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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Summary

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, randomised, placebo-controlled phase 3 trial, patients from 23 Canadian centres were randomly allocated (1:1) with a web-based system and minimisation 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 Organisation 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.

Funding The NCIC CTG's programmatic grant from the Canadian Cancer Society Research Institute.

Introduction

Palliative radiotherapy is effective in treatment of symptomatic bone metastases;[1,2] however, pain flare (defined as temporary worsening of pain in the treated site) is a potential side-effect with an estimated incidence of 30–40% across studies.[3–9] The impact of pain flare can be severe and profound.[10] Pain flare might be due to release of inflammatory cytokines,[11] and so dexamethasone might prevent or attenuate the occurrence of pain flare through its anti-inflammatory action.[12–14] Results of two pilot studies[11,15] have shown the efficacy of dexamethasone given before radiotherapy in successfully preventing pain flare. We did a randomised controlled trial comparing dexamethasone with placebo for reduction of incidence of pain flare in patients receiving a single fraction of palliative radiotherapy.

Methods

Study design and participants

The NCIC Clinical Trials Group (NCIC CTG) Symptom Control 23 (SC.23) study was a randomised, double-blind placebo-controlled trial in patients enrolled at 23 Canadian cancer centres. Patients were recruited after referral for palliative radiation treatment for painful bone metastases.

Eligible patients were aged at least 18 years with a proven diagnosis of cancer and pain corresponding to a site (or sites) of radiologically confirmed bone metastases. Severity of pain had to be scored at least two out of ten on question three of the Brief Pain Inventory, with a stable dose and schedule of narcotic medications prescribed. Patients had to be planning to receive a single 8 Gy fraction of palliative radiotherapy

Lancet Oncol 2015; 16: 1463–72

Published Online October 18, 2015 http://dx.doi.org/10.1016/S1470-2045(15)00199-0

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Research in context

Evidence before this study

Nine studies have documented incidence of pain flare in patients treated with palliative radiotherapy to painful bone metastases. Incidence of pain flare is 30–40%. Dexamethasone has been shown to be a feasible prophylactic against pain flare. Two pilot studies investigating use of 8 mg dexamethasone before treatment for prophylaxis in 33 patients and 8 mg of dexamethasone before radiotherapy and for 3 days after radiation in 41 patients reported that pain flare incidence was reduced to 22–24%.

Added value of this study

Dexamethasone is efficacious in prophylaxis of radiation-induced pain flare. Dexamethasone improved quality of life by reducing nausea and increasing functional activity and appetite, without serious adverse effects.

Implications of all the available evidence

Bone metastases are very prevalent in patients with advanced cancer. Many patients with bone metastases need palliative radiotherapy. Radiation therapy is effective in treatment of painful bone metastases, but with an incidence of 30–40% acute pain flare. Dexamethasone is efficacious in prophylaxis of radiation-induced pain flare. This finding might change the practice of radiation oncologists worldwide. Whether dexamethasone at 16 mg/day would further reduce incidence of pain flare remains unknown.

to one or two target volumes (all machine and beam types allowed). Patients with haematological malignancies were ineligible because steroids constitute anticancer therapy for these patients. Other ineligibility criteria included concurrent use or use within 7 days of the study period of any corticosteroid medication other than topical or inhaled preparations; medical contraindications to corticosteroids such as uncontrolled diabetes, uncontrolled hypertension, or active peptic ulcer; hypokalaemia less than 3·0 mmol/L; random glucose concentration of 13·9 mmol/L or more; or Karnofsky performance status (KPS) of less than 40; and plans to receive cytotoxic chemotherapy within 10 days of radiotherapy. Patients were ineligible if they had clinical or radiological evidence of spinal cord compression, a pathological fracture, or an impending fracture needing surgical fixation. Additionally, patients were ineligible if they needed treatment with a non-steroidal anti-inflammatory drug (NSAID), but patients treated with daily low-dose aspirin for anti-platelet therapy were eligible. Patients who had received previous radiotherapy to study site or sites were also ineligible.

All participating centres received approval from their local research ethics boards, and written consent was obtained from all participants. A study protocol is available online.

For the **study protocol** see http://www.ctg.queensu.ca/public/publications/SC23_public/sc23-Protocol-Amend1-2013DEC19-Public_Secured.pdf

See Online for appendix

Randomisation and masking

Patients were randomly assigned (1:1) to receive either dexamethasone or placebo using a web-based system and minimisation algorithm. Randomisation was stratified according to centre, baseline worst pain score (2–4, 5–6, or 7–10) on question three of the Brief Pain Inventory, primary cancer site (breast, prostate, lung, or other), and number of painful sites receiving radiotherapy (one *vs* two). The randomisation schedule was generated by the NCIC CTG central randomisation manager. Patients, investigators, response assessors, and the study statistician were all masked to treatment allocation; this included use of placebo tablets that were identical in appearance to dexamethasone tablets.

