Pergamon

European Journal of Cancer, Vol. 34, No. 2, pp. 263–269, 1998

Printed in Great Britain
0959-8049/98 $19.00+0.00

PII: S0959-8049(97)10136-8

Original Paper

Bisphosphonates

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INTRODUCTION

THE AIM of this short review is to provide an update on the use of currently available bisphosphonates in cancer patients and to summarise their current indications for the treatment of tumour-induced hypercalcaemia (TIH) and of metastatic bone pain in advanced disease and for the prevention of the complications of breast cancer and multiple myeloma-induced osteolysis. Data with newer bisphosphonates for the treatment of TIH will also be briefly reviewed to indicate what we can expect from these potent drugs.

All bisphosphonates are characterised by a P-C-P bond in their structure, which promotes their binding to the mineralised bone matrix and their subsequent inhibitory effects on bone resorption. The rest of the bisphosphonate molecule varies according to the structural modification of the side chain, features which determine their relative potency, side-effects and probably also their precise mechanism of action. Bisphosphonates localise preferentially to sites of active bone formation and resorption. They can act directly on mature osteoclasts, decreasing their bone resorption activity, notably by lowering H^+ and Ca^{++} extrusion and modifying the activity of various enzymes [1–3]. Alternatively, recent findings suggest that osteoblasts, or at least those lining the bone surface, could also be essential target cells for bisphosphonates with secondary effects on the osteoclasts, probably by changing the secretion of an inhibitor of osteoclast recruitment [4]. Moreover, bisphosphonates can induce osteoclast apoptosis and this effect could also be mediated through the osteoblasts. The relative importance of this osteoblast-dependent inhibitory activity of bisphosphonates compared with a direct inhibition of osteoclast activity or secretory capacity remains to be determined.

Irrespective of the precise mechanism(s) of action, bisphosphonates have been successfully used in the treatment of conditions characterised by a relative or an absolute increase in osteoclast-mediated bone resorption, notably Paget's disease of bone or osteoporosis. In cancer patients, they have become the standard therapy for TIH and a new form of medical therapy for bone metastases.

TUMOUR INDUCED HYPERCALCAEMIA

Increased calcium release from bone is the main cause of hypercalcaemia in cancer patients. Secretion of humoral and paracrine factors by the tumour cells markedly stimulate osteoclast activity and proliferation. Collagen cross-links are also increased in most patients with TIH and their mean level is usually more than 3-fold higher compared with healthy subjects [5]. Moreover, osteoblast activity is often inhibited, leading to a characteristic uncoupling between bone resorption and bone formation [6]. This causes a rapid rise in serum calcium, in contrast to the relatively stable levels of serum calcium seen in primary hyperparathyroidism where bone coupling is usually maintained.

Several studies have established the essential role of parathyroid hormone-related protein (PTHrP) in most types of cancer hypercalcaemia [7, 8]. The kidneys may also contribute to the pathogenesis and maintenance of TIH through a decrease in the glomerular filtration rate and an increase in the tubular re-absorption of calcium, which result from the decreased circulating volume and the specific renal effects of PTHrP. Rehydration has generally mild and transient effects on calcium levels, effecting a median decrease of only 1 mg/dl [9, 10], but it interrupts the vicious cycle of TIH by inhibiting the increased tubular re-absorption of calcium.

Bisphosphonates have become the standard treatment for TIH and they have supplanted all other hypocalcaemic drugs, except corticosteroids for hypercalcaemia of multiple myeloma. Etidronate is the least potent of the clinically evaluated bisphosphonates and it corrects TIH in only one fourth of cases [10]. Clodronate has been given at doses varying between 300 and 1500 mg/day for 1–10 days. A single-day 1500 mg infusion appears to be as efficient as daily 300 mg infusions for 5 days and this therapy achieves normocalcaemia in approximately 80% of cases [11, 12].

Pamidronate is the most useful of the commercially available compounds. It was first administered as daily 15 mg, 2 h infusions that were repeated for up to 10 days. In a multicentre trial, 90% of 132 patients treated in this manner became normocalcaemic after a mean interval of 3–4 days [13]. Such a therapeutic scheme is, however, cumbersome and it was later shown that pamidronate could also be given as a single infusion over 2–24 h. Following a dose–response study, it is recommended that the dose is increased as a function of the pretreatment calcium levels, from 30 mg for calcium levels less than 12 mg/dl up to 90 mg for calcium levels above 16 mg/dl [14]. The existence of a dose–response relationship within the therapeutic range has actually been difficult to demonstrate. Large studies indicate that the

dose–response relationship is particularly evident in patients with an increased tubular re-absorption of calcium and that a dose around 90 mg achieves normocalcaemia in more than 90% of patients (Figure 1) [15]. At these dose levels, the effects on either serum or urinary calcium are not significantly influenced by the tumour type or by the presence of bone metastases. The response to lower doses of pamidronate will, however, be less in patients with humoral hypercalcaemia of malignancy compared with patients with bone metastases [16]. Similarly, the influence of circulating PTHrP on the response to bisphosphonates becomes clearcut when lower doses of pamidronate or less potent compounds are selected [12, 16].

