Dexamethasone Role for Pain Flare Prevention after Palliative Bone Irradiation: A Single Institutional Randomized Trial

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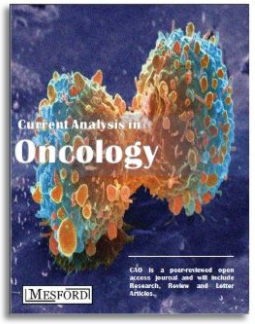

Abstract:

Background: Bone metastasis is the most common cause of cancer-related pain. Radiotherapy is the gold standard palliative treatment of painful bone metastases. However, pain flare is a possible adverse reaction. Dexamethasone is an effective drug to manage the pain flare. This trial will study the dexamethasone role to prevent pain flare, to determine the optimal dose schedule and to evaluate the dexamethasone related complications

Methods: From July 2016 to June 2018, 311 eligible patients with painful bone metastases entered into this three-armed, randomized study. All patients received a single 8 Gy dose of radiotherapy. Group I did not receive dexamethasone. Group II received 8 mg dexamethasone once daily administered: the day before radiotherapy, one hour prior to radiotherapy (the same day of radiotherapy) and one day after completing radiotherapy. Group III received once daily 8 mg dexamethasone given: one hour before irradiation and for two days after completing irradiation.

Results: Of the Group I (110 patients), 45 (40.9%) patients experienced pain flare. Of the Group II (101 patients) and Group III (100 patients), 18 (17.8%) and 16 (16%) patients experienced pain flare. The difference in the incidence of pain flare between the two groups which received steroid and the group which did not receive was statistically significant (P = 0.002), but there was no difference between the two groups which received different schedule of dexamethasone. No dexamethasone related complications were reported.

Conclusion: Dexamethasone significantly decreases the pain flare incidence after palliative bone irradiation. Dexamethasone, at three doses of 8 mg, is a well-tolerated and safe schedule. Three doses schedule of dexamethasone may be considered for patients who undergo palliative radiotherapy for painful bone metastases and have no contraindication for this treatment.

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Bone metastases, Palliative irradiation, Dexamethasone, Pain flare.

INTRODUCTION

Bone metastasis is the most common cause of pain in cancer patients that requires treatment [1, 2].

Over the last decade, external beam radiotherapy has been confirmed by numerous prospective randomized trials as being highly effective in pain relief of painful bone metastases [3]. Thus, refining this treatment is worthwhile. Single fraction radiotherapy of 8 Gray is the gold standard palliative treatment of painful bone metastases, with a pain response rate of more than 60% [4].

Pain flare is unpleasant adverse reaction of palliative radiotherapy of painful bone metastases. Chow et al. defined pain flare as a two-point increase of the worst pain score on an 11-point rating scale, compared to baseline, with the same analgesic dose, or a 25% increase in analgesic dose with the same worst pain score [5].

One study showed that; pain flare incidence was 40% .The majority of the pain flares occurred during the first five days after treatment with 1.5 days median duration. Multiple pain flare occurred in 25% of patients [6].

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In Loblaw trial, the incidence of pain flare was 41% and the difference between single and multiple fractions (57% and 24% respectively) was statistically significant [7].

Patients who had a pain flare experienced a negative effect on quality of life [8]. Most patients increased their pain medication to manage their pain flare with the possible increasing of their cost and side-effects, however, this does not prevent the occurrence of this phenomenon altogether. So the need for prevention of this phenomenon instead of managing it is indicated.

Dexamethasone is an effective drug to manage the pain flare through decreasing the operiostium edema of the irradiated bone. In a few phase II studies that have been completed, this medication succeeded in reducing the incidence of pain flare by 50% from around 40% to 20% [9, 10].

Therefore, this trial will study the dexamethasone role to prevent pain flare, to determine the optimal dose schedule and to evaluate the tolerability of dexamethasone.

MATERIALS AND METHODS

This trial is three-armed, double-blind, placebo controlled randomized trial. It was conducted at clinical oncology and nuclear medicine department from July 2016 to June 2018. Written informed consent was obtained from all patients before registration. This study was authorized by our institutional review board.

