



Mucositis in head and neck cancer patients treated with radiotherapy and systemic therapies: Literature review and consensus statements.



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ABSTRACT

Background: Oral mucositis (OM) due to radiotherapy and systemic therapies in head and neck cancer treatment represents a major problem causing a wide spectrum of clinical signs and symptoms. This adverse event may reduce quality of life, resulting from debilitating oral pain, bleeding, dysphagia, infections, impairment of food intake, high rate of hospitalization and may interfere with the delivery of programmed treatment plans, ultimately jeopardizing patient outcome. Globally, there is a lack of evidence on effective measures for the prevention and treatment of OM, and only scant uniform conclusions and recommendations can be derived from the existing literature and guidelines. A multidisciplinary team of Italian head and neck cancer experts met in Milan 17–18 February 2013 with the aim of reaching consensus on prophylaxis and management of mucositis. The results of the literature review and the statements that achieved consensus are reported and discussed in this paper.

Material and methods: The Delphi Appropriateness Method was used as a structured communication method for achieving consensus. Subsequently, external expert reviewers evaluated the conclusions carefully according to their area of expertise.

Results: This paper presents 13 clusters of statements on prophylaxis and treatment of mucositis that achieved consensus.

Conclusions: OM represents a very stressful situation for head and neck cancer patients submitted to chemo-radiation or exclusive radiation treatment. A multidisciplinary approach is mandatory, but there is still no gold-standard protocol that is prominently better than others.

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1. Introduction

Treatment-induced oral and oropharyngeal mucositis (OM) in head and neck cancer patients (HNCs) undergoing radiotherapy (RT) with or without systemic therapies (SyTh; including chemotherapy and/or targeted therapies) is one of the most debilitating and troublesome acute side effects and profoundly affects quality of life (QoL), because it is associated with symptoms such as pain, bleeding, dysphagia, infections and food intake impairment (Elting et al., 2007; Elting et al., 2008; Raber-Durlacher et al., 2010; Bossi et al., 2014; Farhangfar et al., 2014; Schindler et al., 2015; Mirabile et al., 2015). Moreover, OM is associated with a high rate of hospitalization and may interfere with the delivery of programmed treatment plans (Poulsen et al., 1999; Sutherland and Browman, 2001; Trotti et al., 2003; Wong et al., 2006; Russo et al., 2008).

The multidisciplinary approach of HNCs, (mainly in advanced stages) involves several integrated therapeutic strategies, such as surgery, RT (with standard or altered fractionations), and systemic therapies. This leads to a substantial increase in acute toxicity, requiring adequate management in order to optimize treatment compliance (Beitler et al., 2014; Pignon et al., 2009; Baujat et al., 2010; Blanchard et al., 2011; Marta et al., 2014; Nguyen-Tan et al., 2014).

While other side effects of anticancer treatments, such as emesis, anemia, and neutropenia, are relatively well controlled with validated supportive care, the therapeutic armamentarium

towards mucositis is still scarce. In this regard, mucositis remains an important dose-limiting factor in head and neck cancer (HNC) treatment.

For all these reasons a panel of experts in HNC treatment, such as Medical Oncologists (MOs), Radiation Oncologists (ROs), Oral Care Physicians/dentists (OCPs), infectious disease physicians (IDP), nutritionists, and nurses reviewed the literature with the aim of reaching a consensus on prophylaxis and management of mucositis in RT (±SyTh)-treated patients

The results of the literature review and the statements that obtained consensus are reported and discussed in this paper.

2. Material and methods

The modified Delphi method was used for achieving Consensus, that differs from Delphi method only with regard the procedure of the first round questionnaire, that usually is unstructured and provides open responses, how we explained following (Hasson et al., 2000; Hsu and Sandford, 2007; Loblaw et al., 2012).

The panel, a group of 40 multidisciplinary experts, met in Milan on February 17–18, 2013 and appointed a facilitator board of 5 expert members, from different clinical settings (3 MO, 2 ROs). The facilitator board performed a systematic review of the literature on mucositis associated with RT with or without SyTh in HNCs.

The MEDLINE database was searched for English-language studies published from 1992 to March 2013 containing the terms

mucositis, head and neck cancer, supportive care, healthcare acquired, chemotherapy, cetuximab and radiotherapy.

Potentially relevant abstracts presented at annual meetings of the American Society of Clinical Oncology (ASCO) and the European Society of Medical Oncology (ESMO) were examined. The study selection included the following:

(a) Observational and prospective studies about OM assessment and treatment; (b) randomized, double-blind, placebo-controlled, or uncontrolled studies; (c) retrospective and uncontrolled studies; (d) systematic reviews and metaanalyses; (e) consensus guidelines. Furthermore, electronic search results were supplemented by manual examination of reference lists from selected articles and were periodically updated until April 2014.

Based on this literature review, the facilitators identified a number of key statements, which were differentiated according to the timing of interventions (pre-, during-, and post-treatment) and included an indication of the person in charge of the management of each physical or behavioral social aspect (e.g., physician, nurse, patient, caregiver, etc.).

All experts rated these statements through a three-round process. A scale of 4 steps was used, where 1 was defined as high consensus, 2 was defined as low consensus, 3 was defined as no consensus, and 4 was chosen by panellists when they felt unable to express an opinion.

A web meeting was held before the second rating, where statements were discussed. The statements that received a weak approval (<75%) were deleted or redefined according to the suggestions of the panellists. The final ratings were analyzed to identify the statement that reached consensus.

Each expert (including the facilitator) was equally weighted in the scoring of the statements.

External specialists MOs (JBV, BM), ROs (JL, GS), OCPs (JR-D, RL) reviewed the statements. The statements were then revised according to the suggestions of the external reviewers and where necessary supplemented with newly identified literature; a third-round voting defined the final statements.

The panellists had a new meeting in Milan on 5 May 2014 in order to approve the final version of the statements, together with the statements coming from other working groups and regarding other topics in supportive care in HNC treatment.

3. Results

Statements reaching consensus are listed in Table 1. Thirty statements were presented at the first round of rating, after which 27 statements reached a high level of consensus and 3 were deleted according to the experts' comments.

The statements approved in this first round were presented to the external experts for input, following which some statements were joined together and a statement about Low Level Laser Therapy was introduced. Following revision, 17 statements were grouped in 13 main clusters (see Table 1) and approved during the second consensus meeting in May 2014.

4. Comments

4.1. General statement

- There are some clinical and therapeutic variables increasing the risk to develop more severe mucositis. Pre-treatment identification of these factors may help the physician in anticipating the need for nutritional and analgesic support.

Detecting the presence of certain risk factors, already present at the time of diagnosis, is of paramount importance because their

modulation or elimination might reduce the severity of mucositis during treatment. The risk factors that have been identified as having the potential to influence mucositis have typically been classified in two categories: patient-related and cytotoxic therapy-related (de Castro and Guindalini, 2010; Eilers and Million, 2011).

4.2. Risk factors

4.2.1. Patient related risk factors

- Poor-oral hygiene, periodontal disease

The biological impact of the resident microflora that may aggravate the inflammatory process involved in mucositis, remains to be clarified (Donnelly et al., 2003). In patients with cancer, this delicate balance between harmless commensal bacteria and host-immune-homeostasis can be disturbed by the cancer itself, anti-cancer treatment, and also by supportive therapies, which all may contribute to a shift of the oral microflora from mainly Gram-positive to Gram-negative bacteria (Donnelly et al., 2003). The disruption of this balance may be related to a direct cytotoxic effect on the oral flora, neutropenia, altered salivary output, altered cytokine release, use of antibiotics, pre-existent periodontal disease and/or compromised oral hygiene, and acquisition of hospital-associated pathogens (Meurman et al., 1997). Indeed, the endotoxin lipopolysaccharide (LPS) stimulates activated macrophages to produce inflammatory mediators such as interleukin 1 (IL-1), interleukin 6 (IL-6), tumor necrosis factor-alpha (TNF- α), prostaglandin E2 (PGE2), and matrix metalloproteinases (MMPs) (Castellheim et al., 2009). In addition, oral bacteria and cytokines may enter the bloodstream when the integrity of the oral mucosal barrier is disrupted and may induce fever and infectious complications including sepsis (Mirabile et al., 2015; Laheij et al., 2012; Russi et al., 2014). Recently, the presence of periodontitis-associated bacteria has been related to the onset and worsening of oral ulcerative mucositis (Khaw et al., 2013). In particular, the bacterium *Porphyromonas gingivalis* can inhibit wound healing in an in-vitro model, suggesting disturbed ulceration healing in patients with periodontal disease. Moreover, a more complex association between periodontitis and OM has recently been considered, based on the common features of local and systemic inflammation (Khaw et al., 2013). A small pilot study in RT-treated HNCs, did not demonstrate a significant statistical correlation between periodontitis and OM severity, although a greater proportion of patients with OM had periodontitis (Khaw et al., 2014). A recent systematic review concluded that presently there is inconclusive evidence for preventive oral infection focus elimination to prevent post-RT oral sequelae and that prospective studies are needed (Schuurhuis et al., 2015).

