

## ORIGINAL ARTICLE

## COMPARISON OF ORAL VERSUS INTRAVENOUS CLODRONATE IN PATIENTS WITH SKELETAL METASTASIS WITH RESPECT TO BONE MINERAL DENSITY AND PAIN SCORE

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**Background:** Clodronate is a bisphosphonate available both in oral as well as intravenous formulations. It is one of the effective drugs painful skeletal metastasis. The present study aimed at comparison of oral vs intravenous formulation with regard to improvement in bone mineral density and pain score among patients having skeletal metastasis. **Methods:** Two hundred patients having any cancer with skeletal metastasis were included in the study. They were given either oral Clodronate or intravenous Clodronate for six months and a comparison was made between them with regard to improvement in bone mineral density and pain score. **Results:** Out of 200 patients 135 were males and 65 females with a mean age of 54 years. Mean T score of patients on oral treatment before start of treatment was -2.42 that improved to -2.15 ( $p<0.005$ ) after 6 months of therapy. Mean T-score of patients on intravenous therapy at baseline was -2.37 also improved to -2.11 ( $p<0.005$ ) after 6 months of therapy. The two arms of treatment did not show statistically significant difference in pre- and post-treatment T scores. The mean pain score of the patients receiving oral Clodronate at the start of treatment was 7.33 that improved to 3.13 ( $p<0.005$ ) while among patients on intravenous Clodronate it improved from 7.37 to 3.11 ( $p<0.005$ ). The comparative improvement in pain scores in the two arms was not significantly different ( $p=0.909$ ). **Conclusion:** Clodronate improves both T score on DEXA-scan and pain score among patients with skeletal metastasis irrespective of the route of administration.

**Keywords:** Clodronate, DEXA scan, skeletal metastasis

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### INTRODUCTION

Bone metastases are most frequent in breast and prostate carcinomas, and they affect two thirds to three quarters of patients with advanced disease from these tumours. In addition, lung, thyroid, and renal cell carcinomas metastasize to bone in approximately 30% to 40% of cases.<sup>1</sup> The morbidity associated with metastatic bone disease, often referred to as skeletal-related events or SREs, includes pain that may require opiates, the need for radiotherapy and/or surgery, hypercalcemia, pathologic fractures and spinal cord compression. It is now generally accepted that osteoclast activation is the key step in the establishment and growth of bone metastases. After administration, bisphosphonates bind avidly to exposed bone mineral, and during bone resorption, bisphosphonates are internalized by the osteoclasts and subsequently cause apoptotic cell death. Biochemical data indicate that bone resorption is of importance not only in classic lytic diseases such as myeloma and breast cancer but also in prostate cancer.<sup>2</sup> Thus, the osteoclast is a key therapeutic target for skeletal metastases irrespective of the tissue of origin.

Clodronate being the most cost-effective bisphosphonate is commonly used in oncology practice. The present study compared the effectiveness of this medicine with regard to route of administration by comparing the effect on bone mineral density and pain score. The results may help in guiding towards the

optimum route of administration especially keeping in view the compliance of patients in this part of the world.

### MATERIAL AND METHODS

A total of 200 patients were included in the study who were divided into two groups with one group being given oral and the other one given intravenous Clodronate. Inclusion criteria was patients with a histological diagnosis of primary cancers having positive bone scans for bone metastasis, life expectancy of  $\geq 1$  year, Eastern Cooperative Oncology Group (ECOG) Performance Status of  $\leq 1$ , age  $>18$  years, normal haematological and biochemical profile. Patients with congestive heart failure; Coronary artery disease (CAD); cardiac arrhythmias or uncontrolled hypertension, HIV infection, active clinically serious infections, symptomatic metastatic brain or meningeal tumours, seizures, undergoing renal dialysis, previous or concurrent cancer are excluded from the study. Also, patients receiving previous chemotherapy, immunotherapy or use of biologic response modifiers and pregnant or breast-feeding patients were excluded from the study.

This was a randomized, open-label phase IV post marketing surveillance study. This is conventional treatment protocol for patients with metastatic bone disease. At the base line, apart from routine haematology and chemistry, patients underwent evaluation regarding bone mineral density (BMD) using

DEXA-scan and pain score using visual analogue scale. Two hundred patients were randomized to receive either intravenous Clodronate 1,500 mg once every 28 days or oral Clodronate 1,200 mg once a day on a continuous basis for 6 months. At the end of these 6 months patients were re-assessed for BMD and pain score. Assessment periods consisted of screening visits, monthly visit for 6 months and end of study procedure. Screening visit was used for patient selection based on exclusion and inclusion criteria, tumour staging, prior treatment, documentation like all medicine being used, and relevant medical history. Monthly visit was used for documenting any adverse effect of therapy. End of study procedure was used to fill the case report form (CRF) after 30 days of the last dose of Clodronate.

Bone scan and BMD were performed at the baseline and one month after completion of the 6<sup>th</sup> month of treatment. A comparison was made of the baseline and final assessments done at the completion of 6 months of therapy. Student's *t*-test was used to compare the *T*-scores and pre-and post-treatment pain scores.

