Oral adverse events associated with targeted cancer therapies

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Over the past decade, targeted therapies have emerged as promising forms of cancer treatment and are increasingly included in chemotherapeutic regimens for an ever-growing list of human cancers. Targeted therapies are so-named due to their specific targeting of dysregulated signaling pathways in cancer cells. This enhanced discrimination between tumor and normal cells is a more promising and efficacious approach to cancer treatment than conventional cytotoxic chemotherapy. However, targeted therapies still have side effects, and some manifest in the oral cavity. Oral adverse events tend to be mild and thus may be overlooked in the context of a patient's overarching diagnosis and management. These oral lesions are often noted during an intraoral examination and identified in the context of the patient's medical history and medication list. It is imperative that the dentist be informed of the oral sequelae of targeted therapies. Many of these side effects can be successfully managed in a palliative manner with conservative therapy. This article discusses the clinical presentations and treatment of intraoral adverse events attributable to the following classes of targeted therapies: epidermal growth factor receptor inhibitors, mammalian target of rapamycin inhibitors, angiogenesis inhibitors, and selected tyrosine kinase inhibitors.

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Cancer is the second-leading cause of death in the United States. At some point in time, many dental patients will be undergoing cancer treatment. Conventional chemotherapeutic agents are cytotoxic to all replicating cells and do not target specific cancer cells; many adverse effects are attributable to this lack of discrimination. Many new cancer drugs are referred to as *targeted therapy* because they target dysregulated signaling pathways specific to a particular type of cancer to inhibit cancer cell growth or survival. As these therapies do not simply target any and all replicating cells, their effects promise to be more specific than conventional chemotherapy.[1]

Despite an improvement in their overall side effect profile, targeted therapies still manifest adverse effects, including oral and perioral lesions. This is not an entirely surprising observation, given that many signaling pathways dysregulated in human neoplasia also serve physiologic roles in normal cells.[1]

Targeted therapies come in various forms, such as monoclonal antibodies, small molecules, or protein kinase inhibitors, and most can target several pathways.[2] More specifically, targeted cancer therapies can be classified by the molecule or pathway targeted. These categories include, but are not limited to, epidermal growth factor receptor (EGFR) inhibitors; inhibitors of the mammalian target of rapamycin (mTOR); platelet-derived growth factor receptor (PDGFR) inhibitors; vascular epithelial growth factor (VEGF) and VEGF receptor (VEGFR) inhibitors; multitargeted tyrosine kinase inhibitors; human epidermal growth factor 2 (HER2) inhibitors; BRAF inhibitors; and CD20 antigen inhibitors. Targeted cancer therapy is sometimes used as monotherapy but can also be combined with conventional chemotherapy or radiation.[2,3]

It is important for dentists to be familiar with the oral, head, and neck adverse events associated with targeted cancer therapy. This review presents the most common intraoral adverse events and discusses management strategies that have been reported in the literature.

Targeted therapies and associated oral adverse events

The oral adverse events associated with targeted cancer therapies may differ substantially from adverse events resulting from conventional cytotoxic chemotherapies. Table 1 lists the oral adverse events associated with particular targeted chemotherapies.

EGFR inhibitors

EGFR inhibitors were among the first targeted therapies developed for the treatment of epithelial tumors, including breast, colorectal, kidney, oral, oropharyngeal, and non–small cell lung cancers.[3-5] EGFR inhibitors target and antagonize the

Table 1. Commonly reported oral adverse events in targeted therapy.

Targeted therapy	Common oral adverse events
EGFR inhibitors	
Cetuximab, panitumumab, erlotinib, gefitinib, lapatinib, canertinib, vandetanib	Mucositis, dysgeusia, xerostomia, geographic tongue, dysphagia, pharyngitis; cetuximab or panitumumab may potentiate radiation- or chemotherapy-induced mucositis
mTOR inhibitors	
Sirolimus, temsirolimus, everolimus, ridaforolimus	Mucosal inflammation, mTOR inhibitor–associated stomatitis (aphthouslike ulcers), dysgeusia, mouth pain, pharyngitis, dysphagia
Hedgehog signaling pathway inhibitor	
Vismodegib	Dysgeusia
BRAF inhibitors	
Dabrafenib, vemurafenib	Hyperkeratotic lesions, increased risk of squamous cell carcinoma
Angiogenesis inhibitors and multitargeted tyrosine kinase inhibitors	
Bevacizumab, axitinib, sunitinib, sorafenib, pazopanib, cabozantinib, regorafenib, afatinib dimaleate, dacomitinib	Mucosal sensitivity or pain, erythema, dysgeusia, hypogeusia, ulceration, xerostomia, paresthesia, anesthesia, MRONJ, voice changes, hoarse voice, throat pain, tooth pain (sorafenib tosylate), lichenoid reactions; sunitinib may cause palatal mucosal pigmentation