Procedures

Patients received either 8 mg of dexamethasone (Valeant Pharmaceuticals International, Montreal, QC, Canada) as two 4 mg tablets, or two placebo tablets to be taken orally at least 1 h before the start of radiotherapy (day 0) and then every day for 4 days after radiotherapy (days 1–4), preferably in the morning with breakfast. Patients reported in diaries their worst pain scores from 0 (no pain) to 10 (pain as bad as you can imagine) before radiation and then daily for 10 days after treatment. Patients were asked to indicate whether their pain before radiotherapy was worse, the same, or better than the baseline worst pain and recorded their daily opioid analgesic intake. Additionally, patients completed the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life QLQ-C15-PAL questionnaire,[16,17] the bone metastases module (EORTC QLQ-BM22),[18] and the Dexamethasone Symptom Questionnaire (DSQ)[19] at baseline, and at 10 days and 42 days after radiation treatment. The EORTC QLQ-C15-PAL questionnaire is an abbreviated version of the QLQ-C30 designed for use in palliative care. The questionnaire includes four multi-item scales and six individual items (appendix).[16,17] The EORTC QLQ-BM22 is composed of four subscales: painful sites and pain characteristics on the symptom scale, and functional interference and psychosocial aspects on the functional scale (appendix).[18] All items for the EORTC QLQ-C15-PAL and QLQ-BM22 (except global assessment) are scaled from one (not at all) to four (very much). A high score suggests increased distress in the symptom scale, whereas a high score in the functional scale shows increased functional ability. Each scale is converted to a score ranging from zero to 100. The DSQ captures the adverse events of

dexamethasone on a four-point Likert scale with nine items: insomnia, gastro-oesophageal reflux, agitation, increased appetite, weight gain, acne, hiccups, oral candida, and depression (appendix).[19] We used these methods to assess the hypothesis that improved control of pain flare might favourably affect related patient function reports, and to assess the effects of dexamethasone (favourable or not) on relevant patient-reported outcomes.

Outcomes

The primary endpoint was the per-patient incidence of pain flare that occurred from the time of radiotherapy to 10 days after completion of radiation treatment. Pain flare was defined as either of the following: a minimum of a two-point increase in the worst pain score for the treated site without a reduction in analgesic intake; or a 25% or greater increase in analgesic intake based on daily oral morphine equivalence without a reduction in the worst pain score. If an individual patient experienced more than one episode of pain flare, only the first episode contributed to the primary endpoint. We considered pain flare early in onset if it started on days 0–5, or late in onset if it started on days 6–10. If the pain flare started during days 0–5, but did not return to baseline until days 6–10, the flare was assigned to both days 0–5 and days 6–10 for the appropriate secondary endpoints. If the worst pain score before treatment was nine or ten, the criteria for pain flare were met if the follow-up worst pain score was ten and reported as worse than the worst pain before treatment with no decrease in analgesic intake. To distinguish pain flare from progression of pain, the worst pain score and analgesic intake had to return to baseline levels during the 11-day on-study period.[3]

As a secondary endpoint, the proportion of patients achieving an overall response (complete response plus partial response) at day 42 after radiation therapy was based on the International Bone Metastases Consensus Endpoint definitions.[20] Complete response was defined as a worst pain score of zero at the bony metastatic site, with no concomitant increase in analgesic intake. Partial response was defined as either a reduction in the worst pain score of two or more without analgesic increase or an analgesic reduction of 25% or more from baseline, without an increase in the worst pain score. Pain progression was defined as either an increase in the worst pain score of two or more without analgesic decrease or an analgesic increase of 25% or more from baseline without a decrease in the worst pain score. The remaining patients were classified as having stable pain.[20] Other secondary objectives included were the toxicity of dexamethasone in this setting, comparing the effect of treatments on quality of life using the instruments described above, and studying the relation between pain flare and the eventual response to radiotherapy.

	Dexamethasone (n=148)	Placebo (n=150)
Median age (years [IQR])	68 (58·5–75)	70 (61–77)
Sex		
Male	88 (59%)	82 (55%)
Female	60 (41%)	68 (45%)
Primary cancer site		
Breast	33 (22%)	33 (22%)
Prostate	36 (24%)	38 (25%)
Lung	41 (28%)	43 (29%)
Other	38 (26%)	36 (24%)
Karnofsky performance status		
40–60	30 (20%)	38 (25%)
70–80	93 (63%)	72 (48%)
90–100	25 (17%)	40 (27%)
Worst pain score at baseline		
2–4	34 (23%)	31 (21%)
5–6	41 (28%)	41 (27%)
7–10	73 (49%)	78 (52%)
Index site of radiated bone lesion		
Pelvis, hips, or lower limbs	61 (41%)	45 (30%)
Lumbo-sacral spine	23 (16%)	31 (21%)
Ribs, scapula, sternum, or skull	40 (27%)	39 (26%)
Upper limbs	3 (2%)	7 (5%)
Cervical-thoracic spine	21 (14%)	28 (19%)

Data are n (%), unless otherwise stated.

