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RESEARCH ARTICLE

A PROSPECTIVE COMPARATIVE STUDY EVALUATING THE IMPACT OF HEMI BODY IRRADIATION VS FOCAL RT PLUS ZOLEDRONATE IN MANAGEMENT OF PAINFUL SKELETAL METASTASES

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ABSTRACT

Objectives: The primary objective of our study is to evaluate the effect of Hemi Body Irradiation and Focal Radiotherapy with Zoledronate on pain management in patients with extensive bone metastases after completion of definitive treatment. The secondary objective is to evaluate the toxicities and Skeletal Related Events eg. fracture.

Material and Methods: We have analyzed the difference in pain reduction comparing two groups of patients in a prospective non randomised study . The first group comprised of 10 patients treated with Hemibody Irradiation (HBI), the second one included 14 patients treated with focal radiotherapy and zoledronic acid, 4mg iv, 4 weekly (RT + ZA). In both groups single fraction radiation of 8Gy (UHBI = 6Gy) was given & followed up for 3 months .All patients were assessed before, during and after treatment with a questionnaire that rated the grade of pain, type of analgesic therapy and patient's performance status. Response assessment was done using Visual analogue scale, percentage of pain relief and total score reduction on a scale of 0 - 20. Acute & chronic haematological and GI toxicities were assessed as per standard guidelines. Statistical analysis was done by Chi square test & Mann-Whitney U test.

Results: Long term pain score & total score reduction was more in (RT + ZA) arm (P =0.002 & 0.001) with less toxicity (P=0.002) and SRE.(P=0.324)

Conclusions Focal RT with ZA showed better result on long term pain management and may be preferred in cancer patients with longer median survival. As our sample size was small, study with larger sample size is warranted.

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INTRODUCTION

Many cancers metastasize to bone exhibiting a particular osteotropism. Bone is the third most common metastatic site after the lung and the liver. Bone metastases are more often seen in male patients with lung or prostatic cancer and in female patients with breast cancer. The presence of bone metastases is themost common cause of cancer-related pain (Twycross, 2010 and Morris, 1986), and management, often difficult, requires a multidisciplinary approach to therapy (Nora, 1997), which provides, as appropriate, the use analgesics, bisphosphonates, radiotherapy, chemotherapy, surgery (Mercadante, 1997). Radiotherapy is considered a standard treatment in the management of bone metastases, particularly in presence of pain, risk of pathological fracture or spinal cord compression. Hypofractionated irradiation continues to be the treatment regimen most frequently used (Nora, 1997). Multiple randomized trials have demonstrated the equivalence of single-fraction and multiple-fraction palliative radiotherapy. Bisphosphonates, can reduce pain, the risk of fractures and the development of new osteolytic lesions and consequently improve the quality of life of patients (Mercadante, 1997 and Hoskin) The present study was undertaken to prospectively evaluatethe effect of Hemi Body Irradiation and Focal Radiotherapy with Zoledronate on pain management in patients with extensive bone metastases after completion of definitive treatment in terms of patient comfort,toxicities and logistics.

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METHODS AND MATERIALS

The study was conducted between June 2015 and May 2016 at the Department of Radiotherapy, Medical college Hospital, Kolkata. It was a prospective, Non randomised, single Institutional study. All cases were Histopathologically and/or Radiologically proven cancers with multiple skeletal metastasis having received definitive treatment for primary malignancy, in form of surgery, chemotherapy, hormone/ Biologic therapy, EBRT prior to the beginning of this study. Patients were selected with (Inclusion criteria) ECOG Performance Status ≤3, pain not controlled by analgesic therapy (WHO analgesic ladder) and baseline haemogram within normal limits (Hb> 10 g/dl; TLC> 3500/µl; Platelet count > 100,000/µl). Exclusioncriteria included unconscious, uncooperative patients with or without presence of bed sore, ulceration at the intended area of interest of radiation, compromised liver and renal function, history of recent prior radiation within 6 months to the intended site of radiation, and presence of any cord compression, neuropathy, Superior Vena Cava Obstruction (SVCO), pathological fracture or brain metastasis. Patients were divided into two groups. The first one included 11 patients treated with HBI alone; the second one included 15 patients treated with Focal Radiotherapy with Zoledronic acid (RT + Z) given at a dose of 4 mg/100ml with an infusion of 15' i.v. every 4 weeks. Patients in HBI arm were treated with 8Gy single fraction for LHBI &6Gy single fraction for UHBI, and patients in RT+ZA arm were treated with 8Gy single fraction radiation by 1.25MV Co60 machine (780c THERATRON). Premedications were given accordingly. Patients were followed up at day7,day 15,day 30,day 60& day 90.One patient in HBI arm died and one from RT+ZA arm lost to follow up, hence total no of patients under study became 24.(10+ 14).

