed to mucosal damage due to alterations in the tissue environment.[2] Females receiving high-dose or fluorouracil-based chemotherapy have a higher risk and more severe presentation than males.[19,21] Some genetic polymorphisms, such as those involved in drug metabolism, also increase risk. For example, a polymorphism in the *TNF* gene, with an incidence of ~16% of Japanese populations, has been associated with more severe mucositis when treated with 5-fluorouracil plus cisplatin chemotherapy.[2,22,23] Additionally, impaired dihydropyrimidine dehydrogenase activity in the metabolism of fluoropyrimidine drugs has been shown to have a role in drug-related toxicities. The deficiency of the dihydropyrimidine dehydrogenase enzyme may reduce the patient's capacity to catabolize fluoropyrimidine, increasing risk of stomatitis, among other toxicities.[24]

Extrinsic patient risk factors that increase the risk of developing stomatitis include poor oral health, diet, alcohol use, a history of smoking, and prior treatment with certain chemotherapeutic agents and immune checkpoint inhibitors (ICIs).[2,18,19,25]

Clinical Data and Impact of Stomatitis

The incidence, severity, and duration of stomatitis may reduce patient adherence to treatment or result in early treatment discontinuation given this toxicity can be painful and impact patient quality of life.[12] **Supplementary Table S1** presents the Common Terminology Criteria for Adverse Events (CTCAE) grading for oral mucositis/stomatitis (CTCAE term: mucositis oral).[26] Grade 1 stomatitis is defined by the presence of mild or asymptomatic symptoms, with no intervention indicated, and grade 2 stomatitis is indicated by the presence of moderate pain or ulcer that does not interfere with oral intake, with diet modifications recommended.[26]

In addition to chemotherapy, stomatitis is also associated with various classes of targeted therapies indicated for use in both breast and lung cancer, including endothelial growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) and mTOR inhibitors. In routine clinical practice, these cases are usually mild and well managed with the implementation of basic oral care protocols.[11,27] The incidence of stomatitis with select EGFR TKIs and mTOR inhibitors used for the treatment of non-small cell lung cancer (NSCLC) and breast cancer (BC) that are known to be associated with stomatitis are summarized in **Table 1**. Stomatitis rates vary widely across treatments, even within the same class of therapy.

EGFR inhibitors

In the phase III Lux-Lung 3 study in patients with *EGFR* mutation-positive NSCLC, stomatitis was among the most common treatment-related AE (TRAE) seen in patients who received afatinib. In this group ($n = 229$), treatment-related any-grade stomatitis was reported in 72% and grade ≥3 events were reported in 9% of patients, compared with 15% any-grade and 1% grade ≥3 events in the cisplatin plus pemetrexed comparator group ($n = 111$; **Table 1**).[28] In a phase III trial of dacomitinib versus gefitinib for first-line treatment of *EGFR*-mutated NSCLC (ARCHER 1050), any-grade treatment-emergent stomatitis and grade 3 events were reported in 44% and 4% of patients receiving dacomitinib ($n = 227$), as compared with 18% and <1% in patients receiving gefitinib comparator ($n = 224$), respectively.[30] Similarly, a sub-study of Asian patients enrolled in the ARCHER1050 study reported any-grade and grade ≥3 stomatitis in 51% and 5%, respectively, of patients receiving dacomitinib ($n = 170$), compared with 21% and 1%, respectively, of patients receiving gefitinib ($n = 176$).[29] Across the AURA3 and FLAURA phase III studies in patients with *EGFR* mutation-positive NSCLC treated with osimertinib, any-grade and grade ≥3 stomatitis were reported in 15%-29% and <1% of patients, respectively, compared with 15% and 1% for platinum-pemetrexed and 20% and <1% for standard EGFR TKI comparators, respectively.[31,32] ICI-containing neoadjuvant therapy has been linked with a greater risk of developing stomatitis, including high-grade (grade ≥3) stomatitis, for patients with triple-negative breast cancer (TNBC).[36] In a small meta-analysis investigating the addition of ICIs to neoadjuvant chemotherapy for patients with TNBC, a greater risk of grade ≥3 stomatitis was associated with ICI therapy, with an odds ratio (OR) of 5.78 (95% confidence interval [CI], 1.01-33.05; $P = .05$); however, risk of any-grade stomatitis was not found to be significantly increased, with an OR of 1.23 (95% CI, 0.97-1.56; $P = .09$).[36]

mTOR inhibitors

High rates of stomatitis are commonly seen with the mTOR inhibitor everolimus, used in the treatment of advanced hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2–) BC. In a systematic

Table 1. Stomatitis incidence with selected targeted therapies for the treatment of breast and lung cancer.

