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MODULATION OF TUMOUR-INDUCED BONE RESORPTION BY BISPHOSPHONATES

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Summary—Tumour cells produce systemic or local factors which can stimulate osteoclast development and activity leading to increased bone resorption. The clinical consequences are bone pain, fractures and hypercalcaemia. Inhibitors of osteoclast-mediated bone resorption, such as the bisphosphonates, are now the treatment of choice for tumour-induced hypercalcaemia. Recent evidence indicates that these compounds, especially the newer ones, reduce skeletal morbidity in patients with metastatic bone disease and improve their quality of life. Better understanding of the mechanisms underlying tumour-induced bone resorption and development of more potent and less toxic bisphosphonates will lead to improved management of patients with malignant diseases involving the skeleton.

INTRODUCTION

Bone is recognized as a homeostatic system which in the adult is remodelled by a series of discrete, well characterized morphological events. The remodelling sequence begins with activation of the osteoclasts and osteoclastic resorption leading to the formation of a resorption cavity. This is followed by the formation phase during which osteoblasts synthesize osteoid which undergoes mineralization. The two principal cells for bone remodelling, the osteoclast and osteoblast, originate from different progenitor cells of the bone marrow; the osteoclasts are derived from hemopoietic stem cells while the osteoblasts are the same lineage as bone marrow-derived stromal cells. Osteoblasts communicate with osteoclasts with locally produced cytokines and other factors. Osteoclastic bone resorption is regulated by systemic hormones [e.g. parathyroid hormone (PTH), 1,25-dihydroxyvitamin D (1,25-DHD)], by osteotropic cytokines (e.g. IL-1, IL-6 and M-CSF) and by factors acting directly on the osteoclasts (e.g. retinoic acid and procathepsin D). Factors stimulating bone resorption can act at various stages of the cascade of events leading to the final activation of the osteoclast or may even stimulate the osteoblasts to produce substances which increase osteoclastic bone resorption [1].

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BONE RESORPTION IN MALIGNANT DISEASES

During the course of malignant diseases the skeleton can be affected by humoral or local factors which are produced by the tumour cells and can stimulate osteoclastic activity leading to increased bone resorption. A number of such factors have been identified and have been implicated in the genesis of tumour-induced bone resorption. These include parathyroid hormone-related protein (PTHrP) IL-1 and IL-6, TNFα, TNFβ, TGFα, 1,25-DHD and proteases such as collagenases and plasminogen activators [2, 3]. Tumours probably produce multiple such factors which act in concert and they increase bone resorption resulting in considerable morbidity, namely bone pain, fractures and hypercalcaemia. Different tumour types appear to produce different factors. For example, haematological malignancies induce local osteolysis mainly through the release of osteotropic cytokines (multiple myeloma), though in some malignant lymphomas with hypercalcaemia ectopic production of 1,25-DHD by the lymphomatous tissue has been documented and in the hypercalcaemia of adult T-cell lymphoma/leukaemia PTHrP as well as osteotropic cytokines have been implicated as the major bone resorbing factors [4–8]. Breast carcinomas can induce bone resorption by a variety of mechanisms including the production of proteases, (plasminogen activators, collagenases and cathepsins), of growth factors (TGFα), of prostaglandins or of hormones (PTHrP) [9–14].

Other solid tumours, which do not metastasize to the skeleton frequently, may induce generalized osteolysis through the production of humoral factors and PTHrP is currently thought to be one of the major secreted products [2, 3, 15].

Although it has been suggested that some malignant cells metastatic to the skeleton may resorb bone directly, evidence obtained so far supports the view that in the majority, if not in all cases, tumours induce bone resorption through stimulation of osteoclastic activity. Hence, drugs which suppress osteoclast-mediated bone resorption, such as the bisphosphonates, may reduce the skeletal complications of malignant diseases.