All patients completed a questionnaire before during and after 7,15.30,60& 90 days from the end of radiation therapy. The questionnaire pointed out the pain with a score from 0 (indicating no pain) to 10 (greatestpain possible) using a visual analogue scale (VAS) & Numeric rating scale (NRS), the analgesic therapy assigning a score from 0 to 6 depending on the type of drug used and the frequency of daily intake, valuation of performance status by ECOG, assigning a score from 0 to 4. Thus, a total score was calculated, for each patient, from a minimum of 0 to a maximum of 20. Percentage of pain relief was noted on a scale of 1-5. (1= 0 to 20%, 2= 21 – 40%, 3 = 41-60%,4= 61-80%,5=81-100%).Pain assessment scoring was done as per the 11 point VAS noted on a 10 cm Scale (Simonet *et al*., 1997; Guise *et al*., 2002) or divided one rupee in to 10 equal parts by coins for better understanding locally. Complete bloodcount (CBC) were checked at every follow up visit. History from patient's party or telephonic conversation were done if patient was absent during follow up check up. Informed consent was taken after verbally explaining about the procedure to patients and their family members. No explanation was given about the possible benefits to avoid bias during this study. Statistical analysis done by IBM SPSS software (version 23) with Chi-square test and Non Parametric Mann-whitney U test.

RESULTS

We calculated the number of patients for each score at several time of our observation. From the data collected, the first important observation was the gradual reduction in number of patients with severe pain (NRS = 8-9-10) in the different phases of observation of both treatment groups. Mean pain score before start of treatment was 9.20, mean analgesic score was 4.94& mean total score was 17.08. Patients in both groups had similar pre-treatment pain score and total score but RT + ZA arm started radiation therapy with slightly increased initial pain score (64% v/s 50%) which was statistically insignificant (p = 0.305). In HBI arm percentage of pain relief was more in initial follow up days but was statistically insignificant.(for day7,day 15 p value was 0.789 & 0.585 respectively). On the other hand, Patients in RT + ZA arm showed better pain relief in long term follow up (p=0.02& 0.000 for day60 & day90

Table 1. Baseline demographic and disease characteristics of patients with bone metastases

No of patients HBI	RT + ZA	TOTAL
Sex		
Female	4	6	10
Male	6	8	14
Age Median (range) age, years	56 (45-70)	56 (45-70)	
Histology		
Prostate	5	3	8
Breast	2	5	7
Lung	1	3	4
Cervix	0	1	1
GB	1	1	2
Unknown primary	1	1	2
Metastasis site		
Cervical spine	1	1	2
Thoracic spine	3	4	7
Lumbar spine	4	4	8
Pelvis	3	2	5
Femur	4	5	9
Tibia	2	5	7
Scapula	1	1	2
Humerus	1	1	2
Sternum	1	1	2
Ribs	3	1	4
No. of metastasis site		
1 – 4	3	8	11
More than 4	7	6	13

respectively), whereas patients in HBI arm showed gradual increase in pain score. Total score reduction was more sustained in RT+ZA arm in long term follow up (p= 0.000), though in initial follow ups, total score reduction was more observed in HBI arm. Histology and no of metastasis didn't show any role in pain relief response assessment, but site of metastasis did. (vertebra and pelvis mets showed poorer pain response).

