Prophylaxis for pain flare. A systematic review.

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Conflict of Interest Disclosure
Carles Fabregat Franco, MD

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.

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”

Chow et al. Radiol Oncol 2005
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.
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 Chi² 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.
Results

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 duplicates articles (n = 7)

Studies included in quantitative synthesis (meta-analysis) (n = 6)
## Results

<table>
<thead>
<tr>
<th>Article</th>
<th>Intervention scheme</th>
<th>RT scheme and location</th>
<th>n</th>
<th>Results (incidence)</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase III RCT placebo controlled</td>
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<tr>
<td>Yousef et al 2014</td>
<td>MPN ev 1 day</td>
<td>30 Gy in 3Gy/fr. Vertebral M1</td>
<td>120</td>
<td>6.6% vs 20%. ( p&lt;0.05 )</td>
<td>1++</td>
</tr>
<tr>
<td>Chow et al 2015</td>
<td>Dexa 8mg for 5 days</td>
<td>8Gy single dose Bone M1</td>
<td>298</td>
<td>26% vs 35%. ( p&lt;0.05 )</td>
<td>1++</td>
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<tr>
<td>Phase II non-comparative</td>
<td></td>
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<tr>
<td>Chow et al 2007</td>
<td>Dexa 8mg for 1 day</td>
<td>8Gy single dose Bone M1</td>
<td>33</td>
<td>24%</td>
<td>1+</td>
</tr>
<tr>
<td>Hird et al 2009</td>
<td>Dexa 8mg for 4 days</td>
<td>8Gy single dose Bone M1</td>
<td>41</td>
<td>22%</td>
<td>1+</td>
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<tr>
<td>Comparative cohort studies</td>
<td></td>
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<tr>
<td>Chiang 2013/ Khan 2015</td>
<td>-Naive</td>
<td>-Dexa 4/8mg for 5 days</td>
<td>SBRT Vertebral M1</td>
<td>41/47</td>
<td>19% (dexa) vs 69% (no). ( p&lt;0.05 ) 13% (8mg) vs 25% (4mg). ( p=0.46 )</td>
</tr>
</tbody>
</table>
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 comparative 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 III)

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