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Original Research

A Prospective Randomised Comparative Study to Evaluate the Effect of Single Dose (6.25Gy Vs 8Gy) Palliative Radiotherapy with Zoledronic Acid in Patients with Painful Bone Metastases

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Background: To assess the effectiveness of a single fraction dose of radiotherapy (6.25Gy versus 8 Gy) with zoledronic acid in cancer patients with painful bone metastases in treating pain; quality of life; duration of pain response and incidence of skeletal related events (SREs).

Material and methods: A total of 80 patients with bone metastases presented in the department of Radiation Oncology, S.M.S hospital were randomly assigned to: Group A, received single dose of 6.25Gy with Zoledronic acid 4mg and Group B, received single dose of 8Gy with Zoledronic acid 4mg. The main variable was pain which was assessed with 11 point Numeric pain Rating Score (NRS).

Results: There were total 80 patients, 40 in each group, with mean age 54.6 years and 54.5 years in group A and B respectively. Most frequent primary malignant sites were lung (36.2%), breast (28.7%), and prostate (8.7%). At 4 weeks post radiotherapy, complete response was 25% in group A, 27.5% in group B and overall response was 82.5% in group A, 85% in group B. At 2 months post radiotherapy complete response was observed in 25% of patients in group A, while 30% in group B and overall response in 85 % in group A and 87.5% in group B. Quality of life improved in both groups. Mean duration of pain relief was 13.5 weeks vs. 14.5 weeks respectively in group A and group B.

Conclusion: There was improvement in pain relief and quality of life post radiotherapy in both the groups. On comparison between 2 groups, the overall pain relief was insignificant between the two dose schedules. So a lower dose 6.25Gy is almost as effective as 8 Gy single fractions for treatment of painful bone metastases.

Introduction

Bone metastases are a common manifestation of distant disease from various primary solid cancers, especially arising in the lung, prostate and breast. After lung and liver, bones are the third most common organ affected by distant metastases [1]. The most common sites of metastatic disease are the vertebral column, pelvis, sacrum, and proximal femurs. Within the spine, the lumbar spine is most frequently involved, followed by the thoracic and cervical spines [2]. Bone metastasis presented clinically as localized pain, pathological fracture, and functional and neurological deficits due to compression of peripheral nerves, nerve roots, or the spinal cord. Systemic manifestations of osseous disease include hypercalcemia, fatigue, and anorexia [1].

Radiotherapy is the most effective treatment for bone metastasis. The aims of palliative treatment of bone metastases are pain relief, preservation of function, and conservation of skeletal integrity. For single or limited number of painful sites, local field external beam radiation therapy (EBRT) give pain relief in about 60 to 85 percent of cases, with complete pain response reported in 15 to 58 percent [3]. Analgesic action of radiation is based on that the higher dose of radiation causes reduction of viable tumor cells within the radiation field that result in decrease tumor bulk. Once the tumor cells are removed from the bone, osteoblastic repair restores the integrity of the bone. Reduction of inflammatory cells by radiation decreases the release of chemical mediators and is responsible for the pain response [4]. Bone-targeted agents like bisphosphonates are potent inhibitors of bone resorption. Bisphosphonates reduces bone resorption and increase mineralization by inhibiting osteoclast activity. Bisphosphonates have a direct apoptotic effect on osteoclasts, affect their differentiation and development, and thereby, act as potent inhibitors of bone resorption. Bisphosphonates had shown impact on macrophages, T cells, osteoblasts, and neoplasm cells [5]. Zoledronic acid effectively reduces the threat of SREs and decreases pain severity and improves QOL of patients with metastatic bone disease [6]. The goals of management for patients with bone metastases include highest pain or symptom control, preserving and restoring function, minimizing the risk for skeletal-related events (SREs), stabilizing the skeleton and enhancing local tumor control.