Table 2. Derivation of a symptomatic assessment from a patient completed questionnaire and distribution of score: symptom score expressed as a percentage of maximum total 20 (100%). Parameter

	Description	Score
Pain	NRS = 0	0
	NRS = 1	1
	NRS = 2	2
	NRS = 3	3
	NRS = 4	4
	NRS = 5	5
	NRS = 6	6
	NRS = 7	7
	NRS = 8	8
	NRS = 9	9
	NRS = 10	10
Analgesic use	None	0
	NSAID single dose	1
	NSAID multiple dose	2
	Weak opioid single dose	3
	Weak opioid multipledose	4
	Strong opioids single dose	5
	Strong opioids multiple dose	6
Performance status	Normal	0
	Light work possible	1
	Up and about > 50% of the day	2
	Confined to bed or to chair > 50% of the day	3
	Completely bed-bound	4
Total score	0 - 20	

Table 3. Percentage pain relief at day 7 , day 15, day 30, day 60 & day 90

Patient Count

		pain score reduction d7		
		41-60%	61-80%	Total
treatment modality	HBI	9	1	10
	Focal RT with ZA	14	0	14
Total		23	1	24

Patient Count

		pain score reduction d15		
		41-60%	61-80%	Total
treatment modality	HBI	5	5	10
	Focal RT with ZA	9	5	14
Total		14	10	24

Patient Count

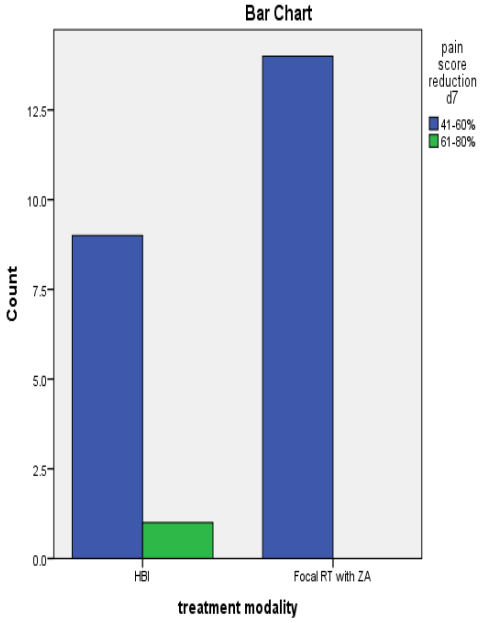
		pain score reduction d30			
		21-40%	41-60%	61-80%	Total
treatment modality	HBI	0	6	4	10
	Focal RT with ZA	0	5	9	14
Total		2	11	11	24

Patient Count

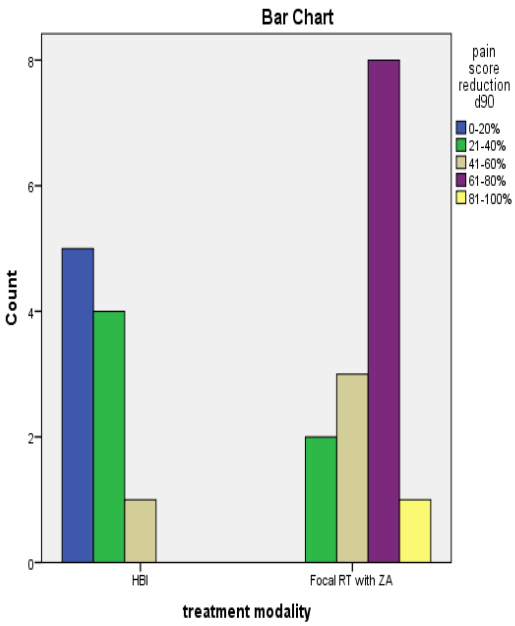
		pain score reduction d60				
		0-20%	21-40%	41-60%	61-80%	Total
treatment modality	HBI	2	3	4	1	10
	Focal RT with ZA	0	0	5	9	14
Total		2	3	9	10	24

Patient Count

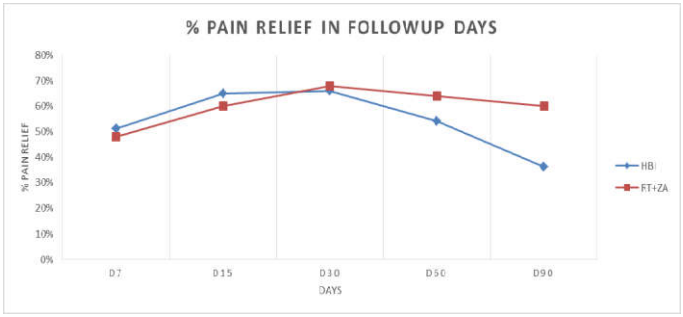
		pain score reduction d90					
		0-20%	21-40%	41-60%	61-80%	81-100%	Total
treatment modality	HBI	5	4	1	0	0	10
	Focal RT with ZA	0	2	3	8	1	14
Total		5	6	4	8	1	24



