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Subjective and metabolic effects of clodronate in patients with advanced breast cancer and symptomatic bone metastases

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Twenty postmenopausal women (aged between 46 and 67 years old) with skeletal metastases from breast carcinoma were treated with clodronate 450 mg i.v. daily for 5 days and thereafter with 100 mg i.m. daily for 10 days. All patients received standard hormonal therapy (tamoxifen). Symptomatic pain (evaluated according to a linear analog scale), performance status (according to Karnofsky), serum alkaline phosphatase, serum creatinine and osteocalcin were measured before and after treatment on days 5, 15, 30 and 45. Scaning by radiology were performed pre- and post-therapy. Bone pain was significantly reduced in 15 out of 20 patients. After clodronate treatment the base line value of circulating osteocalcin (3.2 ± 1.6 ng/ml) showed a significant increase on days 30 and 45 ($p < 0.001$). Radiological assessment of bone lesions showed stable disease in 18 patients and progression in two patients. No adverse side effects were observed. These data show that clodronate provided pain relief in 75% of treated patients and the increase in circulating osteocalcin levels can be considered a marker of the stabilization of skeletal metastatic lesions.

Key words: Bone metastases, breast cancer, clodronate, osteocalcin.

Introduction

The skeleton is a common metastatic site for carcinoma of the breast. Although hormonal treatment, chemotherapy and radiotherapy can produce remissions of varying length, progressive skeletal disease, complicated by bone pain, remains the major problem in these patients. Several clinical studies have indicated that tumor-induced bone resorption may be inhibited by bisphosphonates.[1–3] The bisphosphonates represent a novel class of drugs which have been developed in the last two decades for diagnostic and therapeutic use in various diseases of bone and calcium metabolism. The rationale of their use is that they are capable of inhibiting bone resorption mediated by a wide range of factors such as resorption stimulated by the major calcium regulating hormones, by prostaglandins and cytokines.[4–6] The wide spectrum of inhibitory actions suggests that the bisphosphonates interfere at a distal step in the cellular events leading to bone resorption and, therefore, are capable of decreasing osteoclasic activity,[7] irrespective of the mechanism of its activation.

Clodronate [(dichloromethylene)diphosphonate] belongs to the groups of bisphosphonates which are synthetic analogs of the naturally occurring pyrophosphates. They inhibit osteoclastic bone resorption and are used clinically in the treatment of Paget's disease, and in the therapy of malignant hypercalcemia and osteolytic metastases.[1,2] Moreover, clinical studies showed that clodronate in chemotherapy induces a rapid inhibitory effect upon the osteoclastic-mediated bone resorption and stimulates osteoblastic activity, as suggested by the increase in circulating osteocalcin levels.[8,9]

We present a report of the pilot study conducted on the effects of i.v. and i.m. administration of clodronate in patients suffering from advanced breast cancer with painful osteolytic bone metastases.

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Patients and methods

Patients

Twenty normocalcemic female patients with multiple osteolytic bone metastases of a histologically proven breast cancer were entered in the study. All were aware that they were on an experimental regimen and gave written informed consent. During the study each of the patients continued to receive an unchanging regimen of hormonal therapy with tamoxifen. All of the patients had evidence of metastatic disease of the skeleton based upon radiography and bone scanning.

Criteria for exclusion were life-expectancy of less than 6 months, Karnofsky performance status below 60, creatine clearance of less than 30 ml/min, peptic ulcer and malabsorption. The clinical characteristics of the patients are shown in Table 1.

Methods

All patients received i.v. infusions of 450 mg/day of sodium clodronate (supplied from Boehringer Biochemia Robin SpA, Milano, Italy) dissolved in 500 ml 5% dextrose solution over a period of 2 h for 5 days. Afterwards the treatment was continued for another 10 days with 100 mg of clodronate i.m. dissolved in 3 ml of saline solution.

The intensity of bone pain was assessed by daily consumption of analgesic drugs and by a visual analog scale.[10] Patients' general conditions were rated according to Karnofsky's performance status criteria.[11] We assessed the status of each patient at least once every week for 2 months, as well as the circulating levels of calcium, phosphate, alkaline phosphatase and osteocalcin (radioimmunoassay method with reagent from CIS International, Saclay, France) in basal conditions at day 5 and days 15, 30 and 45 during and after treatment.

Table 1. Clinical characteristics of 20 patients with osteolytic metastases from breast cancer

Mean age (years)	61
Range	46–67
Previous systemic therapy	
chemotherapy	14
hormonal	20
Karnofsky index	
100–80	7
80–60	13
osteolytic bone metastases	
axial	13
long bones	3
both	4
Extra-osseus metastases	9

Statistical analysis

The significance of differences between the two means of biochemical parameters measured pre- and post-treatment was calculated by a variance analysis which was repeatedly used to statistically evaluate the variable examined among patients. Moreover, multiple comparisons against the basal values were performed each time that the time factor indicated that the F-test was considered significant.

