Pergamon

European Journal of Cancer, Vol. 34, No. 6, pp. 820–824, 1998

Printed in Great Britain
0959-8049/98 $19.00+0.00

PII: S0959-8049(97)10155-1

Original Paper

A Randomised Phase II Study of Oral Pamidronate for the Treatment of Bone Metastases from Breast Cancer

R.E. Coleman,[1] S. Houston,[2] O.P. Purohit,[1] R.D. Rubens,[2] A. Kandra[3] and J. Ford[3]

[1]YCRC Department of Clinical Oncology, Weston Park Hospital, Whitman Road, Sheffield S10 2SJ; [2]ICRF Clinical Oncology Unit, Guy's Hospital, London SE1 9RT, U.K.; and [3]Novartis, Basle, Switzerland

47 patients with progressive, painful, predominantly lytic bone metastases from breast cancer were included in a randomised double-blind phase II trial comparing the effects of pamidronate 150 and 300 mg daily. Oral pamidronate produced either sclerosis or stabilisation of lytic metastases for at least 24 weeks in 5 of 24 and 3 of 23 patients at the 300 and 150 mg dose levels, respectively. Evidence of symptomatic improvement was observed in 5 of 22 (23%) and 7 of 22 (32%) patients for symptomatic disease at the respective doses. These improvements were accompanied by a reduction in the rate of bone resorption as shown by suppression ($P = < 0.01$) of urinary calcium and a non-significant fall in deoxypyridinoline. No obvious differences in efficacy were observed between the two dose levels. Gastrointestinal adverse events, principally comprising nausea and vomiting, were the most commonly reported side-effects leading to discontinuation of trial treatment in 4 of 24 and 2 of 23 patients at 300 and 150 mg dose levels, respectively. The poor tolerability of oral pamidronate coupled with the modest clinical effects reported here suggest that oral pamidronate will not replace the current strategy of regular intravenous infusions of pamidronate for the treatment of osteolytic bone disease.

Key words: bone metastases, breast cancer, oral pamidronate
Eur J Cancer, Vol. 34, No. 6, pp. 820–824, 1998

INTRODUCTION

BISPHOSPHONATES ARE potent inhibitors of osteoclast function which, particularly in advanced breast cancer [1, 2] and multiple myeloma [3, 4], are increasingly being incorporated into the management of metastatic bone disease. Clinically important, beneficial effects on skeletal complications [1, 3], bone pain [5], quality of life [1, 3, 5] and evolution of the disease during systemic treatment [6] have been demonstrated. Pamidronate is the most potent and widely tested of the commercially available bisphosphonates in cancer patients and regular intravenous (i.v.) treatments are now established in many countries around the world for the treatment of osteolytic bone metastases from breast cancer and multiple myeloma [7].

To avoid the inconvenience of regular i.v. infusions, an effective oral formulation could be preferable for many patients. Clinical efficacy has already been demonstrated with oral clodronate [2], and a non-standardised oral form of pamidronate has been extensively tested in Holland [8]. In the latter phase III trial, in which cancer patients with bone metastases were given standard therapy either alone or with 300–600 mg of oral enteric-coated pamidronate, a 38% reduction in skeletal complications was seen in patients receiving pamidronate.

In general, bisphosphonates are poorly absorbed and oral administration of amino-bisphosphonates is associated with significant gastrointestinal (GI) side-effects. In the Dutch trial with pamidronate, GI toxicity led to premature discontinuation in 25% of patients receiving 600 mg daily and in 8% given 300 mg. In an attempt to circumvent these problems, Novartis (formerly Ciba) developed a novel capsule formulation of pamidronate each containing several hundred enteric-coated pellets.

In a phase I trial with this new formulation, 104 patients with breast cancer and bone metastases were randomised to receive doses of 75, 150 and 300 mg daily for 4 weeks [9]. Possible pamidronate-related GI toxicity was reported in 6 of

Correspondence to R.E. Coleman.
Received 25 Jul. 1997; revised 20 Nov. 1997; accepted 10 Dec. 1997.

34 (18%), 2 of 34 (6%) and 11 of 36 (31%) patients treated at 75, 150 and 300 mg, respectively. Urinary calcium excretion (UCCR)—a surrogate marker of bone resorption—was reduced equally at doses of 150 and 300 mg, but to a lesser degree at 75 mg.

