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Compte-Rendu du Congrès MASCC/ISOO-Vancouver, juin 2010 « Mucositis » & « Oral Care » Sessions

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CANADA PLACE

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La prise en charge de la Mucite (Mucositis) et les soins bucco-pharyngés en général (Oral Care) ont été parmi les thèmes les plus importants du dernier Congrès MASCC/ISOO.

En plus des sessions orales et posters (18 communications orales et posters sur ce thème), se sont déroulés 2 Workshops sur ce thème:

- 1 workshop d'une journée pleine le 22/6 pour la Mucite (Mucositis Working Group)**
- 1 Workshop d'une 1/2 journée (23/6) pour l' « Oral Care »**



Le Workshop « Mucites » était orienté « Recherche », avec la présentation d'études biologiques et cliniques en cours ou terminées.

Il a été l'occasion de voir exposer 3 communications sur l'intérêt potentiel du Caphosol*, 1 communication sur Loramyc* chez les patients avec xérostomie (RJB) et une communication sur le rationnel et la mise en œuvre de l'essai « Clonidine » (RJB).

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Abstract:

Clonidine is an antihypertensive drug acting through its α_2 -receptor agonist properties. Stimulation of α_2 -receptor is correlated with an increase in the release of pro-inflammatory cytokines (IL1 β , IL6 and TNF α) from macrophages and lymphocytes. In experimental models, clonidine decreases the macrophage cytokine gene expression and shifts the phenotype from pro-inflammatory to anti-inflammatory.

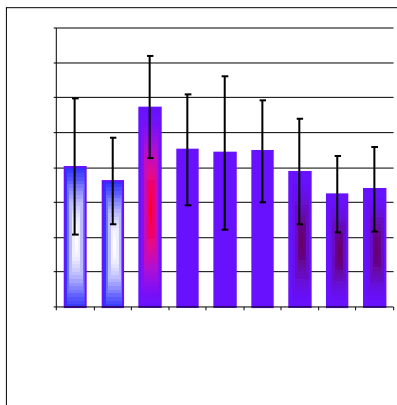
Mucositis is a frequent complication of cancer treatments including chemo and radiotherapy. These treatments lead to the activation of NF- κ B and consequently to the release of IL1 β , IL6 and TNF α . Clonidine through the activation of α_2 -adrenoceptors on macrophages and lymphocytes may decrease the release of the principal mediators of injury in mucositis. In a validated experimental model of oral mucositis (acute radiation in hamsters), clonidine significantly reduced the duration and the severity of mucositis ($p < 0.001$). In ex-vivo experiment on human oral mucosa, clonidine dose-dependently and significantly decreased the release of TNF α induced by substance P.

Lauriad® mucoadhesive buccal tablet (MBT) is an extended release formulation to be applied to the gum that induces rapid, high and prolonged salivary and mucosal concentrations of the active principle and low plasma concentrations. Based on these data, clonidine loaded in the MBT may prevent and treat oral mucositis.

This multicentre, double blind, randomised, placebo-controlled, three-arm study is aimed at comparing the efficacy and safety of clonidine Lauriad® 50 µg and 100 µg MBT to those of placebo in the prevention and treatment of oral mucositis. The objectives of the study are to demonstrate the efficacy of clonidine Lauriad® 50 µg and 100 µg MBT versus placebo, to determine the optimal dose and the plasma and salivary pharmacokinetic parameters of clonidine Lauriad® 50 µg and 100 µg MBT, and to evaluate the quality of life and the local and overall safety in head and neck patients undergoing post-operative concomitant chemoradiation.

