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Pamidronate Infusions as Single-agent Therapy for Bone Metastases: A Phase II Trial in Patients with Breast Cancer

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Pamidronate is a potent biphosphonate which modulates tumour-induced osteolysis (TIO) by inhibiting osteoclast-mediated bone resorption. In a phase II trial, 69 breast cancer patients with symptomatic progressive bone metastases were given infusions of pamidronate 60 mg over 1 or 4 h every 2 weeks for a maximum of 13 infusions or until progressive disease (PD) at any site. No other systemic anticancer therapy was allowed. Pain was measured using a visual analogue scale, mobility using a detailed eight-point questionnaire and analgesic intake using a six-point scale. Improvements in pain, mobility and analgesic scores occurred in 61, 50 and 30% of patients, respectively, with 33, 21 and 16% achieving a 40% improvement for ≥8 weeks. At trial discontinuation, baseline levels of pain and mobility had improved by 27% ($P = 0.001$) and 20% ($P = 0.004$), respectively, despite a one category reduction in analgesic intake in 27% of patients. Using this relatively high dose of pamidronate, symptomatic response was independent of the number of bone metastases and also of infusion rate. The infusions were well tolerated with no major toxicities reported. Pamidronate infusions provide useful palliation for breast cancer patients with symptomatic bone metastases.

Key words: pamidronate, breast cancer, bone metastases, pain
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INTRODUCTION

BONE METASTASES are a major cause of morbidity in advanced breast cancer. Complications include pain, immobility, pathological fracture and tumour-induced hypercalcaemia (TIH) [1–3]. Osteoclast-mediated bone resorption under the paracrine influence of factors derived from tumour cells is the major process leading to bone destruction [4, 5]. Although the mechanisms remain poorly defined, biphosphonates inhibit osteoclasts, a property which has stimulated trials with these agents in metastatic bone disease [6].

Pamidronate (trade name Aredia®) is a potent biphosphonate which is widely registered for the treatment of TIH. Early trials demonstrated that normocalcaemia is restored in approximately 75% of patients using single doses of 30–45 mg [7–9] although subsequent reports indicate that response rates approach 100% when doses of 90 mg are employed [9, 10]. For bone metastases trials, dose selection has been a major challenge. In practice, doses with proven efficacy in TIH have been selected, a reasonable approach given that tumour-induced osteolysis (TIO) is particularly severe in patients with TIH. Based on early experience in TIH [7], doses of 30 mg as 2 h infusions every 2 weeks were employed in initial phase II trials in breast cancer conducted in the U.K. at centres in London and Manchester [11, 12]. During these trials, no specific anticancer therapy was administered, greatly facilitating the response evaluation to pamidronate. Although radiological, subjective and biochemical responses were documented, subsequent analyses have demonstrated that response was transient in patients with high levels of urinary calcium excretion (and, by inference, of bone resorption), suggesting that this dose was suboptimal for patients with extensive disease. Pharmacokinetic studies indicate that body retention of pamidronate is a function of the number of bone metastases, also raising the possibility that modest doses of biphosphonates could be subtherapeutic in patients with extensive skeletal involvement [13].

These considerations prompted an additional phase II trial of

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single-agent pamidronate in breast cancer in which infusions of pamidronate 60 mg were given every 2 weeks. As before, data were collected relating to radiological, subjective and biochemical parameters. To explore the influence of tumour burden on response, the effects were compared in patients with <10 or ≥ 10 bone metastases. The results are compared with those from the earlier studies.

PATIENTS AND METHODS

Breast cancer patients who had failed at least one systemic therapy for metastatic disease were eligible. All patients had symptomatic, progressive, lytic or lytic/sclerotic bone metastases. Extraskeletal disease, when present, was non-life threatening in the immediate future. Patients were to have a baseline white blood cell (WBC) count $\geq 2.5 \times 10^9$/l, platelets $\geq 75 \times 10^9$/l, serum creatinine ≤ 150 μmol/l and bilirubin ≤ 25μmol/l. No prior treatment with bisphosphonates was allowed. During the trial, no systemic anticancer therapy was permitted although hormonal therapy which had been administered for ≥ 3 months was continued in 18 patients to avoid withdrawal responses. Radiotherapy for intractable bone pain was allowed provided it was given to $< 25\%$ of bone lesions. The protocol was approved by local ethical committees and all patients gave informed consent.

