

## Clodronate Therapy in Patients with Breast Cancer and Bone Metastases

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### ABSTRACT

**Purpose:** To assess whether clodronate can reduce frequency of skeletal morbidity in women with lytic bone metastases from breast cancer.

**Methods:** Between 1997 and 2001, 167 patients with stage IV breast cancer with bone metastases, were randomly assigned to receive clodronate at a dose of 1600 mg per day orally for 12 months, in addition to the standard specific anti cancer therapy (87 patients) or standard anti cancer therapy only (80 patients). Skeletal complications, including pathological fractures, the need for radiation to bone or bone surgery, spinal cord compression and hypercalcemia (a serum calcium concentration above 12 mg per deciliter (3.0 mmol per liter) or elevated to any degree and requiring treatment) were assessed monthly. Bone pain, use of analgesic drugs, performance status and quality of life were assessed throughout the trial.

**Results:** There was no significant difference between the two groups at study entry regarding clinical characteristics. The median time for first skeletal complication was significantly less in the control group (6.1 vs 9.7 months,  $p = 0.05$ ). The proportion of patients who had any skeletal complication in the clodronate group was in general less than in the control group but the difference was not statistically significant. Bone pains reduction was higher in the clodronate group than the control group, but the difference was insignificant ( $p = 0.09$ ). Clodronate was generally well tolerated and the main side effects were constipation (32%) flatulence/dyspepsia (17%) and anorexia (8%). The overall survival was not affected by clodronate therapy. The median survival was 14 months in the clodronate group and 13.8 months in the control group.

**Conclusions:** Clodronate is an effective supplement to conventional anticancer treatment for breast cancer with bone metastasis. It reduces skeletal complications and relieves symptoms associated with lytic bone lesions. Further clinical trials that recruit a larger number of patients will be needed to clearly define the role of clodronate in metastatic breast cancer.

**Key Words:** Clodronate - Breast cancer - Bone metastases - Bone pain.

### INTRODUCTION

The skeleton is the most common organ to be affected by metastatic breast cancer and the site of disease which produces the greatest morbidity. Skeletal morbidity includes pain requiring radiotherapy, hypercalcemia, pathological fracture and spinal cord or nerve root compression. From randomized trials in advanced breast cancer [1,2], it can be seen that one of these major skeletal complications occurs on average every three to four months. Additionally, metastatic disease may remain confined to the skeleton with the decline in quality of life and eventual death due entirely to skeletal complications.

There is now a much greater understanding of the mechanism underlying the development of bone metastases. Tumor cells within the bone marrow cavity secrete a variety of cytokines that stimulate osteoclasts to resorb bone, leading to cancer-mediated destruction of the skeleton. Bisphosphonates are potent inhibitors of this osteoclastic resorption [3]. Bisphosphonates are natural compounds that are characterized by containing central structure, that is responsible not only for their binding to the mineralized bone matrix but also for their inhibitory effects on bone resorption [4]. Recent studies also suggest that bisphosphonates cause osteoclast apoptosis, with the appearance of distinctive changes in cell and nuclear morphology and may have direct apoptotic effects on tumor cells [5].

Most experience with bisphosphonates for bone pains is from their use for skeletal metastases from advanced breast cancer. The ma-

majority of early studies were open uncontrolled studies, but subsequently, randomized controlled trials of intravenous pamidronate, clodronate, ibandronate and zoledronate have all demonstrated useful pain relief [6].

In various studies especially on breast cancer, myeloma and prostate cancer, the bisphosphonate, clodronate (dichloromethylene diphosphonate,  $\text{Cl}_2$  MDP) has proved to exert a pain relieving effect on bone pain. It has a high affinity for solid phase calcium phosphate, binds to hydroxyapatite and thus accumulate in bone. Clodronate also has been reported to restore normocalcemia in 40% to 80% of treated patients, depending on the tumor type and dose used [7,8].

The aim of this work is to study the role of oral clodronate in reducing skeletal complications and controlling bone pain in patients with bone metastases from breast cancer.

