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The Clinical and Cost Considerations of Bisphosphonates in Preventing Bone Complications in Patients with Metastatic Breast Cancer or Multiple Myeloma

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Abstract

The bisphosphonates are potent inhibitors of osteoclast-mediated bone resorption and are now the treatment of choice for the management of hypercalcaemia of malignancy. The incidences of hypercalcaemia and other skeletal complications (bone pain, pathological fracture) remain high despite apparent responses to systemic therapy, with particularly high event rates in women with advanced skeletal metastases of breast cancer. This review focuses on studies addressing

the long-term efficacy of bisphosphonates to reduce skeletal complications in breast cancer (5 studies) and multiple myeloma (4 studies), with particular reference to controlled studies of sufficient magnitude and duration to allow confidence in the estimation of efficacy.

Bearing in mind the limitations of differences in trial design and the lack of direct studies comparing drugs, adequate exposure to a bisphosphonate reduces the incidence of skeletal complication by 30 to 40% in both breast cancer and multiple myeloma. Oral clondronate and intravenous pamidronate have similar efficacy in both diseases, but the duration of efficacy may differ between drugs. Both agents have shown intriguing survival benefits in subgroups of patients.

The numbers needed to treat (NNT) to prevent a skeletal complication during one year are lowest in metastatic skeletal disease in breast cancer (NNT < 8) but also compare very favourably with other disease for patients with recurrent non-skeletal breast cancer or multiple myeloma (NNTs 7 to 31 depending on the complication to be prevented). Treatment costs of both breast cancer and multiple myloma are driven by inpatient and outpatient hospital visits so that bisphosphonate regimens should be developed that reduce both.

Further research is required to determine if subgroups of patients can be better identified that will derive particular benefit, or perhaps no benefit at all, from bisphosphonate therapy. It is not known whether more potent bisphosphonates will deliver greater clinical efficacy in the future.

Bone destruction and its clinical sequelae are a significant cause of morbidity in patients with cancer. Furthermore, despite progress in anti-tumour therapy and the use of more aggressive regimens, the incidence of skeletal disease remains high and, in contrast with visceral metastases, is frequently associated with prolonged survival. Bone pain is observed in both osteosclerotic and osteolytic disease, but hypercalcaemia and pathological fracture are most frequently associated with osteolysis. Regardless of the tumour type, there is compelling evidence that this bone destruction is mediated by normal osteoclasts (bone-resorbing cells) stimulated by factors produced by the tumour or by stromal cells in response to the presence of tumour.[1,2]

The bisphosphonates are potent inhibitors of osteoclast-mediated bone resorption (for review, see Fleisch[3,4]). At least 10 bisphosphonates are currently available or in development. The newer bisphosphonates have markedly higher potency than earlier agents but, currently, there are no data to suggest that they will differ in their ultimate therapeutic effect. The greatest experience in malignancy-associated bone disease has been gained with the bisphosphonates, etidronate, clodronate, ibandronate and pamidronate.

These agents are now the treatment of choice for the management of hypercalcaemia of malignancy. Their efficacy in this setting has prompted studies to examine their ability to decrease the incidence of skeletal complications in malignancies, particularly breast cancer and multiple myeloma. This review focuses on studies addressing the long term efficacy of bisphosphonates in breast cancer and multiple myeloma, with particular reference to controlled studies of sufficient magnitude and duration to allow confidence in the estimation of efficacy.

1. The Burden of Skeletal Complications in Malignancy

Tumours commonly associated with the development of skeletal metastases are shown in table I. Breast cancer, prostate cancer and multiple myeloma account for the majority of cases but this varies from country to country. Approximately 30 000 new cases of breast cancer are diagnosed each year in the UK. Of those developing recurrent disease, 30% will develop their first metastases in

bone and skeletal disease will be present in approximately 80% at death. Women with predominantly skeletal disease survive significantly longer than those with visceral disease (particularly liver and CNS metastases). A similar burden of disease is observed in prostate cancer in men. Multiple myeloma affects approximately 3000 new patients each year in the UK with skeletal destruction being a prominent feature at the time of diagnosis.[6]

The most common skeletal complications of neoplasia are hypercalcaemia, bone pain and fractures at both axial and appendicular sites. In contrast with studies documenting the prevalence of skeletal complications in malignancy, there are few data from prospective studies describing the incidence of such complications during the course of the disease. Some estimate of the incidence can be derived from the control arms of placebo-controlled studies of bisphosphonates in myeloma and breast cancer metastatic to bone (table II).[7-17] There are obvious difficulties in extrapolating such data to the routine clinical setting since selection criteria for studies can exclude patients with severe or mild disease, leading, to under- or over-estimation of the incidence, respectively. Furthermore, the methods of reporting incidence are not uniform across the studies. Bearing these limitations in mind, the incidence of skeletal complications is high despite apparent responses to systemic therapy (table II). The incidence and event rates are particularly high in women with advanced skeletal metastases in breast cancer, where approximately 25 to 40% of patients will require radiotherapy for bone pain, 25 to 50% will sustain incident vertebral fractures and a similar proportion may sustain nonvertebral fractures.

Hypercalcaemia is also common, occurring in approximately 30% of patients annually, although the incidence of severe hypercalcaemia (serum calcium adjusted for albumin >3.00 mmol/L) is somewhat lower (approximately 10%). However, it should be noted that the incidence of hypercalcaemia and pathological vertebral fracture is also substantial in women with recurrence apparently limited to soft tissue and visceral sites.

The incidence of complications in myeloma appears to be lower than in patients with skeletal disease in breast cancer but new vertebral fractures occur in about 15 to 30% of patients annually and peripheral fractures occur in approximately 10%.

Multiple complications within an individual are common so that estimates based on events per 100 patient years (table II) exceed estimates of incidence computed as the proportion of patients with each event. The majority of studies that have reported event rates and the number of patients affected, show that the event rates are usually 2- to 3-fold higher (table II).

2. Rationale for Use of Bisphosphonates

Skeletal destruction in osteolysis is mediated by a disruption of normal bone remodelling which accounts for much (>95%) of normal skeletal turnover. Since bone remodelling is a surface-based event, remodelling activity is greater on cancellous than on cortical surfaces. Remodelling of cancellous bone is largely mediated by the activity of bone resorbing cells (osteoclasts) and bone form-

Table I. Features of malignancies affecting the skeleton in the UK

Type of malignancy	New cases per year in UK[5]	Proportion developing skeletal metastases (%)	Median survival[a] (months)
Breast	31 843	80	21
Prostate	15 705	85	30
Thyroid	956	50	–
Kidney	4464	30	–
Lung	37 312	44	4
Multiple myeloma	2860	–	33

a From development of bone metastases.

– indicates data not available.

Table II. Estimated incidences of skeletal complications in patients with multiple myeloma and advanced breast cancer. Data derived from placebo arms of double-blind, controlled trials

Reference	Malignancy	Number of patients	Population	Median duration (months)	Percentage of patients developing complication annually (event rate/100 patient-years)				
					pain[a]	hyper-calcaemia	fracture		
							any	vertebral	nonvertebral
Belch et al.[7]	Myeloma	173	At first treatment	44	– (–)	5 (–)[b]	– (–)	– (–)	8 (–)
Lahtinen et al.[8]	Myeloma	336	At first treatment	24	– (–)	– (–)	– (–)	20 (–)[c]	12 (–)
Brincker et al.[9]	Myeloma	300	At first treatment	18	– (26)	– (13)[d]	– (59)	– (38)[c]	– (21)
Berenson et al.[10,11]	Myeloma	392	On chemotherapy	18	24 (–)	5 (–)[b]	21 (–)	15 (–)	6 (–)
McCloskey et al.[6]	Myeloma	536	At first treatment	31	–	3 (5)[b]	– (39)	31 (35)[e]	3 (4)
Paterson et al.[12]	Breast	173	Bone metastases	14	41 (89)	30 (52)	– (164)	50 (124)[e]	23 (40)
Kanis et al.[13]	Breast	133	Non-bone metastases	20	12 (19)	8 (12)	– (67)	17 (61)[e]	5 (6)
Hortobagyi et al.[14,15]	Breast	382	Bone metastases	10	23 (84)	8 (19)[b]	25 (174)	25 (74)[e]	39 (100)
Theriault et al.[16]	Breast	371	Bone metastases	16	28 (90)	6 (17)[b]	44 (210)	22 (80)[e]	31 (140)
Hultborn et al.[17]	Breast	404	Bone metastases	12	28 (40)	9 (9)[f]	–	–	16[g] (20)

a Pain recorded as number of radiotherapy episodes.
b Serum calcium levels >3.00 mmol/L.
c Subjective radiological reading.
d Serum calcium levels >2.75 mmol/L.
e Using vertebral morphometry (but different criteria).
f Requiring treatment (level not defined).
g Pelvis and long bones only.
– indicates not recorded.

ing cells (osteoblasts). In health, the activity of these 2 cell types are closely linked so that resorption is followed by formation (the process termed 'coupling') and the amount of bone resorbed is replaced by an equal amount of newly formed bone (the process termed 'balance').

