Studi innovativi sul controllo del dolore nella terapia di supporto alla disfagia dolorosa

Dolore e H&N

→ L'importanza del **sintomo dolore** nelle diverse fasi del trattamento

→ Focus sullo **stato dell'arte** nel trattamento del dolore durante le terapie

→**Studi innovativi** sul trattamento del dolore e **suggerimenti pratici**

Già in fase diagnostica….

IASP

PAIN® 152 (2011) 1206–1209

PAIN®

www.elsevier.com/locate/pain

Clinical note

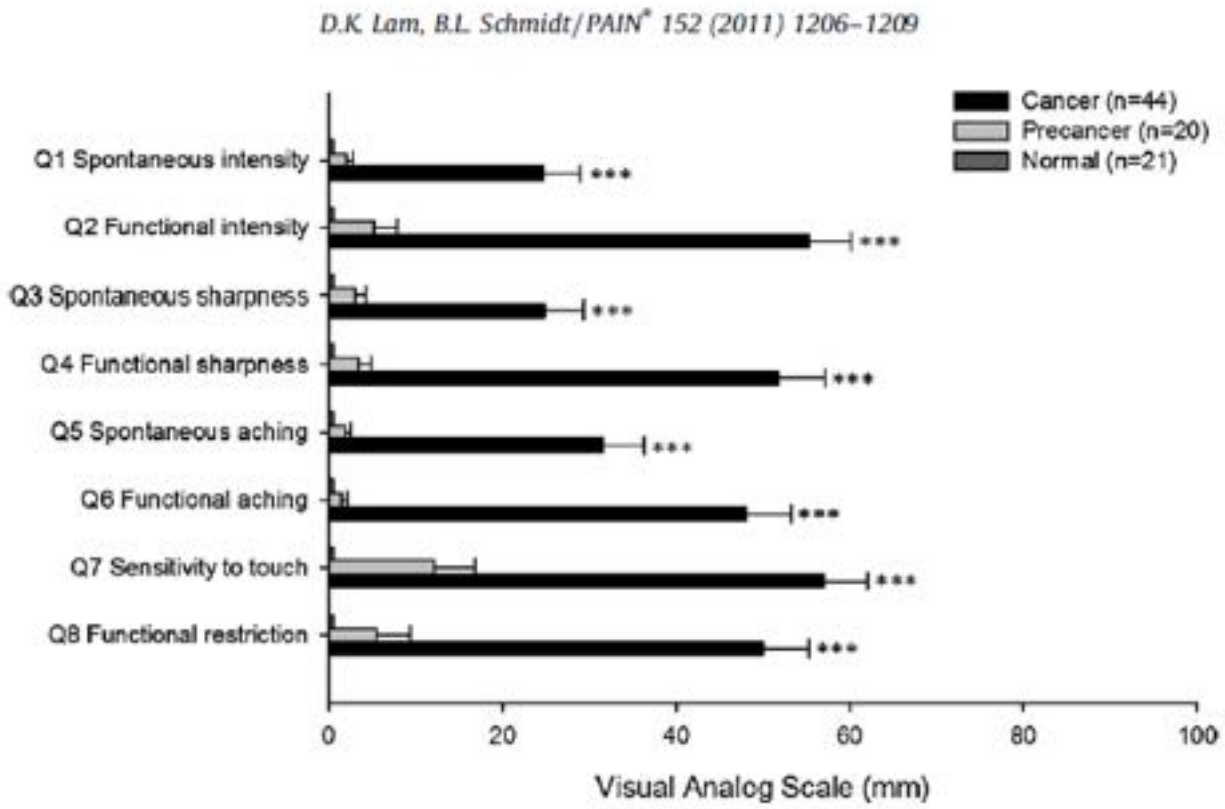
Orofacial pain onset predicts transition to head and neck cancer

David K. Lam [a], Brian L. Schmidt [b,c,*]

[a] *Department of Oral and Maxillofacial Surgery, University of California San Francisco, San Francisco, CA, USA*
[b] *Bluestone Center for Clinical Research, New York University, New York, NY, USA*
[c] *Department of Oral and Maxillofacial Surgery, New York University, New York, NY, USA*

Dal sintomo alla diagnosi?

Intensity of pain able to distinguish form precancerous lesions to oral cancer



Fattore prognostico e predittivo

American Pain Society
RESEARCH
EDUCATION
TREATMENT
ADVOCACY
PUBLISHED BY ELSEVIER

The Journal of Pain, Vol 15, No 10 (October), 2014: pp 1015-1022
Available online at www.jpain.org and www.sciencedirect.com

Survival Patterns in Squamous Cell Carcinoma of the Head and Neck: Pain as an Independent Prognostic Factor for Survival

Cielito C. Reyes-Gibby,* Karen O. Anderson,† Kelly W. Merriman,* Knox H. Todd,*

J Pain 2014

ORIGINAL ARTICLE

The Role of Pain in Head and Neck Cancer Recurrence and Survivorship

Joseph Scharpf, MD; Lucy Hynds Karnell, PhD; Alan J. Christensen, PhD; Gerry F. Funk, MD

Arch Otolar HN Surg 2009

Fattore prognostico e predittivo

BASALE

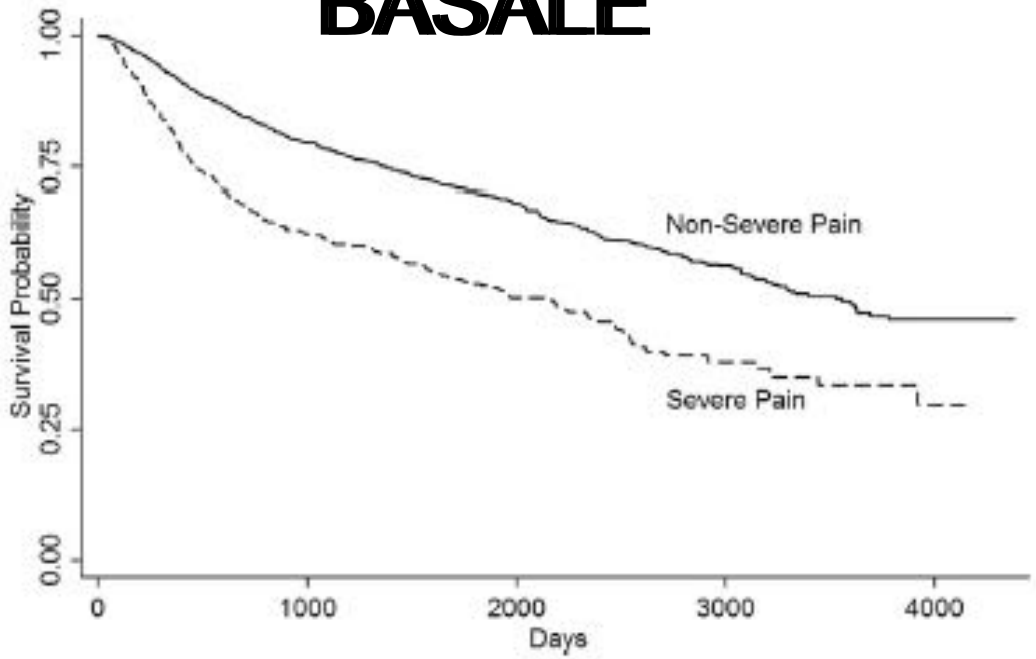


Figure 1. Kaplan-Meier estimates of the effect of pain on survival probability.