Ex-vivo anti-inflammatory effect*

Untreated gingiva
Gingiva treated by 3 µg/ml clonidine
Gingiva stimulated by SP
Gingiva + SP + 0.009 µg/ml clonidine
Gingiva + SP + 0.03 µg/ml clonidine
Gingiva + SP + 0.09 µg/ml clonidine
Gingiva + SP + 0.3 µg/ml clonidine (9 ng/day/5mm ² soit 18 µg/d)*
Gingiva + SP + 0.9 µg/ml clonidine (18 ng/day/5mm ² soit 54 µg/d)*
Gingiva + SP + 3 µg/ml clonidine (90 ng/day/5mm ² soit 180 µg/d)*



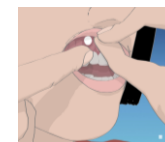
*Significant and dose-dependently decreased of TNF α by clonidine
 Acknowledgments: the authors thank "Gredeco and " Biomodels For their collaboration in the preclinical development

Acute radiation in hamsters**

Group	Days -1 to 20	Days Grade ≥ 3	Days Grade < 3	Total Days	% Days Grade ≥ 3	Chi Sq Vs control	P value
Vehicle		90	102	192	46.9	-	-
Clonidine 100 µg/kg/day		56	136	192	29.2	12.0350	≤ 0.001
Clonidine 300 µg/kg/day		58	134	192	30.2	10.5650	0.001

Lauriad® technology

- Lead product: miconazole Lauriad® 50 mg (Oravig®, FDA approved)
 Topical treatment for oropharyngeal candidiasis. Early and extended release formulation :
- Miconazole salivary concentrations above MIC (1 µg/ml) reached within 1 hour
 - Mean duration of miconazole salivary concentrations above MIC for 13.3 \pm 5.2 hours
 - Once daily application
- Acyclovir Lauriad® 50 mg
 Topical treatment for herpes labialis
- Significant acyclovir salivary concentrations 30 min after application
 - High acyclovir salivary concentrations detectable up to 48 hours
 - Single dose application within 1 hour following the occurrence of prodromal symptoms



A phase II clinical trial – BA2009-28-01

Objectives:

- Primary objective:** to demonstrate the efficacy of clonidine Lauriad® 50 µg and 100 µg MBT versus placebo in the prevention and treatment of chemoradiation therapy induced oral mucositis
- Secondary objectives:** - to determine the optimal dose of clonidine Lauriad® MBT
- To determine the plasma and salivary Pk parameters of clonidine Lauriad® 50 µg and 100 µg MBT
 - To evaluate the quality of life of cancer patients treated with clonidine Lauriad® MBT during chemoradiation therapy
 - To evaluate the duration of MBT adhesion
 - To evaluate the local and overall safety of clonidine Lauriad® MBT
 - To preliminary evaluate the health economics in patients undergoing chemoradiotherapy treated with clonidine Lauriad® MBT

Evaluation criteria:

- Primary endpoint:** comparison between groups of the percentage of patients with an oral mucositis score ≥ 3 using the WHO scale at cumulative radiation dose of 50 Gy
- Secondary endpoints:** - comparison between groups of the percentage of patients with an oral mucositis score ≥ 3 using the WHO scale at cumulative radiation dose of 40 Gy and 60 Gy
- Incidence, duration and total dose of opioids use
 - Number of days during which the use of gastrostomy/nasogastric tube for feeding is necessary
 - Overall and local tolerability
 - Pk plasma and salivary parameters

Conclusions:

- Clonidine definitely showed efficacy in reducing severity of mucositis in a validated animal preclinical model.
- Clonidine effectively reduced the release of TNF α induced by substance P in human oral mucosa
- A phase II clinical trial in patient with Head and neck cancer receiving Chemoradiation therapy is ongoing

Updated Clinical Practice Guidelines for the Prevention and Treatment of Mucositis

