Eur J Cancer, Vol. 28A, No. 4/5, pp. 890–893, 1992.
Printed in Great Britain

0964–1947/92 $5.00 + 0.00

Intravenous Clodronate for the Treatment of Hypercalcaemia in Breast Cancer Patients with Bone Metastases—A Prospective Randomised Placebo-controlled Multicentre Study

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In a double blind randomised multicentre study the effect of intravenous clodronate plus hydration was compared with placebo plus hydration in the treatment of hypercalcaemia in breast cancer patients with bone metastases. The patients were treated either with hydration plus clodronate 300 mg/day or hydration plus placebo, up to 7 days or until serum ionised calcium was below 1.4 mmol/l. 25 patients received clodronate and 19 placebo. A significant difference in favour of clodronate was observed in the time to reach normocalcaemia ($P = 0.004$) and in the number of patients achieving normocalcaemia ($P = 0.0003$). 17 patients of 21 evaluable patients on clodronate achieved normocalcaemia compared with 4 of 19 patients on placebo. The only adverse event clearly associated with clodronate was symptomatic hypocalcaemia in 1 patient. Thus, clodronate seems to be a safe and highly efficacious drug for the treatment of hypercalcaemia in breast cancer patients.
Eur J Cancer, Vol. 28A, No. 4/5, pp. 890–893, 1992.

INTRODUCTION

HYPERCALCAEMIA IS a potentially life-threatening complication of malignancy and occurs most frequently in patients with evidence of bone metastases. Up to 85% of patients with breast cancer develop bone metastases [1] and approximately 15% of these develop hypercalcaemia [2]. In most cases hypercalcaemia in these patients is considered to be caused by increased bone resorption by osteoclasts. Activation of osteoclast activity is probably mediated by a variety of factors such as hormones, growth factors, prostaglandins and cytokines [3]. Previous treatments of hypercalcaemia consisted of hydration, steroids, diuretics, mitramycin and/or calcitonin. All these treatments, however, are associated with different problems such as short duration, toxicity or lack of efficacy.

Clodronate is a bisphosphonate analogue to inorganic pyrophosphate, which resists hydrolysis and inhibits bone resorption by osteoclasts [4]. The intravenous formulation of clodronate has been used in a number of studies in the treatment of hypercalcaemia of malignancy in cancer patients [5–12]. However, these studies mostly included patients with different types of malignancies or did not include appropriate controls. Therefore, data on efficacy and safety from double blind placebo controlled studies are needed. The present study evaluates the efficacy and safety of intravenous clodronate plus hydration compared with placebo plus hydration in the management of hypercalcaemia with bone metastases in breast cancer patients. Ionised serum calcium, which is the physiologically significant parameter and is unaffected by changes in plasma protein levels, was used to determine the degree of hypercalcaemia. The primary efficacy endpoint was time to reach normocalcaemia, defined as serum ionised calcium value below 1.40 mmol/l.

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This paper was presented at the EORTC Breast Cancer Working Conference, 3–6 September 1991, Leuven, Belgium.
Revised and accepted 5 Dec. 1991.

PATIENTS AND METHODS

Female patients with bone metastases due to histologically confirmed breast cancer and hypercalcaemia, defined as ionised serum calcium above 1.60 mmol/l, were hydrated with 2–4 l 0.9% NaCl for 12–24 h. If ionised serum calcium was still above 1.60 mmol/l after hydration the patients were randomly allocated with equal probability to treatment with either clodronate 300 mg/day or placebo, both combined with further hydration. Prior to randomisation the patients were stratified according to the number of previous hypercalcaemic episodes. The treatment was given in a double blind manner. A full medical history and a physical examination were performed for each patient. Patients were excluded, however, if they had any other disease known to cause hypercalcaemia or a serum creatinine >250 μmol/l. Furthermore, any previous treatment with any bisphosphonate or any treatment within 14 days before inclusion in the study with steroids, thiazides, calcitonin or mitramycin led to exclusion. Patients with a history of malignant neoplasms other than breast cancer were also excluded. Stable concomitant therapy of hormone therapy and/or chemotherapy and/or diuretics was allowed but radiation therapy was not allowed during the treatment period. Prior to study entry the patients could also have received surgery for their breast cancer and/or radiotherapy

to the primary tumour site and/or metastatic site. Clodronate and placebo were given intravenously in 500 ml 0.9% NaCl over 3 h once a day. The treatment was continued up to 7 days or until serum ionised calcium was below 1.40 mmol/l. If no response to treatment was observed within 72 h ($S\text{-}Ca^{2+}$ > baseline level) the patient could be withdrawn. The patients were concomitantly given a minimum of 1.5 l 0.9% NaCl daily intravenously. Blood samples were taken daily up to the day after termination of the study. In serum, total and ionised calcium, creatinine, sodium, potassium, magnesium and albumin were determined. In addition, blood counts and liver function tests were performed at entry and on the day after termination of treatment, as well as a collection of a 10–12 h fasting urine specimen. In urine, hydroxyproline, phosphate, calcium and creatinine were determined.