The present study was initiated to confirm the efficacy and tolerability profiles of the 150 and 300 mg doses over a longer treatment period. The primary objective was to determine the proportion of patients who achieved either sclerosis or stabilisation of lytic bone lesions. Secondary objectives included effects on pain, mobility and analgesic use, reduction in biochemical markers of bone resorption and assessment of the tolerability of the two dose levels.

PATIENTS AND METHODS

Patient selection

47 women with a median age of 53 years (range 37–83 years) with metastatic breast cancer and radiologically progressing bone metastases from six centres in the U.K. and Denmark were invited to participate in this randomised double-blind, comparative, multi-centre, phase II trial.

Patients had to have at least two bone metastases visible on plain radiograph with at least one purely lytic lesion for radiological assessment. Metastases present outside the skeleton had to be clinically stable and at sites that were not immediately life threatening. Patients had to have failed to respond to, or relapsed on, at least one previous systemic treatment, have a life expectancy of at least 3 months and adequate haematological, renal and hepatic function.

Patients whose bone metastases were pain free on non-opiate analgesics, with visceral soft tissue disease requiring systemic anticancer treatment, hypercalcaemia of malignancy, proven peptic ulcer, poor performance status unrelated to bone disease (WHO 3–4) and any prior treatment with bisphosphonates within the previous 6 months, were excluded from the study.

All centres obtained local ethical committee approval prior to beginning the trial and written informed consent was obtained from patients before enrolment.

Trial medication and treatment

Patients received either pamidronate 300 mg daily (two capsules of pamidronate 75 mg taken twice daily 30 min before breakfast and 30 min before the evening meal) or pamidronate 150 mg daily when active drug was only included in the capsules taken in the morning with placebo capsules being administered in the evening. Medication was taken with a large glass of water and patients were advised not to lie down immediately after taking medication to avoid prolonged contact of the medication with the oesophageal mucosa. Food and medications containing calcium were not permitted 60 min before and 30 min after taking the trial medication.

During the trial, patients did not receive any other anticancer drug therapy and, in order to prevent confusion with possible hormone withdrawal responses, patients on hormonal agents at trial entry continued to receive the same hormonal treatment, providing this had been unchanged for at least 3 months prior to trial entry. Hormonal agents given for less than 3 months were discontinued.

Patients were not to receive any agents known to influence bone metabolism. Radiotherapy could be given during the trial provided that treatment was given to less than 25% of bone lesions. Lesions irradiated during the trial period or within 6 weeks prior to entry were not used to assess response.

Monitoring response

Patients were assessed at 4-weekly intervals. At each visit, the patients completed questionnaires related to pain, mobility and analgesic use and provided urine and blood samples for the measurement of markers of bone resorption and the various safety parameters, respectively. The investigator also recorded the patient's WHO performance status and plain radiographs of bone lesions were performed before treatment and at weeks 13 and 25.

Objective response. The primary end-point of the trial was the number of patients who developed a response in bone on serial plain radiographs. Skeletal response was defined as either sclerosis within lytic lesions on plain radiographs taken at weeks 13 or 25, or stable disease in bone until at least week 25. To ensure consistency in the assessment of response and the time to progression in bone between the centres, an extramural review of plain radiographs was performed. Two reviewers from each of the participating countries (a clinical oncologist and a radiologist) reviewed the plain radiographs from all randomised patients in that country under blind conditions. The results from this review procedure were used in the analysis of the primary efficacy variable. The results of the plain radiograph appearances as recorded by the investigators were also noted.

Subjective response. To assess symptomatic response, patients were asked to record at each visit the average pain intensity during the previous week according to a six-point scale, along with a modified version of the Oswestry Back Pain Questionnaire [10]. Patients recorded their total analgesic intake during the previous 24 h and this was converted to a seven-point analgesic score. At each visit, the investigator recorded the patient's performance status according to the WHO Scale.