In tumour-associated bone disease, the most frequent disturbances include increases in the rate of turnover, loss of coupling, and an imbalance between resorption and formation. Osteolysis in breast cancer is mediated by increased activity of osteoclasts.[1] There are several candidates for osteoclast activation in breast cancer in addition to the estrogen deficiency induced by chemotherapy, tamoxifen or ovarian ablation. Approximately one-third of women with breast cancer have evidence for parathyroid-like activity[18] related to the expression by tumour tissue of parathyroid hormone-related protein and its endocrine secretion.

Increased osteoclast activity is observed in close proximity to myeloma cells[19-21] and appears to be correlated with the tumour cell burden.[21] Recent evidence suggests that at least 3 cytokines are implicated in the increased osteoclastic activity of myelomatosis, including tumour necrosis factor-β, interleukin (IL)-1 and IL-6.[2,22-25] It is important to realise that cytokines and growth factors released during increased bone turnover may also promote myeloma cell growth and proliferation.[2] The effect of corticosteroids to reduce the synthesis

of these cytokines may explain their value in the treatment of myeloma.[26-28]

In addition, bone is lost because of an imbalance within each remodelling sequence, usually as a result of a decreased amount of new bone formed within erosion cavities combined with an increase in resorption depth. Where bone turnover is additionally accelerated, skeletal losses are amplified. At cancellous sites, the increased depth of erosion transects trabecular plates and rods of bone, thus removing the surface on which new bone formation can occur ('uncoupling'). In addition, the activity of osteoblasts may be reduced, an effect seen frequently in myeloma[19,21] where possible mechanisms include the production of inhibitory factors by myeloma cells.[29,30] Similar relative suppression of osteoblasts has also been described in breast cancer.[31,32]

In addition to malignancy-induced bone loss, women with breast cancer are particularly vulnerable to osteoporosis. At the time of first diagnosis the prevalence of osteoporotic fractures in women with breast cancer approximates that of an age- and gender-matched control population.[33,34] Thereafter, the incidence of vertebral fractures is more than 3-fold higher than in age-matched controls using morphometric criteria to define vertebral fracture[33] and more than 2-fold higher based on radiologists' reports.[34] Premenopausal women who receive adjuvant treatment are at special risk because of early menopause[35-39] or adjuvant ovarian ablation.[40] Tamoxifen, although preventing bone loss in postmenopausal women,[41,42] appears to cause bone loss in premenopausal women, presumably by competitive agonist activity at the estrogen receptor.[37] Moreover, in postmenopausal women fracture risk may even increase after stopping adjuvant endocrine treatment.[43] The effects of treatment of myeloma on bone mass have not received as much attention but beneficial effects have been observed particularly at axial sites.[44]

Irrespective of whether focal or generalised osteolysis occurs, the pathogenesis for increased bone resorption involves disturbances in the normal remodelling mechanisms. It is of relevance that the disruptions induced in remodelling are mediated largely, if not exclusively, by authentic bone cells rather than tumour cells themselves.

3. Long Term Clinical Studies with Bisphosphonates

Although a large number of studies have examined the effects of bisphosphonates in neoplastic bone disease, many have only involved small numbers of patients or examined short term efficacy, and others have been nonblind, uncontrolled studies. Recently, several controlled studies have addressed the use of bisphosphonates early in the course of breast cancer to try to reduce the development of bone metastases but they have not been included in this review of efficacy, which has been restricted to use in patients with more advanced disease. For the purposes of this review, we have focused on randomised, placebo-controlled studies with total sample sizes of more than 100 patients followed for at least 6 months. These can be divided into studies of multiple myeloma (n = 4) and studies in women with metastatic breast cancer (n = 5). The single large double-blind, placebo-controlled study of etidronate in myeloma has not been included as etidronate is not licensed for long term use in malignancy.[7] The studies are reviewed briefly in this section.

3.1 Myeloma

The study by Lahtinen et al.[8] evaluated the efficacy of oral clodronate 2400 mg/day over a 2-year period in 336 patients with stage I to III multiple myeloma. Systemic therapy comprised melphalan and prednisolone with nonresponders subsequently receiving treatment with the MOCCA regimen [methyl] prednisone, vincristine, cyclophosphamide, melphalan and lomustine (CCNU)]. Study medication was given as 800mg (2 capsules) 3 times daily and commenced 4 weeks after the first course of melphalan-prednisolone.

Clodronate treatment was associated with a significant 50% reduction in radiographic progression of osteolytic disease (12 *vs* 24% of patients, p = 0.026), a 25% reduction in the incidence of

vertebral fracture (30 *vs* 40%, nonsignificant). The proportion of patients becoming pain-free was higher in the clodronate group (30 *vs* 15%) but this was not statistically significant from placebo. The incidence of nonvertebral fractures was similar in both groups. The number of deaths was lower during clodronate treatment (54 *vs* 68) but this was also not statistically significant.

In the study by Berenson et al.,[10,11] 392 patients were randomised to receive either placebo or pamidronate 90mg intravenously administered at 4-week intervals over a total follow-up of 21 cycles of treatment. Inclusion criteria comprised patients with stage III multiple myeloma, an unchanged chemotherapy regimen for at least 2 months and an estimated life expectancy of at least 9 months. Patients with recent skeletal complications or renal impairment were excluded. Eligible patients were stratified according to their systemic therapy with stratum 1 consisting of those on initial treatment or with disease controlled by a single drug regimen and stratum 2 comprising those with second-line or subsequent chemotherapy regimens.

Treatment over the first 9 cycles of treatment was associated with a marked reduction (44%) in the incidence of pathological fracture (vertebral and nonvertebral sites), a 36% reduction in radiotherapy requirements to bone but no significant effect on the incidence of severe hypercalcaemia.[11] The reduction in fracture risk was significant in stratum 1 but a trend was observed in patients with more advanced disease. The reduction in radiotherapy requirement was confined to those with more advanced disease (stratum 2).

In contrast, the incidence of pathological fracture and skeletal radiotherapy was similar or greater in the pamidronate group during a further 12 cycles of treatment.[10] For example, in the Kaplan-Meier estimates analysis, the proportion of patients with any skeletal event increased by 17% between 12 and 21 cycles (33 to 50%) in the pamidronate group compared with an increase of 10% (48 to 58%) in the placebo group.[10] Indeed, there is a progressive waning in the apparent efficacy of pamidronate as judged by the relative risks of events in each of the 3-month periods from 9 months onwards.[45] Thus, while the proportion of patients with any skeletal complication remained lower in the stratum 1 patients (37 *vs* 47%), the difference between treatments was no longer significant. In stratum 2, only the requirement for radiotherapy remained significantly lower after 21 cycles but most of this reduction had occurred in the first 9 cycles of treatment. Interestingly, survival in the stratum 2 patients was significantly increased in the pamidronate group [median 21 *vs* 14 months, $p = 0.041$ adjusted for baseline serum β2-microglobulin levels and ECOG (European Cooperative Oncologic Group) performance status]. New or worsening anaemia was noted more frequently in pamidronate-treated patients during the last 12 cycles of therapy (38 *vs* 25%, $p = 0.017$).

