*J Natl Cancer Inst Monogr* (2019) 2019(53): lgz003

doi: 10.1093/jncimonographs/lgz003
Article



ARTICLE

# Oral Pain in the Cancer Patient

Joel B. Epstein, Christine Miaskowski

See the Notes section for the full list of authors' affiliations.
**Correspondence to:** Joel B. Epstein, DMD, MSD, FRCD(C), FDS RCS(Edin), Department of Surgery, Diplomat, American Board of Oral Medicine, Consulting Staff, Division of Otolaryngology and Head and Neck Surgery, City of Hope, 1500 East Duarte Road, Duarte, CA 91010 (e-mail: jepstein@coh.org).

## Abstract

Oral pain due to cancer and associated treatments is common. The prevalence and severity of oral cancer is high. Painful oral mucositis develops in head and neck cancer patients following surgery and associated radiation therapy and/or chemotherapy. In addition, oral pain, including pain from mucositis, occurs in patients receiving chemotherapy for cancers of the hematopoietic system and cancers at other anatomic sites. Despite pain management practices that include high-dose opioid analgesics, patients rarely obtain relief from either head and neck cancer pain or mucositis pain. Because oral pain in cancer patients is likely due to both nociceptive and neuropathic mechanisms, effective management of pain requires treatments for both processes. As knowledge of the pathophysiology of oral pain in cancer patients increases, new approaches for the prevention and management are anticipated. This article focuses on the emerging evidence that supports the molecular mechanisms and the unique oral micro-neuroanatomy that in combination produce the severe oral pain experienced by cancer patients. In addition, this article summarizes the current state of clinical management of oral mucositis pain.

Although the occurrence of pain due to head and neck cancer (HNC) is variable, it is reported to be as high as 85% at diagnosis (1–3). Whereas complete surgical resection provides near complete relief of HNC-related pain, many HNC patients require radiation therapy (RT) with or without chemotherapy, which can lead to long-lasting pain (4). For HNC patients receiving RT, pain intensity increases during treatment, is highest at the 2 week follow-up, and persists at the 3-month follow-up (5). Neuropathic pain descriptors are selected by almost three-quarters of patients (73%), which suggests that neuropathic pain is common in patients with HNC throughout treatment. More than one-half of patients report continuous pain, and approximately 80% of patients report both continuous and intermittent episodes of pain. These findings are supported by other studies that demonstrate that 30% of HNC patients experience neuropathic pain. Mixed nociceptive and neuropathic descriptors were chosen by 93% of HNC patients at diagnosis (6). The affective and evaluative descriptors chosen for HNC pain suggest that this pain has a considerable impact on patients' quality of life even when the intensity is described as low to moderate. These findings suggest that clinicians should consider concurrent management of both nociceptive and neuropathic pain in HNC patients.

Oral mucositis is a toxic effect of systemic chemotherapy, RT to the head and neck region, and targeted therapies. Oral mucositis and associated pain are reported to be the most distressing symptom during and after RT, with increasing pain intensity and pain interference scores by week 3, peaking at week 5, and persisting following therapy (5,7). Mucositis pain interferes with daily activities in approximately one-third of patients and with mood and social activities in 50–60%. Mucositis pain has nociceptive and neuropathic components. Nociceptors are sensitized by pro-inflammatory cytokines (eg, tumor necrosis factor-$\alpha$ [TNF-$\alpha$], interleukin [IL] 2, IL-6) and are stimulated by mediators at the site of tissue inflammation. Combined chemotherapy and RT results in increased frequency, severity, and duration of mucositis and related pain (8).

In addition to mucositis, other sources of oral pain occur in cancer patients. Cytotoxic agents, such as vinca alkaloids, vinblastine, and platinum derivatives, may cause jaw pain and neuropathy. Neuropathies are common in patients with cancer (1.7–5.5%) and may be due to direct effects of tumor, paraneoplastic syndromes, and treatment-related toxicity. Surgical procedures result in acute nociceptive orofacial pain and may lead to painful postsurgical neuropathy and postsurgical fibrosis. In addition to tissue injury at tumor resection, morbidity is

**Received:** January 11, 2019; **Revised:** February 7, 2019; **Accepted:** April 1, 2019

increased by concomitant procedures such as neck dissection. Resection of the mandible inevitably leads to sensory impairment, with 50% of patients experiencing regional hyperalgesia or allodynia. At 2 to 5 years post-maxillectomy, 88–90% of patients report persistent pain. Pain scores following HNC surgery are highest for the oral cavity, followed by the larynx, oropharynx, and nasopharynx. In surgically treated oral cancer patients, functional problems were reported postoperatively in more than 50% of cases, and at follow-up (ie, ≥6 months postsurgery) impairment due to moderate to severe pain was found in 34% of patients. The most frequent pain locations are the shoulder, neck, temporomandibular joint, oral cavity, and the face and other head regions, reflecting morbidity secondary to surgery.

Fortunately, posttreatment symptoms tend to improve with time. In patients with HNC, the postoperative pain experience is characterized by acute pain that persists for 1 to 2 months, with a gradual improvement over time. However, long-term HNC survivors (>3 years) experience statistically significantly more pain and functional problems than matched control subjects, even though a relative return to normal function occurs. Chronic postsurgical pain may involve inflammatory and neuropathic pain mechanisms, depending on the extent of surgery, the treated anatomic location, and/or the addition of adjuvant therapy. Poor efficacy of traditional approaches, consisting primarily of opioid analgesics, has led to the emergence of adjunctive and complimentary methods for pain management in cancer patients (9–11).

Oral pain in cancer patients may be due to the primary disease or to various cancer treatments, including surgery, RT, chemotherapy, and targeted therapies (12). Emerging data suggest that an overlap exists in the molecular mechanisms that generate cancer pain. Moreover, the complex micro-neuroanatomy that innervates the oral cavity likely contributes to the severity, character, and impact of cancer pain. In this review, we present recent evidence on various molecular pathways, as well as the sensory fiber types and receptors that are sensitized and activated leading to oral pain in cancer patients.

## Biology of Oral Pain

### Innervation of the Oral Cavity

An understanding of the nociceptive mechanisms that generate oral pain in cancer patients rests on knowledge of the oral micro-neuroanatomy. Most studies of nociceptors that innervate the oral cavity have examined innervations of the dental pulp. These fibers project mainly to the most rostral part of the long spinal trigeminal nucleus (ie, the subnucleus oralis). In contrast, nociceptive afferents from the remainder of the oral cavity terminate in the subnucleus caudalis or medullary dorsal horn. In order to discuss the nociceptive fibers and pathways that underlie oral pain, comparisons need to be made between the afferent innervation to the trigeminal nucleus caudalis from the trigeminal ganglion (TG) vs the afferent innervation to the spinal dorsal horn from the dorsal root ganglia (DRG). The knowledge base for the latter is larger than for the former.

Afferents for pain are primarily Aδ fibers that convey fast, sharp pain and C fibers that convey slow, burning pain. One distinction between TG and DRG innervation is that trigeminal thermonociceptors have considerably slower action potential conduction velocities and lower temperature thresholds than do DRG thermonociceptors (13). Although a comprehensive compendium of over 40 neuroactive substances and their receptor subtypes in the central terminations of TG neurons in the nucleus caudalis was published (14), no comparison to DRG neurons was cited.

### Neuronal Fibers and Pathways

Like their counterparts in the spinal dorsal horn, the nociceptive Aδ fibers and C fibers of the TG release both glutamate in the nucleus caudalis and neuropeptides (eg, substance P and calcitonin gene-related peptide) in the nucleus caudalis and periphery (Figure 1). The C fibers are differentiated further into two populations (ie, peptidergic and nonpeptidergic C fibers) that are stratified into different lamina and associated with different pain modalities. Neuropeptide release is bidirectional, from both central terminals and peripheral free nerve endings. Peripheral release from peptidergic neurons produces the neurogenic inflammation component of the complex pain response and amplifies nociception of nearby nerve endings. Glutamate signaling likely plays an important role in inflammatory pain (15).

