The role of bisphosphonates in breast and prostate cancers

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Abstract

Bisphosphonate drugs are a group of pyrophosphate analogues which bind avidly to hydroxyapatite bone mineral surfaces and their major action is to inhibit osteoclast activity and thus bone resorption. In oncology, their role in metastatic bone disease is well established, but there is increasing interest in their potential role in preventing and treating cancer-induced bone loss and their possible anti-tumour effects.

Metastatic bone disease is associated with a variety of skeletal complications, including pathologic fractures, bone pain, impaired mobility, spinal cord compression and hypercalcaemia. Intravenous bisphosphonates, particularly zoledronic acid, in conjunction with rehydration, are now established as the treatment of choice for hypercalcaemia. For treatment of bone pain, it has also been shown that bisphosphonates can be an effective supplementary approach to radiotherapy. In breast cancer and myeloma, bisphosphonates have now become part of standard therapy to treat and prevent skeletal-related events (SRE) and, until recently, treatment was largely with intravenous pamidronate or oral clodronate. However, large, randomised, multicentre trials using intravenous administration of the highly potent bisphosphonate zoledronic acid every 3–4 weeks have recently demonstrated a reduction of 20% in the risk of developing an SRE compared with pamidronate for patients with breast cancer. Moreover, these trials have demonstrated, for the first time, that a bisphosphonate significantly reduces the occurrence of skeletal events in hormone-refractory prostate cancer and in non-small cell lung cancer and a range of other solid tumours.

Investigations into the potential of the relatively low potency bisphosphonate, clodronate, for the prevention of bone metastases in breast cancer have produced conflicting data. Further large, randomised studies with clodronate and zoledronic acid are planned and until the results are available it is not possible to identify a definite adjuvant role for bisphosphonates. Evidence is accumulating in vitro that bisphosphonates are also able to directly affect tumour cells, in addition to their effects on osteoclasts, with zoledronic acid being particularly potent.

Over recent decades there has been a significant improvement in cure rates and survival times in certain cancers and the use of chemotherapy and hormone therapy has expanded greatly, leading to increasing numbers of long-term survivors who have received these treatments. Management of treatment-induced bone loss is therefore assuming a greater importance and bisphosphonates represent an attractive treatment option in such patients. Several placebo-controlled trials using oral clodronate, oral risedronate, intravenous pamidronate and intravenous zoledronic acid have all now demonstrated benefits in reducing the loss in bone mineral density.

Introduction

Advanced cancers frequently metastasise to the bone, and the resulting bone destruction is associated with a variety of skeletal complications, including pathologic fractures, bone pain, impaired mobility, spinal cord compression and hypercalcaemia. It is estimated that more than 1.5 million cancer patients worldwide have bone metastases. Current treatment options for patients with bone metastases include radiation therapy, surgery, bisphosphonates and analgesics, in addition to standard anticancer therapy. The primary goal of therapy is to minimise bone pain and morbidity and improve mobility and quality of life.

Bone is not an inert organ. During adult life, the normal bone undergoes a continuous remodelling process of resorption and formation (Mundy 1999). This is normally a tightly co-ordinated process in which initial
osteoclast resorption takes place in discrete ‘packets’, known as bone remodelling units, over a period of about 8 days. This is followed by a more prolonged phase of bone formation (over about 3 months), to repair the defect, mediated by osteoblasts (Turner et al. 1994, Spelsberg et al. 1999).

Pathophysiology of bone metastases

In normal healthy bone there is a steady-state balance, or ‘coupling’, of osteoblastic bone formation and osteoclastic bone resorption, which is lost when tumour cells enter the bone microenvironment. In vitro, breast cancer cells produce parathyroid hormone-related protein (PTHrP) (Guise 2000) which stimulates osteoclastic resorption by increasing osteoblast and stromal cell production of the receptor activator of nuclear factor kB (RANK) ligand (Thomas et al. 1999). RANK ligand binds to its receptor RANK on osteoclast lineage cells, inducing differentiation into mature osteoclasts and stimulation of osteoclast activity (Hofbauer et al. 2000).

Within normal bone, osteoblast secretion of osteoprotegerin (OPG) neutralises RANK ligand, and prevents RANK ligand’s stimulatory effects on osteoclasts. However, in bone harbouring cancer cells there is loss of regulatory control. The MCF-7 oestrogen-dependent breast cancer cell line has been found to decrease osteoblastic OPG mRNA levels (Thomas et al. 1999), so enhancing osteoclast formation. The imbalance is further compounded by release of transforming growth factor-β (TGF-β) and insulin-like growth factor-1 (IGF-1) by resorbing bone. These have been found to act as survival factors for breast cancer cells, promoting tumour production of PTHrP (Guise 2000) and thus allowing a perpetuating cycle of osteolytic bone destruction to be created.

Prostate cancer tends to cause osteoblastic lesions in bone. It is hypothesised that osteoblastic lesions are formed by intense osteoblastic activity, preceded by osteoclastic bone resorption, as indicated by increased levels of urinary markers of osteoclastic bone resorption in prostate cancer patients (Garnero et al. 2000). Conversely, it is also possible that prostate tumour cells can induce metastatic bone lesions that do not involve osteoclastic activity. A recent study (Lee et al. 2002) found that prostate cancer cells (PC-3) implanted into the tibia of SCID mice caused osteolytic lesions, possibly through secretion of RANK ligand. However, when another prostate cancer cell line (LAPC-9) was used, osteoblastic lesions developed even when no osteoclasts were present. This may be partially explained by a previous finding from the same authors that LAPC-9 prostate cancer cells did not secrete RANK ligand, instead producing OPG and interleukin-6 (Lee et al. 2002). It is possible therefore that OPG secretion blocks the formation of osteolytic lesions, whilst interleukin-6 and other bone-stimulatory proteins contribute to the formation of osteoblastic lesions. It is possible that all mechanisms contribute in vivo.

The growth factor endothelin-1 (ET-1) may also be involved in prostate cancer bone metastases. Comparisons with patients with cancer confined to the prostate and normal controls, circulating levels of ET-1 are increased in patients with osteoblastic bone metastases from androgen-refractory prostate cancer (Nelson et al. 1995). ET-1 stimulates osteoblasts and inhibits osteoclast activity (Takuwa et al. 1990, Chiao et al. 2000) in animal models, whilst antagonists of ET have been found to inhibit bone formation in vivo. Furthermore, a recent study (Granchi et al. 2001) found that ET-1 production by prostate cancer cells is reduced by androgens but stimulated in androgen-insensitive prostate cancer cells by factors such as TGF-β. This may be clinically relevant as metastatic prostate cancer typically develops androgen resistance. PTHrP is probably also involved in the pathogenesis of prostate cancer bone metastases, as co-expression of PTHrP and its receptor has been found in both the primary tumour and bone metastases of patients with prostate cancer (Bryden et al. 2002).

Bone marrow stromal cells are important in the pathogenesis of myeloma bone disease (Derenne et al. 1999). Interleukin-6 appears to be an important growth and survival factor for myeloma cells and confers resistance to treatment with dexamethasone, a commonly used treatment for multiple myeloma (Derenne et al. 1999). Metalloproteinases (MMPs), important for normal and malignant remodelling, may also contribute. Bone marrow stromal cells from myeloma patients secrete interstitial collagenases (MMP-1) and gelatinase A (MMP-2). MMP-1 initiates bone resorption (Barille et al. 1997) degrading type I collagen, which becomes a substrate for MMP-2. Malignant plasma cells have been found to upregulate MMP-1 (Derenne et al. 1999) and activate MMP-2.

In myeloma, OPG has recently been found to be a survival factor for myeloma cells in vitro (Shipman & Croucher 2003). OPG, a member of the tumour necrosis factor (TNF) receptor family, has been identified as a decoy receptor for RANK ligand so preventing the latter’s interaction with RANK. This effectively inhibits osteoclastic bone resorption.