Patients with a symptomatic improvement were classified into major and minor symptomatic responders. A major symptomatic response was achieved if *any* of the following main significant improvements occurred and a minor response if *at least two* of the lesser criteria in brackets occurred:

(a) reduction in pain by at least one category of the six-point pain scale at 2 (1) consecutive 4-weekly examinations when compared with baseline;
(b) 20% (10%) improvement in the score of the pain and mobility questionnaire at two consecutive 4-weekly examinations when compared with baseline;
(c) 50% (25%) reduction for at least 2 months in the dose of the most powerful analgesic taken at trial entry.

Biochemical assessment

For the measurement of bone resorption markers, a second void sample of urine following an overnight fast was collected, acidified to prevent precipation of calcium phosphate, frozen at −20°C and subsequently shipped for central analysis. Serum for haematological and biochemical safety data was analysed locally at the participating centres.

Toxicity assessment

All adverse events were recorded and graded according to WHO criteria with the exception of GI toxicity for which a

Table 1. *Grading scheme for gastrointestinal toxicity*

Symptom	Grade 1	Grade 2	Grade 3
Nausea	Not daily, tolerable with or without therapy	Daily, tolerable with or without therapy	Intolerable
Vomiting	Less than three times per week	More than three times per week but not daily	Daily or intolerable
Abdominal pain	Mild, not more than three times per week	Mild, more than three times per week but not daily	Intolerable or daily of any severity
Diarrhoea	Transient, not more than 2 days in duration	Tolerable, more than 2 days in duration	Intolerable or requiring active therapy
Others	Mild	Moderate	Severe

grading system more appropriate for chronic drug administration was used. This is shown in Table 1.

Study size and statistical methods

It was originally planned to treat a total of 52 patients. With an assumed response rate of 15% in each treatment arm and a sample size of 26 patients per treatment group, the probability of observing zero responders was < 1.5% at each dose level. Because of the significant level of GI toxicity and the increasing evidence for the use of intravenous bisphosphonate therapy for metastatic bone disease [1, 5, 6], the trial was closed to enrolment prematurely after only 47 patients had been recruited.

RESULTS

The treatment groups were well matched for baseline characteristics, including weight, time since first bone metastasis, performance status, analgesic score and pain score. The only pretreatment difference between the treatment groups was that the median baseline scores on the pain and mobility questionnaire were 50 and 31% for 300 and 150 mg dose groups, respectively.

The efficacy data are summarised in Table 2. At 300 mg, 5 of 24 patients (21%, 95% confidence interval (CI) 7–42%) achieved a response in bone according to data collected at extramural review. The corresponding figure for the 150 mg dose was 3 of 23 patients (13%, 95% CI 3–33%). Of these 8 responders, 2 at 300 mg had stable disease at week 25, the remaining 6 had sclerosis of lytic bone lesions corresponding to a partial response according to UICC criteria [11]. Interestingly, a partial response was documented by the investigators in only 1 of these 7 responders.

All patients had some degree of pain at trial entry and 22 patients at each dose level were assessable for subjective response. By week 9, 3 patients in each treatment group were pain free. A major symptomatic response was reported in 5 of 22 patients (23%) and 7 of 22 (32%) patients receiving 300 or 150 mg pamidronate, respectively. During the first 3 months, the median score from the pain and mobility questionnaire fell by 25% with pamidronate 300 mg but there was no improvement in scores in the 150 mg dose group. No significant changes in analgesic intake were observed with either dose group and only 6 patients were recorded as improving their performance status.

On external review, 11 patients at each dose level were judged to have progressed in the skeleton during the trial. Median time to progressive disease in bone was 121 and 92 days for patients treated with 300 and 150 mg pamidronate, respectively. This difference was not statistically significant ($P = 0.75$, log rank test). Using data recorded by the investigators, time to progressive disease in bone was somewhat longer, measuring 166 and 124 days in the respective dose groups, a difference which was also not statistically significant ($P = 0.75$, log rank test).

In both treatment groups, UCCR fell to < 50% of the baseline value by week 5 ($P = < 0.01$). There was no clear difference between the two dosage groups. In contrast to the UCCR, the level of pyridinoline excretion remained relatively constant for the duration of the trial, whilst for deoxypyridinoline there was a modest non-significant reduction in levels which was most apparent in the 300 mg dose group. However, the percentage reduction from baseline was much less than for the UCCR and was rarely more than 30% (Figure 1).