The presence of the tyrosine kinase A (TrkA) receptor is the second distinguishing feature of the peptidergic C-fiber population. The TrkA receptor binds nerve growth factor (NGF), which is a hypersensitizing pain mediator (16). The distribution of nonpeptidergic neurons in the TG is distinct. The central terminals of the nonpeptidergic TG neurons have a different distribution in the nucleus caudalis than do their counterpart DRG neurons that terminate in the spinal dorsal horn (17). Furthermore, many of the caudalis neurons receive convergent inputs from skin, tooth pulp, viscera, neck, and muscle and are likely involved in deep pain, spread, referral, and neuroplastic changes.

Two pathways exist that modulate other types of pain, although they may not be involved in oral pain. The first is the phenomena of "Aβ pain" that occurs when damage to C fibers leads to sprouting of nonnociceptive Aβ sensory fibers into the nociceptive C-fiber terminal lamina in the dorsal horn. This phenomena should be greatly reduced in the trigeminal system because most A-beta fibers of the TG terminate in the far rostral subnucleus oralis and pontine sensory nucleus (17). Second, although some nociceptive afferents are susceptible to sympathetic modulation following injury in a variety of pain conditions, in the orofacial region there may be less sympathetic neural reactivity to peripheral injury.

### Sensory Receptors

The transient receptor potential (TRP) family of sensory ion-channel proteins are the sensory receptors on nociceptor peripheral free nerve endings. These receptors are highly expressed on both TG and DRG neurons that convey thermal and chemical nociception and contribute to mechanical hyperalgesia (18). In addition, they are involved in olfaction, taste, and somatosensation (19). For example, in skin and muscle generally, heat hyperalgesia and heat allodynia (ie, perception of a nonnoxious stimulus as noxious) vary with the distribution of TRPV1 and higher-threshold TRPV2 heat receptors (20). TRP receptors implicated in mechanical hyperalgesia include the TRPV1 heat and proton receptor (21), the TRPA1 cold and chemical irritant receptor, the TRPM8 (menthol) cold receptor (16,22), and the TRPV4 osmolarity receptor (18).

#### *Distribution and Modulation of TRP Receptors*

For both the DRG and TG in rats, the TRPV1 and TRPA1 receptors are present only on C fiber terminals, whereas the TRPM8 receptor is present on both C and Aδ fibers (23). Furthermore, these

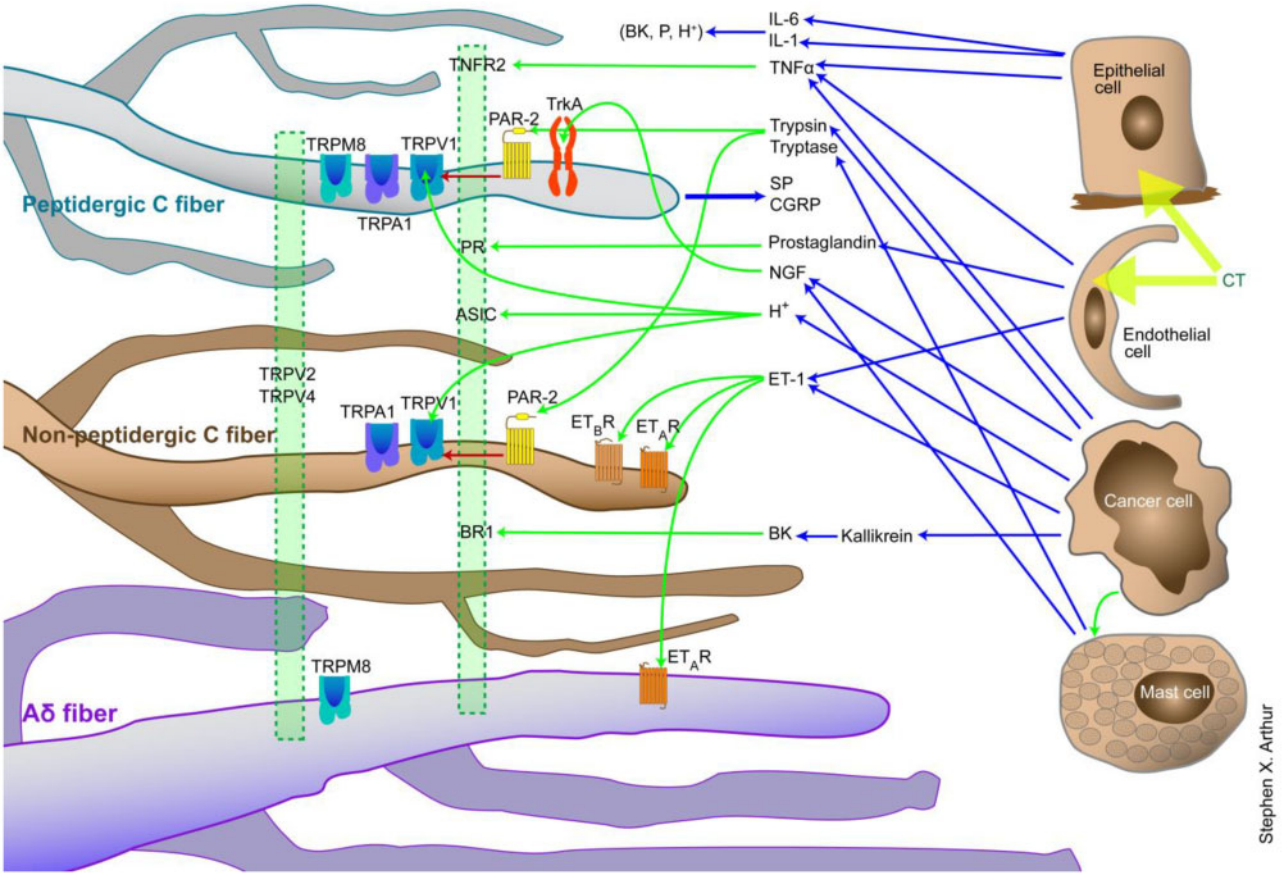


**Figure 1.** Mediators, fiber types, and receptors that convey trigeminal nociception in oral cancer and chemotherapy-induced oral mucositis. Nociceptive receptors and transient receptor potential (TRP) channels are distributed differently across the three main nociceptor fiber types of the trigeminal ganglion (TG). This distribution of receptors is fundamentally different from that of dorsal root ganglia. Those receptors that have not yet been localized to specific trigeminal fibers are indicated generally by a **dashed box** that spans all three fiber types. The **top two cells** on the right indicate mediators secreted by the oral mucosa in response to chemotherapy. Because many oral mucositis patients do not have oral cancer, the mediators of mucositis may not be coexisting with those elicited by the cancer cell. Mediators shown for the cancer and mast cells are not in response to chemotherapy. Secretion of ET-1 from the endothelial cell in response to chemotherapy is hypothesized, but there is not yet direct evidence. The TRP channels may be sensitized by many of the mediators, but their correspondences are not yet specified for the three fiber types of the TG. **Blue arrows** indicate secretion. **Green arrows** indicate activation. **Red arrows** indicate sensitization. ASIC = acid sensing ion channel; BK=bradykinin; BR1 = bradykinin receptor type 1; CGRP = calcitonin gene-related peptide; CT = chemotherapy; ET-1 = endothelin; IL = interleukin; NGF = nerve growth factor; PAR-2 = protease activated receptor type 2; PR = prostaglandin receptor; SP=substance; TNF-α = tumor necrosis factor; TNFR2 = tumor necrosis factor receptor type 2; TrKa=tyrosine kinase A;TRPA1 = transient receptor potential cation channel, subfamily A, member 1; TRPM = transient receptor potential melastatin; TRPV = transient receptor potential vanilloid.

receptors may overlap with other TRP receptors. Most importantly in relationship to oral cancer pain and pain associated with oral mucositis, the TRPM8 receptors are confined to neurons that express TrkA receptors for NGF (23). This localization suggests that, among C fibers, TRPM8 receptors are restricted to the peptidergic population in both the TG and DRG, which contributes to neurogenic inflammation that is modulated by NGF. In rat oral mucosa, the TRPV4 receptor contributes to inflammatory hyperalgesia and is modulated by descending serotonin projections. In addition, a host of peripheral signaling molecules that act through other receptors and second-messenger systems can sensitize TRP receptors (16,21) and may mediate hyperalgesia and allodynia within the microenvironment of oral cancer and mucositis.

