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Treatment of Bone Metastases from Breast Cancer and Myeloma with Pamidronate

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28 patients with progressing painful bone metastases (18 breast cancer, 9 myeloma and 1 low grade lymphoma) received pamidronate 60 mg by 24 h continuous infusion for at least 2 courses (range 2–12). In patients urinary calcium and hydroxyproline excretion significantly decreased in relation to diminution of bone resorption. 9 of 18 breast cancer patients and 8 of 9 evaluable patients with myeloma had symptomatic improvement. Sclerotic areas of previously lytic lesions appeared in 8 breast cancer patients and in 1 myeloma patient. Transient fever developed in 1 patient and local phlebitis in 2. Among the 28 patients, 15 did not receive any anticancer treatment or have any change of the anticancer therapy during pamidronate administration. Of 7 with breast cancer, 4 had an improvement of symptoms and 4 sclerosis on radiographs. Impressive control of symptoms was the major feature of 8 myeloma patients, but only 1 had radiographic sclerosis.
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INTRODUCTION

BONE METASTASES are a frequent cause of morbidity and mortality in cancer patients, causing pain, pathological fractures and hypercalcaemia [1]. They result from accelerated bone resorption induced by the tumour and mediated through an activation of osteoclasts, stimulated by endocrine factors, such as parathyroid hormone related peptides, osteoclast activating factor (OAF), or by paracrine factors such as transforming growth factor alpha and tumour necrosis factor [2–4]. The frequency of bone metastases in breast cancer patients increases during the course of the disease, reaching 50–85% [5–7]. In myeloma, bone involvement is, by definition, 100%. The treatment of bone lesions is directed against the tumour itself (chemotherapy, hormonotherapy or radiotherapy).

Bisphosphonates are structural analogues of pyrophosphate, the natural regulator of bone mineral precipitation and dissolution. Their mechanisms of action are not completely understood. They alter surface hydroxyapatite, impairing osteoclast binding sites [8], and act directly on the mononuclear precursor of osteoclasts [9]. Bisphosphonates have been widely used in benign clinical conditions characterised by increased bone resorption, such as Paget's disease [10] or osteoporosis [11]. In

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malignant diseases they have been used successfully for the control of hypercalcaemia of malignancy [12–14]. The use of bisphosphonates to control the morbidity of bone metastases from breast cancer was then tested in open trials and in a few randomised studies [15–17]: bone pain, fractures and hypercalcaemic events significantly decreased. In myeloma, there are fewer reports and definite conclusions on the role of bisphosphonates cannot be drawn [13, 18].

The optimal dose schedule and route of administration of bisphosphonates are not yet defined. Most clinical studies have tested oral administration at low dosage. Bisphosphonates are poorly absorbed by the gut, 4% [19] or less, and can cause gastric irritation, leading to further dose reduction [17]. A dose-response relation has been demonstrated in the treatment of hypercalcaemia [20, 21] and may be of importance in the treatment of other malignant conditions. Pamidronate is a second-generation bisphosphonate that strongly inhibits bone resorption without interfering with bone mineralisation at clinical doses [8, 22]. It may be superior to other bisphosphonates considering its direct action on osteoclast precursors [9, 23].

In previous studies we have determined the efficacy of pamidronate as a single infusion at high dosage in mild Paget's disease [10] and malignant hypercalcaemia [14, 20]. We therefore did an open phase II study to assess its long-term tolerance and efficacy in breast cancer or myeloma patients with painful, progressing lytic lesions of bone.

PATIENTS AND METHODS

Unselected patients with painful, progressing osteolytic metastases from histologically proven breast cancer or myeloma were studied. A patient with a low grade, diffuse, well-differentiated lymphoma with bone lesions was enrolled in the myeloma group. 1 patient in this group had no bone pain and was not evaluable for symptomatic response. All the patients were normocalcaemic.