Table 1: **Baseline characteristics**

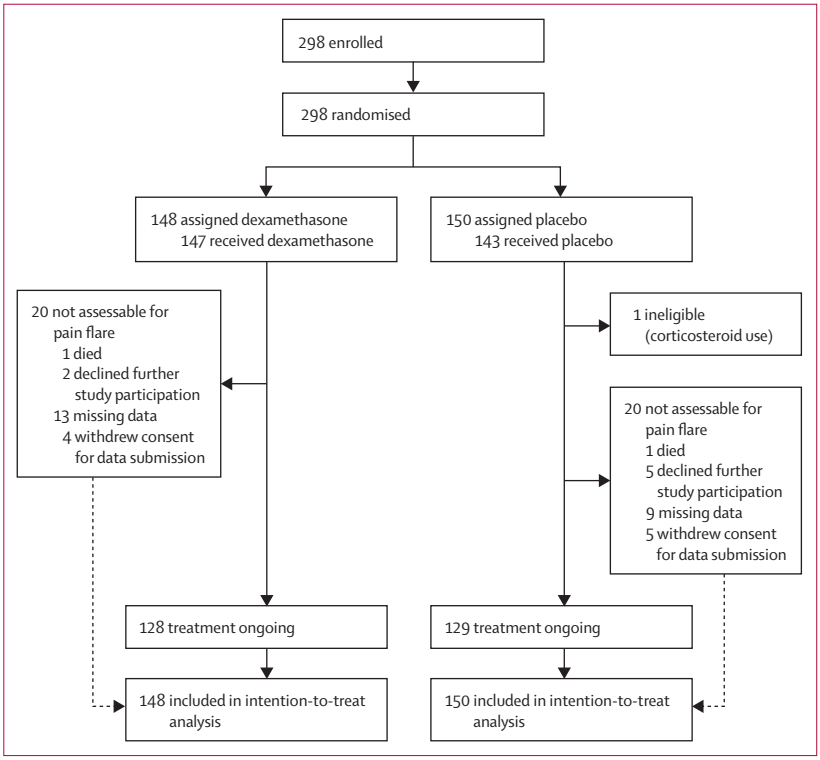

Figure 1: **Trial profile**
Missing data refers to participants without a complete 10-day pain diary.

Statistical analysis

The study was designed as a superiority study. On the basis of previous work,[3,11,15] we hypothesised that the incidence of pain flare with radiotherapy would be reduced from 35% in the placebo group to 15% in the dexamethasone group with dexamethasone. Assuming that 15% of patients would be lost to follow-up or not assessable, we expected the incidence of pain flare for the intention-to-treat analysis would be 45% for the placebo group and 28% for the dexamethasone group. Using two proportions power analysis with Fleiss continuity correction for phase 3 clinical trials[21] and one-sided α of 0·05 and β of 0·1, 149 patients were needed in each group. This sample size also provided sufficient power to statistically assess the patient-reported outcomes.

We assumed patients who were not assessable owing to missing data to have experienced pain flare for the intention-to-treat analysis. We also did a sensitivity analysis that assumed patients with missing data did not have pain flare in both groups. We calculated the difference in pain flare incidence and its 90% CI between groups. We used the Cochran-Mantel-Haenszel test to adjust for stratification factors, except centre, to investigate the difference in pain flare incidence between the two groups,[22] and a logistic regression model with treatment, age (as a continuous variable), sex, primary malignancy, KPS, worst pain score at baseline, and site of painful bone lesion as covariates to correlate baseline factors to pain flare incidence. Additionally, we did another sensitivity analysis favouring the placebo group, assuming all patients who were not assessable with missing data in the treatment group to have pain flare and in the placebo group to have no pain flare.

We assessed patient-reported quality of life with the EORTC QLQ-C15-PAL, QLQ-BM22, and DSQ by comparing mean change scores (baseline to day 10 and day 42) between groups. We tested between-group differences using linear mixed models with the scores, treatment group, and their interaction term as fixed effects. Furthermore, we used paired *t* tests to assess the significance of change scores (baseline to 10 days). We classified the items in each questionnaire into low (not at all, a little) versus high (quite a bit, very much), and we compared the proportion of patients in each item. We selected changes of at least ten points from baseline to represent a clinically meaningful change.[23] All patients who received at least one dose of study drug were included in safety analyses. Safety monitoring was done every 6 months by the NCIC CTG data safety and monitoring committee. All analyses were done with SAS, version 9.2. All p values were two-sided unless otherwise specified. This study is registered with ClinicalTrials.gov, number NCT01248585.

	Dexamethasone (n=148)	Placebo (n=150)
0–10 days		
Not assessable	7 (5%)	11 (7%)
No pain flare	81 (55%)	63 (42%)
Pain progression	21 (14%)	23 (15%)
Pain flare*	39 (26%); sensitivity analysis 26 (18%)	53 (35%); sensitivity analysis 44 (29%)
0–5 days (p=0·03 pain flare *vs* no pain flare)		
Not assessable	6 (4%)	10 (7%)
No pain flare	101 (68%)	77 (51%)
Pain progression	12 (8%)	17 (11%)
Pain flare	29 (20%)	46 (31%)
6–10 days (p=0·4 pain flare *vs* no pain flare)		
Not assessable	7 (5%)	12 (8%)
No pain flare	91 (61%)	82 (55%)
Pain progression	22 (15%)	29 (19%)
Pain flare	28 (19%)	27 (18%)

Data are n (%). *Missing data for 13 patients (dexamethasone group) and nine patients (placebo group).