The superiority of pamidronate over clodronate in patients with TIH has been demonstrated in a randomised trial involving 41 patients, not only in terms of success rate, but more evidently in the duration of normocalcaemia. The median duration of action of clodronate was 14 days compared with 28 days for pamidronate [17]. Evaluation of sensitive and specific markers of bone resorption shows that the acute suppression of bone resorption is identical, but that the duration of suppression is significantly longer after pamidronate compared with clodronate [18].

Oral clodronate is often prescribed after successful intravenous therapy but the efficacy of this strategy has not been systematically examined, and it cannot thus be recommended at the present time.

METASTATIC BONE PAIN AND THE OSTEOLYTIC PROCESS

Biochemical markers of bone resorption are increased in more than 90% of patients with advanced metastatic bone disease [19]. It has been proposed that the propensity of breast cancer cells to metastasise and proliferate in bone could be explained by a 'seed and soil' concept ([20]; see also Yoneda, pp. 240–245). Breast cancer cells (the 'seed') appear to secrete factors, such as PTHrP, potentiating the development of metastases in the skeleton which constitutes a fertile 'soil' rich in cytokines and growth factors that stimulate breast cancer cells growth, including insulin-like growth factors. Local production of PTHrP and of other osteolytic factors such as TGF-α by cancer cells in bone would stimulate osteoclastic bone resorption, partly through the osteoblasts, the proliferation of which may also be inhibited [21]. Such factors probably induce osteoclast differentiation from haematopoietic stem cells and activate mature osteoclasts already present in bone. Increased osteoclast number and activity would then cause local foci of osteolysis, which could further stimulate cancer cell proliferation. It thus appears rational to target bone-resorbing cells for the treatment and perhaps the prevention of tumour-induced osteolysis.

Pain is the most common symptom of metastatic bone disease. It is present in more than half the patients when bone metastases are diagnosed and is almost a constant feature when bone metastases are progressing. External beam radiotherapy remains the treatment of choice for localised bone pain which does not respond to systemic treatment and/or simple analgesics. However, many patients have widespread, often previously irradiated sites of pain and for these patients, effective palliation of symptoms remains difficult.

It has not been convincingly demonstrated that any of the currently available oral bisphosphonates can reduce metastatic bone pain. This was recently confirmed in a placebo-controlled study of oral clodronate in patients with progressing bone metastases, mainly from breast cancer [22].

When pooling the available data from several phase II trials with repeated intravenous pamidronate infusions, relief of bone pain appeared to occur in half the patients [12]. However, the studies were not placebo-controlled and the evaluation was, therefore, open to criticism. Placebo-controlled studies have, nevertheless, confirmed that both clodronate and pamidronate given intravenously can exert significant and rapid analgesic effects [23, 24]. The median duration of symptomatic response is almost 3 months after a single high-dose (120 mg) pamidronate infusion in patients with breast

