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Pain management in head and neck cancer patients undergoing chemo-radiotherapy: Clinical practical recommendations

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ABSTRACT

Pain in head and neck cancer represents a major issue, before, during and after the oncological treatments. The most frequent cause of pain is chemo/radiation related oral mucositis, which involves 80% of the patients and worsens their quality of life inhibiting speaking, eating, drinking or swallowing and sometimes reducing the treatment compliance, the maximum dose intensity and thus the potential efficacy of treatment. Nevertheless pain is still often under estimated and undertreated. An Italian multidisciplinary group of head and neck cancer specialists met with the aim of reaching a consensus on pain management in this setting. The Delphi Appropriateness method was used for the consensus. External expert reviewers evaluated the final statements. The paper contains 30 consensus-reached statements about pain management in HNC patients and offers a review of recent literature in these topics.

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1. Introduction

Thirty-nine studies carried out in head and neck cancer patients showed that pain is present in 50%, 81% and 70% of them respectively before, during and after the oncological treatments. In 36% of the patients pain carried on six months after the end of therapy performed with curative intent and in 30% of the patients the severity of pain was higher than the pre-treatment period.

Systemic therapy associated with radiation is the main treatment of locally advanced head and neck cancer (HNC) patients, increasing overall survival and loco-regional control (Pignon et al., 2009). Acute pain due to inflammation of mucosa (mucositis) and skin in the radiation field (dermatitis), and late pain related to radiation-induced fibrosis (costo-clavicular or temporomandibular joint disorder, trismus, neuropathic pain) impair quality of life (Blanchard et al., 2014) and possibly reduce the chances of cure. Pain is involved in a vicious cycle, consisting of dysphagia, malnourishment, reduced treatment compliance, that may hesitate in a lower dose intensity of systemic therapy or in radiation treatment breaks, so ultimately with a possible interference on chance of tumor control (Bese et al., 2007). The analgesic strategies employed for pain management comprise both local and systemic drugs (Cerchietti et al., 2002; Ling and Larsson, 2011; Bar Ad et al., 2010a). However, there are insufficient evidences to choice one specific analgesic treatment over another (Trotter et al., 2013).

Treatment outcome is the most reported endpoint in the available studies based on head and neck cancer patients, and only a minority of the reports consider specifically pain due to the oncological management and pharmacological strategy to address it. However, pain is considered one of the most troublesome symptom when linked to mucositis, possibly increasing also medical costs among HNC patients treated with chemo-radiation (CRT), proportionally to the severity of the clinical presentation (Trotti et al., 2003; Nonzee et al., 2008).

For all these reasons Italian medical oncologists (MOs), radiation oncologists (ROs) and palliative care specialists met with the aim of reaching a consensus on pain management in CRT-treated HNC pts. The results of the literature review and the statements that obtained consensus are reported and discussed in this paper.

2. Material and methods

The Delphi Appropriateness Method was used for this Consensus (Loblaw et al., 2012). The panel, a group of 37 multidisciplinary experts (MOs, ROs, palliative care specialists and nurses), met in Milan on February 17 and 18, 2013 and appointed a facilitator board of 4 expert members, from different clinical settings (2 MOs, 2 ROs). The facilitator board performed a systematic review of the literature on pain in systemic therapy and CRT-treated HNC patients.

The MEDLINE database was searched for English-language studies published from 1994 to March 2013 containing the terms pain, head and neck cancer, systemic therapy, chemotherapy and radiotherapy.

Potentially relevant abstracts presented at annual meetings of the American Society of Clinical Oncology and of the European Society of Medical Oncology were examined.

The study selection included the following:

(a) observational and prospective studies about assessment and treatment; (b) randomized, double-blind, placebo-controlled, or uncontrolled studies; (c) retrospective and uncontrolled studies; (d) systematic reviews and meta-analyses; (e) consensus guidelines. Furthermore the electronic search results were supplemented by manual examination of reference lists from selected articles.

On the basis of this literature review, the facilitators identified a number of key statements. All the experts rated these statements through a two-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 (<75/100) were redefined according the observations of panellists. The final ratings were analyzed to identify the statement that reached a consensus. Each expert (including facilitator) was equally weighted in scoring the statements. External specialists in Medical Oncology and supportive cancer care reviewed the statements.

3. Results

Consensus-reached statements are listed in Table 1.

