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The Effect of Systemic Steroids on the Incidence of Bone Pain Flare with Palliative Irradiation

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Abstract

Background: A significant number of patients who receive palliative irradiation for painful bone metastases experience pain flare, defined as a distressing transient increase in pain not immediately controlled by additional analgesics. This pain is postulated to be due to edema at the onset of radiotherapy. This study aims to compare the incidence of bone pain flare among patients who receive steroid prophylaxis to those with no prophylaxis treatment.

Methods: From June 2011 to June 2013, 147 eligible patients with painful bone metastases entered into this phase 3 prospective study. We divided patients into two groups. Group A received 8 mg dexamethasone one hour prior to irradiation during the treatment time and for three days afterwards. Group B received no prophylaxis treatment. All patients received radiotherapy at a dose of 2000 Gy/5 fractions. The development of flare was recorded in each group and several factors were examined to determine the presence of an influence on this incidence.

Results: Group A included 68 patients, 11 (16.2%) of whom developed bone pain flare while group B comprised 79 patients, 30 (38%) with bone pain flare. These results indicated that steroid prophylaxis made a statistically significant difference in decreasing pain flare incidence (P=0.0033). No steroid related complications were reported by any of the patients. None of the factors assessed showed a statistically significant effect on flare development (P>0.05).

Conclusion: Administration of 8 mg of dexamethasone an hour prior to irradiation for the treatment period and three days afterwards is effective in significantly decreasing the incidence of pain flare. Dexamethasone is well tolerated and may be recommended for all adult patients who undergo palliative bone irradiation who have no contraindication to this treatment. Larger phase 3 randomized trials are needed to confirm these findings.

Keywords: Dexamethasone, Pain flare, Bone metastases, Palliative radiotherapy

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Introduction

Bone metastasis is a frequent condition seen in oncology practices with a rising incidence due to longer survival of cancer patients.[1] It is the most common cause of cancer-related pain and the most frequent symptom that requires treatment in cancer patients.[2] The primary goal of palliative treatment is to improve quality of life and alleviate patient suffering. Management of bone pain includes analgesics, local treatment as radiation and/or surgery, and systemic treatment that includes hormones, chemotherapy, radioisotopes, and agents such as bisphosphonates.[3] Over the last decade, external beam radiotherapy has been confirmed by numerous prospective randomized trials as being highly effective in pain relief and it is often the pillar of local pain relief.[4] Thus, refining this treatment is worthwhile.

Pain flare, which is a temporary pain increase that occurs immediately or shortly after commencing radiation treatment, has been reported by a significant number of patients.[5] It is hypothesized that pain flare results from edema induced by radiotherapy.[6] Pain flare is defined as a two-point increase of the worst pain score on an 11-point scale of 0 (no pain) to 10 (worst imaginable pain) compared to baseline without a decrease in analgesic intake or as a 25% increase in analgesic intake without a decrease in the worst pain score after radiotherapy according to the International Bone Metastases Consensus Guidelines. Additionally, the self-perceived pain score is required to return to baseline to distinguish it from progressive pain.[5] This phenomenon impacts patients for one to several days during and after treatment.[7] Patients are often directed to take 'breakthrough' pain medication at the onset of pain flare, however, this does not prevent the occurrence of this phenomenon altogether.[8]

Dexamethasone has shown promise in combating this phenomenon. In a few phase II studies that have been completed, this medication succeeded in reducing the number of patients who experienced pain flare from around 40% to 20%.[9] The aim of this phase 3 study was to compare the incidence of pain flare in patients administered 8 mg of dexamethasone one hour before radiotherapy and once daily for three days after completion of a 2000 Gy/5 fraction radiotherapy schedule to patients palliated with the same schedule without steroid prophylaxis, with the intent to determine its efficacy in preventing bone pain flare.

