ORIGINAL ARTICLE

Taylor&Francis healthsciences

Clodronate as a Single-dose Intravenous Infusion Effectively Provides Short-term Correction of Malignant Hypercalcemia

Sari T. Atula, Riitta K. Tähtelä, Jaakko I. Nevalainen and Liisa H. Pylkkänen

From Schering Oy, Clinical Research, Helsinki, Finland

Correspondence to: Sari Atula, Schering Oy, Pasilanraitio 9, PO Box 325, FI-00101 Helsinki, Finland. Tel: +358 9 7088 426. Fax: +358 9 7088 286. E-mail: sari.atula@schering.fi

Acta Oncologica Vol. 42, No. 7, pp. 735–740, 2003

The efficacy and safety of a single intravenous (I.V.) infusion of clodronate 1 500 mg or 900 mg was compared with a single I.V. infusion of pamidronate 90 mg in the treatment of malignant hypercalcemia. Primary efficacy data from two separate, but parallel, randomized double-blind controlled multi-center studies (N = 63), involving patients with malignant hypercalcemia ($S\text{-}Ca_{cor} > 2.68$ mmol/l), were pooled along with results from a study (N = 4), in which an open I.V. phase was followed by a randomized oral phase. The primary efficacy variable, the proportion of normocalcemic patients at day 5 could be evaluated from 51 subjects. Of them, 21 were in the clodronate 1 500 mg group, 10 in the clodronate 900 mg group and 20 in the pamidronate 90 mg group. After the rehydration, the patients were given a single I.V. infusion of clodronate 1 500 mg, clodronate 900 mg or pamidronate 90 mg. The patients were followed up for five days and $S\text{-}Ca_{cor}$ was measured daily. At day 5, a total of 16 patients (76%) in the clodronate 1 500 mg group, six patients (60%) in the clodronate 900 mg group and 17 patients (85%) in the pamidronate 90 mg group were normocalcemic, the differences between the treatment groups being statistically non-significant. The differences in the mean $S\text{-}Ca_{cor}$ between the treatment groups were statistically non-significant. I.V. clodronate given either as 900 mg or 1 500 mg single-dose was safe and well tolerated.

Received 6 November 2002
Accepted 28 May 2003

Hypercalcemia is a severe, often late-stage complication associated with a number of malignancies. Patients with skeletal metastases from lung and breast cancer suffer most frequently from hypercalcemia, but it is also frequent in patients with malignant blood disorders such as multiple myeloma (1). Prompt intervention is needed to prevent the consequences, which can prove fatal. Saline infusions provide an effective initial response by expanding extracellular volume, increasing the glomerular filtration rate and reducing calcium reabsorption. However, rehydration often normalizes calcium levels only partially and temporarily (2). After initial emergency treatment, long-term management of hypercalcemia depends on the effectiveness of antineoplastic drugs in controlling the underlying malignancy.

Most hypercalcemic episodes result from increased bone resorption due to skeletal metastases. The spread of malignant metastatic cells to the bone marrow is hematogenous, stimulating osteoclastic activity and subsequent resorption of surrounding bone by factors such as parathyroid hormone-related protein (PTHrP) (3). Enhanced bone turnover produces numerous cytokines and growth factors, which further stimulate the growth of cancer cells. These molecular interactions form a vicious cycle of metastatic cell growth and osteolysis and may, ultimately, lead to clinical bone metastasis (4). On the other hand, PTHrP secreted by primary or metastatic tumour cells may also cause humoral hypercalcemia by stimulating tubular reabsorption of calcium in the kidneys in the absence of skeletal lesions (5).