Fattore prognostico e predittivo?

POST TX

Table 4. Patient, Disease, and Treatment Characteristics That Predict Recurrence

Variable	No. of Patients[a] (n=191)	% of Patients Diagnosed as Having Recurrence	Multivariate Analysis (n=164)	
			P Value	Hazard Ratio
Posttreatment pain score			.003	3.758
No/low, 0-3	157	9.6		
Moderate/high, 4-10	34	26.5		
Age, y			NA	NA
<60	97	11.3		
60-69	49	14.3		
≥70	45	13.3		
Sex			NA	NA
Men	131	12.2		
Women	60	13.3		
"Combined" stage[b]			NA	NA
Early	75	12.0		
Advanced	104	13.5		
Tumor site			.03	1.968
Larynx	44	2.3		
Oral cavity	88	17.0		
Pharynx	41	17.1		
Treatment			NA	NA
Single modality	103	11.7		
Multimodality	86	14.0		

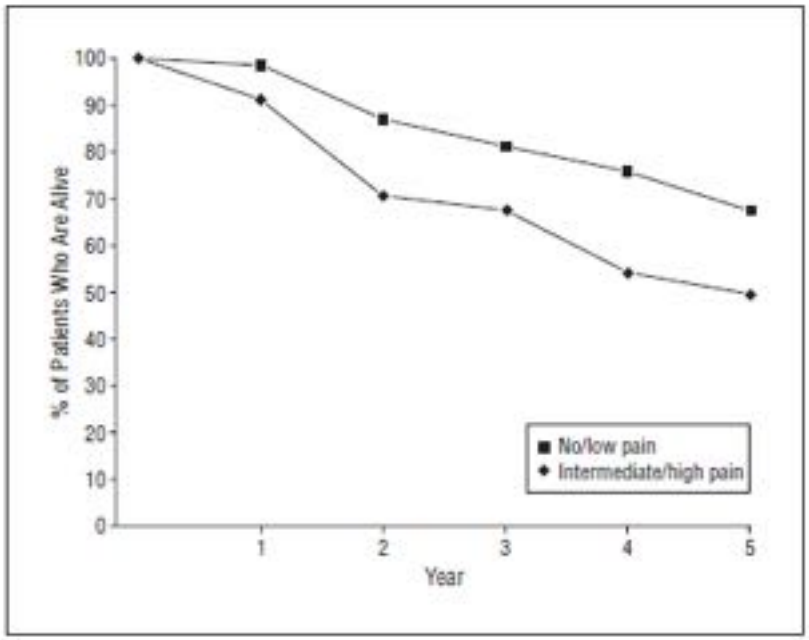
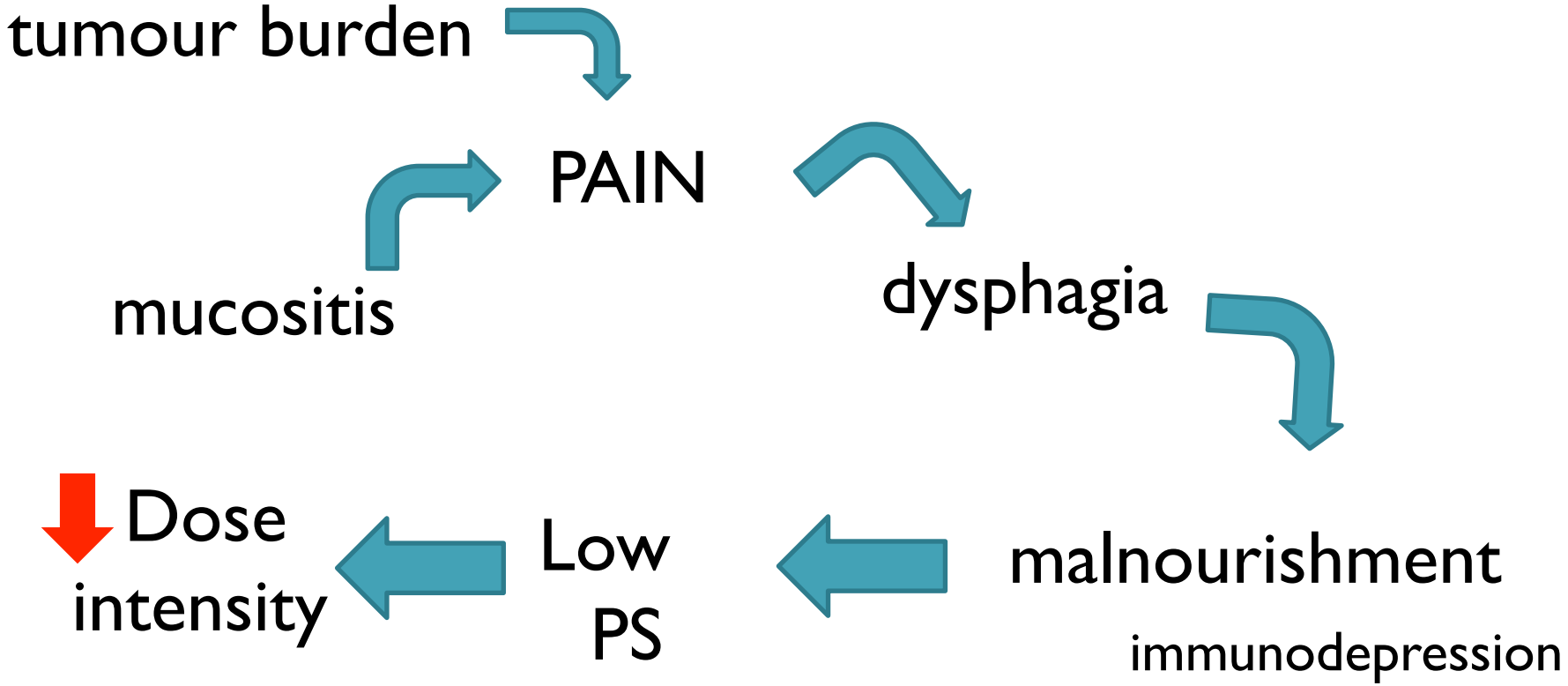


Figure. Five-year disease-specific survival rates by level of posttreatment pain among patients with head and neck cancer (*P*=.04). In year 1, 98.1% of patients with no/low pain (score range, 0-3) (n=157) survived, and 91.2% with intermediate/high pain (score range, 4-10) (n=34) survived; in year 2, 86.6% with no/low pain and 70.6% with intermediate/high pain survived; in year 3, 80.9% with no/low pain and 67.6% with intermediate/high pain survived; in year 4, 75.8% with no/low pain and 54.1% with intermediate/high pain survived; and in year 5, 67.4% with no/low pain and 49.4% with intermediate/high pain survived.

