CLINICAL INVESTIGATION

Assessment and management of mucositis in head and neck cancer patients

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Oral mucositis (OM) is a significant problem in patients with head and neck cancer undergoing chemoradiation treatments. Severe OM develops in more than 90% of patients undergoing combined chemotherapy and radiation. OM is not only painful but also limits adequate nutritional intake and decreases the patient's willingness to continue treatment. When severe, it is responsible for acute and chronic complications such as aspiration, prolonged dysphagia, scarring and fibrosis. In spite of all the advances made in understanding the pathobiology of OM, there is currently no prophylactic therapy with proven efficacy. Strategies to limit the extent of OM and to manage its symptoms include basic oral care, supportive medications, nutritional support and limiting the use of aggressive treatments to high-risk patients. This review focuses on OM recognition, preventive measurements, symptom-management strategies, and identifies current research studies addressing OM prevention.

Keywords: chemotherapy • head and neck cancer • mucositis • nutrition • pain • radiation

Oral mucositis (OM) develops in almost all patients receiving radiotherapy (RT) to the upper aerodigestive tract [1,2]. Patients receiving cumulative radiation doses >5000 cGy, hyperfractionation with dose escalation, accelerated radiation schedules, and/or concomitant chemo-RT (CRT) are more likely to develop OM [3–5]. OM is reported to be of severe intensity by 75–90% of this patient population [6]. OM complications are responsible for reduction in the dose of chemotherapy in approximately 60% of patients and for discontinuation of the chemotherapy regimen in approximately 30% of patients [7]. OM is often difficult to visualize when it occurs in the critical hypopharyngeal, laryngeal and oropharyngeal areas, where OM can be associated with prolonged pain and functional impairment. During therapy, pain is reported in essentially all head and neck cancer patients [8]. Oral discomfort persists in almost a half of patients for extended periods of time, even following resolution of visible OM [8]. OM symptoms and associated comorbidities (pain, dehydration, weight loss, and systemic infections among others [9]) adversely impact quality of life (QOL) and economic outcomes. Pain management is one of the most important aspects of symptom control during head and neck cancer treatment, but it has been shown that few patients are given adequate opioid analgesia [10].

Clinical features of mucositis

The clinical findings of OM are very predictable in patients undergoing radiation treatments to the superior aerodigestive tract [11]. The use of chemotherapy delivered concomitantly with radiation increases the severity and impacts on the time-course of OM. Erythema of the mucosa is noticed at the very beginning of the

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second week of radiation, and focal mucosal ulcers are noticed a few days later. At this stage, patients typically start to complain of pain. Extended areas of confluent mucosal ulceration are usually seen early during the fourth week of radiation. At this point, the ability to continue with a full oral diet is usually compromised. An abrupt appearance of severe, confluent ulcers and/or early initiation of ulceration that affect the keratinized mucosa of the dorsal tongue, gingival, or the hard palate are often associated with an infectious etiology [11,12]. During the fifth and sixth weeks of radiation, a confluent ulcerative lesion covered by a fibrous exudate called pseudo-membrane is usually present. At this stage, patients usually complain of severe pain that is only partially controlled with opioids, and they are unable to continue with an oral diet. The majority of patients suffering from severe OM will need a percutaneous endoscopic gastrostomy (PEG) feeding tube in order to continue with an adequate caloric intake. Severe OM persists for 2–4 weeks after the end of treatment and then it slowly resolves completely [11]. In some patients, limited ulceration in high-dose areas or in the posterior regions of the mucosa may persist for periods as long as several months. Severe OM is associated with systemic signs and symptoms such as weight loss out of proportion to caloric intake, fatigue, anorexia, dehydration, and deconditioning. These signs and symptoms are probably related to the high levels of pro-inflammatory cytokines released during the development of OM [13–16].

