

Dexamethasone in the prophylaxis of radiation-induced pain flare after palliative radiotherapy for bone metastases: a double-blind, randomised placebo-controlled, phase 3 trial

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Abstract: *Background*

Pain flare occurs after palliative radiotherapy, and dexamethasone has shown potential for prevention of such flare. We aimed to compare the efficacy of dexamethasone with that of placebo in terms of reduction of incidence of pain flare. *Methods* In this double-blind, randomized, placebo-controlled phase 3 trial, patients from 23 Canadian centers were randomly allocated (1:1) with a web-based system and minimization algorithm to receive either two 4 mg dexamethasone tablets or two placebo tablets taken orally at least 1 h before the start of radiation treatment (a single 8 Gy dose to bone metastases; day 0) and then every day for 4 days after radiotherapy (days 1–4). Patients were eligible if they had a non-haematological malignancy and bone metastasis (or metastases) corresponding to the clinically painful area or areas. Patients reported their worst pain scores and opioid analgesic intake before treatment and daily for 10 days after radiation treatment. They completed the European Organization for Research and Treatment of Cancer (EORTC) quality of life QLQ-C15-PAL, the bone metastases module (EORTC QLQ-BM22), and the Dexamethasone Symptom Questionnaire at baseline, and at days 10 and 42 after radiation treatment. Pain flare was defined as at least a two-point increase on a scale of 0–10 in the worst pain score with no decrease in analgesic intake, or a 25% or greater increase in analgesic intake with no decrease in the worst pain score from days 0–10, followed by a return to baseline levels or below. Primary analysis of incidence of pain flare was by intention-to-treat (patients with missing primary data were classified as having pain flare). This study is registered with ClinicalTrials.gov, number NCT01248585, and is completed. *Findings* Between May 30, 2011, and Dec 11, 2014, 298 patients were enrolled. **39 (26%) of 148 patients randomly allocated to the dexamethasone group and 53 (35%) of 150 patients in the placebo group had a pain flare (difference 8.9%, lower 95% confidence bound 0.0, one-sided p=0.05).** Two grade 3 and one grade 4 biochemical hyperglycaemic events occurred in the dexamethasone group (without known clinical effects) compared with none in the placebo group. The most common adverse events were bone pain (61 [41%] of 147 vs 68 [48%] of 143), fatigue (58 [39%] of 147 vs 49 [34%] of 143), constipation (47 [32%] of 147 vs 37 [26%] of 143), and nausea (34 [23%] of 147 vs 34 [24%] of 143), most of which were mild grade 1 or 2. *Interpretation* Dexamethasone reduces radiation-induced pain flare in the treatment of painful bone metastases. **Outcome:** dexamethasone decreases radiation-induced pain flare (as well as nausea and improved functional activity and appetite but increased number of high depression scores)

Strengths:

- Randomized, double-blind RCT with efficacious blinding of patients, investigators, response assessors, study statistician
- ITT analysis – assumed patients with missing data had pain flare (both groups) and sensitivity analysis – assumed patients in both groups did **not** have flare
- majority of patients had pain scores of at least 5 at baseline
- analyzed pain based on both subjective patient rating and daily morphine equivalents
- thorough analysis of effect of dexamethasone/placebo on quality of life

Weaknesses:

- 75% of patients had cancer of either breast/prostate/lung – possibly limited applicability to other primaries
- 75-80% of patients relatively high-functioning ($\geq 70\%$ on KPS scale)
- limited information on patient co-morbidities, notably diabetes (although did not that well-controlled diabetes **not** a contra-indication to dexamethasone)
- excluded patients already on corticosteroids
- could have included dexamethasone 4 mg in analysis

Relevance to Palliative Care: Many palliative care patients are referred to our service with pain control as a primary issue. Sources of pain vary but a large number of these patients have bony metastases which may benefit from radiotherapy and although this may eventually improve pain scores it can be associated with pain flare in the interim. This study provides relatively convincing evidence that dexamethasone can decrease the incidence and/or severity of these pain flares with an NNT of 9-11.

