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Single Institutional Comparative Study of Short versus Long Course Radiotherapy for Palliation of Painful Bone Metastasis

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Abstract
Purpose: *External beam radiotherapy is an effective treatment for symptomatic bone metastases. This study aims to compare the 8Gy in single fraction and 30Gy in 10 fractions radiotherapy for palliation of bone metastases in terms of pain relieving efficacy, toxicity and feasibility of different dose schedules.*
Material and Method: *In this two arm, prospective comparative study we enrolled 60 patients of ≥18 years with KPS ≥ 40, histologically proven malignancy with radiologically confirmed, painful bone metastases and randomized (1:1) to receive either 8 Gy in a single fraction or 30 Gy in 10 fractions with Zoledronic acid every 4 weeks for 6 months. Treatment response was determined by Brief Pain Inventory and toxicity assessment was done by CTCAE version 4.03.*
Results: *Overall response was 76.6% in both groups. In 8Gy group complete response and partial response were 36.7% and 40% respectively compared with 30% and 46.7% in 30 Gy group respectively (p =0.76). In both arms frequently reported toxicities were anorexia and anemia. No grade 4-5 toxicity were reported in any patient. Retreatment rate were higher in 8 Gy group than 30 Gy group (10% vs 3.3%, p = 0.61).*
Conclusion: *8Gy/1 fraction is as effective as 30Gy/10 fraction for palliation of painful bone metastasis with less side effects and more feasible for patients and caregivers in terms of treatment duration, cost and hospital visit.*
Keywords: *Painful bone metastasis, Zoledronic acid, radiotherapy, single fraction.*

Introduction

The exact incidence of bone metastases is difficult to determine, but estimates are that >100,000 people in the United States will develop osseous metastatic disease annually[1],[2]. Prostate, breast, and lung cancers are the most common malignancies in adults and are the most common tumours that metastasize to bone [3].

Bone metastases are the most common cause of cancer-related pain[4]. The treatment of pain from bone metastases involves the use of multiple complementary approaches including radiotherapy, surgery, chemotherapy, bisphosphonates, calcitonin, and analgesics [5].

External beam radiotherapy has been reported to be effective in palliating painful bone metastases, with

partial pain relief seen in 80% to 90% of patients and complete pain relief in 50% of patients. Patients who have improvement in pain after radiotherapy may also have improvement in emotional functioning, decreased insomnia and decreased constipation, and overall improvement in quality-of-life scores[6].

There have been multiple randomized, prospective trials in the last 30 years comparing shorter-course, lower–total-dose treatment to the more ―standard longer-course, higher–dose treatment and concluded that Single-dose treatments of 8 Gy provide similar pain relief to longer-treatment regimens (30 Gy in 10 fractions or 20 to 24 Gy in five to eight treatments)[6]. Despite these results, longer courses of treatment to higher total doses of radiation remain the most commonly used schedules in the United States, typically with a regimen of 30 Gy given in 10 treatment fractions over 2 weeks[7].

The use of shorter course of radiation therapy in palliation of symptomatic bone metastases makes it easier for patients and their caregiver to arrange logistics of therapy. One or 2 visits to treatment facility for planning and treatment save time and resources for patients, caregivers and health care providers compared to ≥10 visits.

This study aims to compare the 8Gy single fraction and 30Gy in 10 fractions radiotherapy concurrently with zoledronic acid for palliation of bone metastases in terms of pain relieving efficacy, toxicity and feasibility of different dose schedules.

Aims & Objectives

The purpose of the study is to compare the single fraction radiotherapy and multiple fraction radiotherapy for palliation of radiologically proven bone metastases from solid tumour in terms of:–

- Pain relieving efficacy
- Toxicity
- Feasibility of different dose schedules

Material and Method

This is a single centre, prospective, observational, randomized non-blinded study in which 60 patients of painful bone metastasis were randomized (1:1) to receive either 8 Gy in single fraction on 1 day or 30 Gy in 10 fractions over 2 weeks with Zoledronic acid every 4 weeks for 6 months. All the patients were treated on a telecobalt machine with two-dimensional radiation planning. The inclusion criteria's were age ≥ 18 years, histologically proven malignancy with radiologically proven bone metastases, KPS ≥ 40, worst pain score from BPI ≥ 5 and a signed study specific informed consent given by the patient before randomization. Prior radiation therapy or palliative surgery for same bone metastases, pathological fracture or impending fracture of treatment site, clinical or radiological evidence of spinal cord or cauda equine compression, KPS < 40 and pregnancy or lactation were exclusion criteria for this study. The response to radiotherapy was assessed by BPI questionnaires at 15th and 30th day of start of radiation then monthly up to 6 month Treatment related toxicity assessed by CTCAE version 4.03 during and after radiation therapy at follow up visits. Treatment response is categorized (on worst pain score from brief pain inventory) as follows:- 1)Complete response –A post treatment score of 0; 2)Partial response–A post treatment improvement of pain score ≥ 2 points; 3)Stable response –A post treatment pain score within1 point of initial pain score; 4) Progressive disease -A post treatment increase of pain score ≥ 2 points.