Pamidronate 60 mg was given every 2 weeks, initially as 4 h intravenous infusions in 500 ml of 0.9% saline. It was subsequently decided to test the safety of 1 h infusions and approximately 50% of patients received infusions (in 250 ml of 0.9% saline) at this rate. Thirteen infusions were administered over 6 months, but were discontinued earlier if progressive disease (PD) occurred in bone or extraskeletal sites.

Bone pain and mobility, the primary efficacy parameters, were recorded every 4 weeks. The patients recorded average bone pain intensity during the previous week using a 100 mm visual analogue scale (VAS) (0 mm indicating no pain, 100 mm extremely severe pain). To provide an assessment of mobility, a modified Oswestry Back Pain Questionnaire was completed comprising eight of the original ten questions [14]. Questions relating to pain intensity and sexual function were omitted because they were considered repetitive or irrelevant. The results were expressed on a scale from 0% (no difficulties) to 100% (highest score for difficulties on all items). The physician recorded analgesic intake with a six-point scale: 0 = no analgesics; 1 = simple analgesics or non-skeletal anti-inflammatory drugs (NSAIDs); 2 = simple analgesics and NSAIDs; 3 = moderate analgesics (e.g. codeine); 4 = opiates equivalent to ≤ 40 mg morphine daily; 5 = opiates equivalent to > 40 mg morphine daily. Administered doses of opiates were converted to the morphine equivalent using standard conversion tables [15]. Consistent scoring of analgesic usage across centres was assured using a checklist. Depending on the extent and duration of improvement, patients were classified as showing no improvement, "some" improvement or "marked" improvement for pain, mobility or analgesic usage. Patients with "mild" improvement experienced a 20% reduction (or one category on the six-point scale) in scores for ≥ 8 weeks or a 40% reduction (or two categories on the six-point scale) for ≥ 4 weeks. Patients with "marked" improvement experienced a 40% reduction for ≥ 8 weeks. Because of overlap in the definitions, the number of patients with "some" improvement includes those achieving "marked" improvement.

A skeletal survey (skull, complete spine, chest X-ray and pelvis) was performed at trial entry and after seven and 13 infusions. Bone scans were performed at entry and after 13 infusions. These investigations were also repeated if the patient discontinued prematurely. Based on the bone scan, patients were classified as having < 10 or ≥ 10 bone metastases. Radiological response was defined as follows: partial response (PR), sclerosis of $\geq 25\%$ of baseline lesions; minimal response (MR), sclerosis of $< 25\%$ of baseline lesions; progressive disease (PD), new lytic disease or a $\geq 25\%$ increase in the size of baseline lesions on X-ray, or new lesions on bone scan if accompanied by pain. For both PR and MR, new bone scan foci had to be free of pain with normal X-ray appearances. Recently irradiated lesions were not used to assess response.

Blood parameters: complete blood count, tests of renal and hepatic function, calcium, phosphate and albumin, were measured every 2 weeks. Serum calcium (CA) was "corrected" for the level of albumin using the formula: corrected CA (CCA) = CA (mmol/l) + ((40-albumin (g/l)) × 0.02) [16]. Hyper- and hypocalcaemia were defined as CCA levels of > 2.75 and < 2.00 mmol/l, respectively. Second-void urine samples were collected after overnight fasting every 2 weeks and calcium excretion expressed as the molar ratio of urinary calcium to urinary creatinine (the UCCR). Carcinoembryonic antigen (CEA) and CA-15.3 were measured at baseline and after seven and 13 infusions, or at trial discontinuation, whichever occurred first.

The design of the earlier phase II breast cancer trials was similar, with two major exceptions. Pamidronate 30 mg was given over 2 h every 2 weeks for 6 months, although in Manchester, U.K. [12], the first four infusions were given weekly. In London, U.K., pain was assessed using a six-point categorical scale, ranging from a score of 0 representing no pain to a score of 5 indicating unbearable pain [11].