### *Proportional Comparisons*

A difference in the proportion of TRP receptors found in the DRG and TG neurons was shown only for TRPM8. The number of TRPM8 receptors is 41% higher in TG neurons and is especially abundant in the mandibular nerve region that innervates the tongue (23). Additional anatomic comparisons suggest the following: (1) DRG and TG express TRPV1 on about 45% of nociceptive neurons; (2) tooth pulp-innervating neurons express TRPV1 on 21–34% of neurons with TRPV2 on a separate population of about 32–51% of neurons; and (3) gingival neurons express TRPV1 on about 25% of neurons with TRPVR2 found on another 41% (24). For TRPA1 receptors in the rat TG, 22% are on peptidergic neurons and 44% are on nonpeptidergic neurons (25). Pain-related NGF receptors appear to be increased in the oral cavity because 70% of TG neurons that innervate rat gingivomucosa display TrkA receptors (for NGF) and are probably nociceptive, whereas only about 40% of total TG neurons or those of the maxillary division display TrkA receptors (26).

## Endothelin-1 (ET-1) as an Oral Pain Mediator

ET-1 is a vasoactive peptide that mediates nociception in all three trigeminal nerve branches of the rat (27). The ET-1 and ET-

3 isoforms of endothelin are expressed in the rat TG. The two ET-1 receptor subtypes, $ET_AR$ and $ET_BR$, are expressed across the entire rat TG, including 30% of the TRPV1-positive neurons. The human TG expresses both receptor subtypes (28). It can be inferred that these receptors are transported to the TG peripheral nerve endings, while concurrently the TG neurons secrete ET-1 at peripheral or central terminals—thereby involving ET-1 in TG neurotransmission, neurogenic inflammation, and sensitization to pain. Experimentally, nociceptive responses are elicited when ET-1s are injected into the maxillary lip or temporomandibular joint of the rat, and these effects are reversed by selective antagonists (27). Likewise, both $ET_AR$ and $ET_BR$ receptors contribute to orofacial thermal hyperalgesia induced by trigeminal nerve constriction in rats (29).

#### *ET-1 Receptors: TG vs DRG*

The most prominent and perhaps key difference between TG and DRG nociceptors is displayed by ET-1 receptors. The distribution of ET-1 receptors in the TG and DRG differs dramatically (27). In rat TG neurons, $ET_ARs$ are expressed on both A$\delta$ fibers and nonpeptidergic C fibers. The $ET_BRs$ are expressed on both satellite glial cells and nonpeptidergic C fibers. In the DRG, $ET_ARs$ in rat and rabbit show a reversed pattern of expression on the peptidergic C fibers (neurogenic) instead of the nonpeptidergic ones (not neurogenic). The $ET_BRs$ in the DRG are restricted to glial cells only. The $ET_BRs$ on TG satellite glial cells are highly functional (30), responding strongly to ET-1 and leading to release of calcium from internal stores and to external calcium influx in equal amounts.

#### *A Unique Pathway*

The implication of the above arrangement is that, within the DRG, ET-1 activates only those C fibers that produce neurogenic inflammation and respond to both TRPM8 nociception and NGF. In addition, ET-1 activates these fibers only through $ET_ARs$. Conversely, within the TG, ET-1 activates only those C fibers that do *not* produce neurogenic inflammation and do *not* respond to either TRPM8 sensory receptors or NGF. Furthermore, these specialized C fibers in the TG are activated by *both* $ET_A$ and $ET_B$ receptors and terminate differently in the nucleus caudalis. In contrast, their DRG counterparts terminate in the dorsal horn. Therefore, activation of both $ET_A$ and $ET_B$ receptors on nonpeptidergic C fibers, a feature unique to trigeminal afferents, may be one explanation for the severity of pain in disorders such as oral cancer and oral mucositis. In these conditions, ET-1 may contribute to both sharp and burning pain but not to neurogenic inflammation by conventional release of neuropeptides.

## Oral Cancer Pain

### Epidemiology and Clinical Impact

More than one-half of all cancer patients experience severe, persistent pain during the course of their disease. Almost all oral cancers are painful (31), and up to 85% of patients report pain at the time of diagnosis (32). Pain is one of the primary presenting symptoms for patients with oral cancer and it restricts patients' oral function, including eating, drinking, and speaking (31). For the oral cancer patient, pain is rated as their worst symptom and is the primary determinant of a poor quality of life (31). Pain can occur as a result of surgery, RT, chemotherapy, and/or targeted therapies (12). Pain due to mucositis affects resource utilization and has a dramatic impact on quality of life.

Orofacial pain and mucosal pain are common following cancer therapy, may persist indefinitely, and may be more severe than pain reported at diagnosis (33–35). During their terminal months of life, 85% of oral cancer patients report pain as their most common problem. A number of validated tools are now available to assess oral quality of life including orofacial pain and function during and following cancer therapy (4,31). Following diagnosis and throughout treatment, these patients require routine assessments of their pain and their functional status so that appropriate management can be provided.

Despite current concerns about the chronic use of opioids for chronic noncancer pain (36), opioid analgesics remain the current standard of care for the management of oral cancer pain (37). Although effective in cancer pain, for oral pain, opioids do not provide complete relief and do little to restore function (eg, decreasing pain associated with swallowing). As the oral cancer progresses, increasing doses of opioids may be required and tolerance may develop rapidly. With progressively higher doses, patients may experience numerous side effects (eg, sedation, cognitive changes, nausea, constipation). Pain management regimens should be tailored to provide relief when patients are required to function, especially during meals. In addition, the management strategies need to be directed at both nociceptive and neuropathic pain to achieve optimal pain relief (32).

Total surgical resection of the oral cancer will provide near complete relief of cancer pain (4). However, some patients have severe pain before surgery, some oral cancers are unresectable, some patients are too medically compromised to have surgery, and many patients develop a recurrence of the cancer or a second primary oral cancer. Of course, surgical intervention is associated with postsurgical pain and may be associated with future disability including discontinuity defects, postsurgical fibrosis, and postsurgical neurogenic and neuropathic pain. Patients with advanced stage HNC, those with large primary tumors, those with regional and systemic spread, and those with poor prognostic features following surgery will receive combined chemotherapy and RT. As a result, current therapy involves combined RT and chemotherapy in more than two-thirds of HNC patients. As a consequence, oral mucositis and its associated pain and dysfunction represent a considerable patient and public health problem. In addition, given that approximately 50% of oral cancer patients will not be cured with surgery, chemotherapy, and/or RT (32), the etiology of and improved methods to treat oral cancer pain warrant investigation.

### Etiology

The etiology of oral cancer pain is multifactorial. Pain in cancer patients is hypothesized to be due to tumor mass effects, ulceration, inflammation, and invasion (38,39). Recent evidence suggests that although inflammation does not play a primary role in mediating cancer pain (40), inflammation leads to sensitization and activation of nociceptive mediators that are released by the cancer in the cancer microenvironment. Oral cancer pain is a complex pathologic process and a formidable clinical problem. However, our understanding of the basic neurologic mechanisms that are responsible for generating oral cancer pain and cancer pain in general has improved. It is clear that the symptoms experienced by the patient with oral cancer are a consequence of cellular, tissue, and systemic changes that occur during the phases of carcinogenesis, including proliferation, invasion, and metastasis, and that continue throughout the course of therapy and into survivorship. To execute these

**Table 1.** Nociceptive mediators in oral cancer and chemotherapy-induced mucositis

| Mediator | Oral cancer | Chemotherapy-induced oral mucositis |
|---|---|---|
| Endothelin-1 | Yes | Yes* |
| Nerve growth factor | Yes | Not determined |
| Tumor necrosis factor $\alpha$ | Yes | Yes |
| Prostaglandins | Yes | Yes |
| Bradykinin | Yes | Secondary† |
| Protons | Yes | Secondary† |
| Trypsin | Yes | Not determined |
| Tryptase | Yes | Not determined |

*Speculative, no direct evidence.
†Result of expression of Interleukin-1$\beta$ and Interleukin-6.

cellular processes, oral squamous cell carcinoma cells produce mediators that affect other cells within the cancer microenvironment, such as neurons and immune cells. Table 1 provides a list of these mediators that were reviewed elsewhere (41,42). Oral cancer pain involves crosstalk between the cancer and primary afferent nociceptors and possible contribution from immune cells. One of the experimental challenges of understanding oral cancer pain is that it is difficult to separate one cell and study it in isolation and understand its contribution to oral cancer pain.