Pathobiology of mucositis

The most descriptive biological model for CRT-induced OM was developed by Sonis *et al.* [7,11,13,17]. The model describes five overlapping stages: initiation, up-regulation, message generation, ulceration and healing. The first stage involves the production of reactive oxygen species, CRT-induced direct damage to cells, and the initiation of other biological events that create a cascade of reactions contributing to tissue damage. Activation of the signal transducer and activator of transcription 3 and the NF-κβ leads to an increase in pro-inflammatory cytokines (i.e., IL-6, TNFα). Positive-feedback mechanisms result in amplification and acceleration of the process, which eventually leads to ulceration. Bacterial colonization of the ulcerated mucosa activates macrophages to produce additional inflammatory cytokines to enhance the tissue-damaging process. After completion of the CRT treatment, healing occurs and the epithelium appears normal again.

Assessment of mucositis

To optimize the supportive treatment of mucositis-associated symptoms of patients undergoing CRT treatments of the head and neck area, a formal assessment of OM during treatment is needed [13,14,18,19]. In the literature, different studies use various OM assessment scales to measure the effects of any given preventive or curative therapy for mucositis [11]. The Multinational Association of Supportive Care in Cancer and the International Society for Oral Oncology proposed that an OM assessment tool should be objective, sensitive, validated, reliable and easy to use in all clinical situations and applications. None of the available clinical tools to assess OM meets all the criteria outlined above [7,20]. The Radiation Therapy Oncology Group and European Organization for Research and Treatment of Cancer mucositis grading system and the Objective Mucositis Assessment Scale are mostly descriptive scales that do not consider patient reported variables [21,22]. The World Health Organization scale is easy to use and is based on clinical observation (erythema and ulceration) in combination with the patient's ability to keep an oral diet [11]. The National Cancer Institute Common Terminology Criteria for Adverse Events system is usually used in clinical trials to document the side effects caused by different anticancer therapies. The 4.0 version evaluates OM based on patient-reported variables such as pain, dysphagia and eating behavior, whereas the 3.0 version uses objective findings during the clinical exam such as erythema, ulceration and bleeding [101]. The 4.0 version has the advantage of a better correlation with the changes in QOL during concomitant CRT treatments [23]. Since patient-reported symptoms tend to be more severe than those recorded by physicians, the Oral Mucositis Daily Questionnaire was created to record patient-reported outcomes of OM on a daily basis without requiring clinic visits. This questionnaire, in addition to periodic clinical assessments, may enable clinicians to identify and manage OM more rapidly and to identify improvements with investigational agents more precisely. This is particularly important for patients with larynx, oropharynx and/or hypopharynx cancers, where the direct assessment of mucositis intensity is extremely difficult [6].

Mucositis prevention

There are no therapies with proven efficacy for the prevention of OM (Table 1). In part, this is due to the fact that many trials consider mucositis prevention an 'all or none' goal, and others try to distinguish between reduction of severity and duration of OM as a preventive goal [11]. Although there are no data to support its routine use, basic oral care is generally recommended as a preventive measure and includes frequent brushing in a non-traumatic fashion with a

Table 1. Compounds studied for mucositis prevention in head and neck cancer.

Compound	Study type	Efficacy	Use recommended by current guidelines (ASCO, ESMO, MASCC)
G-CSF	Phase III	No improvement	No
GM-CSF	Phase III	No improvement	No
KGF-1	Phase III	Insufficient data	No
Amifostine	Phase III	Insufficient data	No
Glutamine	Phase III	Insufficient data	No
Benzydamine hydrochloride	Phase III	Effective in patients receiving moderate RT doses	Yes (MASCC, ESMO)
LLLT	Phase III	Insufficient data	No

ASCO: American Society of Clinical Oncology; ESMO: European Society for Medical Oncology; LLLT: Low-level laser therapy; MASCC: Multinational Association of Supportive Care in Cancer; RT: Radiotherapy.

soft brush, flossing as tolerated, frequent rinsing with bland solutions (normal saline with sodium bicarbonate), and moisturizing agents [7,20,24].