All patients gave their consent to participate and the study was approved by the ethical committee at each of the seven participating centres. The primary endpoint was the number of days to reach normocalcaemia (serum ionised calcium < 1.40 mmol/). The analysis was performed using the logrank test. In the logrank analysis all patients were included who had at least one ionised calcium value during treatment available. Two methods were used for the logrank analysis: (a) withdrawals due to lack of efficacy or death were treated as if they had remained hypercalcaemic up to 8 days; other patients with missing data were censored on the last day for which a value was available and (b) all patients with missing data, whatever the cause, were censored on the last day for which a value was available.

The number of patients achieving normocalcaemia was also compared between the two treatments (Fisher's exact test).

RESULTS

44 patients aged between 36 and 82 years were included at 6 Swedish centres and 1 Danish centre. By chance 25 received clodronate (median age 51) and 19 received placebo (median age 55). Of the 44 patients 13 were above 65 years of age. 43 of the 44 patients had bone metastases, but in one of the 43 patients bone metastases was diagnosed one day after entry. 6 patients (4 on clodronate and 2 on placebo) had experienced one or more previous episodes of hypercalcaemia. Prior to study entry, 36 of the 44 patients had received surgery for their breast cancer. 12 patients had received radiotherapy to the primary tumour site alone, 13 to the primary site plus metastatic sites and 6 to metastatic sites alone. 25 patients had been treated with chemotherapy and 29 with hormone therapy.

Of the 44 included patients, 36 patients were hypercalcaemic according to the study definition. For the other 8 patients, 3 patients (on placebo) had ionised calcium values between 1.4 and 1.6 mmol/l, 3 patients had no value available at day of entry (2 on clodronate and 1 on placebo) but had values on day 2 between 1.51 and 2.10 mmol/l and for 2 patients (on clodronate) no ionised calcium value was available (total serum calcium was however increased).

In the analysis of number of days to reach normocalcaemia, 2 patients were excluded due to lack of any value of ionised serum calcium. Thus, 42 patients were included in the analysis of number of days to reach normocalcaemia (log rank test). The result shows that the number of days to reach normocalcaemia was shorter with clodronate than with placebo, regardless of whether method (a) or (b) was used in the logrank analysis. A significant difference in favour of clodronate was shown as well in method (a), $P = 0.0004$, as in method (b), $P = 0.0014$.

In the analysis of number of patients who responded to treatment, defined as ionised serum calcium level below 1.40 mmol/l within 7 days, 4 patients (clodronate arm) of 44 included were excluded because of either too few or lack of ionised serum calcium values. Thus, 21 of the 25 patients in the clodronate arm and 19 in the placebo arm were evaluable for analysis. The individual ionised serum calcium for the 21 patients treated with clodronate are shown in Fig. 1 and for the 19 patients treated with placebo in Fig. 2. 4 of 21 patients treated with clodronate failed to achieve normocalcaemia. In 3 of these patients a fall in ionised calcium from 2.00 to 1.43, 1.70 to 1.40 mmol/l and 2.04 to 1.64 mmol/l, respectively, was observed. The fourth died on day 2 because of progressive disease. Thus, of the 21 evaluable

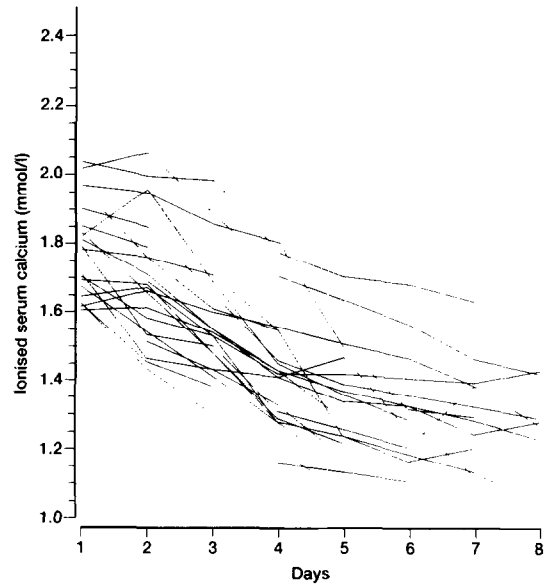

Fig. 1. Individual ionised serum calcium curves for 21 patients treated with clodronate up to 7 days or until normocalcaemia < 1.40 mmol/l.