The main objective of the present study was to assess the effectiveness of a single fraction dose of radiotherapy (6.25Gy versus 8 Gy) with zoledronic acid (ZA) in treatment of pain in patients with painful bone metastases. Secondary objectives were to improve quality of life, mean duration of response and incidence of SREs in cancer patients with painful bone metastases post radiotherapy.

Materials and Methods

Study design

A total of 80 patients with bone metastasis presented in the Department of Radiation Oncology, S.M.S Medical College, Jaipur were randomly assigned into two groups: Group A(study) patients received 6.25Gy/1# with zoledronic acid 4mg iv over 15 min infusion (within 7 days after radiation) every 4 weeks.Group B (control) patients received 8Gy/1# with zoledronic acid 4mg iv over 15 min infusion (within 7 days after radiation) every 4 weeks.

Inclusion and exclusion criteria

The study population comprised patients with bone metastases from histopathological proven primary malignancy. Patients had to meet all the following criteria- age 18-70 years, ECOG performance status 1-3, patients willing to give written informed consent, no treatment with bisphosphonates prior to inclusion, patients having normal hematological and biochemical parameters, no history of previous radiotherapy in same area, no fracture at site of bone metastasis and no history of multiple myeloma.

Treatment and follow up

After locating the site of pain, marker X-ray in treatment position obtained following which they were treated with telecobalt machine (Bhabhatron-II TAW) with a single posterior portal for vertebral metastases and anterio- posterior or posterio-anterior portals for pelvis and long bones. Patients were assessed at baseline before radiotherapy than at 4week, 2 month and 6 month post radiotherapy.

Response assessment

The main variable was pain which was assessed with 11 point Numeric pain Rating Score (NRS) ranging from ‘0’ no pain to ‘10’ worst pain (mild pain 1-3, moderate pain 4-6, severe 7-10). The response was assessed according to WHO criteria with the definition of subjective response as complete response (CR) defined as a complete disappearance of pain with no need for analgesics. Partial response (PR) defined as improvement in pain score by one categories, with pain still existing. No response (NR) defined as the pain remained the same or increased. Response was assessed in form of complete and overall pain relief.

QOL was assessed using EORTC QOL-C30 (version 3) scale as per EORTC guidelines. To evaluate functional status of patients ECOG score was used. Score on this scale ranges from 0 to 5, with high score indicating poor performance of the patient.

Statistics

SPSS statistical software was used for statistical analysis and data entry. Fisher’s exact test was used to assess response between the 2 groups. Qualitative data were expressed in mean and compared by using student t-test and p-test. P value <0.05 considered significant.

Results

There were total 80 patients, 40 in each group, with mean age 54.6 year and 54.5 year in group A and group B respectively. Overall 55% patients were male and 45 % were females. Most frequent primary malignant sites were lung (36.2%), breast (28.7%), and prostate (8.7%) (Table 1).

Variables	Group A (6.25Gy) (%)	Group B (8Gy) (%)
Age (Mean)	55.6	55.5
Sex		
Male	19 (45.5)	25 (62.5)
Female	21 (52.5)	15 (37.5)
Rural	32 (80)	30 (75)
Urban	8 (20)	10 (25)
Primary tumor		
Lung	14 (35)	15 (37.5)
Breast	13 (32.5)	10 (20)
Prostate	2 (5)	5 (12.5)
Head and Neck	3 (7.5)	4 (10)
Renal Cancer	2 (5)	1 (2.5)
Others	8 (20)	8 (20)
Sites of metastases		
Spine	28 (70)	29 (72.5)
Pelvis	4 (10)	6 (15)
Long bones	7 (17.5)	2 (5)
Axial skeleton	1 (2.5)	3 (7.5)
(PS) ECOG>2	10 (25)	8 (20)
ECOG≤2	30 (75)	32 (80)

Table 1. Patient’s demographic and Pathophysiologic Characteristics.

