



Review

Oral complications of targeted cancer therapies: A narrative literature review

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SUMMARY

The aim of the present study was to investigate the available literature regarding the oral side effects or adverse events associated with targeted cancer therapy. Common oral toxicities include the terms mucositis, stomatitis, dysphagia, xerostomia, pharyngitis, and taste alterations. Aims of treatment included molecules and pathways involved in carcinogenesis reported in the literature were EGFR, VEGF, mTOR, mAbs, TKIs, and multi-kinase inhibitors. Common targeted therapies used in clinical practice or under-investigation included cetuximab, panitumumab, erlotinib, sorafenib, sunitinib malate, imatinib mesylate, bevacizumab, trastuzumab, lapatinib, and mTORs. One hundred and forty-three articles were considered relevant and included in this review. The majority of studies did not specifically address oral toxicities or include an oral clinical exam, which may lead to underreported and under-investigated oral toxicities. Further investigation is necessary to determine if the initial impression that targeted therapy produces milder oral toxicities than conventional cancer treatment is accurate.

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Abbreviations: EGFR(1), epidermal growth factor receptor (inhibitors); TKIs, tyrosine kinase inhibitors; mAbs, monoclonal antibodies; RT, radiotherapy; HNSCC, head and neck squamous cell carcinoma; HNC, head and neck cancer; CRC, colorectal cancer; RCC, renal cell carcinoma; NSCLC, non-small cell lung cancer; GIST, gastrointestinal stromal tumors; MMPs, matrix metalloproteinases; VEGF, vascular endothelial growth factor; IRI, irinotecan; CET, cetuximab; mTOR, mammalian target of rapamycin; AEs, adverse events.

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Introduction

Conventional cancer chemotherapeutics carry a heavy toxicity burden. Oral side effects include mucositis, hyposalivation/xerostomia, dysphagia, pharyngitis, infection, discomfort, and taste alterations. Mucositis has been reported to affect many patients receiving high dose conventional chemotherapy.¹ The common clinical presentation of cytotoxic chemotherapy mucositis includes painful inflammation, erythema, and ulcerations of the oral mucosa and digestive tract. As cancer treatment protocols evolve, emphasis is placed on developing therapies specific to neoplastic

tissue to eradicate or control malignancies while maintaining minimal toxicities affecting non-neoplastic tissue. Molecularly targeted cancer therapies have been developed that block the growth and survival of cancer cells by interfering with specific molecules and pathways involved in carcinogenesis. These treatments include anti-tumor monoclonal antibodies (mAbs), small molecules, signal transduction receptor inhibitors, and cancer vaccines. Targeted cancer therapies are indicated in the first and second line treatment of a variety of solid tumors of varying stages including: lung, breast, kidney, colorectal, head and neck, and hematopoietic malignancies.^{2–7} Published studies investigating the safety of targeted therapies have indicated that fewer oral complications are experienced with these agents. Reports to date focus on acute complications with limited information published on chronic complications and survivorship issues.

The side effects from targeted cancer therapies are considered to be mild to moderate, and in most cases substantially less than conventional cancer chemotherapy.⁸ If targeted therapies are combined with conventional cancer therapies previously identified toxicities may be increased in severity or duration. Additionally, adverse events that were unexpected in the preclinical setting may occur.⁹ Oral manifestations of targeted therapies may be independent or additive to oral complications in radiation and conventional chemotherapy. Oral mucositis may present with broad areas of erythema, aphthous-like stomatitis, or compound mucositis associated with conventional therapy.¹⁰ While some molecules have overlapping mechanisms of action and may affect different parts of the same pathway, thus having similar cellular effects, their side effect profiles may differ. Other molecules target multiple pathways and as such have unique molecular signaling effects and side effects. The purpose of this review is to illustrate from the available published literature the nature, variety, and frequency of oral complications associated with the emergence and use of targeted cancer therapies.

