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Osteolytic Bone Metastases in Breast Carcinoma Pathogenesis, Morbidity and Bisphosphonate Treatment

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INTRODUCTION

BREAST cancer is the main cause of death due to malignant disease among women in the Western world [1]. The incidence of bone metastases depends to a large extent on the stage of the tumour at the time of diagnosis and varies markedly in published studies [2–5]. With the help of new histologic techniques, carried out with antiserum against epithelial membrane antigen, tumour invasion in bone marrow is found in a high percentage of patients [6, 7], even in patients with early stage breast cancer at the time of diagnosis. Most bone metastases are of the osteolytic type, are localized mainly in the axial skeleton [3, 5, 8] and may give rise to considerable morbidity.

Morbidity arising from metastatic bone lesions includes pain, pathological fractures, restricted mobility and hypercalcaemia. Galasko [9] reports the occurrence of pain in 50 out of 86 patients (65%) with bone metastases. About 20% of patients suffer pathological fractures [9] and 15% develop hypercalcaemia [10, 11] (Table 1).

General or local osteolytic bone disease obviously is a serious complication of breast carcinoma. Bisphosphonates have proved to be potent inhibitors of bone resorption [72] and the possibility of using them as supportive therapy has been raised. It is thus opportune to briefly review existing data about incidence, detection and pathogenesis of osteolytic bone disease and to discuss available data concerning the efficacy of bisphosphonate treatment.

*Table 1. Morbidity of bone metastases**

Pain	65%
Pathological fractures	20%
Immobility	?
Hypercalcaemia	15%

* Data derived from Galasko [9], Haagensen [10] and Galasko *et al.* [11].

INCIDENCE AND DETECTION OF BONE METASTASES

The reported incidence of bone metastases varies markedly [2–5]. However, only a few studies had a sufficiently long follow-up, that included scintigraphic and radiological assessment [13, 14]. Studies of patients with stage I and II cancer indicated that only a few (< 5%) exhibited signs of skeletal involvement at the time of diagnosis [3–5, 15, 16]. Bone metastases are found with higher frequency (28–75%) in patients with stage III disease [2, 3, 5]; autopsy studies yield an even higher percentage (50–80%) [17–19]. Evaluation of data is hampered by the fact that more than one method of clinical staging is used by the different authors [2, 5, 16].

The isotope bone scan is the method of choice for the detection of metastases [3, 20, 21]. Conventional radiographs remain essential, because both false positive and false negative scans occur [3, 20, 22, 23]. When the two techniques are compared, scanning appears to have a higher sensitivity and abnormalities are visible 2–18 months earlier on scans than on radiographs [9, 24]. In a recent publication [25] it was shown that computed tomography is superior to conventional radiography for the detection of skeletal metastases and should be carried out whenever skeletal scinti-

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graphs are positive and conventional radiographs are normal.

Some authors doubt the value of periodical bone scanning in routine clinical practice. They recommend that this examination be carried out only when indicated by complaints (specifically bone pain) and biochemical abnormalities [16, 26, 27]. Alkaline phosphatase, CEA and gamma GT serum levels are reported to be the most important biochemical parameters in disseminated breast carcinoma [28]. Recent articles consider the urinary excretion of hydroxyproline to be unreliable [28]; metastases in soft tissues also cause elevation of the urinary hydroxyproline excretion [29, 30].

PATHOGENESIS OF SKELETAL METASTASES, OSTEOLYSIS AND HYPERCALCAEMIA

Skeletal metastases

Several hypotheses have been put forward to explain the occurrence of skeletal metastases. Besareb and Caro [31] suggest that excessive PG secretion by the tumour could lead to suppression of the immune system, thus giving the tumour cells the chance to reach certain tissues — especially bone. On the other hand PG might create a 'fertile soil' for some tumour cells, leading to metastases in bone [31]. Once several tumour cells have become embedded, local production of osteolytic substances could result in erosion and thereby permit expansion of the tumour [31, 32]. Finally Orr *et al.* [33, 34] demonstrated that bone is a chemoattractant for breast cancer cells. Type I collagen and its fragments too have a chemotactic effect on breast cancer cells [35]. The possibility that collagen degradation products produced by bone remodelling could be responsible for the chemoattraction of some tumour cells to endosteal bone surfaces has to be considered [36].

Osteolysis

The pathogenesis of the osteolysis around metastatic bone lesions is not yet fully understood. Galasko and Bennett [37, 38] distinguish two mechanisms:

1. bone destruction by metastasized tumour cells and
2. bone destruction by osteoclasts that are activated by mediators secreted by the primary tumour.