PATIENTS

This study included 311 patients with painful bone metastases were randomly distributed between the three arms.

Inclusion criteria: Patients aged ≥ 18 years who have primary solid malignancy with uncomplicated painful bone metastases, , indication for single shot radiotherapy, pain intensity on a numeric rating scale of ≥ 2 as used in the Brief Pain Inventory (BPI) [11], and able to follow instructions.

Exclusion criteria included hematological malignancies, concurrent use of steroid medication or concurrent use of chemotherapy. Patients with contraindication to steroids such as uncontrolled hypertension or diabetes were not eligible for participation. Indication of irradiation of multiple sites and previous irradiated sites for painful bone metastases were not eligible for participation. Those with previous pathological fractures at the study area or with high-risk lesions for pathological fractures were excluded.

TREATMENT REGIMENS

We divided patients into 3 groups; all patients received a single 8 Gy dose of radiotherapy. Group I will not receive dexamethasone. Group II received 8 mg dexamethasone once daily administered: the day before radiotherapy, one hour prior to radiotherapy (the same day of radiotherapy) and one day after completing radiotherapy. Group III will receive 8 mg dexamethasone once daily given one hour before to irradiation and for two days after radiation therapy.

Questionnaire was filled out by patients at baseline, then daily to day 10 and a final one at day 30. The patients were questioned about any changes in their pain.

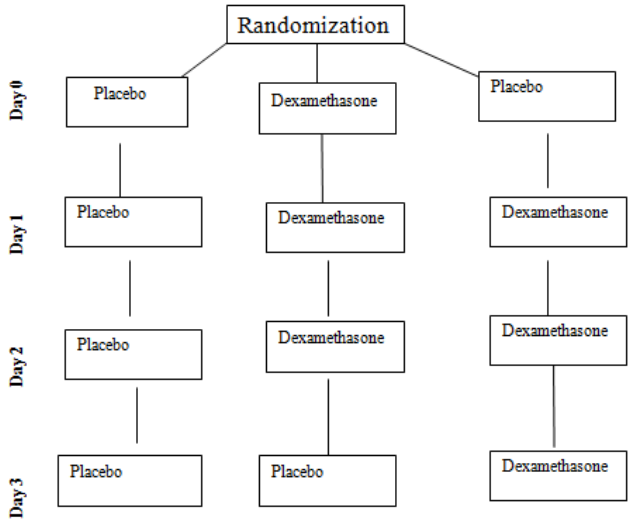
Pain rate (0-10), the Brief Pain Inventory (BPI) and analgesic score were performed to each patient. patients were categorized according to BPI as follows: absence of pain category was 0, mild pain category was 1-4, moderate pain category was 5-6, and severe pain category was 7-10 [12] and according to analgesic score as follows: score 0 was no analgesia, score 1was non-opioids, score 2 was weak opioids, and strong opioids were given a score of 3 [13].

EVALUATE DEXAMETHASONE SIDE EFFECTS

Dexamethasone side effects (fluid retention, increased appetite, mood changes, insomnia, skin rash, stomach upset, hypertension, and hyperglycemia) were evaluated weekly for 4weeks (day 7, 14, 21, 28).

SAMPLE SIZE CALCULATION:

To reduce pain flare by 50% (from 40 to 20%), 100 patients will be required in each arm. To count for possible loss of follow up, 10% (10 patients) will be added in each arm, giving a total of 110 patients per arm. So, to perform this study, 330 patients are needed.



STATISTICAL ANALYSIS PLAN

Patient characteristics were reported as frequencies and proportions. Comparison of occurrence of pain flare and factors which could possibly affect its development between the three arms was assessed using the Chi-Square test. Multivariate cox regression analysis was used to identify prognostic factors. Significance was $P \leq .05$ for all statistical tests.

RESULTS

Patient's characteristics of 311 cases are shown in Table **1**. They were 161 (51.8%) males and 150 (48.2%) females. Median age was 54 years (range: 28 to 74). ECOG performance scores

Table 1. Patients Characteristics.