Oral squamous carcinoma cells produce multiple mediators that sensitize sensory fibers in the cancer microenvironment (41,42). TNF-$\alpha$ was shown to be released from oral squamous cell cancer cells due to treatment increasing inflammation and nociception (43).

One of the most studied cancer pain mediators is ET-1 (44). ET-1 is secreted by multiple cancers, including prostate, breast, colon, hepatocellular, pancreatic, endometrial, lung, pheochromocytoma, and oral squamous cell carcinoma (45). Endogenous ET-1 produced by oral cancer results in mechanical allodynia in a mouse model (45). Patients with oral squamous cell carcinoma have severe pain secondary to mechanical stimulation to which the oral cavity is highly exposed (eg, when hard food contacts the area around the cancer) (4,31). A model that may reflect this type of oral mechanical pain is produced by inoculating a human-derived oral squamous cell carcinoma into the hind paw of a mouse. This mouse model displays the mechanical hyperalgesia that is observed in human oral cancer patients (4,31). Using this mouse model, findings suggest that the nociceptive effect of ET-1 is peripherally mediated in the cancer microenvironment (45). $ET_AR$ antagonism, using the highly selective drug BQ-123 injected directly within the cancer microenvironment, produces antinociception (ie, pain reduction) similar to acutely administered, high-dose, systemic morphine (46). Interestingly, $ET_AR$ antagonism was shown to prevent morphine tolerance (47,48). $ET_{AB}$ antagonism produces antinociception and simultaneously prevents morphine tolerance, suggesting that ET antagonism may be an effective treatment for cancer pain (49).

## Pain Associated With Oral Mucositis Caused by High-Dose Cancer Therapies

### Epidemiology and Clinical Impact

Acute, severe pain from chemotherapy-induced oral mucositis is a clinically and financially significant public health problem (50). Oral mucositis is reported to be one of the most statistically significant toxicities associated with the treatment of HNC as well as in hematopoietic stem cell transplantation (HSCT). In addition, clinically significant oral mucosal injury and pain occur when the oral mucosa is included in the high-dose head and neck radiation portal.

Evidence of severe pain from oral mucositis comes from several sources. Of note, data were derived from a toxicity scale that combines scoring for chemotherapy-induced oral mucositis (51). On this scale, grade III–IV toxicity is a valid indicator of severe pain because these toxicity scores were highly correlated with oral mucositis pain scores. In grade I, oral soreness can occur without lesions. In grade II, pain does not prevent eating or swallowing. The incidence of grade III–IV oral mucositis from regimens that include an anthracycline, taxane, or platinum compound are in the 1–10% range. In contrast, regimens that include fluorouracil vary from 3% to 66%. For other chemotherapy regimens, the incidence of grade III–IV oral mucositis is 2–27% (50). For patients who undergo HSCT without total body irradiation, incidence ranges from 30% to 50% (50). In HNC patients receiving combined chemotherapy and RT, the incidence approaches 100% (8).

A second source of data on severe pain from chemotherapy-induced oral mucositis is the incidence of dose-limiting toxicity that slows or prevents the continuation of treatment (50). For all patients with grade III–IV oral or gastrointestinal (GI) mucositis combined, approximately 30% discontinue the regimen (range, 8–100%) (50). When grade III–IV oral mucositis (without GI mucositis) occurs, patients with solid tumors who receive myelosuppressive chemotherapy had dose reductions in their next cycle twice as often (21% vs 11%) and had twice as many hospitalizations (8 vs 4 days) as those without mucositis. For these patients, the costs of grade I–II and grade III–IV mucositis (combined oral and GI) were $2725 and $5565 per cycle, respectively (52). Other studies found that among all patients with grade III–IV oral mucositis on standard-dose chemotherapy regimens, 70% required feeding tubes and 62% needed to be hospitalized. In addition, while on high-dose chemotherapy for HSCT, 87% of patients needed feeding tubes (50). Patients with oral mucositis during HSCT require approximately 6 more days of opioid analgesics and experience 2 more febrile days than those without oral mucositis (53). These adverse effects are associated with considerable increases in the cost of care. For example, in one study, the additional hospital charges associated with oral mucositis totaled about $42 000 per patient (54). Grades III–IV mucositis (oral and GI) accounted for 3% of resources used during cycles of raltitrexed and 21% during cycles of fluorouracil and leucovorin. Delay in treatment, dose reductions, and/or discontinuation of chemotherapy following episodes of clinically significant mucositis may affect overall cure rates. The costs of care may be affected by the need to support nutrient intake (eg, tube feeding), administer systemic analgesics and intravenous antibiotics, and admit to the hospital and ICU for prolonged periods.

### Etiology in Relation to Pain Mediators

The leading hypotheses for the etiology of oral mucositis include mechanisms of DNA damage, cytokine generation, injury to basal epithelium, and secondary microbial colonization, followed by healing (50). One of the challenges of studying oral mucositis pain has been the limitations of the animal models and the question of whether the animal models recapitulate the

patient's pain condition (55). The development of more sophisticated 3-dimensional oral mucosal models may provide new insights into the mediators that contribute to mucositis pain (56).

As in oral cancer pain, one of the salient molecular pain mediators of oral mucositis pain may be ET-1. This hypothesis is based on the current view of cancer therapy-induced oral mucositis pathobiology (50,57). In the current view, the origin of oral mucositis is primarily connective (ie, endothelial) rather than epithelial tissue. Before any toxic effects of chemotherapy on dividing epithelial stem cells occurs, mucositis is initiated by reactive oxygen species (ROS) in the microvasculature of the submucosal layer. ROS initiate mucositis by activating the transcription factor nuclear factor kB (NF-$\kappa$B), which in turn induces a mucositis pathogenesis process through the actions of various molecular mediators.

In one review (58), two different genetic pathways that are upregulated by NF-$\kappa$B are described. One of these pathways involves the pro-inflammatory cytokines TNF-$\alpha$, IL-1$\beta$, and IL-6, which sensitize pain fibers. ET-1 is induced by this same transcription factor and is activated by oxidative stress. The ET-1 response to oxidative stress is immediate and its regulatory genetic pathways are known. In cultured human coronary-artery smooth muscle cells and endothelial cells, ROS increase preproET-1 mRNA and ET-1 content by activating the promoter site of the precursor preproET-1 (59,60). This upregulation of ET-1 by ROS can occur by activating NF-$\kappa$B (61,62), which in turn can stimulate ET-1 gene expression (63). Further amplification of ET-1 production can then occur by positive feedback because ET-1 in turn stimulates production of more ROS (64,65). In the oral cavity, this overproduction of ET-1 could activate the unique population of trigeminal-system C fibers discussed earlier. Therefore, studies on the role of ET-1 in chemotherapy-induced oral mucositis pain are warranted.

In addition to ET-1, candidate molecular mediators for chemotherapy-induced mucositis pain and hypersensitivity include those associated with oral cancer pain, including TNF-$\alpha$, NGF, bradykinin, prostaglandins, protons, trypsin, and tryptase (Figure 1) (42). Of these candidates, the most promising is TNF-$\alpha$. It is one of the three cytokines induced by NF-$\kappa$B to initiate oral mucositis (54,66,67), and in cancers it directly generates hyperalgesia by activating the TNFR2 receptor on nerve endings. Experimental evidence for its role in oral mucositis pain is that expression of TNF-$\alpha$ mRNA in buccal samples is statistically significantly associated with the worst intensity of treatment-induced oral mucositis pain with swallowing (68). Notable in this study is the large amount of inter-individual variability in the amounts of TNF-$\alpha$ produced. More recently, a compound that inhibits the induction and signaling of TNF-$\alpha$ was found to reduce the incidence of oral mucositis associated with radiochemotherapy in patients with HNC, without reducing the tumor response to radio-chemotherapy (68,69).