It has been shown that monocytes and lymphocytes may play a role in the activation of tumour cells. Substances that are elaborated in the course of the interaction between tumour cells, monocytes and lymphocytes have the property of being able to induce or enhance osteoclastic bone resorption. For instance, tumour cells and monocytes have been shown to be able to stimulate production of an osteoclast activating factor (OAF) by lymphocytes through formation of type E and F prostaglandins, monocytes or tumour cells [39, 40]. Involvement of OAF has been proven in myeloma and lymphoma. A direct influence of PG on the osteoclasts has also been described [41]. *In vitro* monocytes can directly resorb bone without involving either the osteoclasts or PG, via diverse other mechanisms [32, 41]. Though PG has been implicated in breast cancer [42, 43], prostaglandin inhibitors (aspirin, indomethacin) were found to be unable to inhibit osteolysis completely [44]. Mundy [32] considers the role of PG uncertain. Direct resorption of bone by breast cancer cells *in vitro* has been described [45].

Hypercalcaemia

As discussed in the previous section patients with malignancy may exhibit generalized osteolysis in addition to or even without demonstrable metastases. The occurrence of osteolysis may well be responsible for the development of hypercalcaemia in patients with tumours. Even when metastatic lesions are demonstrated in the skeleton of hypercalcaemic patients, it is still possible that the hypercalcaemia is due to the generalized osteolysis rather than to the localized destruction.

Three explanations have been put forward. Mundy [36] suggests that growth factors may bind to PTH receptors in bone. Ectopic PTH production by the tumour tissue itself has also been suggested as a possibility, as has the production of vitamin D like sterols. The importance of sterols has not been generally accepted. The possibility of ectopic PTH production merits further discussion.

A new line of investigation implicates growth factors in osteolytic bone resorption [46]. The function of the peptide epidermal growth factor (EGF) in man is unknown. Tashjian and Levine [47] found that EGF induces bone resorption in neonatal mouse calvaria. This effect was mediated by PG synthesis and was blocked by PG inhibitors. However, in the foetal rat long bone system, the stimulation of bone resorption by EGF is independent of PG generation [48]. Since EGF stimulates mesenchymal cells to divide and thus accelerates proliferative processes, it may resemble the factors involved in oncogenic transformation by retroviruses. Platelet-derived growth factor (PDGF) is the major circulating growth factor for cells of mesenchymal origin. Its behaviour is similar to that of EGF, also with regard to PG synthesis [49]. PDGF is related to the oncogene of simian sarcoma virus. Tumour-derived transforming growth factors (TGFs) are a family of polypeptides which stimulate cell growth and replication. TGFs share some biological properties with EGF [50], but differ

structurally and antigenically. They have been found in and may be responsible for some of the cases of tumour-induced hypercalcaemia.

Differentiation between primary hyperparathyroidism and tumour-induced hypercalcaemia

Differentiation between hyperparathyroidism and tumour-induced hypercalcaemia is difficult biochemically. There are however two parameters that aid in diagnosis: the urinary excretion of calcium is likely to be higher in severe tumour-induced hypercalcaemia than in primary hyperparathyroidism, while the serum calcium values tend to vary over short periods of time in tumour-induced hypercalcaemia and are often quite stable in hypercalcaemia due to hyperparathyroidism. In both cases, however, a low serum phosphate, a decreased tubular phosphate reabsorption (TmP/GFR) (Table 2) and an increased nephrogenous cyclic AMP (NcAMP) production are found. In a minority of their hypercalcaemic tumour patients Stewart *et al.* observed a decreased production of NcAMP [51]. As a rule these patients had breast carcinoma or lymphoma with extensive dissemination to the bones. TmP/GFR was significantly lower in this group of patients; in all other respects, however, they did not differ from tumour patients with an elevated NcAMP. Moreover, uncertainty exists about the incidence of hyperparathyroidism in cancer patients. Some investigators emphasize that hyperparathyroidism might account for many of the tumour-induced hypercalcaemias, but often selected patient populations were studied [52–54]. Moreover, the importance of ectopic parathyroid hormone (PTH) production in this kind of patient has probably been exaggerated in the past. In a comprehensive review article Skrabanek *et al.* [52] found evidence for pseudohyperparathyroidism (or humoral tumour hypercalcaemia/hypophosphataemia) in 61 of 74 surgical patients. Ectopic PTH production could be demonstrated in only a minority of these patients.

It has, however, become clear that in additioin to similarities there are also differences in the biochemical profiles between hyperparathyroidism and tumour-induced hypercalcaemia. In hyperparathyroidism serum 1,25-$(OH)_2$ vitamin D level is high [51] or normal [56], serum iPTH is high [51], calcium absorption in the gut is increased [55], blood pH is low and serum chloride is high [52]. In tumour-induced hypercalcaemia, in contrast, serum 1,25-$(OH)_2$ vitamin D is low, iPTH is low [51], calcium absorption is decreased [55], blood pH is high and serum chloride is low [52] (Table 2]. It is concluded from these data that PTH is not responsible for the hypercalcaemia (and hypophosphataemia) in tumour patients [51]. Characteristic bone histology of the two conditions is different; in hypercalcaemia due to malignancy osteoclasts are increased and osteoblasts and osteoid are practically absent, whereas in hyperparathyroidism both osteoclast and osteoblast activities are increased and the loss of skeletal calcium is minimal [57]. Simpson *et al.* [58] could even exclude ectopic PTH production by the tumours of their patients. They could not detect PTH-*m*RNA in the tumour tissue.