Statistical considerations

Formal statistical testing was performed for the pain and mobility scores. The scores at the following time-points were compared with baseline using the paired *t*-test: at 4 weeks (i.e. after two infusions); at lowest value recorded; and at last value recorded, irrespective of when this occurred. Median time to PD in bone was calculated using the Kaplan–Meier survival function.

RESULTS

69 patients were recruited into the trial from eight centres in four European countries (Table 1). Bone metastases had been present for a median of 20 months, representing the sole metastatic site in 49 patients (71%). Ten or more metastases were present in 44 patients (64%) and 42 patients (61%) had received more than one therapy for metastatic disease.

A median of nine infusions was administered (range 1–13) with 28 patients completing 13 infusions. This corresponds to a median trial duration of 18 weeks (range 2–26). The remaining 41 patients discontinued treatment prematurely for the following reasons: PD in bone ($n = 18$); PD in extraskeletal sites ($n = 5$); patient refusal ($n = 4$); death due to cancer ($n = 3$); hypocalcaemia ($n = 2$); cancer complications ($n = 9$). All 69 patients were included in the analyses.

Changes in pain and mobility scores according to the VAS and the Oswestry Questionnaire, respectively, are shown in Table 2. The mean score at baseline for both parameters was at the midpoint of the respective ranges (49 mm and 46%). Following pamidronate treatment, highly significant improvements were recorded for both parameters at each time-point, with the exception of mobility at week 4. The "last value" recorded is a

Table 1. Patient characteristics

Age (median)	54 years	(range 27–78)
Time since diagnosis of breast cancer (median)	52 months	(range 2–170)
Time since appearance of metastases in any site (median)	25 months	(range < 1–138)
Time since appearance of bone metastases (median)	20 months	(range < 1–135)
Number of bone metastases per patient:		
< 10	25/69 (36%)	
⩾ 10	44/69 (64%)	
Metastases localised to the skeleton	49/69 (71%)	
Prior therapy for metastatic disease		
Nil	2 (3%)	
1 prior therapy	25 (36%)	
⩾ 1 prior therapy	42 (61%)	

Table 2. Changes in pain and mobility scores at defined time-points

Parameter		Baseline	Week 4	Lowest value	Last value
VAS	Mean ± S.D.	49 ± 23	39 ± 23	25 ± 21	36 ± 24
	% change	–	−20%	−49%	−27%
	n	62	54	60	60
	P value (versus baseline)	–	0.02	0.0001	0.001
Mobility score*	Mean ± S.D.	46 ± 23	40 ± 21	33 ± 22	37 ± 23
	% change	–	−13%	−28%	−20%
	n	66	56	60	60
	P value (versus baseline)	–	0.2	0.0001	0.004

VAS, visual analogue scale (scale 0–100 mm).
*Modified Oswestry back pain questionnaire (scale 0–100%).

particularly severe test since it includes the scores of patients at trial discontinuation, including those with PD in bone, in whom symptomatic deterioration may have been present. At this time-point, the pain and mobility scores were improved by 27% ($P = 0.001$) and 20% ($P = 0.004$), respectively. Improvements in pain and mobility were independent of the number of bone metastases (data not shown).

The number of patients with "some" or "marked" improvement in pain, mobility and analgesic intake are shown in Table 3. "Some" improvement in these parameters was seen in 61, 50 and 30% of patients, respectively. "Marked" improvement (representing a 40% improvement or a two-point improvement in analgesic intake for ⩾ 8 weeks) was recorded in 33, 21 and 16% of patients, respectively. 64 patients were taking analgesics at trial entry, with a median score of 3. At some point during the trial, 37% of patients reduced analgesic intake by at least one category. At trial discontinuation, 27% were taking fewer analgesics.

Table 3. Improvements in symptomatic parameters

Parameter	Degree of improvement	Number of patients (%)
Pain (VAS)	"some"	61
	"marked"†	33
Mobility score*	"some"	50
	"marked"†	21
Analgesic score (six-point)	"some"	30
	"marked"†	16

VAS, visual analogue scale.
*Modified Oswestry back pain questionnaire; †Patients with "some" improvement are included in these totals.