Agent	Tumor type	Number of patients	Incidence of stomatitis (%)[a]	
			Any grade	Grade ≥3
EGFR TKIs				
Afatinib	Stage IIIB/IV lung adenocarcinoma	*N* = 229[28]	72	9
Dacomitinib	Advanced NSCLC and *EGFR* mutations	*N* = 170[29]	51	5
	Advanced NSCLC and *EGFR* mutations	*N* = 227[30]	44	4
Osimertinib	Previously untreated, *EGFR* mutation-positive advanced NSCLC	*N* = 279[31]	29	<1
	T790M-positive advanced NSCLC	*N* = 279[32]	15	0
Gefitinib	Advanced NSCLC and *EGFR* mutations	*N* = 176[29]	21	1
	Advanced NSCLC and *EGFR* mutations	*N* = 224[30]	18	<1
mTOR inhibitors				
Ridaforolimus	Multiple tumor types	*N* = 194[33]	55	8
Everolimus	Multiple tumor types	*N* = 3493[17], [b] *N* = 558[c]	43	16
Temsirolimus	Advanced renal cell carcinoma	*N* = 208[34]	41	3
Sirolimus	Recurrent/ refractory solid tumors	*N* = 12[35]	10	2

[a]Stomatitis incidence reported as TEAEs unless otherwise indicated.
[b]Any-grade patient number.
[c]Grade ≥3 patient number.
Abbreviations: EGFR, endothelial growth factor receptor; mTOR, mammalian target of rapamycin; NSCLC, non-small cell lung cancer; TEAE, treatment-emergent adverse event; TKI, tyrosine kinase inhibitor; TNBC, triple-negative breast cancer.

review of 8201 patients with cancer who received everolimus, including 3933 patients with BC, the incidence of stomatitis was 43%; 84% of cases were grade 1-2 and 16% were grade 3-4.[17] The time to onset was approximately 5 days, most frequently occurring in the first cycle of mTOR-inhibitor therapy.[17] mIAS is also common with the use of other mTOR inhibitors, including ridaforolimus, temsirolimus, and sirolimus, with frequencies of any-grade stomatitis of 55%, 41%, and 10%, respectively.[17,33-35]

ADCs

Rates of stomatitis seen with trophoblast cell-surface antigen-2 (TROP2)-directed or DXd-containing ADCs are presented in **Table 2**. As with other classes of agents, stomatitis incidences range widely between agents, with most events being grade 1-2.[37,39,44,48] High rates have been reported for the TROP2-directed ADCs DB-1305 (75%), SHR-A1921 (66%), and sacituzumab tirumotecan (SKB264; 44%-49%, TRAEs).[37-41] Conversely, sacituzumab govitecan and ESG401, which share the same SN-38 payload, show lower incidences, with rates of <15%-17% of any-grade stomatitis.[43,44] These wide-ranging incidences may be influenced by differences in the individual antibody, linker, and/or payload of each ADC.[49,50] A potential pharmacological hypothesis for TROP2 ADC-associated stomatitis is that TROP2 expression on epithelia of the esophagus, tonsil crypts, salivary glands, and mucosal tissues could facilitate increased localized, non-tumor uptake of the payload.[14,15] Indeed, TROP2 has been found to be highly expressed in salivary glands,[51] which play a critical role in maintaining the homeostasis of the oral cavity.[52]

In studies in patients with solid tumors (including NSCLC and BC) who received trastuzumab deruxtecan (T-DXd), reported rates of any-grade stomatitis were 17%-32% and events were mostly low grade (grades 1-2).[45,46] In previously treated patients with advanced *EGFR*-mutated NSCLC receiving patritumab deruxtecan (HER3-DXd), grade 1-2 and grade 3 stomatitis were reported in 11% and 1% of patients, respectively.[47]

Dato-DXd-associated stomatitis

Dato-DXd

Dato-DXd is a novel TROP2-directed ADC that is under clinical evaluation as a treatment for various solid tumors. Dato-DXd comprises a humanized anti-TROP2 immunoglobulin G1 monoclonal antibody covalently linked to a highly potent topoisomerase I inhibitor payload (DXd) via a plasma-stable, tumor-selective, tetrapeptide-based cleavable linker. Binding of Dato-DXd to TROP2-expressing cells leads to internalization of the drug into cancer cells and release of the payload, resulting in DNA topoisomerase I inhibition, DNA damage, and apoptosis. The released payload can also enter neighboring cells in the tumor microenvironment, leading to cell death via a bystander antitumor effect.[53] TROP2 is a transmembrane glycoprotein that is broadly expressed in a variety of solid tumor types, including HR+/HER2– BC, TNBC, and NSCLC.[54,55] High TROP2 expression is associated with poor prognosis in both BC and NSCLC.[54-56] Given its expression profile, TROP2 represents an attractive tumor-associated antigen for ADC therapies that may be effective across a range of tumor types.

