Guidelines for the use of bisphosphonates in bone metastases

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Introduction

Bone is the most frequent site of distant relapse, accounting for around 40% of all first recurrences; among women with advanced metastatic breast cancer, 65% to 75% will develop bone metastases [1]. Bone metastases are associated with a variety of skeletal complications, also known as skeletal-related events (SREs), including bone pain requiring radiotherapy, pathological fractures, hypercalcaemia, and spinal cord compression, which complicate the clinical course and adversely affect quality of life. Therefore, the goals of treatment for bone metastases are to reduce pain and morbidity and to improve quality of life. Current palliative therapy for bone metastases includes primarily external beam radiotherapy, radionuclides, and bisphosphonates.

Bone is not an inert organ. During adult life, the normal bone undergoes a continuous remodelling process of resorption and formation. This is normally a tightly co-ordinated process which takes place in discrete "packets", known as bone remodelling units. Osteoclastic bone resorption takes place first 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. There is normally a fine balance between bone formation and bone resorption, so that the total amount of bone tends to remain fairly constant.

There are many factors involved in the regulation of bone resorption, including agents that enhance or inhibit proliferation of osteoclast progenitors. Of these, osteoprotogerin (OPG) is a natural inhibitor of osteoclast production and activity and is a member of the tumour necrosis factor superfamily. Recent studies on OPG and its binding to RANK (osteoclast differentiation factor) ligand have led to the possibility of new therapeutic agents, based on OPG. Hormonal effects also play a role and, in women, oestrogen is of key importance, a fact that is highlighted by the accelerated phase of bone loss around the menopause, corresponding to the decrease in oestrogen levels.

In the last ten years, the bisphosphonates have emerged as a valuable additional approach to the range of current treatments for metastatic breast cancer. All bisphosphonates are pyrophosphate analogues, characterised by a P–C–P containing central structure rather than the P–O–P of pyrophosphate, and a variable R′ chain which determines the relative potency, side effects and probably also the precise mechanism of action. The P–C–P backbone renders bisphosphonates resistant to phosphatase activity, and promotes their binding to the mineralised bone matrix. Following administration, bisphosphonates bind avidly to exposed bone mineral around resorbing osteoclasts, leading to very high local concentrations of bisphosphonate in the resorption lacunae (up to 1000 μM). On release from the bone surface, bisphosphonates are internalised by the osteoclast, where they cause disruption of the biochemical processes involved in bone resorption. These include destruction of the osteoclast cytoskeleton, disruption of the sealing zone at the bone surface, and loss of the ruffled border across which the hydrolytic enzymes and protons necessary for bone dissolution are normally secreted.

Bisphosphonates also cause osteoclast apoptosis, with the appearance of distinctive changes in cell and nuclear morphology. Although the precise molecular targets responsible for promoting this apoptosis are unknown, the bisphosphonates have recently been shown to inhibit enzymes of the mevalonate pathway which are ultimately responsible for events that lead to the post-translational modification of GTP-binding proteins such as Ras and Rho. Recent studies also suggest that bisphosphonates may have direct apoptotic effects on tumour cells [2].

Following the intravenous administration of a bisphosphonate, approximately 25–40% of the injected dose is excreted by the kidney and the remainder is taken up by bone. All bisphosphonates suffer from poor bio-availability when given by mouth. They must be taken on an empty stomach as they bind to calcium in the diet and may cause gastro-intestinal toxi-

cities such as nausea, vomiting, indigestion and diarrhoea.

Rationale for the use of bisphosphonates

Recent research has increased our understanding of the development of bone metastases as well as the continual interaction between cancer cells and active bone. Tumour cells in the bone marrow cavity secrete a variety of paracrine factors that stimulate bone cell activity. These include parathyroid hormone-related protein (PTHrP), interleukin-6 and endothelin-1. These result in disruption of the normal coupling signals between osteoblast and osteoclast function, with excessive osteolysis being the usual predominant consequence. It is now generally accepted that osteoclast activation is the key step in the establishment and growth of all bone metastases [3]. Biochemical data indicate that bone resorption is of importance not only in classic "lytic" disease but also in patients with sclerotic metastases. Indeed, the values of resorption markers in the latter are at least as high as those seen in patients with lytic metastases [4].