G-CSF is currently used for the primary and secondary prevention of febrile neutropenia in high-risk patients receiving chemotherapy. It also decreases the incidence of OM in the setting of combination chemotherapy for the treatment of solid tumors. In a randomized, double-blind, placebo-controlled trial in patients with squamous cell carcinoma of the head and neck (SCCHN) receiving postoperative RT, G-CSF and placebo were both administered subcutaneously on a daily basis during the course of RT. Unfortunately, only 41 patients were enrolled and the study was closed due to poor accrual. Patients in the study-drug arm were able to complete the radiation course in a shorter period of time (48.4 ± 4.32 days vs 51.6 ± 1 .84 days; p = 0.005) and also had better overall survival (hazard ratio: 0.37; p = 0.037) [25]. On the other hand, a randomized multicentric trial evaluating the preventive effect of G-CSF on patients receiving hyperfractionated RT or CRT showed an unexpected increase in locoregional failures in patients with stage III–IV SCCHN [26]. Some preliminary reports of small studies suggested that GM-CSF might have a preventive effect on the development of OM. To address this issue, the Radiation Therapy Oncology Group designed a placebo-controlled, double-blind, prospective randomized trial in patients undergoing RT with curative intent for tumors of the oral cavity and oropharynx. Patients were randomized to receive either GM-CSF or placebo subcutaneously, three times a week, during the radiation course. There was no protective effect of GM-CSF in terms of severity of OM and no impact on the QOL during and after completion of therapy [27]. These data do not support the standard use of G-CSF or GM-CSF in clinical practice.

KGF-1, a keratinocyte growth factor, exerts cytoprotective effects on epithelial cells. Palifermin (Kepivance; Swedish Orphan Biovitrum, Stockholm, Sweden), an N-terminal, truncated version of KGF, has been used in clinical practice. Two double-blinded, randomized, placebo-controlled trials assessed the efficacy of Palifermin on the prevention of OM in head and neck cancer patients. In the first trial, 186 patients with stages II–IVB carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx received adjuvant therapy after surgical resection. CRT with triweekly cisplatin was the adjuvant regimen used in this trial. Patients were randomly assigned to receive weekly palifermin 120 μg/kg or placebo from 3 days before and continuing throughout CRT. Severe OM was seen in 47 (51%) of 92 patients administered palifermin and 63 (67%) of 94 administered placebo (p = 0.027). Neither patient-reported mouth and throat soreness scores nor treatment breaks differed between treatment arms [28]. In the second trial, patients with newly diagnosed, unresected stage III–IVB squamous cell carcinoma of the oral cavity, oropharynx, nasopharynx, hypopharynx, or larynx receiving CRT with cisplatin (100 mg/m^2 on days 1, 22, and 43) received palifermin (180 μcg/kg) or placebo before starting CRT and then once weekly for 7 weeks. OM was significantly lower for palifermin than for placebo (54 vs 69%; p = 0.041). However, opioid analgesic use, average mouth and throat soreness scores, and CRT compliance were not significantly different between treatment arms [29]. Interestingly, the benefit of palifermin in physician-assessed OM in both trials was not paralleled by a better patient-reported outcome, assessed through the mouth and throat soreness score. Generally, adverse events reported by physicians are less accurate than those reported by patient-reported outcome instruments. Indeed, for OM, some clinicians have proposed replacing physician scales with patient-assessed OM reporting. On the other hand,

it appears that both the patient and clinician provide information of value that, when combined, provides a more accurate understanding of the patient's symptoms [24,30]. Thus, the role of palifermin in OM prevention, along with its safety profile, remains unproven and must be more fully defined in future trials.

Amifostine (WR-1035, Ethyol®; MedImmune Pharma, Nijmegen, The Netherlands) is an organic thiophosphate that initially was thought to have a protective effect on the bone marrow and the GI mucosa in cancer patients receiving CRT. Its mechanism of action is as a free radical scavenger that protects the DNA from direct damage and reduces the levels of pro-inflammatory cytokines that are up-regulated during the course of RT. A literature review on the use of amifostine to prevent OM in patients receiving RT or CRT for SCCHN was unable to give any recommendation for or against its routine use due to inconsistent results [31]. A randomized Phase II study assessed the preventive effect of amifostine on the incidence of severe OM. Head and neck cancer patients with locoregionally advanced disease received definitive CRT with weekly carboplatin/paclitaxel with or without amifostine. The treatment schedule consisted of four weekly doses of carboplatin with an AUC of 1.5 and paclitaxel 45 mg/m^2 concurrently with a concomitant boost radiation technique. The patients that participated in the study were randomized to a daily dose of 500 mg of amifostine administered subcutaneously or no amifostine. The severity of OM and xerostomia was similar in both arms with an incidence of grade III OM of 75% in the group of patients randomized to amifotine and 70% in the group of patient that did not receive the study drug [32]. The results of these studies do not support the use of amifostine for the prevention of OM or xerostomia associated with CRT.