TNF-related apoptosis-inducing ligand (TRAIL/Apo2L), also a member of the TNF receptor family, selectively induces apoptosis of tumour cells in vitro whilst not affecting normal cells. However, Shipman and Croucher (2003) found that recombinant OPG and
natural OPG produced by osteoblast-like cells significantly reduced TRAIL/Apo2L-induced apoptosis of myeloma cells in vitro. This implies that OPG may act as a survival factor for myeloma, although how this translates to the in vivo setting is not yet clear as it is not known how OPG and TRAIL/Apo2L interact within the human bone microenvironment.

Pharmacology of bisphosphonates

Bisphosphonates are stable analogues of pyrophosphates (PPi). PPi has a P–O–P structure (Fig. 1a), whereby two phosphate groups are linked by an oxygen atom. Bisphosphonates, however, have a P–C–P structure, a geminal (central) carbon atom replacing the oxygen (Fig. 1b). Side chains R1 and R2 are attached to the carbon atom and influence the bisphosphonates’ ability to bind to bone, and their anti-resorptive ability. Bisphosphonates containing a primary nitrogen atom in the R2 side chain (for example pamidronate) are more potent than non-nitrogen bisphosphonates (such as clodronate), whilst modifying the primary amine to form a tertiary amine (for example ibandronate) results in even more potent molecules. The most potent bisphosphonates to date appear to be those containing a tertiary amine within a ring structure, such as zoledronate (Fig. 1c) (for full review see Russell & Rogers 1999).

Bisphosphonates bind avidly to hydroxyapatite bone mineral surfaces and are selectively internalised by osteoclasts where they inhibit their activity (Russell & Rogers 1999). Nitrogen-containing bisphosphonates inhibit the mevalonate pathway (Amin et al. 1992), the main target being farnesyl diphosphate synthase (Dunford et al. 2001). Inhibition of the mevalonate pathway leads to loss of important prenylated proteins which are required for post-translation lipid modification (i.e. prenylation) of signalling GTPases, such as Ras, Rho and Rac (Rogers et al. 2000). These regulate a variety of key osteoclast cell functions, such as control of endosomes, integrin signalling, membrane ruffling, control of cell morphology, and loss of these proteins leads to induction of osteoclast apoptosis. Non-nitrogen-containing bisphosphonates have a different mechanism of action. They are metabolically incorporated into non-hydrolysable analogues of ATP (Rogers et al. 1996), ultimately also leading to osteoclast apoptosis. As a consequence of this osteolysis is effectively inhibited.

Anti-tumour effects of bisphosphonates

Increasing evidence is accumulating that bisphosphonates are able to directly affect tumour cells, in addition to their direct effects upon osteoclasts. The potency of the anti-tumour effect in vitro generally mirrors the potency of the anti-resorptive ability with nitrogen-bisphosphonates, in particular, zoledronic acid being the most potent in both respects. Bisphosphonates induce apoptosis of tumour cells and inhibit tumour cell growth, in vitro, of a variety of tumour cell types, including breast (Senaratne et al. 2000, Jagdev et al. 2001a), prostate (Lee et al. 2001), melanoma (Riebeling et al. 2002), osteosarcoma (Mackie et al. 2001, Sonnemann et al. 2001) and myeloma (Shipman et al. 1998) tumour cells. The mechanism of apoptosis, at least for breast and myeloma cells, appears to be through inhibition of the mevalonate pathway for nitrogen-bisphosphonates, as for induction of osteoclast apoptosis (Shipman et al. 1998, Jagdev et al. 2001a).

Nitrogen-bisphosphonates inhibit the adhesion and spreading of human breast, prostate, fibrosarcoma cell lines and human melanoma cell lines cancer cells to and over bone matrix in vitro (van der Pluijm et al. 1996, Teronen et al. 1999, Boissier et al. 2000, Virtanen et al. 2002), whereas non-nitrogen-bisphosphonates have little or no effect. Bisphosphonates also inhibit various MMPs, such as MMP -2, -9 and -12, which are particularly involved in cancer growth and metastases in vitro (Boissier et al. 2000). Interestingly for this particular anti-tumour activity, all bisphosphonates appeared equipotent. Consequently, bisphosphonates are able to inhibit invasion of breast and prostate cancer cells through artificial membrane in vitro (Boissier et al. 2000). This is thought to be due to the effect of bisphosphonates upon MMPs, but recent data reveal, for zoledronic acid at least, that inhibition of invasion may also be due to the effects of zoledronic acid on the mevalonate pathway (Denoix et al. 2003). At a concentration (1μM) that did not modify MMP activity or production, Denoyelle et al. (2003) found that zoledronic acid inhibited breast cancer cell invasion by inhibition of Rho A, as a result of the defective prenylation induced by zoledronic acid.
More recently, possible anti-angiogenic effects of bisphosphonates have been discovered, neo-angiogenesis being a prerequisite for cancer cell growth and spread. Osteoblastic cells in the bone produce both vascular endothelial growth factor (VEGF) and basic fibroblastic growth factor (b-FGF) and vascularisation is needed for osteoclastic bone resorption. Intravenous zoledronic acid (4 mg) or pamidronate (90 mg), given as treatment for metastatic bone disease to breast cancer patients, induced a significant decrease in bone marrow plasma values of b-FGF and in VEGF, 3 days post-infusion (Jagdev et al. 2001b), whilst Santini et al. (2002) found that pamidronate was able to induce significant decreases in serum VEGF of cancer patients with a variety of solid tumours (including non-small cell lung cancer, breast, prostate and bladder cancers) that had metastatised to bone. Significant decreases in serum VEGF level were found 24 h after a 90 mg infusion of pamidronate, with further significant decreases at 2 days. Zoledronic acid and pamidronate have also been shown to decrease b-FGF- and, to a lesser extent, VEGF-induced proliferation of vascular tissue in a murine soft tissue model of angiogenesis (Wood et al. 2002). This indicates that nitrogen-bisphosphonates may have anti-angiogenic potential outside the bone microenvironment, with zoledronic acid the more potent inhibitor of the two compounds on angiogenesis.

Of particular interest is the potential for bisphosphonates, when used in vitro, to enhance the anti-tumour activity of known cytotoxic agents that are commonly used in the clinical setting. Whilst there are data derived from preclinical experiments exploring the potential interactions of various cytotoxic drugs in use for particular tumour types, very little is known about how bisphosphonates may interact with commonly used cytotoxic agents. This is especially pertinent for metastatic breast cancer, as these patients are often managed with a variety of drugs that may well include a bisphosphonate with an anti-hormonal agent or chemotherapy drug. To date, only zoledronic acid has shown synergy in vitro — with paclitaxel or tamoxifen in breast cancer (Jagdev et al. 2000, 2001a) and with dexamethasone in myeloma (Tassone et al. 2000). Other bisphosphonates in combination with cytotoxic drugs have shown additive activity at best, for example ibandronate in combination with the taxanes in breast cancer (Magnetto et al. 1999), or no effect, for example pamidronate in combination with the chemotherapy agent dacarbazine (Riebeling et al. 2002).

The clinical relevance of the anti-tumour effects of bisphosphonates observed in vitro is not yet clear, although attempts have been made to mimic the human situation of metastatic disease using specially designed animal models of bone metastases. One such example is the 4T1 orthotopic murine model (Mundy et al. 2001). In this model, murine mammary tumour cells are injected into the mammary fat pad, and subsequent disease progression mimics the human situation. The primary tumour develops by week 1, liver and lung metastases at week 2, bone and other metastases by week 3 and death by weeks 4 or 5. Using this model, zoledronic acid, given as a single 0.3 μg intravenous injection on day 7 (i.e. when the primary tumour had developed), not only led to a reduction in bone lesions and osteolysis, but interestingly also caused a decrease in bone tumour burden. Non-osseous tumour was not affected however. Other bisphosphonates in similar animal models have either shown no effect (Krempien & Manegold 1993) or an adverse effect (Kostenuik et al. 1993).