The breast cancer group consisted of 25 patients but only 18 were evaluable for long-term results. 7 patients were excluded because of early death due to rapid progression of disease and/or because pamidronate was administered only once. For similar reasons 3 out of 13 patients were excluded in the myeloma group, leaving 10 patients for evaluation. 7 patients with breast cancer and 8 with myeloma had no oncological treatment at all or no modification of the treatment at time of pamidronate administration and follow-up. In the remaining 11 breast cancer and 2 myeloma patients, in whom a new oncological treatment (chemotherapy, hormonotherapy) was started at the same time as pamidronate the treatment was not modified during follow-up. Response to treatment was assessed radiographically, biochemically and symptomatically.

Bone metastases were confirmed by conventional radiographs which were repeated every 3 months. Evaluation of response was done blindly by a radiologist. "Response" was recorded when sclerosis appeared in previously lytic areas. However, the appearance of new lytic areas was considered as "progression" and radiologic stabilisation as "no change". Biochemical indices were monthly serum calcium, phosphate, creatinine, alkaline phosphatase and proteins and urinary calcium, creatinine and hydroxyproline in 2 h morning urine samples [14]. Symptomatic response was assessed by monthly medical evaluation of pain (score 0–10) and by patients' evaluation of pain intensity on an analogue scale (0–10). Antalgic consumption and evaluation of performance status according to Eastern Cooperative Oncology Group criteria [24] were recorded at each visit. Symptomatic response was defined as complete (CR) if pain ceased for at least 2 months according to the medical and patients' evaluations, without pain medication. A partial response (PR) was defined as an improvement of at least 3 points in both evaluation systems, with a decrease in pain medication, for at least 2 months. Other minimal changes, lasting less than 2 months were described as no change (NC).

Table 1. *Characteristics of breast cancer patients*

Patient no.	Age	Menopausal status	TNM	ER/PR (fmol/mg protein)	Time to bone metastases (months)	Previous treatment of bone metastases*	Extraskeletal metastases	Survival	
								Status	Duration (mo)
1	46	Pre	T2N1M0	8.1/12.1	10	MPA	—	Dead	48
2	58	Post	T4N1M1	25.8/29.7	—	Tam	—	Dead	41
3	45	Pre	T2N0M0	16.5/129.5	14	Ooph/4-Epi	Node	Dead	60
4	73	Post	T4N1M0	8.6/20.6	105	Tam	—	Alive	159
5	68	Post	T4N2M0	23.4/38.1	11	Tam/RT	Skin	Dead	58
6	85	Post	T2N1M0	Neg/13	11	RT	—	Dead	20
7	74	Post	T2N1M0	Not done	96	RT	—	Alive	127
8	63	Post	T2N1M0	1.4/3	20	RT	—	Dead	67
9	56	Post	T1N0M0	127.2/9.7	15	Tam/RT	Liver	Dead	36
10	49	Pre	T4N1M0	8.6/20.6	21	Tam/RT	Node	Dead	35
11	53	Post	T2N1M0	Neg/Neg	110	Tam	Node/skin	Dead	119
12	63	Post	T2N0M0	47.7/21.8	36	RT/Tam/MPA	—	Dead	65
13	37	Pre	T2N1M0	26.9/17.1	11	Ooph	—	Dead	51
14	46	Pre	T2N0M0	6.2/87.3	16	Ooph	—	Dead	45
15	45	Pre	T2N1M0	27.5/5.0	13	RT	Liver	Dead	25
16	70	Post	T3N1M0	20.6/36.3	10	—	Liver/skin	Dead	51
17	57	Post	T1N0M0	15.0/189.5	24	RT	—	Dead	97
18	56	Post	T2N0M0	237/116.7	29	—	—	Alive	120

Pre = premenopausal; Post = postmenopausal; TNM = tumour node metastasis; ER = oestrogen receptor; PR = progesterone receptor; Neg = negative; 4-Epi = 4-epirubicin; MPA = medroxyprogesterone; Tam = tamoxifen; RT = radiotherapy and Ooph = oophorectomy.