- Alcohol

Alcohol abuse is a well-recognized risk factor for oral and oropharyngeal cancer cell carcinoma (Toporcov et al., 2015; Hashibe et al., 2007). Alcohol intake is associated with an increased susceptibility of the oral mucosa to acute radiation injury with an increased incidence and severity of mucositis. The normal oral flora metabolizes alcohol into toxic metabolites such as acetaldehyde. Oral mucosa lacks of alcohol dehydrogenase and consequently acetaldehyde may accumulate in the mouth. Thus, the damage of the oral tissues may be ascribed in part to the action of acetaldehyde. In addition, some acute effects can result from a direct action of ethanol and formation of reactive oxygen species (ROS) and fatty acid ethyl esters (FAEEs) (Pöschl and Seitz, 2004). Chronic alcohol consumption is associated with mucosal atrophy and hyper-regeneration of the basal layer cells. Both these mechanisms contribute to increased susceptibility of the mucosa to chemi-

Table 1
Consensus-reached statements.

Clusters	Phase	Item	In charge of
1.	General statement	1a ● There are some clinical and therapeutic variables increasing the risk to develop more severe mucositis. Pre-treatment identification of these factors may help the physician in anticipating the need for nutritional and analgesic support	<ul style="list-style-type: none"> • Clinical Oncologist. • Nurse • Dentist • Patients
2.	Risk factors	<p>2a Patient related risk factors (Non-treatment related risk factors):</p> <ul style="list-style-type: none"> • Poor oral hygiene, • Periodontal disease, • Persistent alcohol or tobacco use, • Xerostomia/hyposalivation, • Low body mass index (BMI <18.5), • Unintentional weight loss before therapy (i.e., >5% weight loss over prior 1 month or >10% in the last 6 months) • Immunosuppression due to comorbidities (such as diabetes mellitus) or aged patients • Female sex. <p>2b Cytotoxic therapy-related risk factors (Treatment related risk factors):</p> <ul style="list-style-type: none"> • Radiotherapy (radiation source, total dose, daily fractionation, and previous RT), • Chemotherapy (dosage, type of drug and timing), and • Bioradiotherapy (RT plus targeted therapy) 	<ul style="list-style-type: none"> • Clinical Oncologist • Nurse Dentist • Patients
3.	Assessment scales	<p>A variety of assessment scales are employed to rate the grade of severity of the oral mucositis (OM)</p> <ul style="list-style-type: none"> ● The most commonly utilized scales are <ul style="list-style-type: none"> a) The National Cancer Institute (NCI)-Common Toxicity Criteria (CTC version 4.0), b) The Toxicity criteria of the Radiation Therapy Oncology Group (RTOG), c) The European Organization for Research and Treatment of Cancer (EORTC), and the criteria set out by the d) World Health Organization (WHO) in 1979 e) Oral Mucositis Assessment Scale (OMAS), f) M. D. Anderson symptom inventory, head and neck module g) OMQD scale ● No evidence-based recommendation is possible about the superiority of one scale over another ● It is appropriate to assess mucositis with both modalities (ORO and PRO instruments) 	<ul style="list-style-type: none"> • Clinical Oncologist • Nurse • Patient
4.	Pre-treatment	<p>Oral hygiene</p> <ul style="list-style-type: none"> • Patient education in oral hygiene techniques is of utmost important: using a soft toothbrush and floss or an interproximal brush, and fluoridated toothpaste to be continued on a lifelong basis <p>Dental examination</p> <ul style="list-style-type: none"> • Control of the pre-existing periodontal and dental disease and a pre-treatment professional dental cleaning may allow a better control of OM • It is recommended that a qualified oral health care team be integrated in a multidisciplinary approach on the basis of well-defined protocols for the pre-treatment, treatment and the follow-up phases 	<ul style="list-style-type: none"> • Clinical oncologist • Nurse • Dentist • Patient
5.		<p>Palifermin</p> <ul style="list-style-type: none"> • The use of recombinant human KGF-1 (palifermin) is not recommended routinely in patients treated for head and neck cancer. 	<ul style="list-style-type: none"> • Clinical oncologist
6.	During treatment	<p>Oral examination</p> <p>1. Evaluating oral hygiene:</p> <ul style="list-style-type: none"> • Basic oral care will reduce the frequency and severity of oral mucositis and its associated pain (the use of soft toothbrushes and not irritating mouthwashes) • Regular oral care with the use of oral mouthwashes is recommended • The use of oral care products not containing alcohol without intense flavor is suggested • No superiority of one mouthwash over saline or bicarbonate rinses has been demonstrated. • Oral prostheses should be kept clean with an antimicrobial solution and their use should be discouraged during night time and in presence of overt oral mucositis <p>2. Assessing mucositis progression:</p> <ul style="list-style-type: none"> • It is recommended to regularly assess oral mucositis at least once-a-week, with instructions to the patient to communicate any further worsening of symptoms in between examinations. When once-weekly irregular assessment instead of daily scoring was evaluated, the incidence of mucositis was underestimated. Whether more frequent assessment generates improved control of OM needs to be confirmed. 	<ul style="list-style-type: none"> • Clinical Oncologist • Dental professional • Nurse • Patient

Consensus-reached statements.

Clusters	Phase	Item	In charge of
7.		<p>Radio-therapeutic precautions:</p> <ul style="list-style-type: none"> • Radiotherapy with the aim of maximal sparing of the mucosa outside any PTV is recommended. • When Intensity Modulated RT (IMRT) is used, the total dose to the mucosa outside the PTV should possibly be planned to be limited to 30 Gy in 6–7 weeks, but this should not jeopardize coverage of the PTV with the prescribed dose. 	<ul style="list-style-type: none"> • Clinical Oncologist
8.	Miscellaneous: statements about the prevention and treatment.	<p>Not-recommended practice</p> <ul style="list-style-type: none"> • Cryotherapy it is not recommended in head and neck cancer patients during (chemo) radiation due to the risk of less tissue oxygenation occurring with vasoconstriction that could impact on treatment efficacy and due to lack of data in this setting, even it was found to be beneficial in patients receiving bolus 5-FU or high dose melphalan • Amifostine is not recommended in patients receiving radiotherapy ± chemotherapy for head and neck cancer, because of its side effects and high cost • Glutamine is not recommended to prevent OM in HNCPS ± CT. • The following topical agents are not recommended for mucositis prevention and treatment: <ul style="list-style-type: none"> ○ Barrier agents such as sucralfate, GelClair®, MuGard® and Mucotrol® ○ Allopurinol gel ○ Chlorhexidine digluconate mouth rinse ○ Povidone-iodine ○ Triclosan mouth washes ○ Isegran mouth washes ○ Aloe vera ○ Granulocyte macrophage colony-stimulating factor ○ Pure natural honey ○ Misoprostol and Prostaglandin E2 ○ Antibiotic + antifungal pastilles (containing polymixin, tobramycin and amphotericin or bacitracin, clotrimoxazole and gentamicine) 	<ul style="list-style-type: none"> • Clinical Oncologist • >Nurse • Patient
9.		<p>Benzydamine mouthwashes</p> <ul style="list-style-type: none"> • Although, the beneficial effects need to be confirmed in larger trials, suggestions are possible about benzydamine mouthwashes to prevent radiation-induced mucositis in HNCPS receiving moderate-dose radiation therapy (up to 50 Gy) without CT. • However, since no direct comparison has been performed with saline or bicarbonate rinses, either agent can be suggested. 	<ul style="list-style-type: none"> • Clinical Oncologist • Nurse
10.		<p>Systemic employment of antibiotics or antiviral agents is not recommended with prophylactic intent in absence of neutropenia; on the other side they are recommended in case of overt infection.</p>	<ul style="list-style-type: none"> • Clinical Oncologist
11.		<p>Antimycotic mycostatin or topical miconazole for prevention</p> <ul style="list-style-type: none"> • Fluconazole can be suggested only in therapeutic setting or with a prophylactic intent in case of patients at high risk of mycosis (chronic steroidal therapy, diabetes). 	<ul style="list-style-type: none"> • Clinical Oncologist
12.		<p>No-suggested practice:</p> <ul style="list-style-type: none"> • No suggestions are possible for topical steroids use in patients receiving radiotherapy +/- chemotherapy for head and neck cancer. • Systemic continuous employment of steroidal therapy for mucositis prevention/treatment is not recommended. • A number of NSAIDS have been evaluated for oral mucositis, including systemic indomethacin and aspirin. • No suggestions is possible about their use in patients receiving radiotherapy +/- chemotherapy for head and neck cancer 	<ul style="list-style-type: none"> • Clinical Oncologist
13.		<ul style="list-style-type: none"> • Low Level Laser Therapy can reduce OM, but vigilance remains necessary and no recommendation is possible. 	<ul style="list-style-type: none"> • Clinical Oncologist

cal or radiotherapeutic agents. Moreover, alcohol predisposes to malnutrition and immunosuppression. Indeed, chronic alcohol consumption results in complex alterations of innate and acquired immune responses (Cook, 1998). Finally, a reduction of the number and the activity of the subset of Natural Killer (NK) lymphocytes has been reported in alcohol-addicted patients, even in absence of cirrhosis (Cook et al., 1991).