Abbreviations: EGFR, epidermal growth factor receptor; MRONJ, medication-related osteonecrosis of the jaw; mTOR, mammalian target of rapamycin.

ligand-binding domain of EGFR, blocking downstream signaling and subsequent cell growth and division.

The most common adverse events associated with EGFR inhibitors affect the skin, including the head and neck region; the reaction frequently appears as a papulopustular eruption with distribution along the trunk and head/neck.[1,3] Additional dermatologic reactions that may occur include xerosis, alopecia, paronychia, onycholysis, and photosensitivity.[3] Adverse events in the oral cavity are most commonly mucositis and less commonly dysgeusia, dysphagia, geographic tongue, pharyngitis, and xerostomia.[3-5] The oral mucositis generated by EGFR inhibitors can range in presentation from erythema to ulceration.[6]

Cetuximab, a monoclonal antibody that targets EGFR, is used in head and neck squamous cell carcinoma, often in combination with chemotherapy or radiation therapy.[1,7] Among EGFR inhibitors, cetuximab produces the greatest variety of oral adverse events.[3] Furthermore, the addition of cetuximab or panitumumab to conventional chemotherapy or radiation therapy has been found to potentiate expected toxicities, such as mucositis.[1,3,7] When cetuximab is used as stand-alone therapy, mucositis is often mild, and thus dose modification or cessation of treatment is not recommended.[7]

Pan-HER tyrosine kinase inhibitors

Overexpression of the HER family signaling pathways plays a role in tumor progression, angiogenesis, metastatic spread, and other malignant processes.[8] Since the HER family signaling pathways are normally involved in cell growth and differentiation, including those of epithelial cells, it is not surprising that the most frequent adverse event reported for pan-HER tyrosine kinase inhibitors is mucositis.[7,8] Afatinib has been approved for the use of *EGFR*-mutated non–small cell lung cancer, and dacomitinib is in the clinical trial phase, yet both have been reported to induce mucositis of varying grades.[7]

Mucositis associated with pan-HER tyrosine kinase inhibitors tends to present as erythema of the nonkeratinized mucosa with superficial ulceration and may also involve the lips.[7] Another drug, lapatinib, a dual kinase inhibitor of EGFR and HER2, can cause low-grade stomatitis as well as dysgeusia and taste alterations.[3]

mTOR inhibitors

mTOR inhibitors (such as sirolimus) have been widely used in the setting of graft-versus-host disease and solid organ transplantation and more recently are used in solid tumor oncology.[9] Temsirolimus, a kinase inhibitor, is indicated for use in renal cell carcinoma. Everolimus is indicated for advanced neuroendocrine tumors of the pancreas, gastrointestinal tract, or lung as well as HER2-negative breast cancer, renal cell carcinoma, and several other less common tumors.[10]

Aphthouslike ulcers, often called *mTOR inhibitor–associated stomatitis* (mIAS), are the most common oral adverse events