Adverse experiences (AEs) were reported by 23 of 24 patients (96%) at 300 mg and 17 of 23 patients (74%) at

Table 2. *Objective and subjective responses to oral pamidronate*

	150 mg ($n = 23$)	300 mg ($n = 24$)
Objective response at EMR	3 PR	3 PR
	0 SD	2 SD
Investigator's objective response	1 PR	0 PR
	2 SD	4 SD
Major subjective response	7/22 (32%)	5/22 (23%)
Minor subjective response	4/18 (22%)	3/20 (15%)

PR, partial response; SD, stable disease; EMR, extramural review.

Table 3. *Adverse events considered to be at least possibly related to oral pamidronate*

	150 mg			300 mg		
	Grade 1	Grade 2	Grade 3	Grade 1	Grade 2	Grade 3
Gastrointestinal*						
Nausea	4	2	0	4	3	1
Vomiting	2	3	0	2	1	2
Diarrhoea	5	2	0	1	1	2
Abdominal pain	1	0	0	0	1	1
Anorexia	0	0	0	2	0	0
Haematemesis	0	0	0	0	1	0
Malaena	0	0	0	0	1	0
Other†						
Dizzyness	1	0	0	0	0	0
Hypertonia	1	0	0	0	0	0
Weight loss	0	0	0	1	0	0
Anaemia	0	0	0	1	0	0

*Graded as per Table 1. †WHO grading.

150 mg. When AEs which the investigators judged to have a 'possible', 'probable' or 'highly probable' relationship to trial treatment were considered, the patient numbers were 13 of 24 (54%) and 7 of 23 (30%) in the respective dose groups (Table 3). Non-GI AEs were clearly related to the underlying cancer. Overall, 18 of 24 (75%) and 6 of 23 (26%) patients experienced GI AEs at 300 and 150 mg, respectively. The numbers were 13 (54%) and 6 (26%) at respective doses when causally related episodes were considered. Premature discontinuation of trial treatment due to GI AEs occurred in 4 (17%) patients at 300 mg and in 2 (9%) patients treated at 150 mg. In 1 patient treated at 300 mg, oesophageal ulceration and bleeding was documented.

Nausea and vomiting were the most frequently reported GI AEs. Nausea, with at the least a 'possible' causality relationship to trial treatment was reported in 9 (38%) and 4 (17%) patients treated at 300 and 150 mg, respectively. The corresponding numbers with vomiting were 7 (29%) and 2 (9%) patients, respectively. One 83 year old woman, receiving concomitant therapy with diclofenac, developed nausea, abdominal pain, haematemesis and melaena 14 days after commencing trial treatment. Gastroscopy revealed moderate oesophagitis, gastric ulceration and two large duodenal ulcers in the first part of the duodenum. The patient recovered from this episode, but died 11 days later due to progressive breast cancer. No significant changes were observed in haematological parameters, liver function tests or renal function.

