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REDUCED MORBIDITY FROM SKELETAL METASTASES IN BREAST CANCER PATIENTS DURING LONG-TERM BISPHOSPHONATE (APD) TREATMENT

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Summary 131 patients with osteolytic metastases from breast cancer were randomised to receive long-term oral treatment with aminohydroxypropylidene-bisphosphonate (APD), 300 mg daily (n = 70), or to act as controls (n = 61) in a multicentre trial. Specific antitumour therapy was at the discretion of the clinician and variable. An interim analysis was made after a median follow-up of 13 months in the APD group and 14 months in the controls. There was a significant reduction in pathological fractures and severe bone pain in the APD group, and hypercalcaemia was prevented. Consequently the necessity for radiotherapy for skeletal complications was more than halved; the number of systemic therapy changes was also reduced. Gastrointestinal side-effects of APD led to a drop-out of 8% of patients. Oral supportive APD therapy is simple and convenient, and significantly reduces skeletal morbidity in advanced breast cancer.

Introduction

BONE metastases occur in up to 85% of patients with advanced breast cancer and can cause pain, fractures, and hypercalcaemia.[1] Hypercalcaemia due to bone metastases or to a more generalised stimulation of bone resorption by a malignancy can be treated effectively with bisphosphonates.[2-5] These compounds are potent inhibitors of bone resorption. The mechanism may involve biochemical effects on bone cells, which have been postulated for disodium clodronate and disodium etidronate, or prevention of osteoclast attachment to bisphosphonate-covered bone matrix,[6,7] as was shown for aminohydroxypropylidene-bisphosphonate (APD), a compound that we developed.[8]

APD inhibits tumour-induced osteolysis in normocalcaemic patients with malignancy.[9] A beneficial effect of bisphosphonates on morbidity due to osteolytic metastases from breast cancer was postulated after a small controlled study with clodronate.[10] During that study, however, the specific anti-tumour therapy was not adjusted in the controls or the treated group when the disease progressed. We report an interim analysis of a prospective open controlled trial of supportive APD treatment on the prevention of morbidity due to progression of metastatic bone disease. The specific antitumour therapy could be adjusted throughout according to clinical need.

Patients and Methods

Patients

Unselected patients with osteolytic metastases of a histologically proven breast cancer were, separately for each of the fourteen centres, randomly allocated to groups for APD treatment or not (controls). Informed consent was obtained. Criteria for exclusion were hypercalcaemia, life-expectancy of less than 6 months, creatinine clearance below 30 ml/min, peptic ulcer, malabsorption, and pregnancy. Details of the groups are shown in table I. At entry into the trial there was evidence of progression of the advanced disease state in all but 1 patient, as assessed according to UICC criteria.[11] The time of entry into this trial was either at first systemic treatment or at a later change of therapy.

At the time of this interim analysis (December, 1986) 131 patients had entered the trial; 70 had received APD for a median follow-up of 13 months (range 1-36). In this group the total duration of observation to date was 957 patient-months. There were 61 controls with a median follow-up of 14 months (range 1-30), equivalent to 868 patient-months.

TABLE I—CHARACTERISTICS OF 131 PATIENTS WITH OSTEOLYTIC METASTASES FROM BREAST CANCER AT START OF TRIAL*

—	APD group (n = 70)	Controls (n = 61)
Age (yr):		
Mean	62	60
(range)	(40–84)	(38–78)
Oestrogen receptor status:		
Positive	44	36
Negative	2	9
Unknown	24	16
Osteolytic bone metastases:		
Axial	39	36
Long bones	3	0
Both	28	25
Extra-osseous metastases	47	41
Previous skeletal complications:		
Hypercalcaemia	5	3
Pathological fractures	8	7
Previous systemic therapy†	51	46
Systemic therapy		
Hormonal	49	40
Chemotherapy	16	15

*All patients were female except 1 in control group.
†One or more types of chemotherapy and/or hormonal therapy.

The APD treatment is intended to be life-long and continuous, irrespective of the occurrence of events related to skeletal morbidity. Trial participation ends with death, with unacceptable APD toxicity, or on request by the patient. Local and systemic antitumour therapy (radiotherapy, surgery, chemotherapy, or hormonal therapy) at the start and during the trial is at the discretion of the clinician. Treatment of hypercalcaemia during the trial with a short course of intravenous APD is allowed in both groups.

APD Treatment

300 mg enteric-coated APD tablets (2 × 150 mg) were given daily, 30 min before meals. The controls did not receive placebo. The APD dose was chosen on the basis of gastrointestinal tolerance. The tablets were prepared by the hospital pharmacy.

Analysis

The patients have been examined three-monthly when clinical data were collected and routine blood tests were done. The study period in this analysis lasted from July, 1983, to December, 1986.