Two additional candidate mediators for mucositis pain are worth noting. First, if NGF plays a role, we might expect it to affect fibers that produce neurogenic inflammation independently of the effects of ET-1. Evidence suggests that NGF is produced in oral squamous cell carcinoma. In addition, NGF appears to have a role in both cancer pain and cachexia in an oral cancer mouse model (70,71). Second, cyclooxygenase-2 expression and upregulation occurs in oral mucositis. However, a controlled clinical trial showed no effect of a prostaglandin antagonist oral rinse on chemotherapy-induced oral mucositis pain (72).

The remaining cancer pain-related candidates listed above (ie, bradykinin, protons, and trypsin-like serine proteases) warrant additional investigation. The primary contribution of ROS-induced cytokines to pain hypersensitivity is thought to be through the potentiation of the inflammatory responses and increased production of these proalgesic agents (16). In particular, serine proteases from human oral squamous cell carcinoma cells cause marked and prolonged mechanical allodynia in mice when administered into the hind paw (73). Whereas the biologic mechanisms of oral cancer pain and mucositis pain are disparate, the activated oral nociceptors responsible for generating oral pain are the same. Overlap of responsible algogens in both painful conditions is likely.

## Clinical Management: Successes and Barriers

### Current Clinical Management

Current recommendations include the use of opioid analgesics to decrease nociceptive pain (74–76). Although opioid use is a focus of recent media attention, the agents are required to effectively manage pain in most patients with HNC. However, many patients report pain characteristics (eg, burning) that can be attributed to neuropathic mechanisms (77). Neuropathic pain is more difficult to manage and opioids have limited efficacy. In addition to the agents cited above, the use of centrally acting antidepressant and anticonvulsant medications and biopsychosocial treatments is warranted (32,78–80). Topical applications for the management of oral pain include the use of local coating agents and locally acting anesthetics and analgesics (81). The potential role for topical oral applications of medications for the management of mucosal neuropathic pain warrants additional clinical trials. Saline mouth rinses, ice chips, and topical mouth rinses containing an anesthetic, diphenhydramine, and a soothing mucosal covering agent are commonly used to provide short-term relief (82). Benzydamine oral rinse is widely used throughout Europe as Tantum Verde (83) with recent evidence of reducing mucositis when used in a preventive oral rinse protocol (84). Other compounded topicals including lidocaine have been used (85).

Opioids are approved for more severe pain. However, a sequential application of acetaminophen, nonsteroidal anti-inflammatory drugs, and opioids alone was shown to be insufficient for relieving the pain of oral mucositis in cancer patients (86). Ketamine (intravenous or oral) may be used in cancer patients to relieve intractable neuropathic pain or to reduce opioid doses (87). Antidepressants or anticonvulsants may be necessary to treat mucositis-induced neuropathic pain.

The anticonvulsant gabapentin is effective for several neuropathic pain syndromes. Administering gabapentin in combination with opiates may be sufficient to adequately manage pain in oral mucositis patients (88,89). For example, cancer patients with oral mucositis were administered gabapentin starting in the second week of RT. By the final week of RT, 71% of the patients required an additional dose of oxycodone equivalent to control the pain. Only 5% of the patients experienced side effects (72,73). In a placebo-controlled study of 128 patients with HNC who were experiencing neuropathic pain, the administration of pregabalin decreased pain intensity and improved mood and quality of life (90). Although not evaluated in HNC, duloxetine is recommended to decrease pain associated with chemotherapy-induced peripheral neuropathy (91). The potential role of cannabinoids was initially evaluated in a study of 74 patients vs control subjects. Cannabis use was associated with decreases in pain, fatigue, and depressive symptoms (92).

Additional research is needed on the potential role of cannabinoids in cancer pain management.

Photobiomodulation (PBM; previously known as low-level laser therapy) is an effective and recommended intervention for the prevention of oral mucositis associated with RT and in HSCT. In addition, PBM reduces the pain associated with oral mucositis (93–96). PBM involves the local application of a coherent, narrow-banded, monochromatic light that has a cytoprotective effect during oxidative stress (93–97). Cancer patients treated with PBM in controlled clinical trials reported statistically significantly lower pain scores after 6 weeks of low-level laser therapy with no adverse effects (97).

In 2014, the Mucositis Study Group of the Multinational Association for Supportive Care in Cancer and the International Society of Oral Oncology (MASCC/ISOO) published an updated clinical practice guideline for the management of oral mucositis (98). Recommendations from this panel were based on evidence from either meta-analyses of randomized controlled trials or data from individual randomized trials. Based on the criteria that this panel used, patient-controlled analgesia with morphine was recommended for the treatment of oral mucositis pain in patients undergoing HSCT. In addition, the panel made the "suggestion," based on the existing evidence, that PBM could be used to reduce the incidence of oral mucositis and its associated pain in patients receiving high-dose chemotherapy or chemoradiotherapy before HSCT and in patients with HNC receiving RT with or without chemotherapy. In addition, based on the available evidence from a number of systematic reviews (9,10,99–103), the MASCC/ISOO panel made a number of suggestions regarding the management of pain associated with oral mucositis, including transdermal fentanyl may be effective to treat pain due to oral mucositis in patients receiving conventional or high-dose chemotherapy with or without total body irradiation; 2% morphine mouthwash may be effective to treat pain due to oral mucositis in patients receiving chemoradiation for HNC; and 0.5% doxepin mouthwash may be effective to treat pain due to oral mucositis (104)

In the MASCC/ISOO guidelines, a number of measures are described that can be used to minimize oral pain. Strict attention to oral hygiene during cancer treatment can reduce the severity of mucositis and associated pain. Patients treated with chemotherapy and/or RT should receive detailed instructions on oral hygiene before their cancer treatment. The patients should provide a return demonstration of the oral hygiene regimen during a pretreatment appointment. Following the visit, the patient should use the regimen on a routine basis throughout the day to remove plaque and loosely adherent necrotic tissue, which will help to minimize bacterial burden and reduce inflammatory mediators. Mechanical debridement and tooth brushing is necessary throughout the day. Use of alcohol-free chlorhexidine oral rinse may reduce pain and improve healing. Patients should be evaluated on an ongoing basis during and following their treatment. Weekly appointments help to motivate patients to adhere to the oral care protocol and allow for the early identification of oral lesions.

### Key Research Questions

Oral cancer pain and oral mucositis pain are complex problems. Several key research questions provide a framework to address and delineate possible underlying mechanisms. These key questions include:

1) What is the effect of chemotherapeutic drugs, targeted therapies, and immunotherapy and combinations with and without RT on the micro-neuroanatomy and electrophysiology of primary afferent nociceptors in the oral cavity?
2) What is the role of traditional nociceptive receptors such as NMDA, TRPV, TRPA, TrkA, and bradykinin?
3) How does the complex of bacterial infection, inflammation, and neurotoxicity lead to pain?
4) Does inhibition of one process break the reciprocal feedback process?
5) Do the currently used animal models of mucositis recapitulate the patient condition, and how can the models and associated nociceptive assays be improved?
6) Does the genomic heterogeneity of individuals explain the varying pain phenotypes seen in patients?
7) Does activation of primary afferent fibers in the oral cancer microenvironment contribute to oral carcinogenesis and explain the evolutionary role of pain in oral cancer?

Clearly, a transdisciplinary approach is required to generate hypotheses and develop a research plan to test them. This comprehensive approach to research will require preclinical and clinical scientists with expertise in trigeminal nociceptive mechanisms, electrophysiology, pharmacology, epithelial cell biology, cancer, epidemiology, genetics, bioinformatics, and symptom management. An increased understanding of the problem will occur through a detailed evaluation of larger patient samples. Comprehensive evaluation of associations between oral mucositis and pain phenotypes and molecular mechanisms (eg, gene expression, genetics, DNA methylation) will identify patients at higher risk as well as identify molecular targets. These studies require the expertise of clinician scientists, molecular geneticists, and computational biologists.