In a model of breast cancer bone metastases (Sasaki et al. 1995), risedronate, a nitrogen-containing bisphosphonate, was administered at a dose of 4 μg/animal per day s.c after osteolytic lesions had developed (day 17) for 10 days, or continuously for 28 days from the point of tumour cell inoculation, or 7 days before tumour cell injection. In all three groups, risedronate inhibited the development of bone metastases and, for those mice receiving continuous risedronate, survival was increased compared with untreated mice. However, whilst risedronate-treated animals had a significant decrease in bone tumour load, there was a greater amount of metastatic invasion into soft tissues surrounding bone when compared with the untreated animals. In contrast, the experimental bisphosphonate YH529, when started the same day as MDA-MB-231 breast cancer cell inoculation into nude mice (20 μg/day s.c. for 4 weeks) reduced non-osseous metastases, in addition to the inhibition of bone lesions and tumour burden in bone (Sasaki et al. 1998).

Collating data accrued from preclinical studies suggest that bisphosphonates not only affect osteoclasts in the bone, but also appear to directly affect tumour cells, albeit within the bone microenvironment. Bisphosphonates may induce tumour cell death directly, for example by induction of apoptosis, or inhibition of their growth and spread, or indirectly by cutting-off their ‘survival factors’, such as TGF-β and IGF-I, which are released from the resorbing bone.

**Clinical uses of bisphosphonates**

In recent years, the opportunities for improving the management of metastatic bone disease have never been greater. Rapid developments are occurring with improvements in reconstructive orthopaedic surgery, the development of bone-seeking radiopharmaceuticals, new endocrine and cytotoxic treatments and, in particular, the development of bisphosphonates to prevent and treat...
skeletal complications. These agents have an increasing role in oncology, not only in the management of metastatic bone disease and skeletal complications, but also for the prevention of cancer treatment-induced bone loss. Additionally, there are increasing data to support the adjuvant use of bisphosphonates in breast cancer, and confirmatory studies are in progress.

Hypercalcaemia of malignancy

Hypercalcaemia is the most common metabolic complication of malignancy, producing many unpleasant gastrointestinal and neurological symptoms. Focal osteolysis by tumour cells, generalised osteolysis by humoral factors secreted by the tumour, increased renal tubular reabsorption of calcium and impaired renal glomerular function may all contribute to the pathophysiology. Intravenous bisphosphonates, in conjunction with rehydration, are now established as the treatment of choice for hypercalcaemia. Some 70-90% of patients will achieve normocalcaemia resulting in relief of symptoms and improved quality of life (Coleman 1998). Zoledronic acid is the most effective bisphosphonate for the acute treatment of this metabolic emergency (Major et al. 2001).

Bisphosphonates for bone pain

Radiotherapy remains the treatment of choice for localised bone pain but many patients have widespread poorly localised, non-mechanical bone pain, while others will experience recurrence of pain in previously irradiated skeletal sites. The bisphosphonates provide an alternative treatment approach to the management of these patients with clinically meaningful pain improvement in around 50% of patients. Until recently it appeared that the intravenous route was necessary for a significant effect on metastatic bone pain. However, recent data with the potent oral amino-bisphosphonate, ibandronate, indicate that this agent also has beneficial effects on bone pain. Pain reduction with bisphosphonates seems to be independent of the nature of the underlying tumour or radiographic appearance of the metastases, with ‘sclerotic’ lesions responding similarly to ‘lytic’ metastases. Additionally, there appears to be an important link between metastatic bone pain and the rate of bone resorption, with subjective response correlating with biochemical response (Vinholes et al. 1996, 1997).

Bisphosphonates to prevent skeletal morbidity in breast cancer

Oral bisphosphonates

The absorption of bisphosphonates from the gut is poor, variable and dramatically inhibited by food intake.

Nevertheless, several studies on oral therapy have been reported, and the role of the oral route is becoming clearer (van Holten-Verzantvoort et al. 1987, 1993, Paterson et al. 1993, Kristensen et al. 1999, Tripathy et al. 2003) (Table 1).

Paterson et al. (1993) randomised 173 patients with bone metastases from breast cancer to receive either clodronate capsules (1600 mg daily) or placebo capsules of identical appearance in addition to appropriate anticancer treatment(s). In the patients who received clodronate, there was a significant reduction in skeletal morbidity. Overall, the combined rate of all skeletal events was 219 per 100 patient years with clodronate compared with 305 on placebo. Most of the benefit could be attributed to the reduction in hypercalcaemic episodes (28 vs 52, \( P < 0.01 \)) and the reduction in frequency of vertebral fractures (84 vs 124 per 100 patient years, \( P < 0.025 \)). There was no significant effect on non-vertebral fractures, radiotherapy requirements, changes in anti-tumour therapy or survival. Oral clodronate was generally well tolerated. These results indicated that oral clodronate can modify the course of skeletal disease in metastatic bone disease from breast cancer. However, at the 1600 mg dose the benefits seen are relatively small, and oral clodronate at this dose is not as effective as intravenous pamidronate in relieving pain or inhibiting bone (Jagdev et al. 2001c). At higher doses (2400 mg), oral clodronate appears to be of similar efficacy to intravenous pamidronate at 60 mg every 3 weeks (Diel et al. 1998a). However, comparison of this probably optimal dose of clodronate with full dose (90 mg) pamidronate or zoledronic acid has not been performed.

There are now no plans for oral pamidronate to be marketed. However, one of the first, randomised trials of bisphosphonate therapy in breast cancer was performed with enteric-coated oral pamidronate (Van Holten-Verzantvoort et al. 1987). One hundred and sixty-one women with bone metastases from breast cancer were randomised to standard anticancer treatment with or without oral pamidronate, initially at a dose of 600 mg/day but subsequently reduced to 300 mg/day because of poor gastrointestinal tolerability. An initial analysis reported a significant reduction in skeletal morbidity with a reduction in pathological fractures, episodes of severe bone pain and hypercalcaemia leading to a reduction in radiotherapy requirements and the need to change the underlying systemic treatment. However, a subsequent analysis revealed that most of this benefit was accrued in the patients who received the initial poorly tolerated dose of 600 mg pamidronate a day (Van Holten-Verzantvoort et al. 1993).

Ibandronate is a highly potent amino-bisphosphonate that is licensed in Europe for the treatment of hypercal-
theless, this new oral agent has obvious attractions to both patients and health care providers but its place in the treatment of metastatic bone disease cannot be defined until comparative data with other bisphosphonates are available.

**Intravenous bisphosphonates**

In the first phase III study of intravenous pamidronate, Conte et al. (1996) randomised 295 patients with breast cancer and bone metastases to standard chemotherapy (generally cyclophosphamide and fluorouracil with one of methotrexate, epirubicin or doxorubicin) alone or chemotherapy plus intravenous pamidronate (45 mg every 3 weeks) — a dose intensity of pamidronate which is now considered suboptimal. A blinded, extramural review of the serial radiographs was performed. There were sufficient imaging studies available to assess response in bone in 224 patients. Of these, 141 (63%) had developed progressive disease in bone, 72 on pamidronate and 69 control patients. A 48% increase in the median time to progression in bone in favour of the patient group which received pamidronate (249 vs 168 days, \( P = 0.02 \)) was identified. Sclerosis of lytic disease was noted in 53 and 65% v 46% (\( P < 0.001 \); delay in first SRE 7.0 vs 13.1 months (\( P = 0.0005 \)).