#### PATIENTS AND METHODS

Between 1997 and 2002, 167 patients with stage IV breast cancer that had at least one lytic metastatic bone lesion, were randomly assigned to receive oral clodronate, in addition to the standard chemo or hormonal therapy (87 patients) or a standard chemo or hormonal therapy only without clodronate (80 patients). The patients were treated at Al-Salama, Dr Baksh and Dr Soliman Fakeeh hospitals at Saudia Arabia. All the patients had Eastern Cooperative Oncology Group (ECOG) scores for performance status [9] of 1 to 3 at time of enrollment and an estimated life expectancy of 6 months. The patients were included in the study if they had skeletal event not less than one month before the study.

*Treatment:* After completion of the initial assessment, a daily oral dose of 1600 mg (4 capsules of 400 mg) was given in two divided doses of 2 capsules on an empty stomach, at least one hour before or after meals. Treatment was continued for 12 months. During the trial, the chemotherapy regimen or hormonal treatment received by individual patient could be changed or discontinued by the treating physician according to disease response.

*Evaluation of response:* All patients were re-evaluated at monthly intervals for skeletal complications, including pathologic fractures,

the need for radiation to bone or bone surgery, spinal cord compression and hypercalcemia (a serum calcium concentration above 12 mg per deciliter or elevated to any degree and requiring treatment). Bone pain, was assessed using a scoring system that quantified both severity and frequency of bone pain. Bone pain scores were calculated by multiplying the score for pain severity (graded from 0 to 3) by the score for pain frequency (0 to 3). A score of 0 indicates no bone pain and a score of 9 indicates constant, severe pain. The use of analgesic drugs and performance status life were assessed throughout the trial. Good response to clodronate therapy was recorded when more than 50% reduction of pretreatment pain was found, while poor response occurred when there was no response or decrease of pain by less than 50% of pain intensity compared with pretreatment assessment.

The regular assessments included also evaluation of progression of disease with development of visceral metastases or new bone metastases. Radiographic surveys of the skeleton and bone scan were performed before entry into the study and every 6 months during the trial. A vertebral fracture was defined as a loss of at least 25 percent of vertebral-body height.

*Statistical analysis:* All relevant baseline data were tabulated and summarized by frequency and percentage for qualitative item and by calculating the mean, the median, extreme values and the standard deviation for quantitative item. Statistical analyses were done using the Chi-square and the Log rank tests.

#### RESULTS

In this trial 167 patients with breast cancer and bone metastases were enrolled; 87 were allocated in clodronate group and 80 patients in the control group. There were no significant difference between the two groups at the study entry with respect to age, menopausal status, grade of tumor, estrogen receptor status, site of metastases and previous or concurrent treatment of cancer (Table 1). In clodronate group, 52 (60%) were post-menopausal, 62 (71%) had grade II tumors and 58 (67%) were estrogen receptor positive patients. Chemotherapy and/or hormonal therapy was given to 95% of the clodronate group patients compared to 94% in the control group patients.

Eighty-seven patients in the study completed 6 months of clodronate treatment at least and were candidates for response assessment. Withdrawal of the drug had occurred in 6 patients. Withdrawal was due to side effects of clodronate in 3, patient choice in 1 and due to unknown causes in 2 patients. Elevated serum calcium was encountered in 6 patients before starting treatment with clodronate, which was controlled within three weeks of starting clodronate therapy. On the other hand, the hypercalcemia encountered in the control group (3 patients) was well controlled by intravenous fluid and steroids therapy.

The median time for first skeletal complication was significantly less in the control group (6.1 vs 9.7 months,  $p = 0.05$ ). Table (2) shows the proportion of skeletal complications in both groups. The proportion of patients who had any skeletal complication in the clodronate group was in general less than in the control group especially at  $\geq 6$  months of treatment, but the difference was not statistically significant. The proportion of patients in the clodronate group who had vertebral pathologic fracture was 18% at 9 months vs 28% in the control group ( $p = 0.16$ ). The proportion of patients in the clodronate group who had any radiation to bone at 12 months was insignificantly lower than that in the control group (31% Vs 40%, respectively).

