Original Article ISSN (O):2395-2822; ISSN (P):2395-2814



# Prospective Randomized Comparative Study of External Beam Radiotherapy Along with Three Weekly Zoledronic Acid versus External Beam Radiotherapy Alone in Metastatic Bone Disease for Palliation of Pain

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Received: January 2021
Accepted: February 2021

## ABSTRACT

**Background:** Metastatic bone disease is common condition that develops in advanced stage of malignancy during the course of their disease. The most prevalent primary sites of bone metastasis are breast, prostate, thyroid, lung, renal cancer. Bone metastasis commonly lead to bone pain and skeletal related events such as pathological fracture, spinal cord compression, palliative radiotherapy, palliative surgery. This study is aimed to assess & compare the pain relief and the time to onset of pain relief obtained with External Beam Radiation Therapy alone versus three weekly Zoledronic acid along with External Beam Radiotherapy. **Methods:** Study was conducted betweenJan 2014 – July 2015.A total of 41 Patients with histopathologically proven malignant disease with clinically & radiologically diagnosed painful bone metastasis were randomly assigned to two arms, A & B. Arm A received palliative EBRT only and Arm B received palliative EBRT along with 3 weekly Inj zoledronic acid 4mg. Pain relief assessed using 0-10 Numeric Pain Rating Scale where '0' represents no pain and '10' represents worst possible pain .The outcome of intervention was assessed at 6th day,10th day,30 days,60 days,90 days & then 3monthly. **Results:** Pain score analysed in the both arms and pain relief is better in arm B which is statistically significant ($p < 0.05$)). Onset of pain relief in arm A is earlier than arm B, but not statistically significant. **Conclusions:** Additional use of Three weekly Inj Zoledronic acid along with EBRT showed better pain relief than EBRT alone for palliation of pain in metastatic bone disease.

***Keywords:*** Metastatic bone disease, palliation of pain, Zoledronic acid.

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## INTRODUCTION

Metastatic disease to the bone are likely to develop bone pain & skeletal related events(SRE) that negatively affects quality of life. Bone pain is the most common symptom that develops from bone metastases. The incidence of bone metastasis varies significantly and it depends on primary sites. The incidence about 70 % to 80 % of patients with breast or prostate cancer and 30 % to 40 % of patients with lung cancer or other solid tumors.[15] The ultimate prognosis for patient with bone metastasis is poor. Overall survival depends on the primary site, single or multiple metastatic sites, presence or absence of visceral metastasis. Mean survival ranges can be 6 months or lower for those with lung carcinoma to several years for those with bone metastases from prostate, breast or thyroid carcinoma. If patients have skeletal metastasis only, their average survival is even longer. It is now generally accepted that osteoclastic activation is the key step in the establishment and growth of bone metastasis. The treatment of bone pain from metastases remains palliative at present. Currently available palliative therapies for patients with painful metastatic bone diseases are multidisciplinary approaches such as medical treatment, external beam radiotherapy, orthopaedic surgery and biologically targeted agents with bisphosphonates or denosumab, radiopharmaceutical agents. The gold standard therapy for palliation of pain in metastatic bone disease remains conventional external beam radiotherapy (EBRT). Over the past 15 years the bisphosphonates have become established as a valuable additional treatment approach for the relief of bone pain across a range of tumor types. Several studies shows that new highly potent Intravenous Inj Zoledronic acid along with palliative EBRT can reduce bone pain and can reduce risk of SRE's.[1] In view of the recent studies, the present study entitled was taken up in an attempt to find out the degree of pain relief, time to onset of pain relief and acute toxicity in the both treatment arms.