**Table 1** Skeletal morbidity in breast cancer

<table>
<thead>
<tr>
<th>Agent and route</th>
<th>No. of patients</th>
<th>Results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pamidronate (600 mg p.o.) vs control</td>
<td>161</td>
<td>Reduced skeletal morbidity rates (SMR), 94 vs 52 events/100 women years (( P &lt; 0.01 )); 600 mg poorly tolerated; no benefit with reduced dose (300 mg)</td>
<td>Van Holten-Verzantvoort et al. (1987, 1993)</td>
</tr>
<tr>
<td>Clodronate (1600 mg p.o.) vs placebo</td>
<td>173</td>
<td>Reduced SMR, 305 vs 219 events/100 women years (( P &lt; 0.001 ))</td>
<td>Paterson et al. (1993)</td>
</tr>
<tr>
<td>Clodronate (1600 mg p.o.) vs control</td>
<td>100</td>
<td>Increased time to first SRE (( P = 0.015 )); improved quality of life</td>
<td>Kristensen et al. (1999)</td>
</tr>
<tr>
<td>Pamidronate (45 mg i.v.) vs control</td>
<td>295</td>
<td>Increased time to bone progression, 168 vs 249 days (( P = 0.02 ))</td>
<td>Conte et al. (1996)</td>
</tr>
<tr>
<td>Pamidronate (90 mg i.v.) vs placebo</td>
<td>382</td>
<td>Reduced proportion experiencing SRE, 65% v 46% (( P &lt; 0.001 )); delay in first SRE 7.0 vs 13.1 months (( P = 0.0005 ))</td>
<td>Hortobagyi et al. (1996)</td>
</tr>
<tr>
<td>Pamidronate (60 mg i.v.) vs control</td>
<td>401</td>
<td>Median time to skeletal progression, 9 vs 14 months (( P &lt; 0.01 ))</td>
<td>Hultborn et al. (1996)</td>
</tr>
<tr>
<td>Pamidronate (90 mg i.v.) vs placebo</td>
<td>374</td>
<td>Reduced proportion experiencing SRE, 67% vs 56% (( P = 0.027 )); delay in first SRE, 6.9 vs 10.4 months (( P = 0.049 ))</td>
<td>Theriault et al. (1999)</td>
</tr>
<tr>
<td>Ibandronate (2/6 mg i.v.) vs placebo</td>
<td>467</td>
<td>Reduced SMR with 6 mg dose; 2 mg ineffective; SMR 2.18 vs 1.61 (( P = 0.03 ))</td>
<td>Body et al. (1999)</td>
</tr>
<tr>
<td>Ibandronate (20/50 mg p.o.) vs placebo</td>
<td>435</td>
<td>Reduced skeletal morbidity with oral ibandronate (20 and 50 mg) 0.65 vs 0.70 vs 1.00 (( P = 0.023 ))</td>
<td>Tripathy et al. (2002)</td>
</tr>
<tr>
<td>Zoledronic acid (4/8 mg i.v.) vs pamidronate (90 mg i.v.)</td>
<td>1130</td>
<td>43% had a SRE with 4 mg zoledronic acid, compared with 45% with pamidronate; 20% risk reduction for an SRE (( P = 0.025 ))</td>
<td>Rosen et al. (2001), Coleman et al. (2002)</td>
</tr>
</tbody>
</table>

SRE, skeletal-related event; i.v., intravenous; p.o., oral

caemia of malignancy, and is in clinical development for both the treatment of metastatic bone disease and the prevention and treatment of osteoporosis. A film-coated tablet has been developed which has been shown to produce a dose-dependent reduction, at doses which are generally well tolerated, in both urinary calcium and collagen cross-link excretion (Coleman et al. 1999). Preliminary reports of phase III, placebo-controlled trials of the oral formulation indicate that the oral formulation is active with a broadly similar impact on skeletal morbidity to that observed in earlier placebo-controlled trials with other bisphosphonates (Tripathy et al. 2002, 2003). The skeletal morbidity period rate, which evaluated the number of 3-month periods on treatment that were complicated by a skeletal-related event (SRE), was significantly less on oral ibandronate (1.0, 0.70 and 0.65 for placebo, 20 mg and 50 mg oral ibandronate daily respectively, \( P = 0.025 \)). However, this analysis is somewhat contrived in that data from the first 3 months on treatment were excluded while complications after study withdrawal were included in the analyses. Neither of these adjustments was pre-planned in the protocol. Nevertheless, this new oral agent has obvious attractions to patients and health care providers but its place in the treatment of metastatic bone disease cannot be defined until comparative data with other bisphosphonates are available.

In the first phase III study of intravenous pamidronate, Conte et al. (1996) randomised 295 patients with breast cancer and bone metastases to standard chemotherapy (generally cyclophosphamide and fluorouracil with one of methotrexate, epirubicin or doxorubicin) alone or chemotherapy plus intravenous pamidronate (45 mg every 3 weeks) — a dose intensity of pamidronate which is now considered suboptimal. A blinded, extramural review of the serial radiographs was performed. There were sufficient imaging studies available to assess response in bone in 224 patients. Of these, 141 (63%) had developed progressive disease in bone, 72 on pamidronate and 69 control patients. A 48% increase in the median time to progression in bone in favour of the patient group which received pamidronate (249 vs 168 days, \( P = 0.02 \)) was identified. Sclerosis of lytic disease was noted in 53 and 44% of pamidronate-treated and control patients respec-
atively. The other major endpoint of this trial was bone pain. A marked improvement in pain was seen more often in the pamidronate-treated group (44 vs 30%, $P = 0.025$), indicating that intravenous pamidronate adds to the symptom relief achieved by chemotherapy alone.

Similar results were reported in a Scandinavian trial (Hultborn et al. 1996). Four hundred and one patients receiving chemotherapy for advanced breast cancer were randomly allocated to receive either an intravenous 60 mg pamidronate infusion every 4 weeks or a placebo infusion — the same dose intensity of pamidronate as that given in the Conte et al. (1996) study. The time to first skeletal complication and number of events was significantly less with pamidronate. The median times to symptoms of skeletal progression were 9 and 14 months for the pamidronate-treated and placebo groups respectively. However, no significant differences in pathological fractures, radiotherapy requirements or the need for a change in systemic therapy were seen.

The results of two double-blind, placebo-controlled trials of 90 mg pamidronate infusions every 3–4 weeks in addition to cytotoxic or endocrine treatments for breast cancer patients with lytic bone metastases really established bisphosphonate treatment in breast cancer as the standard of care (Hortobagyi et al. 1996, Theriault et al. 1999). These two studies were of similar design, with the exception of the systemic anticancer treatment at study entry. The demographic and tumour characteristics were well balanced. The primary endpoint was the influence of pamidronate on SREs, namely: pathological long bone and vertebral fractures, spinal cord compression, radiation for pain relief or to treat or prevent pathological fractures or spinal cord compression, surgery to bone and hypercalcaemia of malignancy (HCM). Treatment effects were expressed in terms of time to first SRE, the proportion of patients experiencing any SRE, the proportion of patients experiencing each individual type of SRE, and the skeletal morbidity rate (SMR) — defined as the number of skeletal events per patient per year. In both studies, pamidronate was well tolerated and no serious drug-related toxicities were identified.

In the chemotherapy study (Hortobagyi et al. 1996), 382 patients were randomised to chemotherapy and either monthly pamidronate ($n = 185$) or placebo infusions ($n = 197$). The time to first SRE (excluding HCM) was 7 months in the placebo group (i.e. with chemotherapy alone) and 14 months in the pamidronate-treated group ($P < 0.01$). The SMR was significantly lower throughout the study period, and at 24 months was 2.5 compared with 3.6 ($P < 0.001$). Benefits were maintained for at least 2 years. The proportion of pamidronate-treated patients with an SRE(s) up to 24 months was 46% compared with 65% for the placebo-treated patients ($P < 0.001$). There were no differences in the types of chemotherapy or the dose intensity of treatments received during the study. The time to a change of treatment and the number of systemic treatments required during the study period were the same for both groups. Pain, analgesic use and ECOG performance status were monitored throughout the study period. As there was inevitably a tendency for the underlying cancer to progress during the study period, there was an overall deterioration in mean performance status, pain and analgesic consumption. However, the deterioration was significantly less in the pamidronate-treated group for all of these endpoints. Quality of life was also better maintained in the pamidronate-treated group, but there were no significant effects on overall survival (14.8 and 13.9 months for the pamidronate- and placebo-treated groups respectively, $P = 0.82$).