Characteristics	Group II (n=101)	Group I (n=110)	Group III(n=100)	*P*-value
Gender				
Male	60(54.6%)	52(51.5%)	49(49%)	0.863
Female	50(45.4%)	49(48.5%)	51(51%)	
Age (years)				
Range	28-74	26-72	24-73	0.761
Median	56	53	55	
PS (ECOG)				
1	40(36.4%)	44(43.6%)	47(47%)	0.632
2	70(63.6)	57(56.4%)	53(53%)	
Primary tumor				
Breast	50(45.5%)	41(40.5%)	47(47%)	
Prostate	22(20%)	30(29.7%)	28(28%)	
Bladder	22(20%)	10(9.9%)	10(10%)	
MUO	4(3.6%)	8(7.9%)	5(5%)	0.765
Lung	3(2.75%)	4(4%)	4(4%)	
Sarcoma	3(2.75%)	4(4%)	3(3%)	
HCC	3(2.75%)	2(2%)	2(2%)	
Colon	3(2.75%)	2(2%)	1(1%)	
Site of irradiated metastases				
Vertebrae	33(30%)	30(29.7%)	27(27%)	
Pelvis	22(20%)	21(20.7%)	24(24%)	0.326
Extremities	55(50%)	50(49.6%)	49(49%)	
Pain Score (0-10)				
Moderate (5-6)	60(54.6%)	44(43.6%)	48(48%)	
Severe (7-10)	50(45.4%)	57(56.4%)	52(48%)	0.514
Analgesic score				
1 (NSAID)	11(10%)	21(20.7%)	9(9%)	
2 (Weak opioids)	49(44.5%)	30(29.7%)	31(31%)	0.473
3 (Strong opioids)	50(45.5%)	50(49.6%)	60(60%)	

were: 1 in 131 (42.1%) patients and 2 in 180 (57.9%) patients. Breast cancer was most common primary tumor site (44.4% of patients). Other sites were the bladder (13.5%), metastases of unknown origin MUO (5.5%), prostate (25.7%), bronchogenic carcinoma (3.5%), sarcoma (3.2%), hepatocellular carcinoma (2.3%) and colon cancers (1.9%).

Extremities were the most frequently irradiated metastatic site in 154 (49.5%) followed by the vertebrae 100 (32.1%), and pelvic bones (25.2%). At presentation, Pain score was moderate in 48.7% and severe in 51.3% of patients. Analgesic score was score 1 in 13.2%, score 2 in 35.4%, and score 3 in 51.4% of patients.

The incidence of pain flare in each group is shown in Table **2**. In Group I, 45 (40.9%) patients experienced pain flare that relieved in 40 (89%) patients within the first week after radiotherapy. Five patients had a prolonged pain flare, which began subsided on day 8 post-radiotherapy. Of the Group II and Group III patients, 18 (17.8%) and 16 (16%) experienced pain flare. In all these patients, pain flare relieved within five days post-radiotherapy.

Table 2. Patients who Experienced Pain Flare in Group I *vs* Group II, III.

Group I No (%)	Group II No (%)	No (%) Group III	P-value
45 (40.9%)	18 (17.8%)	16 (16%)	0.002

The difference in the incidence of pain flare between the two groups which received steroid and the group which did not receive it was statistically significant (P=0.002), but there was no difference between the two groups which received different schedule of dexamethasone, which indicated the effectiveness

of steroid taken with radiotherapy in decreasing the incidence of pain flare (tables **2, 3**). Patients who received dexamethasone did not experience any complications.

Table 3. Patients who Experienced Pain Flare in Group II *vs.* Group III.

Group II No (%)	No (%) Group III	P- value
18 (17.8%)	16 (16%)	0.865

Factors which may affect the development of pain flare were assessed; gender, age, performance status, primary tumor, irradiated site, pain score, or analgesic score did not significantly affect the development of pain flare, but the only factor that affected the development of pain flare was dexamethasone use and the difference was statistically significant (Table **4**).

DISCUSSION

Pain flare incidence is up to 40% of patients with bone metastases treated by palliative radiotherapy [6, 7].

Limited data on bone pain flare has been published. Chow et al. evaluated occurrence of pain flare after painful bone metastases irradiation in 88 patients and found that 12 of 88 patients (14%) had pain flare on day 1; this study confirmed the occurrence of pain flare following radiotherapy in the treatment of painful bone metastases [5].