4. Comments

4.1. General statements:

a In (chemo) radiotherapy-induced mucositis, escalation of pain intensity and pain interference scores generally start at week 3, peak at week 5 and persist for 2–4 weeks after the end of radiotherapy, with a gradual remission of signs and symptoms.
b (Chemo) radiotherapy-induced mucositis pain is frequent (>80%) and interferes with daily activities (33% of pts) and with social activities and mood (50–60% of pts); these consequences greatly affect the patient's overall quality of life and may lead to severe disability, including work absences or loss of active employment.
c Patients may experience long term spontaneous or evoked mucosal pain due to epithelial atrophy, neurologic sensitization and/or neuropathy. Putative risk factors for mucosal sensitivity include: aggressive chemoradiation regimens, xerostomia, and active cigarette smoking. Pain may be evoked by hot or spicy food/liquids, acidic food/liquids and dry air.
d Painful mucositis increase the costs of care (opioid analgesics, tube feeding), is associated with additional admission and prolonged periods in the hospital, leading to delayed, interrupted, or altered cancer therapy protocols that can affect prognosis.
e Mucosal pain may be caused by or exacerbated by oral infections. A careful oral exam to rule out infection since it can be easily treated.

Patients report that mucositis is the most debilitating side effect of their head and neck cancer therapy (Rose-Ped et al., 2002). It is defined as erythematous, inflammatory, and painful ulcerative lesions that occur in the mucosal lining of the mouth, pharynx, oesophagus, and entire gastrointestinal tract secondary to chemotherapy, biologic therapy or radiotherapy.

Multiple mechanisms are involved as the sequential interactions of all cell and tissue types, and various physiological elements (e.g., tissue factors and cytokines) of the oral mucosa.

It primarily affects the non-keratinized tissues, such as the soft palate, the pharynx, the floor of the mouth, and the lateral borders of the tongue. Ulcerations and mucosal infections can hesitate in oedema and inflammation that cause pain.

During the fifth week of RT, when pts have received approximately a radiation of 5000–6000 cGy the highest peak in pain is frequently observed and it is likely to improve not earlier than 2–4 weeks since the completion of RT, and to heal in about two months (Wong et al., 2006).

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Table 1
Consensus-reached statements.

Chapter	Item	Phase	Description	Whom is it in charge of
Pain	1	General statement	• In (chemo) radiotherapy-induced mucositis, escalation of pain intensity and pain interference scores generally start at week 3, peak at week 5 and persist for 2–4 weeks after the end of radiotherapy, with a gradual remission of signs and symptoms • (Chemo) radiotherapy-induced mucositis pain is frequent (>80%) and interferes with daily activities (33% of pts) and with social activities and mood (50–60% of pts); these consequences greatly affect the patient's overall quality of life and may lead to severe disability, including work absences or loss of active employment • Patients may experience long term spontaneous or evoked mucosal pain due to epithelial atrophy, neurologic sensitization and/or neuropathy. Putative risk factors for mucosal sensitivity include: aggressive chemoradiation regimens, xerostomia, and active cigarette smoking. Pain may be evoked by hot or spicy food/liquids, acidic food/liquids and dry air • Painful mucositis increase the costs of care (opioid analgesics, tube feeding), is associated with additional admission and prolonged periods in the hospital, leading to delayed, interrupted, or altered cancer therapy protocols that can affect prognosis • Mucosal pain may be caused by or exacerbated by oral infections. A careful oral exam to rule out infection since it can be easily treated	Oncology Physician—Nurse
Pain	2	Pre-treatment	• Pain correlates with radiation treatment fields, dose and its fractioning; concomitant chemotherapy or cetuximab results in increased frequency, severity and duration of mucositis pain. These factors should be considered when evaluating the patient before the treatment and considering the possible increase in pain intensity during treatment course • When making treatment plans, the ability of a patient to tolerate increased oral pain and higher doses of opioids should be considered. Patients who are frail, elderly or who have severe concurrent medical conditions may have poor tolerance of aggressive medications regimens required to deal with severe oral pain associated with aggressive chemoradiation regimens	Oncology Physician—Nurse
Pain	3	Treatment	• In clinical practice, Numerical rating scale or verbal rating scale or visual analogue scale must be used regularly to assess background, breakthrough and swallow-related pain • Daily pain assessment and a personalized dose and type of medications according to the intensity of pain, rescue medications improve pain control • Increasing evidence supports the importance of continued swallowing effort during and after the course of radiation in order to minimize disuse atrophy and fibrosis and to optimize long term swallow function. Adequate pain managemenr to prevent and to treat the symptom may substantially enhance swallow effort	Oncology Physician—Nurse—Patient
Pain	4	Treatment	• Basic oral care will reduce the frequency and severity of oral mucositis and its associated pain	Oncology Physician—Nurse—Patient
Pain	5	Treatment	• Treatment of painful mucositis may benefit from topical and systemic drugs • However, the use of an opioid-based systemic pain control program is almost always necessary for pain relief • Aggressive measures to prevent and treat opioid-induced side effects is critical in order to optimize patient compliance with pain regimens	Oncology Physician
Pain	6	Treatment	• Topical coating agents may reduce local mucosal sensitivity. • Topical anaesthetics (e.g., Lidocaine 2%) alone or as mixture mouthwashes may be effective but with a short duration of effect (15–30 min) • Topical morphine based mouthwashes is effective for relieving pain with extended duration (4–6 h) and it is probably more effective than topical lidocaine • Topical fentanyl prepared as lozenges is not effective and its use should be avoided • Topical capsaicin may desensitize pts prior to the onset of mucositis but it is poorly tolerated and has no place in clinical practice • Even if mouthwashes of doxepin (tricyclic antidepressant) 0.5% have shown to reduce pain for 4 h or longer, there is no wide application in clinical practice, because no confirmation trials have been published yet	Oncology Physician—Nurse