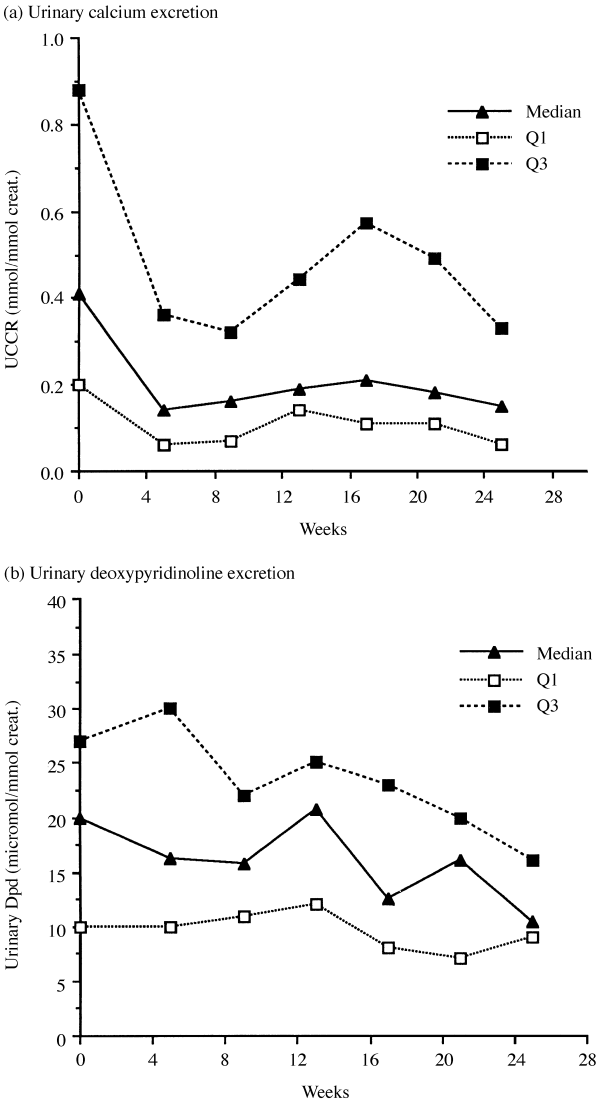

Figure 1. Urinary excretion of calcium (a) and deoxypyridinoline (b). Median, upper and lower quartiles are shown for both resorption markers. Values are expressed as a ratio to creatinine in order to correct for renal function.

DISCUSSION

8 patients in this study (5 at 300 mg and 3 at 150 mg) showed an objective response in bone according to the results obtained at extramural review. In addition, a modest symptomatic response rate was observed along with biochemical evidence of a reduction in bone resorption, with suppression of UCCR and a non-significant reduction in urinary deoxypyridinoline. Responses were seen at both dose levels and no evidence of a dose–response effect for any of the efficacy criteria could be detected in a study of this size. The subjective response criteria used in this study were quite liberal in comparison with other validated pain assessments used in previous studies [5, 12] and, if anything, exaggerated the subjective effects of treatment.

As in previous trials with oral pamidronate [8, 9]. GI AEs were the principal side-effects reported. The 300 mg dose was less well tolerated, with two to three times as many patients experiencing problems compared with the 150 mg dose level. Nausea and vomiting were the most common AEs reported and 6 patients discontinued treatment prematurely due to GI toxicity. Of the 2 patients with GI bleeding, ulceration documented by endoscopy was observed in one which could have been drug related.

The rather modest clinical effects in the context of significant, albeit generally manageable GI side-effects are rather disappointing and less impressive than those reported by van Holten-Verzantvoort and colleagues. However, in their study most of the clinical benefit was seen at the initial protocol dose of 600 mg—a dose which could not be sustained because of toxicity [13].

Although a number of other trials have been initiated in recent years for both the treatment and prevention of metastatic bone disease in breast cancer and multiple myeloma, it seems unlikely that the clinical effects with the oral formulation will match the impressive effects seen with intravenous therapy on bone pain [5], healing of lytic bone lesions [7] and inhibition of skeletal related events [1, 3, 6]. This is almost certainly due to the combination of poor tolerability and the very low absorption of oral pamidronate; with the enteric-coated capsule formulation used in this study, the bioavailability (even in fasting patients) has been shown to be less than 1% (Novartis, data not shown).

GI toxicity is not unique to pamidronate but a characteristic of amino-bisphosphonates in general. Both ibandronate [14] and alendronate [15] have also been reported to produce GI side-effects, notably oesophageal ulceration in the case of alendronate use for osteoporosis. Clodronate does not appear to share this property and has been relatively well-tolerated in most trials reported to date [2, 4]. However, clodronate is a relatively weak bisphosphonate and the clinical results, on indirect comparisons, appear to be less impressive than those obtained with intravenous pamidronate, Although oral clodronate has been shown to reduce skeletal morbidity [2, 4], no significant effects on pain or analgesic consumption have been demonstrated [7].

In conclusion, oral pamidronate was rather poorly tolerated and produced only modest clinical benefit. The intravenous route of administration remains preferable for both pain relief and long-term inhibition of skeletal-related events.