There were 323 three-month evaluation intervals in the APD group and 297 such intervals in the controls. We analysed the occurrence of hypercalcaemia (serum calcium exceeding 2.75 mmol/l), of bone pain severe enough to be a reason for radiotherapy or surgery, and of pathological or imminent fractures. We also evaluated the number of changes of hormonal or chemotherapy regimens caused by progression of osteolytic metastases, the number of radiotherapy or surgical interventions needed for the treatment of bone pain and pathological or imminent fractures, and APD toxicity.

Additionally event-free survival was studied. This is defined as the survival period from the time of randomisation during which none of the following complications occurred: hypercalcaemia, changes of medication, radiotherapy, surgical intervention, death, or APD toxicity leading to drop-out from the trial. Kaplan-Meier curves were plotted for event-free survival, and the treatment and control groups were compared with the log-rank test. Other comparisons were made with the Mann-Whitney test and the χ^2 test.

Results

Events related to skeletal morbidity (ie, hypercalcaemia, changes of systemic medication, radiotherapy, or surgery) can occur alone or combined within a 3-month observation interval, but are referred to as one complication. There were significantly more complications in the controls (67) than in the APD group (32) (table II). In addition the ratio of combined to total complications was significantly higher in the controls (31:67) than in the treated (7:32) group ($p = 0{\cdot}002$). The overall morbidity has been plotted as the cumulative sum of complications during subsequent observation intervals against the cumulative sum of these intervals. The slopes represent the occurrence of complications per unit time and are a measure of morbidity (fig 1). The slopes in both groups were approximately linear throughout the study. With supportive APD treatment morbidity was more than halved.

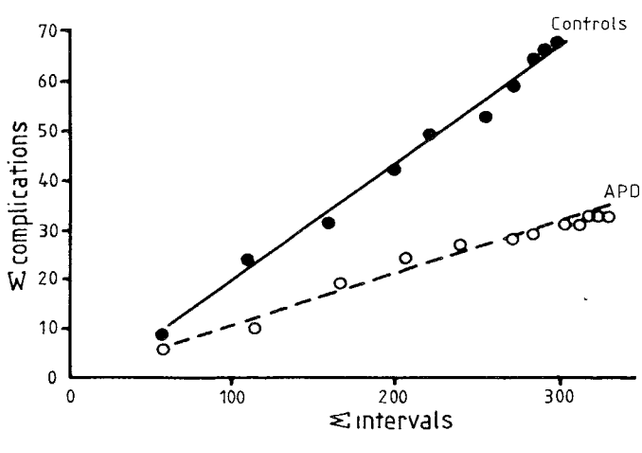

Fig 1—Cumulative sum of complications per 3-month interval by cumulative sum of these intervals.

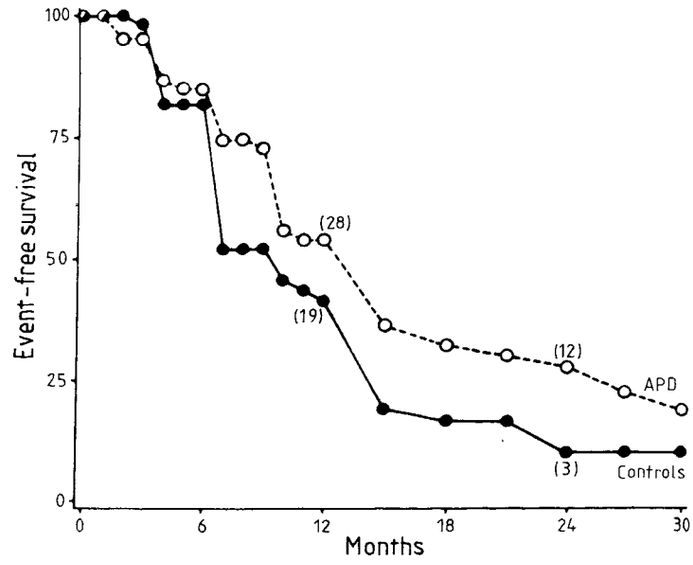

Fig 2—Event-free survival.

Event-free survival (fig 2) was longer for patients receiving APD (median 13 months) compared with the controls (9 months). There was, however, no significant difference between the groups. This may partly be because we included APD toxicity that led to drop-out as an end-point of an event-free interval.