L’impatto del dolore durante il trattamento

L'impatto del dolore durante il trattamento



Pluralità di cause…
non solo da malattia!

review

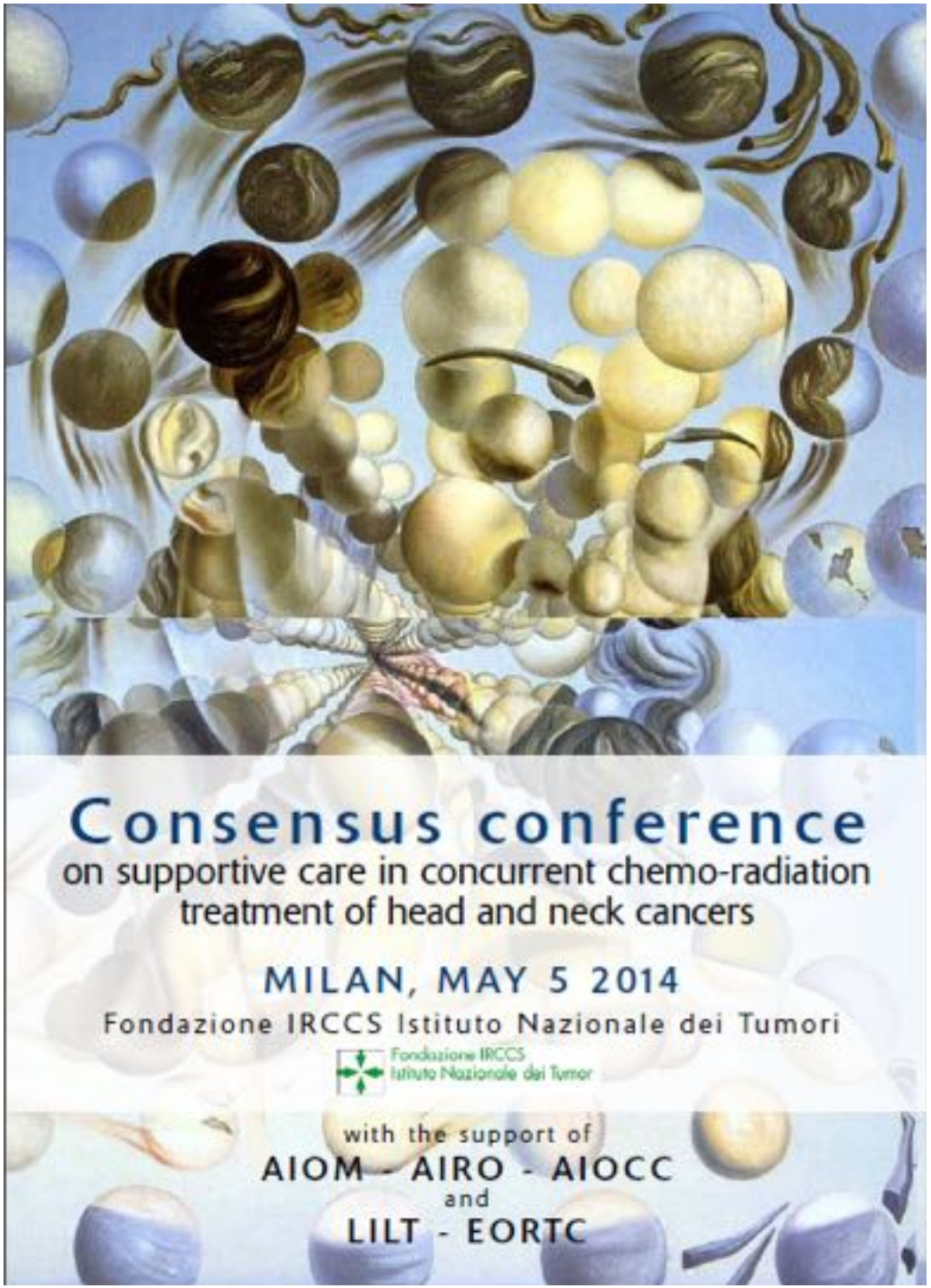
Annals of Oncology 00: 1–10, 2014
doi:10.1093/annonc/mdu011

Pain related to cancer treatments and diagnostic procedures: a no man's land?

C. I. Ripamonti[1*], P. Bossi[2], D. Santini[3] & M. Fallon[4]

[1]Supportive Care in Cancer Unit, Fondazione IRCCS, Istituto Nazionale dei Tumori, Milan; [2]Head and Neck Medical Oncology Unit, Fondazione IRCCS, Istituto Nazionale dei Tumori, Milan; [3]Medical Oncology Unit, Università Campus Bio-Medico, Rome, Italy; [4]St Columba's Hospice Chair of Palliative Medicine, IGMM, University of Edinburgh, Edinburgh, UK

Focus sullo stato dell'arte del trattamento del dolore


Consensus conference
on supportive care in concurrent chemo-radiation
treatment of head and neck cancers
MILAN, MAY 5 2014
Fondazione IRCCS Istituto Nazionale dei Tumori
Fondazione IRCCS
Istituto Nazionale dei Tumori
with the support of
AIOM - AIRO - AIOCC
and
LILT - EORTC

TOPICS

MUCOSITIS

DYSPHAGIA

HEMATOLOGICAL TOXICITY

INFECTIONS

NUTRITION/HYDRATION

PAIN

SKIN TOXICITY

STOMATOLOGICAL PROBLEMS

DURING TREATMENT

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 control may substantially enhance swallow effort.

Consensus conference on supportive care
in concurrent chemo-radiation of head and neck cancers

DURING 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.

Consensus conference on supportive care
in concurrent chemo-radiation of head and neck cancers

DURING TREATMENT
TOPICAL AGENTS

Topical anaesthetics (e.g. Lidocaine 2%) alone or as mixture mouthwashes may be effective but with a short duration of effect (15-30 min).