1. Hortobagyi GN, Theriault RL, Porter L, *et al.* Efficacy of pamidronate in reducing skeletal complications in patients with breast cancer and lytic bone metastases. *N Engl J Med* 1996, **335**, 1785–1791.
2. Paterson AHG, Powles TJ, Kanis JA, *et al.* Double blind controlled trial of clodronate in patients with bone metastases from breast cancer. *J Clin Oncol* 1993, **11**, 59–65.
3. Berenson JR, Lichtenstein A, Porter L, *et al.* Efficacy of pamidronate in reducing skeletal events in patients with advanced multiple myeloma. *N Engl J Med* 1996, **334**, 488–493.
4. Lahtinen R, Laakso M, Palva I, *et al.* for the Finnish Leukaemia Group. Randomised, placebo-controlled multicentre trial of clodronate in multiple myeloma. *Lancet* 1992, **340**, 1049.
5. Purohit OP, Anthony C, Radstone CR, Owen J, Coleman RE. High-dose intravenous pamidronate for metastatic bone pain. *Br J Cancer* 1994, **70**, 554–558.
6. Conte PF, Latreille J, Mauriac L, *et al.* Delay in progression of bone metastases in breast cancer patients treated with intravenous pamidronate. Results from a multinational randomised controlled trial. *J Clin Oncol* 1996, **14**, 2552–2559.
7. Body J-J, Coleman RE, Piccart M. Use of bisphosphonates in cancer patients. *Cancer Treatment Rev* 1996, **22**, 265–287.
8. Holten-Verzantvoort AT van, Kroon HM, Bijvoet OLM, *et al.* Palliative bone treatment in patients with bone metastases from breast cancer. *J Clin Oncol* 1993, **11**, 491–498.
9. Rose C, Ford J, Becher R, *et al.* on behalf of the Aredia international Study Group. Pamidronate disodium (Aredia), dose effect and tolerability evaluation in breast cancer patients with bone metastases, ESMO proceedings. *Ann Oncol* 1992, **3**(Suppl. 5), 85.
10. Fairbank JCT, Couper J, Davies JB, O'Brien JP. The Oswestry low back questionnaire. *Physiotherapy* 1980, **66**, 271–273.
11. Hayward JL, Carbone PP, Heuson JC, Kumaoka S, Segaloff A, Rubens RD. Assessment of response to therapy in advanced breast cancer. *Eur J Cancer Clin Oncol* 1977, **13**, 89–94.
12. Ernst DS, MacDonald RN, Paterson AHG, Jensen J, Bruera E. A double-blind cross-over trial of IV clodronate in metastatic bone pain. *J Pain Sympt Manag* 1992, **7**, 4–11.
13. Holten-Verzantvoort ATM van, Kroon HM, Bijvoet OLM, *et al.* Palliative pamidronate treatment in patients with bone metastases from breast cancer. *J Clin Oncol* 1993, **11**, 491–498.
14. Coleman RE, Purohit OP, Black C, *et al.* Ibandronate: a well tolerated new oral bisphosphonate for the treatment of bone metastases. *The Breast* 1995, **4**(3), 236.
15. De Groen PC, Lubbe DF, Hirsch LJ, *et al.* Oesophagitis associated with the use of alendronate. *N Engl J Med* 1996, **335**, 1016, 1021.

Acknowledgements—The authors would like to acknowledge the following investigators who also recruited patients for this trial. Dr C. Rose, Department of Oncology, Odense Sygehus 5000, Odense, Denmark; Dr H. Mouridsen, Department of Oncology, Rigshospitalet 5074, 2100 Copenhagen, Denmark; Dr C. Hamilton, Department of Radiotherapy, Royal South Hants Hospital, Graham Road, Southampton SO9 4PE, U.K.; Dr J. Maher, Regional Centre for Radiotherapy and Oncology, Mount Vernon Hospital, Northwood, Middlesex HA6 2UB, U.K. The authors also acknowledge the extramural review personnel who were Dr C.J. Tyrell (Clinical Oncologist, Plymouth General Hospital, Plymouth PL4 7JJ, U.K.), Dr M.V. Merrick (Consultant Radiologist, Western General Hospital, Crewe Road, Edinburgh, EH4 2XU, U.K.), Dr D. Ejlertsen (Consultant Oncologist, Aarhus University Hospital, Aarhus, Denmark), Dr A.M. Leffer (Radiologist, Rigshospitalet 5074, 2100 Copenhagen, Denmark).