BISPHOSPHONATES AS PHARMACOLOGICAL TOOLS FOR THE SUPPRESSION OF INCREASED BONE RESORPTION

The bisphosphonates represent a class of drugs which are used in the treatment of skeletal disorders with increasing frequency. All bisphosphonates have a P-C-P bond in their molecule through which they bind strongly to the mineralized bone matrix, a prerequisite for their action on bone resorption. The rest of the structure differs among the various bisphosphonates and it is this part of the molecule which determines their potency, their activity–toxicity ratio and probably their mechanism of action. In particular, the presence of a nitrogen molecule in the backbone structure of the bisphosphonates significantly increases their potency and specificity towards suppression of bone resorption.

The mechanism by which bisphosphonates suppress osteoclastic resorption has not been fully elucidated yet. They can directly affect the function of mature osteoclasts as is the case with clodronate or they may interfere with events preceding the final activation of the osteoclasts, a mechanism relevant to a number of nitrogen-containing bisphosphonates [16, 17]. Studies in our laboratory with different nitrogen-containing bisphosphonates showed that these compounds, at clinically relevant concentrations, are not toxic to the osteoclasts or to their precursors, they do not affect the proliferation of osteoclast progenitors and they do not disturb the chemotaxis or migration of osteoclast precursors to bone. They rather appear to interfere with a bone matrix-related process which is essential for the attachment, terminal differentiation and final activation of osteoclasts [16, 18, 19]. In other words, nitrogen-containing bisphosphonates appear to prevent rather than inhibit osteoclastic resorption.

There is now a number of bisphosphonates at various stages of clinical development. For a distinction of their clinical properties these compounds can be arbitrarily classified into three generations. First generation bisphosphonates are those that exhibit significant activity but cannot be used for the predictive suppression of increased bone resorption (i.e. etidronate). In the second generation belong the bisphosphonates that can induce predictable and complete suppression of increased bone resorption when administered parenterally; an oral formulation, however, cannot be always used for the same purpose because of the low intestinal absorption and the gastrointestinal toxicity which may be induced by doses sufficiently high to achieve this (i.e. pamidronate). We defined as the third generation those bisphosphonates that can be used efficaciously either parenterally or orally for any purpose [20].

TREATMENT OF MALIGNANCY-ASSOCIATED HYPERCALCAEMIA WITH BISPHOSPHONATES

Bisphosphonates have been proven very useful in the management of patients with malignancy-associated hypercalcaemia. Of the three bisphosphonates registered in European countries, clodronate and pamidronate (APD) have been reported to normalize serum calcium concentrations in about 90% of patients with pamidronate being more effective in the recommended doses [21–25]. The newer, even more potent, bisphosphonates currently under development still need to be properly evaluated in clinical practice. When treating patients with malignancy-associated hypercalcaemia with bisphosphonates two additional factors need to be taken into consideration. The first is the need for volume expansion with the administration of normal saline to these patients as volume contraction stimulates renal tubular reabsorption of calcium and aggravates the hypercalcaemia. The second is that factors produced by malignant tumours may act not only on bone to increase osteoclastic resorption but also on the kidney to increase renal tubular reabsorption of calcium, as is the case with some solid tumours secreting PTHrP. In addition, in a small percentage of such tumours circulating concentrations of 1,25-DHD may be high which may further

contribute to the development and maintenance of hypercalcaemia by increasing intestinal calcium absorption [26]. As bisphosphonates act solely on bone and do not affect the intestinal or renal handling of calcium these mechanisms may account for the failure of bisphosphonates to normalize serum calcium concentrations in some patients.

THE EFFECTS OF BISPHOSPHONATES ON SKELETAL MORBIDITY IN METASTATIC DISEASE

One of the most exciting developments in the therapeutic applications of bisphosphonates to oncological patients has been the reduction of skeletal morbidity in patients with metastatic disease.