In the endocrine study (Theriault et al. 1999), 374 patients were randomised to receive hormone therapy with pamidronate ($n = 182$) or placebo ($n = 192$) infusions every month. As in the chemotherapy study, pamidronate reduced the number and rate of SREs. The time to first SRE (excluding HCM) was 6 months in the placebo-treated group, and 10 months in those receiving pamidronate ($P < 0.049$). The benefits of pamidronate were slower to appear than in the chemotherapy study, but again the effect was maintained for at least 2 years. The SMR at 24 months was 2.4 compared with 3.8 ($P = 0.008$), and the proportion of pamidronate-treated patients experiencing an SRE(s) was 56% compared with 67% for the placebo-treated patients ($P = 0.027$). The effects on pain and analgesic consumption were even more clearly evident in this study. Again, there was no difference in survival by treatment group (23.1 and 23.5 months for the pamidronate- and placebo-treated groups respectively, $P = 0.69$).

Zoledronic acid is the most potent bisphosphonate in clinical development. In normocalcaemic patients, a dose-dependent reduction in deoxypyridinoline, a specific marker of bone resorption, was identified (Berenson et al. 2001a). These biochemical responses were at least as large as those previously reported after infusions of 90 mg pamidronate and, subsequently, a randomised, double-blind, dose-finding phase II study of zoledronic acid tested doses of 0.5, 2 and 4 mg zoledronic acid given on a 4-weekly schedule. This study showed that 4 mg zoledronic acid was of similar efficacy to pamidronate and merited formal evaluation and development (Berenson et al. 2001b).

Recently, a large, international, multicentre, stratified, randomised double-blind phase III trial of zoledronic acid compared with pamidronate in the treatment of malignant bone disease in patients with breast cancer has been completed (Rosen et al. 2001). The trial was designed as a
non-inferiority trial in which the primary efficacy variable was the proportion of patients experiencing at least one SRE. Secondary efficacy variables included the time to first SRE, SMR and an Andersen–Gill multiple events analysis (Rosen et al. 2003). The proportion of patients experiencing individual SREs, time to progression, tumour response, performance status, analgesic and pain scores, and markers of bone resorption and formation were also assessed.

One thousand one hundred and thirty patients with advanced breast cancer, and at least one metastatic bone lesion, were randomised to receive either 4 mg zoledronic acid or 8 mg zoledronic acid via a short intravenous infusion, or 90 mg pamidronate via a 2-h-infusion. Treatments were administered every 3–4 weeks. Initially zoledronic acid was administered as a 5-min infusion in 50 ml 0.9% saline or 5% dextrose. This was amended to 15-min infusion in 100 ml saline or dextrose due to concerns over renal toxicity. Similarly, the 8 mg dose of zoledronic acid was reduced to 4 mg due to continuing concerns over renal safety.

An initial analysis of the first 13 months on the study revealed broadly similar results across all three treatment groups (Rosen et al. 2001). Forty-four to forty-six percent of patients experienced at least one SRE. Differences that were seen included a reduction in radiotherapy requirements between the groups treated with 4 mg zoledronic acid and pamidronate groups (15 vs 20%, P = 0.031). More recently, the final 25-month data have become available (Rosen et al. 2003). This has shown superiority for 4 mg zoledronic acid over pamidronate. Using the pre-planned Andersen–Gill multiple event analysis, a reduction of 20% in the risk of developing an SRE was observed (hazard ratio (HR) = 0.799, P = 0.025).

The effects of pamidronate and zoledronic acid on pain scores, analgesic use or performance status were similar. Pain was reduced in all groups and analgesic use was decreased or stabilised. There were no appreciable differences in the response of bone lesions to therapy or the time to progression between the study groups. All markers of bone resorption or formation decreased from baseline to the end of the study. At all time-points, the urinary marker of bone resorption NTX was significantly less in the group treated with 4 mg zoledronic acid compared with the pamidronate-treated group (e.g. 64 vs 57% below baseline at the end of 1 year, P = 0.015). Median overall survival was similar at approximately 2 years in the study groups. The most common adverse events were bone pain, nausea, fever and fatigue and, as with the other adverse effects, they occurred generally with a similar frequency in each group. The incidence of renal dysfunction with 4 mg zoledronic acid (given on the 15-min schedule) was indistinguishable from pamidronate.

Intravenous ibandronate has also been evaluated in advanced breast cancer. Preliminary analysis of a phase III, placebo-controlled trial of monthly infusions in breast cancer has shown a significant reduction in skeletal-related morbidity with 6 mg ibandronate (Body et al. 1999). Additionally, improvements in pain and quality of life were clearly demonstrated at this dose.

**Bisphosphonate treatment for the prevention of bone metastases**

Bone is the most frequent site of distant relapse, accounting for around 40% of all first recurrences (Coleman & Rubens 1987). As discussed earlier, inhibition of bone resorption could have an effect on the development and progression of metastatic bone disease, and indeed the disease process as a whole. The use of adjuvant bisphosphonate treatment is thus a therapeutic strategy of considerable importance.

Several clinical trials using the relatively low potency oral bisphosphonate, clodronate, have been reported (Table 2). In the largest study, 1079 women with primary operable breast cancer were randomised to receive either 1600 mg clodronate daily or placebo for 2 years in addition to standard adjuvant systemic treatment. Recent data presented with a median follow-up time of 5 years revealed a non-significant reduction in the frequency of bone metastases in the clodronate-treated patients (63 (12%) vs 80 (15%) patients, P = 0.127) (Powles et al. 2002). However, during the 2 years on active treatment there was a reduction in bone metastases, but this disappeared on discontinuation of the study drug, suggesting that adjuvant bisphosphonate treatment trials in the future should test a longer duration of treatment. There was no effect on non-bone recurrence (112 (21%) vs 128 (24%) patients, P = 0.26) but, despite little effect on the primary endpoint (bone recurrence), patients randomised to the clodronate arm had a better survival (82 vs 77%, P = 0.047). Of note, some of this benefit was related to a reduction in non-breast cancer deaths in the clodronate-treated patients.

In a second study, Diel et al. (1998b) studied 302 breast cancer patients randomly allocated to either oral clodronate (1600 mg daily, n = 157) for 3 years or a control group (n = 145). These women had no overt evidence of metastatic disease, but were selected for the trial on the basis of immunocytochemical detection of tumour cells in the bone marrow, a known risk factor for the subsequent development of distant metastases. Patients received appropriate adjuvant chemotherapy and endocrine treatment. There were no discernable prognostic or treatment imbalances between the two
groups and the follow-up schedules were similar. The median observation period was 36 months. The incidence of osseous metastases was significantly lower in the clodronate-treated group (11 (7%) vs 25 (17%) patients, \( P < 0.002 \)). There was also an unexpected large reduction in the incidence of visceral metastases in the clodronate-treated group (19 (13%) vs 42 (29%) patients, \( P < 0.001 \)). These results have subsequently been updated (Diel et al. 2000) and show similar results, although the striking effect on extra-skeletal visceral relapse seen in the earlier report was less and no longer statistically significant.