- Tobacco

Cigarette smoke elicits inflammatory processes and impairs the host defence against viral and bacterial agents (Lixuan et al., 2010; Nikota and Stämpfli, 2012). Indeed, cigarette smoke has demonstrated the ability to initiate both innate and adaptive immune responses and to alter bacterial/viral host defence mechanisms. The up-regulation of IL-1 is induced directly by the components of cigarette smoke or by the release of danger associated molecular patterns (DAMP), secondary to cigarette smoke-induced cell death (Nikota and Stämpfli, 2012; Eltom et al., 2011; Doz et al., 2008). Furthermore, cigarette smoke dose-dependently inhibits the induction of an anti-viral state and the production of interferon (IFN) by epithelial cells. As a consequence, the smoke-elicited, exaggerated, and ineffective cellular inflammatory response seems to result in a lower survival in cigarette smoke-exposed mice infected with influenza virus (Robbins et al., 2006; Gualano et al., 2008), or with bacteria (Gaschler et al., 2009). Thus, cigarette smoke activates innate immune processes, altering the immune response without suppressing it. This favors microbial infection and amplifies inflammation (Russi et al., 2014; Sonis et al., 2004).

- Xerostomia/hyposalivation

Hyposalivation due to head and neck RT or chemoradiation may worsen OM. Comorbidities (e.g., Sjogren syndrome) or chronic use of medications, that reduce the salivary flow, may also increase the frequency, intensity and duration of mucositis (Jensen and Vissink, 2014). Changes of the salivary flow rate, salivary pH, and salivary consistency may induce or worsen other symptoms such as oral burning, soreness, halitosis, taste changes, and may impair mastication and speech. These patients are at increased risk of dental caries and osteoradionecrosis (Lovell et al., 2014).

- Low body mass index (BMI <18.5).
- Unintentional weight loss before therapy (i.e., >5% weight loss over the prior month or >10% in the last 6 months).

Several studies have focused on low BMI as a risk factor for overall survival in HNCPS (Ottosson et al., 2014; Pai et al., 2012; McRackan et al., 2008; Liu et al., 2006). Recently, a statistically significant association has been found between low BMI and grade 2–3 mucositis in HNCPS treated with RT (Saito et al., 2012). This finding underlines the need to maintain an adequate nutrition (Zahn et al., 2012). Indeed, an inadequate nutritional intake during RT can impair the multifaceted process of wound healing, and, consequently, the healing of ulcerative OM.

- Immunosuppression due to comorbidities (such as diabetes mellitus) or aged patients

Comorbidities are very common in HNCPS, especially when they have a history of alcohol and tobacco abuse (Boje, 2014). Cardiovascular diseases, renal failure, liver and lung function impairment are frequent, in particular in older HNCPS. Yet, no specific data are available regarding the impact of comorbidity on mucositis incidence and severity because these patients are frequently excluded from curative treatment programs.

Diabetes mellitus

Diabetes mellitus has been considered as an important risk factor for oral cavity pathology (Elting et al., 2007), due to microvascular changes in the gingiva and alveolar mucosa. These changes include the thickening of the capillary basement membrane, narrowing of the lumen and peri-endothelial thickening and stasis in the microcirculation (Emrich et al., 1991). Besides the modification of the vascular wall, the oral microflora is also altered. The predominant microorganisms vary from one study to another, and include: gram negative bacteria, *Staphylococcus epidermidis*, *Campylobacter* and anaerobic vibrios, *Aggregatibacter actinomycetemcomitans* and pigmented bacteroids, including *Prevotella intermedia*, *P. gingivalis* and *Wolinella recta* (Arrieta-Blanco et al., 2003). It has been postulated also that a defect of polymorphonuclear function (i.e., a decrease of chemotaxis, adherence and phagocytosis of peripheral leukocytes) might be a potential risk factor for oral infection in diabetic patients (Mowat and Baum, 1971). Finally, in diabetic patients an abnormal metabolism of collagen has been detected (Arrieta-Blanco et al., 2003), which may contribute to impaired mucosal wound healing during RT.

Aged patients

Although age was considered a risk factor for mucositis, few studies focused on this risk factor and conflicting results have been reported. Potentially, increased OM risk is due to a poor healing capacity in elderly HNCPS, and to the frequent comorbidities associated with older age (Boje, 2014). Yet, Huang et al. compared different radiation doses and fractionations between a cohort of HNCPS of ≥ 75 years and those younger, and found no difference in terms of unplanned RT interruption (18% vs. 19%) and treatment-related deaths (3% vs. 2%), also with hyperfractionated accelerated RT (AF-RT) (Huang et al., 2011). Furthermore, some studies reported that younger patients are at higher risk of mucositis (Pico et al., 1998).

- Gender

Several studies suggested an association between female gender and higher incidence of mucositis grades 3–4 (Sonis et al., 2004; Vokurka et al., 2006).

4.2.2. Cytotoxic therapy-related risk factors

Treatment factors that may impact mucositis severity:

- Radiotherapy

During the past two decades, altered fractionations with or without CT improved locoregional control and survival in HNCPS, at the expense of an increased incidence of OM (33–77% of HNCPS treated with CF-RT and 25–100% of HNCPS treated with altered fractionation (Beitler et al., 2014; Baujat et al., 2010; Wygoda et al., 2012).

Bentzen et al. (2001) reported that unconventional fractionation RT (i.e., Continuous hyperfractionated accelerated RT: CHART) was associated with a greater incidence (75% vs. 44%) and peak severity (60% vs. 34%) of confluent ulcerative mucositis. Highly significant relationships between ulcerative mucositis grade and dysphagia, odynophagia and prescribed narcotics were also observed.

The DAHANCA 6&7 study included 1476 patients eligible for primary RT alone (Mortensen et al., 2012). Compared to standard treatment (5frs/week), AF-RT (6frs/week) significantly increased the use of analgesics (53% vs. 65%), dysphagia (35% vs. 45%), mucosal edema (52% vs. 59%), and mucositis (33% vs. 53%). In addition, in 100 patients randomized between two definitive radiation treatments (i.e., more AF-RT, 7 days a week, and a CF, 5 days a week), even a higher percentage of OM (respectively, 94% vs. 53%) with a longer duration (mean, 4.2 vs. 1.5 wks) was found as compared

to that observed in the DAHANCA study (Skladowski et al., 2006). Confluent mucositis was the main acute toxicity. In a recent randomized controlled study, the altered fractionation was related to an OM incidence in 75% of patients, in comparison to 23% of patients treated with CF (Bourhis et al., 2006). Similar results were found in another series of patients (Altered fractionation 62% vs. CF: 42%) (Cummings et al., 2007). Moreover, with a regimen of AF-RT (radiation doses of 64.8 Gy in 3.5 weeks without CT, 1.8 Gy twice a day/5 days per week) the rate of grade 3 or higher OM was 84%, which was higher than observed with conventional CRT or accelerated CRT (69% and 76%, respectively) (Bourhis et al., 2006).

- Chemotherapy

In the past decade, the intensification of treatment strategy for HNCPS by the addition of concomitant CT led to an improvement of outcomes. Unfortunately, this strategy also led to a higher rate of toxicity (Pignon et al., 2009; Blanchard et al., 2011). Indeed, several authors reported an increased frequency, severity, and duration of OM with concurrent CRT, with grade 3–4 OM ranging from 30% to 84% (Keane et al., 1993; Gibbs et al., 1999; Trotti, 2000; Adelstein et al., 2003; Bernier, 2004, 2009; Bensadoun et al., 2006; Semrau et al., 2006; Vera-Llonch et al., 2006; Mañas et al., 2009; Bourhis et al., 2012; Haddad et al., 2013). Grade 3 and grade 4 incidence of mucositis were reported in 80% and 39% of radio/chemotreated HNCPS (6181 patients in 33 studies), respectively.

Similar results were found by Elting et al. (2007) who reported an overall incidence of 91% (grade 3–4 in 66%) in HNCPS treated with chemoradiation; grade 3–4 mucositis was more frequent in patients with oral cavity or oropharynx primaries, receiving concomitant CT, and treated with altered fractionation schedules.

Indeed, concurrent chemo-radiotherapy seems to lead to an increase of the Biologically Effective dose (BED) as compared to exclusive RT (Kasibhatla et al., 2007; Fowler, 2008; Lee and Eisbruch, 2009), by approximately 8.8 Gy₁₀ (Kasibhatla et al., 2007) to 10 Gy₁₀ (Fowler, 2008), as if an additional 12 Gy given in 6 fractions (Kasibhatla et al., 2007) or 7.2 Gy in 3.6 fractions (Fowler, 2008) had been delivered. Sanguineti et al. (2012) showed that concurrent CT significantly increases the risk of OM in oropharyngeal HNCPS treated with intensity modulated radiation therapy (IMRT) by 4.1 times and 5.1 times, with altered and conventional fractionation (CF), respectively.

These grades of toxicity can cause planned or unplanned radiation treatment breaks that may reduce the beneficial effect of the addition of CT to RT by reducing the tumor BED due to cancer cell repopulation during the breaks (Trotti et al., 2003; Kasibhatla et al., 2007; Fowler, 2008).