Methods

A literature review was completed on MedLine/OVID using the following search terms: monoclonal antibodies, small molecules, stomatitis, and mucositis. A search for “oral” and “targeted anti-cancer therapy” yielded 146 results. Specific drug name searches combined with “adverse events” including “cetuximab, Erbitux” yielded 159 results, “panitumumab, Vectibix” 19 “erlotinib, Tarceva” 175, “sorafenib, Nexavar” 41, “sunitinib malate, Sutent” 13 “imatinib mesylate, Gleevec” 123, “bevacizumab, Avastin” 131, “trastuzumab, Herceptin,” 15, “lapatinib, Tykerb” 31, and “mTOR”. Of these articles 142 were considered relevant and included in this review. Relevant articles included phase I, II, and III studies and case reports that recorded oral complications.

Epidermal growth factor receptor inhibitors (EGFRI)

EGF is important in cellular proliferation and survival. Since EGFR is over-expressed in a variety of solid tumors, its inhibition and regulation has been investigated in the treatment of these neoplasms.¹¹ EGFRI therapy is used in the treatment of epithelial cancers including breast, colorectal, oropharyngeal, non-small cell lung cancer, and renal cell carcinoma.^{12–16}

The most frequent adverse events associated with all EGFRI are cutaneous reactions, particularly dermatologic rash. The rash presents as a papulopustular reaction distributed along the trunk and head and neck and is considered a class reaction. The rash generally resolves without scarring after discontinuation of treatment but may leave hyperpigmentation.^{17,18} Proposed mechanism involves follicular occlusion by keratinocytes leading to an inflam-

matory response. Management includes oral or topical corticosteroids and antibiotics with drug withdrawal in severe cases. The reaction has been reported to occur as late as five months into treatment.¹⁹ Nail changes, xerosis, eyelash abnormalities, and alopecia are other frequently reported toxicities.¹⁷

Cetuximab (Erbitux, ImClone) is a recombinant human/murine mAbs directed toward EGFR and is FDA approved in the United States, Canada, EU, and multiple other countries for treatment of head and neck squamous cell carcinoma (HNSCC) and colorectal cancer (CRC). Cetuximab binds to and competitively inhibits the EGFR that is frequently over expressed in the extracellular domain of cancer cells. This prevents phosphorylation by kinase activation, thereby inhibiting cell growth and promoting apoptosis by decreasing matrix metalloproteinases (MMPS) and VEGF.²⁰ VEGF is a hypoxia-induced growth factor that promotes neovascularization, endothelial maturation, chemotaxis and vasodilatation. Rapidly dividing malignant cells induce VEGF to support the vascular requirements of solid tumors.

Oral toxicities reported include mucositis, xerostomia, dysphagia, and pharyngitis (Figs. 1 and 2). Dysphagia was reported in one study of nasopharyngeal cancer in 5% of patients treated with cetuximab.²¹ Cetuximab associated mucositis appears to present with a general erythema and sensitivity that may be less ulcerative of nonkeratinized mucosa than that typically seen with cytotoxic chemotherapy and radiation therapy.²² Combination therapy with cytotoxic agents may lead to combined presentation of more classical ulcerative mucositis with broad involvement of the oral mucosa including the labial mucosa. In a trial of mCRC comparing irinotecan (IRI) plus cetuximab (CET) to CET alone, fewer patients



Figure 1 EGFRi mucositis.



Figure 2 EGFRi mucositis.

Table 1
Prevalence of oral toxicities in RT and RT plus cetuximab.⁸

	RT alone	RT plus cetuximab
Mucositis	94% Grade 3–5 52%	93% Grade 3–5 56%
Taste Alterations	29% Grade 3–5 0%	28% Grade 3–5 0%
Xerostomia	72% Grade 3–5 5%	71% Grade 3–5 3%
Pharyngitis	26% Grade 3–5 3%	19% Grade 3–5 4%
Voice Alteration	22% Grade 3–5 0%	19% Grade 3–5 2%
Oral Candidiasis	22% Grade 3–5 0%	20% Grade 3–5 0%

experienced grade 3 or 4 stomatitis in the CET alone group with 1 patient versus 5 for CET plus IRI, but evaluation of xerostomia, dysphagia, and pharyngitis were not mentioned in the report.²³