Radiological assessment of response was performed in 61 patients, of whom 2 achieved PR and 8 MR, representing sclerosis in ⩾ 25% and < 25% of bone lesions, respectively. Median time to PD in bone was 168 days. During the trial, 8 patients (12%) received single courses of radiotherapy for bone pain. Data from these patients were not censored. One patient developed TIH with X-ray evidence of PD in bone.

The pamidronate infusions produced rapid sustained reductions in urinary calcium, expressed as the UCCR (upper limit of normal < 0.4 mmol/l:mmol/l). The median last recorded UCCR value for all 69 patients was 0.17, indicating sustained inhibition of bone resorption. In contrast, median levels of CCA and serum phosphate were largely unaffected. There were also no consistent reductions in CEA and CA-15.3, indicating that pamidronate had no antitumour effects.

Tolerability

The infusions were well tolerated. Transient infusion site reactions were reported after 11 infusions, 9 in patients receiving 1 h infusions. Fever was reported in 33 and 3% of patients

receiving 1 and 4 h infusions, respectively, usually after only the first infusion. Transient musculoskeletal discomfort, flu-like symptoms, headache and rigors were reported by 12, 7, 70 and 4% of patients, respectively, usually on only a single occasion, and at both infusion rates. Pamidronate was discontinued in 2 patients because of hypocalcaemia (CCA of 1.79 and 2.03 mmol/l, respectively). One complained of muscle cramps although the second remained asymptomatic. A 78-year-old patient who received 1 h infusions developed WHO grade 1 urea and creatinine levels which may have been drug-related although some values were elevated in the months prior to treatment.

DISCUSSION

This trial evaluated the effects of repeated infusions of pamidronate 60 mg in breast cancer patients with symptomatic bone metastases. No specific anticancer therapy was allowed, which prevented the inclusion of a placebo group on ethical grounds. However, to prevent withdrawal responses, hormonal therapy was continued in 18 patients who were progressing on these agents at trial entry. Limited radiotherapy was given to only 8 patients during the trial. Hence, the symptomatic improvements observed can largely be attributed to pamidronate.

Symptomatic responses were documented at 4 week intervals using patient self-assessment scales. Bone pain was assessed using a VAS, and a detailed mobility questionnaire provided an overview of the influence of pain on everyday activities [14]. In comparison to baseline values, average pain reductions of 20, 49 and 27% were recorded after 4 weeks, at "lowest" and at "last" value, respectively. Average improvements in mobility measured 13, 28 and 20% at these time-points. The changes are clinically relevant and were statistically significant for all comparisons with the exception of mobility at week 4. The patients' last recorded response value on-study constitutes the most severe test in that it includes values from patients with PD in bone, many of whom would have had symptomatic deterioration at that time. For both pain and mobility, this "last" value was lower than the score at week 4, indicating that response was sustained. In contrast, the data at week 4 could represent a placebo effect whilst the "lowest" values may reflect spontaneous fluctuations in the patients' perception of these subjective symptoms. A "marked" improvement in pain and mobility, defined as a 40% reduction in symptom scores lasting for $\geq$ 8 weeks, was observed in 33 and 21% of patients, respectively. Mobility improved to a lesser extent in all analyses, possibly reflecting debility due to cancer.

Analgesic intake was measured using a six-point scale and "marked" reductions, representing a two-point reduction for $\geq$ 8 weeks, were observed in 16% of patients. An additional 14% had lesser reductions in analgesic intake. Analgesics for moderate or severe cancer pain are seldom totally effective and are reduced only if sustained pain reduction occurs. A reduction in pain in the face of stable analgesic intake could be taken as showing patient benefit. In practice, analgesic requirements were reduced in some patients, providing additional evidence of sustained pain reduction.

The observation of pain relief sustained for many weeks in patients with progressive cancer is strong evidence against a placebo response. Sustained improvements were also seen in mobility levels and analgesic intake, both of which are less susceptible to placebo effects. Interestingly, there were no differences between subgroups based on number of bone metastases ($<$ 10 versus $\geq$ 10 bone metastases), suggesting that, at this dosage, response was independent of the extent of skeletal disease.

Sclerosis of lytic bone metastases on X-ray was reported in earlier breast cancer trials where pamidronate was given as single-agent therapy [11, 12]. These observations were confirmed in this trial, although sclerosis in $\geq$ 25% of lesions was seen in only 2 patients, with sclerosis of $<$ 25% of lesions in 8 additional patients.