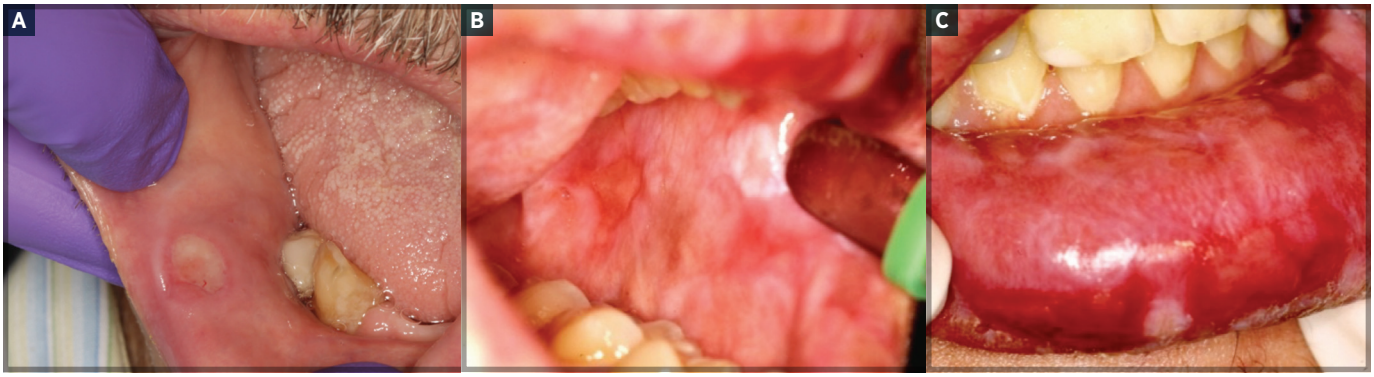

Figure. Oral lesions associated with chemotherapy. A. Mammalian target of rapamycin (mTOR) inhibitor–associated stomatitis (mIAS) associated with sirolimus. (Courtesy of Alessandro Villa, DDS, PhD, MPH, Boston, Massachusetts.) B & C. Conventional cytotoxic chemotherapy–associated mucositis. (Courtesy of Rui Amaral Mendes, DMD, PhD, Cleveland, Ohio.)

associated with mTOR inhibitors.[9,11] The term *mIAS* is preferred to *mucositis* in the setting of mTOR inhibitors, as these lesions differ in clinical presentation, course, and pathophysiology from conventional chemotherapy-associated mucositis (Figure).[9,12] The lesions typically present as multiple, discrete, ovoid, superficial, well-demarcated ulcerations that measure less than 1.0 cm and resemble minor recurrent aphthous stomatitis.[9] Less commonly, they may resemble herpetiform or major recurrent aphthous stomatitis.[7,9] The ulcers of mIAS develop acutely several days after the start of an mTOR inhibitor, are confined to the nonkeratinized mucosa, and may be disproportionately painful considering their small size.[12] The lesions heal spontaneously in less than 1 week without scarring.[9]

Reportedly, mIAS often presents during the first cycle of therapy, and the rate of occurrence and severity of mIAS appear to decrease with subsequent treatment cycles.[7] Between 33.5% and 52.9% of individuals taking mTOR inhibitors experience mIAS.[7] The oral ulcers associated with mTOR inhibitors may result in dose modification or treatment discontinuation.[9,11] In a phase I trial of deforolimus (ridaforolimus), mIAS was documented as the most frequent dose-limiting toxicity.[13]

Other oral and pharyngeal adverse events noted with mTOR inhibitors include dysgeusia, dysphagia, mucosal inflammation, mouth pain, and pharyngitis.[3,9]

Angiogenesis inhibitors and VEGFR-directed multitargeted tyrosine kinase inhibitors

Angiogenesis inhibitors prevent the formation of blood vessels necessary for the delivery of oxygen and nutrients to rapidly dividing cancer cells. Many drugs are classified as angiogenesis inhibitors, including bevacizumab, everolimus, pazopanib, sorafenib, and sunitinib. Angiogenesis inhibitors are indicated for a variety of cancers (including hepatocellular, neuroendocrine, and renal carcinoma) and are being investigated for treatment of other malignancies.

A study of patients taking VEGFR-directed, multitargeted tyrosine kinase inhibitors noted that the oral adverse events were, in descending order, mucosal sensitivity or pain; dysgeusia or hypogeusia; ulceration; xerostomia; and paresthesia or anesthesia.[14] Mucositis/stomatitis has also been reported to occur more often in individuals receiving bevacizumab or aflibercept in combination with 5-fluorouracil–based chemotherapy than in patients receiving chemotherapy alone.[15] Sorafenib tosylate is used in the treatment of hepatocellular and renal cell carcinomas and inhibits multiple targets, including VEGFR-2 and PDGFR-β signaling cascade. The most common adverse event noted with sorafenib tosylate is a characteristic hand-foot-skin reaction; however, a wide variety of oral, pharyngeal, and dental adverse events have been reported, including oral mucosal sensitivity (dysesthesia) without clinical findings, voice changes, hoarse voice, taste alterations, mucositis/stomatitis, glossodynia, throat pain, and tooth pain.[3] Hand-foot-skin reactions tend to occur in areas of mechanical trauma and clinically present as focal blisters and calluslike formations on the palms and soles of the feet.[15] One study reported that patients experienced dry mouth with the use of sunitinib malate.[3]