Table 2: **Incidence of pain flare (intention-to-treat)**

Role of the funding source

The funder of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. EC, RMM, KD, and CFW had access to the raw data. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between May 30, 2011, and Dec 11, 2014, 298 patients from 23 Canadian centres (appendix) were enrolled;

	Dexamethasone			Placebo		
	Early onset (day 0–5)	Late onset (day 6–10)	Overall (day 0–10)	Early onset (day 0–5)	Late onset (day 6–10)	Overall (day 0–10)
Change in pain score	2 (0–8)	2·5 (2–5)	2 (0–8)	2 (0–6)	4 (2–4)	2 (0–6)
Beginning of pain flare after radiation (days)	1 (1–5)	7 (6–8)	1·5 (1–8)	1 (1–5)	6 (6–7)	1 (1–7)
Duration of pain flare (days)	3 (1–8)	1·5 (1–4)	3 (1–8)	2 (1–8)	3 (3–4)	2 (1–8)

Data are median (range).

Table 3: **Change in pain score and duration of pain flare for early and late onset**

148 patients were assigned to the dexamethasone group and 150 to the placebo group (table 1). The median age was 69 years (range 32–96).

Median follow-up was 1·39 months (IQR 1·35–1·46) for all patients, 1·39 months (IQR 1·35–1·47) for the dexamethasone group and 1·39 months (IQR 1·35–1·45) for the placebo group. The most common primary sites were lung (28%), prostate (25%), and breast (22%). 231 (78%) of 298 patients had radiotherapy at one site of bone metastasis (115 [78%] of 148 patients in the dexamethasone group and 116 [73%] of 150 patients in the placebo group), with the remaining patients in each group having radiotherapy at two sites. 40 patients (20 in each group) were not assessable for pain flare incidence in the first 10 days (figure 1).

In the intention-to-treat analysis, 92 patients experienced pain flare on days 0–10: 39 (26%) of 148 patients in the dexamethasone group and 53 (35%) of 150 patients in the placebo group; the absolute difference in pain flare incidence between the two groups was 8·9% (lower 95% confidence bound [CB]: 0·0, one-sided p=0·05). The number of patients who had pain flare in days 0–5 was 29 (20%) in the dexamethasone group and 46 (31%) in the placebo group; the absolute difference was 11·1% (lower 95% CB 2·8, one-sided p=0·03). We identified no difference in pain flare incidence between the two groups on days 6–10 (table 2). The logistic regression model showed that dexamethasone (but not placebo) significantly reduced pain flare (one-sided p=0·05).

In the sensitivity analysis, 70 patients experienced pain flare on days 0–10: 26 (18%) of 148 in the dexamethasone group and 44 (29%) of 150 in the placebo group; the absolute difference in pain flare incidence was 11·8% (lower 95% CB 3·8, one-sided p=0·01). 13 (9%) patients in the dexamethasone group and 31 (21%) patients in the placebo group had pain flare in days 0–5; the absolute difference was 11·9% (lower 95% CB 4·0, one-sided p=0·005). Pain flare incidence did not differ between the two groups on days 6–10 (table 2). The logistic regression model showed that dexamethasone was significantly associated with pain flare reduction on days 0–10 (one-sided p=0·02). Other factors associated with pain flare reduction include male sex (p=0·03), KPS of 70–80 (p=0·02), and KPS of 40–60 (p=0·0007); no other factors were significantly associated with reduced pain flare. When analyses were repeated in both groups separately, no factors were associated with pain flare reduction in the dexamethasone group, whereas in the placebo group, KPS of 40–60 was associated with pain flare reduction (p=0·0015), and having an irradiated bone lesion in the cervico-thoracic spine was associated with pain flare increase (p=0·001). Another sensitivity analysis for pain flare incidence favouring the placebo group showed that 84 patients experienced pain flare, with 39 (26%) of 148 patients in the dexamethasone group and 44 (29%) of 150 patients in the placebo group, with no significant difference in pain flare between the two groups (Cochran-Mantel-Haenszel test one-sided p=0·37).

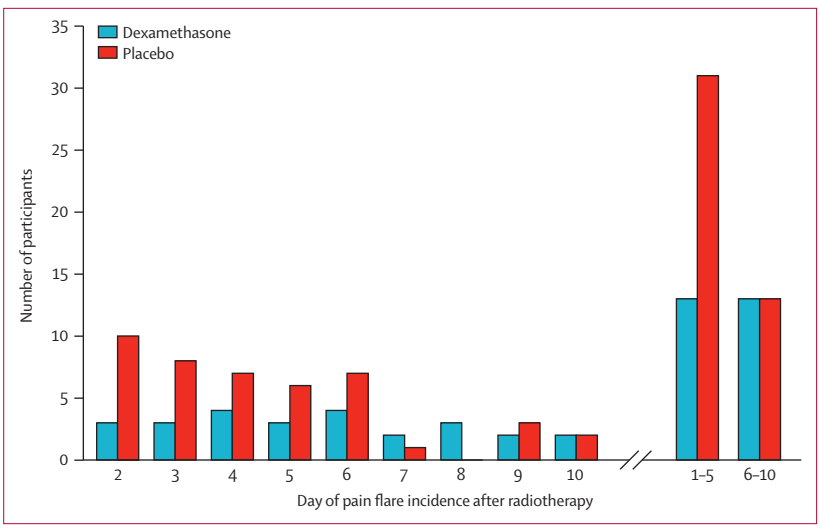

Figure 2: **Daily pain flare incidence**
For the 70 patients who experienced pain flare in the sensitivity analysis. No pain flare occurred in either group on days 0–1.

