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Treatment of bone metastases from breast cancer with (3-amino-1-hydroxypropylidene)-1,1-bisphosphonate (APD)

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Summary Twenty-eight patients with progressive symptomatic bone metastases from breast cancer received (3-amino-1-hydroxypropylidene)-1,1-bisphosphonate (APD) 30 mg in 500 ml of 0.9% saline infused over 2 h every 14 days. No other systemic therapy for breast cancer was prescribed. All patients had progressed on at least one previous systemic treatment. APD was continued until the disease progressed. Patients were assessed for objective response by the UICC criteria. In addition, subjective response was determined by a pain questionnaire.

Radiological evidence of bone healing with sclerosis of lytic disease (UICC partial response) was seen in 4 patients. The median duration of response was 10 months. Eleven patients had stable disease for at least 3 months (median 5 months) and 9 progressed. Symptomatic response occurred in 9 patients and 12 reported an improvement in quality of life. Treatment was tolerated well with no significant toxicity.

In conclusion, long-term inhibition of bone destruction is possible with APD therapy alone and both subjective and objective responses are seen.

Bone metastases are common in advanced breast cancer and a major cause of morbidity. Pain especially, but also pathological fracture, hypercalcaemia and bone marrow infiltration, cause disability. Palliation is possible with radiotherapy or systemic anticancer treatments and the clinical course is often long (Coleman & Rubens, 1987*a*). However, progressive skeletal destruction leads to increasing immobility, a deterioration in quality of life and premature death.

Our understanding of the pathogenesis of skeletal metastases is incomplete but activation of osteoclasts is clearly relevant (Coleman & Rubens, 1985). Tumour cells secrete a variety of paracrine factors which stimulate osteoclastic bone resorption. Normal coupling between osteoclast and osteoblast results in new bone formation although in metastatic bone disease this may be disturbed. Typically in advanced breast cancer resorption predominates and lytic bone metastases develop (Galasko, 1976).

The diphosphonates (biphosphonates) are compounds containing a P-C-P structure by which they bind tightly to calcified bone matrix (Powell & Denmark, 1985). Some, including (3-amino-1-hydroxypropylidene)-1,1-bisphosphonate (APD), are potent inhibitors of bone resorption. The mechanism of action is unclear but may involve direct biochemical effects on the osteoclast (Boonekamp *et al.*, 1986), prevention of osteoclast attachment to the bone matrix (Fleisch, 1982) or inhibition of osteoclast differentiation and recruitment (Boonekamp *et al.*, 1987). APD has been successfully used in the control of a variety of benign conditions characterised by increased bone resorption including Paget's disease (Harinck *et al.*, 1987), disuse and steroid-induced osteoporosis (Hoekman *et al.*, 1985; Reid *et al.*, 1988; Huaux *et al.*, 1985). APD is highly effective also for the control of hypercalcaemia of malignancy (Sleeboom *et al.*, 1983; Ralston *et al.*, 1985; Coleman & Rubens, 1987*b*) and a recent study has shown that APD in combination with systemic anticancer treatment reduces the morbidity caused by tumour-induced osteolysis (van Holten-Verzanvoort *et al.*, 1987).

We have studied the effects of APD on a group of patients with progressive lytic bone metastases from breast cancer. No other systemic anticancer treatment was prescribed allowing a detailed assessment of objective, symptomatic and biochemical response to APD.

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Patients and methods

Twenty-eight patients with progressive symptomatic bone metastases from advanced breast cancer were studied. The median age was 52 (range 32–73). All patients had confirmation of progressive lytic, or mixed lytic and sclerotic, bone metastases on serial radiographs. Skeletal disease was widely disseminated throughout the axial skeleton in all patients. Metastatic disease was confirmed to the bone in 23. In 5 patients stable asymptomatic extra-skeletal disease was present affecting the skin (3 patients), pleura (2 patients) and, in one patient each, breast, lymph nodes, lung and brain.

All patients had received previous systemic treatment; 27 endocrine treatment, 12 chemotherapy and 11 both (Table I). A four week withdrawal period was observed after additive hormone treatment (e.g., progestogens) or chemotherapy. Informed consent was obtained.