Results

Sodium clodronate administration was associated with a mild but not significant decrease in total serum calcium levels (within the normal range) in several patients; basal serum calcium = 9.5 ± 0.4 mg/dl (mean value $\pm$ SD) vs. 9.2 ± 0.3 at the end of the treatment ($p > 0.05$). Mean serum alkaline phosphatase concentration showed a progressive increase (39%) within the first 5–30 days and then slowly decreased. Figure 1 shows the osteocalcin serum levels, measured in basal conditions, during and after clodronate treatment; the differences in levels were significant ($p < 0.001$).

Severe bone pain was present initially in all patients. The intensity of the pain was significantly reduced by clodronate; improvement in pain was observed within 1 week in seven patients (35%) and 10–15 days thereafter in a further eight patients (40%). Only five patients (25%) did not show any symptomatic improvement and two of these required radiotherapy to obtain pain control.

During the study, no patient had to discontinue treatment for acute gastrointestinal and/or renal toxicity. The performance status, according to the Karnofsky scale, was significantly improved in 12 out of 20 patients (60%).

Discussion

Previous studies have demonstrated that osteocalcin blood concentrations increase in Paget's disease, in

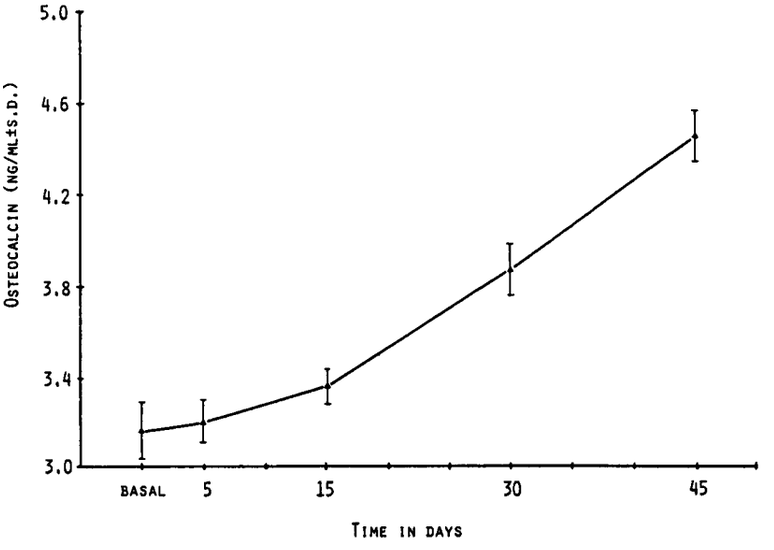

Figure 1. Circulating osteocalcin levels during clodronate treatment.

primary and secondary hyperparathyroidism,[12,13] and in osteoporosis.[14,15] Conflicting results have been reported for cancerous patients with bone metastases.[15,16]

Our laboratory findings related to patients with bone metastases undergoing chemotherapeutic regimen recently demonstrated that the increase in circulating osteocalcin levels can be considered a biological marker of recovered osteoblastic activity.[8] As reported in the literature, bisdiphosphonates are powerful inhibitors of osteoclastic bone resorption and, among these agents, clodronate has proven to be most effective in reducing bone resorption related to metastatic breast carcinoma, myeloma and prostatic carcinoma[2,3,17,18] as well as preventing new bone metastases.[19]

The inhibitory mechanism of bone resorption is still not completely clear. One hypothesis that has been postulated is that the bisphosphonates inhibit osteoclastic activity. In fact, bisphosphonates have been found to enter cells and to have a number of different biochemical effects of relevance in bone resorption such as reducing lactic acid production, and inhibiting lysosomal enzymes and prostaglandin synthesis in bone cells, as well as inhibiting the acidification in the osteoclast.[20-22] A second view postulates that bisphosphonates may maintain a concentration gradient of the drug near the bone surface sufficiently large enough to give a direct influence on osteoclast progenitor cells or on other cell systems that are operative in initiating bone resorption.[23]

Our findings show that clodronate can induce significant pain relief in patients with bone metastases due to breast cancer. Moderate or severe bone pain was present initially in all patients. Of these, 15 out of 20 (75%) appeared to have some degree of improvement of pain and the analgesic consumption was completely abolished in eight out of 20 patients.

Administration of clodronate was also associated with a mild decrease in calcium serum levels while serum alkaline phosphatase concentration, such as osteocalcin, increased in most patients. Increases in alkaline phosphatase and, more specifically, circulating osteocalcin levels, can be considered an index of osteoblastic activation related to skeletal healing and repair, as also reported by other authors.[3,9,18]

The data from these patients indicate that clodronate can significantly inhibit osteoclastic-mediated bone resorption in women with breast carcinoma without undesirable side effects.

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