Clodronate (dichloromethylene bisphosphonate) and pamidronate (3-amino-1-hydroxy-propylidene bisphosphonate) are molecules characterized by two carbon-phosphate bonds. In contrast to clodronate, pamidronate also contains a nitrogen group and therefore belongs to a group of aminobisphosphonates. All bisphosphonates are retained by bone and the extent of retention is directly related to skeletal turnover. Therefore, bisphosphonates bind most readily to regions of pathological bone activity, such as areas of malignant osteolysis. Direct inhibition of osteoclastic bone resorption appears to represent the primary mechanism by which clodronate and pamidronate correct malignant hypercalcemia (6). Clodronate acts by forming intracellularly a complex with ATP to induce

 ISSN 0284-186X
DOI: 10.1080/02841860310013111

apoptosis of osteoclasts (7), whereas aminobisphosphonates induce osteoclast apoptosis by inhibiting the mevalonate pathway and, hence, protein prenylation (8). Since osteolysis is a major factor behind malignant hypercalcemia, the role of bisphosphonates in the treatment of hypercalcemia is likely to be mediated through their effects on osteoclast function.

Bisphosphonates have established their role as a gold standard in the treatment of malignant hypercalcemia during the interval between acute-phase rehydration, as an initial response, and long-term control of the underlying cancer. Parenteral administration is the treatment of choice for rapid and effective treatment of hypercalcemia. Numerous studies show that intravenous (I.V.) clodronate reduces serum calcium in the majority of patients suffering from malignant hypercalcemia (2, 9). Similarly, I.V. pamidronate is effective in cancer-related hypercalcemia (10). When clodronate is used in malignant hypercalcemia, the most common regimen is I.V. infusion of 300–600 mg daily for 3–6 days. However, O'Rourke et al. (11) found that a single I.V. infusion of 1 500 mg clodronate has a similar effect when compared with administration of the same dose over five days.

In this pooled analysis, two doses of clodronate and one dose of pamidronate, given as a single I.V. infusion, were compared—in terms of efficacy and safety—in normalizing malignant hypercalcemia. The analysis covered two multi-center, double-blind, randomized studies and one study in which the open I.V. phase was followed by a randomized and blind oral phase. The selected I.V. clodronate doses were based on previous clinical data relating to the efficacy and safety of clodronate. The dose-response was also assessed by using two different doses of clodronate, 1 500 mg and 900 mg. The selected dose for pamidronate, 90 mg, is widely used for the treatment of malignant hypercalcemia. The primary end-point of this study was to identify the proportion of normocalcemic patients (corrected serum calcium ($S\text{-}Ca_{cor}$) ≤ 2.68 mmol/l) in each treatment group five days after administration of the study drug. The secondary end-point was to assess how $S\text{-}Ca_{cor}$ levels changed during the study period.

MATERIAL AND METHODS

Primary efficacy data from two parallel, randomized, controlled double-blind multi-center studies were pooled for this report. In addition, results from a study involving four patients, for whom the open non-randomized I.V. phase was followed by a randomized blind oral phase, were included in the pooled analyses. Two of the studies were conducted in Europe and one in the USA. The study protocols were approved by local ethics committees prior to the beginning of the studies. These studies were conducted in compliance with good clinical practice (GCP) and the Helsinki Declaration (as amended). All patients gave their informed consent before enrollment to the studies. The study protocols were originally designed to be similar in terms of patient population and primary efficacy variables. However, the study protocols were subsequently amended due to the slow recruitment rate in each study, as presented below in the individual descriptions of the studies. Due to the difficulties in patient enrollment, all three studies were terminated prematurely. Because of the considerable difference between planned and recruited patient numbers, it was decided that data from the studies should be pooled whilst they were actually running.

Inclusion and exclusion criteria and objectives were similar in all studies. Patients had to be at least 18 years of age, with a clinical diagnosis of malignant hypercalcemia ($S\text{-}Ca_{cor} \geq 2.68$ mmol/l). They were required to sign an informed consent form and had to have a life-expectancy exceeding four weeks at the time of enrollment onto the study. Because of short life expectancy, follow-up data were not systemically collected from the patients. Exclusion criteria were as follows: patients with hypercalcemia from any cause other than malignancy, or who had received systemic cancer treatment within four weeks prior to entry into the study, or who had received treatment for hypercalcemia within one week prior to entry into the study (one month in the case of study No 3, with four patients) or who had received bisphosphonates within four weeks prior to entry into the study. After enrollment onto the study patients could be removed either at their own request or on the basis of a physician's decision, if rising $S\text{-}Ca_{cor}$ was regarded as life threatening.