Pain score reduction day 7



Pain score reduction day 90



Line diagram showing % pain relief during follow up days in both arms

Patient Count

		total score reduction d7		
		41-60%	61-80%	Total
treatment modality	HBI	8	2	10
	Focal RT with ZA	14	0	14
Total		22	2	24

Patient Count

		total score reduction d15		
		51-75%	61-80%	Total
treatment modality	HBI	2	8	10
	Focal RT with ZA	4	10	14
Total		6	18	24

Count

		total score reduction d30			
		21-40%	41-60%	61-80%	Total
treatment modality	HBI	2	6	2	10
	Focal RT with ZA	0	1	13	14
Total		2	7	15	24

Count

		total score reduction d60				
		0-20%	21-40%	41-60%	61-80%	Total
treatment modality	HBI	1	4	5	0	10
	Focal RT with ZA	0	0	3	11	14
Total		1	4	8	11	24

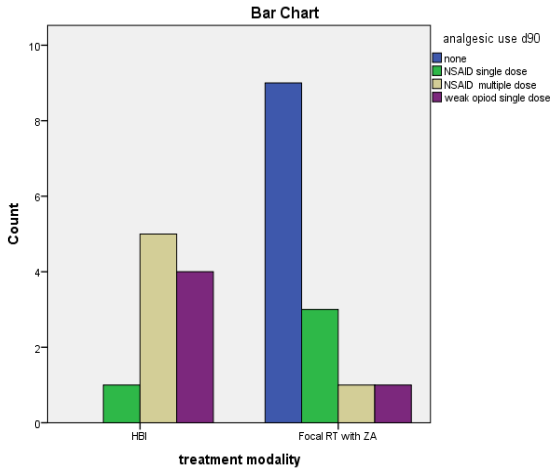
		total score reduction d90				
		0-20%	21-40%	41-60%	61-80%	Total
treatment modality	HBI	3	7	0	0	10
	Focal RT with ZA	0	2	3	9	14
Total		3	9	3	9	24

Statistics

Analgesic score reduction was more in RT +ZA arm in long term follow up.(p value 0.003)

Analgesic score at day 90

Patients in HBI arm developed more SRE (skeletal related events, e.g. fracture) than RT + ZA arm (40% v/s 21.42%, p = 0.324) which did not attain statistical significance.



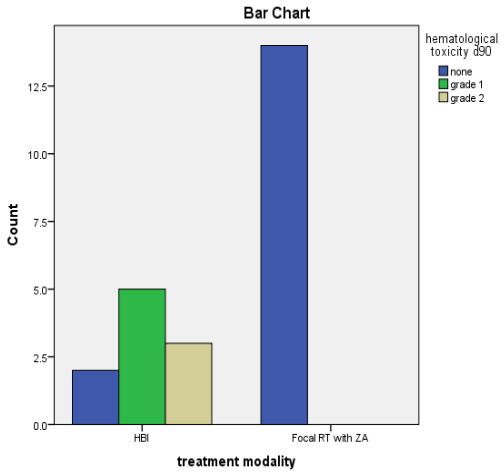
		SRE		
Patient count		no	Yes	Total
treatment modality	HBI	6	4	10
	Focal RT with ZA	11	3	14
Total		17	7	24

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.974[a]	1	**.324**		
Continuity Correction[b]	.282	1	.595		
Likelihood Ratio	.966	1	.326		
Fisher's Exact Test				.393	.296
Linear-by-Linear Association	.933	1	.334		
N of Valid Cases	24				

a. 2 cells (50.0%) have expected count less than 5. The minimum expected count is 2.92.
b. Computed only for a 2x2 table

None of the patients suffered any grade 3 or 4 toxicity. Acute & chronic grade 1&2 hematological toxicities were more in HBI arm(p=0.000) which were manageable.GI toxicities were not significant in any arm of the study. From our observational study, it is relevant a clear potentiation of benefit effects related to palliative radiation therapy in patients receiving also bisphosphonate therapy, so obtaining a better control over pain, a decreased need for pain relief and less toxicities.