The first-in-human clinical evaluation of Dato-DXd in patients with advanced solid tumors was undertaken as part of the ongoing TROPION-PanTumor01 phase I study

Table 2. Incidence of stomatitis with TROP2-directed or DXd-containing antibody-drug conjugates in breast and lung cancer.

Agent	Target	Payload	Tumor type	Number of patients	Incidence of stomatitis (%)[a]	
					Any grade	Grade ≥3
DB-1305	TROP2	DNA topoisomerase I inhibitor	Advanced/unresectable, recurrent, or metastatic solid tumors	*N* = 44[37]	75	23
SHR-A1921	TROP2	DNA topoisomerase I inhibitor	Advanced solid tumors	*N* = 38[38]	66	18[b]
Sacituzumab tirumotecan	TROP2	Belotecan-derivative topoisomerase I inhibitor	NSCLC	*N* = 43[39]	49[b]	9[b]
			Metastatic TNBC	*N* = 59[40]	46[b]	7[b]
				N = 130[41]	44[b]	9[b]
MHB036C	TROP2	DNA topoisomerase I inhibitor	Locally advanced or metastatic solid tumors	*N* = 26[42]	≥25[b], [c]	35[b]
Sacituzumab govitecan	TROP2	DNA topoisomerase I inhibitor SN-38	Metastatic TNBC	*N* = 258[43]	17	2
ESG401	TROP2	DNA topoisomerase I inhibitor SN-38	Advanced or metastatic solid tumors	*N* = 35[44]	<15[c]	0
T-DXd	HER2	DXd	HER2-expressing advanced breast cancer	*N* = 54[45]	32	0
			HER2-expressing advanced solid tumors	*N* = 59[46]	17	2
HER3-DXd	HER3	DXd	Advanced NSCLC	*N* = 225[47]	12	1

[a]Stomatitis incidence reported as TEAEs unless otherwise indicated.
[b]TRAEs are reported.
[c]Exact number not available in reference.
Abbreviations: DXd, topoisomerase I inhibitor payload (exatecan derivative); HER2, human epidermal growth factor receptor 2; HER3, human epidermal growth factor receptor 3; HER3-DXd, patritumab deruxtecan; NSCLC, non-small cell lung cancer; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event; TNBC, triple-negative breast cancer; TRAE, treatment-related adverse event; TROP2, trophoblast cell-surface antigen-2.

(ClinicalTrials.gov Identifier: NCT03401385).[57,58] The safety profile of Dato-DXd in these patients was manageable and treatment discontinuation due to TRAEs was rare.[14,58,59]

Stomatitis is one of the identified AEs of special interest (AESIs) for the Dato-DXd clinical program and is a common TEAE observed in patients with NSCLC or BC who receive Dato-DXd. For the Dato-DXd clinical trial program, stomatitis refers to any event that was coded as any of 26 pre-selected preferred terms, including pharyngeal inflammation and mouth ulceration. A full list of the pre-selected preferred terms is included in the **Supplementary information**. Stomatitis events associated with Dato-DXd are mostly mild or moderate (grade 1-2) and rarely lead to treatment discontinuation.[57,58,60-62] The underlying mechanism(s) of Dato-DXd-associated stomatitis are not fully understood and investigations into the biological underpinnings and risk factor analyses are ongoing.[2,11]

TROPION-PanTumor01 was a phase I dose-escalation study. Given the lack of prior experience with Dato-DXd, the protocol evolved over the course of the study including the addition of recommendations for prophylaxis, early detection, and management of stomatitis. Here, we present insights learned from the evaluation of Dato-DXd across a number of different studies, including phase I TROPION-PanTumor01, phase II TROPION-Lung05 (NCT04484142), phase III TROPION-Breast01 (NCT05104866), and phase III TROPION-Lung01 (NCT04656652), with a focus on management of stomatitis among patients with HR+/HER2– BC, TNBC, and NSCLC who received Dato-DXd (**Table 3**).