Statistics

Statistical analysis was performed with software (SPSS, version 20). Descriptive statistics were used to express the data findings. For categorical variables, Chi square or Fischer exact test was used as appropriate. P values ≤ 0.05 was considered statistically significant.

Results

From 2015 to 2017, 60 patients with painful bone metastases were randomized for the trial, 30 patients to a single fraction and 30 patients to 10 fractions of palliative radiotherapy. Of these patients 50% were male and 50% were female. Age range was 33-84 years (mean – 54.2 years). Majority of the patients

were of KPS between 40 and 70(96.7%). Most common primary tumour was carcinoma breast (33.3%) followed by carcinoma lung (18.3%), carcinoma prostate (18.3%), carcinoma cervix (5.0%), carcinoma gall bladder (5.0%), carcinoma thyroid (5.0%), head and neck cancer (5.0%), colorectal cancer (3.3%) and unknown primary (3.3%). A single patient of carcinoma esophagus (1.7%) and carcinoma pancreas (1.7%) were also included in this trial. Patients with variable sites of bone metastasis were included in this study. Most common site being vertebrae (47.5%), lumbar (36 patients- 17.48%) followed by thoracic (33 patients – 16%), cervical (15 patients – 17.28%) and sacrum (14 patients- 6.8%). Other non-vertebral sites were pelvic bones (29 patients -14.08%), ribs (18 patients – 8.74%), femur (16 patients – 7.77%), humerus (11 patients – 5.34%), scapula (10 patients - 4.85%), clavicle (5 patients 2.43%), skull (5 patients – 2.43%), tibia (2 patients – 0.97%) and fibula, radius and ulna (1 patient – 0.5% to each site). The baseline characteristics of both group patients are summarized in Table 1.

The overall response rate to palliative RT in our study was 76.6%, which was similar in both groups. In single fraction group complete response rate and partial response rate were 36.7% and 40% respectively whereas 20% and 3.3% patients showed stable response and progressive disease respectively. In multiple fraction group complete response rate and partial response rate were 30% and 46.7% respectively whereas 23.3% patients showed stable response (Table 2).

In our study both group patients experienced same toxicity profile. Most common toxicity was anorexia followed by anemia, nausea, vomiting, diarrhoea, leucopenia and thrombocytopenia. Grade 1 toxicity was 20.4% (18.5% vs 22.9%), grade 2 toxicity was 27.8% (26.2% vs 29.5%) and grade 3 toxicity was 8.8% (9.0% vs 8.5%). No grade 4-5 toxicity was experienced by patients during study. No incidence of radiation induced myelopathy or pathological fracture was noted during study period (Table 3).

Reirradiation rate was 10% (n = 3) in 8Gy group and 3.3% (n =1) in 30Gy in 10 fractions group (difference = 6.7%, p = 0.30) within 6 months of follow up.

In single fraction group, patients completed their treatment in 30 days (on average 1day/patient) where as in multiple fraction group; patients completed their treatment in 450 days (on avarage15 days/patient). Thus multiple fraction group patients needed on average 14 additional days to complete treatment.