McCloskey et al.[6] studied a total of 536 patients with newly diagnosed multiple myeloma randomised to receive placebo or clodronate 1600 mg/day in addition to systemic chemotherapy [largely ABCM regimen (doxorubicin, carmustine {BCNU}, cyclophosphamide, melphalan) with or without prednisolone]. Patients over 75 years and those who had received previous chemotherapy were excluded. Treatment with clodronate began 2 to 6 weeks after chemotherapy and was continued indefinitely or until the patient showed evidence of progressive osteolytic lesions or hypercalcaemia requiring treatment other than fluid replacement.

Treatment with clodronate was associated with a 50% decrease in the proportion of patients with severe hypercalcaemia (5.1 *vs* 10.1%, $p = 0.064$) and a similar reduction in reported nonvertebral fractures (6.8 *vs* 13.2%, $p = 0.036$). Fewer patients receiving clodronate sustained incident vertebral fractures (38 *vs* 55%, $p = 0.012$) and patients also lost less height over 3 years compared with those receiving placebo (2.0 ± 0.7 *vs* 3.4 ± 0.7cm, $p = 0.011$). The incidence of pathological fracture and hypercalcaemia were consistently lower in the clodronate groups throughout 4 years of follow-up. The frequencies of back pain and poor performance status were significantly lower at relapse in clodronate than in placebo-treated patients (10.9 *vs*

19.9%, $p < 0.05$, and 18.3 *vs* 30.5%, $p < 0.025$, respectively). There was no difference in survival between the clodronate- and placebo-treated patients. However, in a *post hoc* subgroup analysis, patients without vertebral fracture at entry, clodronate was associated with increased survival (median survival 1362 *vs* 1094 days, $p < 0.05$).

In the study by Brincker et al.,[9] 300 patients with newly diagnosed, previously untreated multiple myeloma were randomised to receive placebo or oral pamidronate 300 mg/day (2 divided doses of 150mg). Patients were excluded if they had a poor prognosis (survival expected to be <3 months), active peptic ulceration or renal impairment. Systemic treatment consisted mainly of melphalan and prednisolone with a subset of patients also receiving interferonα-2b. Study treatment started after the first course of chemotherapy and the median duration of treatment was 18 months.

Treatment with pamidronate was associated with a significant reduction in bone pain (0.58 *vs* 0.80 mean events/year, $p = 0.04$) and a significant prolongation of the time to first severe bone pain (1003 *vs* 565 days, $p = 0.005$) as judged by the investigators. However, patients' perceptions of pain and analgesic consumption were similar in the 2 treatment groups. The number of pathological fractures and requirement for surgery were lower in the pamidronate-treated patients, but the differences were not statistically significant. Despite a reported nonsignificant difference in the incidence of vertebral collapses (0.29 *vs* 0.38 mean events/year), height loss was noted to be significantly less in the pamidronate group (1.5 *vs* 3cm, $p = 0.02$). Survival was similar in patients receiving pamidronate or placebo.

3.2 Advanced Breast Cancer

Paterson et al.[12] studied 173 women with bone metastases randomised to receive clodronate 1600 mg/day or an identical placebo. The median time from the onset of distant metastases to study entry was approximately 1 year and systemic endocrine or chemotherapy were similar in both groups. Placebo-treated patients were more likely to have metastatic disease confined to bone only at entry, but this did not alter the subsequent incidence of events or survival.

Clodronate significantly reduced the incidence of hypercalcaemia (28 *vs* 52 events/100 patient years, $p < 0.01$) and vertebral fractures (84 *vs* 124 events/100 patient years, $p < 0.025$). The requirement for skeletal radiotherapy was reduced but not statistically significant with the benefit being most marked at axial sites. There was no difference in the incidence of nonvertebral fractures but the event rate was low. Overall, there was a 27% decrease in the number of morbid skeletal events (219 *vs* 305 events/100 patient years).

In the study by Hortobagyi et al.,[14,15] 382 women with stage IV cancer and at least 1 predominantly lytic metastasis at least 1cm in diameter were included in the study. All patients were receiving chemotherapy at entry, had an estimated life expectancy greater than 9 months and had not sustained any skeletal events in the 2 weeks before study entry. Patients received either placebo or pamidronate 90mg intravenously at 4-week intervals and treatment was continued for up to 2 years.

In the first year of treatment,[14] pamidronate reduced the incidence of nonvertebral fractures (20 *vs* 30%, $p = 0.02$), radiotherapy to bone (19 *vs* 33%, $p = 0.002$), hypercalcaemia (6 *vs* 12%, $p = 0.03$) and the requirement for surgery (4 *vs* 10%, $p = 0.02$). There was no apparent effect on the proportion of patients sustaining vertebral fractures (23 *vs* 19%, $p = 0.37$) but the time to first skeletal complication was longer in the pamidronate group.

During the second year of treatment,[15] the incidence of nonvertebral fracture and surgery remained lower in the pamidronate-treated patients. In contrast, the incidences of hypercalcaemia, radiotherapy to bone and vertebral fracture derived from the Kaplan-Meier estimates between 15 and 24 months were similar or higher in the pamidronate group than with placebo (4 *vs* 3% for hypercalcaemia, 17 *vs* 13% for vertebral fracture and 14 *vs* 7% for radiotherapy to bone).[15] The overall incidence remained lower in the pamidronate

group because of the marked effect in the first year of treatment.

The primary aim of the double-blind study by Kanis et al.[13] was to examine the effect of oral clodronate 1600 mg/day on the incidence of skeletal metastases. 133 women with recurrent breast cancer but no radiographic or scintigraphic evidence of skeletal metastases were studied for up to 3 years.

The number of skeletal complications was relatively low, but clodronate was associated with a significant reduction in the event rate (71 *vs* 97 events/100 patient years, $p < 0.01$). Trends for reductions in the incidence of all individual skeletal complications (hypercalcaemia, vertebral fracture, nonvertebral fractures and radiotherapy to bone) were reported in the clodronate group. More importantly, treatment with clodronate was associated with a nonsignificant reduction in patients developing skeletal metastases (23 *vs* 28%) but the number of metastases was markedly reduced (32 *vs* 63, $p < 0.005$). There was no difference in survival between the treatment groups.

In the study by Theriault et al.,[16] 371 women with stage IV cancer and at least 1 predominantly lytic metastasis at least 1cm in diameter were included. All patients were receiving hormonal therapy at entry, had an estimated life expectancy greater than 9 months and had not sustained any skeletal events in the 2 weeks before study entry. Patients received either placebo or pamidronate 90mg intravenously at 3- to 4-week intervals and treatment was continued for up to 2 years.

In the first year of treatment, pamidronate reduced the incidence of radiation to bone ($p = 0.005$). A trend for reduction was observed in pathological fractures ($p = 0.108$), largely mediated by a nonsignificant reduction in nonvertebral fractures. There was no significant effect on the proportion of patients sustaining vertebral fractures, spinal cord compression, hypercalcaemia or surgery to bone. The time to first skeletal complication was longer (10.4 *vs* 6.9 months, $p = 0.049$) in the pamidronate group.

By the end of the second year of treatment, pamidronate treatment was associated with a significantly lower cumulative incidence of hypercalcaemia (4 *vs* 10%, $p = 0.036$) with nonsignificant reductions in radiation to bone (31 *vs* 40%, $p = 0.058$), nonvertebral fracture (36 *vs* 40%, $p = 0.498$) and surgery to bone (7 *vs* 11%, $p = 0.245$). The proportion of patients sustaining vertebral fractures or spinal cord compressions were also similar in the 2 groups. It is of interest to note that the differences in incidence rates between the pamidronate and placebo groups that did occur were largely observed in the first 12 cycles of treatment.