Clinical pharmacology data

An exposure-response analysis was performed to evaluate stomatitis events (the preferred term "stomatitis") from the NSCLC cohort of TROPION-PanTumor01 across a range of Dato-DXd doses.[59] Patients with NSCLC enrolled in this trial received Dato-DXd in 4-, 6-, 8-, or 10-mg/kg doses (*N* = 188) and reported stomatitis more frequently in earlier treatment cycles, with a median time to first event (onset time) of 8 days, and 72% of first events occurring in cycle 1. Most stomatitis events in TROPION-PanTumor01 were grades 1-2.[17,59] The incidence of any-grade stomatitis increased in a dose-dependent manner. In the 4-mg/kg dose group, 21 patients (42%) experienced any-grade stomatitis, which is comparatively lower than the incidences in the 6-, 8-, and 10-mg/kg dose groups, where it was reported in 30 (60%), 44 (55%), and 4 (50%) patients, respectively. Grade 1 stomatitis occurred in 17 (34%), 18 (36%), 16 (20%), and 1 (13%) patients in the 4-, 6-, 8-, and 10-mg/kg dose groups, respectively. Grade 2 stomatitis was reported by 4 (8%), 11 (22%), 24 (30%), and 2 (25%) patients, while grade ≥3 stomatitis was observed in 0, 1 (2%), 4 (5%), and 1 (13%) patients in the 4-, 6-, 8-, and 10-mg/kg dose groups, respectively. Further analyses of the quantitative exposure response for safety revealed a positive correlation between both the incidence and onset time of stomatitis and the log-transformed average concentration of Dato-DXd. Additionally, the geographic location of the participants (Japan compared with the USA) and sex (female) were significant covariates affecting the incidence of any-grade and grade ≥2 stomatitis.

Clinical safety data from TROPION-PanTumor01

TROPION-PanTumor01 enrolled the first patient on February 7, 2018, and the initial guidelines for stomatitis management were implemented on June 9, 2021. Implementation occurred toward the end of enrollment in the NSCLC cohort of the study (data cutoff date was July 30, 2021), and midway

through the HR+/HER2– BC and TNBC cohorts (first patient enrolled with TNBC: June 30, 2020; first patient enrolled with HR+/HER2– BC: March 15, 2021). More specific and stringent guidelines for stomatitis management were implemented between October 5, 2021, and February 12, 2023.[65] The current guidelines for stomatitis management were therefore implemented after most patients were enrolled and treated in TROPION-PanTumor01.

In TROPION-PanTumor01, the overall incidence of any-grade stomatitis (grouped preferred terms; **Supplementary information**) in the lung and breast cohorts was 70%-90% in patients treated with 6 mg/kg Dato-DXd (**Table 4**).[58] Most of these events were mild to moderate. In the combined 6-mg/kg and 8-mg/kg TNBC groups ($n = 44$), grade 1, 2, and ≥3 stomatitis was reported in 17 (39%), 13 (30%), and 5 (11%) patients, respectively. In the 6-mg/kg HR+/HER2– BC group ($n = 41$), grade 1, 2, and ≥3 stomatitis was observed in 18 (44%), 15 (37%), and 4 (10%) patients, respectively (**Table 4**). In the 6-mg/kg NSCLC group ($n = 50$), grade 1, 2, and ≥3 stomatitis was seen in 18 (36%), 15 (30%), and 2 (4%) patients, respectively (**Table 4**). The median onset time for stomatitis was 11 days in the NSCLC cohort (4-8 mg/kg dose). There was only 1 (2%) discontinuation of Dato-DXd due to stomatitis in a patient with HR+/HER2– BC and there were no discontinuations due to stomatitis in NSCLC or TNBC.[57,58]

Clinical safety data from TROPION-Breast01, TROPION-Lung01, and TROPION-Lung05

In contrast to TROPION-PanTumor01, management guidelines were in place throughout the entirety of TROPION-Breast01 (first patient enrolled: October 18, 2021) and the majority of TROPION-Lung01 (first patient enrolled: December 21, 2020) and TROPION-Lung05 studies (first patient enrolled: March 29, 2021). The guidelines further evolved with ongoing clinical experience, and the most current oral care plan was in place for the latter half of TROPION-Breast01, TROPION-Lung01, and TROPION-Lung05.

Table 3. Dato-DXd monotherapy clinical trials in NSCLC, TNBC, and HR+/HER2– BC.