Delayed wound healing and the possibility of medication-related osteonecrosis of the jaw (MRONJ) are of great concern to the dental provider.[3,16] Antiangiogenic therapy is a risk factor for MRONJ.[17-19] An analysis of 3 large prospective trials (n = 3560) of bevacizumab use in advanced breast cancer populations showed a modest 0.3%-0.4% incidence of MRONJ; however, patients exposed to both bisphosphonates and bevacizumab had a 0.9%-2.4% incidence of MRONJ.[17]

Other multitargeted tyrosine kinase inhibitors

Imatinib mesylate is a tyrosine kinase inhibitor targeting PDGF, *bcr-abl* fusion gene, and c-kit signaling.[3] It is most commonly used in the treatment of chronic myeloid leukemia and gastrointestinal stromal tumors and may be used as a second-line combination treatment for malignant melanoma, epithelial ovarian cancer, and pancreatic cancer.[3]

Commonly reported oral adverse events include oral lichenoid reactions, stomatitis, and taste alterations.[3] Oral lichenoid reactions to imatinib mesylate can present as white reticular striae surrounded by erythema on the oral mucosa; the lesions may or may not be ulcerated.[3,20] In a case report, oral lichenoid lesions were reported to resolve after cessation of imatinib mesylate therapy and responded to topical steroids.[20] Additionally, diffuse palatal mucosal pigmentation may be seen in patients taking long-term imatinib therapy for chronic myeloid leukemia.[21]

BRAF inhibitors

BRAF inhibitors, such as dabrafenib and vemurafenib, are used in the treatment of *BRAF*-mutated metastatic melanoma.[7] Observed adverse reactions include hyperkeratotic lesions of the skin and oral mucosa and secondary squamous cell carcinoma (SCC).[7] Oral hyperkeratotic lesions have been described as multifocal and can be found on both the keratinized and non-keratinized mucosa, including the buccal mucosa, tongue, attached gingiva, and hard palate.[7] There has been a single case report of an SCC that developed in a hyperkeratotic lesion of the labial mucosa in a patient taking vemurafenib.[22] While the case reports of BRAF inhibitor–induced oral SCCs are rare, cutaneous SCCs (typically of the keratoacanthomatous variant) have been more frequently reported in patients taking these medications.[7,23]

There are no standardized recommendations for treating BRAF inhibitor–induced oral adverse events. Expert opinion recommends completion of routine oral examinations and biopsy of keratotic lesions.[7]

Hedgehog pathway inhibitors

Hedgehog pathway inhibitors are used to treat basal cell carcinoma.[4] Dysgeusia is a common adverse event (58%-63%) in patients taking vismodegib. In one trial, 23% of subjects reported that dysgeusia was so severe that it caused changes to their diet.[4] Prior to initiating treatment, the oncologist should inform patients about this potential adverse effect and possibly refer them to a dietitian to prevent significant weight loss.[7] Return of taste is expected after the discontinuation of the hedgehog pathway inhibitor.[4]

Anti-CD20 monoclonal antibodies

Rituximab and obinutuzumab are monoclonal antibodies targeting CD20 antigens on B cells. Anti-CD20 antibiodies have several indications, including non-Hodgkin lymphoma and chronic lymphocytic leukemia. Oral adverse events are rare, but several case reports have reported lichenoid reactions and Stevens-Johnson syndrome.[24-27] Other adverse events that may occur include reactivation of latent viral infections, such as herpes simplex virus, with risk for dissemination.[26]