In addition to the well recognised release of bone cell activating factors from the tumour, it is now appreciated that release of bone-derived growth factors and cytokines from resorbing bone can both attract cancer cells to the bone surface and facilitate their growth and proliferation [3]. Inhibition of bone resorption could therefore have an effect on the development and progression of metastatic bone disease, and is an adjuvant therapeutic strategy of potential importance.

Biochemical markers of bone metabolism

Since bone remodelling is a metabolically dynamic process, the status of the process may be reflected in the levels of certain serum and urinary metabolites. In the case of metastatic bone disease, measurement of the levels of these metabolites may be exploited as biochemical markers (also known as bone markers) to monitor progress of the disease and the effectiveness of therapy, such as bisphosphonates.

Type I collagen is the predominant protein in bone, comprising 95% of the extracellular, non-mineral bone matrix. Procollagen, a protein rich in the hydroxylated amino acids hydroxyproline and hydroxylysine, is secreted from the osteoblast before undergoing cleavage of both the N-terminal and C-terminal regions to yield the native Type I collagen. Both the N-terminal fragment, known as Type I procollagen N-terminal propeptide (PINP) and the C-terminal fragment, known as Type I procollagen C-terminal propeptide (PICP) can be used as bone formation markers, as can other markers of osteoblast activity such as bone-specific alkaline phosphatase and osteocalcin.

Type I collagen is helical except for regions at the N-terminus and C-terminus which are known as N-telopeptide (Ntx) and C-telopeptide (Ctx). Different molecules of Type I collagen can be cross-linked through three hydroxylysine residues to form pyridinium rings (PYD), while deoxypyridinoline crosslinks (DPD) result from the combination of two hydroxylysine and one lysine residues. Breakdown of bone by osteoclasts releases bone mineral (primarily calcium and phosphate), as well as Type I collagen fragments such as Ntx, Ctx, PYD, DPD, hydroxyproline and other non-collagenous protein metabolites. These products of bone formation and breakdown appear in the serum and are excreted largely unchanged by the kidney. They can be determined quantitatively by a range of commercially available analytical techniques such as ELISA and HPLC.

Bisphosphonates for bone pain

Although radiotherapy is the treatment of choice for localised bone pain, many patients have widespread poorly localised bone pain and others will experience recurrence of bone pain in previously irradiated sites. The bisphosphonates provide an alternative treatment approach for the relief of bone pain. To obtain optimal analgesic effects, the intravenous route is necessary [5], at least until more potent and well tolerated oral bisphosphonates have been developed. The effect of bisphosphonates on pain seems to be independent of the nature of the radiographic appearance of the metastases, with sclerotic lesions responding similarly to lytic metastases. A direct comparison of intravenous ibandronate and single fraction radiotherapy for metastatic bone pain (RIB trial) is ongoing in the UK.

Bisphosphonates to prevent skeletal morbidity

Oral bisphosphonates

The absorption of bisphosphonates from the gut is poor, variable, and dramatically inhibited by food intake. Nevertheless, three randomised studies in advanced breast cancer have been performed, two stud-

Table 1
Effects of bisphosphonates on skeletal morbidity: results of randomised trials, breast cancer