Consensus conference on supportive care
in concurrent chemo-radiation of head and neck cancers

DURING TREATMENT
TOPICAL AGENTS

Topical morphine is effective
for relieving pain
and it is probably more effective
than topical lidocaine

Consensus conference on supportive care
in concurrent chemo-radiation of head and neck cancers

DURING TREATMENT
TOPICAL AGENTS

Pain 105 (2003) 265–273

PAIN

www.elsevier.com/locate/pain

Potential utility of the peripheral analgesic properties of morphine in stomatitis-related pain: a pilot study

Leandro C.A. Cerchietti[a,b,*], Alfredo H. Navigante[a,b], Miguel W. Körte[c], Alejandro M. Cohen[d], Patricia N. Quiroga[d], Edda C. Villaamil[d], Marcelo R. Bonomi[b,e], Berta M. Roth[a,e]

Consensus conference on supportive care
in concurrent chemo-radiation of head and neck cancers

DURING TREATMENT
TOPICAL AGENTS

Effect of Topical Morphine for Mucositis-Associated Pain following Concomitant Chemoradiotherapy for Head and Neck Carcinoma

Leandro C. A. Cerchietti, M.D.[1]
Alfredo H. Navigante, M.D., Ph.D.[1]
Marcelo R. Bonomi, M.D.[2]
Mariel A. Zaderajko, M.D.[2]
Pablo R. Menéndez, M.D.[2]
Catalina E. Pogany, M.D.[2]
Berta M. C. Roth, M.D.[2]

TABLE 2
Primary End Points after the Treatment

End points	Group MO (n = 14)	Group MG (n = 12)	P value[a]
Duration of severe functional impairment (days mean ± SD)	1.85 ± 1.53	7.67 ± 4.3	**0.017**
Duration of severe pain (days mean ± SD)	5.07 ± 1.79	8.58 ± 2.65	**0.032**
M3H-NRS (1st–3rd quartile)	6 (5–6.75)	7.5 (6.16–8.83)	**0.038**

Consensus conference on supportive care
in concurrent chemo-radiation of head and neck cancers

DURING TREATMENT
TOPICAL AGENTS

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.

Consensus conference on supportive care
in concurrent chemo-radiation of head and neck cancers

DURING TREATMENT
SYSTEMIC DRUGS

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.

Consensus conference on supportive care
in concurrent chemo-radiation of head and neck cancers

DURING TREATMENT
SYSTEMIC DRUGS

An effective pain regimen should include a

fixed and breakthrough medication

with an appropriate dose and schedule for each.

Consensus conference on supportive care
in concurrent chemo-radiation of head and neck cancers

DURING TREATMENT
SYSTEMIC DRUGS

Odynophagia should be considered breakthrough pain to be treated with appropriate breakthrough medication dosing.

DURING TREATMENT
SYSTEMIC DRUGS

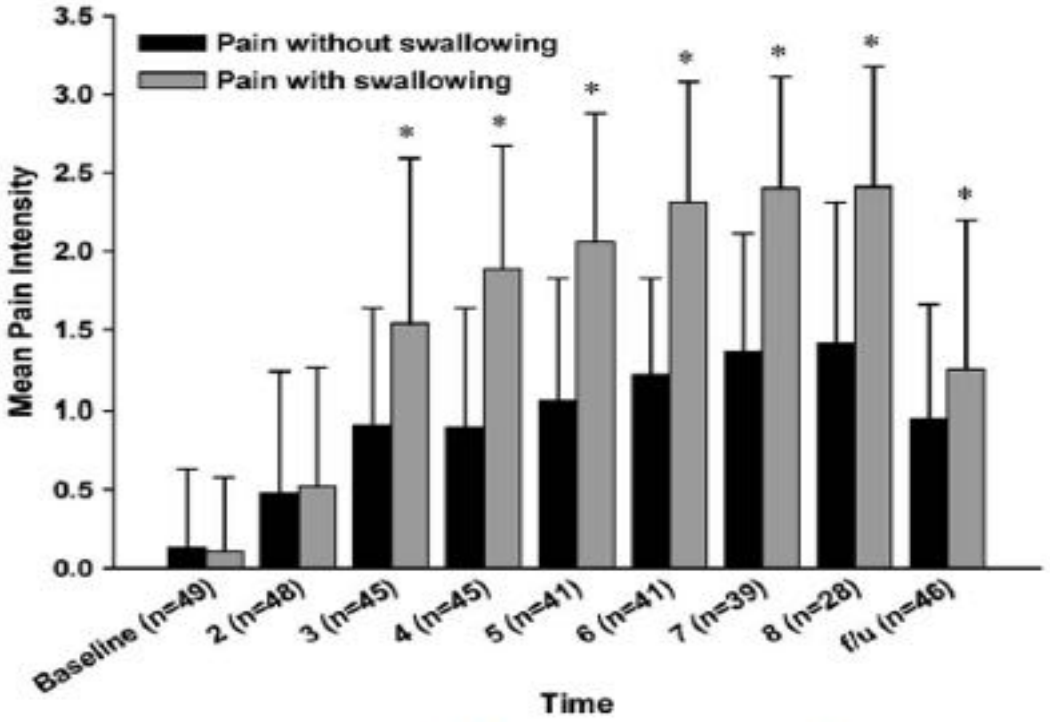


Fig. 2. Average weekly pain ratings using the MacDibbs Mouth Assessment Tool with patients swallowing and not swallowing on a 0–3 scale. Significant differences (*) were found from Week 3 to follow-up ($P = 0.001$). F/U = follow-up. Values are plotted as means ± SD.

Consensus conference on supportive care
in concurrent chemo-radiation of head and neck cancers

DURING TREATMENT
SYSTEMIC DRUGS

Preventive administrations of breakthrough pain medication a half hour before eating may improve swallow function.

Transmucosal intranasal route administration of fentanyl is a rationale approach to odynophagia treatment.

Original Article

Gabapentin for the Treatment of Pain Syndrome Related to Radiation-Induced Mucositis in Patients With Head and Neck Cancer Treated With Concurrent Chemoradiotherapy

Voichita Bar Ad, MD[1]; Gregory Weinstein, MD[2]; Pinaki R. Dutta, MD, PhD[1]; Arie Dosoretz[3]; Ara Chalian, MD[2]; Stefan Both, PhD[1]; and Harry Quon, MD[1]

Cancer 2010

DURING TREATMENT
SYSTEMIC DRUGS

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.

Consensus conference on supportive care
in concurrent chemo-radiation of head and neck cancers

Head & Neck Oncology

BioMed Central

Research

Open Access

Neuropathic and nociceptive pain in head and neck cancer patients receiving radiation therapy

Joel B Epstein[†1,3,4], Diana J Wilkie[*†1,2], Dena J Fischer[†3], Young-Ok Kim[†2] and Dana Villines[†3]

Address: [1]University of Illinois Cancer Center, University of Illinois, Chicago, USA, [2]University of Illinois College of Nursing, University of Illinois, Chicago, USA, [3]University of Illinois College of Dentistry, University of Illinois, Chicago, USA and [4]Univerity of Illinois College of Medicine, University of Illinois, Chicago, USA

Email: Joel B Epstein - jepstein@uic.edu; Diana J Wilkie* - diwilkie@uic.edu; Dena J Fischer - fischerd@uic.edu; Young-Ok Kim - ykim2@uic.edu; Dana Villines - dvilli1@uic.edu

* Corresponding author †Equal contributors

DURING TREATMENT
SYSTEMIC DRUGS

Patients with musculoskeletal pain may benefit from adjunctive medications such as non-steroidal inflammatories (systemic and topical) and anti-spasmodics.