Study	Patient population	Regimen
Advanced/metastatic NSCLC		
TROPION-PanTumor01 (NCT03401385)[57]	Advanced/metastatic NSCLC	Dato-DXd
TROPION-Lung01 (NCT04656652)[63]	Advanced/metastatic NSCLC With or without actionable genomic alterations Disease has progressed on prior therapies	Dato-DXd versus docetaxel
TROPION-Lung05 (NCT04484142)[62]	Previously treated non-small cell lung cancer with actionable genomic alterations	Dato-DXd
Advanced/metastatic BC		
TROPION-PanTumor01 (NCT03401385)[58]	Advanced/metastatic TNBC and HR+/HER2– BC	Dato-DXd
TROPION-Breast01 (NCT05104866)[64]	Inoperable or metastatic HR+/HER2– BC 1 or 2 prior lines of systemic chemotherapy with progression on, or not suitable for, endocrine therapy	Dato-DXd versus investigator's choice chemotherapy

Abbreviations: BC, breast cancer; Dato-DXd, datopotamab deruxtecan; HER2–, human epidermal growth factor receptor 2-negative; HR+, hormone receptor-positive; NSCLC, non-small cell lung cancer; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1.

Table 4. Stomatitis in patients with breast or lung cancer treated with Dato-DXd from TROPION-PanTumor01, TROPION-Breast01, TROPION-Lung01, and TROPION-Lung05.

	TROPION-PanTumor01			TROPION-Breast01	TROPION-Lung01	TROPION-Lung05
Patients, *n* (%)[a]	**TNBC[b] (*N* = 44)**	**HR+/HER2– BC (*N* = 41)**	**NSCLC (*N* = 50)**	**HR+/HER2– BC (*N* = 360)**	**NSCLC (*N* = 297)**	**NSCLC (*N* = 137)**
Oral mucositis/stomatitis (overall)[c]	35 (80)	37 (90)	35 (70)	200 (56)	160 (54)	90 (66)
Grade 1 TEAE	17 (39)	18 (44)	18 (36)	91 (25)	79 (27)	45 (33)
Grade 2 TEAE	13 (30)	15 (37)	15 (30)	84 (23)	62 (21)	30 (22)
Grade ≥3 TEAE	5 (11)	4 (10)	2 (4)	25 (7)	19 (6)[d]	15 (11)

In TROPION-Breast01, only treatment-related AESIs were reported, whereas TROPION-PanTumor01, TROPION-Lung01, and TROPION-Lung05 report treatment-emergent AESIs.
[a]Percentages are based on the overall number of patients within each cohort.
[b]Data are reported for patients who received either Dato-DXd 6 mg/kg ($n = 42$) or 8 mg/kg ($n = 2$).
[c]Oral mucositis/stomatitis as a medical concept that refers to any event that was coded as any of the 26 pre-selected preferred terms.
[d]One patient had grade 4 stomatitis in TROPION-Lung01.
Abbreviations: AESI, adverse event of special interest; BC, breast cancer; Dato-DXd, datopotamab deruxtecan; HER2–, human epidermal growth factor receptor 2-negative; HR+, hormone receptor-positive; NSCLC, non-small cell lung cancer; TEAE, treatment-emergent adverse event; TNBC, triple-negative breast cancer.

Among 360 patients with HR+/HER2– BC treated with Dato-DXd in TROPION-Breast01, most stomatitis events were mild to moderate, with 91 (25%) and 84 (23%) patients with grade 1 and 2 TRAEs, respectively. Grade ≥3 stomatitis events were reported in 25 (7%) patients (**Table 4**). Stomatitis led to treatment interruption in 5 (1%) patients and treatment discontinuation in 1 (<1%) patient in the Dato-DXd group.[66,67]

In TROPION-Lung01, in patients with NSCLC (n = 297), most stomatitis events were similarly mild to moderate. Treatment-emergent grade 1 and 2 stomatitis was reported in 79 (27%) and 62 (21%) patients, respectively, with 19 patients (6%) experiencing grade ≥3 events. Stomatitis associated with Dato-DXd resulted in a low discontinuation rate (2 [<1%] patients) and a low treatment interruption rate (13 [4.4%] patients) in TROPION-Lung01.[68]

In TROPION-Lung05, in patients with NSCLC with actionable genomic alterations (n = 137), the majority of stomatitis events were again mild to moderate. Treatment-emergent grade 1 and 2 stomatitis was reported in 45 (33%) and 30 (22%) patients, respectively, and 15 (11%) patients reported a grade ≥3 event.[62]