## RESULTS

Out of 200 patients 135 were males and 65 females. Mean age of the patients who received oral Clodronate was 64.5±7.94 years while those receiving intravenous Clodronate was 61.12 ±9.65 years.

Mean *T* scores on DEXA scan pre-and post-treatment for both oral and intravenous Clodronate are shown in Table-1. Also shown are the *p*-values for comparison between pre/post and oral/intravenous.

Similarly, the main pain scores pre-and post-treatment for both oral and intravenous Clodronate are shown in Table-2 along with the *p*-values for both the comparisons.

The improvement in *T* score and pain score after 6 months of treatment was significant for both the groups independently showing the beneficial effects of both the treatment arms. However, the comparative improvement in post treatment *T* and pain scores in the two arms was not statistically significant confirming that oral Clodronate was as effective as IV Clodronate.

**Table-1: Comparison of T scores**

Route of administration	T-score on DEXA scan		<i>p</i> -value (pre- vs post)	<i>p</i> -value (oral vs IV)
	Pre-Treatment	Post Treatment		
	Mean	Mean		
Oral Clodronate	-2.46±0.29	-2.09±0.55	<0.001	0.48
IV Clodronate	-2.34±0.43	-2.07±0.38	<0.001	

**Table-2: Comparison of pain scores**

Route of administration	Pain score		<i>p</i> -value (pre- vs post)	<i>p</i> -value (oral vs IV)
	Pre-Treatment	Post Treatment		
	Mean	Mean		
Oral Clodronate	7.16±1.04	3.11±1.29	<0.001	0.69
IV Clodronate	7.56±0.63	3.07±0.94	<0.001	

## DISCUSSION

Although radiotherapy is the treatment of choice for localized bone pain, bisphosphonates provide an additional treatment approach for the relief of bone pain across a range of tumour types. Additionally, the bisphosphonates have become the standard of care for the treatment and prevention of skeletal complications associated with bone metastases in patients with breast cancer and multiple myeloma. More recently, they have also demonstrated benefits in patients with bone metastases secondary to other cancers including prostate cancer, lung cancer, and other solid tumors.<sup>3</sup> The absorption of bisphosphonates from the gut is poor, variable, and dramatically inhibited by food intake. Nevertheless, oral Clodronate has been shown in randomized trials to have good clinical efficacy in breast cancer and multiple myeloma.<sup>4,5</sup> For most patients with multiple myeloma intravenous bisphosphonates have become routine clinical management for most patients with multiple myeloma. Both zoledronic acid<sup>6</sup> and pamidronate<sup>7</sup>, but not ibandronate, have shown comparable efficacy with the choice of preferred agent depending largely on cost and convenience. Over the past 10 years bisphosphonates have become established as a valuable additional approach to the range of current treatments. Bisphosphonates are analogues of pyrophosphate, characterized by a phosphorus-carbon-phosphorus (P-C-P) containing central structure that binds to bone and a variable side chain that determines the relative potency, side effects, and the precise mechanism of action.<sup>8</sup> As already described bisphosphonates act through their anti-osteoclastic activity. Also, bisphosphonates have shown some anti-tumour activity as well.<sup>9</sup> Thus bisphosphonates can improve the overall survival mainly through their activity against bone metastasis. Consensus guidance recommendations indicate that all patients with multiple myeloma and radiologically confirmed bone metastases from breast cancer should receive bisphosphonates from the time of diagnosis and continue indefinitely.<sup>10,11</sup> Bisphosphonates should be administered not only to patients of metastatic bone disease from a primary breast tumour but from other primaries like lung, prostate, renal and thyroid as well.

This study shows a significant improvement in parameters under study, i.e., pain score and bone mineral density calculated by visual analogue scale *T* scores respectively. The mean pain score overall in the two arms before Clodronate was administered was 7.13 and it decreased down to 3.12 after 6 months of therapy with Clodronate. So Clodronate did provide significant clinical benefit overall. But there was no difference when the two arms of study when compared mutually. Mean bone mineral density also improved significantly after six months of therapy but as with pain score, the

difference was not significantly different when the two arms were compared with each other. This showed that there is no clinical difference whether Clodronate is administered intravenously or orally. While selecting the route of administration, other factors can be taken into account like compliance, cost difference and logistics etc. Recently the impact of bisphosphonates on breast cancer incidence and recurrence was studied by evaluating the results of ABCSG-12 trial, AZURE trial and ZO-FAST trial. The current conclusion is that ongoing breast cancer adjuvant clinical trials may provide more evidence regarding the potential of bisphosphonates for breast cancer prevention.<sup>12</sup> Bisphosphonate Clodronate is a pro-drug that has been shown to have potent anticancer activity in non-small-cell lung cancer cells.<sup>13</sup>

## CONCLUSION

Use of Clodronate in patients with bone metastasis confirmed by bone scan significantly reduces pain and increases the bone mineral density. The route of administration was not found to be an important factor in this setting. Other factors like patient compliance, cost, availability and logistics should be considered while selecting the route of administration.

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