In a multicentric Canadian trial [6], the incidence of pain flare was 40% (44/111) of patients who received single and multiple fractions. The incidence of pain flare was 39% (27/70) of patients treated with a single 8 Gy whereas 41% (17/41) who received 20 Gy/5 fractions. In the present study, there was a similar pain flare incidence (40.9%, 45/110) observed in Group I patients that received no dexamethasone.

Yousef *et al.* found that pre-emptive methylprednisolone infusion (5 mg/kg) the day just before initiation of radiotherapy significantly reduced pain flare and improves functional motor status after short-term radiotherapy in patients with vertebral metastases [14] , suggesting that usage of steroid may decrease pain flare incidence .

Chow study [9], included 33 patients received a single dose of 8 mg dexamethasone that was given one hour before the single

Table 4. Multivariable Cox Proportional Hazard Models for Pain Flare.

	HR (95% CI)	P Value
Gender Male Female	1.36(0.94-1.92)	0.31
Age (years) <55 ≥55	0.73(0.65-1.82)	0.25
PS (ECOG) 1 2	0.62(0.49-1.78)	0.12
Primary tumor Breast Non-breast	1.01 (0.66 – 1.53)	0.95
Site of irradiated metastases Vertebrae Pelvis Extremities	0.49 (0.14 – 1.62)	0.42
Pain Score (0-10) Moderate (5-6) Severe (7-10)	0.94(0.58-1.66)	0.41
Analgesic score 1 (NSAID) 2 (Weak opioids) 3 (Strong opioids)	0.98(0.68-1.56)	0.11
Dexamethasone use No Yes	2.49 (1.39 – 4.48)	0.002

fraction radiotherapy, showed pain flare incidence of 24%. Dexamethasone was well tolerated. However most of the pain flares occurred after 24 hours after radiotherapy, suggesting that a longer treatment time might be useful.

In another study [10], included 41 patients received 8 mg dexamethasone before single fraction palliative radiotherapy and then daily for three consecutive days showed an overall pain flare incidence of 22%, with a median duration of one day. This study supports long course of dexamethasone may decrease pain flare incidence.

In Chow randomized trial , 298 patients were randomly allocated to receive either 8 mg dexamethasone or placebo taken orally at least 1 h before the start of radiation treatment and then daily for 4 days after radiotherapy. This study showed that dexamethasone reduced the incidence of pain flare from 35% to 26% (p= 0.05) [15].

In a recent randomized study , included 295 patients who allocated to receive: [group A] placebo before start of radiotherapy (day 1) and then for 3 days afterwards, [group B] 8 mg dexamethasone (day 1) followed by 3 days of placebo, or [group C] four daily 8 mg doses of dexamethasone (days 1-4). Pain flare incidence was 50% intention-to-treat (ITT) or 25% sensitivity analyses (SA) for group A, 34% or 16% for group B, and 44% or 25% for group C (ITT; p= 0.06 and SA; p= 0.15). This trial concluded that no significant effect of dexamethasone on the incidence of pain flare after palliative radiotherapy for painful bone metastases [16].

In the present study, the pain flare incidence observed in 16.9% (34/201) of patients from the group II and III who received dexamethasone. This decreased incidence of pain flare in this study may be due to the relatively prolonged dexamethasone intake.

Our results showed a statistically significant decrease (P=0.002) in the incidence of pain flare between the two groups which received steroid and the group which did not receive it, but there was no difference between the two groups which received different schedule of dexamethasone , which indicated that steroid taken with radiotherapy effectively decreased the incidence of pain flare .These dexamethasone schedules and doses were safe and well tolerated as no steroid toxicity was reported.

Any of studied factors significantly affected the development of pain flare, but the only factor that affected the development of pain flare was dexamethasone use.

CONCLUSION

Dexamethasone significantly decreases the incidence of pain flare after palliative radiotherapy for painful bone metastases. Dexamethasone, at three daily doses of 8 mg, is a well-tolerated and safe schedule. Three doses schedule of dexamethasone may be considered for all adult patients who undergo palliative radiotherapy for painful bone metastases and have no contraindication for this treatment.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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