In summary, before management guidelines were implemented in the clinical development program, stomatitis rates were 70%-90% across cohorts in the phase I TROPION-PanTumor01 study. After recommendations were in place, stomatitis rates dropped to 54%-66% in the phase II-III TROPION-Breast01, TROPION-Lung01, and TROPION-Lung05 studies. The incidences of grade 1 and 2 stomatitis were reduced in TROPION-Breast01, TROPION-Lung01, and TROPION-Lung05 compared to those seen in TROPION-PanTumor01, while grade ≥3 events were consistently low (≤11%) across trials. However, a limitation to the recommendations provided in later clinical trials is that adherence was not mandatory; therefore, in some cases, poor compliance may have reduced their overall effectiveness. Studies are ongoing to explore the potential impact of stomatitis prophylaxis in more detail.

Prophylaxis and management of Dato-DXd-associated stomatitis

Current clinical recommendations for prophylaxis of Dato-DXd-associated stomatitis

The current prophylaxis guidelines for Dato-DXd-induced stomatitis, based on clinical trial experience, are summarized in **Figure 2** (Step 1). These guidelines have evolved with ongoing clinical trial experience, and the history of updates to these guidelines have been reported separately.[65] Prior to starting Dato-DXd treatment, current recommendations are for patients to initiate a prophylactic daily oral care plan with education about the importance of oral hygiene and hydration, and strongly recommend prophylactic utilization of a steroid-containing mouthwash. Oral care plan recommendations include the following: gentle brushing of teeth after meals and before bed using a soft toothbrush and bland fluoride-containing toothpaste, flossing daily unless it causes pain or bleeding, and use of a steroid-containing mouthwash daily (if available) while on treatment with Dato-DXd. For example, dexamethasone oral solution 0.1 mg/mL (10 mL, 4 times daily, swish for 1-2 minutes then spit out), or a similar mouthwash regimen using an alternative steroid advocated by institutional/local clinical practice guidelines is highly recommended; an oral nystatin suspension, or other topical antifungal agents, may be considered ≥15 minutes after the steroid-containing mouthwash. The recommendation for care in countries with limited access to steroid-containing mouthwash is to use a bland non-alcoholic and/or bicarbonate-containing mouthwash (4-6 times per day). Additionally, prophylactic cryotherapy (ice chips or ice water held in the mouth throughout the infusion) can be considered.

Rationale for the use of steroid-containing mouthwash and cryotherapy for stomatitis prophylaxis

The Multinational Association of Supportive Care in Cancer and International Society for Oral Oncology evidence-based clinical practice guidelines recommend a range of measures for the management of stomatitis.[69] A basic oral care plan, incorporating patient education and multi-agent combination oral care, is still considered best practice. A previous study investigating the use of professional oral care to prevent stomatitis in patients receiving everolimus and exemestane found that professional oral care reduced the incidence and severity of stomatitis.[70] In addition, the use of supplementary interventions such as oral cryotherapy are recommended for certain patients with stomatitis.[69]

Prior to clinical trials assessing the use of steroid-containing mouthwash in the management or prophylaxis of drug-induced stomatitis in patients with cancer, information around the use of steroid treatment for stomatitis was limited to those used to treat aphthous ulcers.[71,72] The efficacy of topical corticosteroids in treating recurrent aphthous ulcers and stomatitis is potentially due to decreased lymphocyte production and the underlying inflammatory response.[73] The SWISH study was a US-based, phase II, open-label trial that assessed the use of dexamethasone mouthwash (0.5 mg/5 mL oral solution) to prevent stomatitis in patients with HR+/HER2– BC who received everolimus and exemestane.[72] Compared with patients who received everolimus plus exemestane in the multicenter, phase III BOLERO-2 study,[74] the use of dexamethasone mouthwash reduced the proportion of any-grade and grade ≥2 stomatitis by 61% and 91%, respectively, after 8 weeks.