Table 2. Breast cancer patients

Patient no.	No. of courses	Drug treatment	Symptoms: Response	Symptoms: Duration (mo)	Bone radiology: Response	Bone radiology: Duration (mo)	Reasons for going off-study
Oncological treatment or change of previous hormonotherapy							
1	4	None	PR	14	Sclerosis	12	Node and cutaneous metastases
2	5	None	PR	8	Sclerosis	24	Liver metastases
3	3	Ooph*	PR	6	Sclerosis	8	Bone progression
4	10	Tam†	CR	12	No change	12	Bone progression
5	7	Tam†	NC	—	Sclerosis	6	Bone progression
6	6	None	NC	—	Progression	—	Bone progression
7	6	None	NC	—	Progression	—	Bone progression
Oncological treatment started at time of pamidronate							
8	8	CMF	NC	—	No change	10	Bone progression
9	4	AG	NC	—	Progression	—	Liver and bone progression
10	3	MPA	NC	—	Progression	—	Brain and bone progression
11	3	MPA	PR	5	Sclerosis	14	Marrow involvement
12	2	AG	NC	—	Progression	—	Liver and bone progression
13	8	MPA	CR	11	Sclerosis	12	Bone progression
14	7	MPA	PR	5	Sclerosis	8	Meninges and bone progression
15	5	MPA + 4-Epi	PD	—	Progression	—	Bone progression
16	3	MPA	PR	3	Progression	—	Liver and bone progression
17	3	4-Epi	NC	—	Progression	—	Stroke
18	12	Tam	PR	11	Sclerosis	31	Bone progression

*Oophorectomy 1 year before.
†Tamoxifen for the 3 previous years.
CMF = cyclophosphamide methotrexate 5-fluorouracil; 4-Epi = 4-epirubicin and AG = aminogluthetimine. CR = complete response, PR = partial response, NC = no change.

Pamidronate (Ciba-Geigy) was given at 60 mg intravenously as a 24 h continuous infusion every month for 4 courses, then every 3 months until progression of disease. A portable infusor (Travenol R, Travenol Laboratories) was used in most patients. The pump, which contained 60 ml (60 mg drug) was fixed to the arm of the patients, allowing outpatient treatment.

RESULTS

Breast cancer

Patients' characteristics and results are summarised in Tables 1 and 2. The median number of pamidronate courses was 4 (range 2–12). Plasma calcium decreased from 2.51 (mean, S.D. 0.05) mmol/l to 2.40 (0.04) mmol/l ($P < 0.05$, t test) 6 months after treatment. No hypocalcaemia occurred. Plasma creatinine and phosphate remained unchanged. Urinary hydroxyproline and calcium excretion are shown in Fig. 1. The fall in urinary calcium excretion (65% after 1 month and 42% after 6 months) and hydroxyproline (about 35%) suggested an important reduction in bone resorption in all cases. No episodes of hypercalcaemia or pathological fractures were observed during follow-up.

No side-effects occurred except for 2 episodes of superficial phlebitis that resolved quickly at the end of infusion. No fever or haematological changes were recorded.

Radiologically, new sclerotic areas of previously lytic lesions appeared in 8 patients (44%), stabilisation in 2 patients (12%), and progression with worsening of the lysis in 8 patients (44%). The radiological response lasted for a median of 12 months (6–31). Among the 8 patients with sclerosis, 6 had a PR of bone pain with an improvement of performance status, 1 had a CR for 11 months and 1 had no change. 1 patient with radiological stabilisation had a symptomatic CR and 1 patient with worsening of lytic lesions had a transient amelioration of pain for 3 months. As a whole 9 patients (50%) had a symptomatic response for a median of 8 months (3–14). The small number of patients precluded detection of a correlation between symptomatic or radiological response and any of the patients' characteristics.