Table 1 Pre-treatment characteristics of eligible patients

Characteristics		8 Gy/1# group (n =30)	30 Gy/10# group (n=30)	Total
Age, years	Mean	54.9	53.5	54.2
	Median	53.5	50	51.5
	Range	33-84	34-82	33-84
Sex (%)	Male	16 (53.3)	14 (46.7)	30 (50)
	Female	14 (46.7)	16 (53.3)	30 (50)
KPS (%)	80	1(3.3)	0(0)	1(3.3)
	70	3(10)	1(3.3)	4(13.3)
	60	11(36.7)	12(40.0)	23(38.3)
	50	10(33.3)	13(43.3)	23(38.3)
	40	5(16.7)	4(13.3)	9(15)
Primary cancer site (%)	Breast	9 (30)	11(36.6)	20 (33.3)
	Prostate	4(13.3)	7 (23.3)	11 (18.3)
	Lung	5(16.7)	6 (20)	11 (18.3)
	Cervix	3(10)	0 (0)	3 (5.0)
	Gall bladder	2(6.6)	1(3.3)	3 (5)
	Thyroid	2(6.6)	1(3.3)	3 (5)
	Head and neck	2(6.6)	1(3.3)	3 (5)
	Colorectal	2(6.6)	0 (0)	2 (3.3)
	Esophagus	0 (0)	1(3.3)	1 (1.7)
	Pancreas	0 (0)	1(3.3)	1 (1.7)
	Unknown primary	1(3.3)	1(3.3)	2 (3.3)
Site of bone metastases (%)	Cervical vertebrae	5 (5)	10 (9.3)	15(7.2)
	Thoracic vertebrae	17 (17)	16(14.9)	33 (16)
	Lumbar vertebrae	19 (19)	17 (15.8)	36 (17.4)
	Sacrum	6 (6)	8 (7.4)	14 (6.7)
	Pelvic bones	12 (12)	17 (15.8)	29 (14)
	Other	40 (40)	39 (36.4)	79 (38.1)
Worst pain score on BPI	5-6	8 (26.6)	6 (20)	14 (23.3)
	7-10	22 (73.3)	24(80)	46 (76.6)

Table 2: Response to treatment, as measured by BPI worst pain score

Response	8 Gy/1# group (n =30)	30 Gy/10# group (n=30)	P value
Complete	11 (36.7)	9 (30.0)	0.698
Partial	12 (40.0)	14 (46.7)	
Stable	6 (20.0)	7 (23.3)	
Progressive disease	1 (3.3)	0 (0.0)	

Table 3: Toxicity of treatment

Adverse events	Toxicity grade	8 Gy/1# group (n =30)	30 Gy/10# group (n=30)
Anemia (%)	Grade 1	5 (16.6)	1 (3.3)
	Grade 2	9 (30)	16 (53.3)
	Grade 3	12 (40)	11 (36.7)
	Grade 4	0 (0)	0 (0)
Leucopenia (%)	Grade 1	7 (23.3)	9 (30)
	Grade 2	1 (3.3)	2 (6.6)
	Grade 3	0 (0)	0 (0)
	Grade 4	0 (0)	0 (0)
Thrombocytopenia (%)	Grade 1	2 (6.6)	1 (3.3)
	Grade 2	0 (0)	0 (0)
	Grade 3	0 (0)	0 (0)
	Grade 4	0 (0)	0 (0)
Nausea (%)	Grade 1	7 (23.3)	10 (33.3)
	Grade 2	9 (30)	12 (40)
	Grade 3	1 (3.3)	3 (10)
	Grade 4	0 (0)	0 (0)
Vomiting (%)	Grade 1	9 (30)	11 (36.6)
	Grade 2	4 (13.3)	7 (23.3)
	Grade 3	1 (3.3)	1 (3.3)
	Grade 4	0 (0)	0 (0)
Anorexia (%)	Grade 1	5 (16.6)	10 (33.3)
	Grade 2	18 (60)	18 (60)
	Grade 3	4 (13.3)	2 (6.6)
	Grade 4	0 (0)	0 (0)
Diarrhoea (%)	Grade 1	4 (13.3)	5 (16.6)
	Grade 2	14 (46.6)	7 (23.3)
	Grade 3	1 (3.3)	1 (3.3)
	Grade 4	0 (0)	0 (0)

Discussion

In this study most common primary diagnosis with bone metastases was Breast cancer (33.3%) followed by ca lung (18.3%) and ca prostate (18.3%). According to Coleman RE (2004) [8] prevalence of metastatic bone disease is highest in breast and prostate cancer, with both together accounting for 80% of all cases. One other study conducted by Body JJ (1992)[9], the most common bone metastasizing tumour were breast cancer (47% to 85%), prostate cancer (33% to 85%) and lung cancer (32% to 60%). The reason for lower incidence of breast cancer, prostate cancer and lung cancer in our study may accounted for the small sample size in our study, increased incidence of these diseases in developed countries on account of their better socioeconomic status and longer life expectancy.

The overall response rate in this study was 76.6%, which was similar in both groups. These results are equivalent to the results reported in the international literatures. In the Dutch Bone Metastases Study the overall response rate was 71%[10]. In the Bone Pain Trial Working Party Report[11] 78% of patients experienced some degree of pain relief. In RTOG 97-14 trial [7] the overall response rate was 66%. In an updated meta-analysis reporting 25 randomized trials by Chow E et. al revealed the overall and complete response rates were 60% and 23% respectively in single-fraction arm versus, 61% and 24% respectively in multiple-fraction arm, again demonstrating equal efficacy[12].