The impact of dexamethasone mouthwash was also evaluated for prevention of chemotherapy-induced stomatitis in a multicenter, randomized, controlled, open-label, phase II study in women receiving chemotherapy for BC.[75] The incidence of stomatitis was 55% in the control group compared with 38% in those receiving dexamethasone mouthwash. In addition, the severity of stomatitis was lower in those who used dexamethasone mouthwash, and 87% of patients adhered to the mouthwash regimen.[76] Alternative steroid mouthwash formulations have also been evaluated for the prophylaxis or treatment of stomatitis following cancer treatment and have shown reductions in the incidence and severity of stomatitis.[77,78]

In a meta-analysis evaluating the efficacy of oral cryotherapy in the prevention of chemotherapy-induced stomatitis in 14 randomized controlled trials, treatment with oral cryotherapy was associated with a significantly reduced risk of developing stomatitis of any grade (risk ratio 0.66, 95% CI, 0.58-0.75, $P < .05$).[79]

Given the supporting data available, guidelines for an oral care plan, including the recommendation to use a

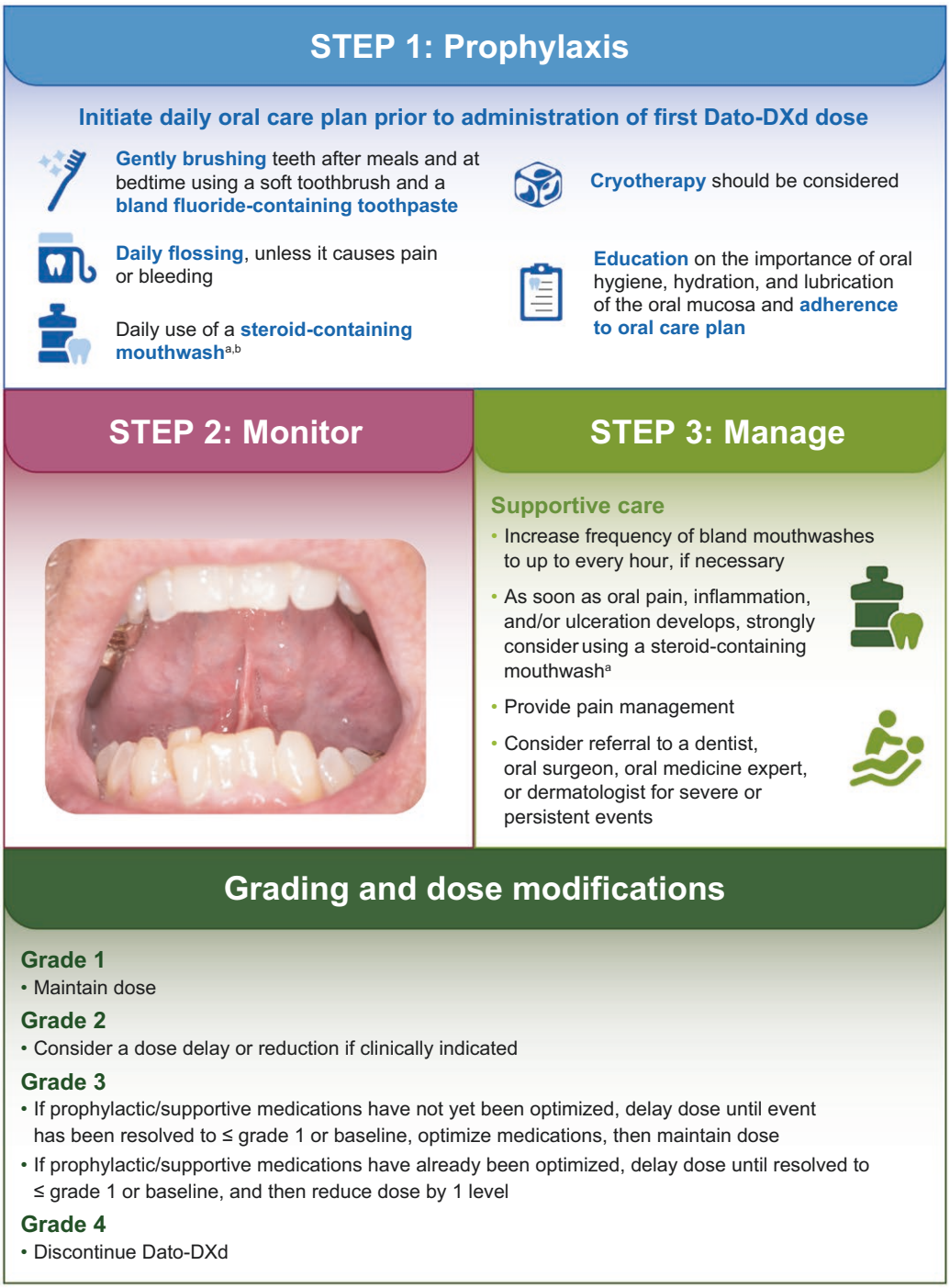

Figure 2. Stomatitis management recommendations.These guidelines reflect those that were in place in the clinical development program from December 5, 2022, and are continually being updated with the emergence of new safety data. [a]For example, Dexamethasone 0.1 mg/mL oral solution (10 mL, 4 times per day, swish for 1-2 minutes then spit out). Similar mouthwash regimens using an alternative steroid can be used as advocated by institutional/local guidelines. Oral nystatin suspension or other topical antifungal agents can be used ≤15 minutes after the steroid-containing mouthwash as advocated by institutional/local guidelines. [b]In the absence of a steroid-containing mouthwash, daily use of an inert, bland mouthwash is acceptable. For example, non-alcoholic and/or bicarbonate-containing mouthwash (4-6 times per day). [c]Doxepin 0.5%, viscous lidocaine 2%. Abbreviations: Dato-DXd, datopotamab deruxtecan. Reprinted from Cancer Treatment Reviews, Vol 125, Heist R, et al., Clinical management, monitoring, and prophylaxis of adverse events of special interest associated with datopotamab deruxtecan, pg 102720, 2024, with permission from Elsevier.

steroid-containing mouthwash (in regions where available), as well as consideration of cryotherapy during infusions, were developed and implemented during clinical trials for the management of Dato-DXd-associated stomatitis.

Current clinical recommendations for managing Dato-DXd-associated stomatitis

Current management guidelines for Dato-DXd-induced stomatitis are summarized in Figure 2 (Step 3). These include

increased use of a bland non-alcoholic and/or bicarbonate-containing mouthwash (up to every hour) and suitable pain management based on local/institutional clinical practice guidelines (eg, doxepin 0.5%, viscous lidocaine 2%). If any oral pain, inflammation, and/or ulceration is experienced, then a steroid-containing mouth rinse 4 times daily (eg, dexamethasone 0.1 mg/mL, 10.0 mL, swish for 1-2 minutes then spit out, or local alternative) should be considered if not already in use. An oral nystatin suspension or topical antifungal agent may also be considered ≥15 minutes post steroid-containing rinse. If events are severe or persist, it is recommended to refer to a dentist, oral surgeon, or dermatologist based on local practice patterns.