The exciting findings of the Powles et al. (2002) and Diel et al. (2000) studies must, however, be viewed in the light of a further trial which produced conflicting results. Saarto et al. (2001) randomised 299 women with primary node-positive breast cancer to oral clodronate (1600 mg daily, \( n = 149 \)) or a control group (\( n = 150 \)). The median follow-up was 5 years. Treatment with clodronate in this study did not lead to a reduction in the development of bone metastases (29 (19%) vs 24 (16%) patients, \( P = 0.27 \) for the clodronate-treated and control groups respectively). Additionally, the development of non-skeletal recurrence was significantly higher in the clodronate-treated group (60 (40%) vs 36 (24%) patients, \( P = 0.0007 \)) and, most importantly, the overall 5-year survival was significantly lower in the clodronate-treated group (70 vs 83%, \( P = 0.009 \)). It is possible that there were some prognostic imbalances favouring the control group but the safest assumption is to consider that the Diel et al. (2001) and Saarto et al. (2001) studies cancel each other out and probably reflect the usual heterogeneity of results seen in relatively small studies of adjuvant breast cancer treatments.

To identify a definite adjuvant role for bisphosphonates will require further large randomised studies. The National Surgical Adjuvant Breast Project is close to completing accrual to a placebo-controlled trial of oral clodronate (\( n \geq 3000 \)) in an attempt to resolve the value or otherwise of the adjuvant clodronate. However, with the anticipated event rate in this study dominated by stage I patients, definitive results are unlikely to emerge before 2007–2008. A large adjuvant trial of zoledronic acid in stage II/III breast cancer patients is underway, but again results are unlikely to be available before 2008.

**Bisphosphonates to prevent skeletal morbidity in breast cancer**

Although bisphosphonates have traditionally been evaluated in patients with osteolytic lesions associated with breast cancer and multiple myeloma, they have also been shown to reduce biochemical markers of bone resorption in patients with osteoblastic bone lesions associated with advanced prostate cancer (Garnero et al. 2000). Additionally, several phase II studies have assessed bone pain and analgesic usage, and demonstrated some benefit in these acute end points (Elomaa et al. 1992, Kylmala et al. 1994, 1997, Pelger et al. 1998, Coleman et al. 1999, Heidenreich et al. 2002). However, these trials were statistically under-powered to detect significant effects on skeletal complications, and the results were not sufficiently convincing to lead to either the regulatory approval or widespread use of bisphosphonates for metastatic bone disease in prostate cancer. Furthermore, until recently, randomised, placebo-controlled trials of bisphosphonates had failed to demonstrate a significant reduction in skeletal complications from bone metastases in patients with advanced prostate cancer in (Table 3).

**Oral bisphosphonates**

In 57 patients with hormone-refractory prostate cancer (HRPC) and bone pain at study entry, Smith (1989)

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**Table 2** The use of adjuvant 1600 clodronate given orally in primary operable breast cancer trials. Average follow-up time was 4.5–5.5 years

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Period of clodronate treatment (years)</th>
<th>Occurrence of bone metastases (clodronate vs placebo)</th>
<th>Occurrence of non-bone metastases (clodronate versus placebo)</th>
<th>Deaths (clodronate vs placebo)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1079</td>
<td>2</td>
<td>At 2 years 2 vs 5% ( (P = 0.016) )</td>
<td>At &gt; 2 years 21 vs 24% ( (P = 0.26) )</td>
<td>At 2 years 8 vs 8% ( \text{approx.} )</td>
<td>Powles et al. (2002)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>At &gt; 2 years 10 vs 10% ( (P = 0.73) )</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>299</td>
<td>3</td>
<td>21 vs 17% ( (P = 0.27) )</td>
<td>43 vs 25% ( (P = 0.009) )</td>
<td>At 5 years 30 vs 17% ( (P = 0.01) )</td>
<td>Saarto et al. (2001)</td>
</tr>
<tr>
<td>302</td>
<td>2</td>
<td>14 vs 24% ( (P = 0.044) )</td>
<td>16 vs 26% ( (P = 0.091) )</td>
<td>At 5 years 10 vs 22% ( (P = 0.002) )</td>
<td>Diel et al. (1998b, 2000)</td>
</tr>
</tbody>
</table>

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concluded that intravenous etidronate (5 mg/kg) followed by oral etidronate (400 mg/day) had no significant effects on pain levels or analgesic usage over and above placebo. A more recent clinical trial involving 208 patients investigated both pain and analgesic usage. In this study, intravenous clodronate was added to a background treatment of mitoxantrone and prednisolone. The study also included objectively measurable skeletal complications as clinical endpoints. No significant differences between clodronate and placebo were seen (Ernst et al. 2002).

The Medical Research Council in the UK has performed a moderate-sized phase III trial of oral clodronate in 311 men with metastatic bone disease from prostate cancer (Dearnaley et al. 2003). Quite a high dose of oral clodronate (1040 mg Loron twice daily) was administered for a median duration of 43 months. After a median follow-up of 59 months, the inevitable deterioration in performance status over the course of the study was significantly less in the clodronate-treated group (HR = 0.71, P = 0.008). A slight advantage in favour of clodronate in the risk of symptomatic progression in bone (the primary endpoint of the study) was observed (median 24 vs 19 months, HR = 0.79, P = 0.066). There was also a trend towards improved survival with clodronate (median 37 vs 28 months, HR = 0.80, P = 0.082). However, none of these differences was statistically significant, and the study was probably under-powered to show the likely impact of a bisphosphonate on the course of the disease. There are no phase III data available on the use of oral ibandronate in prostate cancer.

Intravenous bisphosphonates
Pamidronate has been studied in patients with advanced prostate cancer (Lipton et al. 2002). In a multicenter, randomised, placebo-controlled trial, 236 prostate cancer patients with bone metastases were treated with intravenous pamidronate (90 mg) or placebo every 3 weeks for 9 months. This trial assessed bone pain as the primary endpoint and included an assessment of skeletal events (defined as pathological fracture, spinal cord compression, requirement for palliative radiotherapy or surgery to bone, or hypercalcaemia of malignancy) as a secondary endpoint. Patients in this trial had very advanced disease (median baseline prostate-specific antigen=97.8 ng/ml in the pamidronate-treated group), very high levels of bone resorption and substantial bone pain at study entry. As in

Table 3  The efficacy of bisphosphonates in randomised, placebo-controlled trials in patients with bone metastases secondary to prostate cancer

<table>
<thead>
<tr>
<th>Agent and route</th>
<th>No. of patients</th>
<th>Results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etidronate</td>
<td>57</td>
<td>No significant benefits</td>
<td>Smith et al. (1989)</td>
</tr>
<tr>
<td>5 mg/kg (i.v., days 1–3), then 400 mg/day (oral)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clodronate</td>
<td>75</td>
<td>↓Pain and analgesic use (1st month only)</td>
<td>Elomaa et al. (1992)</td>
</tr>
<tr>
<td>3200 mg/day (1st month), then 1600 mg/day (oral)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clodronate</td>
<td>57</td>
<td>↓Pain by 10% (non-significant)</td>
<td>Kylmala et al. (1994, 1997)</td>
</tr>
<tr>
<td>300 mg/day (i.v., days 1–5), then 1600 mg/day (oral)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clodronate</td>
<td>55</td>
<td>No significant benefits</td>
<td>Strang et al. (1997)</td>
</tr>
<tr>
<td>300 mg/day (i.v., days 1–3), then 3200 mg/day (oral)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clodronate</td>
<td>208</td>
<td>↓Pain (non significant)</td>
<td>Ernst et al. (2002)</td>
</tr>
<tr>
<td>1500 mg (i.v.) every 3 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pamidronate</td>
<td>236</td>
<td>No significant benefits in pain or proportion of patients with SREs</td>
<td>Lipton et al. (2002)</td>
</tr>
<tr>
<td>90 mg (i.v.) every 3 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>643</td>
<td>↓Proportion of patients with ≥1 SRE (P = 0.021)</td>
<td>Saad et al. (2002)</td>
</tr>
<tr>
<td>4 mg (i.v.) every 3 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clodronate</td>
<td>311</td>
<td>↓Proportion of patients with ≥1 SRE (41 vs 49%, P = NS) Improvement in time to progression (24 vs 19 months, P = NS)</td>
<td>Dearnaley et al. (2001)</td>
</tr>
<tr>
<td>1040 mg/day (oral)</td>
<td></td>
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</tr>
</tbody>
</table>

NS, not significant.
the previous trials, pamidronate did not reduce the incidence of skeletal events and had only a slight effect on bone pain.