More than 90% of all HNC are squamous cell carcinomas.²⁴ In recurrent or metastatic HNSCC, cetuximab may be used alone or in combination with RT.²⁵ Adverse events from RT are extensively documented and can have a severe negative effects on quality of life.²⁶ Concurrent administration of cetuximab and RT or previous RT makes the etiology of oral side effects difficult to distinguish. A 2006 phase III trial involving 400 patients compared patients treated with RT alone and RT plus cetuximab. The reported grade 3 and above adverse events did not differ significantly between these two groups, while the RT plus cetuximab group had significant prolonged disease-free survival (Table 1).⁸

However, a retrospective review article with meta-analysis reported cetuximab plus RT to have a higher reported prevalence of mucositis compared to RT with cytotoxic therapy or RT alone.²⁷ A small study of 13 patients reported enhanced toxicity with cetuximab in HNC with a high number (31%) requiring a treatment break due to skin toxicity and/or mucositis.²⁸ The majority of the phase I–III studies do not mention oral adverse events associated with cetuximab, which may be due to under-reporting or to less severe or frequent adverse events compared to other EGFR tyrosine or multi-kinase inhibitors, and suggest a need for further evaluation.^{29–37}

Panitumumab (Vectibix, Amgen) is a fully humanized IgG2 k mAb EGFR. In combination with oxaliplatin-based chemotherapy, it is approved for first line treatment of wild-type KRAS expressing CRC that exhibits disease progression after administration of fluoropyrimidine, oxaliplatin, or irinotecan therapy in the US and EU.^{38,39} Fully-human mAbs were developed for their potential to decrease immunogenicity, making the administration more tolerable than chimeric monoclonal antibodies. Oral side effects are generally reported as grade 1–2.^{38,39} Several safety studies reported stomatitis as “mild to moderate”,⁴⁰ and present in 7%,⁴¹ 18%,⁴² and 23%.⁴³ Mucosal inflammation was less frequently reported with 6% below grade 3 and 1% of patients above grade 3.⁴¹

Erlotinib (Tarceva, Genentech) and gefitinib (Iressa, Astra Zenica) are small molecule TKIs of EGFR, regulating cellular pathways by reversibly inhibiting ATP binding in tumor cells.^{44–46} They have been investigated as second-line or adjunctive treatment for NSCLC,^{47,49} HNSCC,⁴⁶ and showed a modest increase in survival in a small number of pancreatic cancer patients.⁴⁸ Erlotinib is approved by the FDA and EMA for maintenance therapy for NSCLC. TKIs have similar side effect profiles to monoclonal antibody EGFR inhibitors (cetuximab and panitumumab) as they share a common pathway in their mechanism of action, with skin rash being reported in most patients. Reported non-dermatological side effects of TKIs that are not common in mAb inhibitors include interstitial lung disease, diarrhea, and hepatic function complications.⁴⁹ A 2005 study of previously treated NSCLC patients found 19% of

Table 2
Prevalence of reported oral toxicities with mTORs.

	Everolimus	Temsirolimus	Placebo	Deforolimus
Stomatitis	31% ⁶¹ 30% ⁶² 36.5%, grade 3–4 2.2% ⁶³ 40% ⁵⁸	20% ⁶⁴	6.1% ⁶³ 8% ⁵⁸	
Mucositis		19% ⁶⁴		
Aphthous		4% ⁶⁴		
Ulcerations		3% ⁶⁴		63% grade 1–2 ⁵⁹ 16% grade 3–4 ⁵⁹
Mucosal inflammation	14% 1% grade 3 ⁵⁸		2% ⁵⁸	

* Include oral pain, mucosal inflammation and stomatitis.