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## MATERIALS & METHODS

Study was conducted between Jan 2014 – July 2015.A total of 41 Patients with histopathologically proven malignant disease with clinically & radiologically diagnosed painful bone metastasis

were randomly assigned to two arms, A & B. Arm A received palliative EBRT only and Arm B received palliative EBRT along with 3 weekly Inj zoledronic acid 4mg.Patients of both treatment arms received External beam radiotherapy with a total dose of 30 gray in 10 fractions @ 2 Gy /fraction over two weeks. EBRTwas delivered using Cobalt-60 machine.The first dose of Injection zoledronic acid was given on the first day of EBRT. The dose of Inj.Zoledronic acid was reduced if Baseline Creatinine clearance(CrCl) is ≤60ml/minute which are as follows:

**Table 1: Reduced doses for patient with baseline CrCl ≤ 60ml/min**

| Baseline CrCl (mL/min) | Recommended dose of inj. Zoledronic acid |
|---|---|
| > 60 | 4.0 mg |
| 50-60 | 3.5 mg |
| 40-49 | 3.3 mg |
| 30-39 | 3 mg |

Pain relief assessed using 0-10 Numeric Pain Rating Scale where '0' represents no pain and '10' represents worst possible pain. Diagnosis of bone metastasis was made with clinical and radiological examinations. The outcome of intervention was assessed at 6th day, 10th day, 30 days,60 days,90 days and thereafter 3monthly. Out of 41 patients 4 patient lost to follow-up and 2 patient died due to non -cancer causes and finally total 35(Arm A-17 and Arm B-18) patients analysed. Statistical analysis was made by SPSS version 20.

## RESULTS

Total of 44 patients were assessed for eligibility for the study. Out of these, 41 patients were randomized after fulfilling the inclusion and exclusion criteria. Patients were randomized into two arms –Arm A &B. Arm A: those patients receiving only EBRT and Arm B: those patients receiving EBRT along with Injection Zoledronic acid 3 weekly. Out of 41 patient 4 patient lost to follow-up and 2 patient died due to non -cancer causes. So, at the end of study, only 35 patients were eligible for analysis with 17 patients in arm A and 18 patients in arm B.
Pain score analysed in the both treatment arms and mean pain score more improved in arm B which is statistically significant (p< 0.05)) in later periods of follow-up treatment [Vide Table 2,Figure 1&2].

**Table 2: Mean pain score**

| | ARMS | No of patients | Mean pain score | P-value |
|---|---|---|---|---|
| Pretreatment | A | 17 | 8.47 | 0.880 |
| | B | 18 | 8.50 | |
| Follow up at 6 th day | A | 17 | 7.71 | 0.830 |
| | B | 18 | 7.67 | |
| Follow up at 10 th day | A | 17 | 7.12 | 0.088 |
| | B | 18 | 6.44 | |
| Follow up at 30 th day | A | 17 | 5.18 | < 0.001 |
| | B | 18 | 2.44 | |
| Follow up at 60 th day | A | 17 | 3.18 | < 0.001 |
| | B | 18 | .94 | |
| Follow up at 90 th day | A | 17 | 1.18 | 0.036 |
| | B | 18 | .78 | |

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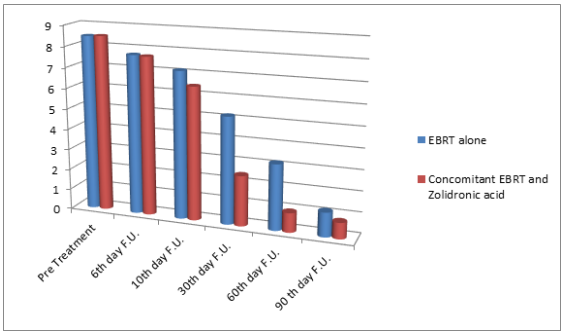


**Figure 1: Bar diagram of mean pain score in both treatment arms in follow up period of our study**

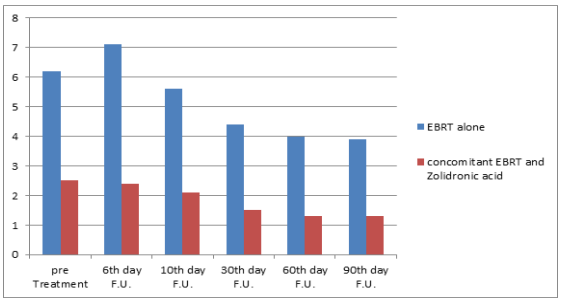


**Figure 2: Bar diagram of mean pain score in both treatment arms in follow up(FU) period of other study.[1]**

The Onset of pain relief analysed in both treatment arms. The chi-square statistics is 1.85 & the p value is .397. There is no significant difference in Onset of pain relief between the two treatment arms [Vide Table 3]