Bone pain evaluation showed that fifty-five patients (63%) in the clodronate group experienced good response with more than 50% reduction in bone pain with decreased analgesic therapy requirements. Eighteen patients experienced bone pain reduction within the first two months of clodronate treatment. The response in the control group was found in 37 patients (46%) and poor or no response in 43 patients (54%). Although the response in clodronate group was higher than that in control group, the difference was not statistically significant ( $p = 0.09$ ) (Fig. 1).

Clodronate was generally well tolerated and few side effects were recorded the main side effects were on the gastrointestinal tract especially constipation which occurred in 32% of patients, flatulence/dyspepsia in 17% and anorexia in 8% of patients. Other minor side effects reported were nausea (3%), intolerance to the drug (2%) and allergic skin rash (1%). There

was no reported hematological, renal or hepatic toxicity in this study (Table 3).

The overall survival was not affected by clodronate therapy. The median survival was 14 months in the clodronate group and 13.8 months in the control group.

Table (1): Clinical characteristics of the 167 patients in the study.

Characteristic	Clodronate group	Control group
Number of patients	87	80
Age range (median $\pm$ SD)	33-71 (50 $\pm$ 10.7)	38-72 (52.5 $\pm$ 10.5)
<i>Menopausal status:</i>		
Pre-menopausal	35 (40%)	29 (36%)
Postmenopausal	52 (60%)	51 (64%)
<i>Pathological grades:</i>		
Grade I	4 (5%)	13 (16%)
Grade II	62 (71%)	42 (53%)
Grade III	21 (24%)	25 (31%)
<i>ER status:</i>		
Positive	58 (67%)	48 (60%)
Negative	17 (19%)	17 (21%)
Unknown	12 (14%)	15 (19%)
<i>Metastases in addition to bone:</i>		
None	55 (60%)	46 (58%)
Liver	13 (15%)	14 (17%)
Lung	12 (14%)	13 (16%)
Brain	3 (3%)	3 (4%)
Other	7 (8%)	4 (5%)
<i>Specific therapy:</i>		
Chemotherapy	41 (47%)	44 (55%)
Hormonal therapy	35 (40%)	26 (32%)
Both	7 (8%)	7 (9%)
None	4 (5%)	3 (4%)
<i>Concomitant analgesic therapy:</i>		
NSAIDs	50 (57%)	36 (45%)
Narcotic drugs	19 (22%)	25 (31%)
Both	18 (21%)	19 (24%)
<i>ECOG performance score:</i>		
0	22 (25%)	24 (30%)
1	44 (50%)	32 (40%)
2	17 (20%)	18 (23%)
3	4 (5%)	6 (7%)
<i>Serum calcium:</i>		
Normal	52 (60%)	41 (51%)
High	6 (7%)	3 (4%)
Unknown	29 (33%)	36 (45%)
<i>Serum CA-15-3:</i>		
Normal	17 (20%)	17 (21%)
High	59 (68%)	48 (60%)
Unknown	11 (12%)	15 (19%)

Table (2): Incidence of skeletal complications by the end of 3,6,9,12 months of clodronate treatment.

Type of skeletal complication and duration of clodronate treatment (months)	Clodronate group (N=87) No. (%)	Control group (N=80) No. (%)	p-value
<i>Vertebral pathologic fracture:</i>			
3	13 (15)	14 (18)	0.65
6	15 (17)	20 (25)	0.22
9	16 (18)	22 (28)	0.16
12	20 (23)	25 (31)	0.23
<i>Non-vertebral pathologic fracture:</i>			
3	19 (22)	18 (23)	0.92
6	23 (26)	26 (33)	0.39
9	28 (32)	32 (40)	0.29
12	29 (33)	32 (40)	0.37
<i>Spinal cord compression:</i>			
3	4 (5)	4 (5)	0.9
6	9 (10)	9 (11)	0.85
9	9 (10)	10 (13)	0.66
12	13 (15)	14 (18)	0.65
<i>Radiation to bone:</i>			
3	16 (18)	18 (22)	0.51
6	19 (22)	26 (32)	0.12
9	26 (30)	29 (36)	0.38
12	27 (31)	32 (40)	0.23
<i>Surgery to bone:</i>			
3	1 (1)	1 (1)	0.95
6	1 (1)	2 (3)	0.51
9	2 (2)	3 (4)	0.58
12	3 (3)	4 (4)	0.62
<i>Hypercalcemia:</i>			
3	1 (1)	1 (1)	0.95
6	2 (2)	2 (3)	0.92
9	3 (3)	4 (5)	0.62
12	3 (3)	5 (6)	0.40