In the study conducted in the USA, 36 patients were enrolled. A total of 27 patients were enrolled onto one of the studies conducted in Europe and four patients onto the other.

Treatments

All patients in the studies were initially rehydrated with I.V. saline infusion for at least 24 hours, to obtain a urine output of at least 50 ml/hr. Clodronate (disodium clodronate tetrahydrate, BONEFOS®, Schering Oy, Turku, Finland) is available in 300 mg ampoules; five ampoules (for 1 500 mg dosing) or three ampoules (for 900 mg dosing) were diluted in 500 ml of isotonic saline. Pamidronate (disodium pamidronate pentahydrate, AREDIA®, Ciba Pharmaceuticals, Summit, New Jersey, USA) is available in 30 mg vials, which was reconstituted with 10 ml of sterile water to achieve a final concentration of 3 mg/ml. Three 30 mg vials were further diluted in 500 ml of isotonic saline to obtain the treatment dose of 90 mg. In all studies the study drugs were administered as a single I.V. infusion over four hours. The doses were not repeated. Because of minor differences in the study settings after the rehydration phase, the treatments are described separately below. The number of patients enrolled is shown in Table 1.

Table 1

Number of randomized patients by treatment groups

Study	Clodronate 1 500 mg	Clodronate 900 mg	Pamidronate 90 mg	Total
1	20	1	15	36
2	8	10	9	27
3	4	0	0	4
Total	32	11	24	67

Study No 1. After adequate rehydration, patients with S-$Ca_{cor} > 3.00$ mmol/l and serum creatinine (S-crea) ≤ 220 μmol/l were randomized to receive either 1 500 mg clodronate or 90 mg pamidronate as a single I.V. infusion over four hours. The infusion was not repeated during the study. After the amendment to the study protocol, the patients with S-$Ca_{cor} > 2.68$ mmol/l but ≤ 3.00 mmol/l were randomized to receive 900 mg clodronate as a single I.V. infusion. However, only one patient received 900 mg infusion openly. The patients were followed for five days. The I.V. phase was followed by a randomized double-blind oral phase; however, oral data were not pooled for these analyses.

Study No 2. After adequate rehydration, patients with S-$Ca_{cor} > 2.68$ mmol/l and S-crea ≤ 220 μmol/l were randomized to receive 1 500 mg clodronate, 900 mg clodronate or 90 mg pamidronate, as a single I.V. infusion over four hours. The dose was not repeated during the study. The patients were followed for five days.

Study No 3. After adequate rehydration, patients with S-$Ca_{cor} > 2.68$ mmol/l but ≤ 3.00 mmol/l received 900 mg clodronate openly as a single I.V. infusion over four hours. Patients with S-$Ca_{cor} > 3.00$ mmol/l received 1 500 mg clodronate openly as a single I.V. infusion over four hours. The study was terminated prematurely due to the slow recruitment rate. The I.V. phase was followed by randomized double-blinded oral phase; however, oral data were not pooled for these analyses.

Measurements

In all the studies S-Ca_{cor} was calculated using the formula: S-Ca + 0.02 X (40 − S-Alb), where albumin is expressed as g/l to avoid fluctuations in S-Ca levels due to albumin binding. S-Ca_{cor} measurement and toxicity assessment were performed daily. S-crea and serum phosphate were also measured daily in studies 1 and 2. A complete blood cell count was taken and hepatic enzymes were measured on entry and on the last day of the study.

Adverse events

Adverse events were reported throughout the study and reasons for premature termination were recorded.

Statistics

The overall difference between the three treatment groups in terms of the proportion of normocalcemic patients at day 5 was tested by Fisher's exact test (2-tailed). An exact 95% confidence interval was estimated for each proportion and the difference of the proportions. Statistical analysis of S-Ca_{cor} was performed by repeated measurements analysis of variance. Comparison of treatments was done by linear contrasts. Statistical analyses were performed by using the SAS®System (Version 6.12) and StatXact-5.