Materials and Methods

From June 2011 to June 2013, 147 eligible patients with painful bone metastases treated at the Radiation Oncology Department of the South Egypt Cancer Institute were enrolled in this phase 3 prospective study. Informed consent was obtained from the patients after approval of the protocol by an Institutional Review Board of South Egypt Cancer Institute, Assiut University. Inclusion criteria were: age above 18 years, histologically or cytologically proven malignancy and the presence of painful bone metastases documented by radiological imaging within six months prior to commencing the treatment. Patients were required to have an ECOG performance status of 2 or less and the ability to state their pain score at the most painful bony metastatic sites planned for radiotherapy. Patients were required to have a baseline pain score of 2 or more on a scale of 0-10 as used in the Brief Pain Inventory (BPI)[10] at all metastatic sites planned for radiotherapy. Exclusion criteria included hematological malignancies (leukemia, Hodgkin or non-Hodgkin lymphoma or plasma cell dyscrasia, and multiple myeloma) as steroids constitute anticancer treatment for these patients. Concurrent use of steroid medication within seven days of commencing radiotherapy, other than topical or inhaled preparations was not allowed. Patients with medical contraindication to steroids such as uncontrolled diabetes or hypertension were not eligible for participation. Those with previous pathological fractures at the study area or with radiological evidence of high-risk lesions for pathological fractures in the femora, tibiae, fibula, humeri, radii or ulnae at the site(s) to be treated and followed in the study (lytic lesions >3 cm or >50% cortical erosion of bone diameter)

Table 1. Patients' characteristics.

Characteristics	Group A (n=68)	Group B (n=79)	Total (n=147)	*P*-value
Gender				
Male	30 (44.1%)	35 (44.3%)	65 (44.2%)	0.928
Female	38 (55.9%)	44 (55.7%)	82 (55.8%)	
Age (years)				
Range	26-74	23-71	23-74	
Median	55	54	55	
PS (ECOG)				
1	25 (36.8%)	29 (36.7%)	54 (36.7%)	0.963
2	43 (63.2%)	50 (63.3%)	93 (63.3%)	
Primary tumor				
Breast	33 (48.5%)	37 (46.8%)	70 (47.6%)	0.838
Non-breast	35 (51.5%)	42 (53.2%)	77 (53.4%)	
•Bladder	7 (10.3%)	12 (15.2%)	19 (12.9%)	
•MUO	9 (13.2%)	8 (10.1%)	17 (11.6%)	
•Prostate	4 (5.9%)	7 (8.9%)	11 (7.5%)	
•Lung	4 (5.9%)	6 (7.6%)	10 (6.8%)	
•Sarcoma	5 (7.4%)	3 (3.8%)	8 (5.4%)	
•HCC	2 (2.9%)	4 (5.1%)	6 (4.1%)	
•Colon	4 (5.9%)	2 (2.5%)	6 (4.1%)	
Site of irradiated metastases				
Vertebrae	31 (45.6%)	38 (48.1%)	69 (46.9%)	0.514
Pelvis	20 (29.4%)	17 (21.5%)	37 (25.2%)	
Extremities	17 (25.0%)	24 (30.4%)	41 (27.9%)	
Pain Score (0-10)				
Moderate (5-6)	27 (39.7%)	36 (45.6%)	63 (42.9%)	0.473
Severe (7-10)	41 (60.3%)	43 (54.4%)	84 (57.1%)	
Analgesic score				
1 (NSAID)	9 (13.2 %)	14 (17.7%)	23 (15.6%)	0.326
2 (Weak opioids)	29 (42.6%)	36 (45.6%)	65 (44.2%)	
3 (Strong opioids)	30 (44.1%)	29 (36.7%)	59 (40.1%)	

were excluded. Previous radiotherapy to the sites treated and followed in the study was not allowed. Patients planned to receive cytotoxic chemotherapy during the on-study period (from the first day of radiotherapy until ten days after the end of treatment) were not allowed to participate in this trial.

Radiation doses to the vertebrae were prescribed to the mid-vertebral body, with inclusion of one vertebra above and below the clinically apparent lesion. A mid-plane dose was prescribed for opposing fields, taking into account the normal tissue tolerance of the structures included in the treatment volume. Long bone metastases were treated with at least a 2 cm margin proximal and distal to the clinically evident lesion. Patients were treated with anterior/posterior fields or a single direct field. They were grouped into two groups - both received 2000Gy/5 fractions. Group A received two, 4 mg dexamethasone tablets once daily administered one hour prior to radiotherapy and for three days after completing radiotherapy. Group B received no prophylaxis treatment. Primary endpoint of the study was to determine