Table (3): Side effects of clodronate in 87 patients in the study group.

Side effects	Number of patients
Constipation	33 (38%)
Flatulence/dyspepsia	18 (21%)
Anorexia	8 (9%)
Nausea	3 (3%)
Intolerance	2 (2%)
Allergic skin rash	1 (1%)

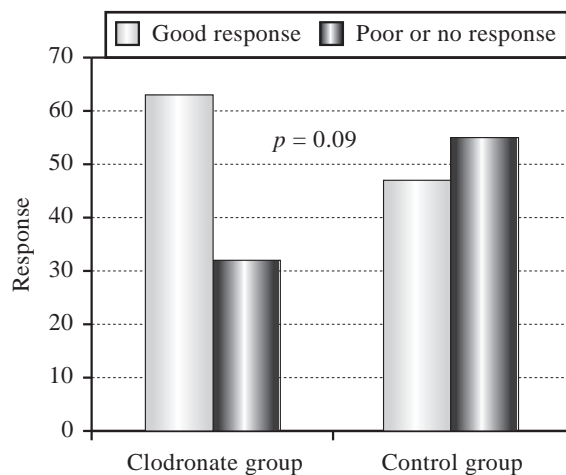


Fig. (1): Pain response in clodronate and control groups.

## DISCUSSION

The morbidity from bone metastases in patients with breast cancer represents a significant health problem and the major clinical manifestation involves osteolytic bone destruction. Depending on the extent of the disease and the site of metastases, patients may be asymptomatic, develop pathological fracture, hypercalcemia, or experience chronic debilitating pain with a significant compromise in quality of life [10].

Besides analgesics drugs, radiotherapy and surgery, there was no specific treatment for cancer-related bone metastases. Cytotoxic chemotherapy or hormonal agents used systemically are associated with only temporarily control of systemic disease. The ultimate prognosis in patients with metastatic breast cancer of the bone is generally poor, but a proportion of these patients may survive longer and this require palliative treatment of the symptoms and complications related to their bone metastases.

The potential value of bisphosphonates in metastatic bone disease was first appreciated in the early 1980. A series of phase II studies demonstrated the activity of bisphosphonates used as single agents in controlling symptomatic osteolytic bone metastases and reducing bone pain. The first prospective placebo-controlled series, on women with metastatic breast cancer, was reported by Elomaa et al. [11] and further analyses of the material were reported in subsequent publications [12,13]. In the original study

a daily dose of 1600 mg clodronate was administered orally for one year to 17 patients and placebo to 17 patients. The results were much more favorable in the first group with decreased analgesic consumption, a lower number of pathological fractures, fewer episodes with hypercalcaemia and reduced need for palliative radiotherapy.

In our study, the median time for first skeletal complication was significantly lower in the control group than in the treated group (6.1 vs 9.7 months,  $p = 0.05$ ). There was a trend for a lower incidence of skeletal complications in the clodronate group compared to the control group, but the difference did not reach statistical significance probably due to the relatively small number of patients.

In breast cancer patients, eight placebo-controlled trials with clodronate or pamidronate have shown retarded progression of lytic bone lesions and decreased frequency of hypercalcaemia, pathological fractures and bone pain [1,2,14-19]. In one study, Kanis et al. [14] evaluated the effects of clodronate on the incidence of skeletal metastases and associated morbidity in women with advanced breast cancer. Patients were either treated with clodronate 1,600 mg/day (66 patients) or placebo (67 patients) for 3 years. Clodronate appeared to decrease the number of patients with multiple fractures. The use of clodronate was associated with a marked and significant decrease in the number of skeletal lesions observed. Trends favoring clodronate use were noted for the frequency of hypercalcaemia, radiotherapy for bone pain and vertebral and non-vertebral fractures with a 26% overall reduction in event rate.