RESULTS

Patient characteristics

A total of 67 patients, 24 males and 43 females, with malignant hypercalcemia, were enrolled onto the three studies. All patients completed the five-day study period. There were, therefore, no study dropouts during the I.V. phase of the studies. However, efficacy data were available only for 51 patients. Table 1 shows patient numbers by treatment group and study.

The baseline characteristics for the 51 patients with the efficacy data available, by the treatment group, are shown in Table 2. The treatment groups were well balanced at baseline regarding the demographic factors age, BMI and blood pressure. Also, the cancer types for the patients by the treatment group are shown in Table 2.

Normocalcemic patients

In all treatment groups that were studied, the proportion of normocalcemic patients increased at a fairly steady rate from the first day of the study up to day 5 (see Fig. 1). At day 5, S-Ca_{cor} data were available for a total of 51 patients. A total of 16 patients (76.2%) in the clodronate 1 500 mg group, 17 patients (85.0%) in the pamidronate group and six patients (60.0%) in the clodronate 900 mg group were normocalcemic (S-Ca_{cor}). No statistical differences were found between the treatment groups at day 5 in terms of achievement of normocalcemia: all p-values were > 0.15. A 95% confidence interval (CI) for the proportion of normocalcemic patients was 53%–92% in the clodronate 1 500 mg group, 26%–88% in the clodronate 900 mg group and 62%–97% in the pamidronate 90 mg group. Although the difference between the clodronate 1 500 mg group and the pamidronate group is small (8.8%), the current data are not conclusive for ruling out clinically meaningful differences between the treatments and are insufficient for demonstrating equivalence (95% CI for the difference: 17.7, −33.2). For other comparisons between the treatment groups, see Table 3, which shows differences between the proportions of normocalcemic patients at day 5 with exact 95% CI. As can be seen from Fig. 1, the clodronate 1 500 mg and pamidronate groups resembled one another closely, regard-

Table 2

Baseline characteristics of the patients with efficacy data available

Variable	Clodronate 1 500 mg N = 21	Clodronate 900 mg N = 10	Pamidronate 90 mg N = 20
Ca_{cor} (mean, mmol/l)	3.45	3.21	3.45
Sex (M/F)	4/17	0/10	10/10
Age (mean, yrs)	52.4	57.5	53.3
BMI (mean, kg/m^2)	23.5	25.7	26.1
Blood pressure (mean, mmHg)	130/77	130/75	126/78
Cancer type:			
Breast cancer	9	4	4
Lung	6	1	4
Lymphoma	2	2	2
Myeloma	1	0	3
Kidney	0	2	0
Unknown primary	0	0	2
Other types, one each	Prostate, colon, pancreas	Bladder	Skin, esophagus, pleura, cervix, tongue

Abbreviation: BMI = body mass index.

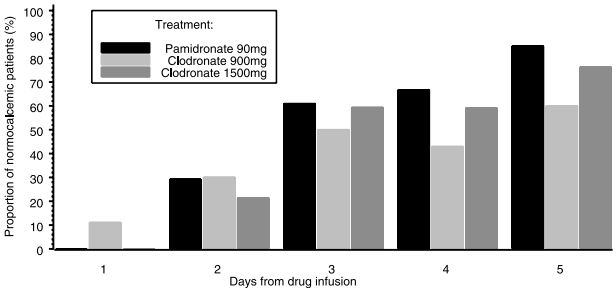

Fig. 1. The proportion of normocalcemic patients in the treatment groups during the study. The differences between the treatment groups in the achievement of normocalcemia were not statistically significant.

ing the speed with which normocalcemia was achieved during the study.

S-Ca_{cor} levels

Total S-Ca_{cor} decreased significantly during the study ($p < 0.0001$), with mean S-Ca_{cor} returning within the reference range by day 5, the final day of the study. At day 5, S-Ca_{cor} was 2.52 mmol/l in the clodronate 1 500 mg group, 2.57 mmol/l in the clodronate 900 mg group and 2.44 mmol/l in the pamidronate 90 mg group. Mean S-Ca_{cor} decreased significantly in each treatment group ($p < 0.0001$ for all treatment groups, see Fig. 2) and the extent of the decrease in S-Ca_{cor} reached the same level in all treatment groups by day 5.