The magnitude of the clinical problem can be appreciated if one considers that malignancies account for about 20% of deaths in developed countries; on average 70% of patients with malignant diseases experience pain during the course of their disease and in 35–40% of them the pain is due to bone involvement [27]. Open or controlled studies with bisphosphonates employing a variety of treatment schedules have been performed mainly in patients with breast carcinoma metastatic to bone and with myeloma [28–33]. Results have invariably shown a beneficial effect of the bisphosphonate therapy on skeletal morbidity. In 1987, our group reported the interim results of a randomized long-term phase III study of continuous supportive treatment with oral pamidronate to patients with breast carcinoma and osteolytic metastases [34]. Results showed a significant reduction in the morbidity due to bone metastases in the pamidronate-treated patients as compared to the control group. This trial has now been completed. Analysis of the effects of pamidronate treatment on some aspects of the quality of life of these patients showed a significant reduction in bone pain and in mobility impairment in the pamidronate-treated patients [35]. In addition, skeletal morbidity—assessed as occurrence of hypercalcaemia, bone pain requiring radiotherapy or surgery and imminent pathological fractures—was significantly reduced in the pamidronate-treated group (van Holten, in preparation).

TOWARDS PROTECTION OF SKELETAL INTEGRITY IN METASTATIC DISEASE

Two important issues emerged from the above mentioned studies. The first was that the effect of pamidronate on quality of life occurred primarily soon after initiation of treatment; prevention of morbidity was not complete and a gradual increase in bone pain and mobility impairment with time followed. The second was that the effects on skeletal morbidity appeared to be dose-dependent. This was shown in a subgroup of patients who were started on a higher dose of pamidronate and were continued on a lower. These patients showed the greatest reduction in skeletal morbidity and a prolongation of the skeletal event-free period (van Holten, in preparation). A higher dose of oral pamidronate may, however, induce gastrointestinal side-effects which limit the administered dose to a level not exerting full efficacy. To improve, therefore, the response-rate in these patients and to achieve, possibly, full arrest of the progression of metastatic skeletal disease it is necessary to advise different therapeutic strategies and/or to use bisphosphonates with increased potency and reduced toxicity.

We have previously shown that dimethylation of the nitrogen molecule of pamidronate increases the specificity of the bisphosphonate towards bone resorption and decreases its non-specific metabolic effects [18]. This bisphosphonate, dimethyl-APD, was shown *in vitro* and *in vivo* to be more potent than pamidronate and full efficacy of an oral formulation on bone resorption was demonstrated in patients with Paget's disease of bone. In addition, dimethyl-APD given orally did not induce any gastrointestinal side-effects [20].

To assess the efficacy of dimethyl-APD in tumour-induced bone resorption we performed a phase II open study in 16 patients with malignancy-associated hypercalcaemia (breast carcinoma 11 patients; renal carcinoma 2 patients; multiple myeloma 1 patient; undifferentiated carcinoma of unknown origin 1 patient; and urinary tract carcinoma 1 patient). Dimethyl-APD was administered orally, 200 mg/day, for a maximum period of 7 days (range 3 to 7). As shown in Fig. 1 the treatment suppressed bone resorption effectively; urinary Ca/Cr, OHP/Cr and PO4/Cr ratios decreased significantly resulting in a reduction in serum calcium concentrations (corrected for albumin binding) from a mean of 3.47 ± 0.14 to 2.46 ± 0.06 mmol/l (normal range 2.20–2.55 mmol/l) 1 day after stopping treatment (Fig. 2). All but 2 of the patients became normocalcaemic. In these 2 patients a significant reduction in serum calcium concentrations was