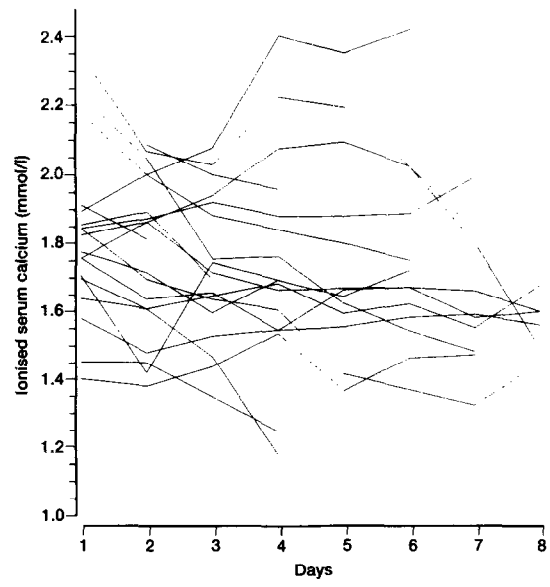

Fig. 2. Individual ionised serum calcium curves for 19 patients treated with placebo up to 7 days or until normocalcaemia < 1.40 mmol/l.

Table 1. Number of patients who responded to treatment and the number of days for these patients to reach normocalcaemia

	No. of patients		
No. of days	Clodronate	Placebo	Total
2	0	1	1
3	2	0	2
4	5	2	7
5	7	0	7
6	2	0	2
7	1	1	2
Total	17	4	21

patients on clodronate, 17 (81%) became normocalcaemic within 7 days. In the placebo arm 4 patients out of 19 (21%) became normocalcaemic within 7 days. The difference between the two treatments were significant in favour of clodronate (Fisher's exact test, $P = 0.0003$). Number of days to reach normocalcaemia for those patients who responded to treatment is shown in Table 1.

The mean values for serum ionised calcium at start and end of the study were also calculated. At day of entry, the clodronate group ($n = 20$) had a mean of 1.76 mmol/l and the placebo group ($n = 18$) a mean of 1.83 mmol/l. At end of study the mean were 1.26 mmol/l for the clodronate group and 1.66 mmol/l in the placebo group. 6 patients were excluded as 4 patients had missing ionised calcium values, 1 patient died on day 2 and 1 was withdrawn on day 2 because of progressive disease (placebo).

Data on urinary concentration of hydroxyproline and calcium were available only in a limited number of patients. The calcium to creatinine ratio (mmol/mmol) was only available for 7 patients on clodronate and 6 patients on placebo. However, the mean value for clodronate fell from 2.24 to 0.56 and a slight decrease was observed for placebo (2.48 to 2.17). In the analysis of the hydroxyprolin/creatinine ratio (μmol/mmol), 6 patients were available for analysis in the clodronate group and 6 in the placebo group. A fall in the clodronate arm from 75 to 39 was observed and a rise in the placebo arm from 63 to 86.

Adverse events were reported for 5 patients on clodronate and one on placebo. 1 patient died during treatment with clodronate due to progressive malignant disease with liver failure, progressive bone metastases and hypercalcaemia. Liver and renal failure had been present at the time of entry into the study. 1 patient had diarrhoea for 24 h, 1 day after end of treatment. Fluid retention was reported in 2 patients probably due to excess of daily rehydration and 1 patient developed mild paraesthesia. 1 patient on placebo was withdrawn because of pulmonary oedema, somnolence and severe deterioration due to progressive disease.

Haematology and clinical chemistry values at the start and end of study treatment were also investigated. Hypocalcaemia was observed in 4 patients on clodronate post treatment. 3 patients were asymptomatic but 1 patient on clodronate developed mild paraesthesia in her hands and feet for 2 days. No significant change in median values for haematological parameters for either treatment was observed.

Hypokalaemia was observed in 8 patients on clodronate and 9 on placebo, and hypomagnesaemia in 4 cases on clodronate and 4 on placebo. A fall in median values for urea was observed in both groups but most marked in the placebo arm. However, no significant changes in median serum creatinine for either treatment was observed. Median values for serum bilirubin, ALAT and ASAT showed no significant change for either treatment.