	Dexamethasone (n=147)		Placebo (n=143)	
	Grade 1–2	Grade 3–5	Grade 1–2	Grade 3–5
Bloating	46 (31%)	1 (1%)	37 (26%)	0
Nausea	34 (23%)	0	34 (24%)	0
Fatigue	56 (38%)	2 (1%)	46 (32%)	3 (2%)
Bone pain	50 (34%)	11 (7%)	48 (34%)	20 (14%)
Anorexia	14 (10%)	1 (1%)	12 (8%)	1 (1%)
Hyperglycaemia	0	3 (2%)*	0	0
Constipation	46 (31%)	1 (1%)	37 (26%)	0

Only patients who received treatment are included. *Two were grade 3 and one was grade 4. All other numbers listed under grade 3–5 were grade 3.

Table 4: **Adverse events**

Patients in the dexamethasone group had greater reduction in mean pain scores (day 10 *vs* pretreatment) compared with those in the placebo group, but the reduction was not significant (–2·37 *vs* –1·85, p=0·09). The reduction was significant between groups for days 0–5, favouring the dexamethasone group (–1·79 *vs* –1·09; p=0·01). We identified no difference in mean pain scores for days 6–10 compared with baseline for either group (table 3). The median cumulative oral morphine equivalence was 228 mg (IQR 27–785) in the dexamethasone group and 224 mg (IQR 42–695) in the placebo group over the 10 days following radiotherapy. There was no difference between the two treatment groups (p=0·92). Additionally, analgesic intake did not differ between the groups from days 0–5 or days 6–10.

Daily incidence rates of pain flare are shown in figure 2. For the 70 patients who experienced pain flare in the

sensitivity analysis (26 in the dexamethasone group and 44 in the placebo group), 44 (63%) had onset within days 0–5 (13 in the dexamethasone group and 31 in the placebo group). 26 patients (13 in the dexamethasone group and 13 in the placebo group) had late-onset pain flare on days 6–10.

64 patients in the dexamethasone group responded to radiation treatment at day 42 (29 complete responses

