# Reduction of visible bone metastases by clodronate therapy in breast cancer

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**Summary**

The current report describes a 57-year-old patient with multiple bone metastases 14 years after her initial treatment for breast cancer. The only therapy the patient received for her osteolytic lesions was oral clodronate (800 mg/daily), as she refused any other kind of treatment. On bone scintigraphy the number of visible bone metastases diminished slowly and after two years only a few minor lesions could be seen. Together with this report the value of oral clodronate as anti-osteolytic therapy in breast cancer patients is discussed.

*Key words:* Bone metastases; Breast cancer; Clodronate therapy; Reduction.

## Introduction

Bone metastases are the most common sign of a disseminated breast cancer. In one-quarter of women with advanced breast cancer the skeleton is the only detectable site of metastases. It is estimated that up to 90% of patients dying with breast disease have bone metastasis [1]. The median duration of survival in patients with bone metastases alone is 24 months; 20% of patients are alive at five years [2]. The duration of survival of patients with visceral involvement is much shorter, usually a matter of a few months [3]. Thus, patients with bone metastases have skeletal morbidity for a significant portion of their remaining years. Chemotherapy, hormonal therapy, local radiation or surgery can lead to symptomatic relief, however the majority of patients will have progressive osteolysis under these treatments.

Tumour-induced osteolysis or lytic bone disease is mediated by osteoclast activation. Interfering with these bone-resorbing cells appears to be a logical target for the treatment and the prevention of this tumour-induced osteolysis. Biphosphonates have an affinity for bone and are preferentially delivered to sites of increased bone formation or resorption [4]. Once deposited on the surface of the bone, the biphosphonates are ingested by osteoclasts that are engaged in bone resorption, leading to an inhibition of osteoclast function [5]. Several double-blind randomised trials have shown that the use of biphosphonates in breast cancer patients significantly reduces the number of skeletal events and the incidence of hypercalcemic episodes [5-7]. In this context we wish to report our observation of a breast cancer patient with bone metastases, where treatment with oral clodronate not only prevented the development of new bone metastases, but also reduced the existing bone lesions.

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## Case Report

At the age of 40, the patient was diagnosed with acute myeloid leukaemia (AML) of the monoblastic type. The initial treatment consisted of adriamycin, vincristine and cytosine arabinoside. A complete remission was achieved with this therapy. At the age of 42 she was diagnosed and treated for an extensive ductal carcinoma in situ of the left breast. The treatment was performed in another hospital and consisted of a mastectomy with axillary lymph node dissection. All the 19 removed lymph nodes were tumour-free and no further adjuvant therapy was given. At the age of 43, three years after her initial diagnosis of AML, the patient relapsed of this disease. Again complete remission was achieved, this time with daunorubidomycin, vincristine, cytosine and arabinoside followed by treatment with amsacrine, azacytidine and cytosine arabinoside. A second recurrence of AML occurred nine years after the first relapse. Again a complete remission was achieved this time with amsacrine and etoposide followed by mitoxantrone and cytosine arabinoside and finally by a bone marrow transplantation. Following this treatment she went into complete remission of AML and has remained in this condition for more than seven years now. Five years after the autologus bone marrow transplant and 14 years after the diagnosis of breast cancer the patient consulted the emergency ward because of a sudden pain in the right half of the chest. The diagnosis of a spontaneous fracture of the 9th right rib was made. Bone scintigraphy revealed multiple hyperfixation spots, compatible with bone metastases (Figure 1a). Except for the 9th rib fracture no osteolytic change was seen with conventional X-ray examination. Clinical examination, mammography and ultrasonography excluded a tumour in the right breast. Peripheral blood examination showed slight anaemia (Hb 10.9 g/dl), normal thrombocyte and leukocyte counts with a normal white cell differential count. It was concluded that the bone metastases were of breast cancer origin, which had been diagnosed 14 years earlier. The patient refused all invasive investigations and any kind of chemotherapy, radiotherapy or hormonal treatment. The only medication the patient received was clodronate 2 x 400 mg daily and painkillers when needed. Over time the number of bone metastases slowly decreased. At present more than two years after the diagnosis of the bone metastases, only minor lesions can be seen on bone scintigraphy (Figure 1b) and the quality of life has considerably improved.

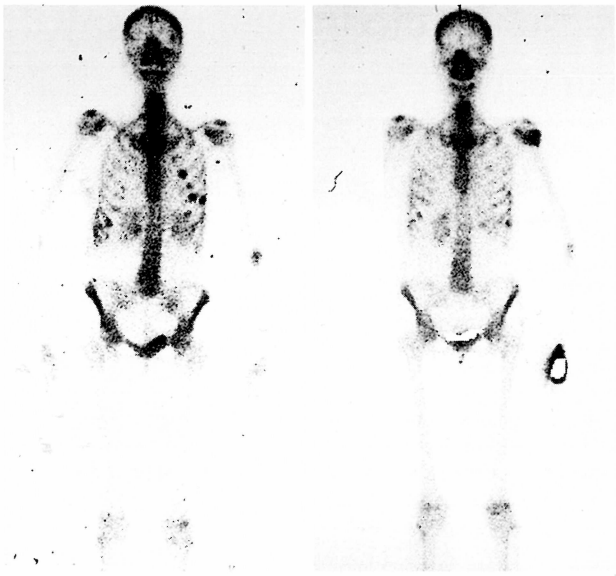

Figure 1. — Bone scintigraphy: (a) before treatment revealing multiple hyperfixation spots, compatible with bone metastases and (b) two years after treatment with 2 x 400 mg clodronate daily.

## Discussion

Bone metastases are the first sign of relapse in about half of the patients with breast cancer. If a ductal carcinoma in situ is treated by mastectomy, there is only a very small risk for an occult carcinoma in the residual breast tissue. In these cases, the local relapse rate and mortality rate is estimated to be as high as 3.1% and 2.5%, respectively [8]. Therefore the present case showing occurrence of bone metastasis 14 years after a mastectomy for an in situ carcinoma has to be considered a rare event.

In physiological circumstances the osteoclasts resorb bone during remodelling and repair [9]. Pathological situations arise when there is only excessive bone resorption, resulting in osteolysis. Osteolytic lesions can cause a wide range of complications including bone pain, impending fractures, pathologic fractures, hypercalcemic episodes and spinal cord compression [4]. Biphosphonates are internalised by osteoclasts, where they cause a disruption of the bone resorption process.

Over the years several studies have used bisphosphonates to reduce skeletal complications of bone metastases, both in patients with breast cancer and in those with multiple myeloma. The outcome of these studies showed a decrease in bone pain, sclerosis of lytic lesions, reduction in pathological fractures and hypercalcemia. The significant reduction in skeletal morbidity led to a significant decrease in the need to perform radiotherapy and surgery to the bone [10]. Another advantage was that the treatment could be used in previously irradiated or operated skeletal sites.

The current case describes a reduction of the number of visible bone metastases on bone scintigraphy and a diminishing of the related symptoms. This case is unique due to the fact that the patient only received oral clodronate. The optimal dose of oral clodronate is probably 1600 mg daily [10], however only 4 to 5% of it is absorbed. Oral therapy is considered to be safe and has a low rate of side-effects [10].

Until now, there are three published studies, which indicate a role for oral clodronate in the prevention of bone metastases [6-10]. Reducing the problems associated with bone metastasis will have a significant impact on the quality of life. The current case history illustrates an important role for biphosphonates in metastasized breast cancer patients. Further research is required in order to confirm and to elucidate this role.

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