DURING TREATMENT
AFTER TREATMENT

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

Consensus conference on supportive care
in concurrent chemo-radiation of head and neck cancers

Studi innovativi:
…ne abbiamo la necessità?

JOURNAL OF ORAL & MAXILLOFACIAL RESEARCH Trotter et al.

Pharmacological and Other Interventions for Head and Neck Cancer Pain: a Systematic Review

Patrick B. Trotter[1], Lindsey A. Norton[1], Ann S. Loo[1], Jonathan I. Munn[1], Elena Voge[1,2], Kim W. Ah-See[3], Tatiana V. Macfarlane[1]

"Randomized trial" "head and neck" "pain" 1947+:

13 studies included

"There is insufficient evidence from RCT of HN cancer pain to advise on an optimal intervention"

Trattamento del ….dolore da trattamento!

Individualized pharmacological treatment of oral mucositis pain in patients with head and neck cancer receiving radiotherapy

Ingrid Stenstrom Ling · Britt Larsson

Supp Care Cancer 2011

"….individualized pain treatment with systemic analgesics exploited to the highest degree **was insufficient**.
Future development of pharmacological possibilities for treatment of OM-related pain is urgent."

Vol. 32 No. 1 July 2006 Journal of Pain and Symptom Management 27

Original Article

Mucositis Pain Induced by Radiation Therapy: Prevalence, Severity, and Use of Self-Care Behaviors

Piera C. Wong, RN, MS, Marylin J. Dodd, RN, PhD, FAAN,

J Pain Sympt management 2006

"…. Pain from radiation therapy (RT)-induced mucositis is a **significant clinical problem** for patients with head and neck cancer (HNC)…
…However, **more severe pain with swallowing** was not managed well throughout the study."

Andamento temporale in RT

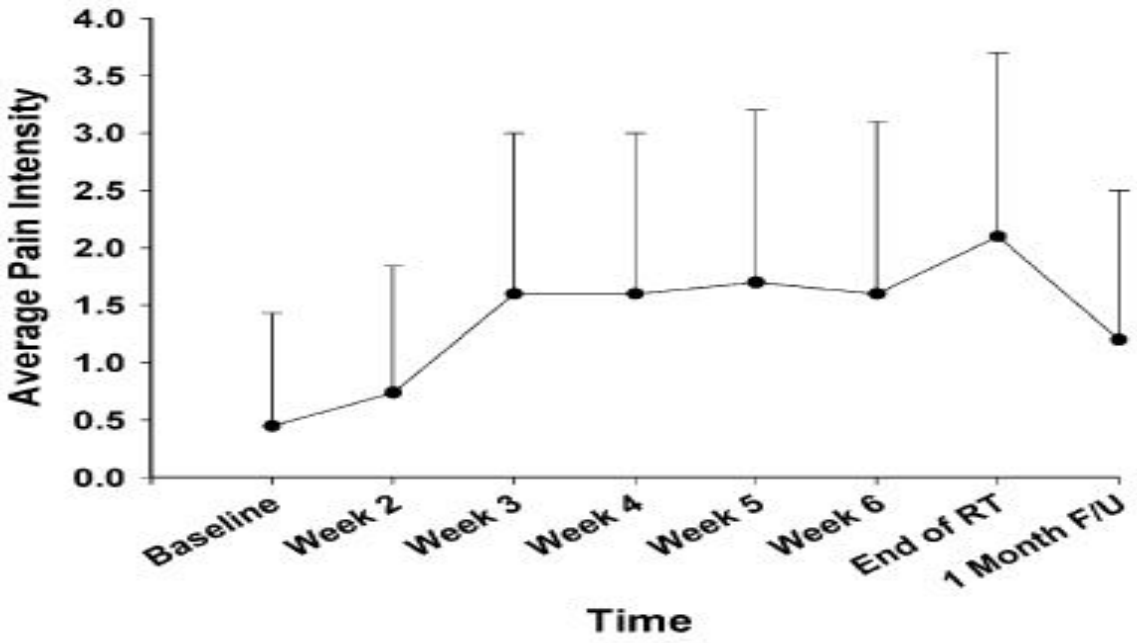


Fig. 1. Self-Care Diary of average pain intensity over time ($n = 49$) on a 0–4 scale. RT = radiation therapy; F/U = follow-up. Values are plotted as means ± SD.