Complete response rate achieved in our study was 33.3% and partial response rate was 43.3% which is also equivalent to the Dutch Bone Metastases Study [10] (complete response rate 35%) and systemic review by Sze et al[13] (complete response rate 32%-34%).

In single fraction group complete response rate and partial response rate were 36.7% and 40% respectively whereas 20% and 3.3% patients showed stable response and progressive disease respectively. In multiple fraction group complete response rate and partial response rate were 30% and 46.7% respectively whereas 23.3% patients showed stable response.($p = 0.698$). In study RTOG- 9714 complete and partial response rates were 15% and 50%, respectively, in the single-fraction arm compared with 18% and 48%, respectively, in the multiple-fractions arm ($p = 0.6$) [7]. In a Subset Analysis of Radiation Therapy Oncology Group Trial 97-14 by David D. Howell complete and partial response rates were 19% and 51%, respectively in the single-fraction arm compared with 17% and 45% respectively in the multiple-fractions arm ($p=0.59$)[7]. Another study conducted by Akhil kapoor et al in north west India

showed complete and partial response rates 22% and 36%, respectively, in the single-fraction arm compared with 17% and 43%, respectively, in the multiple-fractions arm[14]. These large multicentric randomized trials [7], [14], [15] and two updated meta-analysis[12] have found no significant difference in probability of achieving pain relief with different fractionation schedules of localized RT in painful uncomplicated bone metastases. Our findings are also in agreement, showing no significant difference in pain reliving efficacy with treatment either using 8Gy in single fraction or 30 Gy in 10 fractions. Although this study revealed a higher rate of complete response in both arms than these previous trials, this difference may be accounted for smaller sample size and use of zoledronic acid in every 28 days in patients of both arms of our study.

In this study retreatment rate was 10% and 3.3% in single fraction and multiple fraction group respectively which is not significant (p=0.3). In RTOG 9714 trial retreatment rates were 18% and 9% in single fraction and 10 fraction arm(p<0.001) [7]. The meta-analysis by Chow et al reported retreatment rate of 20% and 8% in single fraction and multiple fraction groups (p<0.00001) [12]. This difference can be accounted by smaller sample size and short duration of follow-up in our study.

In this study treatment response had assessed by brief pain inventory. Mean score for all scores of brief pain inventory showed a downward trend throughout treatment although fall was less steep after 1st or 2nd month. Mean pain scores started to increase after 4th or 5th month in both arms. Statistical analysis revealed no significant difference between single fraction and multiple fraction arms in mean scores of brief pain inventory during treatment as well as during follow-up.

In our study most common toxicity was anorexia followed by anemia, nausea, vomiting, diarrhoea, leucopenia and thrombocytopenia. Grade 1 toxicity was 20.4% (18.5% vs 22.9%), grade 2 toxicity was 27.8% (26.2% vs 29.5%) and grade 3 toxicity was 8.8% (9.0% vs 8.5%). A greater incidence of toxicities were noted in multiple fraction arm, although this difference was statistically not significant (p>0.05). The higher grades of toxicities were reported in patients receiving palliative chemotherapy during follow-up. No grade 4 toxicity was experienced by patients during study. No incidence of spinal cord myelopathy or pathological fracture was noted during study period. These toxicities were well manageable by either hospitalization or OPD basis. RTOG 9714 trial [7] reported that more patients had acute grades 2-4 toxicities in multiple fraction arm (17%) than in single fraction arm (10%), this difference was significant (p=0.002). This difference can be accounted due to palliative chemotherapy or hormonal therapy in 60% patients during follow-up period in our study.

The use of single fraction radiotherapy in our trial saved on average additional 14 days of patients and their caregivers to complete their treatment. It saved direct and indirect costs of additional leave from work, travel, lodging and childcare; and work of healthcare providers and radiation therapists. The use of single fraction radiotherapy also reduced use of telecobalt machine.

Conclusion

With this study we concluded that 8Gy in single fraction is as effective as 30Gy in 10 fractions for palliation of bone metastases with fewer and manageable side effects. This short course radiation therapy is feasible for patients, caregivers, healthcare providers and radiation therapists. It also reduces excess burden of telecobalt machines especially in developing countries where enough radiation machines are already lacking.

Conflict of interest

We certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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