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Table 1 (*Continued*)

Chapter	Item	Phase	Description	Whom is it in charge of
Pain	7	Treatment	Systemic drugs The WHO describes the principles of pain management and the analgesic ladder indicates the management of pain according to the type and intensity of pain experienced by the patient • Patients often experience difficulty with swallowing during and after surgery or radiation-based treatments. Under these circumstances, transdermal fentanyl can provide consistent and effective pain relief • An effective pain regimen should include a fixed and breakthrough medication with an appropriate dose and schedule for each • Odynophagia should be considered as incidental breakthrough pain to be treated with appropriate rescue medications Preventive administrations of rescue short release medications with a short half hour before eating may improve swallow function • Transmucosal intranasal route administration of fentanyl is a rational approach to odynophagia treatment • Mucositis is frequently associated with a neuropathic pain Even if high doses of gabapentin have been reported to reduce the need for high total dose of opioids, neuropathic pain control remains a critical item with very frequent failures	Oncology Physician
Pain	8		• Patients with musculoskeletal pain in the jaws, neck and shoulders secondary to tumor or treatment should be considered for orthopedic evaluation and physical therapy and/or lymphedema therapy where appropriate • Patients with musculoskeletal pain may benefit from adjunctive medications such as non-steroidal inflammatories (systemic and topical) and anti-spasmodics	Oncology Physician
Pain	9	Post-treatment	• Patients treated with aggressive multi-modality regimens may develop central pain disorders characterized by the following: widespread, non-anatomical distribution of pain, persisting beyond expected tissue healing time, more constant and unremitting, and associated with high levels of disability • Patients with jaw, neck and shoulder dysfunction related to tumour or treatment induced lymphedema and fibrosis may experience acute and long term musculoskeletal pain. • As pain intensity decreased, opioids should be tapered. It must be recognized that a cohort of patients may require long term opioid analgesics due to persistent spontaneous or evoked mucosal pain	Oncology Physician

The prevention or reduction of intensity and duration of oral mucositis is important to permit the administration of the full dosage of cancer treatment and thereby potentiate the curative or control intent of treatment.

4.2. Pre-treatment evaluation statements

a Pain correlates with radiation treatment fields, dose and its fractioning; concomitant chemotherapy or cetuximab results in increased frequency, severity and duration of mucositis pain. These factors should be considered when evaluating the patient before the treatment and considering the possible increase in pain intensity during treatment course.
b When making treatment plans, the ability of a patient to tolerate increased oral pain and higher doses of opioids should be considered. Patients who are frail, elderly or who have severe concurrent medical conditions may have poor tolerance of aggressive medications regimens required to deal with severe oral pain associated with aggressive chemoradiation regimens.

4.2.1. Assessment

a In Clinical practice Numerical rating scale or verbal rating scale or visual analogue scale must be used regularly to assess background, breakthrough and swallow-related pain.
b Daily pain assessment and a personalized dose and type of medications according to the intensity of pain improve pain control.