- Bioradiotherapy (RT plus targeted therapy)

In the pivotal randomized trial of Bonner et al. the addition of cetuximab to RT significantly improved locoregional progression, progression free survival and overall survival without exacerbating common adverse events, including ulcerative mucositis. In particular, grade 3–4 OM was observed in 52% of the HNCPS in the group of RT alone and 56% in the group of RT plus cetuximab (an epidermal growth factor receptor (EGFR) inhibitor; $p = 0.44$) (Bonner et al., 2006).

However, the results of this first trial were questioned by further studies that pointed out a greater incidence of mucositis when EGFR inhibitor treatment was added to RT (Walsh et al., 2011). Walsh et al. (2011) retrospectively reviewed acute toxicity in 2 cohorts of HNCPS treated with RT plus either cetuximab or cisplatin. The cetuximab-treated HNCPS experienced a significantly higher frequency of grade ≥ 3 OM ($p = 0.014$), skin dermatitis ($p = 0.0004$), weight loss $\geq 10\%$ ($p = 0.03$), and enteral feeding requirement

($p = 0.05$) than cisplatin-treated HNCPS did. Other recent papers reported a rate of grade 3–4 OM ranging between 45–74% (Pryor et al., 2011; Alongi et al., 2012; Rampino et al., 2012; Valeriani et al., 2012; Lefebvre et al., 2013; Levy et al., 2014; Pergolizzi et al., 2011; Merlano et al., 2011). In particular, Lefebvre et al. (2013) showed no statistically significant difference of grade 3–4 OM incidence after induction CT followed by concurrent platinum-based CRT versus concurrent bioradiotherapy (46% vs. 45%), whereas Levy et al. (2014) recorded a statistically significant difference between the severity of OM in patients treated with bioradiotherapy versus those treated with chemioradiotherapy (51% vs. 34%, $p = 0.01$) (Haddad et al., 2013; Bonner et al., 2006).

Moreover, Pryor et al. (2011) described a distinctive pattern of severe anterior stomatitis with concurrent cetuximab and RT, different from that of conventional OM described with CRT or AF-RT. Cetuximab-RT treated patients experienced higher rates of grade ≥ 3 cheilitis (26% vs. 6%, $p = 0.01$) and anterior stomatitis (38% vs. 6%, $p = 0.002$), although these structures received low RT doses (i.e. median maximum dose to the lips 9.3 Gy and to the anterior oral cavity 20 Gy).

4.3. Statements about assessment tools

A variety of assessment scales are employed to rate the severity of OM. The most commonly utilized scales are the National Cancer Institute (NCI)-Common Toxicity Criteria (CTC version 4.0), the Toxicity criteria of the Radiation Therapy Oncology Group (RTOG), the European Organization for Research and Treatment of Cancer (EORTC), the criteria set out by the World Health Organization (WHO) in 1979, the OM Assessment Scale (OMAS), M.D. Anderson symptom inventory-head and neck module (MDASI-HN), and the OMQD scale.

- No evidence-based recommendation is possible about the superiority of one scale over another

The diagnosis of mucositis is mostly based on clinical manifestations. Frequently, it is necessary to establish a correct differential diagnosis with other pathological conditions because mucositis can be complicated by bacterial, viral, and fungal superinfection (Köstler et al., 2001). Viral infections may differ clinically from mucositis because they may also affect the keratinized mucosa of the hard palate, gums, and back of the tongue. In controversial cases, exfoliative cytology and microbiological cultures are necessary for a definitive differential diagnosis (Stokman et al., 2003). In addition, mycotic infections may be frequent and generally caused by *Candida albicans* or other candida spp., such as *krusei*, *tropicalis*, *parapsilosis* spp., or *Aspergillus* spp. (Stokman et al., 2003).

The clinical course of OM with conventional RT techniques (2 Gy per day for 5 days per week to a total cumulative dose of 60–70 Gy) is predictable. Erythema of the mucosa appears together with mild to moderate pain, but without evident ulcerative changes after a cumulative dose of 10 Gy. Atrophic changes in the epithelium usually occur at a total dose of 16–22 Gy. In this phase, discomfort increases and analgesic therapy may be necessary. At a cumulative dose ≥ 30 Gy, ulcerative lesions are frequent on the movable mucosa of the cheeks, lips, ventral and lateral tongue. Involvement of the more heavily keratinized sites such as the dorsal tongue, gingiva and hard palate is uncommon in OM. Ulcerative OM lesions are irregular, frequently associated with erythema and often covered by pseudomembranes. In this phase the patient is often very symptomatic and cannot eat normally. Ulcerative lesions may persist for 2–4 weeks after the completion of RT.

The persistence of severe ulcers lasting until 5–7 weeks after the end of treatment are frequent in HNCPS treated with CRT (Köstler et al., 2001; Stokman et al., 2003). Post-RT chronic mucosi-

tis has also been described (Stokman et al., 2003). However, with IMRT technique this scenario may change (Sanguineti et al., 2006; Rosenthal et al., 2008a; Nagarajan, 2015; Kruser et al., 2013).

A variety of assessment scales are employed in order to grade the severity of OM. An ideal OM assessment tool should be objective, sensitive, validated, reliable, and easy to use in all clinical situations. The scale should be able to measure proper parameters of OM across different treatment modalities, including CT, RT and CRT or bio-radiotherapy. In addition, it should measure both the mucosal damage and the patient's functional capabilities relative to the oral status (e.g., the ability to eat, to speak). Although a number of different tools have been used to assess OM severity, unfortunately none of these have been universally recognized because they did not meet all the criteria mentioned above. The most commonly utilized scales are the National Cancer Institute (NCI)-Common Toxicity Criteria (CTC version 4.0) from the USA, the Toxicity criteria of the Radiation Therapy Oncology Group (RTOG), the European Organization for Research and Treatment of Cancer (EORTC), and the criteria set out by the World Health Organization (WHO) in 1979, and the OM Assessment Scale (OMAS) (Sonis et al., 2004; Rosenthal et al., 2007; Ctae Panel, 2006; National Cancer Institute, 2009; Cox et al., 1995; Organization WH, 1979; Sonis et al., 1999). Most of the scales that are used in daily clinical practice are based on the measurement of oral symptoms, signs and functional disturbances. Some scales primarily focused on operator-rated observation (ORO-scale) of mucosal tissue injury (e.g., erythema, ulceration) and have particular value in clinical trial-based assessment of OM. The World Health Organization (WHO) Oral Toxicity Scale, for example, combines signs of mucosal damages (erythema and ulceration) with functional impairment, while the RTOG criteria are based only on a general description of mucosal damage intensity. The OMAS scale, on the contrary, measures the size of ulceration or pseudomembrane and the extent of mucosal erythema at nine anatomical sites of the oral cavity. Finally, the National Cancer Institute (NCI)-Common Toxicity Criteria (CTC version 4.0) assesses OM according to objective signs (erythema, ulceration, and bleeding) and subjective variables as pain, dysphagia, and eating behavior. There is still a lack of a universally accepted scale to report mucositis (Denis et al., 2003; Liu et al., 2012). Mixed scales like WHO offer the benefit of a more comprehensive appraisal of the signs and symptoms of mucositis; however, the limits of this assessment lie in the fact that the evaluation is filtered by the physician judgement, not being directly reported by the patient.

- It is appropriate to assess mucositis with both modalities (ORO and PRO instruments)

As reported in other cancer patient settings, adverse events reported by ORO-scales are less accurate than those reported by PRO instruments (Fromme et al., 2004). The ORO tools are frequently not able to correlate the severity of mucosal damage (erythema or ulceration) either with the experience of the patient (e.g., his/her well-being) or with the loss of specific functions (e.g., speech, eating, swallowing). Obviously, it is crucial to determine the impact of each acute treatment-related toxicity (e.g., OM) on the HNCPS' QoL (QoL). PRO-scales seem to be more reliable in describing the impact of the toxicity on QoL and patient's compliance to the treatment. According to these considerations, PRO's have been recommended by the US national Institutes of Health for optimal patient care (Nih, 2002). Indeed, some clinicians have proposed replacing ORO with PRO-assessed mucositis reporting (Epstein et al., 2007; Murphy et al., 2010). When the mouth soreness severity was scored by using a PRO-scale such as the OM Daily Questionnaire (OMQD), functional Assessment of Cancer therapy (FACT-G), Esophagus Cancer subscale (ECS) QOL, and Functional

Assessment of Chronic Illness Therapy (FACT)-Fatigue subscale, even a mild mouth soreness score was associated with a substantial decrease of QoL (Elting et al., 2008).

Several PRO tools have been proposed. The OM Weekly Questionnaire-Head and Neck Cancer (OMWQ-HN), a validated instrument for measuring the impact of mucositis in HNCPS receiving (chemo) radiotherapy, was able to differentiate patients reporting worsening from those reporting no change or improvement in their status. Yet, no direct comparisons have been made between different OM ORO-tools (Epstein et al., 2007). Murphy et al. have designed a PRO tool focused on the identification of high-impact and high-risk toxicities in CRT-treated HNCPS, by selecting specific questions for HNCPS and by excluding both the general symptoms (such as fatigue, nausea/vomiting, gastrointestinal symptoms) and mood disorders (such as depression, anxiety, social phobia and avoidant behaviors) (Murphy et al., 2010). The updated version (VANDERBILT HEAD AND NECK SYMPTOM SURVEY VERSION 2.0), although waiting for a further validation, seemed reliable to record the prevalence of adverse oral health outcomes in HNCPS (Cooperstein et al., 2012). Rosenthal et al. showed that the MDASI-HN was more accurate than FACT-HN tool in capturing the actual severity of radiation-related OM (Rosenthal et al., 2008b; Greco et al., 2015). This tool was based on the identification of symptom's burden by cluster analysis after their identification during treatment (either systemic and local symptoms). It seemed very promising for the early detection of the need for therapeutical interventions (Rosenthal et al., 2014). Presently, the most reasonable approach for recording the side effects of CRT treatment should include both PRO- and ORO-tools.