	Dexamethasone						Placebo						p value	
	n*	Baseline score (mean [SD])	Score change at day 10 (mean [SD])	Improved at day 10	Stable at day 10	Worsened at day 10	n*	Baseline score (mean [SD])	Score change at day 10 (mean [SD])	Improved at day 10	Stable at day 10	Worsened at day 10	χ^2 test	M-H test
EORTC QLQ-C15-PAL														
Physical	139	74·82 (22·60)	−1·6 (23·4)	33 (29%)	39 (35%)	41 (36%)	143	71·72 (27·40)	−3·4 (19·0)	25 (22%)	44 (39%)	43 (38%)	0·485	0·392
Dyspnoea	138	24·88 (27·92)	−0·3 (25·1)	25 (22%)	63 (56%)	24 (21%)	143	23·31 (29·35)	2·8 (19·8)	10 (9%)	78 (72%)	21 (19%)	0·017	0·175
Pain	137	62·77 (24·94)	−11·2 (29·7)	53 (48%)	31 (28%)	26 (24%)	142	64·44 (27·38)	−5·6 (30·6)	50 (46%)	29 (27%)	29 (27%)	0·861	0·648
Insomnia	139	38·61 (32·66)	0·9 (35·5)	34 (30%)	48 (42%)	31 (27%)	143	35·43 (32·19)	0·6 (29·3)	26 (24%)	57 (52%)	27 (25%)	0·355	0·715
Fatigue	139	45·20 (27·89)	5·1 (27·7)	35 (31%)	33 (29%)	44 (39%)	141	47·99 (27·28)	4·1 (23·4)	30 (27%)	42 (38%)	39 (35%)	0·414	0·995
Appetite	139	33·81 (35·66)	−2·7 (28·6)	28 (25%)	59 (52%)	26 (23%)	143	34·73 (36·23)	4·5 (35·1)	20 (18%)	60 (54%)	32 (29%)	0·376	0·173
Nausea	139	19·42 (29·46)	−0·6 (27·8)	22 (19%)	70 (62%)	21 (19%)	142	17·84 (27·12)	8·0 (29·8)	16 (14%)	61 (54%)	35 (31%)	0·080	0·037
Constipation	137	31·87 (34·27)	2·7 (32·8)	21 (19%)	64 (58%)	26 (23%)	143	34·73 (35·80)	−1·5 (31·8)	22 (20%)	68 (61%)	22 (20%)	0·789	0·599
Emotional	138	69·93 (26·01)	−1·6 (28·8)	33 (29%)	42 (38%)	37 (33%)	143	68·07 (27·30)	0·3 (21·3)	29 (26%)	52 (46%)	31 (28%)	0·396	0·861
EORTC QLQ-BM22														
Painful sites	139	36·38 (17·92)	−4·1 (19·5)	43 (38%)	46 (41%)	24 (21%)	143	34·30 (17·80)	−1·8 (18·5)	29 (26%)	54 (48%)	29 (26%)	0·147	0·089
Pain characteristics	139	47·52 (22·33)	−9·4 (27·4)	65 (58%)	18 (16%)	30 (27%)	143	44·09 (21·83)	−2·7 (23·1)	51 (46%)	25 (22%)	36 (32%)	0·185	0·131
Functional interference	139	51·09 (22·54)	−10·5 (22·4)	51 (45%)	45 (40%)	17 (15%)	143	49·68 (23·06)	−3·8 (20·7)	33 (29%)	54 (48%)	25 (22%)	0·045	0·018
Psychosocial aspects	139	51·01 (18·68)	−0·4 (18·6)	33 (29%)	46 (41%)	34 (30%)	143	48·62 (20·63)	1·3 (18·3)	31 (28%)	40 (36%)	41 (37%)	0·568	0·443
DSQ														
Reflux	138	18·13 (24·54)	6·0 (29·5)	20 (18%)	60 (54%)	31 (28%)	142	18·12 (27·02)	1·9 (31·1)	22 (21%)	54 (51%)	30 (28%)	0·855	0·799
Insomnia	137	34·55 (33·19)	1·5 (33·3)	30 (27%)	55 (49%)	27 (24%)	142	30·75 (33·70)	1·5 (31·4)	28 (26%)	52 (48%)	28 (26%)	0·952	0·782
Increased appetite	138	9·42 (20·13)	7·2 (27·9)	12 (11%)	69 (62%)	30 (27%)	141	8·98 (19·47)	−0·6 (20·9)	14 (13%)	81 (75%)	13 (12%)	0·020	0·023
Hiccups	137	8·27 (20·52)	2·4 (20·8)	8 (7%)	91 (81%)	13 (12%)	141	6·38 (17·33)	3·5 (16·5)	5 (5%)	85 (80%)	16 (15%)	0·594	0·314
Weight gain	138	7·00 (15·83)	0·6 (20·2)	12 (11%)	84 (76%)	14 (13%)	142	7·98 (20·22)	−2·2 (18·7)	13 (13%)	83 (80%)	8 (8%)	0·469	0·302
Agitation	136	31·86 (30·33)	3·0 (28·3)	20 (18%)	63 (57%)	28 (25%)	142	28·87 (28·69)	1·9 (30·0)	21 (20%)	57 (53%)	29 (27%)	0·874	0·976
Acne	138	2·42 (9·56)	3·0 (19·3)	4 (4%)	99 (88%)	9 (8%)	142	3·52 (12·99)	0·6 (14·4)	6 (6%)	94 (87%)	8 (7%)	0·773	0·580
Oral candida	138	2·42 (13·14)	1·2 (11·8)	3 (3%)	100 (90%)	8 (7%)	141	1·18 (7·36)	1·3 (12·1)	2 (2%)	100 (94%)	4 (4%)	0·492	0·489
Depression	31	7·53 (22·29)	3·2 (18·0)	1 (5%)	18 (86%)	2 (10%)	34	1·96 (7·96)	3·0 (17·5)	1 (5%)	19 (86%)	2 (9%)	0·998	0·985

M-H=Mantel–Haenszel. EORTC QLQ-C15-PAL=European Organisation for Research and Treatment of Cancer quality of life QLQ-C15-PAL. EORTC QLQ-BM22=the bone EORTC quality of life metastases module. DSQ=dexamethasone Symptom Questionnaire. *The number of patients with quality of life data at baseline; data not available for all patients at day 10.

Table 5: **Quality of life at baseline and day 10**

and 35 partial responses), as did 52 patients in the placebo group (32 complete responses and 20 partial responses). The proportion of patients achieving an overall response was not significantly different between groups (43% in the dexamethasone group and 35% in the placebo group; p=0·15). Whether a patient developed pain flare or not was not predictive of response to radiation in either group.

In the dexamethasone group, three patients had biochemically identified hyperglycaemic events, but no patients developed any clinical symptoms needing admission to hospital (table 4). All three patients stopped study medication as a result of the hyperglycaemic events. Two of these three patients had pre-existing diabetes, and one patient developed biochemical hyperglycaemia when put on dexamethasone 16 mg/day during radiation treatment for brain metastases. No serious adverse events were reported at the 6-week follow-up in both groups. 26 deaths (11 in the dexamethasone group and 15 in the placebo group) occurred in the study period. 24 of these deaths were due to cancer (ten in the dexamethasone group and 14 in the placebo group), two were due to unknown causes, and no patients died of causes related to the study medication.

The compliance rates for the quality of life assessment using QLQ-C15-PAL-15, QLQ-BM-22, and DSQ were similar in the two groups: 99% at baseline, 84% at day 10, and 82% at day 42 for both the dexamethasone and placebo groups. Patients in the dexamethasone group had significantly reduced nausea and functional interference, and improved appetite at day 10 compared with baseline. At day 10, a larger proportion of patients in the dexamethasone group than in the placebo group had significantly reduced nausea and functional interference, and improved appetite. At day 42, patients in the dexamethasone group were also slightly improved in physical domain (p=0·05) and insomnia (p=0·09; table 5) compared with patients in the placebo group. The groups did not differ significantly in DSQ scores at baseline or at day 10 (table 4). At day 42, significantly more patients reported high depression scores in the dexamethasone group (seven [8%] of 93) than in the placebo group (one [1%] of 88; p=0·04).