Despite the failures of other bisphosphonates, zoledronic acid was investigated in patients with advanced prostate cancer to determine if the increased potency of this compound would translate into improved clinical benefits for this patient population. Six hundred and forty-three patients with HRPC and documented bone metastases were randomised to one of three different treatment groups: 4 mg zoledronic acid \( (n = 214) \), 8 mg zoledronic acid \( (n = 221) \) or placebo \( (n = 208) \) (Saad et al. 2002). In the 8 mg arm, the dose was reduced by a protocol amendment to 4 mg because of concerns over renal safety, and conclusions on the efficacy of this cohort are difficult to make. Zoledronic acid or placebo were administered as a 15-min, 100 ml intravenous infusion every 3 weeks for 15 months followed by an extension phase of a further 10 months. All patients received daily oral supplements of calcium and vitamin D. The disposition, demographics and prognostic factors of patients in the zoledronic acid and placebo treatment groups were well balanced. The primary endpoint was the proportion of patients with a skeletal event, defined as pathologic fracture, spinal cord compression, requirement for radiation therapy to treat bone pain, requirement for surgery to bone, or changes in chemotherapy resulting from bone pain.

Zoledronic acid was significantly more effective than placebo across all primary and secondary endpoints. The 4 mg zoledronic acid treatment group achieved significant reductions in the proportion of patients with any skeletal complication (33 vs 44% with placebo, \( P = 0.021 \)) or pathologic fracture (13 vs 22% with placebo, \( P = 0.015 \)) compared with the placebo-treated group. Furthermore, there were consistent reductions in the proportion of patients with each type of skeletal complication, including non-vertebral fractures. Zoledronic acid (4 mg) was still significantly superior to placebo when fractures were excluded, indicating that the beneficial effect was not simply a result of the prevention of osteoporotic fractures. Zoledronic acid also prolonged the time to first skeletal complication by more than 4 months \( (P = 0.011) \). Using the protocol-specified Andersen–Gill multiple-event analysis, it was calculated that 4 mg zoledronic acid reduced the overall risk of skeletal complications by 36%.

Zoledronic acid reduced bone pain compared with placebo at all time-points, and these differences were significant at 3 and 9 months. Significant reductions in markers of bone resorption were documented for the zoledronic acid-treated group compared with the placebo-treated group throughout the duration of the study. Despite the favourable effects on skeletal morbidity, there were no significant effects on disease-related endpoints such as time to progression and survival.

As a class, bisphosphonates are known to affect renal function. However, the risk of renal function deterioration in patients treated with zoledronic acid (4 mg via a 15-min intravenous infusion) was similar to that of placebo-treated patients. The only adverse events that occurred at increased frequency with the zoledronic acid-treated group compared with the placebo-treated group were fatigue, anaemia, myalgia and pyrexia. The majority of these events were manageable with simple supportive care measures and are as expected with any intravenous amino-bisphosphonate therapy.

**Optimum use of bisphosphonates in metastatic bone disease**

Criteria for the point at which bisphosphonates should be started and stopped in the course of metastatic bone disease need to be determined. Because of the logistics and cost of bisphosphonate treatment for all patients with metastatic bone disease, certain empirical recommendations on who should receive treatment are needed. These should take into account the extent of disease, the life expectancy of the patient, the probability of the patient experiencing an SRE and the ease with which the patient can attend for treatment (or be treated by a domiciliary service) (Plunkett & Rubens 2003).

Current international guidelines (Hillner et al. 2000a) suggest that women with bone metastases from breast cancer should receive bisphosphonates from the time of diagnosis, particularly if they have already experienced a skeletal event. In the context of life-threatening visceral disease, immediate bisphosphonate treatment for bone metastases from breast cancer is of lower priority, particularly if the bone disease is asymptomatic. It is hoped that biochemical monitoring of bone resorption may prove to be relevant in identifying patients most likely to experience a reduction in skeletal morbidity from bisphosphonate treatment.

Because bisphosphonates are providing supportive care, reducing the rate of skeletal morbidity but not necessarily abolishing it, the criteria for stopping their administration are different from those used for classical anti-neoplastic drugs. They should not be stopped when a skeletal event occurs, or when there is progression in bone, but be continued for as long as bone disease is a clinically relevant problem. If bisphosphonate treatment is stopped, bone resorption rates will increase within a few weeks and this will put the patient at even higher risk for subsequent events. The pharmacodynamics of bisphosphonates in metastatic bone disease is very different (much shorter duration of action) than that observed in benign bone disease or postmenopausal osteoporosis.
Despite the obvious clinical benefits of bisphosphonates, it is clear that only a proportion of events are prevented and some patients do not experience a skeletal event despite the presence of metastatic bone disease. It has been impossible to predict whether an individual patient needs, or will benefit from, a bisphosphonate. Overall, bisphosphonates reduce the frequency of skeletal events by 25–40%. However, bisphosphonates are a relatively costly additional intervention in cancer care which is now potentially applicable to a very large proportion of patients with advanced malignancy. The cost effectiveness of routine long-term treatment has been questioned (Hillner et al. 2000b, Body 2003) and prioritisation of bisphosphonate use is needed.

A recent preliminary report of the use of the bone resorption marker NTX suggests that biochemical monitoring may be useful to identify patients at high risk of skeletal complications. In this study of 121 patients with metastatic bone disease, monthly measurements of urinary NTX during treatment with a range of bisphosphonates were made (Brown et al. 2003a). All SREs, plus hospital admissions for control of bone pain, and death during the period of observation were recorded. NTX was strongly correlated with the number of SREs and/or death \( (P < 0.001) \). Patients with NTX values above 100 nmol/mmol creatinine were many times more likely to experience an SRE/death than those with NTX below this level \( (P < 0.01) \). Subsequently, these data have been confirmed by evaluation of the large data set of patients with bone metastases included in the phase III development programme of zoledronic acid. In this study, elevated NTX levels were highly predictive of skeletal events, progression in bone and death (Brown et al. 2003b). These observations suggest that a more cost-effective use of bisphosphonates might be to reserve them until patients have NTX levels above either 50 or 100 nmol/mmol creatinine, and adjust the dose and schedule to maintain a normal (< 50 nmol/mmol creatinine) rate of bone resorption. Randomised trials to assess this approach are planned.

Use of bisphosphonates in the management of treatment-induced bone loss

Over recent decades there has been a significant improvement in cure rates and survival times in certain cancers. Over the same period, the use of adjuvant chemotherapy and hormone therapy has expanded greatly. Thus there are increasing numbers of long-term survivors who have received these treatments. Whilst initial attention has naturally been focused on treatment of the malignancy, recent studies have highlighted the possible long-term detrimental effects of cancer treatments on the skeleton, with accelerated bone loss, which may lead to osteoporosis. The morbidity associated with osteoporosis, leading to debilitating fractures, chronic pain and increased hospitalisation can have a significant negative impact on quality of life.

There is an increasing awareness of the need for research into the occurrence and management of therapy-induced osteoporosis and a number of recent studies have been carried out, particularly in breast and prostate cancer. Such studies require the monitoring of bone mineral density (BMD), which can be measured by a range of techniques. However, dual energy X-ray absorptiometry (DEXA) scan remains the gold standard for measurement of BMD and enables quantitative assessment of BMD at specific regions of the body, the two most commonly measured being the lumbar spine and proximal femur. WHO criteria for osteopenia and osteoporosis have now been defined according to DEXA scan measurements (WHO Organization Technical Report 1994).