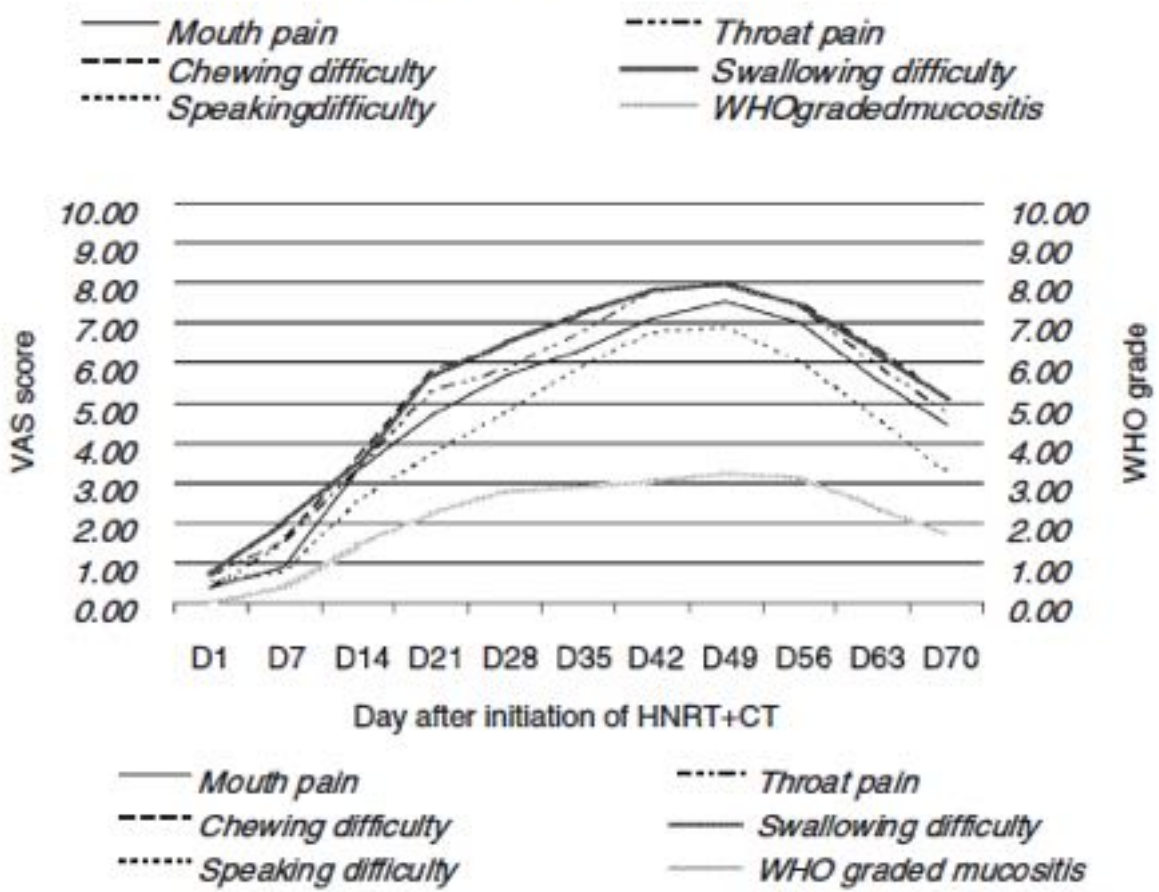
Impatto in QoL

Support Care Cancer (2010) 18:1477–1485
DOI 10.1007/s00520-009-0771-7

ORIGINAL ARTICLE

Severe oral mucositis associated with cancer therapy: impact on oral functional status and quality of life

Karis Kin-Fong Cheng · S. F. Leung



Studi innovativi recenti

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

Randomized double-blind placebo-controlled trial of celecoxib for oral mucositis in patients receiving radiation therapy for head and neck cancer

Rajesh V. Lalla [a,*], Linda E. Choquette [a], Kathleen F. Curley [a], Robert J. Dowsett [a], Richard S. Feinn [b], Upendra P. Hegde [a], Carol C. Pilbeam [a], Andrew L. Salner [c], Stephen T. Sonis [d], Douglas E. Peterson [a]

Studi innovativi recenti

- ✓ Incl: HN pts, RT ≥ 50 Gy +/- CT
- ✓ Random: celecoxib 200 mg vs placebo (20 pts x 2)
- ✓ Valutazioni: mucosite WHO, OMAS, CTC, entità dolore, uso oppioidi, tipo dieta
- ✓ Risultati: nessuna differenza per tutti gli endpoint

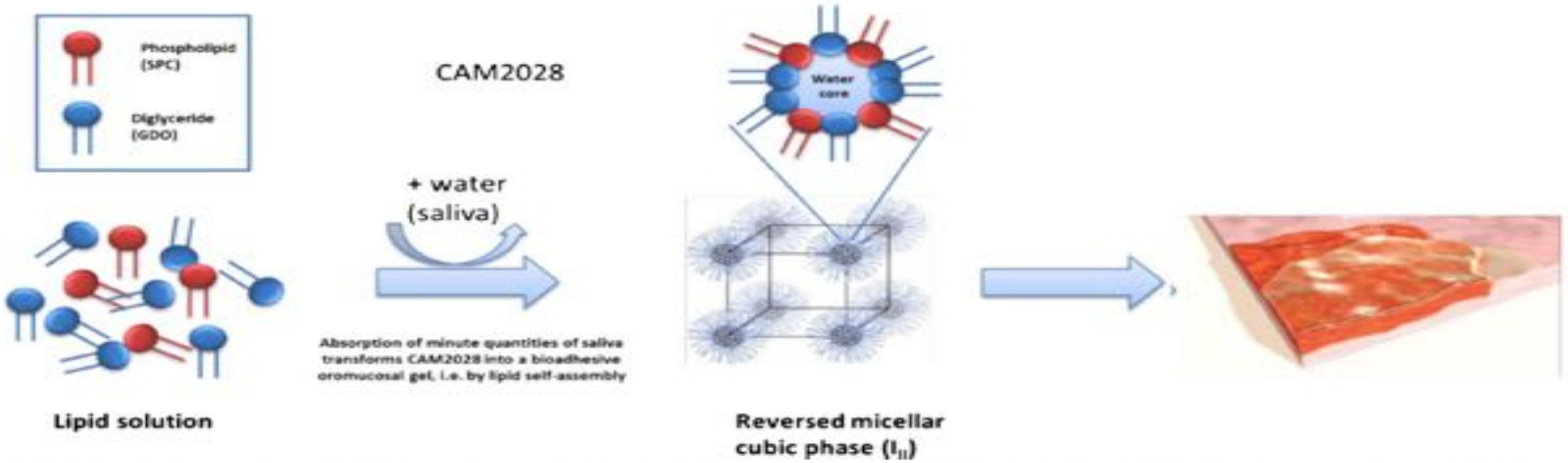
Studi innovativi recenti

Support Care Cancer (2014) 22:1557–1562
DOI 10.1007/s00520-014-2117-3

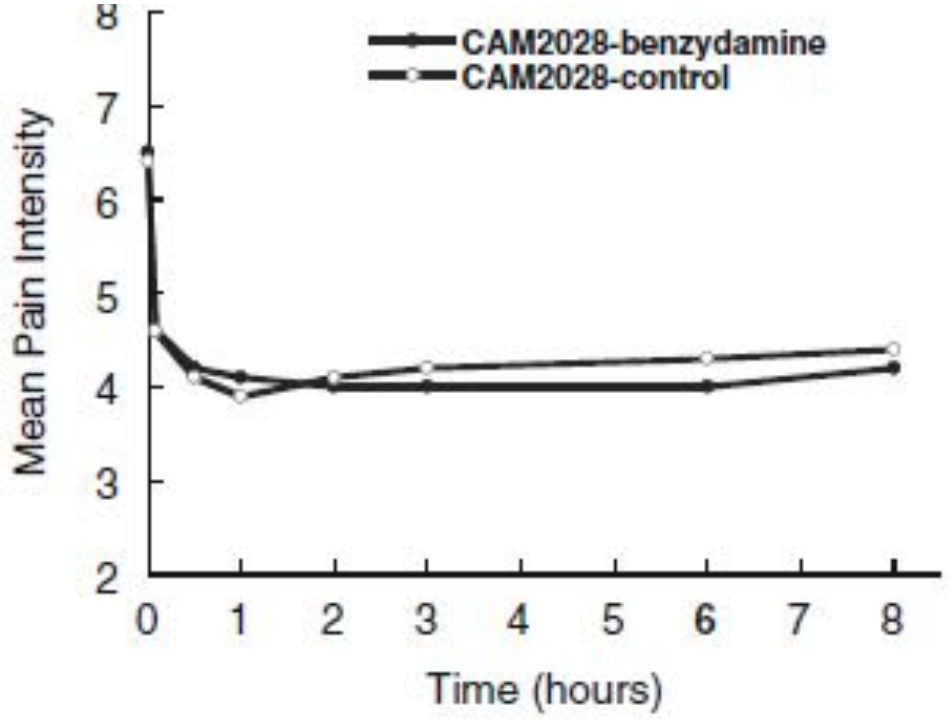
ORIGINAL ARTICLE

Treatment of oral mucositis pain following radiation therapy for head-and-neck cancer using a bioadhesive barrier-forming lipid solution

