Oral Complications of Nonsurgical Cancer Therapies

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KEYWORDS

• Mucositis • Osteonecrosis • Medication related osteonecrosis of the jaws • Cancer • Immunosuppression • Chemotherapy • Radiotherapy • Hematopoietic stem cell transplantation

KEY POINTS

- There are a variety of nonsurgical cancer treatment modalities, such as chemotherapy, radiotherapy, hematopoietic stem cell transplantation, and targeted therapy.
- Each modality uses various protocols, medications, and techniques, and therefore a wide range of oral complications occur.
- The complications may be specific to the mouth, affecting the oral mucosa, salivary glands, dentition and gingivae; the complications may also affect the musculoskeletal system or sensory system.
- Complications may be non–tissue specific, such as bleeding, infection, secondary malignancy, and developmental disturbances.
- The range and severity of oral complications highlight the importance of appropriate management to optimize oral function, quality of life, and well-being.

Introduction

The aim of this article is to review the oral complications of nonsurgical cancer therapy. Novel treatments and advances in existing treatments come with a new set of side effects and complications, particularly in the radiation oncology and immunotherapy fields. This section will cover the oral complications following nonsurgical treatment modalities: chemotherapy, radiotherapy (RT), chemoradiotherapy, hematopoietic stem cell transplantation (HSCT), and targeted therapy.

Table 1 lists oral complications, organized according to the tissue affected. The text expands on most of these complications and when applicable refers to detailed reviews. The clinical photos show the plethora of oral complications.

Oral mucosal complications

Mucositis

- The toxicity of chemotherapy, RT or combination affecting the oral mucosa, causing inflammation and tissue damage is termed oral mucositis. Clinically, it manifests as painful erythema and ulcerations.
- The incidence of oral mucositis varies according to treatment modality. For chemotherapy-associated mucositis, the cytotoxic agents used and the intensity of the regimen are among the main factors that determine the severity of the mucositis. In HSCT and hematologic malignancies, neutropenia is an additional risk factor. In head and neck cancer treated with RT the field of oral mucosa receiving weekly cumulative doses of approximately 10 Gy is at the greatest risk for lesions of mucositis. The use of concomitant chemoradiotherapy increases the risk for mucositis, as does the introduction of targeted therapy.[1] The wide range of mucosal responses to the same cancer treatment regimens have not been explained,[2,3] and the role genetics plays in these oral manifestations has recently gained attention.[4]
- The clinical features include localized or generalized denudation of the oral mucosa; frank ulcers on the nonkeratinized mucosa covered with fibrinous pseudomembranes are also seen (Fig. 1). The pain may be so severe that oral intake is impaired, cancer treatment is interfered with, opioid use increases, hospitalization is prolonged, and quality of life is reduced. Furthermore, oral mucositis may increase the risk of systemic spread of infection.[5]
- The differential diagnosis includes infection and drug eruptions. Local trauma from sharp anatomic structures or restorative materials may further irritate the injured

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Table 1 Oral complications associated with nonsurgical cancer therapy

Category	Tissue	Oral complication	Early presentation	Late presentation
Tissue-specific manifestations	Mucosa	Mucositis	+	+
		Anemia-related mucosal changes: atrophy and burning, paleness	+	—
		Neutropenic ulcer	+	—
		Lichenoid, erythema, and ulcers (cGVHD)	—	+
		Pyogenic granuloma	—	+
		Targeted therapy—associated stomatitis	+	+
		Targeted therapy—associated lichenoid	+	+
		Chemotherapy-associated pigmentation	—	+
		Targeted therapy—associated pigmentation	—	+
	Salivary glands	Salivary hypofunction	+	+
		Sialoadenitis	+	+
		Mucocele (cGVHD)	—	+
	Musculoskeletal complications	Osteoradionecrosis	—	+
		Drug-induced osteonecrosis of the jaw	—	+
		Impaired mastication	+	+
		Swallowing disorders	+	+
		Speech disorders	+	+
		Fibrosis + scarring + trismus (limited neck and shoulder mobility)	—	+
		Loss of elasticity, reduced range of motion and limited mouth opening (scleroderma-like GVHD)	—	—
	Sensory disturbances	Dysgeusia	+	+
		Neuropathy − dental/orofacial	—	+
		Tooth hypersensitivity	—	+
	Teeth and gingivae	Increased dental demineralization and caries	—	+
		Pulp necrosis/obliteration (cGVHD)	—	+
		Gingival enlargement	—	+
		Desquamative gingivitis (cGVHD)	—	+
		Acute periodontal infections	+	+
		Preexisting chronic periodontal infections	+	+
Non—tissue specific manifestations	Bleeding	Thrombocytopenia	+	+
		DIC	+	+
	Infection	Viral	+	+
		Bacterial	+	+
		Fungal	+	+
	Malignancy	Squamous cell carcinoma	—	+
		Posttransplant lymphoproliferative disorder	—	+
		Postradiation sarcoma	—	+
	Developmental	Developmental disturbances of teeth and craniofacial growth in pediatric patients	—	+

Abbreviations: cGVHD, chronic graft-versus-host disease; DIC, disseminated intravascular coagulation.

mucosa. Additional differential diagnoses depend on the cancer treatment modality. For chemotherapy-associated oral mucositis, the clinician should consider for differential diagnosis neutropenic ulcers. For HSCT-associated mucositis the differential diagnosis of the ulcerations may be neutropenic ulcers or acute graft-versus-host disease (GVHD). For RT-associated mucositis, if the findings are localized to the surgical site, postoperative complications should be suspected as differential diagnosis.

- Evidence-based clinical practice guidelines for the management of mucositis were developed by Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO).[6] The most recent edition suggests treatments as outlined on Table 2. The MASCC/ISOO guidelines are being updated at this time.
- Chronic forms of oral mucositis were described after RT. Two subtypes were suggested: (1) persistent type, when the lesions do not heal within 3 months after the completion of the RT and (2) recurrent type, when new discrete ulcers wax and wane after the completion of RT.[7]

Neutropenic ulcer

- Neutropenic patients may present with ulceration of the nonkeratinized mucosa, with no obvious infectious cause or correlation to cytotoxic therapy.
- The incidence is unknown because most of the literature is based on case reports or small case series.
- Clinically, the ulceration may be surrounded by a diffuse area of erythema (Fig. 2). The ulcerative lesions vary in shape and size, ranging from irregular elliptical shapes to extensive amorphous lesions. The ulcerations may be deep and occur simultaneously in multiple sites. The