**Table 3: Onset of pain relief in both treatment arms Onset of pain relief.**

| Post RT | arm A(n=17) | arm B(n=18) |
|---|---|---|
| 3rd day | 13 | 10 |
| 7th day | 2 | 3 |
| 14th day | 2 | 5 |

Grades of acute Toxicity analysed in the both treatment arms and there is no significant difference in Grades of acute toxicity between two treatment arms [Vide Table 4]

**Table 4: Grades of acute toxicity in both treatment arms**

| Toxicity | Grades | Arm A | Arm B | Total | P value |
|---|---|---|---|---|---|
| Skin | 1 | 5 | 5 | 10 | .714393. |
| | 2 | 3 | 2 | 5 | |
| Upper G.i | 1 | 3 | 4 | 7 | .459426 |
| | 2 | 4 | 2 | 6 | |
| | 3 | 1 | 0 | 1 | |
| Lower G.I. | 2 | 2 | 3 | 5 | .273322. |
| | 3 | 1 | 0 | 1 | |
| Haematological (anaemia) | 1 | 1 | 2 | 3 | .497374 |
| | 2 | 4 | 3 | 7 | |
| | 3 | 1 | 0 | 1 | |

There is no significant difference in Grades of acute toxicity between two treatment arms.

## DISCUSSION

In our study, age of the patient at presentation ranged from 30 years to 70 years with majority of patient in their 5th and 6thdecades (37.1% and 34.3% respectively).Salonia et al in his study of 1107 patients reported majority of age of presentation of bone metastases is in the 6thdecades and above.[4]

In our study vertebra was the most common bone involved(80%).Among the vertebra involved, thoracic vertebra constituted the majority (50%).It was followed by lumber vertebra and cervical vertebra. Asdourian et al reported that axial skeleton is the common site of bone metastases most commonly occurring in spine & pelvis. The lumbar spine is the single most frequent site of bone metastases.[3]

In our study 17.1% of patients experienced complete relief and 82.9% patients expresses partial pain relief. Findings are consistent with the published study such as Okawa T et al 1988. But, Tong et al reported that 53% of patients obtaining complete relief but the rest of the patients experiencing partial relief.[5]

The present study showing significant improvement in the mean numeric pain rating score in patients with painful bone metastases. Our result is comparable with findings of published study.[1,6]

The present study also compares the time to onset of pain relief between the treatment arms. All of the patients reported onset of improvement within the first 3 weeks of starting EBRT/EBRT along with zoledronic acid. This findings is consistent with the findings of published study.[7]

In our study, skeletal related events seen in 6 patients in arm A and 1 patient in arm B. Findings are consistent with the published study. Systematic review and meta-analysis revealed that bisphosphonates can reduce the risk of developing SREs, and help control bone pain.[17]

In our study, acute toxicity such as skin toxicity, anemia, upper G.I. and lower G.I. toxicities are comparable in both treatment arms. All the toxicities observed and managed with conservative treatment.

In our study, we observed the statistically significant difference in mean pain score between two treatment arms in follow-up period from week 4 to week 12 and compared with our findings with previous studies in [Figure 2]. The result of our study provides reflection of reduction of bone pain in both arms as supported by other studies.[1,6]

## CONCLUSION

We conclude in this study that three weekly Inj. Zoledronic acid along with EBRT is more effective treatment option alone with better pain relief than EBRT & similar toxicity profiles and justifies the use of concomitant use of EBRT and Inj. Zoledronic acid. However, further studies with large sample size and long term follow-up are necessary to draw a definite conclusion.

Compliance with Ethical Standards

Ethical approval: All procedures followed were in accordance with the ethical standards of the ethical committee on human experimentation (Institutional) and with the Helsinki Declaration of 1975.

Informed consent taken from each patient before randomization.

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**How to cite this article:** Ghosh BN, Chandra B, Mukherjee P, Kumar S. Prospective Randomized Comparative Study of External Beam Radiotherapy Along with Three Weekly Zoledronic Acid versus External Beam Radiotherapy Alone in Metastatic Bone Disease for Palliation of Pain. Ann. Int. Med. Den. Res. 2021; 7(2):RD18-RD21.

**Source of Support:** Nil, **Conflict of Interest:** None declared