DISCUSSION

This investigation confirms that hydration plus clodronate is efficacious in the treatment of hypercalcaemia due to malignancy in breast cancer patients. In this report as opposed to previous studies ionised serum calcium were used to measure the efficacy of the treatment. In addition, it also shows that only continuous hydration of the patient is not enough in the treatment of the hypercalcaemia due to malignancy. Earlier studies showed a heterogeneity concerning doses administered, duration of therapy and patient populations [5–12]. However, in two studies [7, 12] the same intravenous dose of 300 mg/day and duration of therapy has been used with total serum calcium as the parameter and the results were similar to the present study. Most patients reach normocalcaemia within 5 days of treatment which is in agreement with previous results with clodronate [5, 6, 9, 12]. In some studies single dose intravenous therapy with clodronate also seems to be effective [7, 10, 11] and normocalcaemia was reached within 5 days [10, 11]. Further investigations are warranted to elucidate which dosage method is optimal for intravenous administration of clodronate in the treatment of hypercalcaemia caused by different malignancies. In our study as well as in other investigations [6, 9–12] both calcium/creatinine and hydroxyproline/creatinine ratios were decreased.

In general adverse events were well balanced between the two treatment groups except for hypocalcaemia. Hypocalcaemia was observed in 4 patients in the clodronate group. 1 of these patients developed mild paraesthesiae for 2 days. When calcium values were normalised a complete regression of symptoms occurred. It was also noticed that this patient received treatment 1 day after normocalcaemia was reached, a fact that might have contributed to the observed symptoms. The only adverse event that could be related to the clodronate treatment with certainty was thus hypocalcaemia.

In conclusion, this double blind study confirms that clodronate is a potent agent and well tolerated in the treatment of hypercalcaemia in breast cancer patients with bone metastases.

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Eur J Cancer, Vol. 28A, No. 4/5, pp. 893–895, 1992.
Printed in Great Britain

0964–1947/92 $5.00 + 0.00

Breast Cancer After a Negative Screen: Follow-up of Women Participating in the DOM Screening Programme

Cecile T.M. Brekelmans, Hubertine J.A. Collette, Corinne Collette, Jacques Fracheboud and Frits de Waard

First-round screening results for women participating in the DOM project (a screening programme for early detection of breast cancer) are described for the age groups 40–49 and 50–64 at entry. In the younger age group, a low pick-up rate (1.96 per 1000) in proportion to the expected incidence rate in the absence of screening (1.46 per 1000) was found. For the older age group, these rates were 4.25 and 2.03, respectively, per 1000. Interval cancers occurred (relatively) more frequently in younger women. After 2 years the ratio between interval-cancers and screen-detected tumours was about 1:1 in the younger age group and 1:2.5 in the older age group. These different results can be caused by too low a sensitivity of mammography and/or a higher tumour growth rate at a young age. The sensitivity of the screen at various periods of follow-up, was compared: a rapidly decreasing sensitivity of mammography was seen for women under the age of 50, in contrast to a slower decrease for women over this age. This rapid decrease may be caused by a relatively high tumour growth rate in younger women.
Eur J Cancer, Vol. 28A, No. 4/5, pp. 893–895, 1992.

INTRODUCTION

In 1974, a population-based non-randomised screening programme for the early detection of breast cancer was started in the city of Utrecht (The Netherlands), the DOM project. In the beginning it was limited to the 1911–1925 birth cohort (women aged 50–64 at entry). The study design and results for this birth cohort have been described previously [1, 2]. From 1981 on other birth cohorts, including women aged 40–49, were also invited [3].

This gave us the opportunity to study the effect of screening in various age groups. It is known from other projects that screening results for women under the age of 50 are not promising [4–8]. One of the parameters to evaluate the (early) effect of screening is the number of cancers occurring after a negative screen, the so-called interval cancers.

High numbers of interval cancers within 2 years after a negative screen in women under the age of 50 are described [9, 10]. This can be explained by too low a sensitivity of mammography or a high tumour growth rate in young women. In order to differentiate between these two possibilities, information on age-specific tumour growth rate and distribution of the preclinical detectable phase is needed.

The purpose of this paper is to add some material to the discussion on whether or not to screen women under the age of 50.

PATIENTS AND METHODS

In 1974–1987, four successive birth cohorts of women living in the city of Utrecht and its suburbs, were invited for screening, with different study designs.

In this study we were interested in the 2-year follow-up of women after the first negative screen. For this reason the 1911–1925 birth cohort, that was offered a second screen after 1 year, was excluded.

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This paper was presented at the EORTC Breast Cancer Working Conference, 3–6 September 1991, Leuven, Belgium.
Revised 16 Dec. 1991; accepted 17 Dec. 1991.