C Fabregat[1], S Almendros[2], A Navarro[2], J Gonzalez[3]
1. Medical Oncology department. Catalan Institute of Oncology. Barcelona, Spain.
2. Radiation Oncology department. Catalan Institute of Oncology. Barcelona , Spain.
3. Palliative Care Unit. Catalan Institute of Oncology., Barcelona, Spain.

Prophylaxis for pain flare. A systematic review.

Conflict of Interest Disclosure

Carles Fabregat Franco, MD

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Has no real or apparent conflicts of interest to report.

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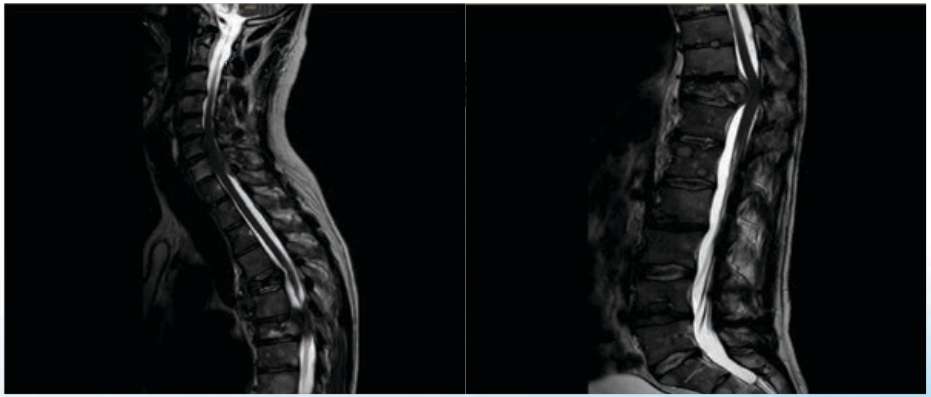
Background

Bone metastases are the most common cause of cancer-related pain and other bone events as fractures, spinal cord compression, hypercalcemia…

Radiotherapy has positioned as one of the most effective treatments to improve both.



KM Foley et al. NEJM 1985.
K Harris et al. Eur J Caner 2009.
S Lutz et al. Int J Radiat Oncol 2011 (Update 2017)

Background

The cytotoxicity of radiation triggers an inflammatory response led by pro-inflammatory cytokines as IL-8 and IL-10.

This inflammatory response can originate a transitory worsening of the pain. This phenomenon is called **"pain flare"**(PF). The most accepted definition is (Chow 2005):

> "The worsening in basal pain without a reduction in the analgesic intake or an increase of 25 percent of the analgesic intake without an improvement of the worst pain score"

E Chow et al. Radiot Oncol 2005
A Bushehri et al. Ann Palliat Med 2016

Background

PF is described in virtually **40% of the patients treated with radiation therapy**.

It usually appears during the first 5 days after the beginning of radiotherapy.

Some immunosuppressive strategies could be useful preventing this phenomenon. For instance: Hyperfractionated radiotherapy or the use of **glucocorticoids**.

We should bear in mind that immunosuppressive treatments have adverse effects, and the fact that these treatments could decrease the efficacy of new immunotherapies.

E Chow et al. Radiot Oncol 2005
A Gomez-Iturriaga et al. BMC Palliat Care 2015
FMY Lim et al. Curr Opin Support Palliat Care 2017

Endpoints

Primary endpoint: to give a comprehensive overview of prophylactic interventions studied to prevent PF and their efficacy grade.

Secondary endpoints: to determine the kind of intervention, the dosage and way of administration, as well as the related toxicity.

Design

Search strategy: MEDLINE, SCOPUS AND COCHRANE LIBRARY.

We designed a search based on the intervention, the comparison, the problem and the population using MeSH and derivative terms. We followed the PRISMA rules for systematic reviews, and we published the protocol in PROSPERO.

Two review authors (CFF and SAS) independently screened all identified titles and abstracts against the inclusion criteria. Potentially relevant reports were reviewed by all authors.

C Fabregat et al. PROSPERO 2018

Statistical analysis

We compared the all the patients who had received prophylaxis (GROUP 1) with the patients which hadn't received any prophylaxis (GROUP 2), using Chi^2 or Fisher exact test when necessary and we extracted the relative risk reduction (RRR)

We planned to extract the RRR using data from randomized and placebo-compared studies, trying to strengthen the results.

Certainty of confidence

The quality of evidence for the outcomes was assessed using the SIGN method, as well as following the GRADE working group methodology.

We assessed the possible risk of bias for each study using the Cochrane Collaboration tool.