## Strategies to Promote the Development and Funding of Future Research

Funding for biomedical research is under tight fiscal constraints at the national level. Securing new and continued funding is a challenge for even highly experienced, independent investigators. The complexity of cancer pain, including pain caused by oral cancer as well as oral mucositis, requires substantial and sustained sources of funding. The statistically significant amount of patient morbidity and substantial health-care costs associated with mucositis and pain warrant that creative partnerships among the federal government, pharmaceutical companies, cancer foundations, patient advocacy groups, and philanthropists be explored as potential sources of funding.

The precise causes of oral pain in cancer patients, whether from primary oral cancer or secondary to treatment for another cancer, remain unknown. Oral pain in these patients remains difficult to treat during and early following cancer therapy and throughout survivorship (105). Treatment should be directed at the mechanisms that underlie this pain. With this approach, it is estimated that patient satisfaction with pain management can be achieved 70–97% of the time (106). Novel approaches for prevention and management are likely to emerge from continued research into the molecular aspects of oral pain in cancer patients.

## Notes

Affiliations of authors: Department of Surgery, City of Hope, Duarte, CA (JBE); Department of Surgery, Cedars-Sinai Health

System, Los Angeles, CA (JBE); Seattle Cancer Care Alliance, Seattle, WA (JBE); Department of Physiological Nursing, University of California San Francisco, San Francisco, CA (CM).

The authors have no conflicts of interest or funding to disclose.

Writing assistance was provided by Stephen Arthur. The illustration was designed and produced by Stephen Arthur.

For support see Funding Acknowledgement section of Monograph.

## References

1. Cuffari L, Tesseroli de Siqueira JT, Nemr K, et al. Pain complaint as the first symptom of oral cancer: a descriptive study. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2006;102(1):56–61.
2. Holländer-Mieritz C, Johansen J, Johansen C, et al. Comparing the patients' subjective experiences of acute side effects during radiotherapy for head and neck cancer with four different patient-reported outcomes questionnaires. *Acta Oncol*. 2019;58(5):603–609.
3. Carpén T, Sjöblom A, Lundberg M, et al. Presenting symptoms and clinical findings in HPV-positive and HPV-negative oropharyngeal cancer patients. *Acta Oto-Laryngol*. 2018;138(5):513–518. Erratum in: *Acta Otolaryngol*. 2018; 138(7):675.
4. Kolokythas A, Connelly ST, Schmidt BL. Validation of the University of California San Francisco oral cancer pain questionnaire. *J Pain*. 2007;8(12): 950–953.
5. Epstein JB, Wilkie DJ, Fischer DJ, et al. Neuropathic and nociceptive pain in head and neck cancer patients receiving radiation therapy. *Head Neck Oncol*. 2009;1:26. doi.10.1186/1758-3284-1-26.
6. Potter J, Higginson IJ, Scadding JW, et al. Identifying neuropathic pain in patients with head and neck cancer: use of the Leeds assessment of neuropathic symptoms and signs scale. *J R Soc Med*. 2003;96(8):379–383.
7. Chen SC, Liao CT, Chang JT. Orofacial pain and predictors in oral squamous cell carcinoma patients receiving treatment. *Oral Oncol*. 2011;47(2):131–135.
8. Modi BJ, Knab B, Feldman LE, et al. Review of current treatment practices for carcinoma of the head and neck. *Expert Opin Pharmacother* 2005;6(7): 1143–1155.
9. Peterson DE, Öhrn K, Bowen J, et al. Systematic review of oral cryotherapy for management of oral mucositis caused by cancer therapy. *Support Care Cancer*. 2013;21(1):327–332.
10. Migliorati C, Hewson I, Lalla RV, et al. Systematic review of laser and other light therapy for the management of oral mucositis in cancer patients. *Support Care Cancer*. 2013;21(1):333–341.
11. Yarom N, Ariyawardana A, Hovan A, et al. Systematic review of natural agents for the management of oral mucositis in cancer patients. *Support Care Cancer*. 2013;21(11):3209–3221.
12. Al-Ansari S, Zecha JA, Barasch A, et al. Oral mucositis induced by anticancer therapies. *Curr Oral Health Rep*. 2015;2(4):202–211.
13. Cuellar JM, Manering NA, Klukinov M, et al. Thermal nociceptive properties of trigeminal afferent neurons in rats. *Mol Pain* 2010;6:39. doi: 10.1186/1744-8069-6-39.
14. Lazarov NE. Comparative analysis of the chemical neuroanatomy of the mammalian trigeminal ganglion and mesencephalic trigeminal nucleus. *Prog Neurobiol*. 2002;66(1):19–59.
15. Haas HS, Linecker A, Pfragner R, et al. Peripheral glutamate signaling in head and neck areas. *Head Neck*. 2010;32(11):1554–1572.
16. Basbaum AI, Bautista DM, Scherrer G, et al. Cellular and molecular mechanisms of pain. *Cell* 2009;139(2):267–284.
17. Sessle BJ. Orofacial pain. In: H Merskey, JD Loeser, R Dubner, et al., eds. *The Paths of Pain, 1975–2005*. Seattle: IASP Press; 2005:131–150.
18. Alessandri-Haber N, Dina OA, Chen X, et al. TRPC1 and TRPC6 channels cooperate with TRPV4 to mediate mechanical hyperalgesia and nociceptor sensitization. *J Neurosci*. 2009;29(19):6217–6228.
19. Gerhold KA, Bautista DM. Molecular and cellular mechanisms of trigeminal chemosensation. *Ann N Y Acad Sci*. 2009;1170:184–189.
20. Rau KK, Jiang N, Johnson RD, et al. Heat sensitization in skin and muscle nociceptors expressing distinct combinations of TRPV1 and TRPV2 protein. *J Neurophysiol*. 2007;97(4):2651–2662.
21. Nilius B, Owsianik G, Voets T, et al. Transient receptor potential cation channels in disease. *Physiol Rev*. 2007;87(1):165–217.
22. Colburn RW, Lubin ML, Stone DJ Jr, et al. Attenuated cold sensitivity in TRPM8 null mice. *Neuron*. 2007;54(3):379–386.