404 women with bone metastases (lytic or blastic) in breast cancer were randomised to receive intravenous pamidronate 60mg every 4 weeks ($n = 201$) or a placebo infusion ($n = 203$) in the study by Hultborn et al.[17]. All patients were receiving systemic therapies at the discretion of the attending physician and had an estimated life expectancy greater than 3 months. Previous bisphosphonate therapy led to exclusion from the study. Treatment was envisaged for up to 2 years with the median time on allocated treatment being 12 and 11.5 months in the pamidronate and placebo groups, respectively.

Pamidronate use was associated with a significant reduction in the cumulative incidence of all skeletal symptom events (pain increase, hypercalcaemia, fractures and pareses). The time to these events was significantly longer in the pamidronate group (11.8 *vs* 8.4 months, $p = 0.0058$). However, only symptoms of skeletal progression (essentially pain, 151 *vs* 214 events) and hypercalcaemia requiring treatment (5 *vs* 17 events) were significantly reduced by pamidronate. There was no significant effect on long bone or pelvic fractures (38 *vs* 39), spinal pareses (5 *vs* 6), palliative radiotherapy requirements (73 *vs* 81) or stabilising surgery (13 *vs* 17). There were no differences in the number of patients requiring changes in anti-tumoral therapies or survival (18.3 months).

4. Efficacy of Bisphosphonates in Reducing Skeletal Complications

It is important to note that to date there have been no direct comparative studies of long term bisphosphonates in malignancy. Differences in patient selection, concomitant therapies and the assessment of outcome complicate any attempt to draw comparisons between the various trials. These limitations need to be borne in mind when the efficacy in each of the clinical trials is expressed in a unified way, e.g. as a percentage reduction in the incidence of skeletal complications.

4.1 Prevention of Hypercalcaemia

The definition of hypercalcaemia has varied between studies, with thresholds for serum calcium levels ranging from 2.6 (adjusted for serum albumin) to 3.0 mmol/L (usually referred to as severe hypercalcaemia). However, mild hypercalcaemia is not always actively treated, so that some studies have utilised the higher threshold (e.g. 3.0 mmol/L), a level at which clinical intervention (usually rehydration, corticosteroids if appropriate and possible use of bisphosphonates) is required. All but 2 of the 9 placebo-controlled studies have shown marked reductions in the incidence of hypercalcaemia during treatment with a bisphosphonate (table III).

Surprisingly, intravenous pamidronate did not reduce the incidence of hypercalcaemia in patients with multiple myeloma,[10,11] whereas the same regimen or a lower dose effectively reduced the incidence in patients with metastatic breast cancer at least in the first year of therapy.[14,15,17] This may be a chance finding due to a relatively low number of events in the myeloma study. Alternatively, it may indicate that the inhibition of bone resorption by this regimen in myeloma is suboptimal, possibly requiring an increased dose or an increased frequency of administration. It is of interest that the effects of intravenous pamidronate on other skeletal complications appeared to be most marked within the first 9 months of the study. Event rates

Table III. Reduction in skeletal complications of malignancy in double-blind, placebo-controlled studies of clodronate and pamidronate. Values in parentheses show the p-values from the relevant studies

Reference	Tumour	n	Agent	Dose	Population	Estimated reduction in event rate (%)			
						radiotherapy	hyper-calcaemia	fracture	
								vertebral	nonvertebral
Lahtinen et al.[8]	Myeloma	336	Clodronate	2400mg	At first treatment	NE (NS)	NR (NS)	–25 (NS)	0 (NS)
McCloskey et al.[6]	Myeloma	536	Clodronate	1600mg	At first treatment	NE (NS)	–60 (0.06)	–45 (0.001)	–45 (0.025)
Brincker et al.[9]	Myeloma	300	Pamidronate	300mg	At first treatment	–27 (NS)	–62 (NS)	–24 (NS)	–43 (NS)
Berenson et al.[10]	Myeloma	392	Pamidronate	90mg 4-weekly	On chemotherapy	–27 (0.06)	+13 (NS)	–41 (0.005)	NE (NS)
Paterson et al.[12]	Breast	173	Clodronate	1600mg	Bone metastases	–16 (NS)	–46 (0.01)	–32 (0.025)	–20 (NS)
Kanis et al.[13]	Breast	133	Clodronate	1600mg	Soft tissue metastases	–20 (NS)	–39 (NS)	–22 (0.1)	–75 (0.1)
Hortobagyi et al.[15]	Breast	382	Pamidronate	90mg 4-weekly	Bone metastases	–49 (0.001)	–67 (0.005)	–39	–34 (0.001)
Theriault et al.[16]	Breast	371	Pamidronate	90mg 3-/4-weekly	Bone metastases	–45 (0.011)	–65 (0.037)	–23 (0.43)	–36 (0.36)
Hultborn et al.[17]	Breast	404	Pamidronate	60mg 4-weekly	Bone metastases	–10 (NS)	–71 (<0.05)	NE	–3 (NS)[a]
Weighted mean reduction in multiple myeloma						–27	–37	–37	–32
Weighted mean reduction in breast cancer						–31	–63	–30	–28

a Pelvic and long bone fractures only.

n = number of patients; **NE** = not evaluable from the data presented; **NR** = not reported; **NS** = not statistically significant.

thereafter did not differ between placebo- and pamidronate-treated patients.

Continuous administration of oral bisphosphonate appears to consistently reduce the incidence of hypercalcaemia, although not all studies have had sufficient power to detect this at a statistically significant level (table III). In the myeloma study of Lahtinen et al.,[8] the total number of hypercalcaemic events was not recorded. However, mean serum calcium values were significantly lower in clodronate-treated patients at 1 year (2.40 *vs* 2.45 mmol/l, $p < 0.05$) and 2 years (2.43 *vs* 2.46 mmol/l, $p < 0.05$) of follow-up. This occurred despite the baseline mean values being higher in the clodronate group (2.66 *vs* 2.60 mmol/l). The prevalence of hypercalcaemia (serum calcium adjusted for albumin >2.65 mmol/L) was recorded at baseline, after 1 year and at the end of the 2-year follow-up. There was no difference in the prevalence at the earlier time points, but at 2 years hypercalcaemia was 36% lower in patients receiving clodronate 2400 mg/day (4.6 *vs* 7.2%, nonsignificant).[8]

It is of interest that in an unpublished analysis of compliance from the study of Paterson et al.,[12] the effect of partial and full compliance was similar on pathological fracture and radiotherapy requirements, but partially compliant patients had a higher incidence of hypercalcaemia. These observations support the notion that hypercalcaemia may be the first complication to manifest in patients with inadequate suppression of bone resorption.

In summary, adequate exposure to a bisphosphonate appears to reduce the incidence of hypercalcaemia with estimated reductions of 63 and 37% in the number of events in breast cancer and multiple myeloma, respectively (table III).

4.2 Pathological Fracture

The acquisition of data on fractures differs for vertebral and nonvertebral fractures. Whereas most nonvertebral fractures are clinically obvious, vertebral fractures may be difficult to detect. Assessment of the latter can be undertaken by visual assessment of changes in shape between radiographs but vertebral fractures frequently involve subtle changes. The major limitation of purely visual assessments is that they are very subjective and lead to poor concordance between classifications by different radiologists. For this reason, information on vertebral fractures is increasingly obtained using morphometric evaluations of radiographs.[46] Such approaches involve the measurement of vertebral heights on lateral spine radiographs and compare vertebral height ratios with appropriate reference data. The attraction of such approaches is that they standardise the definition of vertebral fracture and, by choosing more stringent criteria for deformity, increase the specificity of the evaluations.[47-49] The outcome of differences in detection of vertebral and nonvertebral fracture is that the effects of treatments on each type of fracture are usually reported separately.