During TIO, calcium is liberated from bone and excreted in the urine, resulting in relative hypercalciuria. Urinary calcium excretion, expressed as the UCCR, is a recognised marker of bone resorption [17]. UCCR levels decreased markedly following treatment with pamidronate and low levels were sustained for the duration of the trial, indicating prolonged inhibition of TIO.

Approximately 50% of patients received pamidronate infusions at 60 mg/h. Despite this 4-fold increase in infusion rate, the infusions were well tolerated. A 78-year-old patient with a prior history of renal insufficiency developed WHO grade 1 elevations of urea and creatinine after rapid infusions, but this episode may not have been drug-related. The predominance of fever and infusion-site reactions in patients receiving rapid infusions may represent a chance phenomenon and all other adverse events were equally distributed between the groups.

Table 4. Overview of phase II trials with pamidronate in breast cancer

Trial [reference]	London [11]	Manchester [12]	Present trial
Dose of pamidronate	30 mg every 2 weeks	30 mg weekly × 4 then every 2 weeks	60 mg every 2 weeks
No. of patients	27	19	69
Median time (months) since metastases appeared in any site	35	19	25
No. (%) of patients with bone metastases as only metastatic site	22/27 (85%)	11/19 (58%)	49/69 (71%)
Pain improvement	Six-point scale (mean)	VAS (mean)	VAS (mean)
	Baseline 2	Baseline 69 mm	Baseline 49 mm
	Last observation* 2	Last observation 40 mm	Last observation 36 mm
	$P = 0.60$	$P = 0.001$	$P = 0.001$
UCCR (median)	Baseline 0.56	Baseline 0.85	Baseline 0.47
(upper limit of normal	Week 4 0.26	Week 5 0.10	Week 4 0.11
0.4 mmol/l:mmol/l)	Last observation* 0.46	Last observation 0.26	Last observation 0.17

VAS, visual analogue scale; UCCR, urinary calcium/creatinine ratio. *Last measured value, irrespective of when this occurred.

This trial demonstrates that pamidronate can be safely infused at rates of up to 60 mg/h with a corresponding increase in patient convenience.

Comparison with other phase II trials

Biphosphonates target preferentially sites of bone metastases, and pharmacokinetic studies indicate that body retention of pamidronate after infusion (mainly in bone) is proportional to the number of bone metastases [13]. This suggests that when a fixed dose is given to a heterogeneous group of patients, efficacy might be compromised in patients with extensive skeletal involvement due to the delivery of a lower fractional dose at each metastatic site. To explore the relationship between the extent of skeletal involvement, the pamidronate dose and response, data from this trial have been compared with earlier breast cancer trials (Table 4). By combining information relating to the median time since the appearance of metastases at any site with the number of patients with only bone metastases, a comparison can be made of the average skeletal burden in patients across the trials. Thus, patients in London, U.K. [11], in whom 85% had only bone metastases, and metastatic disease had been present for a median of 35 months, had more extensive skeletal involvement on average than in Manchester, U.K. [12] where the corresponding figures were 58% and 19 months. The patients in the present trial occupy an intermediate position. At the London centre [11], pamidronate 30 mg did not produce sustained reductions in pain, and bone resorption was only temporarily inhibited, as shown by transient falls in urinary calcium, suggesting that this dose was inadequate for patients with longstanding disease. In contrast, significant pain relief and sustained reductions in UCCR were observed in Manchester, U.K. [12] where patients with more recent (and presumably less severe) skeletal involvement received a similar dose, although the initial administration of four infusions at weekly intervals may have contributed to the more favourable outcome. In the present trial, 60 mg were administered every 2 weeks and sustained improvements were observed in both parameters. At this dose level, response was independent of the extent of skeletal involvement as shown by similar efficacy in patients with < 10 or ≥ 10 bone metastases.

In summary, infusions of pamidronate 60 mg every 2 weeks provide useful palliation in breast cancer patients with symptomatic bone metastases. This dose can be safely infused over 1 h, thereby minimising patient inconvenience. In comparison to many anticancer agents, pamidronate is remarkably well tolerated.

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