When the treatment groups were compared, there were no significant differences between them during the study in terms of S-Ca_{cor} changes (all p-values > 0.15). The change in S-Ca_{cor} was 25% in the clodronate 1 500 mg group (95% CI 21%–29%), 20% in the clodronate 900 mg group (95% CI 13%–26%) and 26% in the pamidronate 90 mg group (95% CI 22%–30%).

Table 3

Differences between the treatment groups in proportions of normocalcemic patients at day 5 with exact 95% CIs

	Difference in %	Exact 95% CI for the difference
Pam 90 mg–Clod 1 500 mg	85.0 − 76.2 = 8.8	(−17.7, 33.2)
Pam 90 mg–Clod 900 mg	85.0 − 60.0 = 25.0	(−9.7, 60.0)
Clod 1 500 mg–Clod 900 mg	76.2 − 0.0 = 16.2	(−18.6, 53.0)

Abbreviations: Pam = pamidronate, Clod = clodronate, CI = confidence interval.

Adverse events

Mild or moderate hypocalcemia, observed in three patients (clodronate 1 500 mg: two patients, pamidronate: one

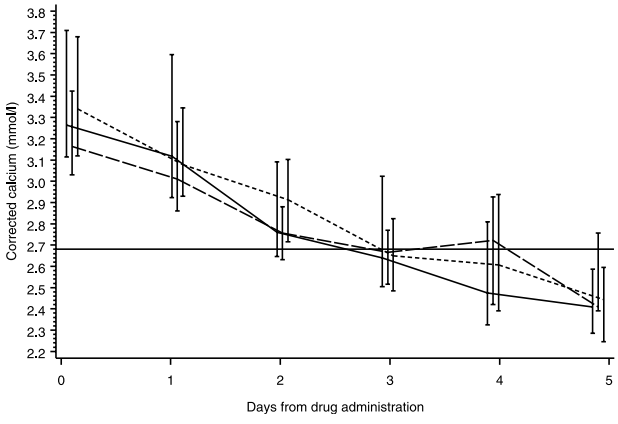

Fig. 2. The median and quartile ranges for changes in S-Ca_{cor} levels in each treatment group during the study. The mean calcium levels reached normocalcemic level by day 3 in all treatment groups. The differences between the treatment groups in the changes of calcium levels were not statistically significant. Treatment: — Pamidronate 90 mg; – – – clodronate 900 mg; --- clodronate 1 500 mg.

patient) during the study, was reported as being related to the study drug. The patients were reported to have suffered the following serious adverse events during the study, all of which were assessed as being unrelated to the study drug: urinary tract infection, leading to sepsis; Staphylococcus infection; subdural hematoma; congestive heart failure, accompanied by right pleural effusion and mild chest pain. An S-crea value of 336 μmol/l was measured for one patient in the clodronate 1 500 mg group at the end of the study. However, this patient had diabetes mellitus and raised S-crea was regarded as unrelated to the study drug. Mean S-crea for all patients with data available was ≤ 125 μmol/l on entry to the study before the rehydration. Towards the end of the study mean S-crea followed a slightly downwards trend, at ≤ 105 μmol/l for all study groups at the last day on the study, reflecting the improvement in renal function associated with decreasing S-Ca. In conclusion, there were no safety concerns in this study and both study drugs were safe, bearing in mind the limitations imposed by a short study period.

DISCUSSION

Hypercalcemia is a frequent complication in advanced malignant diseases. For example, 10–20% of women with breast cancer suffer from hypercalcemic episodes (12). In a retrospective survey, 7.2% of all cancer patients admitted to the oncology unit in a hospital in UK were hypercalcemic (13). Hypercalcemia is the most common potentially life-threatening endocrinological complication of cancer. The therapeutic approach needs to combine speed and efficacy, if potentially lethal consequences are to be avoided. Bisphosphonates, such as clodronate, have been shown to be very effective in the treatment of hypercalcemia, and are now a crucial part of the standard care. I.V. clodronate is often used for this indication with a dose of 1 500 mg administered as 300 mg doses in five consequent days. In clinical practice, it would be desirable to reduce the period of I.V. administration for clodronate from five days to a more convenient four-hour period.