4.2.2. Pain control

1. Increasing evidence supports the importance of continued swallowing effort during and after the course of radiation in order to minimize disuse atrophy and fibrosis and to optimize long term swallow function. Adequate pain management to prevent and to treat the symptom may substantially enhance swallow effort.
2. Basic oral care will reduce the frequency and severity of oral mucositis and its associated pain.
3. Treatment of painful mucositis may benefit from topical and systemic drugs.
4. However, the use of an opioid-based systemic pain control program is almost always necessary for pain relief.
5. Aggressive measures to prevent and treat opioid-induced side effects is critical in order to optimize patient compliance with pain regimens.

4.2.3. Topical drugs

a Topical coating agents may reduce local mucosal sensitivity.
b Topical anaesthetics (e.g., Lidocaine 2%) alone or as mixture mouthwashes may be effective but with a short duration of effect (15–30 min).
c Topical morphine based mouthwashes is effective for relieving pain with extended duration (4–6 h) and it is probably more effective than topical lidocaine.
d Topical fentanyl prepared as lozenges is not effective and its use should be avoided.

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e Topical capsaicin may desensitize pts prior to the onset of mucositis but it is poorly tolerated and has no place in clinical practice.
f Even if mouthwashes of doxepin (tricyclic antidepressant) 0.5% have shown to reduce pain for 4 h or longer, there is no wide application in clinical practice, because no confirmation trials have been published yet.

Currently, the mucositis-induced pain management includes the use of topical anesthetics and systemic analgesics. Systemic administration of opioids may be complicated by well-known side effects, namely nausea, vomiting, mental clouding, constipation, sedation and tolerance, that should be assessed frequently and prevented whenever possible. Basic and clinical research suggest that the analgesic effects of exogenous opioids administered as mouth washing are particularly prominent in patients with painful inflammatory conditions (Cerchietti et al., 2002) and could be an effective and safe therapy to relieve pain, decreasing the duration of functional impairment and reducing side effects. The analgesic efficacy of morphine administered topically in mucositis-induced pain deserves further study to better define the dosage of the morphine relieving pain and also the possible presence of the drug in the blood (Cerchietti, 2006).

In HNC patients, pain due to mucositis may presents also as incidental breakthrough pain (BTP), a transitory exacerbation of pain that occurs against a background of stable pain otherwise adequately controlled by around-the-clock opioid therapy with a prevalence of 48% (average of 3.85 episodes per day) of which more than 50% of episodes were of gradual onset but with severe intensity (Bhatnagar et al., 2010). Incident pain was the predominating one (50%) followed by spontaneous (25%) and end of dose failure (20%), while in 5% of the cases the nature of pain was unknown or mixed. Actually, the majority of pain episodes were associated with some precipitating factor (Bhatnagar et al., 2010).

In this setting it may arise in response to a predictable stimulus such as swallowing or it may be related to a specific predictable trigger as incident predictable pain (Ripamonti et al., 2012) (IP-BTP).

Uncontrolled pain may lead to a decrease in overall swallowing effort. An adequate use analgesics contributes to maintain swallowing ability, to regularly perform specific swallowing exercises, in order to reduce aspiration and to earlier recover a sufficient oral intake (Bese et al., 2007).

The optimal control of BTP may allow to limit the dosage of background drugs employed. The most effective way of administration was judged to be transmucosal intranasal route. In fact, in patients with head and neck cancer, oral transmucosal administration could be difficult because of sticky saliva, xerostomia or oral ulcerations.

Fentanyl nasal spray (FNS), in other setting of diseases, was shown to be efficacious and well tolerated, providing faster onset of analgesia than immediate-release morphine (Fallon et al., 2011; Portenoy et al., 2010; Davies et al., 2011).

Unfortunately, these studies did not investigate the ability of FNS to prevent or reduce the intensity of BTP in HNC patients, absolutely neglecting the importance of odynophagia control. Recently, Bossi et al. published an experience concerning the feasibility and the activity of fentanyl pectin nasal spray against incidental feeding BTP due to chemoradiation-induced oral and oropharyngeal mucositis in HNC patients (Bossi et al., 2014).

4.2.4. Systemic drugs

a The WHO describes the principles of pain management and the analgesic ladder indicates the management of pain according to the type and intensity of pain experienced by the patient.
b Patients often experience difficulty with swallowing during and after surgery or radiation-based treatments. Under these circumstances, transdermal fentanyl or subcutaneous opioids can provide consistent and effective pain relief.
c An effective pain regimen should include a fixed and rescue medication (short release opioids) with an appropriate dose and schedule for each.
d Odynophagia should be considered as incidental breakthrough pain to be treated with appropriate rescue medications. Preventive administrations of breakthrough pain medication a half hour before eating may improve swallow function.
e Trans mucosal intranasal route administration of fentanyl is a rational approach to odynophagia treatment.
f Mucositis is frequently associated with a neuropathic pain.
g Even if high doses of gabapentin have been reported to reduce the need for high total dose of opioids, neuropathic pain control remains a critical item with very frequent failures.
h Patients with musculoskeletal pain in the jaws, neck and shoulders secondary to tumour or treatment should be considered for orthopaedic evaluation and physical therapy and/or lymphedema therapy where appropriate.
i Patients with musculoskeletal pain may benefit from adjunctive medications such as non-steroidal inflammatories (systemic and topical) and anti-spasmodics.