Discussion

Compared with placebo, dexamethasone reduced incidence of pain flare in our study and was accompanied by a reduction in nausea and improvement in functional activity and appetite, without serious adverse effects. Nine previous studies[3–9,11,15] have documented the incidence of pain flare in patients treated with palliative radiotherapy to painful bone metastases (table 6). The incidence of pain flare is 30–40%. Hird and colleagues[10] interviewed patients who developed pain flare. Patients reported that pain flare interfered with daily activities and general functioning, and was associated with anxiety and worry about the success of treatment. 85% of patients preferred prophylaxis for management of pain flare to an increase in analgesic use when pain flare occurred, leaving them at risk of associated adverse events including dry mouth, drowsiness, and constipation.[10]

Dexamethasone has been shown to be a feasible prophylactic against pain flare. Two pilot studies[11,15] investigating use of 8 mg dexamethasone before treatment for prophylaxis in 33 patients, and 8 mg dexamethasone before radiotherapy and for 3 days consecutively after radiotherapy in 41 patients, reported that pain flare incidence was reduced to 22–24%.

Yousef and El-Mashad[24] randomised 120 patients with vertebral metastases treated with 30 Gy in ten fractions to receive a 24-h infusion of methylprednisone (5 mg/kg) or normal saline infusion the day before initiation of radiotherapy. Four (7%) patients in the steroid group and 12 (20%) patients in the placebo group had pain flare (p<0·05). The mean duration of pain flare was 1·25 days in the steroid group and 3·75 days in the placebo group. However, the dose of methylprednisolone in their study was much higher than doses typically used for pain management. A 5 mg/kg dose in a 70 kg patient converts to a dexamethasone dose of 66 mg/day. Their reported pain flare incidence was lower than those reported in the literature. With 2-week radiation and the scientific literature suggesting that pain flare often occurs during the first 5 days after the radiation, the efficacy of a single infusion with a biological half-life of 18–36 h to cover the entire 3 weeks at risk would be questionable. Additionally, we anticipated that oral treatment strategies would be necessary to enable adoption, rather than admitting patients to hospital for a 24-h infusion.

We postulated that the incidence of pain flare for days 0–10 in the intention-to-treat analysis would decrease from 45% to 28% with dexamethasone prophylaxis, a difference of 17%. However, the between-group difference was 8·9% in the intention-to-treat and 11·7% in the sensitivity analyses. The sensitivity analysis for pain flare incidence favouring placebo did not show any significant difference between the two groups in pain flare incidence. The number needed to treat (NNT) increased from our initial hypothesis of six to an observed NNT of 11 in the intention-to-treat analysis and nine in sensitivity analysis. The relative risk of reduction of pain flare with dexamethasone compared with placebo in days 0–10 would be 25% in the intention-to-treat and 40% in the sensitivity analyses. Despite this higher NNT, our observations of reduced incidence of pain flare and an associated improvement in quality of life scores in nausea, functional interference, and appetite lead us to conclude that prophylactic use of dexamethasone should be adopted as standard of care for patients receiving palliative radiotherapy for treatment of painful bone metastases.

Bone metastases are very prevalent, and many patients with bone metastases need palliative radiotherapy.

	Study design	Population	Incidence of pain flare (%)	Time to pain flare, duration of pain flare	Intervention with dexamethasone
Kirkbride and Aslanidis (1996)[7]	Prospective; monitored short-term toxicity and pain relief at 2 weeks and 1 month after treatment	n=16; 12 Gy in one fraction	5 (31%) of 16 patients	Not reported	NA
Foro et al (1998)[9]	Prospective, randomised study comparing response rates; pain relief assessed with a visual analogue scale every 3 months for 1 year	8 Gy in one fraction, 15 Gy in three fractions, or 30 Gy in ten fractions	15% of patients receiving 8 Gy in one fraction	Not reported	NA
Roos et al (2005)[8]	Prospective; flare effect defined as temporary increase in pain within a week of commencing radiation treatment, and graded on a 3 point numerical scale (1=mild, 2=moderate, 3=severe)	n=272; randomised to receive 8 Gy in one fraction or 20 Gy in five fractions	Overall 20 (10%) of 194	Within 1 week	NA
Chow et al (2005)[5]	Prospective; medications and pain score (0–10 score) collected at baseline, daily during treatment, and daily for 10 days after treatment	n=88; 8 Gy in one fraction or 20 Gy in five fractions	14% on day 1 and 2 for patients who received 8 Gy in one fraction; 15% on day 1 for patients who received 20 Gy in five fractions; overall range of pain flare 2–16%	14% at day 1 and 16% at day 2 after treatment	NA
Loblaw et al (2007)[3]	Prospective; medications recorded, and pain measured using the Present Pain Intensity at baseline, in a daily diary for the first week after treatment, and at 14 days, 1 month, and 3 months after treatment	n=44; randomised to receive 8 Gy in one fraction or 20 Gy in five fractions	41%	Median duration of 3 days	NA
Chow et al (2007)[11]	Prospective; medications and pain score recorded using the BPI at baseline, and daily for 10 days after treatment	n=33; 8 Gy in one fraction	24% had pain flare during 10-day follow-up	Of the 24% who had pain flare, two patients had a 1-day pain flare on day 3, three patients had 1-day pain flare on day 7, three had prolonged pain flare (one on days 2–4, one on days 4–6, and one on days 3–8)	Two tablets of 4 mg dexamethasone by mouth 1 h before radiation treatment
Hird et al (2009)[4]	Prospective; pain and medications were recorded with the BPI at baseline and then with a daily diary during treatment and 10 days after completion of treatment	n=111; 8 Gy in one fraction or multiple fractions	Overall incidence of 40%; for patients treated with 8 Gy in one fraction, incidence was 39%, and 41% for those treated with multiple fractions	Pain flare occurred within first 5 days after radiation in 80% of patients	NA
Hird et al (2009)[15]	Prospective; pain, medications, and quality of life recorded through the BPI and EORTC QLQ-C30 at baseline, daily for 10 days, and at 6 weeks after, treatment	n=41; 8 Gy in one fraction	22% experienced a total of 11 pain flares	Median duration of pain flare was 1 day, and these occurred on days 1, 2, and 4; two separate 3-day pain flares occurred on days 6 and 8. Six (55%) of 11 pain flares occurred on day 5	Dexamethasone 8 mg orally at least 1 h before radiotherapy and 8 mg daily for 3 days consecutively after treatment
Gomez-Iturriaga et al (2014)[6]	Prospective; worst pain scores and analgesic consumption were measured before, daily during, and 10 days after treatment	n=94; multiple fractions	45%	Median duration of 2 days; most (88%) pain flares occurred in days 1–5	NA

