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Agents Affecting Osteolysis in Patients with Breast Cancer

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Summary. *Aspirin and indomethacin, flurbiprofen, synthetic human calcitonin, and mithramycin were assessed for their anti-osteolytic properties in patients with breast cancer and painful skeletal metastases.*

Some patients responded with pain relief to aspirin/indomethacin (2/10), flurbiprofen (2/9), calcitonin (2/7), and mithramycin (3/8). Objective evidence of reduction of osteolysis occurred with flurbiprofen, mithramycin, and calcitonin, but not with aspirin and indomethacin. A sustained reduction in hydroxyproline occurred with flurbiprofen (2/8) and mithramycin (2/8). A reduction of hypercalcaemia occurred with flurbiprofen (2/4), calcitonin (1/1), and mithramycin (2/4).

These findings indicate that these agents have no place as primary therapeutic agents for osteolytic bone metastases but they may be useful as an adjuvant to other therapy.

Introduction

The spread of breast cancer to bone with release of osteolytic substances by the tumour cells gives rise to skeletal destruction, hypercalcaemia, and increased urinary hydroxyproline excretion. Various anti-osteolytic agents have been identified, and we have, therefore, examined some of these for possible anti-osteolytic properties in patients with bone metastases.

Breast tumour-mediated osteolysis can be reduced in vitro by aspirin or indomethacin, both inhibitors of prostaglandin synthesis [6]. These agents can also reduce serum calcium in some cases of hypercalcaemia complicating renal, lung and pancreatic carcinomas [1, 11]. Calcitonin has been shown to be capable of reducing bone pain [5] and serum calcium [2] in some patients with skeletal metastases. Mithramycin has also been found to be anti-osteolytic in vitro [4] and is effective in reducing serum calcium in breast carcinoma [12].

We have, therefore, tested these agents and a new prostaglandin synthetase inhibitor, flurbiprofen, in vivo for their effects on osteolysis in breast carcinoma.

Patients, Materials and Methods

Twenty-two patients with histologically proved breast carcinomas and radiological evidence of widespread osteolytic bone metastases were studied on 34 separate occasions, for periods ranging from 5–400 days (Table 1). None of the patients had other known skeletal, endocrine, or cardiovascular diseases but 13 patients were hypercalcaemic (serum calcium > 2.6 mmol/litre) at the time of study. Patients were given soluble aspirin (BPC), indomethacin (Indocid; Mercke, Sharpe & Dohme), flurbiprofen (Froben; Boots), synthetic human calcitonin (CIBA-Geigy) or mithramycin (Mithracin; Pfizer). The dose schedules and routes of administration are shown in Table 1.

In a separate study, five patients were given three doses of 1 mg synthetic human calcitonin at 2-hourly intervals, and urine was collected every 2 h for hydroxyproline measurement.

Serum calcium (Technicon: autoanalyser) and the urinary hydroxyproline excretion measured as hydroxyproline: creatinine ratio (OHP/Cr) were estimated before, at weekly intervals during, and after the study in an early morning urine sample [9]. Hydroxyproline excretion has previously been shown to reflect the degree of osteolysis in breast carcinoma [8]. 99m-Technetium polyphosphate bone scanning and skeletal radiographs were carried out before and at the end of each study period. Pain and analgesic requirements were assessed weekly by a single independent observer utilising a questionnaire detailing site, character and degree of pain, analgesic requirements, disturbance of sleep, and degree of mobility.

All but four patients had received hormone treatment or chemotherapy in the past. None, however, had received active anticancer therapy, hormone therapy or ablative surgery, for at least four weeks before each agent was commenced. Sufficient paracetamol or opiates were administered to control pain prior to study but no new analgesic therapy was instituted during the study period.

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Table 1. Agents used and response obtained with each

Agent	Indomethacin/aspirin	Flurbiprofen	Calcitonin	Mithramycin
Dose and Method of administration	2700 mg soluble aspirin and 75 mg indomethacin *or* 300 mg indomethacin daily PO	300 mg daily PO	1 mg daily SC	1 mg twice weekly IV
Number of patients	10	9	7	8
Number with hypercalcaemia	4	4	1	4
Duration of treatment (days)	5–8	21–28	21	28–400
Response; i.e., reduction of				
1. Bone pain/analgesic requirements	2/10	2/9	2/7	3/8
2. Serum calcium	0/4	2/4	1/1	2/4
3. OHP/Cr	0/10	2/8	0/6	2/8
Bone scan	–	4/4 increased uptake	5/5 increased uptake	2/8 increased uptake 2/8 decreased uptake
Bone X-rays	–	0/7 improved	0/7 improved	1/8 improved with sclerosis

Results

1. Indomethacin/Aspirin

Therapy with indomethacin and/or aspirin significantly relieved pain in two out of ten patients for the 8 days of the study, and this was associated with some improvement of general performance in these patients. This was not accompanied by a concomitant fall in serum calcium or urinary hydroxyproline.

