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REVIEW

MASCC/ISOO Clinical Practice Statement: Management of oral complications of targeted therapy

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Abstract

Purpose A MASCC/ISOO Clinical Practice Statement (CPS) is aimed at generating a concise tool for clinicians that concentrates practical information needed for the management of oral complications of cancer patients. This CPS is focused on the management of oral complications of targeted therapy.

Methods This CPS was developed based on critical evaluation of the literature followed by a structured discussion of a group of leading experts, members of the Oral Care Study Group of MASCC/ISOO. Targeted agents were identified using the National Cancer Institute's list of Food and Drug Administration approved targeted therapy drugs. The information is presented in the form of succinct bullets and tables to generate a short manual about the best standard of care.

Results Oral toxicities secondary to targeted therapy include various mucosal conditions, gingival conditions, jawbone disease, dysesthesia, taste change, and dry mouth. For the purpose of this CPS, we focused on oral mucosal conditions, gingival conditions, taste change, and dysesthesia. The treatment of oral toxicities depends on the symptom severity. Topical steroids and immunomodulators are often used as first-line therapy for oral mucosal toxicities. Treatment approaches for oral dysesthesia and taste change primarily revolve around symptoms management. Typically, therapy protocols align with the therapeutic algorithms employed for other neuropathic pain conditions, incorporating topical pharmacological interventions to achieve relief. Other oral toxicity requires a more specific approach.

Conclusion Management of oral toxicities from targeted molecular therapies is designed to alleviate patient discomfort and optimize treatment outcomes. Collaboration between medical and oral health professionals is necessary for best management practices.

Keywords Cancer · Oral complications · Targeted therapy

Introduction

Targeted molecular therapies have changed the treatment landscape and improved the prognosis of many cancer patients. Recent literature has shown that several targeted agents are associated with oral toxicities to the mucosa, jaw bones, and salivary glands as well as other oral tissues [1, 2]. The management strategies for these oral complications are not well established.

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The Oral Care Study Group (OCSG) of the Multinational Association of Supportive Cancer MASCC/International Society of Oral Oncology (ISOO) developed a Clinical Practice Statement (CPS) to provide a general overview of the management of oral complications secondary to targeted therapy.

Types of oral manifestations/adverse effects

- Aphthous-like lesions (e.g., Mammalian Target of Rapamycin (mTOR) Inhibitors and fibroblast growth factor receptor inhibitor) [3, 4].
- Oral mucositis or stomatitis (anti-epidermal growth factor receptor (anti-EGFR) monoclonal antibodies (e.g., panitumumab), vascular endothelial growth factor receptor (VEGFR) inhibitors (e.g., sorafenib, sunitinib, pazopanib, and cabozantinib))[5]. As the early literature about targeted therapy combined various types of ulcerative conditions, the terms oral mucositis and stomatitis are used in this CPS to refer to non-specific ulceration or erosion.
- Oral dysesthesia (e.g. VEGFR-2 inhibitors, such as sorafenib, sunitinib, regorafenib, cabozantinib) [6, 7]. Refers to a burning sensation or generalized hypersensitivity in the absence of abnormal findings.
- Dysgeusia (e.g., bevacizumab)[8].
- Dry mouth/xerostomia (e.g., cabozantinib, regorafenib, sunitinib)[9]
- Lichenoid lesions (e.g., rituximab, imatinib)[10].
- Hyperkeratotic lesions and possible increased risk of squamous cell carcinoma (SCC) (e.g., dabrafenib and vemurafenib) [11, 12].
- Geographic tongue either developing de novo or worsening of pre-existing geographic tongue (e.g., bevacizumab, sorafenib, sunitinib) [13]
- Gingival overgrowth (vemurafenib) [14].
- Increased gingival bleeding (e.g., bevacizumab, sunitinib) [15]
- Delayed healing (e.g., bevacizumab) [16].
- Medication-related osteonecrosis of the jaw (e.g., denosumab) [17].
- Additional targeted therapy toxicities were reported; however, other than diagnosing it, no immediate intervention is needed (e.g., oral hyperpigmentation in patients receiving tyrosine kinase inhibitors such as imatinib) [12].
- Of note, an oral co-diagnosis may present unrelated to the targeted therapy. This CPS will not address concurring oral diagnoses.