4.4. Pre-treatment statements:

4.4.1. Oral hygiene

- Patient education in oral hygiene techniques is of utmost importance: using a soft toothbrush and floss or an interproximal brush, and fluoridated toothpaste to be continued on a lifelong basis.

4.4.2. Dental examination

- The control of the pre-existing periodontal and dental disease and a pre-treatment professional dental cleaning may allow a better control of OM.
- It is recommended that a qualified oral health care team be integrated in a multidisciplinary approach on the basis of well-defined protocols from pre-treatment phase, during treatment, and follow-up.

Oral care has been often recommended to reduce the incidence and severity of OM.

Recommendations regarding oral care based on systematic reviews are available and have been regularly updated (Eilers and Million, 2011; Lalla et al., 2008; Rubenstein et al., 2004; Bensinger et al., 2008; Keefe et al., 2007; Niscola et al., 2012; Lalla et al., 2014), although the evidence for the use of oral care protocols is weak and the amount of data is limited. However, a multidisciplinary strategy might improve the care of HNCPS, even if its benefit has not been widely studied, yet. An experienced dentist is necessary in this team due to the need to integrate oral, dental and medical care. A recent study (Friedland et al., 2011) showed a better 5-year survival in 395 patients managed in the multidisciplinary clinic or team setting compared to 331 HNCPS managed outside of an multidisciplinary approach. Keefe et al. included a interdisciplinary approach for supportive care in HNCPS' treatment guideline (Keefe et al., 2007; Niscola et al., 2012; Lalla et al., 2014).

4.4.3. The use of recombinant human KGF-1 (palifermin) is not recommended routinely in patients treated for head and neck cancer

Keratinocyte growth factor (KGF) is a fibroblast growth factor (FGF-7) that stimulates cell proliferation, migration, differentiation, survival, DNA repair, and induces detoxification from reactive oxygen species (Finch and Rubin, 2006; Finch et al., 1989). Recombinant human KGF (palifermin; N23-KGF) is approved for use in patients with hematologic malignancies receiving myelotoxic therapies requiring hematopoietic stem cell support (Sonis, 2009).

Le et al. (2011) reported a lower incidence of severe mucositis (weekly 180 g/kg Palifermin 54% vs. placebo 69%; $p=0.041$), in a multicenter, randomized, placebo-controlled, double-blind trial in 188 locally advanced HNCs treated with definitive conventional CRT (radiation 2 Gy/day). The median time to develop severe OM was delayed (47 vs. 35 days), the median duration of severe OM was shortened (5 vs. 26 days). However, the differences were not significant for PRO measures, because the average mouth and throat soreness scores did not differ between the 2 arms. In addition, opioid analgesic use and CRT compliance were not different. Median follow-up for patients who were alive at last contact was 25.9 months (range, 0.7–48.4 months) in the palifermin arm and 25.0 months (range, 0.7–45.9 months) in the placebo arm indicating no apparent difference in survival curves between treatment arms.

Henke et al. (2008) in a similar phase III study obtained similar results in the postoperative setting. The incidence of severe mucositis was reduced in patients treated with weekly 120 μ g/kg of palifermin (51%) compared to controls (67%; $p=0.027$). The median duration of severe OM (4.5 days vs. 22 days) and time to onset (4.5 days vs. 22 days) were also superior in the palifermin group compared to placebo. No differences were reported in PROs. The median follow-up for all patients was 32.8 months (palifermin, 24.7 months [range, 0.5–50.5]; placebo, 34.5 months [range, 0.2–50.6]). Overall survival (hazard ratio, 0.96; 95% CI, 0.54–1.71) was similar between treatment arms.

No data about a possible imbalance of Human Papilloma Virus (HPV)-status between the arms have been reported. Indeed, concerns exist about a potential stimulation by palifermin of primary or secondary tumor growth, since epithelial tumors have receptors for KGF. However, xenograft models have demonstrated that palifermin neither stimulates tumor growth nor confers tumor protection from CT and in vitro study of human head and neck cancer cell lines has shown neither growth stimulation nor alteration in radiosensitivity from KGF exposures up to 2 days (Brake et al., 2008; Ning et al., 1998). Trials with longer follow-up are needed to confirm the role of palifermin as potential inducer of tumor growth. Thus, additional data are needed to assure safety of the drug.

Therefore, based on these trials we could not definitely establish the clinical relevance of the extensive use of palifermin in HNCs treated with RT or RCT. Indeed, the reported reduction of the rate of mucositis with palifermin did not translate in fewer RT breaks or a lower average Mouth and Throat Soreness (MTS) scores. Last but not least, palifermin is relatively expensive and cost-benefit will have to be demonstrated in HNCs (Bossi et al., 2012).

4.5. Treatment statements: oral examination

4.5.1. Evaluating oral hygiene:

- Basic oral care will reduce the frequency and severity of oral mucositis and its associated pain (the use of soft toothbrushes and non-irritating mouthwashes).
- Regular oral care with the use of oral mouthwashes is recommended.
- The use of oral care products not containing alcohol without intense flavor is suggested.

- No superiority of one mouthwash over saline or bicarbonate rinses has been demonstrated.
- Oral prostheses should be kept clean with an antimicrobial solution and their use should be discouraged during night time and in presence of overt oral mucositis.

Oral care has been often recommended by several authors to reduce the incidence and severity of OM (Lalla et al., 2008; Rubenstein et al., 2004; Bensinger et al., 2008; Keefe et al., 2007; Niscola et al., 2012; Lalla et al., 2014). The management of pre-existing periodontal and dental disease may lead to a better control of OM. Thus, qualified oral health care teams have to be integrated in a multidisciplinary approach on the basis of well-defined protocols prior to treatment, during treatment, and during follow-up (Beech et al., 2014; Moore et al., 2012; Chl et al., 2010). A randomized controlled trial was undertaken to compare the effect of an oral care protocol to no oral care protocol in delaying the onset of OM and reducing oral injury in 30 nasopharyngeal cancer patients undergoing RT. Later onset of OM and a lesser degree of oral injury were recorded in the oral care protocol group (Shieh et al., 1997). The importance to plan a simple and inexpensive oral care protocol for reducing OM was also underlined by several authors for different cancer patients (Santos et al., 2011; Qutob et al., 2013; Hogan, 2009). The updated MASCC/ISOO guidelines for the management of OM recommended the development of oral care protocols with patient and staff education on the daily application of this protocol to reduce the incidence of pain and mucositis in patients treated with RT (Lalla et al., 2014; McGuire et al., 2013a). However, considering the lack of evidence on the choice of one product over another, normal saline and sodium bicarbonate mouthwashes or oral mouthwashes not containing alcohol and without intense flavor are considered helpful for oral care.

4.5.2. Assessing mucositis progression

When once-weekly irregular assessment instead of daily scoring was evaluated, the incidence of mucositis was underestimated. Whether a more frequent assessment could generate an improved control of OM needs to be confirmed. Thus, in patients receiving RT \pm CT for HNC it is recommended to regularly assess OM at least once-a-week, advising the patient to communicate any further worsening of symptoms. Presently, there are no recommendations regarding the optimal timing for OM assessment. Wygoda et al. evaluated severity of acute mucosal reactions caused by CF-RT and AF-RT regimens according to frequency and regularity of scoring. A significant difference in the incidence of mucositis between the CF-RT and AF-RT groups was noted, mainly in weeks 4–6 of irradiation. Comparing the irregular once-weekly assessment arm with the daily assessment arm, the incidence of mucositis was underestimated by approximately 20–36% in the once-weekly arm. Even a regular thrice-weekly scoring moderately underestimated the incidence of OM compared with daily scoring (Wygoda et al., 2009). Whereas both for patients and physicians, daily or three times a week evaluation can be a huge burden, our recommendation is to regularly evaluate OM at least once-at-week, and to advise patients to communicate any further worsening of symptoms.

4.6. Radiotherapeutic precautions

- RT with the aim of maximal sparing of the mucosa outside any Planned target Volume (PTV) is recommended.
- When intensity modulated RT (IMRT) is used, the total dose to the mucosa outside any PTV should be planned to be limited to 30 Gy in 6–7 week, but this should not jeopardize coverage of the PTV with the prescribed dose.