APD (Ciba-Geigy Pharmaceuticals Ltd., Horsham) was given every 14 days at a dose of 30 mg by intravenous infusion in 500 ml of normal (0.9%) saline over 2 h. Treatment was continued until progression of disease. The median number of APD treatments was eight (range 2–34). No other systemic anticancer treatment was prescribed. Radiotherapy

Table I Previous treatments

	No. treatments	*No. patients*
Endocrine		
Adjuvant	0	27
	1	1
Advanced diseased	0	1
	1	13
	2	8
	3	4
	4	1
	5	1
Chemotherapy		
Adjuvant	0	24
	1	4
Advanced disease	0	16
	1	8
	2	3
	3	1
Radiotherapy to bone metastases		
	No	5
	Yes	23

to painful sites of disease and analgesics were given as necessary.

Objective, symptomatic and biochemical response to treatment were assessed. The UICC response criteria (Hayward *et al.*, 1977) were used to assess objective response. A partial response was recorded when radiological evidence of sclerosis within previously lytic bone metastases was seen with no evidence of new lesions. The response category 'no change' indicated stabilisation of disease on plain radiographs for at least 3 months. An increase in the size of one or more baseline lesions or the appearance of new lesions was recorded as progressive disease. Purely sclerotic lesions were considered unassessable.

Two methods were used to assess symptomatic response: (1) a questionnaire recording pain intensity, analgesic consumption, mobility and performance status completed by the patient at each visit. A 'pain score' was derived from this information and expressed as a percentage of the maximum possible score (Table II); (2) a single question to the patient at 3 months (or sooner in the event of progressive disease) inquiring of the overall effect of treatment on quality of life.

Markers of bone metabolism used to follow the biochemical response to treatment were serum calcium, alkaline phosphatase and osteocalcin (BGP) and urinary calcium excretion. Monthly serum measurements of calcium, creatinine, alkaline phosphatase and phosphate were performed on a morning blood sample using a standard multi-channel autoanalyser. Serum for osteocalcin measurements was stored at −20°C and determined by radioimmunoassay using the Immuno Nuclear Osteocalcin RIA kit (Price *et al.*, 1980). A spot sample of urine was collected after an overnight fast and voiding of urine in the morning for measurement of urinary calcium excretion (Nordin, 1976). All samples were collected on the morning before treatment with APD.

Results

Response of skeletal disease to treatment was assessable in 24 patients (Table III). In 4 patients assessment was not possible because of either extra-skeletal progression (2 patients) or lack of follow-up data (2 patients). Radiographic evidence of bone healing (Figures 1 & 2) was seen in 4/24

Table II Derivation of pain score from questionnaire

Parameter	*Description*	*Score*
Pain	None	0
	Mild	1
	Moderate	2
	Severe	3
	Very severe	4
	Intolerable	5
Analgesic use	None	0
	Simple analgesic or NSAID	1
	Simple analgesic + NSAID	2
	Moderate analgesic (e.g. DF118)	3
	Opiates (<40 mg morphine daily)	4
	Opiates (>40 mg morphine daily)	5
Mobility	Normal	0
	Vigorous exercise/activity impaired	1
	Climbing stairs/walking/bending impaired	2
	Difficulty with dressing/washing	3
	Difficulty with all activities	4
	Totally dependent and bedbound	5
Performance status	Normal	0
	Light work possible	1
	Up and about >50% of the day	2
	Confined to bed >50% of the day	3
	Completely bedbound	4
Symptom score expressed as a percentage of maximum total		19 (100%)

Table III Response data ($n=28$)

Objective bone response (UICC)		
Partial response	4 (9, 9, 12, 18+ months)	
Stable disease	11 (median 5 months, range 3–7 months)	
Progressive disease	9	
Not assessable	4 – extra-skeletal progression: 2 – lost to follow-up: 2	
Subjective response		
	Global[a]	*Pain score*[b]
Improvement	12	9
No change	6	11
Deterioration	8	4
Not assessable	2	4

[a]Patient assessment of overall subjective benefit from APD treatment; [b]Derived as shown in **Table II**.