Tatiana Hadjieva · Eva Cavallin-Ståhl · Margareta Linden · Fredrik Tiberg



- ✓ Incl: HN pts con 2 sottosedi cavità orale/ orofaringe , 3-4 settimana di RT, mucosite WHO ≥2, dolore ≥ 6
- ✓ Random: CAM2028 placebo vs CAM2028 benzidamina (32 pts) day 1-3 con cross
- ✓ Valutazioni: dolore a 5 min – 1h - 6h - 8h



Studi innovativi recenti

VOLUME 32 · NUMBER 15 · MAY 20 2014

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Doxepin Rinse Versus Placebo in the Treatment of Acute Oral Mucositis Pain in Patients Receiving Head and Neck Radiotherapy With or Without Chemotherapy: A Phase III, Randomized, Double-Blind Trial (NCCTG-N09C6 [Alliance])

James L. Leenstra, Robert C. Miller, Rui Qin, James A. Martenson, Kenneth J. Dornfeld, James D. Bearden,

- ✓Incl: RT (+/- CT) su 1/3 cavità orale, dolore ≥4 NRS
  Nr = 155 pts
- ✓ Random: sciacqui con doxepina / placebo die 1; placebo/doxepina die 2
- ✓Valutazioni: dolore a 5-15-30-60 min
- ✓Endpoint: riduzione AUC pain

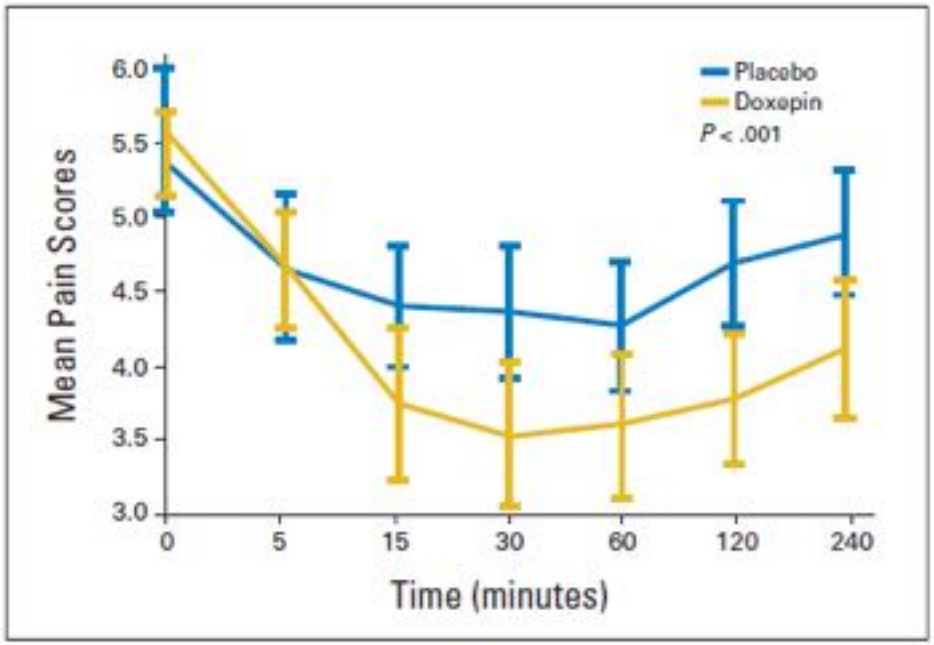


Fig 3. Average mouth and throat pain score over time, doxepin versus placebo, phase 1.

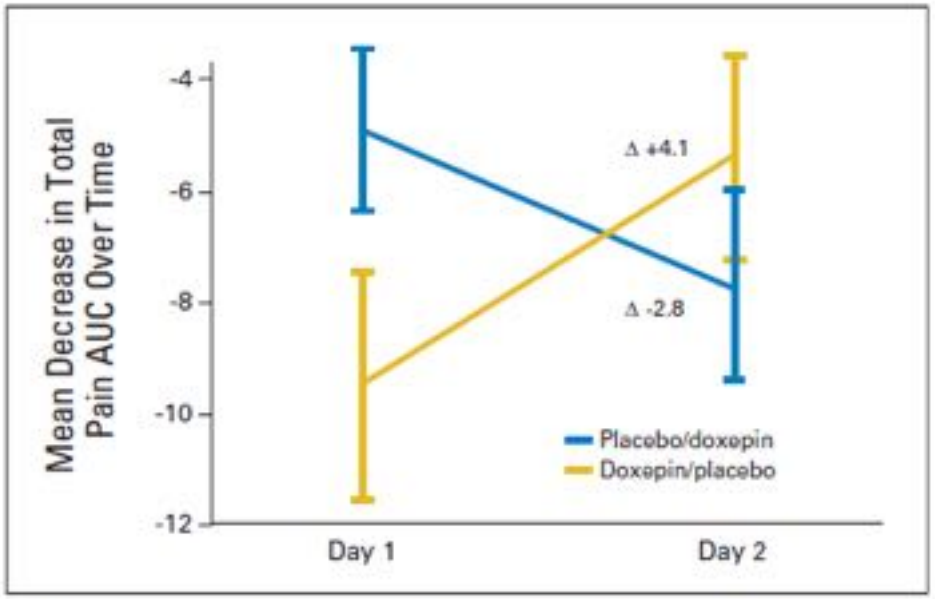


Fig 2. Crossover analysis of area under the curve (AUC) mouth and throat pain score, phases 1 and 2.

Studi innovativi in corso!

Positive Phase II preliminary results of Validive® for the prevention of Severe Oral Mucositis in Head and Neck cancer patients

Positive Phase II preliminary results of Validive®

For the prevention of Severe Oral Mucositis in Head and Neck cancer patients

- Significant reduction of incidence of severe mucositis
- Improved oral mucositis related symptoms and decreased adverse events related to radiotherapy
- Good Safety profile
- Strong Compliance to treatment

Studi innovativi in fieri

PEctin Rapid Fentanil Efficacy Clinical Trial For pAin at Swallowing undergoing radioTherapy

A multicenter randomized open trial to evaluate the efficacy of fentanyl pectin nasal spray (FPNS) versus Physician Choice (PC) - Usual Care (UC), in reducing incidental predictable breakthrough pain (IP-BTP) at swallowing in patients with head and neck cancer undergoing radiotherapy

ClinicalTrials.gov Identifier:
NCT01980498

Study phase

Multicenter, randomized, open-label phase IIIb study

Setting

In head and neck cancer care units in 20/25 Italian sites.