23. Kobayashi K, Fukuoka T, Obata K, et al. Distinct expression of TRPM8, TRPA1, and TRPV1 mRNAs in rat primary afferent neurons with adelta/c-fibers and colocalization with trk receptors. *J Comp Neurol*. 2005;493(4):596–606.
24. Stenholm E, Bongenhielm U, Ahlquist M, et al. VRl- and VRL-l-like immunoreactivity in normal and injured trigeminal dental primary sensory neurons of the rat. *Acta Odontol Scand*. 2002;60(2):72–79.
25. Kim YS, Son JY, Kim TH, et al. Expression of transient receptor potential ankyrin 1 (TRPA1) in the rat trigeminal sensory afferents and spinal dorsal horn. *J Comp Neurol*. 2010;518(5):687–6698.
26. Gaspersic R, Kovacic U, Cor A, et al. Expression of TrkA receptor for neurotrophins in trigeminal neurons innervating the rat gingivomucosal tissue. *Neurosci Lett*. 2007;418(3):253–256.
27. Chichorro JG, Fiuza CR, Bressan E, et al. Endothelins as pronociceptive mediators of the rat trigeminal system: role of ETA and ETB receptors. *Brain Res*. 2010;1345:73–83.
28. Uddman R, Tajti J, Cardell LO, et al. Endothelin ETA and ETB receptor expression in the human trigeminal ganglion. *Neuro Endocrinol Lett*. 2006;27(3): 345–349.
29. Chichorro JG, Zampronio AR, Cabrini DA, et al. Mechanisms operated by endothelin ETA and ETB receptors in the trigeminal ganglion contribute to orofacial thermal hyperalgesia induced by infraorbital nerve constriction in rats. *Neuropeptides*. 2009;43(2):133–142.
30. Feldman-Goriachnik R, Hanani M. Functional study of endothelin B receptors in satellite glial cells in trigeminal ganglia. *Neuroreport*. 2011;22(10): 465–469.
31. Connelly ST, Schmidt BL. Evaluation of pain in patients with oral squamous cell carcinoma. *J Pain*. 2004;5(9):505–510.
32. Epstein JB, Elad S, Eliav E, et al. Orofacial pain in cancer: part II—clinical perspectives and management. *J Dent Res*. 2007;86(6):506–518.
33. Murphy BA, Dietrich MS, Wells N, et al. Reliability and validity of the Vanderbilt head and neck symptom survey: a tool to assess symptom burden in patients treated with chemoradiation. *Head Neck*. 2010;32(1):26–37.
34. Epstein JB, Hong C, Logan RM, et al. A systematic review of orofacial pain in patients receiving cancer therapy. *Support Care Cancer*. 2010;18(8):1023–1031.
35. Murphy BA, Beaumont JL, Isitt J, et al. Mucositis-related morbidity and resource utilization in head and neck cancer patients receiving radiation therapy with or without chemotherapy. *J Pain Symptom Manage*. 2009;38(4): 522–532.
36. Paice JA. Navigating cancer pain management in the midst of the opioid epidemic. *Oncology*. 2018;32(8):386–390, 403.
37. Paice JA. Cancer pain management and the opioid crisis in America: how to preserve hard-earned gains in improving the quality of cancer pain management. *Cancer*. 2018;124(12):2491–2497.
38. Portenoy RK, Ahmed E. Cancer pain syndromes. *Hematol Oncol Clin North Am*. 2018;32(3):371–386.
39. Romero-Reyes M, Salvemini D. Cancer and orofacial pain. *Med Oral Patol Oral Cir Bucal*. 2016;21(6):e665–e671.
40. Harano N, Ono K, Hidaka K, et al. Differences between orofacial inflammation and cancer pain. *J Dent Res*. 2010;89(6):615–620.
41. Schmidt BL, Hamamoto DT, Simone DA, et al. Mechanism of cancer pain. *Mol Interv*. 2010;10(3):164–178.
42. Benoliel R, Epstein J, Eliav E, et al. Orofacial pain in cancer: part I—mechanisms. *J Dent Res*. 2007;86(6):491–505.
43. Scheff NN, Ye Y, Battacharya A, et al. Tumor necrosis factor alpha secreted from oral squamous cell carcinoma contributes to cancer pain and associated inflammation. *Pain*. 2017;158(2):2396–2409.
44. Barr TP, Kam S, Khodorova A, et al. New perspectives on the endothelin axis in pain. *Pharmacol Res*. 2011;63(6):532–540.
45. Pickering V, Jordan RC, Schmidt BL. Elevated salivary endothelin levels in oral cancer patients—a pilot study. *Oral Oncol*. 2007;43(1):37–41.
46. Schmidt BL, Pickering V, Liu S, et al. Peripheral endothelin A receptor antagonism attenuates carcinoma-induced pain. *Eur J Pain*. 2007;11(4):406–414.
47. Bhalla S, Ciaccio N, Wang ZJ, et al. Involvement of endothelin in morphine tolerance in neuroblastoma (SH-SY5Y) cells. *Exp Biol Med*. 2006;231(6): 1152–1156.
48. Bhalla S, Matwyshyn G, Gulati A. Morphine tolerance does not develop in mice treated with endothelin-A receptor antagonists. *Brain Res*. 2005; 1064(1–2):126–135.
49. Kopruszinksi CM, dos Reis RC, Gambeta E, et al. Blockade of endothelin receptors reduces tumor-induced ongoing pain and evoked hypersensitivity in a rat model of facial carcinoma induced pain. *Eur J. Pharmacol*. 2018;818:132–140.
50. Sonis ST, Elting LS, Keefe D, et al. Perspectives on cancer therapy-induced mucosal injury: pathogenesis, measurement, epidemiology, and consequences for patients. *Cancer*. 2004;100(9 Suppl):1995–2025.
51. Schubert MM, Williams BE, Lloid ME, et al. Clinical assessment scale for the rating of oral mucosal changes associated with bone marrow transplantation. Development of an oral mucositis index. *Cancer*. 1992;69(10):2469–2477.
52. Elting LS, Cooksley C, Chambers M, et al. The burdens of cancer therapy. Clinical and economic outcomes of chemotherapy-induced mucositis. *Cancer*. 2003;98(7):1531–1539.
53. Vera-Llonch M, Oster G, Ford CM, et al. Oral mucositis and outcomes of autologous hematopoietic stem-cell transplantation following high-dose melphalan conditioning for multiple myeloma. *J Support Oncol*. 2007;5(5):231–235.
54. Sonis ST, Oster G, Fuchs H, et al. Oral mucositis and the clinical and economic outcomes of hematopoietic stem-cell transplantation. *J Clin Oncol*. 2001;19(8):2201–2205.
55. Viet CT, Corby PM, Akinwande A, et al. Review of preclinical studies on treatment of mucositis and associated pain. *J Dent Res*. 2014;93(9):868–875.
56. Lambros MP, DeSalvo MK, Mulamalla HC, et al. Genome wide expression after different doses of irradiation of a three-dimensional (3D) model of oral mucosal. *Genom Data*. 2016;7:137–139.
57. Sonis ST. Oral mucositis. *Anticancer Drugs*. 2011;22(7):607–612.