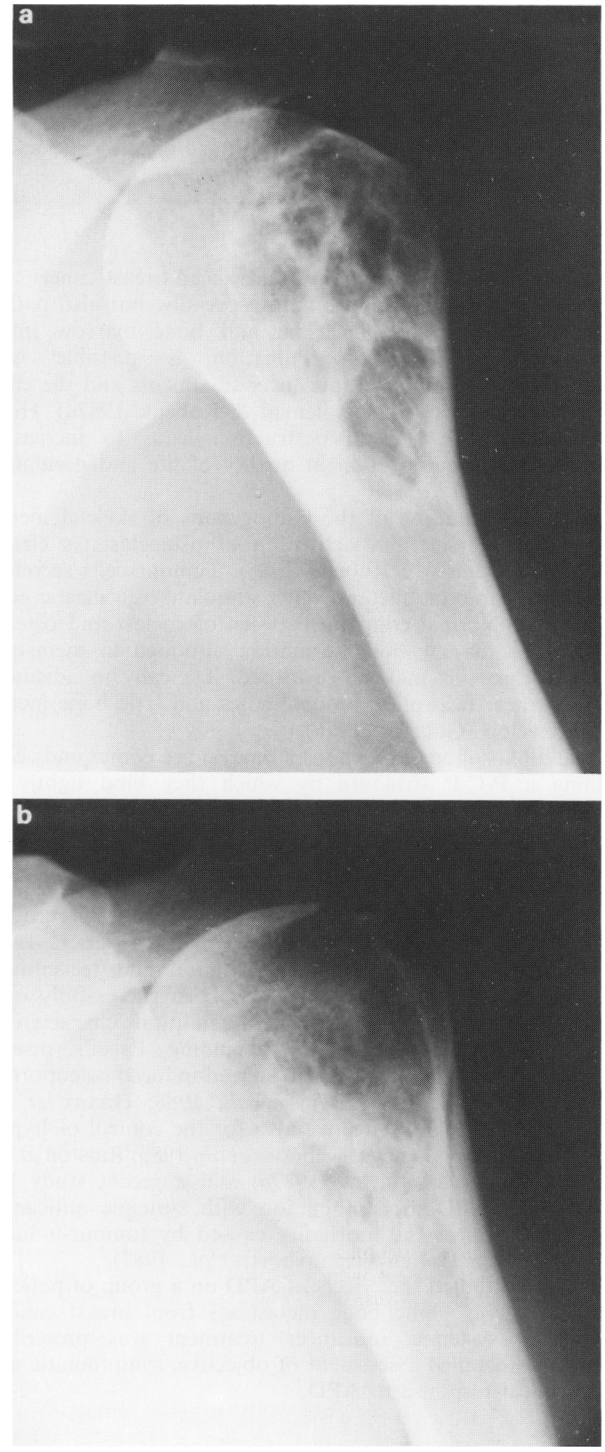

Figure 1 Plain radiographs of the left upper humerus (a) before and (b) 6 months after treatment with APD. The lytic lesion has undergone sclerosis.