The life-expectancy of the patients randomized in the current studies was expected only to exceed four weeks. Moreover, the patients had advanced terminal malignancy with a serious metabolic disorder, hypercalcemia. These facts lead to difficulties in enrolling eligible patients. As it turned out, the gap between planned and actual patient numbers was substantial in all three studies. Consequently, statistical analyses of individual studies were under-powered, and this needs to borne in mind when interpreting the results. When the difficulties in recruitment became obvious while the studies were still ongoing, it was decided to pool the efficacy data to obtain more accurate and reliable results. To the best of our knowledge this is the largest study to be published comparing I.V. clodronate and pamidronate in the treatment of malignant hypercalcemia.

With respect to the demographic factors and baseline S-Ca_{cor} levels, the clodronate 1 500 mg and pamidronate groups were the two that were reasonably well balanced. Mean S-Ca_{cor} was naturally lower in the clodronate 900 mg group at baseline on account of the study design for the two pooled studies, which allowed patients with moderate hypercalcemia only (S-Ca_{cor} 2.68–3.0 mmol/l) to receive this lower dose of clodronate. Total baseline resemblance between the groups could not be achieved on account of the relatively small number of patients in each treatment group.

The clinical efficacy of a single I.V. dose of pamidronate for the treatment of malignant hypercalcemia has been confirmed (10) and it was, therefore, chosen as a reference therapy for clodronate. The dose—90 mg—at which pamidronate is given has been proven to be clinically effective (14) and is widely used. On the final day of the study, no statistically significant differences were seen between the treatment groups in terms of the proportion of patients in whom normocalcemia was achieved, although the point estimates favour pamidronate over both clodronate doses. In light of the small number of patients included, the possibility of true differences between treatment groups cannot be excluded. However, when it comes to the achievement of normocalcemia, there seems to be no major difference between high-dose clodronate and pamidronate, a finding which accords with the results obtained by Purohit et al. (15) from 41 cancer patients. These results are also in line with earlier experience showing that preclinical difference in chemical potency between clodronate and pamidronate does not seem to produce an obvious difference in clinical efficacy, as also suggested by Major et al. (16).

Mean S-Ca_{cor} decreased to normocalcemic levels in all treatment groups by final day of the study. The results were also suggestive of a slight dose-relationship between the clodronate groups, showing that 1 500 mg clodronate was somewhat better than 900 mg clodronate in reducing the mean S-Ca_{cor}, judging by the proportion of normocalcemic patients on the final day of the study. While mean S-Ca_{cor} was found in the statistical analysis to be at almost the same level amongst all groups on day 5, a minimal advantage was seen for the clodronate 1 500 mg and pamidronate groups, compared with the clodronate 900 mg group. In the light of these results, it would appear that 1 500 mg clodronate, which is a currently recommended dose for I.V. administration, is probably clinically closer to 90 mg pamidronate than is 900 mg of clodronate. This finding is in line with the results found by Purohit (15), reporting a decrease in serum calcium of parallel magnitude for both the clodronate 1 500 mg and pamidronate 90 mg groups when the study medication was administered I.V. over four hours to 41 patients. In an open study by O'Rourke et al. (11), normocalcemia was achieved more rapidly following a single I.V. dose of 1 500 mg clodronate than a 300 mg I.V.

dose daily for five days, even though the extent of the decrease in urinary calcium was parallel at both doses.