IMRT represents the standard technique for RT of HNCPS (Kouloulis et al., 2013). In addition to a better dose conformation, the IMRT provides the possibility of dose-escalation with a better normal tissue sparing (e.g., parotid glands) (Marta et al., 2014). In clinical practice, IMRT reduces the incidence of grade 2–3 xerostomia in HNCPS without compromising loco-regional control and overall survival (Kouloulis et al., 2013; Fang et al., 2008). Yet, IMRT is still associated with substantial acute toxicity, namely OM, that also limits the therapeutic potential of this technique (Sanguineti et al., 2011; Wang et al., 2012; Gomez et al., 2009). The use of multiple nonuniform intensity beams results in a more heterogeneous dose distribution within both target volumes and normal tissues compared with opposed lateral beams using 3D-conformal radiation therapy. A typical seven- or nine-field IMRT plan for tumors of the oropharynx uses beams that enter or exit through the oral cavity during the entire course of treatment. Conversely, the 3D conformal opposed lateral beams would spare the majority of the oral cavity for most if not the entire duration of radiation course. Grade 2 or more acute mucositis was reported in 66% of 35 patients with oral cavity cancer who received postoperative IMRT (Narayan et al., 2008). Elting et al. showed that the use of IMRT was not associated with a higher risk of grade 3 mucositis compared with CFRT, but was associated with significantly longer durations of mucositis ($p < 0.01$) (Elting et al., 2007). Vergeer et al. showed lower rates of acute mucositis during radiation with IMRT as compared to 3D-CRT, which they explained by the use of a simultaneous intergrated boost technique with lower dose per fraction to the electively treated areas and the longer overall treatment time of radiation (Vergeer et al., 2009). With IMRT, a large volume of the anterior part of the oral cavity was frequently exposed to low/intermediate dose, due to the use of multiple oblique fields. In 12 patients, cumulative doses to the oral cavity of less than 32 Gy were associated with minimal acute mucositis while a dose greater than 39 Gy was associated with longer duration of mucositis (Narayan et al., 2008). Shogan et al. showed a statistically significant correlation between acute mucositis grade and percentage of volume of oral cavity receiving 15, 30, 40, and 45 Gy (Shogan et al., 2005).

Several studies were recently published that investigated whether part of the mucosa that is not overlapping with the PTV can be spared during the planning process. Sanguineti et al. investigated the potential “mucosa sparing” effect of IMRT by considering the wall of oropharyngeal mucosa as an organ at risk (Sanguineti et al., 2006). They showed that IMRT can spare more mucosal volume respect to 3D-conformal RT, and when the maximum dose to the mucosa was setted below 30 Gy, they recorded a decrease of 20% and 12% of the percentage of mucosa volume exposed to a dose equivalent to 30 Gy and 70 Gy in 3 and 7 weeks, respectively. The authors showed that IMRT with an oral mucosal dose constraint below of 30 Gy could potentially reduce the rate of OM without a detrimental effect on PTV. Moreover, they found a significant correlation between the absolute amount of OM that received 9.5 Gy per week and the need of or dependence on a feeding tube during IMRT in oropharyngeal cancer (Sanguineti et al., 2011). The reduction of OM volume that receives more than 9.5–10 Gy/week to less than 50–60 cc may result in a significantly lower risk of requiring percutaneous endoscopic gastrostomy (PEG). Recently, a prospective, randomized clinical trial has been conducted to investigate IMRT with or without oral sparing for oral tongue squamous cell carcinoma (SCC) in order to compare the incidence and severity of acute mucositis in multiple oral cavity sites (Wang et al., 2012). In 24/48 patients with oral tongue SCC treated with postoperative IMRT, the mucosa including the bilateral cheeks, upper lip, and lower lip was defined as a single organ-at-risk (OAR) and was given <32Gy. Compared to the group of unspared oral mucosa, the single-OAR-saving technique had less grade 2 and 3 mucositis in the constrained-dose areas in the spared oral mucosa group (0%

and 25% vs. 45.8% and 54.2%, respectively; $p < 0.001$). Moreover, the spared oral mucosa group recorded a significant reduction in the use of analgesics ($p < 0.043$) and intravenous antibiotics ($p < 0.039$). Notably, no recurrences were detected in the vicinity of the spared oral mucosa (the united site) during a median follow-up time of 30 months. Although the definition and contouring of the oral mucosa volume in a reproducible and consistent way may still appear problematic, the spare of oral mucosa with IMRT seems a promising and attractive approach in order to decrease the severity of acute mucositis and improving QoL (Dean et al., 2015).

At any rate, some technical devices such as the positioning of the patient with hyperextended neck or some oral or lingual immobilizing tools can help to reduce the exposure of oral mucosa to high doses of radiation therapy

4.7. Statements about the prevention and treatment of mucositis: not recommended practice

4.7.1. Cryotherapy

- Cryotherapy is not recommended in HNCPS during (chemo) radiation due to the risk of less tissue oxygenation occurring with vasoconstriction that could impact on treatment efficacy and due to lack of data in this setting, even it was found to be beneficial in patients receiving bolus 5-FU or high dose melphalan.

Cryotherapy has largely been utilized since 1990 in order to reduce OM in cancer patients undergoing systemic CT. Clinical trials as well as meta-analyses have confirmed its clinical benefit in reducing OM incidence and/or severity in this setting of patients (Peterson et al., 2013). Since the mechanism of action of hypothermia is based on the effect of local vasoconstriction in the mucosa of the oral cavity, cryotherapy has not been used in HNCPS treated by either CT or CRT, because it has been postulated that the effect of vasoconstriction might be detrimental for the local control of the cancer itself. Therefore, no studies have been published regarding the use of cryotherapy for HNCPS' mucositis. Consequently, its use cannot be recommended in HNCPS (Keefe et al., 2007; Lalla et al., 2014; Peterson et al., 2013).

4.7.2. Amifostine

- There is insufficient evidence to support the use of amifostine for the prevention and treatment of OM in CRT HNCPS.
- Amifostine is not recommended in patients receiving radiotherapy ± chemotherapy for head and neck cancer, because of its side effects and high cost.

Amifostine is a radioprotective agent that scavenges radiation-induced free radicals and has been shown to protect normal tissues from adverse effects of radiation in various experimental models. In HNCPS, several trials, many of them suffering of statistical bias, have compared amifostine with no treatment or placebo and they indicate a weak unreliable evidence of amifostine effectiveness in preventing HNCPS' OM (Veerasarn et al., 2006; Bourhis et al., 2000; Kouloulis et al., 2004). A recent metanalysis showed that Amifostine was significantly effective in lowering mucositis, xerostomia and dysphagia incidence in patients treated with exclusive RT, while no reduction of side effects was recorded in the CRT group (Guertal, 2014). On the other hand, a randomized phase III study has demonstrated that the daily administration of i.v. Amifostine can successfully reduce the incidence and severity of acute and chronic xerostomia without reducing the severity of acute mucositis (amifostine vs. no treatment: G3-4 OM 35% vs. 39%) (Brizel et al., 2000). In conclusion, there are conflicting results on the efficacy of i.v. Amifostine in reducing OM incidence in this setting of patients, so

it can not be recommended for the prevention and treatment of OM in CRT HNCPS (Gu et al., 2014; Büntzel et al., 1998; Antonadou et al., 2002; Büntzel et al., 2002; Vacha et al., 2003; Buentzel et al., 2006; Suntharalingam et al., 2004).

Similar results have been also reported for subcutaneous Amifostine (Haddad et al., 2009).

4.7.3. Glutamine

- Glutamine is not recommended to prevent OM in HNCPS ± CT

L-Glutamine (GLN) is a nonessential amino acid that has a variety of applications in naturopathic medicine. It has been postulated that in the critically ill patient, GLN becomes an essential amino acid for recovering, restoring, and repairing cells. There have been some questions in regard to the GLN use in this patient population considering the fact that it is a preferred energy source for enterocytes, lymphocytes, and for malignant cells, as well. The review by Savarese et al suggested that the clinical role of GLN in the prevention of CT and RT-induced toxicity is evolving (Savarese et al., 2003). Indeed, the trials regarding GLN supplementation are scarce and the quality of evidence is low. In a double-blinded, placebo-controlled study, a significant ($p=0.035$) lower incidence of mucositis was shown in 14 patients receiving L-alanyl-L-glutamine than in 15 patients receiving placebo (Cerchiatti et al., 2006). Furthermore, GLN significantly decreased CRT-induced mucositis severity in the oral cavity, pharynx and larynx compared with placebo in 40HNCPS (Tsujiimoto et al., 2015). However, considering the substantial heterogeneity among these studies and the small series of patients, the panelists concluded that there is inadequate evidence of benefit of glutamine in reducing or preventing HNCPS' mucositis (Yarom et al., 2013).

4.7.4. The following topical agents are not recommended for mucositis prevention and treatment:

- Barrier-protective agents such as sucralfate, GelClair[®], MuGard[®] and Mucotrol[®]

Barrier-protective agents such as sucralfate, GelClair[®] and Mucotrol[®] are self-applied by patients in an attempt to cover ulcerated mucosa and reduce symptoms. **Sucralfate** is an aluminum salt of sulfate sucrose. It has been used since 1968 for the treatment of duodenal ulcers. In several studies, prophylactic oral rinsing with sucralfate did not prevent oral ulcerative mucositis (Carter et al., 1999; Epstein and Wong, 1994; Evensen et al., 2001; Lievens et al., 1998; Meredith et al., 1997; Makkonen et al., 1994; Cengiz et al., 1999; Franzén et al., 1995; Etiz et al., 2000). A randomised trial with 20 subjects reported that **GelClair[®]** was no more effective than standard practice (sucralfate and mucaïne) in relieving the pain associated with RT-induced OM (Barber et al., 2007). Only one small study reported on the efficacy of **Mucotrol[®]** in reducing the incidence of mucositis, which was attributed to its local analgesic, antioxidant and immunomodulatory activity and wound-healing properties (Naidu et al., 2005).