At 4 weeks post radiotherapy, complete pain response was 25% in group A, 27.5% in group B and overall response was 82.5% in group A, 85% in group B. At 2 months post radiotherapy complete

response was observed in 25% of patients in group A, while 30% in group B and overall response in 85 % in group A and 87.5% in group B. No significant difference in pain response was observed between the two groups (P value >0.05). At 4 weeks of radiotherapy ECOG performance status improved in 65% and 70% patients from baseline, which improved in 70% and 75% patients both groups respectively at 2nd month post radiotherapy (Table 2).

		Group 1 (N=40) (%)	Group 2 (N= 40) (%)	P-value
		6.25Gy	8Gy	
4 week	CR	10 (25)	11 (27.5)	
	PR	23 (57.5)	23 (57.5)	0.81
	OR	33 (82.5)	34 (85)	
2 months	CR	10 (25)	12 (30)	
	PR	24 (60)	23 (57.5)	0.84
	OR	34 (85)	35 (87.5)	
6 monts	CR	0	0	
	PR	7 (17.5)	8 (20)	1
	OR	7 (17.5)	8 (20)	

Table 2. Pain Response after 4 Week, 2 and 6 Month.

EORTC Quality of life improved in both groups. Mean scores increased in both groups from baseline, at 2 month mean scores were highest which had shown improved global quality of life of patients, thereafter scores decreased with the time (Table 3).

Mean scores	Baseline	1 month	2 month	6 month
Group1	28.5	44.6	45	16.9
Group2	29.6	45.2	46.9	16.4

Table 3. Mean Scores EORTC Global Quality of Life at Baseline, 4 week, 2 and 6 month.

The mean duration of response was 13.57 and 14.54 weeks in group A and group B respectively. The difference between the groups were not statistical significant (p-value 0.34) (Table 4).

Groups	Group 1 (6.25 Gy)	Group 2 (8 Gy)	P value
Mean duration of response (Weeks)	13.57	14.54	0.34

Table 4. Mean Duration of Response.

Reduction of analgesic use was observed at 4^{th} week after radiotherapy in 50% and 55%patients in group A and B respectively (Table 5).

	4 week (%)	2 months (%)	6 months (%)
Group 1	20 (50)	20 (50)	4 (10)
Group 2	22 (55)	22 (55)	5 (12.5)

Table 5. Patients with Decreased Analgesics Requirement.

Overall skeletal related events (SRE) occured in 20% and 15% patients of group A and group B. The adverse reactions were 12.5% and 22.5% in group A and group B respectively. Most frequent adverse reaction were nausea, vomiting and fever, higher in group B. No significant difference (p-value 0.7) were observed between two groups (Table 6).

	Group1	Group 2	P value

Patients with SREs	8 (20)	6 (15)	0.76
Patients with Adverse reactions	5 (12.5)	9 (22.5)	0.78

Table 6. Patients with SREs and Adverse Reactions.

At 4-weeks follow up 65 % and 70 % patients, and at 2 month 70 % and 75% patients had shown improved performance status which further decreased to 17.5% and 20% at 6th month of follow up in group A and group B respectively (Table 7).

	4 week (%)	2 month (%)	6 month (%)
Group1	26 (65)	28 (70)	7 (17.5)
Group2	28 (70)	30 (75)	8 (20)

Table 7. Patients with Improved ECOG Performance Status.