The guidelines for grade 1 stomatitis events are to maintain the dose of Dato-DXd and optimize the aforementioned prophylactic and supportive medications. Grade 2 guidelines involve considering a dose delay or reduction if clinically indicated and optimizing prophylactic and supportive medications as above. For grade 3 events, if prophylaxis and supportive medications have not yet been optimized, guidance is to delay the dose until resolved to grade ≤1 or baseline, optimize medications, and then maintain the dose. If prophylaxis and supportive medications have already been optimized, the guidance is to delay the dose until resolved to grade ≤1 or baseline, then reduce the dose by 1 level. Grade 4 guidelines are to discontinue the patient from the study treatment.

Conclusions

Stomatitis is a common yet manageable AE seen with many cancer therapies. As for any anticancer agent, it is important to balance patient benefit and improved outcomes against observed toxicities. Here, we have summarized stomatitis incidence in patients receiving Dato-DXd, with a focus on the TROPION-PanTumor01, TROPION-Breast01, TROPION-Lung01, and TROPION-Lung05 studies. The current risk-benefit profile seen with Dato-DXd is encouraging, supporting its continued development and future clinical use if approved by regulatory authorities.

Given the evidence for steroid-containing mouthwash use both for prophylaxis and treatment of stomatitis, specific management recommendations were developed during the first-in-human TROPION-PanTumor01 study and incorporated into subsequent trials. These provide clinicians with a multidisciplinary approach to stomatitis management that incorporates prevention, early detection, close monitoring, appropriate management, and dose modification. Importantly, following the implementation of a stringent oral care plan, overall stomatitis rates were reduced in subsequent studies.

Looking ahead, an improved mechanistic understanding and elucidation of risk factors for Dato-DXd-related stomatitis should translate to even more effective prophylactic strategies and improved clinical management for this common toxicity.

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Conflicts of interest

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Data Availability

De-identified individual participant data and applicable supporting clinical trial documents may be available on request at Vivli-Center for Global Clinical Research Data. In cases where trial data and supporting documents are provided pursuant to our company policies and procedures, Daiichi Sankyo, Inc., will continue to protect the privacy of our clinical trial patients. Details on data sharing criteria and the procedure for requesting access can be found online.

Supplementary material

Supplementary material is available at *The Oncologist* online.

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