2. Flurbiprofen

This agent seemed as effective as indomethacin in relieving pain (2/9 patients). These two patients had an associated improvement in performance but pain returned on cessation of the drug. The serum calcium fell in two out of four, although not to normal levels, and the hydroxyproline excretion was reduced in two out of eight patients, one of whom also showed a fall in serum calcium. All bone scans showed increased uptake but skeletal radiographs showed no change at the end of the study period.

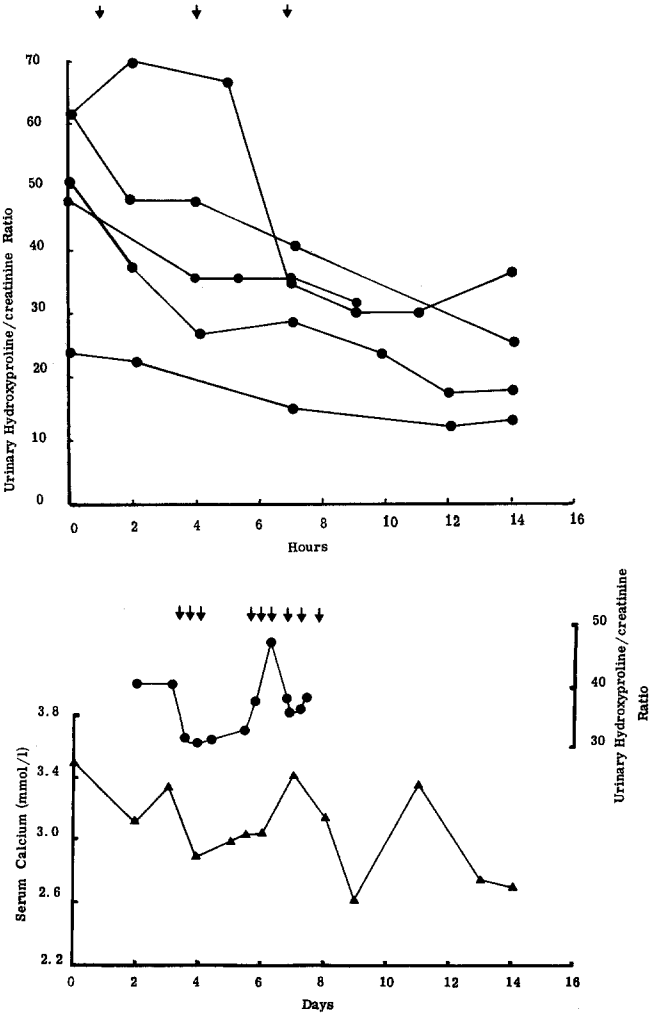

Fig. 1. The effect of synthetic human calcitonin on serum calcium and hydroxyproline excretion. The *arrows* indicate the times of administration of 1 mg synthetic human calcitonin. The top figure indicates response of hydroxyproline excretion to this treatment in five consecutive patients and the lower figure shows the transient fall in serum calcium and hydroxyproline excretion in a single patient. ●, urinary hydroxyproline: creatinine ratio (normal range 10–35); ▲, serum calcium (mmol/litre) (normal range 2.1–2.6 mmol/litre)

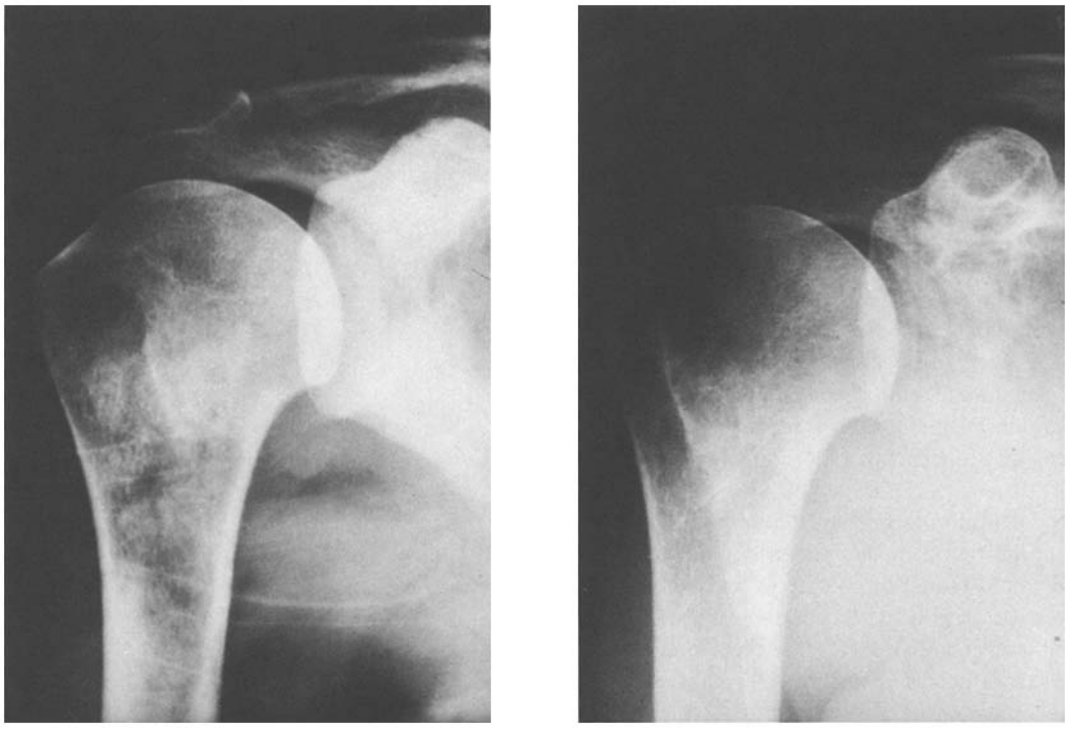

Fig. 2 a and b. Response of bone metastases to mithramycin injections. **a** R humerus berfore treatment; **b** R humerus after treatment