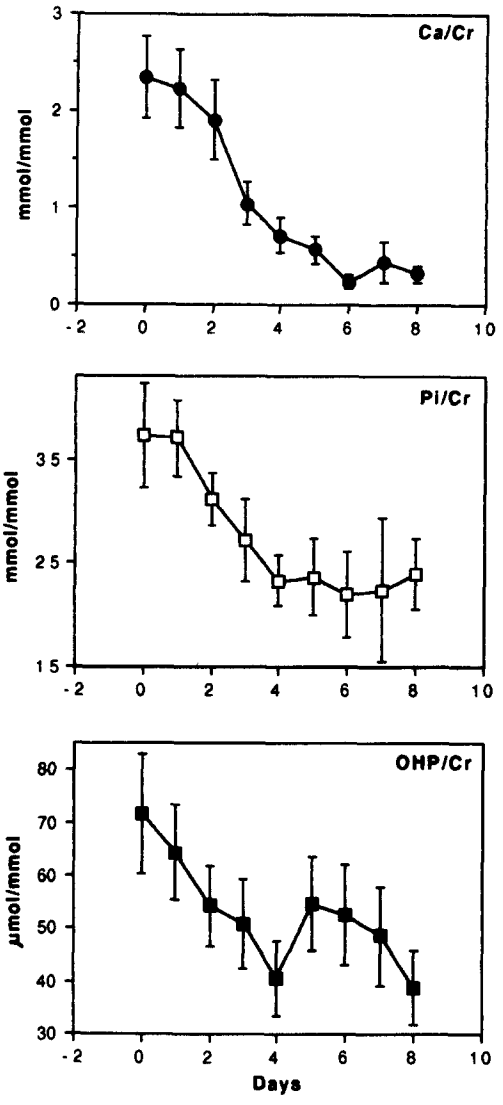

Fig. 1. Urinary excretions (mean ± SE) of calcium (Ca), phosphate (PO_4) and hydroxyproline (OHP) in relation to creatinine (Cr) in 16 patients with malignancy-associated hypercalcaemia during treatment with oral dimethyl-APD 200 mg/day.

also observed. In the first, with breast carcinoma, serum calcium concentration decreased from 3.73 to 2.91 mmol/l while in the second, with a carcinoma of the urinary tract, it decreased from 3.90 to 2.61 mmol/l.

These results demonstrate the efficacy of oral dimethyl-APD in suppressing tumour-induced bone resorption and make this, or other bisphosphonates with a similar pharmacological profile, a very promising compound for the improved management of skeletal morbidity in patients with malignancies metastatic to bone, such as breast carcinoma, multiple myeloma or, as suggested more recently, carcinoma of the prostate.

UNRESOLVED ISSUES

All the evidence obtained so far strongly suggests that supportive treatment of patients with malignant diseases and skeletal involvement with bisphosphonates, especially the newer ones, adds a new beneficial dimension to the palliative management of these patients.

These studies, however, do not address a very important issue, namely the use of bisphosphonates for the prevention of bone lesions in patients with tumours known to metastasize frequently to bone who have not yet developed bone metastases. Breast carcinoma is a typical example of such tumours. Our phase III study of pamidronate treatment of patients with advanced disease but no bone metastases progresses slowly due to the natural history of bone metastases in breast carcinoma. Although 50 to 70% of these patients will develop at some stage symptomatic bone metastases, these may take longer to appear and any possible protection of the skeleton has to be evaluated against the effects of long-term treatment with bisphosphonates especially in patients who are free of any sign of advanced disease (skeletal or extra-skeletal) and no evidence of increased bone resorption. Limited evidence obtained so far during long-term treatment of patients with osteoporosis with pamidronate showed no adverse effects on bone metabolism but it must also be emphasized that the dose used in osteoporosis is lower than that required to suppress bone resorption in tumour patients [36]. The issues of optimal treatment strategies and of the long-term effects of bisphosphonates on bone remodelling need to be addressed before engaging in long-term preventive trials in patients with breast carcinoma.

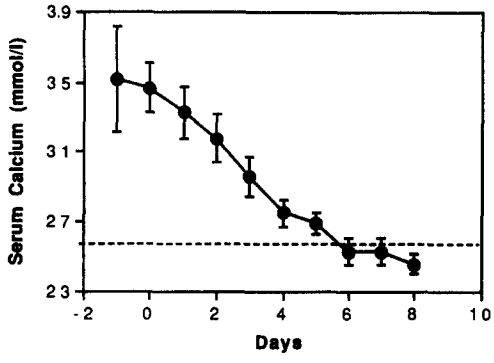

Fig. 2. Serum calcium concentrations (mean ± SE) in 16 patients with malignancy-associated hypercalcaemia during treatment with oral dimethyl-APD 200 mg/day. Day 8 represents values obtained 1 day after stopping treatment.

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