Recently, a randomized trial with the mucoadhesive hydrogel **MuGard[®]** has been published, showing a reduction of patient-reported oral soreness and WHO mucositis grade during RT vs. a sham placebo mainly consisting of bicarbonate rinses (Allison et al., 2014). The results of this trial are promising, but it should be cautiously considered because efficacy assessments were limited to only 78 of 120 enrolled subjects who documented daily study medication use during the first 2.5 weeks following radiation therapy. The reduced compliance during the trial is a concern for transferability of this result to clinical practice. Additionally, although set up as a double-blind study, the use of a sodium bicarbonate rinse as a control for a viscous mucoadherent gel may not be optimal.

- Allopurinol gel

No difference between allopurinol and placebo in HNCPS receiving RT ± CT has been demonstrated, even if some results suggest that allopurinol gel application can mitigate inflammatory reactions associated to RT-induced OM and dermatitis (Abbasi Nazari et al., 2007; Kitagawa et al., 2008). Recently, a film dosage form containing allopurinol seems to be useful to prevent or treat mucositis (Murata et al., 2012). In summary, most of the studies have not shown a real utility of this agent either for the prevention or the treatment of OM (Jensen et al., 2013).

- Chlorhexidine-digluconate

Chlorhexidine mouthwashes were compared with placebo in 25 patients treated with RT, showing a detrimental effect (Foote et al., 1994). Significantly lower mucositis scores were reported with 1% povidone-iodine mouthwashes, in respect to 0.12% chlorhexidine (Madan et al., 2008). Conversely, Meca reported that chlorhexidine digluconate significantly reduced the Mutans Streptococci count and induced a significant improvement of RT side effects, such as mucositis and candidosis (Meca et al., 2009). Yet, the use of bioadhesive chlorhexidine gel 0.2% did not contribute to a clinical improvement of the RT-CT induced OM (Diaz-Sanchez et al., 2015). Finally, the randomized clinical trial of Lanzos et al. detected no significant differences between chlorhexidine and placebo group (Lanzós et al., 2010; McGuire et al., 2013b).

- Povidone-iodine, triclosan mouth washes, Isegran mouth washes

Topical antibacterial agents have been proposed for the reduction of OM (Saunders et al., 2013).

Among these, **Povidone-iodine**, typically used to disinfect skin wounds, showed a modest efficacy compared to sterile water or intensive dental hygiene protocols (Adamietz et al., 1998; Rahn et al., 1997). Conversely a multicenter, randomized trial, showed no difference between Povidone-iodine and saline mouthwashes (Vokurka et al., 2005). **Triclosan**, another broad-spectrum antibacterial agent, did not reduce OM in 24HNCPS, compared to sodium bicarbonate mouthwash (Satheeshkumar et al., 2010). **Isegran**, an analog of protegrin-1 with broad-spectrum antimicrobial activity, was utilized either in CT or CRT protocols. Randomized studies demonstrated lack of efficacy of Isegran in reduction or prevention of OM (Lalla et al., 2014; Saunders et al., 2013).

- Aloe vera

Two papers reported different results about Aloe Vera efficacy (Su et al., 2004; Puataweepong et al., 2010). Furthermore, recently Ahmadi et al. stressed the potential usefulness of Aloe vera mouthwash as alternative agent for treating RT-induced OM and candidiasis in HNCPS (Su et al., 2004; Puataweepong et al., 2010; Ahmadi, 2012; Sahebjamee et al., 2014). Although numerous studies have been published about Aloe Vera, the only randomized one showed no advantage for Aloe Vera vs. placebo (Yarom et al., 2013; Su et al., 2004).

- Granulocyte macrophage colony-stimulating factor

Granulocyte colony-stimulating factor (G-CSF) showed no statistically significant difference compared to placebo in patients treated with RT or CRT (Su et al., 2006).

Several series showed some effects of granulocyte-macrophage colony-stimulating factor (GM-CSF) in preventing mucositis in

HNCPs receiving CT or CRT, used both as mouthwashes and subcutaneously (Raber-Durlacher et al., 2013; Saarihahti et al., 2002; Mantovani et al., 2003; Masucci et al., 2005; Makkonen et al., 2000; McAleese et al., 2006).

On the other hand, the Radiation Therapy Oncology Group conducted a double-blind, placebo-controlled, randomized study to test the efficacy and safety of GM-CSF in reducing the severity and duration of mucosal injury and pain (mucositis) associated with curative RT in HNCPs. There was no statistically significant difference in the average mean mucositis score in the GM-CSF vs. placebo arms by a *t* test ($p=0.4006$) (Ryu et al., 2007). Consequently, no recommendation can be given about the use of GM-CSF in this setting of disease.

- Pure natural honey

Several studies showed that prophylactic use of pure natural honey was effective in reducing mucositis in HNCPs (Biswal et al., 2003; Motallebnejad et al., 2008; Rashad et al., 2009; Bardy et al., 2012). However, in view of the considerable statistical heterogeneity of these studies with a high risk of statistical biases, these results should be interpreted with caution (Song et al., 2012; Richards, 2012; Clarkson et al., 2010). Recently, a randomized placebo-controlled trial showed that manuka honey was poorly tolerated and did not reduce CRT-induced mucositis (Hawley et al., 2014).

- Misoprostol and Prostaglandin E₂

Misoprostol, a prostaglandin E₁ analog, is an effective radioprotector in animal studies. Sixty-nine patients were treated with RT and either misoprostol tablet or an identical placebo tablet. No advantage was seen in the misoprostol group (Hanson et al., 1995). In a randomized, double-blind, placebo-controlled trial of misoprostol in HNCPs, topical misoprostol was ineffective in reducing the severity of radiation-induced mucositis in patients receiving radical dose RT (Veness et al., 2006). Prostaglandin E₂ lozenges were found to be ineffective either in the prevention or treatment of HNCP/leukemia OM (Porteder et al., 1988; Labar et al., 1993; Kühner et al., 1986; Pretnar et al., 1989; Nicolatou-Galitis et al., 2013).

- Antibiotic + antifungal pastilles (containing polymixin, tobramycin and Amphotericin or bacitracin, clotrimoxazole and gentamicine)

Antibiotic + antifungal pastilles (containing polymixin, tobramycin and amphotericin) were compared with a placebo: the selective oral flora elimination did not result in a reduction of radiation-induced mucositis (Stokman et al., 2003; Wijers et al., 2001). Antimicrobial lozenge (bacitracin, clotrimazole, and gentamicin) was assessed in a multicenter, double-blind, prospective, randomized trial aimed to reduce RT-induced mucositis in HNCPs. There were no statistically significant differences between the arms in terms of extension of severe mucositis or RT delays (El-Sayed et al., 2002). Finally, the use of oral antimicrobials does not seem to impact QoL (Duncan et al., 2005).

4.8. During treatment

4.8.1. Benzydamine mouthwashes

- Suggestions are possible about benzydamine mouthwashes to prevent radiation-induced mucositis in HNCPs receiving moderate-dose radiation therapy (up to 50 Gy) without CT.

Benzydamine mouthwash was compared to placebo in several trials and in all of them some statistically significant differences in

favour of benzydamine have been reported although all these studies suffered from some statistical bias (Samaranayake et al., 1988; Epstein et al., 1989; Kazemian et al., 2009; Roopashri et al., 2011). In a randomized double-blind study, Epstein et al. showed a reduction of erythema and ulceration in benzydamine group compared to the placebo group in patients treated with a cumulative doses of 50 Gy (exclusive RT) (Epstein et al., 2001). These results have also been confirmed by Cheng, although in a small series of patients (Kin-Fong Cheng and Ka Tsui Yuen, 2006).

- The beneficial effects, however, need to be confirmed in a larger trial. Based on the Epstein's study, benzydamine mouthwashes have been recommended for prevention of radiation-induced mucositis in HNCPs receiving moderate-dose radiation therapy, without concomitant chemotherapy (Keefe et al., 2007; Lalla et al., 2014). However, since no direct comparison has been performed with saline or bicarbonate rinses, either agent can be suggested. No evidence of benefit with Benzydamine mouthwash has been recorded in patients submitted to CRT treatment (Prada and Chiesa, 1987; Prada et al., 1985).
- Antimycotic mycostatin or topical miconazole for prevention.

The only data coming from randomized study are derived from patients with leukemia treated with CT or bone marrow transplantation. It showed no difference between the use of nystatin mouth rinses (with or without clorexidine) and saline rinses (Epstein et al., 1992). Furthermore, the topical application of miconazole oral gel was ineffective in reducing the incidence of OM in leukemia pediatric patients (Rojas de Morales et al., 2001). Thus, no evidence in favour of prophylaxis with these 2 agents can be derived.