Glutamine is one of the most important sources of energy for the constant cell renewal of the GI tract epithelium. During a normal metabolic state, the human body has a large repository of glutamine. There is strong evidence that during many catabolic states, such as sepsis or cancer, the body's glutamine stores are depleted [33]. It has been shown that head and neck cancer patients receiving cancer treatments have depleted stores of glutamine with the consequent increased risk of CRT-induced toxicities [34,35]. The supplementation of glutamine to this patient population may reduce the side effects of different cancer treatments. The protective effect of glutamine administered orally on the incidence of OM was assessed in head and neck cancer patients. In a double-blinded placebo-controlled trial, patients with head and neck cancer receiving definitive or postoperative RT were randomized to receive daily oral glutamine suspension (16 g) or placebo. Patients were instructed to swish the test solutions four times per day during the course of radiation. There was a shorter duration of severe OM assessed clinically in the group of patients receiving glutamine. No difference in the severity and duration of OM was reported by the patients [34]. In a second double-blinded, placebo-controlled study, the safety and OM-preventive effects of glutamine administered intravenously were assessed in head and neck cancer patients receiving definitive CRT. Patients were blindly assigned to receive either intravenous L-alanyl-L-glutamine 0.4 g/kg weight/day or an equal volume of saline (placebo) during chemotherapy days. There was a higher incidence of patients suffering severe OM in the placebo group compared with the glutamine group (67 vs 14%; p = 0.007). Another interesting finding of the study was that patients receiving the study drug experienced less pain and had fewer PEG tube insertions for nutritional support compared with the group of patients receiving placebo [35]. The difference in these results might be partially explained by the fact that oral glutamine is usually absorbed in the upper part of the jejunum and only a small fraction can be detected in the portal vein. The rest is utilized mainly by enterocytes and immune competent cells of the upper part of the GI tract. In addition, when the portal blood reaches the liver, more glutamine is utilized before a smaller fraction of the enterally provided glutamine can appear in the general circulation to become available to different tissues. In contrast, parenterally provided glutamine is distributed to the different tissues of the body in relation to the bloodflow distribution between these tissues and organs [33]. Currently, the use of glutamine for prevention of mucositis in head and neck cancer patients is not recommended by international guidelines [18–20].

Benzydamine hydrochloride, a nonsteroidal agent with analgesic, anesthetic, anti-inflammatory and antimicrobial properties, has been found to be efficacious for both stomatitis and RT-induced OM. The safety and preventive effect of 0.15% benzydamine oral rinse on the incidence of OM were prospectively assessed in patients with head and neck cancer. Patients receiving RT to the head and neck area were included in a double-blinded placebo-controlled trial. Study patients were instructed to rinse with 15 ml for 2 min, 4–8 times daily before and during RT, and for 2 weeks after completion. Patients were evaluated clinically on a weekly basis before, during and up to 3 weeks after the completion of treatment. In the Benzydamine group, there was a 30% reduction in the incidence of erythema and radiation-induced ulcers.

Of note, one third of patients receiving the study drug did not experience any signs of radiation-induced ulcers, as opposed to 18% of patients who received placebo ($p = 0.037$). Patients receiving benzydamine rinses experienced a significant delay in the need for opioid analgesics when compared with the group receiving placebo ($p < 0.05$). It is important to note that benzydamine did not show any clinical benefit in the group of patients that underwent a full course of accelerated RT [36]. A second study was performed to assess the preventive effect of oral rinses of benzydamine in the incidence of OM. Patients receiving a definitive course of RT or CRT as primary treatment for cancers of the head and neck area were included in the study. Subjects were randomized to receive an oral rinse of either benzydamine or placebo. The group of patients receiving the study drug had a 44% incidence of severe OM that compared favorably with the 79% incidence observed in the group receiving placebo ($p = 0.001$) [37]. The results of these trials support the prophylactic use of benzydamine oral rinses in patients receiving a standard course of radiation [18,20]. However, it is unclear if patients receiving concomitant CRT would benefit from it considering the small number of cases treated with this modality in both trials [36,37].