Agent and route	*n*	Results	Investigator [Ref.]
Pamidronate 600 mg p.o. vs. control	161	Reduced skeletal morbidity rate (SMR) 94 vs. 52 events/100 women years ($P \leq 0.01$) 600 mg poorly tolerated No benefit with reduced dose (300 mg)	Van Holten [8,9]
Clodronate 1600 mg p.o. vs. placebo	173	Reduced SMR 305 vs. 219 events/100 woman years ($P \leq 0.001$)	Paterson [6]
Clodronate 1600 mg vs. control	100	Increased time to first SRE ($P = 0.015$) Improved quality of life	Kristensen [7]
Pamidronate 45 mg i.v. vs. control	295	Increased time to bone progression 168 vs. 249 days ($P = 0.02$)	Conte [12]
Pamidronate 90 mg i.v. vs. placebo	382	Reduced proportion experiencing SRE 65% vs. 46% ($P \leq 0.001$) Delay in first SRE 7.0 months vs. 13.1 ($P = 0.0005$)	Hortobagyi [14]
Pamidronate 60 mg i.v. vs. control	401	Median time to skeletal progression 9 vs. 14 months ($P \leq 0.01$)	Hultborn [13]
Pamidronate 90 mg i.v. vs. placebo	374	Reduced proportion experiencing SRE 67% vs. 56% ($P = 0.027$) Delay in first SRE 6.9 months vs. 10.4 ($P = 0.049$)	Theriault [15]
Ibandronate 2/6 mg i.v. vs. placebo	467	Reduced SMR with 6 mg dose. 2 mg ineffective SMR 2.18 vs. 1.61 ($P = 0.03$)	Body [20]
Ibandronate 20/50 mg p.o. vs. placebo	435	Reduced skeletal morbidity with oral ibandronate 20 and 50 mg 0.65 vs. 0.70 vs. 1.00 ($P = 0.023$)	Tripathy [11]
Zoledronic acid 4/8 mg i.v. vs. pamidronate 90 mg i.v.	1130	43% had a SRE with 4 mg zoledronic acid, compared to 45% with pamidronate. 20% risk reduction for an SRE ($P = 0.025$)	Rosen [18], Coleman [19]

ies (one placebo controlled) with clodronate [6,7] and one open study with pamidronate [8] (Table 1).

Paterson and colleagues 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) [6]. The patients in each study group were comparable in their clinical, radiographic and biochemical characteristics. 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 to 305 on placebo. Most of the benefit was accounted for by a reduction in hypercalcaemic episodes (28 vs. 52, $P \leq 0.01$) and the incidence of vertebral fractures (84 vs. 124 per 100 patient years, $P \leq 0.025$). There was no significant effect on non-vertebral fractures, radiotherapy requirements, changes in antitumour therapy or survival. A reduction in the absolute number of patients requiring spinal radiotherapy in the clodronate treated group (32 vs. 42) was seen, but there was no significant effect of clodronate treatment on the overall spinal radiotherapy requirements (75 vs. 89 courses per 100 patient years, P = NS). 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, the benefits seen were relatively small and the overall clinical utility of clodronate will remain poorly defined in advanced breast cancer until the publication of studies comparing clodronate with an aminobisphosphonate.

There are now no plans for oral pamidronate to be marketed. However, van Holten and colleagues reported an influential study of enteric-coated oral pamidronate [8]. 161 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 gastro-intestinal tolerability. This was not a placebo-controlled study and took 6 years to recruit, suggesting possible selection bias. 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 accrued

from the patients who received the initial poorly tolerated dose of 600 mg pamidronate a day [9].

Ibandronate is a highly potent amino-bisphosphonate that is licensed in Europe for the treatment of hypercalcaemia of malignancy, and 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 crosslink excretion [10]. 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 [11]. This new oral agent has obvious attractions to both patients and health care providers, but the place of ibandronate 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. randomised 295 patients with breast cancer and bone metastases to standard chemotherapy (generally cyclophosphamide and fluorouracil with one of methotrexate (CMF), epirubicin (FEC) or doxorubicin (FAC)) alone or chemotherapy plus intravenous pamidronate 45 mg every 3 weeks — a dose intensity of pamidronate which is now considered suboptimal [12]. A blinded, extra-mural review of the serial radiographs was performed. There were sufficient imaging studies available to assess response in bone in 224 patients. 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 who received pamidronate (249 vs. 168 days, $P = 0.02$) was identified. Sclerosis of lytic disease was noted in 53% and 44% of pamidronate and control patients, respectively. The other major endpoint of this trial was bone pain. A marked improvement in pain was seen more often in the pamidronate group (44% vs. 30%, $P = 0.025$), indicating that intravenous pamidronate adds to the symptom relief achieved by chemotherapy alone. There were also fewer complications in the pamidronate-treated group, including fewer long bone fractures (4 vs. 12), and a longer median time to requirement for radiotherapy (697 days vs. 571 days). Chemotherapy-related side-effects and overall survival were not influenced by pamidronate.

