Hypercalcemia in patients with breast cancer: a survival study

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Abstract: In a retrospective study survival after hypercalcemia in breast cancer patients has been investigated. A group of 72 patients were treated with bisphosphonate APD [3-(amino-1,1-hydroxypropylidene)bispophonate] and third-generation amino-containing bisphosphonates between January 1980 and October 1992. A median survival of 4.5 months was found. In a multivariate analysis, four independent prognostic factors for survival have been found: the interval between first relapse and hypercalcemia, sites of metastases at the moment of hypercalcemia, primary treatment, and the level of serum alkaline phosphatase. Patients with a "flare" reaction on tamoxifen treatment and patients with a normal serum alkaline phosphatase level and bone metastases only had a prolonged survival. Hypercalcemia associated with visceral metastases carried a very poor prognosis. The level of serum calcium in this series of patients was no prognostic indicator for survival.

Key words: Hypercalcemia – Breast cancer – Bisphosphonates – Tamoxifen – Serum calcium – APD

Introduction

Breast cancer is the most frequent malignant tumor in women of Western Europe. In the Netherlands women have a 1:12 chance of developing this disease before the age of 75 (Cleton 1988). Approximately half of these women will develop metastases and 70% of these patients eventually have symptomatic bone metastases. Hypercalcemia is a common complication of breast cancer and is usually associated with bone metastases.

The bisphosphonate APD [3-(amino-1,1-hydroxypropylidene)bispophonate] is a very effective compound to treat hypercalcemia (Coleman and Rubens 1987a; Coleman 1992; Sleeboom et al. 1983; Harinck et al. 1987). During the last 10 years all patients presenting with symptomatic hypercalcemia in our hospital have been treated with APD and, from 1988 on, also with third-generation amino-containing bisphosphonates (dimethyl-APD and EB1053). Although treatment with bisphosphonates is very effective in normalizing serum calcium levels, it is not yet known whether it prolongs survival. The few studies on survival of hypercalcemic breast cancer patients report a dismal median survival of 2–3 months (Coleman 1985; Coleman and Rubens 1987b; Brada et al. 1990; Kristensen et al. 1992; Grutters et al. 1993).

Patients and methods

Patients. The records of breast cancer patients who were admitted to our hospital for treatment for hypercalcemia between January 1980 and October 1992 were reviewed. Entry criteria to this study were breast cancer, hypercalcemia and specific antihypercalcemic treatment with bisphosphonates.

Patients were found through the hospital cancer registry and the files of the laboratory for clinical chemistry. A selection was made on the basis of the level of serum calcium. In a first screening of the patients' charts it appeared that only those patients who had had at least two determinations of a high serum calcium had been treated with APD and were therefore suitable for this study. Although a normal range of serum calcium in our laboratory is from 2.25 mmol/l to 2.55 mmol/l, only patients with calcium levels over 2.65 mmol/l were used for the analysis. Serum calcium levels were adjusted for albumin concentration; for each 1 g/l below 42 g/l albumin, 0.0175 mmol/l was added to the uncorrected value of the serum calcium. All studied patients with a corrected serum calcium below 3.00 mmol/l had had at least two measurements before initiation of a calcium-lowering treatment. A total of 72 patients were entered into this study.

The clinical data obtained from the patients' files included the date of the first diagnosis of breast cancer, the treatment of the primary tumor, adjuvant radiotherapy or systemic treatment, the date and site of the first relapse and any systemic treatment. Data on the physical examination, bone scan, radiological investigation and sonography or computed tomography scan of the liver were available. Detailed data of the clinical chemistry, especially serum calcium, serum phosphate, and albumin levels, were recorded. Symptoms related to hypercalcemia, including malaise, confusion, stupor, anorexia, pain, polyuria and polydipsia, constipation, nausea and vomiting, were also recorded. Sites of metastatic disease were defined according to the UICC classification, involving three categories: soft tissue, bone and visceral (Van der Schueren et al. 1991). When the disease involved more than one category, the patient was classified by the category associated with the worst prognosis, irrespective of the extent of involvement.
Treatment. The standard treatment for hypercalcemia started with rehydrating the patient with at least 2 l i.v. saline. Patients who maintained an elevated serum calcium level were treated with i.v. bisphosphonates. Altogether, 49 patients were treated with APD (15 mg/day in 500 ml saline, infused over 2 h, for a period of more than 2 days after restoration of the serum calcium level); 23 patients were treated in experimental studies with more potent third-generation bisphosphonates. In the majority of patients (56%) the systemic treatment was changed after they manifested hypercalcemia; 26 patients received maintenance treatment with oral APD.

Statistical methods. Statistical analysis was carried out using the Cox method for multivariate regression (Cox 1972). The SPSS program was used for statistical calculations. Survival curves were calculated using the Kaplan-Meier method (Kaplan and Maier 1958).

Results

Patients

The patients' characteristics are presented in Table 1. Two patients are still alive, the other 70 were followed until death.

All patients except 2 had bone metastases; 1 patient had metastases in soft-tissue areas only, the other patient had visceral metastases (in the liver) only. Although metastases were not a criterion for selection, all patients had hematogenic metastases (35 patients visceral and bone metastases, 35 patients bone metastases only). Most patients had bone metastases at four or more sites. Almost 80% of the patients had a serum calcium level higher than 3.0 mmol/l.

Effect of APD treatment

Out of 72 patients, 62 became normocalcemic within 7 days of treatment, median: 3.5 days. Seven patients had a delayed response, requiring 8–19 days. A single patient did not respond to APD treatment and was hypercalcemic for 34 days until she died. Two patients died within 3 days after the treatment was initiated. Of the total research population, 96% of the patients responded to treatment with APD or dimethyl-APD, and 90% of the responders normalized within 7 days.

Survival

Survival was measured from the time of diagnosis of hypercalcemia (Fig. 1). Two patients were still alive when this series was analyzed. Survival until analysis was used in this study. The median survival was 4.5 months (range 0–61 months). Figures 2, 3 show survival after the first relapse and diagnosis of breast cancer respectively. Thirty-four patients had one or several episodes of recurrent hypercalcemia. Eleven patients died during a hypercalcemic episode, 3 during the first episode of hypercalcemia, 3 during a second episode, 4 during a third episode and 1 patient died during a fifth episode of hypercalcemia.

Hypercalcemia occurring within 2 weeks from the start of tamoxifen treatment was considered as a “flare” phenomenon. Eight patients developed such a flare; their median survival was 16 months. When these patients were excluded from the analysis, the median survival of the remaining 64 patients decreased from 4.5 to 3 months.

![Fig. 1. Survival of 72 hypercalcemic patients with breast cancer. Survival is calculated from the date of presentation of hypercalcemia . . . , 95% confidence interval](image)