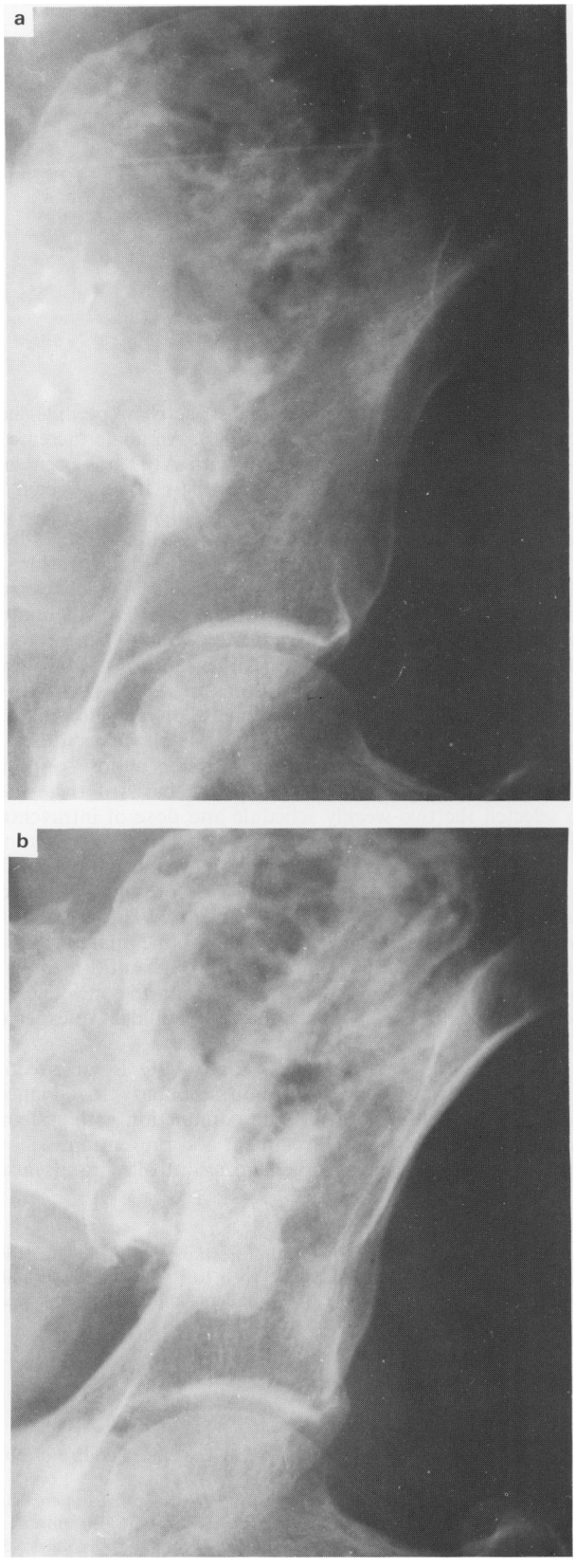

Figure 2 Plain radiographs of the left ilium (a) before and (b) 6 months after treatment with APD. The lytic areas in the ilium have undergone sclerosis.

patients (17%), in whom sclerosis of lytic lesions occurred with no evidence of new lesions. The sites undergoing sclerosis were outside the fields of previous radiotherapy.

The median duration of response was 10 months (range 9–18+). In one responding patient APD was stopped after 6 months' treatment and progression of disease was visible on plain radiographs 3 months later. APD was resumed but on this occasion the patient failed to respond. One patient remains on APD, in remission and off all analgesics, at 18 months. Two responding patients subsequently developed progressive disease outside the skeleton (liver 1 pt., skin 1pt.) necessitating a change of treatment. Restaging at this time showed no evidence of progressive skeletal disease. Stabilisation of previously progressive bone disease for a minimum of 3 months (median 5 months, range 3–7 months) occurred in 11 patients (46%). Two had radiological evidence of sclerosis but radiographs of other sites showed new lytic areas. In 6, extraskeletal progression occurred, necessitating a change in treatment, before any evidence of deteriorating skeletal disease. The median time to progressive bone disease was 16 weeks (range 5–78+ weeks) and occurred within 3 months in 8 patients (33%). The median duration of survival has not been reached but is more than 38 weeks.

The mean pain score fell from 53% to 49% after 3 months' treatment. This change was not significant but 9 patients showed a >10% improvement in symptom score. In 5 patients dramatic symptomatic improvement occurred allowing a major increase in mobility. All of these patients remain pain free more than a year later, 4 having discontinued opiate analgesia. All patients with symptomatic improvement had stabilisation of disease or bone healing on plain radiographs. Twelve patients reported global improvement in quality of life (Table III), 11 with stable or improving radiological signs. Six patients reported a cyclical pattern to their pain with improvement after treatment and an increase in pain during the few days before the next dose of APD.

Morbidity resulting from bone metastases included pathological fracture, cord compression, marrow infiltration and hypercalcaemia and these events are summarised in Table IV. Three patients were hypercalcaemic at the start of treatment. APD corrected the serum calcium to normal but recurrence of hypercalcaemic refractory to further doses of APD and progressive bone metastases developed in 2 within 3 months.

A transient but significant fall in serum calcium was seen at 1 month (Table V). The fall in urinary calcium excretion was more marked and persisted throughout treatment. A fall in urinary calcium excretion was seen in 23/25 (92%) patients with serial measurements. Despite inhibition of bone resorption there was no suggestion of inhibition of osteoblast activity. Levels of serum alkaline phosphatase activity and osteocalcin increased, although not significantly, during treatment.

APD was tolerated without serious toxicity. No gastrointestinal toxicity or alopecia was seen. Renal function as determined by serum creatinine was unaffected. Slight elevation of liver transaminases (1–2 times normal upper limit) occurred in 7 patients. This was of uncertrain significance but in 3 patients was attributable to the development of liver metastases. One patient had a mild pyrexia on the evening of treatment (on 2 occasions). Two patients developed lymphopenia (lymphocyte count $<0.5\times10^{9}l^{-1}$) and another two

Table IV Complications of metastatic bone involvement

	Temporal relationship to APD treatment		
Morbidity	*<1 month before*	*during*	*<1 month after*
Radiotherapy to painful bone lesions	4	5	2
Pathological fracture of long bone	0	1	2
Spinal cord compression	0	4[a]	0
Hypercalcaemia	3[b]	1	0
Leuco-erythroblastic anaemia	0	3	0

[a]Three at a site of progressive vertebral collapse and one due to epidural extension of the tumour; [b]Hypercalcaemia controlled by APD but returned during treatment in two patients.