Objective

To provide a practical guide for clinicians on management of oral toxicities from targeted therapy based on the current best standards of care for these oral complications.

Methods

The National Cancer Institute list (https://www.cancer.gov/about-cancer/treatment/types/targeted-therapies/approved-drug-list) of targeted therapy drugs approved by the U.S. Food and Drug Administration for certain types of cancer was used as the source of agents (see Appendix). Hormones, radioactive compounds, cytotoxic chemotherapy, and agents that function through the activation of the immune system against cancer were excluded from this list. A literature search of PubMed was conducted to assess the current management strategies of the oral toxicities secondary to targeted therapies. During the development of the manuscript, point questions that deemed a closer look were generated, and a literature search was done to ensure accuracy of information. Following discussion by an international working group of the OCSG of MASCC/ISOO, this CPS was reviewed and approved by two independent boards: the ISOO Advisory Board and the MASCC Guidelines Committee. The Statement follows the MASCC/ISOO Guidelines Policy. This OCSG CPS excludes osteonecrosis of the jaw due to targeted therapy and immune-related adverse events from immune checkpoint inhibitors. Please refer to the 2019 MASCC/ISOO/American Society of Clinical Oncology (ASCO) Clinical Practice Guideline Summary for the management of medication-related osteonecrosis of the jaw [17].

Management

General implications

The goal of treatment of oral toxicities secondary to targeted therapy is to relieve pain and accelerate the healing of existing lesions and to manage oral symptoms (Table 1). Recurrence may occur upon discontinuation of the topical therapy while the targeted therapy continues. Therefore, a dialogue with the patient about the course of the oral condition and the expected treatment outcomes should take place.

Table 1 The main components of the management approach for various oral complications of targeted therapy

Oral complication	Main components of the management approach
For all oral mucosal complications	• Maintain good oral hygiene • Avoid irritating food • Use mild-flavored fluoridated toothpaste • Use topical anesthetics for pain control, if needed • Rinse with saline or sodium bicarbonate solution to improve OH • Maintain hydration
Aphthous-like lesions	• Corticosteroids (topical, intralesional, and/or systemic)
Oral mucositis or stomatitis due to targeted therapy	• Corticosteroids (topical, intralesional, and/or systemic) • Antifungals if oral candidiasis is superimposed (topical or systemic)
Oral dysesthesia	• GABA analogs or benzodiazepines (topical or systemic)
Dysgeusia	• Food enhancement/personalized nutritional counseling • Zinc supplements • GABA analogs or benzodiazepines (topical) • Taste may improve after discontinuation of the offending medication
Dry mouth/xerostomia	• Please refer to the MASCC/ISOO CPS about management of salivary gland hypofunction and xerostomia [18]
Lichenoid lesions	• Corticosteroids if symptomatic (topical, intralesional, and/or systemic) • Long-term surveillance; biopsy if SCC or oral dysplasia is suspected
Hyperkeratotic lesions	• Long-term surveillance; biopsy if SCC or oral dysplasia is suspected
Geographic tongue	• Corticosteroids if symptomatic (topical)
Gingival enlargement	• Spontaneous improvement with discontinuation of the offending agent • Maintain good oral hygiene • Rinse with saline or sodium bicarbonate solution • Professional dental hygiene treatment may be needed
Gingival bleeding	• Topical hemostatic agents such as aminocaproic acid 5% solution • Educate the patient about the role of meticulous OH in preventing gingival bleeding

SCC, squamous cell carcinoma; *mTOR inhibitors*, mammalian target of Rapamycin inhibitors; *CPS*, clinical practice statement; *GABA*, gamma-aminobutyric acid