Breast cancer

Osteoporosis in breast cancer patients is likely to be of growing importance due to the increasing incidence of the disease, coupled with significant improvements in survival (expectations are that the 10-year survival will soon exceed 70%; Parkin et al. 2001). There is an increased risk of osteoporosis for women with breast cancer because of treatment-induced premature ovarian failure, direct effects of chemotherapy on bone and effects of the breast cancer itself (Mincy 2003). Women in this group are also less likely to receive hormone replacement therapy because of the perceived risk of further breast cancer. Vertebral collapse with fracture is a common consequence of osteoporosis and Kanis et al. (1999) showed that women with breast cancer suffered almost five times as many vertebral fractures after diagnosis as age-matched postmenopausal women without a history of breast cancer. Approximately 22% of women are premenopausal at diagnosis of breast cancer and more than 60% will experience ovarian failure within 1 year of presentation due to the effects of adjuvant chemotherapy (Pfeilschifter & Diel 2000).

Several studies have shown that this chemotherapy-induced early menopause can lead to significant loss in bone density (Headley et al. 1998, Miller & Klibanski 1999). Although direct effects of chemotherapy on bone can occur (Wheeler et al. 1995), secondary premature ovarian failure is the major mechanism of bone loss (Shapiro et al. 2001) with rapid bone loss (> 5%) in the first few years.
In addition to the effects of chemotherapy, hormonal therapies may also contribute to bone loss. This includes tamoxifen in premenopausal women (Powles et al. 1996). Following encouraging results from recent studies of drugs such as anastrozole and letrozole, it is likely that the long-term use of aromatase inhibitors in breast cancer will increase. However, it is increasingly clear that these agents will enhance bone loss (Cummings et al. 1998, Goss et al. 2001, Harper-Wynne et al. 2001). This was demonstrated in the recent anastrazole, tamoxifen alone or in combination (ATAC) study. In this study, postmenopausal women with invasive breast cancer were treated with surgery ± radiotherapy ± chemotherapy as clinically indicated. In the overall study, anastrozole showed significant superior efficacy in terms of disease-free survival and also a significant reduction in contralateral breast cancer, compared with tamoxifen alone (ATAC Trialists Group 2002). However, there was a significant 60% increase in fracture rate. In addition to the main study, a bone sub-protocol was carried out on 308 patients to determine treatment effects on BMD and bone metabolism (Eastell et al. 2002). After 1 year, increased bone turnover and a decrease of BMD in the spine (−2.6%) and at the hip (−1.7%) was seen with anastrozole compared with an increase in BMD in the spine (1.0%) and the hip (0.5%) with tamoxifen.

Bisphosphonates are among a number of agents that have a role in treating or preventing bone loss in long-term survivors of breast cancer. Studies using daily oral clodronate have shown a significant reduction in bone loss after chemotherapy (Saarto et al. 1997, Powles et al. 1998). A double-blind, placebo-controlled study using the oral bisphosphonate risedronate showed that BMD at the lumbar spine and proximal femur decreased in the placebo-treated group but increased in the risedronate-treated group, with the differences being statistically significant (Delmas et al. 1997). Preliminary results of a study carried out by the Austrian Breast Cancer Group (Gnant et al. 2002) also suggest that 3-monthly zoledronic acid protects against bone loss associated with anastrozole therapy in premenopausal breast cancer patients receiving ovarian suppression with goserelin and either tamoxifen or anastrozole. If the initial findings are sustained, this schedule is likely to become widely used in standard care. Recently, however, Reid et al. (2002) studied the effects of even less frequent dosing of zoledronic acid in postmenopausal women with low bone density but no history of breast cancer. They found that the mean increase in BMD at lumbar spine and hip was 4.6 and 3.3% respectively, when the zoledronic acid was given as an annual 4 mg intravenous infusion. This was as effective as more frequent dosing and, because of this extremely convenient schedule, there is great interest in investigating the use of less frequent dosing of zoledronic acid to prevent bone loss in breast cancer patients.

Prostate cancer

Osteoporosis is also a common disease in men. For example, about 30% of all hip fractures occur in men and the associated mortality rate is greater than in women (Seeman 1999). One of the major causes of osteoporosis in men is hypogonadism (Bilezikian 1999).

The annual incidence for development of prostate cancer in the USA is approximately 198 000 (Greenlee et al. 2001). Many of these men are at risk of developing osteoporosis, largely because of the androgen-deprivation therapy (ADT) they receive for their cancer. ADT may be achieved either by bilateral orchiectomy or, increasingly, by the use of a gonadotrophin-releasing hormone (GnRH) agonist. These treatments are being introduced earlier and earlier in the course of the disease with the result that many men experience many years of androgen suppression. ADT results in substantially reduced serum concentrations of testosterone (to less than 5% normal level) and oestradiol (to less than 20% of normal level) (Leuprolide Study Group 1984, Smith et al. 2001). ADT is thus a major cause of hypogonadism in these patients.

It might be expected that androgen deprivation would lead to increased bone loss and increased fracture rate and this has been investigated in a number of recent studies in prostate cancer patients. As yet there appear to have been no large prospective studies of the relationship between fracture rate and ADT in prostate cancer patients and current evidence relies upon retrospective studies (Smith 2003). In one of these studies, in 235 patients with prostate cancer, fractures occurred much more frequently in those treated with bilateral orchiectomies (13.6%) compared with those not treated with ADT (1.1%, P < 0.001) (Daniell et al. 1997). Two studies investigating ADT using GnRH agonist in over 400 patients in total, provide strong evidence that ADT increases the incidence of osteoporotic fractures (Townsend et al. 1997, Hatano et al. 2000), but appropriate prospective trials are desirable to confirm and extend these findings.

For assessment of the effect of ADT on BMD, prospective studies have been performed, although patient numbers have been small (11–35). Significant loss in BMD has been observed within 6 months of commencement of a GnRH agonist (Diamond et al. 1998), and Smith (2003) has reviewed four prospective studies in non-metastatic prostate cancer patients receiving ADT (Eriksen et al. 1995, Maillefer et al. 1999, Daniell et al. 2000, Berutti et al. 2002). In the various studies, measurements after 1 year showed a mean reduction in BMD of between 0.6
and 9.6% at the hip and between 2.3 and 4.6% at the lumbar spine.

As the potential scale of the problem is being realised, attention is not only focusing on measuring bone density in such patients to assess those at risk, but also on therapeutic options such as bisphosphonates to prevent or treat therapy-related bone loss in prostate cancer. One of the first studies of a bisphosphonate in this area was the use of etidronate in 12 patients with disseminated prostate cancer, 6 months after treatment with a GnRH agonist (Diamond et al. 1998). The mean lumbar spine BMD decreased following treatment with a GnRH agonist, but increased by 7.8% ($P < 0.05$) 6 months after commencement of etidronate treatment. More recently, pamidronate has been shown to prevent loss in BMD in patients with locally advanced prostate cancer (Smith et al. 2001) and in a study in patients with prostate cancer and bone metastases, who had received ADT for at least 6 months, Diamond et al. (2001) showed that pamidronate significantly increased the BMD in the hip and spine.

A very recent, multicentre prospective study has evaluated the potent bisphosphonate, zoledronate, in locally advanced or recurrent prostate cancer (Smith et al. 2003). At 1 year, in the zoledronic acid arm, BMD increased by 5.3% at the lumbar spine and 1.1% in the total hip. In the placebo arm, the BMD decreased by 2% in the lumbar spine and 2.8% in the total hip. This important study demonstrates that zoledronic acid can not only maintain but actually increases BMD during ADT. These studies suggest that 3-monthly intravenous administration of potent bisphosphonates may be sufficient to maintain BMD, but further studies are needed to determine whether this translates to a corresponding advantage in reducing osteoporotic fractures.

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