In the subgroup of 7 patients with no oncological treatment or no concomitant modifications of their treatment, a radiological response was noted in 4 patients, no change occurred in 2 patients and progression in 1. Symptomatic improvement was recorded in 4 patients, 3 of whom had radiological response and

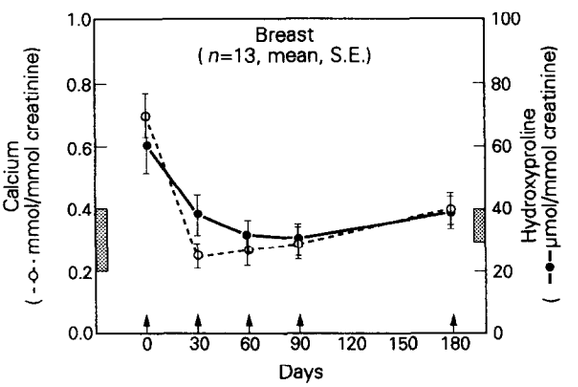

Fig. 1. Urinary calcium and hydroxyproline excretion in breast cancer patients. Arrow = 60 mg pamidronate. Shading = normal range.

Table 3. Myeloma patients' characteristics and results

Patient no.	Age	Stage	No. of courses	Drug treatment	Symptoms: Response	Symptoms: Duration (mo)	Bone radiology	Follow-up (mo)
Oncological treatment or change of previous therapy								
1	61	II A	9	None	Ineval*	—	Sclerosis	24
2	77	III A	8	None	PR	18	NC	24
3	37	I A	8	None	CR	18	NC	24
4	83	II A	7	None	PR	16	NC	16
5	72	II A	4	MEL-Pred†	PR	9	No data	12
6	55	III A	4	None	CR	10	NC	10
7	72	II A	6	None	PR	6	NC	12
8	72	DWDL IV	10	CLB-Pred	CR	24	NC	24
Chemotherapy started at time of pamidronate								
9	67	II A	7	MEL	NC	—	NC	16
10	57	II A	6	MEL-Pred	PR	12	NC	12

*Inevaluable, no bone pain.
DWDL = diffuse well-differentiated lymphoma. MEL-Pred = melphalan-prednisone (†for the 3 previous months).
CLB-Pred = chlorambucil prednisone for the 3 previous years.

1 had no change. The symptomatic improvement lasted from 6 to 14 months.

The reasons for stopping pamidronate are recorded in Table 2. Extraskeletal progression occurred in 7 patients, among whom 3 had no concomitant bone progression.

Myeloma patients

Patients' characteristics and results are reported in Table 3. The median age was 64 (39–83) and median follow-up was 17 months (12–22). A median of 7 courses was given (3–10).

Urinary calcium and hydroxyproline excretion are shown in Fig. 2. A fall in both variables occurred rapidly and plateaued at 50% of the initial values during follow-up. Plasma calcium decreased slightly and remained significantly lower after treatment (Fig. 3). The other indices (plasma phosphate, protein, creatinine and alkaline phosphatase) did not change significantly.

Except for 1 patient who had a transient increase in temperature, no side-effects were recorded. Most patients were treated as outpatients with no sign of phlebitis.

Radiological sclerosis was noted only in 1 patient. In the other patients no major changes of bone lyses or porosis could be demonstrated. On the other hand, symptomatic response was dramatic, occurring in 8 of the 9 evaluable patients (89%) among whom 3 had a CR lasting 10 to 24 months and 5 a PR lasting a median of 12 months (6–18).

In the subgroup of 8 patients without concomitant chemotherapy or any change in their oncological treatment, all, including the 1 with low grade lymphoma, showed a dramatic decrease or disappearance of their symptoms. Except for 1 patient who developed sclerosis of a previously lytic lesion, no significant changes of bone appearance were observed on plain radiographs. In 2 patients, an increase of paraprotein secretion was noted during the period of pain control.