Low-level laser therapy (LLLT) is a local application of a monochromatic, narrow-band, coherent light source. LLLT is recommended for prevention and treatment of OM in patients receiving high-dose chemotherapy for hematopoietic stem-cell transplant [20]. It is important to note that there are some inconsistencies in the reported clinical benefits of LLLT due to the lack of standardized laser parameters and differences in the dose levels described in the literature. The mechanism of action of LLLT is still unclear, but it seems to have a protective effect at the cellular level during the periods of oxidative stress in patients receiving radiation treatments to the head and neck area [38]. In a recent meta analysis on the preventive effect of LLLT, a reduction in the incidence of severe OM was observed. Interestingly, there was a larger clinical benefit in terms of OM prevention when the analysis was restricted to the trials that included patients who received doses higher than 1 J [38]. Moreover, in a double-blinded, randomized trial comparing two different LLLT groups: group 1 (660 nm/15 mW/3.8 J/cm^2/spot size 4 mm^2) and group 2 (660 nm/5 mW/1.3 J/cm^2/spot size 4 mm^2) that were administered daily during the full course of RT, it was shown that patients randomized to the high LLLT (group 1), had less severe OM and reduced pain during the radiation treatment [39]. Currently, there are several ongoing clinical trials for OM prevention; most of which are focusing on the anti-inflammatory properties of the studied compounds (Table 2).

Mucositis-associated pain

OM pain is reported in essentially all head and neck cancer patients [8] and interferes with daily activities in approximately a third of patients and with social activities and mood in 50–60% of patients receiving RT or concurrent CRT treatments for head and neck malignancies [40]. Pain usually arises as a consequence of activation of primary nociceptive afferents by tissue-damaging stimuli and processing of this activity within the nociceptive system. Pain may also arise by activity generated within the nociceptive system without adequate stimulation of its peripheral sensory endings. This type of pain is called neuropathic and is defined as pain initiated or caused by a primary lesion or dysfunction in the nervous system [41]. In a study of patients with tumors of the upper aerodigestive tract, which assessed the incidence and type of pain prospectively, neuropathic pain was diagnosed in 56% of studied subjects. In most of the cases, neuropathic pain was part of a mixed picture [42]. Approximately a third to a half of patients with severe OM develop concomitant local infections with Candida species and Herpes virus family [12,43,44]. Patients with local infections usually report higher pain and dysphagia and complain of a 'neuropathic' component during the pain episodes. Although current guidelines do not recommend the prophylactic use of antimycotics, antivirals and/or antibiotics, this component is very important to recognize in order to provide adequate pain relief using etiological targeted measures [12,18,19,44,45]. This subset of patients may often require increased doses of systemic analgesics, as well as additional local anesthetic or analgesic agents [43,44].

Opioid use for management of mucositis-associated pain

Morphine is the classic example of an analgesic opioid. Its effects on analgesia, as well as many of its side effects, are a result of its binding capacity to the opioid receptors in the central nervous system and to the receptors located on the peripheral nerve terminals. There are strong data obtained from basic research, as well as clinical experience, which support the premise that morphine still has potent analgesic effect when applied locally in the setting of painful conditions associated with tissue damage due to inflammatory events [46–48]. Morphine seems to be the opioid of choice to use topically for the management of OM-associated pain for two reasons. First, the opioid ligands with a preference for μ-receptors

Table 2. Clinical trials in development for mucositis prevention.