As regards pain response, our results revealed that 55 patients (63%) showed good response to oral clodronate 1600 mg per day, with more than 50% reduction in bone pain with decreased analgesic requirements therapy. Although the response in clodronate group was higher (63%) than that in control group (47.5%), the difference was not statistically significant ( $p = 0.09$ ). A significant useful pain relief was reported in different other studies of bisphosphonates used for skeletal metastases [1,2,6,15,18,20]. Clodronate is not a first-line drug for bone pain, but considering other effects on skeletal morbidity, it is an important alternative or complement to other treatment options in

resistant pain problems. The degree of pain relief with clodronate therapy varies in different studies and difficult to compare, as the assessment of pain relief has not been performed in a standardized way.

Hypercalcaemia of malignancy occurs in approximately 5% to 10% of all patients with malignant diseases. It is particularly frequent complication in patients with metastatic breast carcinoma and lung cancer as well as myelomatosis and certain other malignancies [4]. The efficacy of clodronate in malignancy-induced hypercalcaemia has been documented in several clinical trials. Six out of 87 patients in this study had elevated serum calcium before clodronate therapy and normalization of serum calcium occurred shortly after initiation of oral clodronate therapy. In another study, Elomaa & Blomqvist [21] reported that clodronate inhibits lytic bone destruction, prevents bone fractures and relieve bone pain in addition to the reduction of hypercalcaemia mortality and morbidity caused by osteolysis due to malignancy.

There is considerable disagreement on the choice of bisphosphonate and the optimum route of administration. The American Society of Clinical Oncology (ASCO) recommended the use of intravenous pamidronate in favor of oral alternatives [22]. A preliminary report of a comparison of oral clodronate (2400 mg daily) versus intravenous pamidronate (60mg every 3 weeks) or clodronate (900 mg every 3 weeks) has been published [23]. This suggested little difference between iv pamidronate and oral clodronate in preventing vertebral fractures but confirmed the superiority of iv therapy for relieving bone pain. A smaller detailed short-term study revealed that the usual dose of clodronate (1600 mg daily), with or without an intravenous loading dose, was less effective than monthly pamidronate in inhibiting bone resorption, as measured by collagen cross-link excretion and relieving bone pain [24]. The symptomatic efficacy appeared to be dose dependent, particularly for the oral agents, because of poor absorption.

Future trials using a new generation of more potent bisphosphonate-zoledronate and ibandronate may offer more effective palliative options. The optimum time in the course of the disease to start bisphosphonates remains uncertain, but once treatment is initiated, patient

should continue to receive bisphosphonate treatment for as long as the skeleton is the dominant site of metastases.

Clodronate was well tolerated without any serious adverse events with its use. The main side effects of clodronate in this study were gastrointestinal upset in the form of constipation (38%), flatulence and dyspepsia in (21%) and anorexia (9%). Hannuniemi and colleagues [25] reported that the incidence of gastrointestinal disturbances with oral administration of clodronate ranged from 2 to 10%. Others have indicated that approximately 10% of patients receiving clodronate orally at dosages of 1600 mg/day or higher developed gastrointestinal disturbances [4]. The results of a recent long-term randomized placebo-controlled trial of 1079 breast cancer patients, spanning a total time-period of 11 years, confirmed the favourable tolerability and safety profile of oral clodronate when given as a dose of 1600 mg daily for two years [26].

In conclusion clodronate is an effective supplement to conventional anticancer treatment for the reduction of skeletal complications and the relief of symptoms associated with lytic bone lesions due to metastatic breast cancer. Further clinical trials that recruit a larger number of patients will be needed to clearly define the role of clodronate in metastatic breast cancer.

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