Oral mucosal toxicities

- The treatment plan is driven by the patient's level of symptoms, and type of clinical presentation.
- Topical treatment is preferred for most oral mucosal toxicities secondary to targeted therapy, and include pain medications and corticosteroids. There are several topical medications available, in different potency, concentration, and form. No standard treatment is available for hyperkeratotic lesions secondary to dabrafenib and vemurafenib. As new literature becomes available, the therapeutic approach may become more specific.
- The mainstay treatment for immune-mediated oral mucosal lesions is topical steroids (Table 2). Corticosteroid gels are usually recommended for single oral lesions only and can be applied to the affected site. For extensive gingival lesions, the gel may be placed in a stent. Solutions as a swish and spit formulation may be used for extensive oral mucosal involvement. Some agents may be compounded as a solution (e.g., clobetasol or budesonide) when a more potent steroid is needed. A gradual tapering is suggested when the symptoms improve. Creams and ointments are usually used for lip conditions, and if indicated, a short course is preferred to reduce tissue atrophy. Topical immunomodulators may be used for steroid-resistant oral lesions (e.g., tacrolimus paste, pimecrolimus cream). Additional agent with immunomodulating effect is minocycline that may be prescribed as 0.5% solution for aphthous-like lesions. Systemic therapy and/or intralesional steroid injection (e.g., with triamcinolone 10–15 mg triamcinolone per cm^2 of ulceration) is reserved for localized oral ulcers unresponsive to topical therapy. Of note, the use of topical immunosuppressive agents may lead to the development of secondary oral candidiasis. Treatment of oral candidiasis is with topical and/or systemic antifungal agents. As topical steroid therapy poses a low risk of glucocorticoid-induced adrenal insufficiency, screening for adrenal insufficiency should be pursued if a patient feels unwell.
- Palliating oral pain and improving oral intake may be achieved with topical anesthetics, although the effect may be transient. Likewise some patients may have difficulty using topical medications due to severe oral pain. In these cases, patients may be instructed to rinse with a topical anesthetic first and then use the recommended agent. Topical pain medications include benzydamine hydrochloride 0.15%, dyclonine hydrochloride 1%, viscous lidocaine

Table 2 Common topical immunosuppressive agents for oral application (modified from Elad et al. [19])

Purpose	Topical agents	Daily dose
Reduce inflammation and accelerate healing (secondary pain relief)**,***	Dexamethasone 0.5 mg/5 mL (0.01%) elixir or solution	5 mL × 1–4/day; swish and spit
	Dexamethasone 0.4 mg/mL (0.04%) solution *	5 mL × 1–4/day; swish and spit
	Prednisolone 3 mg/mL (0.3%) solution	5 mL × 1–4/day; swish and spit
	Budesonide 0.3–0.6 mg/mL (0.03–0.06%) solution *	5 mL × 1–4/day; swish and spit
	Clobetasol 0.5 mg/mL (0.05%) solution *	5 mL × 1–4/day; swish and spit
	Tacrolimus 0.1 mg/mL (0.01%) solution *^	5 mL × 1–4/day; swish and spit
	Clobetasol 0.05% gel	× 1–3/day; apply a thin film on the affected site
	Bethametasone 0.05% gel	× 1–3/day; apply a thin film on the affected site
	Fluocinolone 0.05% gel	× 1–3/day; apply a thin film on the affected site
	Triamcinolone 0.1% ointment	× 1–3/day; apply a thin film on the affected site
	Tacrolimus 0.1% ointment^	× 1–3/day; apply a thin film on the affected site
Management of neuropathic pain**,***	Gabapentin 250 mg/5 mL solution*	5 mL × 1–4/day; swish and spit
	Clonazepam 0.1–0.5 mg/mL solution*	5 mL × 1–4/day; swish and spit
Management of acute pain	Benzocaine 20% paste	× 1–3/day; apply a thin film on the affected site
	Lidocaine 2% viscous solution	5 mL × 1–4/day; swish and spit
	Doxepin HCl 0.5% solution *	5 mL × 1–4/day; swish and spit
	Morphine sulfate 0.2% solution *	5 mL × 1–4/day; swish and spit

*May not be commercially available, and thus may need to be compounded

**It is advised to rinse with the solution for 5 min and avoid rinsing/drinking for approximately 30 min after the rinse in order to reduce washout effect