NA=not applicable. BPI=Brief Pain Inventory.

Table 6: **Summary of the scientific literature**

16 898 courses of radiation were delivered to 8601 patients with bone metastases during 2007–11 in British Columbia (4225 courses per year).[25] Between 1984 and 2012, 97 150 patients in Ontario received 186 694 radiation courses to bone metastases (6668 courses per year).[26] Using the US National Cancer Database to identify patients treated for osseous metastases from breast, prostate, and lung cancer, 24 992 patients were treated with radiation during 2005–11 for bone metastases (4165 patients per year for the three primary cancer sites).[27] A Norwegian national registry-based study[28] reported that 14 380 radiation courses were delivered to bone metastases in 1997–2007 (1438 courses per year). A retrospective review[29] of radiotherapy databases at two large Australian institutions identified 8211 radiation courses for bone metastases in 5683 patients for 1997–2009 (684 courses per year). Despite an NNT estimate of 9–11, many patients will benefit from dexamethasone prophylaxis of radiation-induced pain flare in treatment of bone metastases. Additionally, dexamethasone is a co-analgesic.

Dexamethasone reduced nausea and functional interference, and improved appetite, at day 10 compared with baseline, although these results should be interpreted with caution because several comparisons are made. Radiation oncologists often prescribe

dexamethasone (typically 8–16 mg/day) to patients with brain metastases undergoing whole brain radiation during the entire period of radiation treatment without serious adverse effects.[30,31] Short-term use of dexamethasone at 8 mg/day for prophylaxis of radiation-induced pain flare in treatment of bone metastases should not pose a challenge, provided caution is taken in patients at risk of dexamethasone-induced hyperglycaemia, such as those with pre-existing diabetes. Whether dexamethasone at 16 mg/day would have further reduced incidence of pain flare is unknown.

We excluded patients with previous radiation to the study site (or sites). However, some patients might have been treated before to other sites of metastatic involvement, with or without having experienced pain flare. In theory, anticipatory effects might affect clinical course later during disease trajectory, similar to anticipatory nausea in chemotherapy. Additional radiological features or comorbidities might be risk factors for pain flare. Many patients have bone metastases plus osteoporosis, compression fractures, degenerative spine or hip disorders, narrowing of the spinal canal, or neuroforamina. Some of these disorders might predispose the patient to pain from increasing swelling. Additional research into these potential predisposing factors is warranted.

Bone metastases are very prevalent in patients with advanced cancer. Radiation therapy is effective in treatment of painful bone metastases, but with an incidence of 30–40% acute pain flare; we have shown that dexamethasone is efficacious in prophylaxis of radiation-induced pain flare in our study.

Contributors

EC, RMM, KD, AN, AF, CFW, JSYW, MB, CD, and RKSW were responsible for the study design. EC, AN, PC, PW, SA, JK, ARD, AM, AF, JSYW, KD, MB, and RKSW accrued recruited patients at the participating centres and assisted in data collection. Data analysis and major manuscript writing were completed by EC, RMM, KD, AF, CFW, JSYW, MB, CD, and RKSW. All authors assisted in manuscript review and appraisal.

Declaration of interests

AN is on advisory boards for Sanofi, Janssen, and Astellas, and received a grant from AstraZeneca, and congress support from Sanofi. All other authors declare no competing interests.

Acknowledgments

This study was supported by the NCIC CTG's programmatic grant from the Canadian Cancer Society Research Institute. We thank Bingshu Chen and Dongsheng Tu for help with statistical analysis, all the patients who participated, and the research teams.

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