the change in pain flare incidence among those who received dexamethasone compared to those who received no prophylaxis treatment. A secondary endpoint was to assess the tolerability of dexamethasone at this dose for this time period. The patients were questioned about change in pain, requested to avoid changes in analgesic intake, report changes if they occurred, and were asked to rate their pain from 0-10 for each day from the start of the radiation treatment until ten days after completion of treatment. The BPI worst pain score categorization was as follows: (0) absence of pain, (1-4) mild pain, (5-6) moderate pain, and (7-10) severe pain.[9] For each patient, an analgesic score was assigned according to the ongoing analgesia received by the patient. No analgesia was scored as (0), non-opioids were given a score of (1), weak opioids (i.e., codeine) were scored as (2), and strong opioids (i.e., morphine, fentanyl) were given a score of 3.[11] Statistical analysis was performed with GraphPad Prism 5, employing the chi square test to compare percentages in the two groups.

Results

Group A consisted of 68 patients and Group B included 79 patients. The general characteristics of the patients were fairly homogenous in the two groups (Table 1). There were 65 (44.2%) males and 82 (55.8%) females who participated in this study. Median age of the participating patients was 55 years (range: 23 to 74). ECOG performance scores were: 1 in 54 (36.7%) patients and 2 in 93 (63.7%) patients. The most common primary tumor site was the breast in 70 (47.6%) patients. Other sites were the bladder (12.9%), metastases of unknown origin MUO (11.6%), prostate (7.5%), bronchogenic carcinoma (6.8%), sarcoma (5.4%), hepatocellular carcinoma HCC (4.1%) and colon (4.1%) cancers. Vertebrae comprised the most frequently irradiated metastatic site, accounting for 46.9%, followed by the extremities (27.9%), and pelvic irradiation (25.2%). Pain score, at presentation, was moderate in 42.9% and severe in 57.1% of participants. Analgesia prior to the start of radiotherapy that continued until ten days after completion was in the form of NSAIDs for 15.6% of patients and scored as 1, 44.2% received weak opioids with a score of 2, and 40.1% were on strong opioids.

Table 2. Patients who experienced pain flare.

Group A (n=68)	Group B (n=79)	*P*-value
No (%)	No (%)	
11 (16.2)	30 (38.0)	0.0033

The patients in each group were followed up from the first day of radiotherapy until ten days after completion of radiotherapy. Table 2 shows the assessed incidence of pain flare in each group. Of the 68 Group A patients, 11 (16.2%) experienced pain flare. Of these, 10 (90%) had increased pain that returned to baseline during radiotherapy treatment and in the five days after treatment. Only one patient had a prolonged pain flare that lasted five days, which began on day three of radiotherapy and subsided on day seven post-radiotherapy. Of the group that received no steroids (n=79), 30 (38%) experienced pain flare. The majority, 26 (86.7%), had their self-perceived pain increase back to baseline within the first five days post-radiotherapy. The remainder of patients had their pain return to baseline from six to ten days after radiotherapy. The difference in the incidence of flare in the two groups was statistically significant (P=0.0033), as shown in Table 2, which indicated that 8 mg dexamethasone taken one hour prior to each radiotherapy session and for three days after completion effectively decreased the incidence of pain flare. No dexamethasone related complications were reported by any of the patients.

Factors which could possibly affect the development of pain flare were analyzed. There were no statistically significant differences (P>0.05) in the numbers of patients who experienced pain flare in terms of gender, age, performance status, primary tumor, site irradiated, pain score, or analgesic score in either group as illustrated in Table 3.

Table 3. Effect of different factors on the development of pain flare.