Management of oral adverse events

The US Food and Drug Administration currently uses the Oral Mucositis Assessment Scale, which is graded based on size and location of erythema or ulceration.[6] Concerns regarding the inadequacy of existing mucositis grading scales in assessing mIAS have been previously mentioned by Peterson et al.[12] They noted that a mucositis scale based only on the size of a lesion may underestimate the severity in patients with mIAS, in whom the lesion may be small yet the pain level and negative impact on quality of life may be significant, requiring dose adjustment or interruption of treatment.[12] Several suggestions have been made for creating class-specific grading scales that characterize specific oral adverse events and assess quality of life.[6,12,28] One such scale for mIAS was proposed by Boers-Doets & Lalla.[28] The Skin Toxicity Study Group of the Multinational Association of Supportive Care in Cancer has proposed and created a dermatologic adverse event scale for EGFR inhibitors that grades oral mucositis based on lesion presentation, pain, and the resulting limitations on oral intake.[6]

Occasionally, terms such as *mucositis* and *stomatitis* have been used inconsistently for oral lesions associated with targeted cancer therapies.[9] It is recommended that the term *stomatitis* be used for any inflammatory condition of the oral tissue that is not associated with chemotherapy or ionizing radiation and the term *mucositis* be used in the setting of chemotherapy- or radiation therapy–induced damage of the mucosa.[29] In addition, it is preferable to refer to mTOR inhibitor–associated lesions as *mIAS* rather than *mucositis*, since the lesions have been found to be distinct from cytotoxic therapy–related mucositis.[9,12,29]

Current understanding of the pathophysiology of oral adverse events from targeted cancer therapy is limited, yet this knowledge is essential to determining the best management strategies. One area of future research will include evidence-based treatment for oral adverse events secondary to targeted cancer therapies. For now, clinicians should use their best judgement and understanding of the potential underlying mechanism when choosing therapies to treat oral complications. A summary of management strategies is provided in Table 2.

Expert-based recommendations have been provided for management of mucositis/stomatitis caused by targeted therapies, including EGFR and mTOR inhibitors.[7,29] Preventive measures are key and similar to those recommended before the start of conventional head and neck radiation or chemotherapy, including a comprehensive oral examination and elimination of sources of infection and trauma.[7] One phase 2 prevention trial (known as the *SWISH trial*) reported that use of a prophylactic dexamethasone oral rinse helped to reduce the incidence of mIAS in patients receiving everolimus/exemestane for metastatic breast cancer.[7] During treatment with agents that may cause mIAS, mucositis, stomatitis, or lichenoid reactions, patients should avoid commonly irritating agents such as alcohol- or peroxide-based mouthwashes, spicy foods, and sharp foods that may traumatize the mucosa. Additionally, good oral hygiene should be emphasized, as it may help to prevent or decrease the severity of mucositis.[7]

Diffuse oral mucositis associated with EGFR inhibitors, mIAS, and symptomatic lichenoid reactions can be treated with topical steroid rinses such as 0.05 mg/5 mL–dexamethasone solution. Localized lesions can be treated with topical steroid gels such as 0.05% clobetasol propionate. Additionally, topical antifungal therapy may be administered concomitantly with topical steroids for prevention of an opportunistic candidal infection. Concomitant use of topical steroids and antifungals is recommended on a case-by-case basis, especially if patients have additional risk factors, such as hyposalivation.[7]

For mild to moderate oral pain, local anesthetic mouthwashes can be used. Patients can be instructed to "swish for 1 minute and spit" with 5 mL of 2% lidocaine solution (not to exceed 4.5 mg/kg or a total of 300 mg) or formulations of "magic" mouthwash that may contain both a topical steroid and local anesthetic. Systemic analgesics (ie, opioids) should be reserved for more severe cases, and such prescriptions should be considered in consultation with the treating oncologist.

Specific recommendations for treatment of mIAS (based on the National Cancer Institute's mucositis grading scale) were

Table 2. Management of oral adverse events associated with targeted therapies.

Oral adverse event	Management strategies

Mucositis/ stomatitis (including mIAS)	• Eliminate sources of trauma and infection.
	• Maintain oral hygiene.
	• Prescribe topical steroids gels or rinses:
	  ○ 0.05 mg/5 mL dexamethasone solution.
	  ○ 0.05% clobetasol propionate.
	• Prescribe topical anesthetics (2% viscous lidocaine solution).
	• Prescribe systemic analgesics.