DISCUSSION

Bisphosphonates are powerful inhibitors of bone resorption. They have been used against tumour-induced hypercalcaemia [12–14] and as a supportive treatment in patients with bone metastases from breast cancer [15–17], myeloma [18] and prostatic cancer [25]. In our study, pamidronate was administered

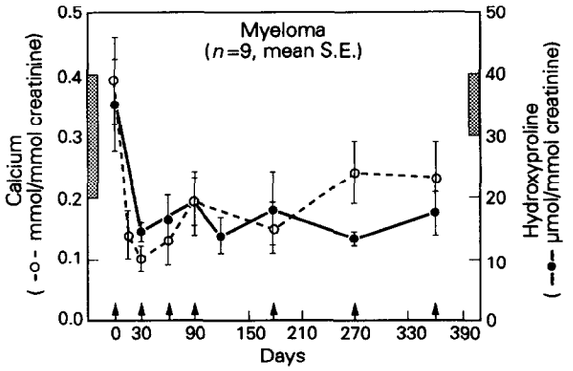

Fig. 2. Urinary calcium and hydroxyproline excretion in myeloma patients.

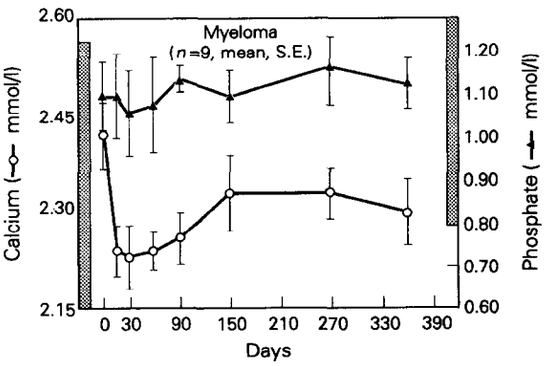

Fig. 3. Serum calcium and phosphate levels in myeloma patients.

in a 24 h intravenous infusion in patients with metastatic breast cancer or myeloma. The important reduction in bone resorption reflected by the drop in urinary hydroxyproline and calcium excretion in both groups of patients confirmed the efficacy of a single infusion of APD, as reported in malignant hypercalcaemia [14, 20]. The appearance of areas of sclerosis of previously lytic bone metastases was observed in half of the patients with breast cancer and in 1 with myeloma. This finding suggested a positive calcium balance due to decreased local and general bone resorption.

To define better the clinical impact of pamidronate, we selected subgroups of patients who did not receive any antitumour treatment or had no change of their oncological treatment while developing painful lytic bone lesions. Improvement of bone pain, with reduction of antalgic consumption and increased mobility occurred in half the breast cancer patients and in all myeloma patients. All these patients had stable disease or sclerosis on bone radiographs. In a breast cancer study, where pamidronate was given intravenously at 30 mg over 2 h every 14 days, symptomatic improvement was described in 42% of the cases [15]; and in a myeloma study, in which dichloromethylene diphosphonate was given orally, a striking decrease of pain occurred in all 7 patients [18]. Our results were similar. The antalgic mechanism of bisphosphonates is not known, but could be mediated through a reduction or an inhibition of lactic acid production [23], lysosomal enzymes [26], or prostaglandin synthesis [27] by osteoclasts. An anti-inflammatory effect on macrophages and secretion of cytokines could also be involved [28].

Radiological assessment of skeletal morbidity is an insensitive method and must be regarded with caution. Subjectivity in interpretation of mixed lytic and blastic areas in plain radiographs made us use a blind control by a radiologist. A lytic lesion is not evident until the destruction of spongy bone reaches 30–50%, and healing of bone may not become apparent within a few months. A difference in the rate of bone sclerosis was seen between breast cancer and myeloma lesions. Similar findings are suggested by other studies. 1 among 7 patients in the myeloma study developed sclerosis [18], and 4 of the 28 patients in the breast cancer study [15]. No pathological fractures, cord compression or episodes of hypercalcaemia developed during treatment.

Pamidronate had no obvious antitumour effect in this population with advanced disease. Extraskeletal metastases appeared in 3 patients with breast cancer and paraprotein increased in 2 patients with myeloma, while symptoms and radiological lesions were controlled by pamidronate.

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