Factor	Group A Flare/no flare (%)	*P*-value	Group B Flare/no flare (%)	*P*-value
Gender				
Male	4/30 (13.3%)	1.000	16/35 (45.7%)	0.247
Female	6/38 (15.8%)		14/44 (31.8%)	
Age (years)				
<55	4/34 (11.8%)	0.512	12/39 (30.8%)	0.260
≥55	7/34 (20.6%)		18/40 (45.0%)	
ECOG PS				
1	4/25 (16%)	0.976	11/29 (37.9%)	0.995
2	7/43 (16.3%)		19/50 (38.0%)	
Primary tumor				
Breast	6/33 (18.2%)	0.663	17/37 (45.9%)	0.171
Non-breast	5/35 (14.3%)		13/42 (31.0%)	
Site irradiated				
Vertebrae	5/31 (16.1%)	0.983	14/38 (36.8%)	0.979
Pelvis	3/20 (15.0%)		7/17 (41.2%)	
Extremities	3/17 (17.6%)			
Pain score (0-10)				
Moderate (5-6)	7/27 (25.9%)	0.137	13/36 (36.1%)	1.000
Severe (7-10)	4/41 (9.76%)		17/43 (39.5%)	
Analgesic score				
1 (NSAID)	2/9 (22.2 %)	0.853	4/14 (28.6%)	0.448
2 (Weak opioids)	5/29 (17.2%)		11/36 (30.5%)	
3 (Strong opioids)	4/30 (13.3%)		15/29 (51.7%)	

Discussion

Limited data on bone pain flare has been published. The most prominent data has been generated by multicenter pilot studies by Chow et al. at the Toronto Sunnybrook Odette Cancer Center. These researchers have documented the occurrence of pain flare using both single fraction (8 Gy) and multiple fraction (20 Gy in 5 fractions) palliative radiotherapy.[5] In a trial conducted in three Canadian centers,[12] the overall pain flare incidence was 44/111 (40%) during radiotherapy and within ten days following its completion in patients who received single and multiple fractions. Patients treated with a single 8 Gy dose reported a pain flare incidence of 39% (27/70) whereas 41% (17/41) who received 2000 Gy/5 fractions reported pain flare. Another smaller study by Chow demonstrated an incidence of pain flare of 2%-16% during the study period of single fraction radiation and after ten days.[5] In the present study patients received 2000 Gy/5 fractions. There was a similar pain flare incidence observed in 38% (30/79) of patients from the group that received no prophylaxis treatment. This phenomenon has shown a severe impact on patient function as documented from interviewing a subset of patients from the second pilot study.[13] The reason for the major impact on patients' lives is that once it occurs, patients are usually directed to take 'break-through' pain medication at its onset. However not even opioids prevent the phenomenon completely and patients still experience some exacerbation of their initial pain.[14]

Dexamethasone, a synthetic glucocorticoid used as an anti-inflammatory or immunosuppressive agent, was administered in an 8 mg dose taken at least one hour prior to a single 8 Gy palliative radiotherapy treatment to prevent pain flare,[6] as this process has been postulated to result from an inflammatory process that occurs with bone irradiation. This single dose of dexamethasone decreased the incidence of flare to 24% (8/33) in this phase 2 trial. Another multicenter pilot study[15] used an 8 mg dose of dexamethasone given one hour prior to single fraction radiotherapy and each morning for three days following treatment. This regimen resulted in a pain flare incidence of 22% with no dexamethasone-related adverse events reported. These studies prompted us to conduct this phase 3 prospective study to compare the effect of dexamethasone on pain flare.

Our results showed a statistically significant decrease (P=0.0033) in the incidence of pain flare with the use of dexamethasone in the mentioned doses, from 38% (30/79) to 16% (11/68), with no dexamethasone related adverse effects. The slightly additional decrease in the development of pain flare achieved in the present study compared to the majority of previous pilot studies might be attributed to the relatively prolonged steroid intake compared to the intake with the single fraction irradiation schedules. This dose of dexamethasone was proven to be safe and well tolerated as none of the patients reported steroid-related adverse effects. No factor proved to be related to the risk of developing bone pain flare in our study, thus no specific group of patients were found to be more susceptible for flare.

Conclusion

Dexamethasone, at a dose of 8 mg, taken one hour prior to radiotherapy for the treatment duration of 2000 Gy/5 fractions and three days afterwards is a well tolerated safe dose of steroids. This dose may be considered for all adult patients who undergo radiotherapy and have no contraindication for this treatment. Dexamethasone significantly decreases the incidence of bone pain flare as experienced by approximately 40% of patients in the majority of studies whose pain was not immediately controlled by changing medication. Thus pain flare has been shown to impact patients' tolerance to treatment. Larger phase 3 randomized trials are recommended to confirm these findings.

Conflict of Interest:

No conflict of interest is declared.

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