Population

158 patients, 79 per arm.

Study design

Randomization

Patients treated with analgesic opioids at a stable dose equivalent to 60 mg oral morphine to control background pain but with uncontrolled pain at swallowing (moderate/severe intensity: ≥ 4 on a NRS 0-10).

- *Informed consent acquired*
- *Inclusion/exclusion criteria verified*

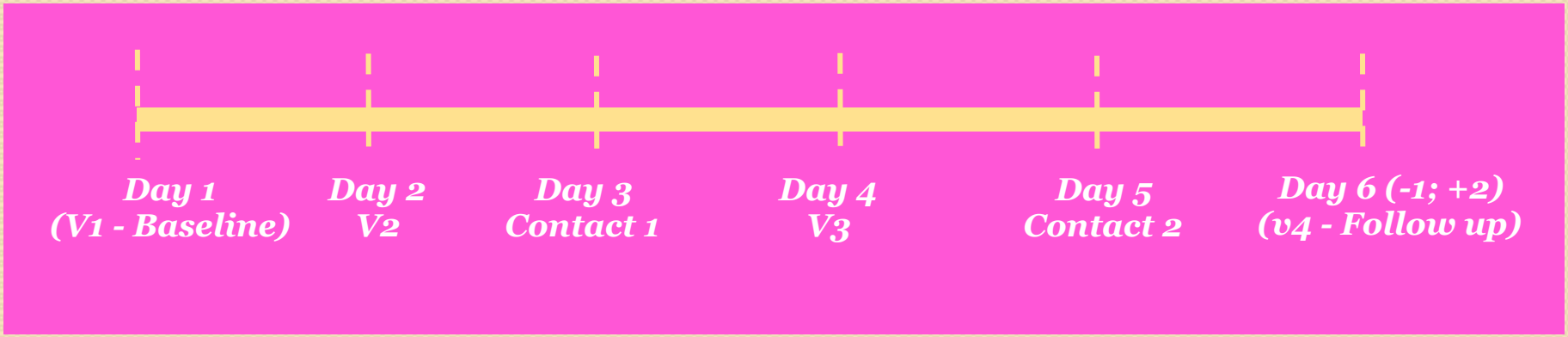
Randomization 1:1

Fentanyl pectin nasal spray (FPNS)	*Physician choice-Usual Care (PC-UC)*

Random assignment is guaranteed by randomization software that allows a stratification of patients per centre in order to obtain a balance between the two treatment groups.

Study timeline

Study timeline



Each patient will assume the drug no more than 3 episode a day (at main meals: breakfast, lunch and dinner) for 15 episodes in total in 5/6 consecutive days.

At each episode the patients will record the pain at baseline (before drug administration), and 10, 20 30 minutes after assuming FPNS or PC-UC and records it in the diary.

Studi innovativi in fieri

ORAL MUCOSITIS-INDUCED PAIN DURING CONCOMITANT CHEMORADIOTHERAPY FOR HEAD &NECK CANCER:

RANDOMIZED DOUBLE BLIND TRIAL TO COMPARE THE EFFECT OF MORPHINE MOUTHWASHES VERSUS PLACEBO MOUTHWASHES IN REDUCING THE USE OF SYSTEMIC FENTANYL OR MORPHINE THERAPY

Studi innovativi in fieri

Study phase

Multicenter, randomized, double blind, phase III study

Setting

In head and neck cancer care units in 15 Italian sites.

Population

140 patients, 70 per arm.

Studi innovativi in fieri

Primary endpoint

To compare the analgesic efficacy of morphine mouthwashes with placebo in terms of difference in total dose requirement of systemic opioids. This may result in improved oral cavity pain control and a reduction of main opioids related side effects..

Indicazioni pratiche

- Identificare **il paziente e il periodo a rischio** e monitorarlo strettamente
  Target: pz malnutrito – disidratato – 4° 5° settimana di terapia – mucosite – HPV pos -…

- **Monitoraggio frequente,** il dolore muta rapidamente (scale NRS, VAS, questionari, etc.)

Indicazioni pratiche

- Scegliere **farmaco più adatto**:
  secondo gradino si/no – cerotto più facilmente gestibile – attenzione dolore neuropatico

- Background and **BTP**

- Farmaci **adiuvanti**

Indicazioni pratiche

- Prevenire **effetti collaterali** di oppiacei
- Farmaci **locali** +/- sistemici
- Educare i **caregivers**
- **Non avere paura** della morfina e similari

Dolore: CASI CLINICI/1

Maschio, 66 anni

Tumore orofaringeo cT4 CN2a HPV neg in fumatore

Scelta terapeutica: IMRT + CDDP x 3

PS 1, BMI 18, weight loss 6% peso corporeo ab initio

Terapia concomitante: bisoprololo, cardioASA

Alla 12 seduta di RT sviluppa mucosite G2.

Calo ponderale di 2 Kg (60→58 Kg).

Algia modesta alla alimentazione

Che programma di terapia antalgica?

1) No farmaci: modifica dieta + anestetico locale prima di mangiare (lidocaina); counseling e sciacqui con acqua e bicarbonato

2) Paracetamolo 1 g x 3

3) Codeina + paracetamolo 1 x 3

4) Identificare intensità numerica (numeric rating scale) e personalizzare la scelta sulla base di colloquio su altre valutazioni accessorie

Dolore: CASI CLINICI/2

Maschio, 62 anni

Tumore laringeo cT4 cN2c

Scelta terapeutica: laringectomia totale → IMRT + CDDP x 3

PS 1, BMI 20, weight loss 3% dopo la chirurgia (80 Kg)

Terapia concomitante: metformina – cardioASA – duloxetina - BDZ

Alla 20 seduta di RT sviluppa algia alla deglutizione (NRS 6/10); background pain controllato

Calo ponderale di 2 Kg (78→76 Kg)

In terapia con Fentanyl 25 mcg/72 ore

<u>Che programma di terapia antalgica?</u>

UNMET NEEDS nel Paziente H&N

- Necessità di studi clinici
- Impatto dolore su QoL
- Ruolo dei Rapid-onset opioids
- Dolore neuropatico
- Ruolo dei trattamenti adiuvanti e delle strategie complementari
- Informare pazienti e caregivers

Grazie!

paolo.bossi@istitutotumori.mi.it