In conclusion, there was no major difference in terms of clinical efficacy in normalizing S-Ca_{cor} between I.V. clodronate 1 500 mg and pamidronate 90 mg, although, due to the low power in the study, a clinically relevant difference in efficacy cannot be excluded. Additionally, there seems to be no differences during the study between the treatment groups in terms of S-Ca_{cor} levels or of the speed with which normocalcemia was achieved. While it is difficult to assess safety data obtained from terminally ill patients with multiple problems related to the cancer and to associated forms of treatment, no specific concerns were found with regard to side effects. In particular, no renal function problems, as measured by S-crea, were observed during the study when study drugs were given as a single I.V. dose over four hours. Besides being effective for acute hypercalcemia as an I.V. formulation, clodronate treatment can be continued after the I.V. phase, using the oral formulation in order to maintain normocalcemia. However, it needs to be acknowledged that whereas single-dose pamidronate is known to retain a considerable fraction of the patients in a normocalcemic state for some time, no such data are available for single-dose clodronate. Taken together, the data available provide no preference for choosing either single-dose I.V. clodronate or pamidronate for the acute correction of malignant hypercalcemia.

REFERENCES

1. Guise TA, Mundy GR. Cancer and bone. Endocrine Rev 1998; 19: 18–54.
2. Witte RS, Koeller J, Davis TE, et al. Clodronate—a randomized study in the treatment of cancer-related hypercalcemia. Arch Intern Med 1987; 147: 937–9.
3. Guise TA, Yin JJ, Taylor SD, et al. Evidence for a causal role of parathyroid hormone-related protein in the pathogenesis of human breast cancer-mediated osteolysis. J Clin Invest 1996; 98: 1544–9.
4. Yoneda T, Michigami T, Yi B, Williams PJ, Niewolna M, Hiraga T. Actions of bisphosphonate on bone metastasis in animal models of breast carcinoma. Cancer 2000; 88: 2979–88.
5. Grill V, Rankin W, Martin TJ. Parathyroid hormone-related protein (PTHrP) and hypercalcemia. Eur J Cancer 1998; 34: 222–9.
6. Hughes DE, MacDonald BR, Russell RGG, Gowen M. Inhibition of osteoclast-like cell formation by bisphosphonates in long-term cultures of human bone marrow. J Clin Invest 1989; 83: 1930–5.
7. Selander KS, Mönkkönen J, Karhukorpi E-K, Härkönen P, Hannuniemi R, Väänänen HK. Characteristics of clodronate-induced apoptosis in osteoclasts and macrophages. Mol Pharmacol 1996; 50: 1127–38.
8. Coxon FP, Helfrich MH, van't Hof RJ, et al. Protein geranylgeranylation is required for osteoclast formation, function, and survival: Inhibition by bisphosphonates and GGTI-298. J Bone Miner Res 2000; 15: 1467–76.
9. Rotstein S, Glas U, Eriksson M, et al. Intravenous clodronate for the treatment of hypercalcaemia in breast cancer patients with bone metastases—a prospective randomised placebo-controlled multicentre study. Eur J Cancer 1992; 28A: 890–3.
10. Gucalp R, Theriault R, Gill I, et al. Treatment of cancer-associated hypercalcemia. Arch Intern Med 1994; 154: 1935–44.
11. O'Rourke NP, McCloskey EV, Vasikaran S, Eyres K, Fern D, Kanis JA. Effective treatment of malignant hypercalcemia with a single intravenous infusion of clodronate. Br J Cancer 1993; 67: 560–3.
12. Diel IJ, Mundy GR. Bisphosphonates in the adjuvant treatment of cancer: experimental evidence and first clinical results. Br J Cancer 2000; 82: 1381–6.
13. O'Rourke NP, McCloskey EV, Kanis JA. Tumour induced hypercalcaemia: A case for active treatment. Clin Oncol 1994; 6: 172–6.
14. Nussbaum SR, Younger J, VandePol CJ, et al. Single-dose intravenous with pamidronate for the treatment of hypercalcemia of malignancy: Comparison of 30-, 60-, and 90-mg dosages. Am J Med 1993; 95: 297–304.
15. Purohit OP, Radstone CR, Anthony C, Kanis JA, Coleman RE. A randomized double-blind comparison of intravenous pamidronate and clodronate in the hypercalcemia of malignancy. Br J Cancer 1995; 72: 1289–93.
16. Major PP, Lipton A, Berenson J, Hortobagyi G. Oral bisphosphonates. Cancer 2000; 88: 5–14.