Table V Effect of APD on biochemical markers of bone metabolism

	Month		
	0	*1*	*3*
Serum calcium (NR 2.1–2.6 mmol l^{-1})	2.39 (0.04)	2.29[a] (0.04)	2.39 (0.12)
Serum alkaline phosphatase (NR 80–300 Iu l^{-1})	507 (52)	652 (76)	562 (81)
Serum osteocalcin (NR 1.8–4.6 ng ml^{-1})	4.0 (0.53)	4.6 (0.69)	4.5 (0.63)
Urinary calcium/creatinine ratio (<0.4 mmol mol^{-1})	0.87 (0.13)	0.32[b] (0.06)	0.40[b] (0.09)

Values given are mean+s.e.m. Significantly different from month 0 value: [a]$P<0.05$, [b]$P<0.01$; NR=normal range for our hospital.

hyperphosphataemia (serum phosphate >1.5 mmol l^{-1}). Two patients had grand mal convulsions; in one cerebral metastases were detected on CT brain scan but in the other no metabolic or structural cause could be found. No further fits since stopping APD have occurred and to date, metastatic disease has not developed in the central nervous system.

Discussion

In this study we have shown that APD, in the absence of any other systemic treatment for breast cancer, is able to halt the metastatic destruction of bone. Seventeen per cent showed evidence of bone healing on plain radiographs and 46% stabilisation of disease. Accompanying this was a reduction in pain score and increased mobility. Symptomatic response was occasionally dramatic and osteolytic destruction inhibited for many months. Although not formally tested there was an indication that APD improved quality of life. Treatment was well tolerated.

Biochemical improvement has been noted in previous studies of diphosphonates in metastatic bone disease (van Holten-Verzantvoort *et al.*, 1987; Elomaa *et al.*, 1983; van Breukelen *et al.*, 1974; Siris *et al.*, 1980), and a reduction in morbidity reported in placebo-controlled studies (van Holten-Verzantvoort *et al.*, 1987; Elomaa *et al.*, 1983). Inhibition of new lesion formation has been noted in animal (Jung *et al.*, 1984) and human studies (Elomaa *et al.*, 1985) but none have reported radiological improvement in metastatic bone disease.

The diphosphonates possess no cytotoxic or immunosuppressive activity (Garattini *et al.*, 1987) and so the structural improvement in bone lesions in some patients needs alternative explanation. In metastatic bone disease bone formation and resorption rates are typically increased (Delmas *et al.*, 1987; Coleman *et al.*, 1988). Specific inhibition of bone resorption stops the efflux of calcium from the skeleton while continuing osteoblast activity permits new bone formation to occur (Parfitt, 1980). An acute increase in the bone mass following treatment with APD has been seen in normal rat bone (Reitsma *et al.*, 1980), bone affected by the mouse 5T2 multiple myeloma (Radl *et al.*, 1985) and patients with steroid-induced osteoporosis (Reid *et al.*, 1988).

The optimum schedule and route of administration of APD has not been defined. We have shown previously that a single intravenous dose of 15–30 mg of APD will control hypercalcaemia secondary to advanced breast cancer for a median of 11 days (Coleman & Rubens, 1987*b*). Multi-dose and single dose intravenous infusions of APD appear to be equally effective in the treatment of hypercalcaemia of malignancy (Yates *et al.*, 1987) and above a dose of 0.25 mg kg^{-1} there does not appear to be a dose–response relationship (Body *et al.*, 1987). On the basis of these data we selected the two-weekly schedule and dose of intravenous APD used in this study.

Extra-skeletal progression was common and the reason for changing treatment in 12 patients. This presumably reflects the lack of specific anticancer treatment. Whether this had any influence on the development of bone marrow infiltration and spinal cord compression through intra-medullary and epidural extension is speculative, but the incidence of these complications was higher than we would have expected (Coleman & Rubens, 1987*a*).

In conclusion, we have shown that APD is an effective drug for inhibiting bone resorption secondary to advanced breast cancer. The role of APD in conjunction with systemic antitumour therapy for the treatment and prevention of bone metastases is now being studied in a controlled randomised trial.

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