The pathogenesis of radiation-induced mucositis is multifactorial and appears to be more complex than direct damage to the epithelium (Lalla et al., 2008; Treister and Sonis, 2007). Recent studies have demonstrated that HNC patients develop nociceptive and neuropathic pain during their radiotherapy course, suggesting the need to treat both types of pain (Epstein et al., 2009).

Neuropathic pain could be also caused by tumor infiltration or due to paraneoplastic or treatment-induced polyneuropathy and it may be adequately controlled by opioids alone ± adjuvant drugs (Ripamonti et al., 2012). Although opioids are the mainstay for the treatment of cancer pain management, their use is limited not only by common side effects but also by the fact that neuropathic pain sometimes poorly responds to narcotics alone (Cherry et al., 1994; Diekenson, 1994; Portenoy, 1994; Tan et al., 2010).

Also amitriptyline and gabapentin has been effectively used to treat multiple neuropathic pain syndromes but only limited data are available in HNC patients pain (Tan et al., 2010; Rose and Kam, 2002; Backonja et al., 1998; Vinik, 2005; Rowbotham et al., 1998; van de Vusse et al., 2004; Bar Ad et al., 2010b).

Opiates and gabapentin are believed to interact favorably through a simultaneous decrease in hyper excitation and increased inhibition of nociception (Kerskinbora et al., 2007) in a synergistic effect (De la O-Arciniega et al., 2009) that even enhances analgesic effect of morphine and better relieve neuropathic pain in cancer pts than opioid escalating doses (Kerskinbora et al., 2007; Gilron et al., 2005) with a beneficial effect on daily activity, mood, sleep, and quality of life (Backonja et al., 1998; Gilron et al., 2005). So that this combination may represent a potential first-line regimen for pain management in cancer pts (Kerskinbora et al., 2007), suggesting the possibility of satisfactory results maintaining low-dose opioids and consequently reducing the risk of adverse side effects traditionally associated with narcotics.

Nevertheless, given the potential benefits of gabapentin in combination with opioids for the treatment of pain syndromes related to radiation-induced mucositis, randomized clinical trials are needed to establish the role of this analgesic combination in this group of cancer patients.

4.3. Post-treatments statements

a Patients treated with aggressive multi-modality regimens may develop central pain disorders characterized by the following: widespread, non-anatomical distribution of pain, persisting

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beyond expected tissue healing time, more constant and unremitting, and associated with high levels of disability.

b Patients with jaw, neck and shoulder dysfunction related to tumor or treatment induced lymphedema and fibrosis may experience acute and long term musculoskeletal pain.

c As pain intensity decreased, opioids should be tapered. It must be recognized that a cohort of patients may require long term opioid analgesics due to persistent spontaneous or evoked mucosal pain.

5. Conclusions

Patients undergoing radiotherapy for the head and neck malignancies develop painful mucositis, which often result in decreased oral intake, weight loss, quality of life deterioration, and unforeseen treatment interruptions (Trotti et al., 2003; Russo et al., 2008). Concurrent administration of systemic therapy to radiation is associated with a significantly increased frequency, severity, and duration of oral mucositis (Trotti et al., 2003) that may impact on treatment itself. In order to better manage this adverse event, it is necessary to standardize clinical management and treatment according to international guidelines.

Since very little has been written concerning pain in HNC patients undergoing curative radiation and systemic therapy, our review aimed to obtain some indications for pain management from literature and to draw up recommendations/suggestions for HNC patients, based on the consensus among multidisciplinary health professionals. Nevertheless there are still unmet needs that necessitate further studies: the role of rapid onset opioids, the best management of neuropathic pain in this setting, the analyses of the pain impact on the quality of life, the role of adjuvant pain medications and complementary strategies, and, in the end, more specific clinical trials in HNC patients subset.

Conflict of interest

The authors have no financial and personal relationships with other people or organizations that could in appropriately influence (bias) this work.

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