***Patients should be informed that the effect may develop over a few weeks–months; not to be discouraged if the initial response is delayed or partial

^ The clinician should be aware of the caution note in the manufacturer information sheet (Black Box: skin malignancies and lymphoma reported following topical calcineurin inhibitor use, causal relationship not established; avoid continuous long-term use). No specific data on malignant transformation following oral topical application

2%, and benzocaine 10%. Topical antihistamines may also provide a local anesthetic effect. Patients should be advised to avoid gargling with the local anesthetic, as it may lead to an unpleasant choking sensation. The clinician might consider limiting the number of daily applications, as systemic absorption exists despite topical application. Up to five daily rinses of standard local anesthetic are generally considered safe. The dental/medical team may consider adjusting the frequency of use and potency of the agent recommended, depending on the severity of the oral toxicity.

- If the targeted therapy is delivered simultaneously or shortly after conventional chemotherapy, it may be challenging to identify to which agent the oral complication is related, if at all. In such cases, the timeline of the oral toxicity development relative to the initiation of the cancer treatment should be considered. Unless there is an indication that the etiology is related to the targeted therapy, the assumption is that the mucosal toxicity is due to conventional oral mucositis (i.e., oral mucositis secondary to chemotherapy) and should be treated accordingly [17]. An indication for targeted therapy being the etiology may be an oral presentation that differs from conventional oral mucositis such as aphthous-like lesions, or a rapid change in the clinical presentation following the addition of the targeted therapy. According to the half-life of each targeted agent, it may be possible to perform a diagnosis by a temporary suspension of the targeted treatment.
- Application of topical treatments can be challenging in pediatric patient populations. Younger pediatric patients may be unable to hold mouthwash, and compliance may be limited with other oral formulations too. Pharmacologic compounding and behavioral techniques may be needed to overcome these barriers.

Oral dysesthesia

- Management of oral dysesthesia focuses on symptom relief, and regimens typically follow the treatment algorithm for other neuropathic pain disorders. Systemic or topical clonazepam, gabapentin, and antidepressants may be used to control the oral symptoms. Topical anesthetics may be helpful for sensitivity/burning control. As new evidence is being published, photobiomodulation may become a treatment option.
- Blood testing may identify systemic factors that contribute to the oral sensitivity, such as iron or vitamin deficiencies. If so, these deficiencies may be addressed by supplements.

Dry mouth

- Dry mouth is a layperson term to describe either xerostomia, defined as a subjective feeling of dry mouth, or salivary gland hypofunction, defined as an objective low saliva secretion.
- Treatment of xerostomia aims to relieve symptoms and, in patients with salivary gland hypofunction, the aim is to increase the salivary flow rate. Please refer to the dry mouth CPS for management strategies [18].

Additional clinical considerations

- Proper description of the oral adverse effects will help with the diagnosis and direct the treatment accordingly. Clinicians are advised to be aware that some oral adverse effects may have symptoms without apparent abnormal findings. It is helpful to familiarize with these conditions (e.g., dysesthesia, glossodynia, burning sensation of the mouth, xerostomia, dysgeusia).
- Most recommendations for oral toxicities (excluding mucositis) are based on expert opinion or extrapolated from data on oral diseases with similar manifestations.
- Oral hygiene is important to prevent secondary infections. Furthermore, in the case of salivary gland hypofunction, it will reduce the risk for dental caries. The patient should be advised about the importance of the daily self-practice oral hygiene, as well as about having a regular dental checkup with the primary dentist.
- A targeted therapy agent may be used as a carrier for cytotoxic drugs (e.g., enfortumab vedotin-ejfv). If oral toxicity develops, it will likely have the clinical presentation of the cytotoxic therapy-related oral toxicity. However, unique reactions to the vehicle molecule cannot be excluded.
- A consultation with an oral medicine professional is preferred for the management of oral complications secondary to cancer therapy. In some cases, depending on the severity of the oral complications and response to therapy, patients may require discontinuation or reduction of the targeted agent. A collaboration between the oral medicine professional and medical team members is ideal to identify the best treatment option.
- Comorbidities and medication use as well as previous treatment should be considered, as they may be associated with an increased risk of oral toxicities.
- Oral infections (bacterial, fungal, and recrudescent viral infections) may develop in the setting of neutropenia and should be considered in myelosuppressed patients. The clinical presentation is usually different from that of other oral mucosal toxicities. An oral culture, blood tests, or a biopsy may be required in some cases for a definitive diagnosis.
- For other targeted therapy-related oral lesions that are asymptomatic and not suspicious for oral cancer, an annual oral and dental exam is advised in patients with no special concerns, as is commonly done in the general population.
- Depending on the country, there might be variabilities in the regulation of the medications used for the treatment of oral toxicities.
- More interventions may become available in the future as the literature develops.