Lichenoid reaction	• Apply topical steroid gels or rinses.
Xerostomia	• Maintain oral hygiene. • Apply topical fluoride treatments. • Prescribe artificial saliva substitutes.
MRONJ	• Counsel patients about MRONJ risk prior to procedures. • Minimize trauma during procedures. • Prescribe antiseptic mouthrinses. • Prescribe systemic antibiotics. • Prescribe systemic analgesics. • Perform local debridement. • Severe cases may require surgical resection and reconstruction.
Dysgeusia	• Consider consultation with dietitian. • Taste usually returns after discontinuation of medication.
Oral hyperkeratotic lesion	• Perform routine oral examination. • Biopsy keratotic lesions.

Mucosal sensitivity or pain in the absence of mucosal lesions	• Consider prescribing palliative rinses:
	  ○ "Magic" mouthwash (solution of antihistamine, topical local anesthetic, and antacid)[a], swish and spit.
	  ○ Clonazepam solution (0.1 mg/mL), swish and spit.

Abbreviations: mIAS, mammalian target of rapamycin (mTOR) inhibitor–associated stomatitis; MRONJ, medication-related osteonecrosis of the jaw.

[a]Magic mouthwash usually contains at least 3 ingredients and can be tailored to the needs of the patient's condition; other compounds may include a corticosteroid, an antibiotic, or an antifungal agent.

outlined by Vigarios et al.[7,30] Usually no treatment is required for grade 1 mIAS, while clinicians may consider topical steroids or intralesional steroid injections (eg, triamcinolone) for grade 2 mIAS. In the case of grade 3 mIAS, systemic steroids (eg, 1 mg/kg of prednisone or an equivalent) have been suggested. A grade 3 reaction occasionally may require mTOR inhibitor dosage adjustment in consultation with the treating oncologist.[7] For severe cases of mIAS, low-level laser therapy—when used with topical steroids—is thought to provide some pain relief and possibly promote healing, but additional data are needed.[7]

For dysgeusia, no current standard treatment exists; however, the elimination of other contributing factors, such as smoking, poor oral hygiene, and sources of infection, have been recommended.[7] Research on zinc supplementation as a treatment option for dysgeusia in cancer patients has yielded mixed results.[4,31,32] Patients taking vismodegib may experience significant changes in taste. This expected adverse event should be discussed with the patient prior to the initiation of therapy, and consultation with a dietitian may considered to prevent significant weight loss.[7]

For patients experiencing medication-induced xerostomia, vigilant oral hygiene and dietary recommendations to reduce cariogenic habits are recommended for prevention of caries. Over-the-counter artificial saliva substitutes are available for temporary relief of symptoms. Topical fluoride treatment should be prescribed for patients at high risk of developing caries due to hyposalivation.

Since antiangiogenic agents are a risk factor for MRONJ, these patients should be treated with the same precautions as those who are receiving bisphosphonate treatment, including an oral examination, education about MRONJ, and dental treatment, if needed, prior to initiation of therapy.[7] Management of MRONJ relies on expert opinion, because no standardized treatment recommendations exist. Treatments at various stages may include antiseptic mouthrinses (eg, chlorhexidine), systemic antibiotics, pain medications, local debridement, and, in severe

cases, surgical resection and reconstruction.[7] Specialists in oral medicine as well as oral and maxillofacial surgeons can be consulted if a practitioner is not comfortable with the diagnosis or treatment options.

Conclusion

Oral adverse events associated with targeted cancer therapies are thought to be mild, but there is growing evidence of their negative impact on a patient's quality of life. Reactions to drugs such as mTOR inhibitors may demonstrate a severity level that interferes with the cancer treatment. It is necessary to characterize the oral adverse events seen in patients taking targeted cancer therapies, as the effects may be significantly different from adverse events arising from conventional cytotoxic chemotherapies. These adverse events should be distinguished from each other, such as in a case of mucositis and mIAS. A comprehensive oral and dental examination is often recommended for patients prior to the initiation of any oncologic treatment, and patients may require further evaluation by a specialist in oral medicine if oral adverse events are noted during treatment.

Increasing awareness among general practitioners in recognizing, grading, and accurately documenting oral adverse events associated with targeted cancer therapies will help increase the understanding of their incidence, pathophysiology, and impact on patients and ultimately will improve patient care. A basic understanding of management strategies will also allow dentists to provide comprehensive care to their patients.

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