*Table 2. Comparison of primary hyperparathyroidism (HPT) with tumour-induced hypercalcaemia (TIH)**

	HPT	TIH
Serum PO_4^{3-}	↓†	= ↓
TmP/GFR	↓	↓
Ca^{2+} excretion (urine)	= ↑‡	↑ ↑
Ca^{2+} absorption (gut)	↑	↓
Serum iPTH	↑	(=) ↓
Serum 1.25 $(OH)_2$ Vit D	= ↑	= ↓
Blood pH	↓	↑

* data derived from Stewart *et al.* [51], Skrabanek *et al.* [52] and Coombes *et al.* [55].
† ↑ increased; ↓ decreased; = normal.
‡ relative to degree of hypercalcaemia.

TREATMENT OF HYPERCALCAEMIA AND OSTEOLYTIC METASTASES

Hypercalcaemia

Secondary disturbance of renal function is mainly responsible for the life threatening character of the tumour-induced hypercalcaemia. The most significant of these are a decline in glomerula filtration rate, sodium loss and reduced concentrating capacity [59–61]. The last, combined with vomiting and reduced fluid intake, may lead to contraction of the extracellular volume, which causes an increase of an already high fractional reabsorption of calcium. Because of the sodium diuretic effect of calcium and the contraction of the extracellular volume the reabsorption of sodium which is associated with calcium reabsorption will increase. This results in a further increase in serum calcium and the creation of a vicious circle which may lead to a threateningly fatal situation.

The treatment of tumour-induced hypercalcaemia should rest on the following principles (beside treatment of the tumour):

the abolition of the contraction of the extracellular volume,
the facilitation of calcium elimination by the kidney and
the inhibition of bone resorption.

Treatment with saline infusion alone practically never leads to normocalcaemia [62, 63]. In some cases the serum calcium even increases. The same holds true when one tries to increase urinary calcium excretion with the help of forced diuresis

by saline infusion combined with furosemide [64–67].

Treatment with calcitonin, which has a natriuric and thereby also a calciuric effect and inhibits bone resorption has a predictable calcium lowering effect but seldom leads to normocalcaemia. The excess of serum calcium decreases by approximately 60% [68]. As is the case with furosemide treatment, almost immediately after the discontinuation of calcitonin the serum calcium starts to rise. The effect of glucocorticoids and indomethacin in tumour-induced hypercalcaemia is usually unpredictable and disappointing. [69].

A good result may be attained with mithramycin. Multiple applications of 25 μg/kg body wt normalizes the serum calcium in approx. 85% of the patients [68]. After more than two applications on consecutive days, however, the possibility of serious liver damage and haematological toxicity increases.

Because of gastro-intestinal side-effects oral administration of inorganic phosphate is unsuitable for the acute treatment of hypercalcaemia. Intravenous phosphate almost immediately decreases the serum calcium; the effect is great, dose dependent and short-lived. The rapid fall of calcium can cause hypotension, and precipitation of calcium phosphate an acute renal insufficiency, therefore a too rapid decline in serum calcium must be avoided. Phosphate treatment is, therefore, not ideal [32, 69].

The introduction in 1979 of bisphosphonates for hypercalcaemia treatment was a significant improvement [12]. Three bisphosphonates are currently used. They are the disodium salts of 3-amino-1-hydroxypropylidene-1, 1-bisphosphonate (APD) [12], 1-hydroxy-ethylidene-1, 1-bisphosphonate (EHDP) [71] and dichloromethylidene bisphosphonate (Cl_2MDP) [70–75]. All three are given preferentially by the intravenous route and infused, together with sodiumdichloride 0.9% over periods of 2 hr (APD) or more (EHDP and Cl_2MDP). The dose is 15 mg per day in the case of APD and 500–2500 mg/day for the other two. All three are efficacious inhibitors of osteoclastic bone resorption, but they differ in two respects. APD has far greater potency than the two others [76]. EHDP is the least potent and may block bone mineralization [77]. There may be several mechanisms of action, including inhibition of bone recognition by osteoclasts and direct toxicity to the osteoclast of mineral-bound bisphosphonate [78]. No side-effects have been seen with intravenous APD; EHDP, when infused too rapidly, has cuased irreversible renal damage; that the same is the case with Cl_2MDP is unlikely [79, 80]. The occurrence of leukemia in three Cl_2MDP treated patients is probably not related to the drug [71].