Compound	Type of study	Sponsor	Estimated enrollment (n)	Estimated completion date
Hydrogel coating agent (MuGard)	Phase IV	Access Pharmaceuticals	120	November 2012
Oral immunomodulatory solution	Phase III	Centre Val d'Aurelle - Paul Lamarque	160	December 2013
Anti-IL-6 Ab (Ald-518)	Phase II	Alder Biopharmaceuticals	96	February 2013
Lactobacillus brevis CD2	Phase III	NCCTG/NCI	148	July 2013
Lactococcus lactis secreting trefoil factor 1	Phase III	Actogenix	Not available	Not available
Honey mouthwash	Phase II	Cyprus University of Technology	60	June 2013

NCCTG: North Central Cancer Treatment Group; NCI: National Cancer Institute.

are generally more potent when applied locally [49]. Second, morphine has shown a low transmucosal and sublingual absorption. The absorption capacity of any given drug depends on the pK of the drug, the pH of the absorbing tissue and on the solubility of the drug in lipids [50–52]. Considering that morphine has a low solubility in lipids and has a high pK, it is the drug of choice to apply on an inflamed tissue with a low pH such as the oral cavity of a patient suffering OM. In a study performed on head and neck cancer patients with primary tumors of the nasopharynx, oropharynx and oral cavity treated with CRT, 26 patients were randomized to either morphine mouth washes or a formulation of 'magic mouth wash'. In the morphine arm, patients were instructed to use an oral rinse of 15 ml 2‰ morphine solution (2000 mg morphine diluted in 1000 ml of water) on an 'as-needed' basis, every 3 h. The magic mouth wash group used a mixture of magnesium aluminum hydroxide, viscous lidocaine and benadryl on an 'as needed' basis, every 3 h. Patients received instructions to avoid swallowing the oral rinses and to hold the mouthwash for 2 min. The duration of pain reported by patients was 3.5 days shorter in the morphine group. As expected, most of the patients randomized to the magic mouth wash group needed the addition of systemic opioids for pain control [24]. In a two block-design pilot study on patients with locoregionally advanced primary tumors of the upper aerodigestive tract receiving definitive treatment with concomitant CRT, different morphine dosing and pharmacokinetic analysis of the solution were performed. The first group of patients suffering from painful OM was randomized into two different dose levels of morphine oral rinses. The first group received 15 ml of 1‰ morphine solution, and the second group received the morphine solution diluted at 2‰. In an extended phase (second block), 22 patients were included to assess the efficacy and safety of the morphine solution diluted at 2‰. The group of patients receiving the oral morphine solution with the higher dose (2‰) had better pain control than the group of patients receiving the lower dose (1‰). Interestingly, there were no detectable concentrations of morphine that could be of clinical significance in the subgroup of patients who underwent pharmacokinetic studies [43].

The use of systemic opioids for the management of OM associated pain was assessed prospectively in the setting of bone marrow transplant. Fentanyl, a synthetic opioid that can be administrated intravenously or subcutaneously, produces short-acting analgesic activity. The low molecular weight, high potency, and high lipid solubility of fentanyl can be easily delivered via the transdermal therapeutic system with variable dosages (12.5, 25, 50, 75 and 100 µg/h). As such, fentanyl is steadily released from a 72-h reservoir by diffusion through a controlled-release membrane, and then absorbed into the microcirculation through the skin. Two prospective trials showed that the routine use of transdermal fentanyl reduced the intensity of pain and improved the QOL of patients suffering from severe OM [53,54]. In our experience, due to the inability of most head and neck cancer patients suffering from severe OM to swallow the sustained-release opioid formulations, the transdermal use of fentanyl becomes the opioid of choice to use in this setting.

Adjuvant analgesic therapies

In those patients with OM-associated neuropathic pain or a mixed picture, adjuvant systemic therapies should be considered [55]. Two retrospective studies on head and neck cancer patients treated with RT

or CRT showed that by adding gabapentin up to a median dose of 2.700 mg/day, the opioid requirements in order to obtain good pain control seemed to be reduced [56,57]. In a randomized trial of opioids versus tricyclic antidepressants for the management of OM-associated pain in head and neck cancer patients undergoing RT, it was shown that, although opioids generally produced greater pain relief, up to 40% of patients achieved sufficient pain control on tricyclic antidepressants alone [58]. Even though there are no randomized trials on the addition of anticonvulsivants and antidepressants to opioids for the management of mucositis-associated pain with neuropathic features, this data support their use in this clinical setting.