4.2.1 Nonvertebral Fracture

Fractures at all sites other than the thoracic and lumbar spine are usually included in the category of nonvertebral fractures. The actual sites of fracture are rarely recorded in published reports and it is therefore not possible to comment on issues such as the method of recording simultaneous multiple fractures (e.g. do multiple rib fractures count as 1 event or more?) and further fracture or re-fracture within a bone. The site of fracture has a significant impact on the patient and healthcare resources.[50] For example, long bone fractures usually require hospitalisation and surgical fixation[50] and this has a significant bearing on the costs of therapy. It is usual practice to exclude fractures, particularly long bone fractures, which occur as the result of significant trauma (e.g. road traffic accidents). It should also be noted that the incidence of long bone fractures is relatively low compared with vertebral fracture in both breast cancer and myeloma (table II) so that the sample sizes of most studies are too small to detect significant effects.

Six of the 9 studies highlighted in this review support the conclusion that long term treatment with a bisphosphonate reduces the incidence of nonvertebral fractures. Two studies have shown statistically significant reductions in the proportion of patients sustaining nonvertebral fractures.[6,15]

A second study with clodronate in breast cancer also showed a borderline effect.[13] Nonsignificant decreases were observed in patients with myeloma with oral pamidronate[9] and in patients with breast cancer with oral clodronate.[12] No apparent effect was observed in 2 studies of myeloma[8,10] and 1 breast cancer study.[17] The reasons for these results are unclear. In addition to the usual possibilities of inadequate dose and poor compliance, the explanation may relate to differences in recording of nonvertebral fractures.

As stated previously, the costs of long bone fractures are greater as they require hospitalisation and surgical fixation. Three studies have reported either a reduction in long bone fractures (82% effect)[6] or in the requirement for surgery (58 and 55%, respectively).[9,15] Reductions in appendicular fractures have been reported with bisphosphonates in other diseases, particularly postmenopausal osteoporosis.[51,52]

4.2.2 Vertebral Fracture

Vertebral fractures are one of the most frequent complications of malignancy (tables II and III). They may result directly from the metastatic process or alternatively reflect the effect of systemic treatment on gonadal function and bone loss.[33,35,37,39] Regardless of the mechanism, bisphosphonate therapy should be expected to decrease the incidence of vertebral fracture. Comparison between the studies in this review is complicated by the lack of uniformity in the method of defining both prevalent and incident vertebral fractures. All evaluable studies demonstrate a 20 to 45% reduction in vertebral fracture event rates and in 3 of the 8 studies the reduction in risk was significant.[6,10,12] In all of the other studies, similar reductions in the incidence of vertebral fractures were observed and the lack of significance may partly relate to the type of analysis undertaken. For example, Lahtinen and colleagues[8] observed a 25% reduction in patients sustaining vertebral fractures but did not report the total number of fractures in each group. Hortobagyi et al.[15] reported that intravenous pamidronate had no significant effect on reducing the number of patients reporting fractures but the total numbers of fractures were 39% lower during pamidronate therapy.

It is likely that much of the discrepancy between studies lies in the lack of consensus on the definition of vertebral fracture. This lack of standardisation also raises the question of the clinical relevance of vertebral fractures recorded during clinical trials. There are obvious clinical correlates of vertebral fracture that can be examined but unfortunately have not been reported in the majority of clinical trials. These include back pain and height loss.[49] In women with advanced metastatic breast cancer, the requirement for radiotherapy to the spine is about 2-fold higher than that to the peripheral skeleton and there is a clear association between incident vertebral fractures defined morphometrically and the requirement for spinal radiotherapy.[12] Therefore, it is likely that the reduction in radiotherapy requirements or back pain reported in most studies is at least partially mediated by a decrease in the incidence of clinically relevant vertebral fractures.

A clear relationship exists between vertebral fractures and height loss with a progressive increase in height loss occurring with increasing numbers of prevalent and/or incident vertebral fractures.[49] Prevention of clinically relevant vertebral fractures should therefore decrease height loss and this has been demonstrated in myeloma using clodronate 1600 mg/day over 3 to 4 years from initial diagnosis.[6] A reduction in height loss has also been reported during oral pamidronate therapy.[9] Despite a reported nonsignificant difference in the incidence of vertebral collapses, height loss was noted to be significantly less in the pamidronate group (1.5 *vs* 3cm, $p = 0.02$) suggesting problems with the definition of vertebral collapses rather than the efficacy of the drug. There was no difference in reported height loss between etidronate-treated patients and placebo-treated patients in the study by the National Cancer Institute of Canada Clinical Trials Group.[7] The latter study also showed no effect of treatment to reduce deterioration in the vertebral index, a subjective grading system for vertebral deformity.

The conclusion by Brincker and colleagues,[9] reiterated by other authors, that oral pamidronate is ineffective in myeloma is almost certainly incorrect and results from a combination of low event rates (thus low statistical power) and inaccurate assessments of incident vertebral fractures.[9,53] In summary, a significant reduction of pathological fracture incidence (vertebral and/or nonvertebral fractures) is reported in 5 of the 9 studies in this review. The estimated treatment effects are very similar for both vertebral (30 to 37% reduction) and nonvertebral fractures (28 to 32% reduction) and are also similar in breast cancer and myeloma. The conclusion that long term bisphosphonate therapy can reduce the incidence of vertebral and nonvertebral fractures is supported by the available data.

4.2.3 Bone Pain

Like vertebral fracture, the assessment of bone pain is also fraught with difficulties, particularly in long term studies, and has rarely been performed in an adequate manner. The relationship between reported pain, direct pain assessments and radiotherapy requirements is complex and is illustrated by the observations of Hultborn and colleagues.[17] In their study in patients with metastatic breast cancer, pamidronate use was associated with a highly significant reduction ($p = 0.006$) in symptoms of skeletal progression, largely reflecting pain, but had no significant effect on the requirement for palliative radiotherapy and no significant reduction in bone pain assessed by visual analogue scale.[17]

The effect of high dose intravenous or intramuscular bisphosphonates to treat bone pain in malignancy in the short term is well documented.[54-58] However, long term intervention studies have demonstrated that the incidence and severity of bone pain can be reduced. In myeloma, for example, the proportion of patients who were pain-free at 24 months of follow-up in the Finnish study increased from 24% at entry to 54% during clodronate therapy ($p < 0.001$) compared with an increase from 29 to 44% in the placebo group ($p < 0.01$).[8] However, the difference between the groups was not statistically significant. Similarly, in the Medical Research Council (MRC) VIth Myeloma Trial,[6] the increased frequencies of back pain and poor performance status associated with disease relapse were significantly lower in clodronate than in placebo-treated patients (10.9 *vs* 19.9%, $p < 0.05$, and 18.3 *vs* 30.5%, $p < 0.025$, respectively).[6] Reductions in bone pain and analgesic consumption have also been noted in small double-blind studies and nonblind, controlled studies in myeloma.[20,59,60] Intermittent intravenous pamidronate has also shown reductions in pain scores at least during the first 9 cycles of treatment.[11]

In a combined analysis of the studies by Hortobagyi et al.[14,15] and Theriault et al.[16] of pamidronate in breast cancer, bone pain was assessed by a pain score that reflected both severity and frequency of pain, and quality of life was measured using the Spitzer Index.[61] The treatment was associated with a significant reduction in the deterioration of bone pain between the first and last visits for each patient (0.72 ± 3.49 *vs* 1.65 ± 3.40 in pamidronate and placebo groups, respectively, $p < 0.001$). The deterioration in quality of life was also less marked in the pamidronate group (-1.80 ± 2.81 *vs* -2.13 ± 2.63), although this was not statistically significant ($p = 0.088$).[61]

Many studies, particularly those in breast cancer, have utilised skeletal radiotherapy requirements as a surrogate for pain assessment (tables II and III). Decreases in radiotherapy requirements have been observed during treatment with oral and intermittent intravenous bisphosphonates.[12,14,15] In myeloma, intermittent pamidronate appears to decrease the requirements for radiotherapy in patients with more advanced disease receiving second-line chemotherapy but had no effect in patients with less advanced disease.[10,11] The latter outcome is similar to that observed in the MRC Myeloma Trial with clodronate where the event rate for radiotherapy was low.[6]

4.2.4 Survival

In breast cancer, liver and CNS metastases exert a greater influence on survival than skeletal metastases, thus perhaps limiting the success of skeletal therapies in improving survival. Theoretical con-

cerns have been raised about the possible detrimental effects of bisphosphonates to increase non-skeletal metastases. Such concerns have arisen from the belief that a metastasis that is prevented from seeding to bone may implant in visceral sites, leading ultimately to a decrease in patient survival. Two studies with newer, highly potent bisphosphonates in an animal model of breast cancer have suggested that such a scenario may be possible.[62,63] However, these findings are not reflected in the available data from human studies.