Our experience covers 150 consecutive patients with hypercalcaemia of malignancy, treated with intravenous APD, for 5 consecutive days in most. In 95% the serum and urine calcium was normalized and in the remainder nearly so, within 3–10 days [81]. This was associated with significant improvement of renal function and correction of hypomagnesemia. Since treatment is always followed by adjustment of chemotherapy, normocalcemia is generally maintained and continuation of bisphosphonate is superfluous. For EHDP and Cl_2MDP the efficacy is approx. 20% lower. Only APD [72–74] and Cl_2MDP [82] are efficacious when given orally, but, since bisphosphonates are not well absorbed and since hypercalcaemia is frequently associated with nausea and vomiting, the intravenous route is to be preferred.

A last resort for hypercalcaemia treatment is hemodialysis but in view of the efficacy of previous modalities, this should hardly ever be necessary.

Osteolytic metastases

In contrast to the many treatment modalities in tumour-induced hypercalcaemia there is as yet no accepted treatment available (beside chemotherapy and/or radiotherapy) for bone metastases. Moreover, follow-up investigations are complicated. Most studies thus have focused on hypercalcaemia.

A first pilot study on the inhibitory effect of APD on osteolytic lesions in eight patients with breast cancer (five with hypercalcaemia) and six with myeloma (two with hypercalcaemia) was carried out by van Breukelen *et al.* [12]. In this study it has been demonstrated that bone resorption is inhibited by APD in normocalcaemic tumour patients. APD was administered for a short period (about 12 days) and the study was uncontrolled. Subsequently several fairly short-term studies on the efficacy of Cl_2MDP were carried out [69, 73, 85–87]. The evidence that bisphosphonates inhibit bone resorption is based on direct observations *in vitro* [76, 77]. In clinical studies their effect is associated with a rapid and concomitant reduction of the urinary excretion of calcium and hydroxyproline together with an increase of calcium absorption, confirming that their action is associated with inhibition of bone resorption [12, 82–84].

Elomaa's investigation [88] is the only prolonged controlled study of patients with carcinoma of the breast. Seventeen patients with breast cancer that had invaded the skeleton were placed on Cl_2MDP therapy (for 3–9 months) additional to their original cancer therapy. They experienced fewer episodes of hypercalcaemia, developed fewer new bone lesions and used analgesics less often than the 17 patients of the control group [88] (Table 3). The favourable results of bisphosphon-

ate treatment in tumour-induced hypercalcaemia and the results of the study of Elomaa *et al.* [88] indicate that bisphosphonates play an active role in the inhibition of osteolysis in metastatic bone lesions and that this effect is a long-term one.

*Table 3. Results of bisphosphonate (dichloro methylidene bisphosphonate = Cl_2 MDP) treatment of breast carcinoma with osteolytic metastases (placebo controlled)**

	Cl_2MDP	Placebo
	Number of patients	
Total	17	17
Use of analgesics	15	3
Radiotherapy because of pain or prevention of fractures	3	10
Hypercalcaemia	1 (mild)	4 (all†)
Skeletal scintigraphy:		
↓ tracer uptake in bone metastases	47%	17%
↑ tracer uptake in bone metastases	31%	63%
tracer uptake unchanged in bone metastases	22%	20%
new bone metastases	3	11
X ray:		
↑ size of bone metastases	5	10
↓ size of bone metastases	0	0
Fractures	1	1

* Data derived from Elomaa *et al.* [88].

SUMMARY

In this review different aspects of osteolytic bone metastasis of breast carcinoma including morbidity, pathogenesis, accompanying hypercalcaemia and treatment, are discussed. Bone metastases occur in many patients with breast cancer (percentages of up to 85% have been reported); although patients seldom die of bone metastases morbidity is pronounced. Literature data point out that humoral factors, such as prostaglandins and the recently described growth factors are of importance beside cell interactions between monocytes, lymphocytes, osteoclasts and tumour cells. Nowadays, no significance is attributed to parathyroid hormone (PTH) overproduction in this respect. The differential diagnosis between primary hyperparathyroidism and tumour-induced hypercalcaemia is not always easy biochemically; combinations of both do occur less frequently than has been assumed in the past. A new and promising line of investigations involves the growth factors, which can increase osteolytic bone resorption and may bind to epidermal growth factor (EGF) or PTH receptors, thus inducing some of the biological effects of PTH (including hypercalcaemia). Until recently it was exceedingly difficult to treat tumour-induced hyper-calcaemia (TIH) (the acute condition). Since the availability of the bisphosphonates dichloromethylidene bisphosphonate (Cl_2MDP) and 3-amino-1-hydroxypropylidene-1, 1-bisphosphonate (APD) this treatment has become very simple. Preliminary results, derived from the literature, point out that bisphosphonate treatment might also be effective in providing long-term control.

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