Nutritional support during treatment

In patients with malignancies of the upper aerodigestive tract, an adequate nutritional support is needed during the course of definitive CRT with curative intent. It has been shown that the lack of such a supportive therapy increases the risk of interruptions during the course of treatment, reducing the likelihood of tumor control and overall survival [59]. Regular dietary counseling during the course of CRT appears to maintain or to improve nutritional status [60]. Moreover, it has been shown that patients who meet protein-related goals during the course of RT have less severe OM [61]. The use of prophylactic enteral feeding to maintain adequate nutritional status during the course of CRT has been recommended for patients with pretreatment body-mass index of less than 20, large primary tumors and/or hypopharyngeal involvement, and/or with the presence of dysphagia before treatment is started [62]. The duration of PEG tube feeding is considerably longer than that of nasogastric tube feeding [62,63]. However, a recent randomized trial on the prophylactic use of PEG tube in patients with advanced head and neck cancer treated with curative intent showed that prophylactic PEG tube was associated with significantly earlier start and longer use of enteral nutrition, fewer malnourished patients over time, and with improved health-related QOL at 6 months post-treatment. Interestingly, the group receiving the PEG tube prophylactically rated higher physical function, role function, and cognitive function. They also had significantly less fatigue and feelings of illness [64]. It has also been shown that there is a significant relationship between percent creatinine, or blood urea nitrogen rise, and percent body-weight loss during concomitant CRT in patients without an adequate nutritional support. Dehydration associated with severe dysphagia during CRT may be one of the causative factors [65]. In our experience, the routine addition of daily parenteral hydration during the last 2 weeks of RT is associated with improved renal function and less fatigue. The above data highlights the importance of the routine nutritional counseling, the prophylactic use of PEG tubes, and of hydration beyond standard hydration during cisplatin administration for those patients with advanced head and neck tumors treated with concomitant CRT therapy.

Future perspective

The increased understanding of the molecular mechanisms that underlie the etiology of OM offers new targets for potential therapeutic interventions. Different topical and systemic medications have been studied for prevention and treatment of OM in head and neck

Executive summary

Background
- Oral mucositis (OM) is a frequent and a dose-limiting toxicity of concomitant chemoradiotherapy delivered to the head and neck area.

Mucositis prevention
- There are no defined strategies yet for preventing mucosal injury or lessening its severity.

Mucositis-associated pain
- OM pain is reported in essentially all head and neck cancer patients receiving concomitant chemoradiotherapy.
- Adequate oral hygiene and topical and systemic analgesics remains the cornerstone of symptomatic treatment.

Nutritional support
- The use of prophylactic percutaneous endoscopic gastrostomy is associated with significantly earlier start and longer use of enteral nutrition, fewer malnourished patients over time, and with improved health-related quality of life.
- The addition of parenteral hydration during the last weeks of radiotherapy is associated with improved renal function and less fatigue.

Future perspective
- Currently, there are several ongoing clinical trials for OM prevention; most of which are focusing on the anti-inflammatory properties of the studied compounds.

cancer patients, but a single efficacious intervention or agent for the prophylaxis or management of CRT-induced OM has not yet been identified. However, there are several ongoing clinical trials for OM prevention; most of which are focusing on blocking the inflammatory process responsible for the tissue damage associated with CRT. Adequate oral hygiene and topical and systemic analgesics remain the cornerstone of symptomatic treatment. In addition, patients with local infections usually report higher pain and dysphagia and complain of a 'neuropathic' component during the pain episodes. This component is very important to recognize in order to provide adequate pain relief using measures such as antimicotics, antivirals and/or antibiotics. In those patients with OM-associated neuropathic pain or a mixed picture, adjuvant systemic therapies with anticonvulsants or antidepressants should be considered in order to optimize the opioid analgesic window. The importance of an early nutritional counseling, it should also be emphasized, along with the prophylactic use of PEG tubes and hydration beyond standard hydration, during cisplatin administration for those patients with advanced head and neck tumors treated with CRT.

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- ■ of interest
- ■■ of considerable interest

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