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Considerable progress in research and clinical application has been made since the original guidelines for managing mucositis in cancer patients were published in 2004, and the first active drug for the prevention and treatment of this condition has been approved by the United States Food and Drug Administration and other regulatory agencies in Europe and Australia. These changes necessitate an updated review of the literature and guidelines. Panel members reviewed the biomedical literature on mucositis published in English between January 2002 and May 2005 and reached a consensus based on the criteria of the American Society of Clinical Oncology. Changes in the guidelines included recommendations for the use of palifermin for oral mucositis associated with stem cell transplantation, amifostine for radiation proctitis, and cryotherapy for mucositis associated with high-dose melphalan. Recommendations *against* specific practices were introduced: Systemic glutamine was *not* recommended for the prevention of gastrointestinal mucositis, and sucralfate and antimicrobial lozenges were *not* recommended for radiation-induced oral mucositis. Furthermore, new guidelines suggested that granulocyte-macrophage-colony stimulating factor mouthwashes *not* be used for oral mucositis prevention in the transplantation population. Advances in mucositis treatment and research have been complemented by an

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Jeffrey Jones, Lowell Anthony, Jo Bowen, Adam S Garden, Ian Hewson, Fred Spijkervet, Richard Logan, Inger von Bultzingslowen, Mike Brennan, Andrea Stringer, Andrei Barasch, Kathryn Damato, Sharon Elad, Arnold Altman, Loree Oberle-Edwards, Judith Johnson, Patricia Wienandts, M. Elvira P. Correa, [Rene-Jean Bensadoun](#), and [Rajesh V. Lalla](#).



Le Workshop « Oral Care » a été focalisé sur la publication prochaine (effective en août 2010) d'une revue systématique sur l'ensemble des complications bucco-dentaires des traitements anti-cancéreux, en 12 articles (12 groupes de travail): xérostomie, trismus, ostéoradionécrose, infections bact., virales, fongiques, ostéonécrose aux biphosphonates, cpk dentaires...

Publi: JSCC août 2010, vol. 18, n°8, pp. 975-1106.



Cette Revue de la Littérature (2000-2009) est le résultat d'une collaboration étroite entre experts d'une trentaine de pays européens, américains, asiatiques et océaniens, dans le but de fournir des guidelines actualisées sur la prise en charge préventive et curative de ces complications.

Il y a malheureusement encore beaucoup de travail à faire pour que ces guidelines soient réellement basées sur l'évidence (evidence based-medicine), car les études randomisées sont particulièrement pauvres dans ce domaine.

Seul le sujet de la Xérostomie induite a bénéficié de nombreux essais récents, mettant en lumière le rôle majeur de la RCMi (IMRT) dans la prévention de l'hyposialie radio-induite, grâce à la préservation des parotides +++

La prévention du trismus radio-induit comme la prévention de l'ostéoradionécrose radio-induite devraient également bénéficier de ces nouvelles techniques d'irradiation ORL +++

A systematic review of trismus induced by cancer therapies in head and neck cancer patients

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Abstract

Purpose This systematic review represents a thorough evaluation of the literature to clarify the impact of cancer therapies on the prevalence, quality of life and economic impact, and management strategies for cancer-therapy-induced trismus.

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Methods A systematic literature search was conducted with assistance from a research librarian in the databases MEDLINE/ PubMed and EMBASE for articles published between January 1, 1990 and December 31, 2008. Each study was independently assessed by two reviewers. Taking into account predetermined quality measures, a weighted prevalence was calculated for the prevalence of trismus. The level of evidence, recommendation grade, and guideline (if possible) were given for published preventive and management strategies for trismus.

Results We reviewed a total of 22 published studies between 1990 and 2008. Most of them assessed the prevalence of this complication, and few focused on management. The weighted prevalence for trismus was 25.4% in patients who received conventional radiotherapy and 5% for the few intensity-modulated radiation therapy studies. No clear guideline recommendations could be made for the prevention or management of trismus.

Conclusions Newer radiation modalities may decrease the prevalence of trismus compared to conventional radiotherapy. Few studies have addressed the quality of life impact of trismus, and no studies were identified to assess the economic impact of trismus. The few preventive and management trials identified in the literature showed some promise, although larger, well-designed studies are required to appropriately assess these therapies before recommendations can be provided.

Keywords Cancer therapy · Trismus · Management strategies



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