patients experienced grade 2 and below mucositis, 1% above grade 3, and 1% of patients required treatment discontinuation or interruption due to stomatitis.⁴⁷ Another study did report mucositis attributable to erlotinib, but further information on oral toxicities is not reported.⁵⁰ Studies evaluating the safety and efficacy of erlotinib and gefitinib do not report oral side effects either due to under-reporting, or few or mild adverse events.^{51–56}

mTORs are inhibitors of the mammalian target of rapamycin and are used in the treatment of RCC and for their immunosuppressive effects to prevent graft versus host disease following transplantation. Rapamycin (sirolimus) is a macrocyclic lactone, produced by a soil bacterium, which inhibits progression of IL-2 stimulated T-cells from the T1 to the S phase. Rapamycin inhibits angiogenesis and endothelial cell proliferation and decreases VEGF.⁵⁷ Because the mechanism of action is interference with intracellular pathways regulating growth, proliferation, and angiogenesis, mTOR inhibitors may be effective in situations where VEGF antibodies or inhibitors have previously failed. A large multicenter randomized, double-blind, placebo-controlled phase III trial of patients treated with everolimus for relapsed mRCC after treatment with VEGF targeted therapy reported the most common events as stomatitis, rash, fatigue or asthenia, and diarrhea. Ulceration of mucosal surfaces involved includes non-keratinized oral tissues such as labial and buccal mucosa and the ventral surface of the tongue and floor of the mouth. The term stomatitis is preferred over mucositis to assist in distinguishing mTOR associated mucosal ulceration from mucositis seen in radiotherapy and cytotoxic chemotherapy. Stomatitis seen with mTOR inhibitors presents with discrete aphthous-like ulcerations in contrast to ulceration associated with radiotherapy and chemotherapy. Stomatitis was reported in 40% of all patients, with 3% experiencing grade 3 reactions. Mucosal inflammation of grade 2 or less was reported in 14% of patients, while 1% of patients reported grade 3 events.⁵⁸ A phase I trial of the mTOR ridaforolimus reported mouth sores, including mouth pain, mucosal inflammation, and stomatitis in 78% of patients. Ulcers were more frequent at doses above 12.5 mg/d. The patients were treated symptomatically and usually achieved complete recovery. These reactions appear less frequent and severe at subsequent administration. A high percentage of patients (66%) reported dermatologic events.⁵⁹ A phase I study of a major metabolite of sirolimus reported 21% of patients with taste perversions, 71% with grade 2 and below mucositis, reported as 1–2 aphthous-like lesions in the mouth and tongue, and only 4% with grade 3 mucositis. These oral ulcers were dose dependent and resolved despite continued drug therapy⁶⁰ (Table 2).^{58,59,61–64}

Imatinib mesylate (Gleevec/Gilvec, Novartis) is a TKI that selectively targets platelet derived growth factor- receptor (PDGF-R),

Table 3
Prevalence of oral toxicities with imatinib mesylate.

	<Grade 2
Stomatitis	10.6% ⁷⁶
Dysgeusia	39% ^{*78}
Taste alterations	12.8% ⁷⁷

* In combination with docetaxel.

c-kit, and the abl-bcr fusion gene. Imatinib mesylate is used in the treatment of abl-bcr + chronic myeloid leukemia and gastrointestinal stromal tumors and also has been investigated as a second-line or combination treatment for malignant melanoma and epithelial ovarian and pancreatic cancers.^{19,65,66}

The current literature consists primarily of drug trials and safety studies, phase I–III trials, and case reports. Five case reports were identified, involving oral lichenoid reactions, presenting as erythematous reticular plaques on oral mucosa with or without ulceration.^{67,68} All reported drug withdrawal and/or treatment with oral or topical corticosteroids led to a complete remission of the oral lesions.^{67,69–71} Other drug trials reported no oral side effects and few reported stomatitis and taste alterations^{65,66,72–75} (Table 3).^{76–78}

Sorafenib tosylate (Nexavar, Bayer and Onyx) is a small molecule Raf multi-kinase inhibitor that is used in the treatment of RCC and unresectable hepatocellular carcinoma, and is has been investigated in the treatment of a number of other tumors including thyroid carcinoma, breast, lung, HNC and melanoma.^{79–81} Sorafenib inhibits VEGF, PDGF, and TK.⁸² Current investigations reveal that 60% of patients report “hand-foot-skin reaction”, characterized by plantar hyperkeratosis, paresthesia, burning, and cutaneous lesions.⁸⁰ Oral side effects include voice changes/hoarse voice, taste alterations, mucositis/stomatitis, tongue pain, throat pain, tooth pain, and one study reported mild gum bleeding. The side effects are generally reported as grade 2 or below with few grade 3 events, including mucositis/stomatitis and tongue/tooth pain (Table 4).^{21,81–96}