4.8.2. Systemic employment of antibiotics or antiviral agents is not recommended with prophylactic intent in absence of neutropenia; on the other side they are recommended in case of overt infection

Interventional strategies that have targeted the oral microflora have been unsuccessful (Donnelly et al., 2003; Laheij et al., 2012; Spijkervet et al., 1990). Antimicrobial agents have no effect in contrasting mucositis. A randomized study between an oral paste containing either a placebo or a combination of the antibiotics polymyxin E, tobramycin, and amphotericin B with the aim of selectively eradicating the aerobic Gram-negative bacteria of the oral cavity, did not result in a reduction of radiation-induced mucositis (Wijers et al., 2001). The use of systemic Clarithromycin has been related to a reduction of OM in patients undergoing bone marrow transplantation, while no studies have been published about HNCPs (Hanson et al., 1995; Yuen et al., 2001). In the absence of studies on this topic, we do not recommend the prolonged use of systemic antibiotic therapy for OM prophylaxis in patients with normal PMN count, also considering the potential risk of selecting resistant bacteria (Saunders et al., 2013). The same considerations have been made with regard to the use of systemic antiviral agents. At the moment, there are no data in the literature indicating their real effectiveness in reducing the incidence of OM in HNCPs (Saunders et al., 2013; Bergmann et al., 1995; Bublely et al., 1989). Systemic antibiotics or antiviral agents are to be used in case of overt infection (bacterial and/or viral) of the oral cavity, after a specific diagnosis of the causative agent involved.

4.8.3. Prophylactic treatment with fluconazole reduced the risk of mycotic infections during RT. However, there are conflicting results about the impact of fluconazole therapy on the development of mucositis (likely due to variable discrimination of candidiasis and mucositis), thus its use cannot be suggested for the management of mucositis

4.8.3.1. *Fluconazole can be suggested only in therapeutic setting or with a prophylactic intent in case of patients at high risk of mycosis (chronic steroidal therapy, diabetes).* Clinical oral fungal infection represents a frequent infectious complication in HNCs. During RT, the prevalence of oral colonization was 37.4%, mainly by *C. albicans* (Bubley et al., 1989). An Italian study reported oropharyngeal mycosis (OPM) in 42.4% of people >70 years and in 58.2% of younger individuals ($p=0.0042$), and in 68.6% of women versus 50.8% of men ($p=0.0069$) (Busetto et al., 2013). Moreover, patients with OPM had longer hospitalization ($p=0.0002$) and longer (>12 days) treatment interruptions ($p=0.0288$). The prophylactic treatment with fluconazole reduced the risk of mycotic infections in a non-randomized study by Nicolatou-Galitis et al. (2006). These authors recorded a statistically significant reduction of the rate of OM (14% vs. 44% $p=0.018$). In other retrospective series, prophylactic fluconazole had significantly decreased grade ≥ 2 mucositis compared to an usual care group (70.6% vs. 89.3%, $p=0.003$) (Rao et al., 2013). Conversely Corvò et al. (2008) confirmed the reduction of the oropharyngeal candidiasis incidence in the group of patients receiving fluconazole prophylaxis in a double-blind controlled trial, but they found no difference in the incidence of mucositis (10% in fluconazole and placebo group). In the light of the literature findings, no recommendation can be made about the utility of prophylaxis with fluconazole for OM in the HNCs treated with RT. However it remains the treatment of choice in case of overt fungal infection in immunocompromised patients (Saunders et al., 2013; Pappas et al., 2009). Finally, it can be judiciously used with prophylactic intent in case of such patients at high risk of mycosis (chronical steroidal therapy, diabetes), balancing against the risk of emergence of resistant strains.

4.9. During treatment: non-suggested practice

4.9.1. No suggestion is possible for topical steroids use in HNCs receiving RT \pm CT

- Systemic continuous employment of steroidal therapy for mucositis prevention/treatment is not recommended

Steroids are considered powerful anti-inflammatory drugs. On the basis of this anti-inflammatory effect, they have been widely used in clinical practice. Even in patients with mucositis of the oral cavity the use of steroids, especially as components of magic-mouthwash, is a widespread practice, although there are no studies that prove their effectiveness (Chan and Ignoffo, 2005; Dodd et al., 2000). Steroidal drugs have also been used as a systemic therapy for the control of mucositis of the oral cavity. Yet, few studies have been published with conflicting results. No efficacy has been reported with prednisone given orally (40 mg/day) for 8 days in 32 HNCs in a randomized, double-blind, placebo-controlled study (Leborgne et al., 1998). Therefore, no support can be drawn from the literature about the efficacy of steroidal drugs on prevention of OM in HNCs (Nicolatou-Galitis et al., 2013). Finally, we discourage the continuous employment of systemic steroidal therapy for mucositis prevention/treatment because there are no data regarding its usefulness in the face of the high incidence of side effects such as immunosuppression, hypertension, diabetes, and risk of gastric perforation.

4.9.2. A number of NSAIDs have been evaluated for OM, including systemic indomethacin and aspirin

- No suggestions are possible about their use in HNCs receiving RT \pm CT

In recent years, the recognition that the mucositis evolves also through a complex cascade of mainly inflammatory events has been provided numerous targets for intervention that are still being

explored (Lalla et al., 2006). Indeed, Sonis enriched the knowledge of the pathogenesis of oral mucosal inflammation with new data on innate and adaptive immune responses to cell death (Russi et al., 2014; Sonis, 2004). The key mechanism by which OM starts is considered a complex inflammatory process that begins early with transient erythema (Russi et al., 2014) even in the absence of other clinical signs. Thus, the use of anti-inflammatory drugs has been considered very attractive in order to prevent or reduce the OM in HNCs. Although a large series of these drugs has been tested in this setting, no evidence about their usefulness has been shown until now (Saunders et al., 2013).

4.9.3. Low level laser therapy may reduce OM severity, but vigilance remains necessary and no recommendation is possible

Low-level laser therapy (LLT) is a noninvasive modality for prevention and management of oral mucositis. LLLT changes the production of intracellular reactive oxygen species (ROS) by acting on mitochondrial respiration. These changes result in fibroblast proliferation, collagen synthesis, decrease of the inflammatory response, increased angiogenesis and tissue repair (Moshkovska and Mayberry, 2005). In addition, these changes causes alteration of excitation and nerve conduction in peripheral nerves and stimulation of release of endogenous endorphins (Chow et al., 2009).

Although there is evidence for the benefit of LLLT in stem cell transplant recipients and the potential of LLLT to reduce OM and OM-associated pain in HNCs is promising (Arun Maiya et al., 2006; Arora et al., 2008; Simões et al., 2009; Zanin et al., 2010; de Lima et al., 2010; Carvalho et al., 2011; Gouvêa de Lima et al., 2012; Gautam et al., 2013; Arbabi-Kalati et al., 2013; Schubert et al., 2007), vigilance remains necessary with respect to its potential growth stimulating effect on tumor cells. In addition, The need of standardization of methods and the absence of a diffuse expertise with this modality make recommendation not possible.

5. Conclusions

OM represents a very stressful situation for HNCs submitted to CRT or exclusive RT. Mucositis is the result of a complex biological process and, therefore, several different management approaches have been proposed, but there is still no gold-standard protocol that is prominently better than others. The range of interventions includes mucosal surface protectants, anti-inflammatory formulations, antimicrobials, growth factors, and a plethora of other miscellaneous agents. Despite all these options, a uniform approach to mucositis prevention and treatment, sustained by a strong evidence base, is lacking.

The new technologies and radiotherapeutic techniques such as IMRT may provide useful tools to spare salivary glands and to reduce the volume of oral mucosa irradiated with doses higher than 30–32 Gy. This radiotherapeutic approach seems to be related to a lower incidence of high grade OM, but the magnitude of the OM symptoms continues to be extremely important from the point of view of HNCs. Although many molecules, drugs and other measures have been proposed to prevent OM, standardized approaches have not been defined up to now. Currently, a multidisciplinary approach is mandatory in HNCs. Therefore, well-orchestrated procedures by oral health care professionals, radiotherapists, oncologists, and surgeons are desirable. Moreover, recent studies focus on identifying genetic polymorphisms associated with the risk to develop OM. This can contribute to better definition of the etiopathogenesis and individualized management of OM. Finally, in the last decade the innate and adaptive immune responses to cell death have been integrated into the pathogenesis model of OM. This will open new scenarios to be explored in the field of OM prophylaxis.

Despite of a clear need for more research, recommendations for prevention/treatment of OM based on consensus might be useful, particularly in the context of well-structured multidisciplinary supportive cancer care.

Conflict of interest

The Authors have no financial and personal relationships with other people or organisations that could inappropriately influence (bias) this work.

Dr. Lalla serves as a consultant for Dara Biosciences, Ingalpharma, and Sucampo Pharmaceuticals.

Disclaimer

This Consensus Paper is informational in nature. The authors caution that the strategies described in this paper might not be suitable for every, or any, purpose or application. This Consensus Paper cannot substitute for the individual judgment brought to each clinical situation by the patient's health care providers. As with all clinical materials, the Consensus Paper should be used with the clear understanding that continued research and practice could result in new knowledge or recommendations.

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