The majority of studies in this review have either shown a nonsignificant trend towards increased survival or no difference in survival between bisphosphonate- and placebo-treated patients. In the small double-blind, controlled study of Elomaa and colleagues,[64,65] survival was significantly increased during bisphosphonate treatment in patients with advanced breast cancer primarily as a result of a reduction in deaths associated with skeletal complications. However, despite a significant reduction in bone metastases, a beneficial effect on visceral metastases and survival has not been observed in a large, double-blind, placebo-controlled study with clodronate in women with primary breast cancer.[66]

However, this does not mean that certain subgroups of patients might derive a survival benefit from bisphosphonate therapy. Indeed, an increased survival in women with bone micrometastases at first diagnosis has recently been reported from a nonblind, controlled study with clodronate in which the reduction in visceral metastases was similar to that observed in bone metastases.[67] In addition, an increased median survival of 8 months was observed in women aged 50 years of age or less in the trial of pamidronate reported by Theriault and colleagues.[16] As the authors quite rightly acknowledge, this may be overstated as it represents a univariate *post hoc* subgroup analysis and there was no overall effect on survival. The mechanism by which pamidronate may confer a survival advantage in younger women is unclear and draws no speculation from the authors.[16,61] In addition, there is no comment on the effects on survival in older patients in whom one might expect to see a potentially detrimental effect of pamidronate given the overall similar survival in the 2 treatment groups. Further multivariate analyses are required to adjust for any other prognostic variables which might have influenced these observations.

Soft tissue disease is not a concern in the majority of patients with myeloma and several studies have suggested that inhibition of skeletal disease may be associated with improved survival in certain subgroups of patients. For example, there was no difference in overall survival between the clodronate and placebo treated patients in the VIth MRC Trial but in patients without vertebral fracture at entry, clodronate was associated with increased survival (median survival 1362 *vs* 1094 days, $p < 0.05$).[6] Intermittent pamidronate has been associated with improved survival of similar magnitude in patients receiving second-line chemotherapy.[10] Finally, in a prospective, nonblind, controlled study of 341 patients, treatment with clodronate from diagnosis in patients with stage I to III myeloma was associated with a longer time to radiographic progression (14.6 *vs* 11.2 months) and a significant survival advantage (median survival 46 *vs* 36 months, $p < 0.009$).[68] The nonparallel design of the latter study hinders the conclusion that the effect was entirely due to clodronate, but it is important to note that the same chemotherapy regimen was used throughout the period of study.

It is important to remember that the survival advantages of bisphosphonates have only been apparent in subgroup analyses and ideally require confirmation in appropriately designed clinical trials.

5. Costs of Long Term Bisphosphonate Therapy in Malignancy

Long term bisphosphonate therapy in malignancy is commonly regarded as relatively expensive. A total of 4 economic studies have been published, 3 of which have addressed the use of oral clodronate,[50,69,70] and another the use of intrave-

nous pamidronate.[71] Again, comparisons between studies are hindered by differences in the measurement of study outcomes and the use of multiple outcomes prevents attempts at comparative cost-effectiveness analyses. Furthermore, most studies have not collected information on quality of life to allow derivation of costs per quality-adjusted life year (QALY).

The use of clodronate in the Finnish Myeloma Study[8] was not found to significantly increase treatment costs in an analysis published by Laakso and colleagues.[70] They noted that the benefits of clodronate on the skeleton (a 50% reduction in patients with progressive osteolysis) were associated with a nonsignificant 12% reduction in hospital costs due to a lower requirement for hospitalisation. The concomitant use of clodronate was associated with a 22% increase in overall costs of treatment [278 *vs* 227 Fmk (Finnish markka) daily].

A more robust analysis of the costs of treatment with clodronate in myeloma was undertaken more recently[50] using data derived from the MRC VIth Myeloma Trial.[6] Using a state-transition model for the first 4 years of the study and resource utilisation data from trial investigators, the authors estimated the mean costs of each transition state and each skeletal complication. Clodronate was found to reduce the mean costs of skeletal complications by 50% from £2860 to £1376 over the 4 years of treatment. The costs of clodronate itself increased the overall management costs by £3377 (from £19 557 to £22 934), an increase of 17%. This estimate was shown to be robust (£2605 to £4150) [1997] by sensitivity analysis.[50] It should be borne in mind that the additional cost does not take into account any additional benefits over and above a reduction in the costs of skeletal complications, most notably any gains in quality of life.

In an analysis of hospital costs associated with osteolytic metastases, Biermann and colleagues[69] suggested that significant savings could be made if clodronate reduced the incidence of skeletal complications by at least 20%. The studies included in this review suggests that such a reduction in hypercalcaemia, bone pain and pathological fractures is realistically achieved during bisphosphonate therapy. However, in a recent cost-effectiveness analysis of pamidronate usage in metastatic breast cancer, the authors concluded that the treatment is associated with high incremental costs per adverse event avoided.[71] This analysis was based on information on event rates and efficacy of pamidronate derived from the studies of Hortobagyi et al.[14,15] and Theriault et al.[16] with a number of well documented assumptions being used in the model. The resulting cost-effectiveness ratios were $108 200 and $305 300 (1998 $US) per QALY in women treated with chemotherapy or hormonal therapy, respectively. The costs of pamidronate and costs associated with pathological fractures that were asymptomatic or treated conservatively were the major cost drivers in the model. A reduction in drug costs by 38% would have resulted in a significant reduction in skeletal events at no extra cost (cost equivalence) and the authors proposed a number of mechanisms by which this might be achieved.[71] The suggestions that a dose reduction or an increase in treatment intervals could be beneficial are difficult to recommend given the available data. However, it should be noted that half of the cost reduction could be achieved if the need for an intravenous infusion could be avoided altogether.

Hospitalisation is the major cost driver in the management of patients with multiple myeloma, accounting for 32% of the total cost over the first 4 years after diagnosis.[50] In addition, outpatient and day-ward attendances accounted for a further 28% of the overall cost of managing patients, whereas chemotherapy accounted for only 5%. Therefore, treatment regimens that reduce the use of secondary care resources will reduce the overall cost of managing patients with multiple myeloma even if they do not lead to cost savings.

However, the achievement of cost savings depends not only on the reduction by treatment but in the incidence of these complications in the population being treated. Thus, the failure of Bruce et al.[50] to reproduce Biermann's[69] finding of potential cost savings probably results from the lower

incidence of skeletal complications in the MRC VIth Myeloma Trial.[6] It is certainly clear that the numbers needed to treat (NNT) will be greater in multiple myeloma and early breast cancer than in women with established skeletal metastases in breast cancer (table IV). However, even in myeloma the NNTs compare very favourably with the use of treatments as secondary prevention in other diseases, such as stroke reductions in patients with a previous stroke or transient ischaemic attack.[72,73]

6. When to Introduce and Discontinue Therapy

None of the studies carried out to date have specifically addressed the questions of when bisphosphonate therapy should be introduced and discontinued. However, it is clear that long term bisphosphonate therapy shows benefits when given early in the course of the disease[6,8,66-68] or at later stages in breast cancer and myeloma.[10-14]

In myeloma, the progression of skeletal disease is probably at its most active at or around the time of diagnosis, as judged by biochemical markers of bone turnover and the high prevalence of baseline fractures. These observations combined with the apparent survival benefit in patients with a lower burden of skeletal disease at diagnosis suggest that treatment should probably be commenced as early as possible. The higher incidence of breast cancer makes the possible use of bisphosphonates in all women at the time of diagnosis problematic and perhaps undesirable. Targeting of women at high risk of skeletal metastases would seem a reasonable approach (larger tumours, axillary node involvement, bone marrow involvement) but the optimal duration of therapy is not yet known. In women with advanced skeletal metastases, it might also be possible to target individuals at highest risk of skeletal complications but no studies have yet addressed this specific question. Guidelines have been proposed and, while they appear sensible, it is important to note that they have not been validated.[74]

The decision of if and when to stop treatment is also difficult. It is important to remember that myeloma and metastatic breast cancer are presently incurable diseases and osteolysis will continue throughout their course. The speed of offset of the action of the bisphosphonates is unknown but is likely to be greater in malignancy than in other diseases associated with lower rates of bone turnover. Two double-blind, controlled studies in patients with breast cancer have suggested that the risk of skeletal disease increases within a few months after stopping bisphosphonate treatment.[65,66] A third controlled but nonblind study suggests a more prolonged effect.[67] At present it would seem reasonable to continue treatment with bisphosphonates indefinitely.