Discussion

Bone metastases are one of the common complication of various solid cancer. Bone metastases are clinically apparent in about 14-70% of the cancer patients [1]. There are various treatment modalities used for management of painful bone metastases; analgesic drugs, surgery, chemotherapy, radiotherapy and hormonal therapy, bisphosphonates alone or in combination. Many trials have been demonstrated that radiotherapy is the main modality for treatment of painful bone metastases with single or multiple fractionation regimens [7]. Results of our study were similar with a study conducted by the Nabila et al where complete pain relief at 8 week were 23.3% and 26.7% in two group respectively, statistically not significant [8]. In our study, more than 80% patients got pain relief at 4-weeks post radiotherapy (82.5% in groups A & 85% in group B respectively which was maintained up to 2 months. A systematic meta analysis by Chow at el reported that highest overall pain relief was 81% and 72% in 6Gy and 8Gy groups respectively. Jeremic et al reported on a study that estimated the efficacy of high single doses (4, 6, and 8 Gy, respectively) of radiation on pain relief. Among the 327 patients, 109 cases received 4 Gy, 108 received 6 Gy, and 110 cases received 8 Gy. Overall response to radiation was 59% in 4Gy arm, 73% in 6Gy arm and 78% in 8Gy arm [9]. A prospective single arm study with 6 Gy single fraction RT shown response in 88% patients [10]. This difference could be attributed to difference in the type of pain scales used or difference in response criteria addition of Zoledronic acid [11]. Several retrospective and prospective randomized studies have shown that single fraction of radiotherapy is as effective as multi fractionation regimen in improving mobility, function and quality of life of patients with painful bone metastasis [7, 12]. In our study overall skeletal related events (SRE) occurred in 20% and 15% patients of group A and group

B. Most frequent SRE were re-irradiation 15% and 10%, spinal cord compression(SCC) was in 1 (2.5%) and 2 (5%) patients respectively, 1 patient developed fracture in 6.25 Gy arm. In Manas et al study, skeletal events were 23.53% and 19.4% in 6Gy vs 8 Gy respectively [13]. Clemons MJ et al conducted prospective study evaluated the impact of second-line zoledronic acid on pain, quality of life, and markers of bone turnover. Patients received monthly zoledronic acid (4 mg) for 3 months. Thirty-one women completed this study and by week 8, patients had experienced significant improvements in pain control ($P < 0.001$). In our study SRE were similar to this study which had shown that zoledronic acid reduces the incidence of SRE in patient with bone metastasis [14]. Clinical studies have shown the synergistic effect of bisphosphonates with combination of radiotherapy in metastatic bone disease. A pilot study of 45 patients with bone metastases treated with a total dose of 30-40Gy over 3-4.5 weeks in combination with iv ibandronate 10 monthly cycle reported, the pain score had fallen from baseline from 6.3 to 0.8 ($p<0.001$) at three months after completion of therapy; use of analgesics reduced from 84% to 24% ($p<0.001$). Significant

difference were observed between two groups [15].

Performance status at 4-weeks follow up improved in 65 % and 70% patients which was decreased to 17.5% & 20% at 6th month of follow up in group A and group B respectively. There was no significant statistical difference in patients with improved performance status in both groups at any time during follow up. A study by Jilla et al which reported an improvement in performance status in about 65% patients in all the groups at 4-weeks follow up [16]. Overall EORTC global quality of life mean score improved post radiotherapy in both the arms which was maximum at 2 month of follow-up. Other domains of functional scales like physical functioning (PF2), Role functioning (RF2) and social functioning (SF) mean scores improved in both the arms highest score improved at 2 month. After that at end of 6 months quality of life scores decreased. The difference in domains of questionnaires was not statistically significant between the arms. In present study, the mean duration of pain relief among responders was 13.57 and 14.54 weeks in the group A and group B respectively. There was no significant statistical difference (p-value>0.05) in the mean duration of response among these groups. A study by Jilla et al, mean duration of response in 8 Gy arm was 12 weeks and Manas et al reported 11.7 weeks & 17.4 weeks of mean duration of response in 6 Gy and 8Gy arms respectively [13, 16].

In conclusion, there was improvement in pain relief and quality of life post radiotherapy in both the groups. On comparing the two groups, overall pain relief difference was insignificant. So a lower dose 6.25Gy with zoledronic acid is almost as effective as 8 Gy single fraction with zoledronic acid for treatment of pain in patients with painful bone metastases.

Acknowledgments

Statement of Transparency and Principals:

· Author declares no conflict of interest

· Study was approved by Research Ethic Committee of author affiliated Institute .

· Study’s data is available upon a reasonable request.

· All authors have contributed to implementation of this research.

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