DISCUSSION

Metastatic bone disease is the major cause of morbidity in patients with cancer. Bone fractures, hypercalcaemia, neurologic deficits and reduced activity associated with bone metastases result in an overall compromise of patient's quality of life. Bone is not an inert body, undergoes continuous remodelling process with phases of resorption and formation (Mundy, 1987). This process is closely coordinated by osteoclasts, responsible for the phase of resorption, and by osteoblasts regulating a more prolonged phase of bone formation. When the bone becomes the seat of metastases, its normal process of turnover is compromised (Mercadante, 1997). The treatment of pain related to bone metastases re-quires a multidisciplinary approach and the radiation therapy is considered a standard treatment used in bone metastases, when there is pain, risk of pathological fracture, and spinal cord compression. It's an effective symptomatic treatment of bone pain localized (Poulson *et al*., 1989; Hoskin, 1995), resulting in a palliative effect within 4 - 6 weeks in about 80% of patients treated. In this context, EBRT is an established modality of palliation of pain, which is neither very costly nor involves logistics of morphine supply and disposal, nor any intervention like nerve blocks or any major systemic complication. In case of widespread bone involvement, the question now is of sequencing, i.e., palliative hypofractionated radiotherapy like 30 Gy in 10 # or 20 Gy in 5 #. In this regard, HBI has been tried and has often proved efficacious in pain palliation. Bisphosphonates have an increasingly important role in oncology, management of bone metastases, in the prevention of skeletal complications. They showed to reduce skeletal morbidity in breast cancer, the level of pain, analgesic consumption, and lead to an improvement in quality of life of the patient (Coleman-Robert, 2000). Bisphosphonates, in addition to inhibiting the function of osteoclasts, they also cause apoptosis, but it seems to have a direct effect on the type of apoptotic tumour cells, as has been demonstrated by studies in vitro on tumour cells of breast cancer, the prostate, melanoma, osteosarcoma, myeloma (Senaratne *et al*., 2000; Jagdev *et al*., 2001; Lee *et al*., 2001; Riebeling *et al*., 2002; Mackie *et al*., 2001; Shipman *et al*., 1998). Radiotherapy and bisphosphonates, therefore, through their effects on cellular homeostasis, play a major role in the treatment of bone metastases. In addition, due to the effect of bisphosphonates radiosensitizer, the combination of bisphosphonates and radiation therapy can improve the effectiveness of the latter (Ugur-Ural *et al*., 2008). *Krempiem et al.* have investigated the possible benefit of this combination on the process of re-calcification and stabilization of osteolytic bone metastases in animal tumour models, demonstrating that the addition of early bisphosphonate, clodronate in this case and radiation therapy, significantly improved the density and bone microstructural parameters (Krempiem *et al*., 2003). *Kouloulias et al.* in a clinical trial of 33 patients with bone metastases from breast cancer, showed that the combination of radiation therapy and treatment with bisphosphonates induced a clinical improvement after 6 months of therapy compared with the control baseline in terms of bone density, pain control, performance status, biochemical markers of bone resorption and quality of life. They also showed a higher clinical benefit-instrumental on bone re-calcification in the combination of radiotherapy and bisphosphonates, com-pared to that obtained by radiotherapy alone (Kouloulias *et al*., 2003). Currently, many patients receiving bisphosphonates in combination with radiation therapy, as documented by a study by Rosen *et al.* (2003), and a review of *Hoskin* (2003). From our study we observed that combination of focal radiotherapy(to the point of maximum tenderness) & Zoledronic acid leads to an increased response to radiation treatment, with a greater reduction in pain in the long run, a reduced need for pain relief and better performance status. So this can be an effective way for palliation of Painful Bone Mets in Cancers which have better overall survival like Breast, Lymphoma, Cervix etc. In view of paucity of Indian data &as our sample size was small, Study with larger sample size is genuinely warranted.

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