There has been some concern about resistance developing to bisphosphonates in the later stages of malignant disease but there is little or no evidence that this is a clinically relevant problem. An increased incidence of skeletal events has been noted in only a few studies. For example, in patients with myeloma receiving intermittent pamidronate the incidence of fracture was similar or slightly higher than in those receiving placebo during the later stage of treatment and contrasted with

Table IV. Estimates of numbers needed to treat (NNT) for 1 year to prevent 1 skeletal complication (hypercalcaemia, vertebral or nonvertebral fracture). The risk is computed as the mean event rate per 100 patient-years, weighted by study size from table II. The relative risk (RR) during treatment with a bisphosphonate is derived from table III. Numbers in parentheses represent the NNT if the risk of event was 50% higher or 50% lower than estimated (or, alternatively, if the reduction in risk was 50% greater or 50% lower)

Disease	Hypercalcaemia			Vertebral fracture			Nonvertebral fracture		
	risk	RR	NNT	risk	RR	NNT	risk	RR	NNT
Myeloma	9	0.63	30 (20-60)	36	0.63	8 (5-15)	10	0.68	31 (21-63)
Breast cancer									
soft tissue metastases only	12	0.61	21 (14-43)	61	0.78	7 (5-15)	6	0.25	22 (15-44)
bone metastases	20	0.37	8 (5-16)	86	0.70	4 (3-8)	81	0.72	4 (3-8)

a marked reduction during earlier cycles of treatment.[10,11] The reasons for this are not clear but are more likely to represent either an insufficient dose or frequency in patients with advancing disease rather than resistance to treatment. The possibility that more frequent exposure may prevent this waning of effect is supported by the observation that there did not appear to be a reduction in the efficacy of oral clodronate, administered daily, in the MRC VIth Myeloma Trial.[6] A remote possibility is that long term pamidronate, like etidronate, may impair mineralisation of bone and this might mask the benefit accruing from inhibition of bone resorption.[7,75]

It is important to remember that the occurrence of complications is reduced but not totally prevented by bisphosphonates. The onset of a complication in a treated patient should therefore be regarded as an indication to consider more aggressive bisphosphonate therapy rather than to deem it a treatment failure and to discontinue therapy. The use of biochemical markers of bone resorption to monitor osteolysis and adequacy of response to bisphosphonates is undergoing evaluation and may improve clinical decision-making.[54,76,77]

7. Dose, Safety and Tolerability

In contrast with long term etidronate, mineralisation defects are rare during treatment with pamidronate and have not been observed with clodronate therapy in breast cancer and myeloma.[36,78-81] Furthermore, fractures heal normally during drug administration.[64,82]

The inhibition of bone resorption by pamidronate and clodronate consistently lowers serum calcium values but symptomatic hypocalcaemia is rare. The concomitant use of other specific inhibitors of bone resorption [e.g. other bisphosphonates, calcitonin and plicamycin (mithramycin)] has shown more rapid rather than more profound responses in patients with hypercalcaemia.[83]

Despite concerns that intravenous bisphosphonates may impair renal function when given by bolus injection,[84] no systematic change in renal function has been observed during intravenous pamidronate or after oral treatment with clodronate as judged by sequential measurements of serum creatinine levels. Clodronate, pamidronate and alendronate have been associated with transient rises in hepatic transaminases but the increases in alanine amino transferase (ALT) and aspartate amino transferase (AST) are not marked and rarely exceed twice the laboratory reference range.[85]

Oral administration of pamidronate is associated with a higher incidence of upper gastrointestinal adverse events.[9,86] Similar events have been reported with alendronate, another aminobisphosphonate.[87] The majority of controlled prevention studies have therefore used either intermittent intravenous infusions of pamidronate, or oral clodronate given daily.

7.1 Pamidronate

Pamidronate is a more potent inhibitor of bone resorption than clodronate and studies suggest that the duration of the effect after intravenous therapy in hypercalcaemia is longer with pamidronate.[88] Many clinical studies indicate that it is rapidly effective in suppressing bone turnover. The usual dose of pamidronate has been 90mg given as a single dose intravenously at 3- to 4-week intervals, a dose that has largely derived from studies of the median duration of action in hypercalcaemia. Some uncertainty remains about the optimal dose and frequency of administration,[89] but the 90mg dose has shown significant beneficial effects in reducing and/or delaying skeletal morbidity in controlled studies.[10,11,13,14]

A potential advantage of intravenous pamidronate is enhanced compliance with treatment but this has not been formally documented. A 4-weekly cycle may coincide with visits to hospital for chemotherapy and this route of administration is therefore attractive. However, for long term treatment the necessity for intravenous infusion may be costly and inconvenient.

Unwanted effects of pamidronate include transient fever, bone pain, episcleritis, iritis and thrombophlebitis at the infusion site.[90,91] It does not readily impair the mineralisation of bone and has

not shown adverse effects on bone formation during oral use in myeloma.[92] However, osteomalacia has been reported after multiple high dose intravenous therapy in Paget's disease of bone.[75] The use of pamidronate and other aminobisphosphonates is associated with a transient leucopenia and a rise in body temperature, chills, myalgia and malaise during the early phase of treatment.[93-96] Lymphopenia occurs more consistently than fever and is evident by 24 hours, followed later by a fall in neutrophil counts. The effect is usually transient and the clinical significance of decreases in subpopulations of circulating lymphocytes (natural killer cells, T cells, and CD4+ and CD8+ T cell subsets) is not clear. It is thought to represent an acute phase reaction and is associated with the expected changes in serum zinc levels and in acute phase proteins.[93,94] Finally, there may be a greater degree of bone marrow suppression in patients with myeloma receiving long term intravenous pamidronate with more frequent development or worsening of anaemia.[10]

7.2 Clodronate

The largest, controlled studies with clodronate in preventing skeletal complications in malignancy have used 1600 to 2400 mg/day orally. Like pamidronate, the optimal dose is not well established but a 4-week dose response study has been undertaken in osteolysis of malignancy. In this double-blind, placebo-controlled study, a daily dose of clodronate 1600mg decreased urinary hydroxyproline and calcium creatinine ratio significantly, whereas a less complete response was observed with a dose of 400 mg/day.[97] A larger dose (3200 mg/day) had no added effect over the 1600mg dose. Persistence of inhibition of bone resorption with longer exposure has been shown directly by histological assessment after 6 months treatment with clodronate 1600 mg/day in women with recurrent breast cancer.[81]

All bisphosphonates are poorly absorbed from the gastrointestinal tract and this has been cited as a reason to avoid their use in malignancy.[53] However, this conclusion is countered by a large body of evidence demonstrating efficacy of oral bisphosphonates in tumour-induced osteolysis and other metabolic bone diseases including Paget's disease of bone and osteoporosis (postmenopausal and corticosteroid-induced).[51,52,98-100] In one study in 24 healthy volunteers, intestinal absorption of clodronate was 2.36% and generally lies between 1 to 3% of the administered dose.[101,102] This is approximately 3-fold higher than the aminobisphosphonates such as alendronate.[103]

The time to reach peak serum concentration is approximately 0.5 hours, suggesting an upper gastrointestinal site of absorption and a post-dose interval of 30 to 60 minutes is recommended before consuming anything other than water. It should be noted that the rate of absorption and bioavailability is reduced to one-third when clodronate is taken half an hour after a fat-loaded meal. This effect may even persist up to 2 hours after a meal,[104] so that a single daily dose before breakfast appears the most appropriate regimen. Despite variable intestinal absorption between and within individuals, the variability in integrated urinary excretion of clodronate falls progressively over time with repeated doses of clodronate.[105] This suggests that despite low oral bioavailability, the exposure to clodronate during long term treatment is relatively constant.