58. de Araujo AA, Varela H, de Medeiros CA, et al. Azilsartan reduced TNF-alpha and IL-1beta levels, increased IL-10 levels and upregulated VEGF, FGF, KGF, and TGF-alpha in an oral mucositis model. *PLoS One*. 2015;10(2):e0116799.
59. Kahler J, Ewert A, Weckmüller J, et al. Oxidative stress increases endothelin-1 synthesis in human coronary artery smooth muscle cells. *J Cardiovasc Pharmacol*. 2001;38(1):49–57.
60. Kahler J, Mendel S, Weckmüller J, et al. Oxidative stress increases synthesis of big endothelin-1 by activation of the endothelin-1 promoter. *J Mol Cell Cardiol*. 2000;32(8):1429–1437.
61. Busse R, Fleming I. Endothelial dysfunction in atherosclerosis. *J Vasc Res*. 1996;33(3):181–194.
62. Geng Z, Rong Y, Lau BH. S-allyl cysteine inhibits activation of nuclear factor kappa B in human T cells. *Free Radic Biol Med*. 1997;23(2):345–350.
63. Bierhaus A, Chevion S, Chevion M, et al. Advanced glycation end product-induced activation of NF-kappaB is suppressed by alpha-lipoic acid in cultured endothelial cells. *Diabetes*. 1997;46(9):1481–1490.
64. Dong F, Zhang X, Wold LE, et al. Endothelin-1 enhances oxidative stress, cell proliferation and reduces apoptosis in human umbilical vein endothelial cells: role of ETB receptor, NADPH oxidase and caveolin-1. *Br J Pharmacol*. 2005;145(3):323–333.
65. Pollock DM, Pollock JS. Endothelin and oxidative stress in the vascular system. *Curr Vasc Pharmacol*. 2005;3(4):365–367.
66. Hall PD, Benko H, Hogan KR, et al. The influence of serum tumor necrosis factor-alpha and interleukin-6 concentrations on nonhematologic toxicity and hematologic recovery in patients with acute myelogenous leukemia. *Exp Hematol*. 1995;23(12):1256–1260.
67. Epstein JB, Silverman S Jr, Paggiarino DA, et al. Benzydamine HCl for prophylaxis of radiation-induced oral mucositis: results from a multicenter, randomized, double-blind, placebo-controlled clinical trial. *Cancer*. 2001; 92(4):875–885.
68. Fall-Dickson JM, Ramsay ES, Castro K, et al. Oral mucositis-related oropharyngeal pain and correlative tumor necrosis factor-alpha expression in adult oncology patients undergoing hematopoietic stem cell transplantation. *Clin Ther*. 2007;29(11; supp l):2547–2561.
69. Watanabe T, Ishihara M, Matsuura K, et al. Polaprezinc prevents oral mucositis associated with radiochemotherapy in patients with head and neck cancer. *Int J Cancer*. 2010;127(8):1984–1990.
70. Kolokythas A, Cox DP, Dekker N, Schmidt BL. Nerve growth factor and tyrosine kinase A receptor in oral squamous cell carcinoma: is there an association with perineural invasion? *J Oral Maxillofac Surg*. 2010;68(6): 1290–1295.
71. Ye Y, Dang D, Zhang J, et al., Nerve growth factor links oral cancer progression, pain, and cachexia. *Mol Cancer Ther*. 2011;10(9):1667–1676. doi: 10.1158/1535-7163.MCT-11-0123.
72. Lalla RV, Gordon GB, Schubert M, et al. A randomized, double-blind, placebo-controlled trial of misoprostol for oral mucositis secondary to high-dose chemotherapy. *Support Care Cancer*. 2012;20(8):1797–1804.
73. Lam DK, Schmidt BL. Serine proteases and protease-activated receptor 2-dependent allodynia: a novel cancer pain pathway. *Pain* 2010;149(2): 263–272.
74. McDermott, JD, Eguchi M, Stokes WA, et al. Short- and long-term opioid use in patients with oral and oropharynx cancer. *Otolaryngol Head Neck Surg*. 2018;160(3):409–419. doi:10.1177/0194599818808513.
75. Giusti R, Bossi P, Mazzotta M, Filetti M, Iacono D, Marchetti P. The use of fentanyl in pain management in head and neck cancer patients: a narrative review. *Br J Pain*. 2018;12(3):155–162.
76. Saraswathula A, Chen MM, Medumbai SC, Whittemore AS, Divi V. Persistent postoperative opioid use in older head and neck cancer patients. *Otolaryngol Head Neck Surg*. 2018;160(3):380–387. doi: 10.1177/0114599818778276.
77. Arantes D, Costa N, Resende T, et al. Dental approach of orofacial pain in head and neck cancer patients. *J Clin Exp Dent*. 2018;10(11):e11082–e11090.
78. Newport K, Coyne P. Topical cocaine for relief of mucosal pain. *J Pain Palliat Care Pharmacother*. 2010;24(2):149–151.
79. Davis MP. Recent development in therapeutics for breakthrough pain. *Expert Rev Neurother*. 2010;10(5):757–773.
80. Gatti A, Reale C, Luzi M, et al. Effects of opioid rotation in chronic pain patients: ORTIBARN study. *Clin Drug Investig*. 2010;30(suppl 2):39–47.
81. Lee HS. Recent advances in topical anesthesia. *J Dent Anesth Pain Med*. 2016; 16(4):237.
82. Lalla RV, Sonis ST, Peterson DE. Management of oral mucositis in patients who have cancer. *Dent Clin North Am*. 2008;52(1):61–77.
83. Wu JC, Beale KK, Ma JD. Evaluation of current and upcoming therapies in oral mucositis prevention. *Future Oncol*. 2010;6(11):1751–1770.
84. Chitapanarux I, Tungkasamit T, Petsuksiri J, et al. Randomized control trial of benzydamine HCL vs sodium bicarbonate for prophylaxis of concurrent chemoradition-induced oral mucositis. *Support Care Cancer*. 2018;26(3): 879–886.
85. Mogensen S, Treldal C, Kristensen CA, et al. Effect of bupivacaine lozenges on oral mucositis pain: a randomized controlled multicenter phase II study. *Pain Rep*. 2017;2(5):e619.
86. Ling IS, Larsson B. Individualized pharmacological treatment of oral mucositis pain in patients with head and neck cancer receiving radiotherapy. *Support Care Cancer*. 2011;19(9):1343–1350.
87. Paice JA, Ferrell B. The management of cancer pain. *CA Cancer J Clin*. 2011; 61(3):157–182.
88. Bar Ad V, Weinstein G, Dutta PR, et al. Gabapentin for the treatment of pain related to radiation-induced mucositis in patients with head and neck tumors treated with intensity-modulated radiation therapy. *Head Neck*. 2010;32(2):173–177.
89. Bar Ad V, Weinstein G, Dutta PR, et al. Gabapentin for the treatment of pain syndrome related to radiation-induced mucositis in patients with head and neck cancer treated with concurrent chemoradiotherapy. *Cancer*. 2010; 116(17):4206–4213.
90. Jiang J, Li Y, Shen Q, et al. Effect of pregabalin on radiotherapy-related neuropathic pain in patients with head and neck cancer: a randomized controlled trial. *J Clin Oncol*. 2019;37:135–143.
91. Hershman DL, Lacchetti C, Dworkin RH, et al. Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol*. 2014;32(18):1941–1967.
92. Zhang H, Xie M, Archibald SD, Jackson BS, Gupta MK. Association of marijuana use with psychosocial and quality of life outcomes among patients with head and neck cancer. *JAMA Otolaryngol Head Neck Surg*. 2018;144: 1017–1022.
93. Bjordal JM, Bensadoun RJ, Tunèr J, et al. A systematic review with meta-analysis of the effect of low-level laser therapy (LLLT) in cancer therapy-induced oral mucositis. *Support Care Cancer*. 2011;19(8):1069–1077.
94. Carvalho PA, Jaguar GC, Pellizzon AC, et al. Evaluation of low-level laser therapy in the prevention and treatment of radiation-induced mucositis: a double-blind randomized study in head and neck cancer patients. *Oral Oncol*. 2011;47(12):1176–1181.
95. Arun Maiya G, Sagar MS, Fernandes D. Effect of low level helium-neon (He-Ne) laser therapy in the prevention & treatment of radiation induced mucositis in head & neck cancer patients. *Indian J Med Res*. 2006;124(4):399–402.
96. Bensadoun RJ, Nair RG. Low-level laser therapy in the prevention and treatment of cancer therapy-induced mucositis: 2012 state of the art based on literature review and meta-analysis. *Curr Opin Oncol*. 2012;24(4):363–370.
97. Marin-Conde F, Castellanos-Cosano L, Pachon-Ibariez J, Serrera-Figallo MA, Gutierrez-Perez JL, Torres-Lagares D. Photobiomodulation with low-level laser therapy reduces oral mucositis caused by head and neck radiochemotherapy: prospective randomized controlled trial. *Int J Oral Maxillofac Surg*. 2018; doi:10.1016/j.ihom.2018.12.006. [Epub ahead of print]
98. Keefe DM, Schubert MM, Elting LS, et al. Updated clinical practice guidelines for the prevention and treatment of mucositis. *Cancer*. 2007;109(5):820–831.
99. McGuire DB, Fulton JS, Park J, et al. Systematic review of basic oral care for the management of oral mucositis in cancer patients. *Support Care Cancer*. 2013;21(11):3165–3177.
100. Jensen SB, Jarvis V, Zadik Y, et al. Systematic review of miscellaneous agents for the management of oral mucositis in cancer patients. *Support Care Cancer*. 2013;21(11):3223–3232.
101. Saunders DP, Epstein JB, Elad S, et al. Systematic review of antimicrobials, mucosal coating agents, anesthetics, and analgesics for the management of oral mucositis in cancer patients. *Support Care Cancer*. 2013;21(11):3191–3207.
102. Nicolatou-Galitis O, Sarri T, Bowen J, et al. Systematic review of anti-inflammatory agents for the management of oral mucositis in cancer patients. *Support Care Cancer*. 2013;21(11):3179–3189.
103. Nicolatou-Galitis O, Sarri T, Bowen J, et al. Systematic review of amifostine for the management of oral mucositis in cancer patients. *Support Care Cancer*. 2013;21(1):357–364.
104. Lalla RV, Bowen J, Barasch A, et al. MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. *Cancer*. 2014; 120(10):1453–1461.
105. Wulff-Burchfield E, Dietrich MS, Ridner S, Murphy BA. Late systemic symptoms in head and neck cancer survivors. *Support Care Cancer*. 2018; doi: 10.1007/s00520-018-4577-3.
106. von Gunten CF. Pathophysiology of pain in cancer. *J Pediatr Hematol Oncol*. 2011;33(Suppl 1):S12–S18.