Similar results were reported in a Scandinavian trial [13]. 401 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 was given in the Conte 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 and placebo groups, respectively. No 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 to 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 [14,15]. These two studies were of similar design, with the exception of the systemic anticancer treatment at study entry, and 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 [14], 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 group ($P \leq 0.01$). The SMR was significantly lower throughout the study period, and at 24 months was 2.5 compared with 3.6 ($P \leq 0.001$). Benefits were maintained for at least 2 years. The proportion of pamidronate patients with an SRE(s) up to 24 months was 46% compared with 65% for the placebo patients ($P \leq 0.001$). 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 Eastern Cooperative Oncology Group (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 group for all of these endpoints. Quality of life was also better maintained in the pamidronate group. There was no difference in survival by treatment group, with the Kaplan–Meier estimate of median survival being 14.8 and 13.9 months for the pamidronate and placebo groups respectively ($P = 0.82$).

In the endocrine study [15], 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 group, and 10 months in those receiving pamidronate ($P \leq 0.049$). The benefits of pamidronate were slower to appear than in the chemotherapy study, but again the effect was maintained for at least two years. The SMR at 24 months was 2.4 compared with 3.8 ($P = 0.008$), and the proportion of pamidronate patients experiencing an SRE(s) was 56% compared with 67% for the placebo 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 with the Kaplan–Meier estimate of median survival being 23.1 and 23.5 months for the pamidronate and placebo groups, respectively ($P = 0.69$).

Zoledronic acid is the most potent bisphosphonate in clinical development. In hypercalcaemia of malignancy zoledronic acid has been shown to be superior to pamidronate [16]. In normocalcaemic patients, a dose-dependent reduction in deoxypyridinoline, a specific marker of bone resorption was identified. These biochemical responses were at least as large as those previously reported after infusions of pamidronate 90 mg, 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 [17].

Recently, a large international, multicentre, stratified, randomised double-blind, phase III trial of zoledronic acid compared to pamidronate in the treatment of malignant bone disease in patients with breast cancer has been completed [18]. 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. 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.

1130 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 three to four weeks. Initially, zoledronic acid was administered as a 5-min infusion in 50 ml of 0.9% saline or 5% dextrose. This was amended to 15-min infusion in 100 ml of 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 has been published [18]. 44–46% of patients experienced at least one SRE. This was similar across all three treatment groups. Differences that were seen included a reduction in radiotherapy requirements between the zoledronic acid 4 mg and pamidronate groups (15% vs. 20%; $P = 0.031$). This difference was most marked in the breast cancer patients receiving hormonal therapy (16% vs. 25%; $P = 0.022$). More recently, the final 25-month data have become available [19]. This has shown superiority for zoledronic acid 4 mg 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 0.799; $P = 0.025$).

There were no significant differences between the bisphosphonate treatments in pain scores, analgesic use or performance status. Pain was reduced in all groups, and analgesic use 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-study. At all time points, the urinary marker of bone resorption NTX was significantly less in the zoledronic acid 4 mg group compared to the pamidronate group (e.g. 64% vs. 57% below baseline at the end of one 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 fre-

quency 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 SRM with ibandronate 6 mg [20]. Additionally, improvements in pain and quality of life were clearly demonstrated at this dose. Full publication of these data are anticipated in 2003.

Optimum use of bisphosphonates in metastatic bone disease

Criteria for when in the course of metastatic bone disease bisphosphonates should be started and stopped 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 a SRE, and the ease with which the patient can attend treatment (or be treated by a domiciliary service) [21].