As expected with an orally administered bisphosphonate, the incidence of lower gastrointestinal adverse effects is higher, with diarrhoea being reported significantly more frequently during clodronate treatment than placebo. The frequency of diarrhoea appears to be highest in the early months of treatment and is usually of mild degree with little or no impact on patients wishing to discontinue treatment.[6,38] Unlike oral pamidronate and alendronate, the frequency of upper gastrointestinal adverse effects is not increased during therapy with clodronate[38,106] and, in particular, there appears to be no increase in the frequency of oesophagitis.[9,87] These observations have led to the clinical use of doses of clodronate taken during the night when patients awaken for

other reasons, a suggestion that may improve compliance but has not been formally tested.

No idiosyncratic or systematic effect has been found in haemoglobin, white blood cell count or platelets during treatment with clodronate.

8. The Future: Prevention of Skeletal Metastases

The prevention of skeletal metastases is probably the ultimate goal of bone-active therapies. Increasing evidence from animal studies suggests that bisphosphonates administered shortly before or concurrently with the injection of tumour cells can reduce the number and extent of skeletal metastases.[62,63] In women with breast cancer and skeletal metastases, an apparent effect of clodronate to reduce further skeletal metastases was observed by Elomaa and colleagues[64,65] during treatment over a 1-year period and the effect appeared to wane during a further year of follow-up off treatment. This small, double-blind, placebo-controlled study was of insufficient size (a total of 34 patients) to exclude statistical error or biases resulting from patient selection. In addition, the study involved women with widespread skeletal metastases which complicates the interpretation of isotope bone scans and radiographs, particularly in women receiving systemic therapies and bone active agents. For this reason, studies examining the incidence of metastases in women without evidence of skeletal involvement are preferable.

In a study of 133 women with soft tissue or visceral recurrence of breast cancer in whom there was no apparent scintigraphic or radiographic evidence of skeletal disease at study entry, clodronate 1600 mg/day was found to significantly reduce the number of detectable skeletal metastases by approximately 50%.[13] There was no significant reduction in the number of patients developing metastases but the study was of insufficient power to detect such an effect. Nevertheless, clodronate appeared to provide a degree of skeletal protection by inhibiting the progression of existing micrometastases and/or preventing the seeding of new metastases to bone.

Two recent nonblind, controlled studies have given conflicting results. In the study of Saarto and colleagues,[106] 299 women with primary breast cancer and nodal involvement were randomised to receive clodronate 1600 mg/day for 3 years (n = 149) or no bisphosphonate treatment (control group, n = 150). All patients received adjuvant therapy: premenopausal CMF (cyclophosphamide, methotrexate, fluorouracil) chemotherapy and postmenopausal antiestrogens with a minimum follow-up time of 5 years. Bone metastases were detected in 39 (26%) patients in the clodronate group and in 27 (18%) in the controls ($p = 0.09$). The development of nonskeletal metastases (visceral and local) was significantly higher in the clodronate group at 67 (45%) compared with the controls at 41 (27%) [$p = 0.001$]. The overall survival and disease-free survival were significantly lower in the clodronate group compared with the controls.

A contrasting effect was observed in the other prospective, randomised, nonblind study of clodronate.[67] The presence of marrow micrometastases at the time of diagnosis was the main inclusion criteria for this study and a total of 302 women with newly diagnosed breast cancer were recruited. All patients had undergone iliac crest bone marrow aspiration at baseline and were deemed to be at high risk of skeletal metastases because of the presence of breast cancer cells detected by an immunocytological marker. In addition to systemic therapy, 157 patients were randomised to receive treatment with clodronate 1600 mg/day with treatment lasting for 2 years and an additional follow-up for 1 year. 145 women didn't receive clodronate and were followed as controls. Treatment with clodronate was associated with a 55% reduction in the incidence of distant metastases (bone or visceral) [13 *vs* 29%, $p < 0.001$]. Bone metastases were observed in only 8% of clodronate-treated patients compared with 17% of controls, representing a reduction of 53% ($p = 0.003$). Intriguingly, treatment with clodronate was also associated with a reduction in visceral metastases (8 *vs* 19%, $p = 0.003$) and a significantly better survival with only

6 patients (4%) having died compared with 22 patients (15%) in the control group (p = 0.001). It is important to note that essentially all of the reduction in metastases occurred within the first 12 to 14 months and the incidence thereafter was similar in the treated patients and controls. In addition, there appears to be little or no offset of action suggesting that the early effect persists for at least 5 years, more consistent with a prevention of metastases than a simple prolongation of the metastases-free interval.

The results from these 2 studies are difficult to reconcile, but the nonblind nature of the studies needs to be borne in mind. Furthermore, at least in the study of women with node positive breast cancer, there is evidence of a chance mismatch of the 2 study groups at baseline with the placebo group having a significantly greater proportion of patients with progesterone-receptor positive tumours and a similar trend for oestrogen-receptor positivity. These discrepancies could certainly influence differences in tumour-responsivity between the treatment groups in favour of the placebo arm.

However, it is perhaps of most relevance that a much larger prospective, double-blind, placebo-controlled study has also examined the issue of prevention of bone metastases.[66] Almost 1100 women with primary operable breast cancer and no evidence of distant metastases were randomised in a double-blind study to receive 2 years of treatment with oral clodronate 1600 mg/day or an identical placebo.[66] Study treatment could commence within 6 months of primary diagnosis and patients are being followed for at least 5 years. The effect of clodronate to reduce treatment-induced bone loss in a subgroup of patients with repeated bone density measurements over 2 years has recently been published.[38] An interim analysis has shown a 33% reduction in the incidence of bone metastases in clodronate-treated patients [Hazard ratio 0.67, 95% confidence interval (CI): 0.43 to 1.06] with the effect being most marked over the treatment period (Hazard ratio 0.51, 95% CI: 0.30 to 0.88). In contrast with the nonblind study of Diel et al.,[67] the relapse rate for non-osseous metastases was the same in clodronate and placebo treated patients (Hazard ratio 0.93, 95% CI: 0.0.69 to 1.24). There was a nonsignificant trend for improved survival in clodronate-treated women (69 *vs* 80 deaths) at the cut-off date for the interim analysis.[38]

The results of this double-blind study suggest that clodronate can reduce the incidence of skeletal metastases in women with primary breast cancer with no adverse effect on visceral metastases. Further studies are required to determine the optimal duration of treatment and how to best target the treatment to women at highest risk of metastases.

9. Conclusion

The rationale for the use of bisphosphonates in tumour-induced osteolysis is well established.[79] The evidence to date supports the view that although systemic chemotherapy is effective in reducing bone resorption, bone destruction continues in myeloma and breast cancer so that supplementary bone protection should be considered. Long term treatment with clodronate or pamidronate has been shown to modify the progression of skeletal disease. Despite the reservations of some authors, the efficacies of oral and intravenous bisphosphonates seem similar in breast cancer and myeloma.[53] The NNTs, particularly in metastatic breast cancer, compare very favourably with the use of treatments as secondary prevention in other diseases.

Further research is required to determine if we can better identify subgroups of patients who will derive particular benefit, or perhaps not benefit at all, from bisphosphonate therapy. The use of biochemical markers of bone resorption and formation to evaluate the risk of skeletal disease and its response to treatment also requires further study.

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