Appendix

FDA-approved targeted agents for cancer therapy

Abemaciclib; acalabrutinib; ado-trastuzumab; afatinib; alectinib; alemtuzumab; alpelisib; amivantamab-vmjw; apalutamide; asciminib; avapritinib; axicabtagene; axitinib; belantamab; belinostat; bevacizumab; bexarotene; binimetinib; blinatumomab; bortezomib; bosutinib; brentuximab; brexucabtagene; brigatinib; cabozantinib-s-malate; capmatinib; carfilzomib; ceritinib; cetuximab; ciltacabtagene; cobimetinib; copanlisib; crizotinib; dabrafenib; dacomitinib; daratumumab; dasatinib; denileukin; denosumab; dostarlimab-gxly; duvelisib; elotuzumab; enasidenib; encorafenib; enfortumab; entrectinib (Rozlytrek); erdafitinib; erlotinib; everolimus; fam-trastuzumab; fedratinib; fulvestrant; gefitinib; gemtuzumab; gilteritinib; glasdegib; ibritumomab; ibrutinib; idecabtagene; idelalisib; imatinib; infigratinib; inotuzumab; iobenguane; ipilimumab; isatuximab-irfc; ivosidenib; ixazomib; lanreotide; lapatinib; larotrectinib; lenvatinib; lisocabtagene; loncastuximab; lorlatinib; lutetium; margetuximab-cmkb; midostaurin; mobocertinib; mogamulizumab-kpkc; moxetumomab; naxitamab-gqgk; necitumumab; neratinib; nilotinib; niraparib; obinutuzumab; ofatumumab; olaparib; osimertinib; pacritinib; palbociclib; panitumumab; pazopanib; pemigatinib; pertuzumab; polatuzumab; ponatinib; pralsetinib; ramucirumab; regorafenib; ribociclib; ripretinib; rituximab; romidepsin; rucaparib; ruxolitinib; sacituzumab; selinexor; selpercatinib; selumetinib; siltuximab; sirolimus; sonidegib; sorafenib; sotorasib; sunitinib; tafasitamab-cxix; tagraxofusp-erzs; talazoparib; tamoxifen; tazemetostat; tebentafusp-tebn; temsirolimus; tepotinib; tisagenlecleucel; tisotumab; tivozanib; trametinib; trastuzumab; tucatinib; vandetanib; vemurafenib; venetoclax; vismodegib; zanubrutinib; ziv-aflibercept

Note: The list was last accessed from the National Cancer Institute website for FDA-approved targeted agents for cancer therapy on May 2024.

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Declarations

Competing interests N. Yarom, C. Hong, C. Fulop, and S. Elad reported no relevant financial or non-financial interests to disclose. A. Villa is a consultant for Merck, K Pharmaceuticals, Afyx Therapeutics, and Lipella Pharmaceuticals. J.B. Epstein is a consultant for Rakuten, Sanotize, Janssen, and Neilsen. P. Bossi is a consultant for Merck, Sanofi-Regeneron, and Merck Sharp & Dohme.

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Disclaimer The MASCC/ISOO OCSG Statements have been developed to facilitate expert-opinion-based management of oral complications of cancer and cancer therapy, where high-quality evidence is lacking. Clinicians should use their judgment when making treatment decisions for individual patients. Statement authors and the MASCC/ISOO do not guarantee or take responsibility for the clinical outcomes in individual patients.

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