Current international guidelines 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, bisphosphonate treatment for bone metastases from breast cancer is probably unnecessary, 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 SMR but not necessarily abolishing it, the criteria for stopping their administration are different from those used for classical antineoplastic drugs. They should not be stopped when a skeletal event occurs, or when there is progression in bone.

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 is currently 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 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 [22]. 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 a SRE/death than those with Ntx below this level ($P < 0.01$). Thus a more cost-effective use of bisphosphonates might be to reserve them until patients have an 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.

Prevention of bone metastases

Encouraging animal studies with a variety of animal tumour models and a range of bisphosphonates have shown inhibition of bone metastasis development and a reduction in tumour burden within bone [23]. More recently, several clinical trials have been reported using the relatively low potency oral bisphosphonate, clodronate (Table 2). In the largest study, 1079 women with primary operable breast cancer were randomised to receive either clodronate 1600 mg daily or placebo for two 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, $P = 0.127$) [24]. However, during the two 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%, $P = 0.047$).

Table 2
The use of adjuvant clodronate in primary operable breast cancer trials

Number of patients	Period of clodronate treatment (years)	Occurrence of bone metastases (clodronate vs. placebo)	Occurrence of non-bone metastases (clodronate vs. placebo)	Deaths (clodronate vs. placebo)	Author [Ref.]
1079	2	At 2 years, 2% vs. 5% $P = 0.016$ At >2 years, 10% vs. 10% $P = 0.73$	At >2 years, 21% vs. 24% $P = 0.26$	At 2 years, 8% vs. 8% (approx.) At 5 years, 17% vs. 22% $P = 0.047$	Powles et al. [24]
299	3	21% vs. 17% $P = 0.27$	43% vs. 25% $P = 0.009$	At 5 years, 30% vs. 17% $P = 0.01$	Saarto et al. [27]
302	2	14% vs. 24% $P = 0.044$	16% vs. 26% $P = 0.091$	At 5 years, 10% vs. 22% $P = 0.002$	Diel et al. [25,26]

In all cases, 600 mg clodronate was given orally. Average follow-up time was 4.5–5.5 years.

In a second study, Diel et al. 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 [25]. 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 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 group (19 (13%) vs. 42 (29%) patients, $P < 0.001$). These results have subsequently been updated [26] 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 and Diel studies must, however, be viewed in the light of a further trial which produced conflicting results. Saarto et al. [27] 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 and control groups, respectively). Additionally, the development of non-skeletal recurrence was significantly higher in the clodronate group (60 (40%) vs. 36 (24%) patients, $P = 0.0007$) and, most importantly, the overall five-year survival was significantly lower in the clodronate 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 and Saarto studies cancel each other out and probably reflect the usual heterogeneity of results seen in relatively small studies of adjuvant treatment.

To identify a definite adjuvant role for bisphosphonates will require further large randomised studies. The National Surgical Adjuvant Breast Project (NSABP) have recently started a placebo controlled trial of oral clodronate ($n \geq 3000$) in an attempt to resolve the value or otherwise of adjuvant clodronate. Adjuvant trials are just beginning with zoledronic acid. It is hoped that the added potency of zoledronic acid may have beneficial effects, not only through the inhibition of bone resorption, but also through direct effects on tumour cells in the bone marrow. There is increasing evidence, from a range of cell line experiments, that zoledronic acid can inhibit tumour cell adhesion and invasion [28]. Additionally, zoledronic acid promotes apoptosis both directly and in synergy with paclitaxel [29]. These effects are mediated through the mevalonate pathway using the same molecular pathway that aminobisphosphonates exploit to inhibit osteoclast function. Finally, there are experimental data from animal models that indicate that zoledronic acid can suppress angiogenesis [30].

Conclusions

The management of bone metastases requires an experienced multi-disciplinary team to ensure timely diagnosis and the appropriate integration of local and systemic treatments. The effects of tumour cells

on bone cell function, especially osteoclast activity, underpin the rationale for the use of bisphosphonate treatment to reduce skeletal morbidity. These bone-specific treatments are now an accepted part of routine clinical management.

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