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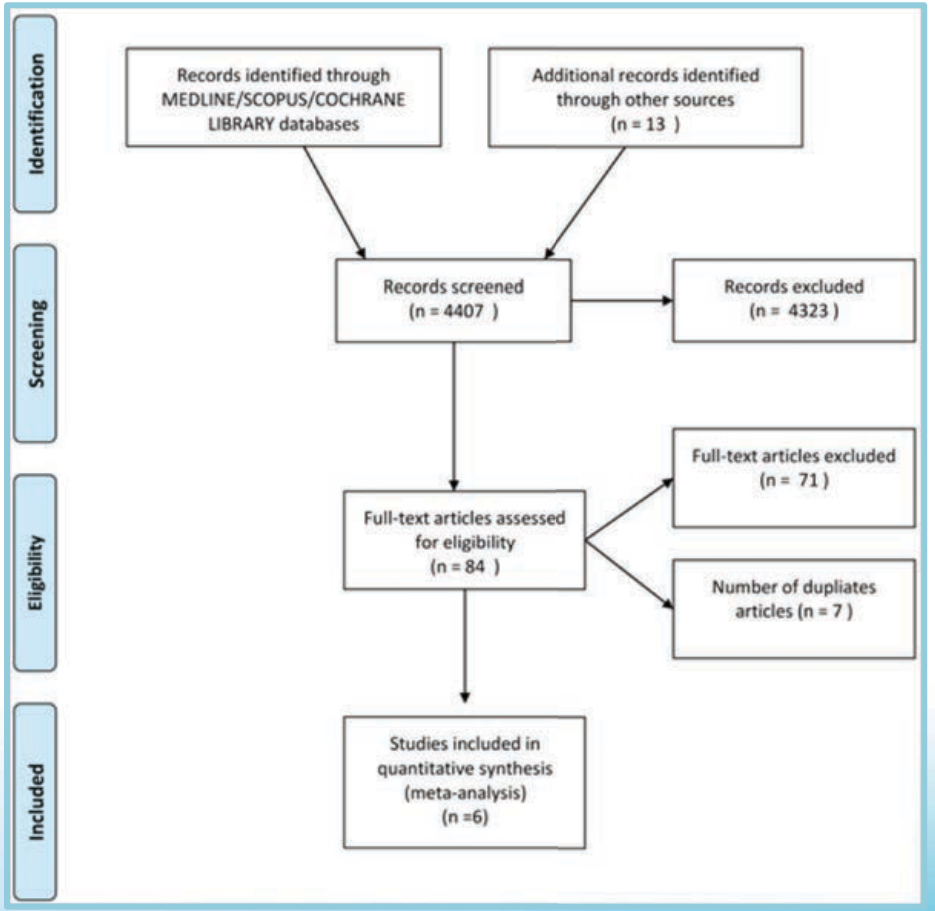
Results


Identification
Screening
Eligibility
Included
Records identified through MEDLINE/SCOPUS/COCHRANE LIBRARY databases
Additional records identified through other sources (n = 13)
Records screened (n = 4407)
Records excluded (n = 4323)
Full-text articles assessed for eligibility (n = 84)
Full-text articles excluded (n = 71)
Number of dupliates articles (n = 7)
Studies included in quantitative synthesis (meta-analysis) (n =6)

Results

Article	Intervention scheme	RT scheme and location	n	Results (incidence)	Evidence
Phase III RCT placebo controlled					
Yousef et al 2014	MPN ev 1 day	30 Gy in 3Gy/fr. Vertebral M1	120	6,6% vs 20%. *p<0,05*	1++
Chow et al 2015	Dexa 8mg for 5 days	8Gy single dose Bone M1	298	26% vs 35%. *p<0,05*	1++
Phase II non-comparative					
Chow et al 2007	Dexa 8mg for 1 day	8Gy single dose Bone M1	33	24%	1+
Hird et al 2009	Dexa 8mg for 4 days	8Gy single dose Bone M1	41	22%	1+
Comparative cohort studies					
Chiang 2013/ Khan 2015	-Naive -Dexa 4/8mg for 5 days	SBRT Vertebral M1	41 47	19% (dexa) vs 69% (no). *p<0,05* 13% (8mg) vs 25% (4mg). *p=0,46*	2-

Results

Pool analysis:

Global

580 patients, 329 receiving prophylaxis and 251 with no-prophylaxis.
28% of the whole patients experienced PF. 21% prophylaxis vs 37% non-prophylaxis.
RRR 43% [confidence bound (CB) of 26-57%, p-value <0.05].

RCT

418 patients, 208 receiving prophylaxis and 210 with no-prophylaxis.
26% of the whole patients experienced PF. 21% prophylaxis vs 31% non-prophylaxis.
RRR 33% [confidence bound (CB) of 7-52%, p-value <0.05].

The prospective cohort study comparing with their historical cohort demonstrated a RRR of 72% [CB 48-85%]. This study showed no differences when comparing 4 vs 8 mg.

Results

No grade 3-4 toxicity was reported in 4 studies. One RCT described a 2% of grade 3-4 hyperglycemia in the dexamethasone group compared with 0% in placebo group.

Nevertheless, the addition of dexamethasone was accompanied by an improvement in other symptoms like nausea, functional activity and appetite.

One study reported significant differences using the BPI index in favour of 4mg compared with 8mg, in terms of walking ability and relations with others.

None of the articles reported predictive factors of the use of corticoids to prevent pain flare.

Limitations

There were only 5 studies suitable for inclusion. 3 of them were compartive with placebo and 2 were RCT.

We found articles in three big medical and scientific databases, however we didn't have access to all database to complete the search.

There were discrepancies in patient characteristics and outcomes within the two RCT.

Conclusions

Glucocorticoids are effective as a preventive treatment for PF (Grade ⨁⨁⨁O)

Currently, orally dexamethasone in 8mg od for 5 days from the first day of RT is the best studied scheme.

We should study further the best scheme of corticoids, to try to decrease the dose down to the minimum effective.

We consider that a short course of corticoids has no significant toxicities in these patients.

THANK YOU FOR YOUR ATTENTION

ICO
Institut Català d'Oncologia

Generalitat de Catalunya

IDI BELL
Institut d'Investigació Biomèdica de Bellvitge

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