Sunitinib malate (Sutent, Pfizer) is an orally administered TKI of VEGF and PDGF that is approved for RCC and GIST after imatinib failure or intolerance. The most commonly reported AEs include diarrhea, fatigue, nausea, stomatitis, and hand-foot syndrome.^{97,98} Grade 1 or 2 stomatitis has been reported in 17–20%⁹⁹ and 25%⁹⁸; grade 3 was reported in 1%⁹⁸ and 3% of patients.⁹⁹ Dry mouth is reported in 11% of patients in one study.⁹⁸ A Japanese study reported

Table 4
Prevalence of oral toxicities with sorafenib.

Reported side effect	% > Grade 2	
Xerostomia	5.2% ²¹	
	6% ⁸²	
	23% ⁸⁵	
Mucositis/stomatitis	11% ⁸⁶	2% ^{91,92}
	11.3% ⁸⁷	3% ⁹³
	12.9% ²¹	9% ⁹⁴
	15% ⁸⁸	
	19% ⁹⁶	
	21% ⁸⁵	
	21.6% ⁸¹	
	35% ⁸³	
	35% ⁹⁶	
	35.7% ⁸⁹	
38% ⁹⁰		
Voice changes/hoarse voice	6–11% ⁸²	
	6.2% ⁸⁷	
Taste alterations	12.2% ⁹⁵	
	22% ⁸²	
	25% ²¹	
	39% ⁸⁴	
Throat pain	10.7% ⁸⁹	
Tongue or tooth pain	11–14% ⁸²	5% ⁸²

grade 1, 2, and 3 stomatitis in 32%, 15% and 4%, respectively. Grade 1 and 2 dysgeusia was reported by 32% and 16% of patients. In study arm of previously treated patients, stomatitis of grade 1, 2, and 3 was reported in 23%, 12% and 4%, and dysgeusia of grade 1 and 2 was reported in 46% and 8% of patients, respectively.¹⁰⁰

Bevacizumab (Avastin, Genentech) is an anti-VEGF IgG mAbs that inhibits angiogenesis, indirectly preventing tumor growth by neutralizing the activity of the VEGF.¹⁰¹ Adverse events are hematological toxicities, neutropenia, hemorrhage, with hypertension being most frequently reported.^{102–106} Bevacizumab is also used to treat macular age-related degeneration via intra-vitreous injection.^{107,108} It is currently under investigation and used in the treatment of glioblastoma,¹⁰⁹ mRCC,¹¹⁰ NSCLC,¹¹¹ and mCRC^{110,103,106} in both the U.S. and E.C. Wound healing complications are possible due to bevacizumab's anti-angiogenic properties and may have a possible effect on jaw wound healing after dental surgery. There is a current recommendation to avoid major surgery within 28 days of administration (FDA), but the implications for oral surgery are yet to be determined. Co-administration with IV bisphosphonates has been identified as a possible contributor to development of bisphosphonate related osteonecrosis of the jaw.^{112–114} Although the impact of antiangiogenics on development of osteonecrosis of the jaw is unknown, small case reports have reported a significant increase in ONJ in patients concurrently receiving antiangiogenic agents and IV bisphosphonates.¹¹⁵ One small pediatric study reported grade 1 mucositis in greater than 10% of patients.¹¹¹ Gingival bleeding has been reported, but is rare.^{116,117} Additional oral side effects are generally not reported.^{51,52,118–122}

Trastuzumab (Herceptin, Genentech) is a recombinant, human IgG mAb that binds to HER2 and inhibits tumor cell proliferation. HER-2 has been estimated to be over expressed in 30% of BC.¹²³ Immunohistochemistry to quantify the expression of HER2 from 0 to 3+ and FISH positivity has been shown to predict the tumor's susceptibility to trastuzumab. The need for additional histological testing may delay time to treatment initiation and increases the total cost of treatment.