Table II shows the occurrence of skeletal morbidity and its recurrence. This aspect of recurrence is not covered in the cumulative sum plot or in event-free survival analysis. Hypercalcaemia did not occur in the APD group, compared with 13 episodes in 8 patients (18 episodes per 100

TABLE II—OCCURRENCE OF MORBIDITY VARIABLES

—	No of events per patient				Total no of events	Event rate*	p
	None	1	2	⩾3			
Hypercalcaemia							
APD	70†	0	0	0	0	0	<0·002
Controls	53	3	5	0	13	18	
Bone pain							
APD	60	9	1	0	11	14	<0·003
Controls	37	18	4	2	33	45	
Pathological fractures‡							
APD	67	3	0	0	3	4	<0·01
Controls	49	10	2	0	14	19	
New medications							
APD	47	20	2	1	27	34	<0·07
Controls	30	19	6	6	53	73	
Radiotherapy							
APD	60	9	1	0	11	14	<0·001
Controls	36	19	4	2	34	47	
Surgery							
APD	69	1	0	0	1	1	NS
Controls	58	2	1	0	4	5	
Complications§							
APD	42	25	2	1	32	40	<0·002
Controls	23	23	6	9	67	92	

*Events per 100 patient-years.
†No of patients.
‡Including imminent fractures: 2 in APD and 7 in control group.
§Isolated or combined occurrence of any variable.
NS = not significant.

patient-years) in the controls. Bone pain was a frequent complication, occurring in the controls 45 times per 100 patient-years. This frequency was significantly reduced by APD to 14 per 100 patient-years. The number of pathological or imminent fractures was also significantly decreased from 19 in the controls to 4 in the APD group per 100 patient-years. In both groups imminent fractures accounted for half the total. Although the number of medication changes given for the progression of osteolytic lesions was more than halved by APD, this reduction was not significant because the proportion of patients with a single change was similar in both groups. In contrast the reduction in radiotherapy for bone lesions was significant. Surgery for skeletal complications was too infrequent in both groups for any meaningful conclusions to be made for this variable.

Side-effects

We had originally investigated a daily APD dose of 600 mg. This proved to be unacceptable because of nausea and vomiting, leading to an early drop-out of a quarter of the APD patients. This compelled us to reduce the dose to 300 mg daily, which proved satisfactory. Side-effects, mainly nausea, now caused a drop-out of 8%. The present report pertains to the 300 mg patient group. Various non-gastrointestinal and non-skeletal effects were reported in the APD group. None of these were unexpected in breast cancer patients and they cannot on present information be ascribed to APD.

Discussion

This interim analysis of 131 patients showed that supportive APD treatment of patients with advanced breast cancer more than halved the requirement for specific therapies due to metastatic bone disease. APD treatment is simple and well tolerated. The incidence of pathological (including imminent) fractures and severe bone pain was significantly reduced. Further development of tumour hypercalcaemia was also prevented. When skeletal complications occurred, they tended to be less severe in the APD group. The median event-free survival in the APD group was longer than in the control group, although this difference was not significant.

Bisphosphonates are small molecules with a P-C-P terminal by which they adhere to a calcified bone matrix. They inhibit osteoclastic bone resorption.[6,7] APD probably acts through inhibition of the attachment of osteoclasts and their precursors to bone.[6] APD, etidronate, and clodronate have been successfully used in diseases with severe osteoclastic bone resorption.[7,12,13] The efficacy of oral and intravenous APD in Paget's disease and tumour hypercalcaemia has been widely reported.[2,3,9,12,14] Several small controlled trials of bisphosphonate treatment have been done in metastatic bone disease[5,10,15-17] and have suggested suppression of the morbidity from bone metastases.

We used a feasible long-term supportive regimen. APD was effective when used to supplement the optimum basic therapy. This may explain why we saw no effect on survival so far. Elomaa et al[15] did find an effect on survival. During the present trial, however, in contrast with the Elomaa study, adequate intervention was not withheld when needed in either group.

Despite beneficial effects on bone, morbidity was not completely prevented, with the probable exception of hypercalcaemia. This limitation may merely indicate that the therapeutic potential of bisphosphonates has not been fully exploited. The oral dose, which seems to be the maximum tolerated, is in the low region of the dose-response curve. It is equivalent to 3 mg intravenously, a route which had a dose-response relation from a low of 2 mg to a maximum of 20 mg in a study in Paget's disease.[12] However, routine use of intravenous APD would be inconvenient in the long term.

Third-generation aminobisphosphonates are now being developed which may couple lower toxicity with higher efficacy than APD.[18] Our results suggest that such efforts might completely prevent complications from metastatic bone disease, which is a major cause of morbidity in patients with advanced breast cancer.

The following clinicians also crontributed patients to this trial: H. P. Sleeboom, Leyenburg Hospital, The Hague; R. Bieger, Bronovo Hospital, The Hague; P. H. T. J. Slee, St. Jozef Hospital, Gouda; D. Pott Hofstede, Streekziekenhuis, Hilversum; C. A. M. Swart, Mariastichting, Haarlem; K. J. Roozendaal, Onze-Lieve-Vrouw Gasthuis, Amsterdam; F. D. Posma, Streekziekenhuis, Almelo; W. P. M. Breed, St Catharina Ziekenhuis, Eindhoven; J. H. van Lijf, Ziekenhuis "De Ziekenzorg", Enschede; and J. R. van der Meij, Diaconessenhuis Voorburg.

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