3. Calcitonin

High-dose synthetic human calcitonin (Fig. 1) produced an acute fall in urinary hydroxyproline excretion. The effect was maximal at 8 h but within 24 h the OHP/Cr had reached pretreatment values.

Daily injections of calcitonin produced significant pain relief in two of seven patients and reduction in serum calcium in the single hypercalcaemic patient, but did not produce a sustained fall in the hydroxyproline excretion over 3 weeks in any patient. As with flurbiprofen, all bone scans showed increased isotope uptake. No improvement in skeletal radiographs was seen.

4. Mithramycin

Three of the eight patients experienced significant relief of pain with a concomitant decrease in analgesic requirements. Severe immobilising pain was completely relieved in one patient within 3 weeks of commencing treatment; stopping the drug caused recurrence of symptoms, which were relieved when mithramycin was re-instituted 2 weeks later. She continued on mithramycin with complete pain relief for over 12 months. A further patient had complete relief of pain, which recurred when the therapy was stopped, but failed to respond when the drug was withdrawn and recommenced.

The serum calcium fell in two of four patients with hypercalcaemia, one of whom experienced pain relief. The hydroxyproline excretion fell in the one patient who had continuous pain relief for 12 months; the bone scan improved and radiological skeletal survey showed evidence of widespread sclerosis and healing of lytic bone deposits (Fig. 2). None of the remaining seven patients showed any change in either scan or skeletal survey, but improvement in the latter would not be expected to occur in patients treated for less than 6 weeks.

Discussion

Skeletal metastases from breast carcinomas respond poorly to chemotherapy, which is generally effective in controlling disease at other sites [10]. For this reason we have investigated the mechanism of tumour-induced osteolysis.

Although prostaglandin synthetase inhibitors appear effective in vitro [6], they are clearly of little value when given in the maximum tolerated clinical doses. Some patients (4/19) experienced reduction of analgesic requirements and significant relief of pain with associated reduction of hydroxyproline excretion, although generally these agents did not appear to influence sekeletal destruction. This suggests that hypercalcaemia, osteolysis, and continued bone destruction in patients with estab-

lished bone metastases may not be prostaglandin synthesis-dependent or that if mediated by prostaglandins, this is in excess of the inhibitory capability of these drugs. This is supported by the observations of Galasko and Bennett [3] concerning the morphological appearances of osteolytic deposits, suggesting that the early-stages of tumour invasion of bone is characterised by osteoclastic bone destruction whereas the later stages are not. Early development of VX2 tumour deposits in the rabbits femur associated with osteoclastic resorption can be inhibited by indomethacin, whereas later nonosteoclastic resorption cannot. This correlates with the suggested role for prostaglandin synthesis in osteoclastic bone resorption [7] and implies that osteolysis by established bone metastases is independent of prostaglandin synthesis.

Synthetic human calcitonin caused an acute reduction in hydroxyproline excretion in our patients, which probably represents a rapid reduction in osteolysis. The effect is transient, however, and a rapid rebound occurs following withdrawal of therapy (Fig. 1). We therefore attempted to use longer-term administration of smaller doses. Only two of seven patients responded with reduction of bone pain, but this was not accompanied by a fall in hydroxyproline excretion. Larger, more frequent doses, may prove more effective.

Mithramycin produced a convincing reduction of osteolysis in at least one patient for more than 1 year. The bone healing and repair seen in this patient may reflect inhibition of DNA-dependent RNA synthesis in the osteoclasts or other cells responsible for bone destruction by the tumour, although it is doubtful whether this drug can significantly inhibit protein synthesis in vivo. Alternatively, mithramycin has been shown to inhibit the synthesis of prostaglandins by inhibiting the synthesis of arachadonic acid (L. Levine, personal communication), an essential precursor of prostaglandin synthesis. This block may be more effective than that of aspirin-like drugs and account for its improved anti-osteolytic efficacy. This makes the use of a combination of aspirin-like drugs with mithramycin an attractive possibility.

Failure to control osteolysis in most patients with metastatic breast cancer results in severe morbidity, and pathological fractures and hypercalcaemia occur in patients who would otherwise be moderately well.

None of the agents evaluated in this study is sufficiently anti-osteolytic to be considered as single-agent therapy for bone metastases. However, the combination of antiosteolytic therapy with chemotherapy for treatment of osteolytic bone metastases is an alternative possibility.

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