A retrospective study of 48 patients reported the most common side effects as fever and chills, infusion reactions, diarrhea, headache and nausea. These events are usually more severe during the first administration and may taper off with subsequent treatments.^{122,123} Side effects not associated with dose limiting toxicity, such as nerve damage, myelosuppression, and mucositis, are typically experienced with conventional chemotherapy and can be managed with discontinuation of therapy or supportive care.

In a study comparing administration of docetaxel and vinorelbine with or without trastuzumab did not report an increase in stomatitis.¹²⁴ A Swedish study reported similar toxicity profile.¹²⁵

Lapatinib (Tykerb, GlaxoSmithKline) is a tyrosine kinase inhibitor of EGFR and HER2 inhibiting ATP binding to signal receptor proteins, approved in 2007 in combination with capecitabine (Xeloda, Genentech) for patients with advanced BC. A study by Harrington found that radiation mucositis and dermatitis was not increased in HNSCC patients treated with chemoradiation compared to published reports of radiation adverse events.¹²⁶ Other studies reported stomatitis grade 2 in 21%¹²⁷ and grade 1 in 13%.^{128,129} Taste alterations/dysgeusia were reported as grade 2 in 10%,¹²⁹ one out of twelve patients reported taste changes¹³⁰ and two patients reported chalky taste.¹³¹ A number of studies did not report oral side effects.^{132–140}

Discussion

The difficulty with determining the prevalence of oral side effects from drug safety studies lies in the limited studies and poten-

tial unreported or uninvestigated symptoms. Many phase I–III studies limit oral symptom investigation to “mucositis/stomatitis”, which does not include other potential oral complications such as xerostomia, dysgeusia, odynophagia, and pharyngitis. Most studies, including phase III trials utilize the Common Toxicity Criteria Adverse Events reporting, which often relies upon spontaneous patient report, leading to probable under-reporting. Relying on patient reports of serious adverse events (SAEs) in oncology leads to underreporting of SAE in clinical oncology trials. In one study 2.4 times the number of SAEs was recorded using structured case report forms and causality assessments were 3.5 times more common in primary data sources than IRB SAE descriptions (93% versus 26%, $p < 0.05$).¹⁴¹ This has been shown in assessment of oral mucositis in oncology, a structured patient evaluation form is not utilized including oral AEs and lack of specific oral clinical exam can lead to misdiagnosis or under diagnosis of oral lesions and complications.^{142,143}

We are not aware of any reviews to date that include comprehensive data on the oral cavity side effects of targeted therapy. Through our review of the current literature, it is apparent that the data collected on oral cavity side effects of targeted therapy is limited in quality and quantity.

Although oral mucosal manifestations that limit therapy have not been associated with use of targeted therapies alone, mucosal damage may impact quality of life, oral intake, and may be painful, particularly when multi-modality therapy is employed. Oral mucositis compounded with gastrointestinal upset, dysphagia, altered taste, and dry mouth can significantly limit a patient’s intake of solids and liquids and complicate optimal nutrition and quality of life. For a good response to treatment, side effect profiles must be minimized in order to maintain an appropriate risk/benefit ratio. It is important to categorize the entire spectrum of drug related toxicities, including oropharyngeal toxicities, in order to convey an accurate message to patients regarding the nature of their treatment and to develop adjunctive therapy to prevent or minimize these toxicities. While prospective studies assessing oral complications of targeted therapies are lacking, initial studies have indicated oral complications may include oral mucosal inflammation and ulceration, dry mouth, and taste change, which may have impact upon quality of life and nutritional and caloric intake. With anticipated increasing use of targeted therapies as single agents and combined with cytotoxic chemotherapy and radiation therapy may cause enhanced and additional oral symptoms. As current reports are primarily based upon spontaneous report of symptoms the nature, frequency and severity of the oral effects may not be clearly understood. In addition, the mechanisms involved that may lead to oral complications may provide insight into prevention and therapeutic strategies to improve patient care. Prospective studies with patient reported oral symptoms and function using validated instruments and specific clinical evaluation of the oral cavity and oral function are warranted.

Conflict of interest

The authors deny any actual or potential conflict of interest including any financial, personal, or other relationships with other people or organizations within that that could inappropriately influence or bias their work.

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