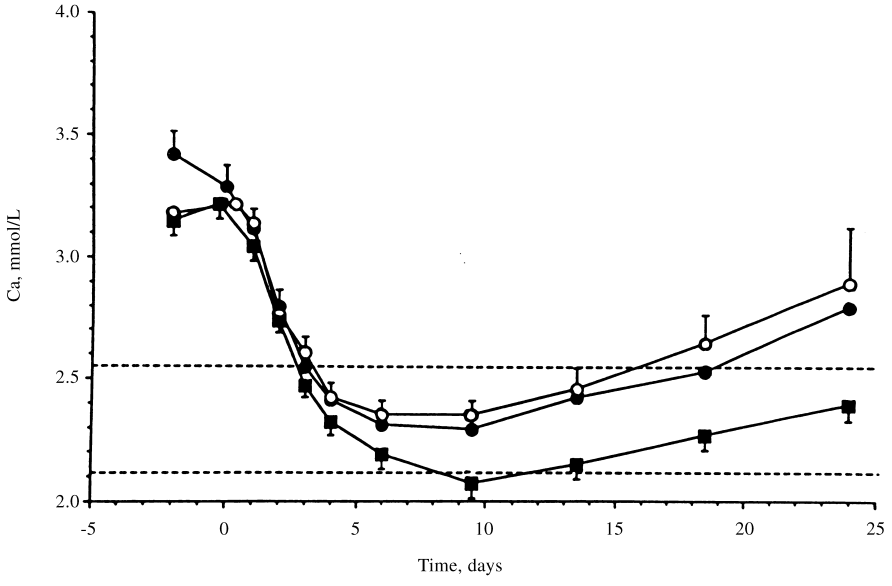

Figure 1. Effects of pamidronate therapy on the decrease of serum calcium (Ca) in 160 hypercalcaemic cancer patients. The patients were divided according to median dose received (●, 0.5 mg/kg, $n = 35$; ○, 1.0 mg/kg, $n = 52$; ■, 1.5 mg/kg, $n = 73$). The broken lines indicate the limits of normal values. Reproduced with permission of *Ann Oncol* 1994, 5, 359–363.

cancer [25]. Preliminary data indicate that modern markers of bone matrix resorption, such as the N-telopeptide of type I collagen (NTx), correlate with the analgesic effects of pamidronate and follow a similar time course. For example, patients with initial NTx levels more than twice the normal values and who have elevated values after therapy only rarely respond to classical doses of pamidronate [24]. It remains to be seen if higher doses of pamidronate or newer more potent compounds would be more useful.

The optimal dose remains to be defined, especially as it is probably a function of the disease type and stage. A dose of 60–90 mg pamidronate every 3–4 weeks can, for the time being, be recommended for palliation of bone pain. Intravenous clodronate will also relieve pain but its shorter duration of action would dictate a rather impractical regimen of administration probably every 10–14 days. The optimal timing of bisphosphonate administration in patients with painful bone metastases is still poorly defined and the role of bisphosphonates as an alternative or an adjunct to radiotherapy requires further study.

Regular pamidronate infusions can also induce recalcification or sclerosis of osteolytic lesions, achieving a partial objective response by conventional UICC criteria in approximately one fifth of the patients [12]. This phenomenon of recalcification appears to be similar to that which can be achieved by conventional hormono- or chemotherapy. This has been confirmed by sequential CT-scans of a target lesion, but the clinical implications and the benefit of these findings remain to be demonstrated, as it could merely represent the ablation of the lytic component in osteolytic/osteoblastic bone metastases. Similarly, an increase in the objective bone response rate to chemotherapy has been shown in a large randomised clinical trial when patients were receiving chemotherapy plus pamidronate as compared to chemotherapy alone, 33 versus 18%, respectively [26].

PREVENTION OF COMPLICATIONS OF METASTATIC BONE DISEASE IN BREAST CANCER

The combination of occasional poor tolerance from gastrointestinal side-effects and the low absorption of oral bisphosphonates, implying the need for high-doses, is still an obstacle to their development as oral drugs in cancer patients. However, oral bisphosphonates can be useful in routine clinical practice and two large-scale studies in patients with breast cancer metastatic to the skeleton, one with clodronate and one with pamidronate, indicate that the administration of oral bisphosphonates until death can reduce the frequency of morbid skeletal events. The clodronate study was randomised, double-blind, placebo-controlled and included 173 patients with breast cancer metastatic to bone [27]. In the clodronate-treated group (1600 mg/day), there was a significant reduction in the incidence of hypercalcaemic episodes, number of vertebral fractures and in the rate of vertebral deformity. The combined rate of all morbid skeletal events was reduced by 28% (Figure 2).

In another prospective, large-scale, but unblinded trial, including 161 patients with a median follow-up of 1.5 years, the total number of complications was reduced by 38% [28]. The incidence of hypercalcaemia, bone pain and symptomatic 'imminent' fractures was reduced by 65, 30 and 50%, respectively. There was also a significant decrease in the need for systemic treatment changes and for radiotherapy by 35 and 33%, respectively. However, these positive effects may have been overestimated by the open nature of the trial. Moreover, the authors could not detect significant effects on either the skeletal event-free period, the survival, or the radiological appearance of the lytic lesions.

The poor and variable absorption of the existing compounds, the requirement to take the drug after fasting, the occasional intolerance superimposed on the frequent digestive complaints and early satiety of cancer patients and the need for doses of bisphosphonates higher in tumour-induced osteolysis than in benign conditions, all make the intravenous route often more attractive than the oral route in cancer patients with established bone metastases. However, the choice can depend on individual circumstances. For example, the oral route will be preferred for many patients on hormonal therapy, especially if the bone disease is not rapidly evolving. The cost–benefit ratio of such an early intervention is unfortunately unknown and will certainly be greatly influenced by local factors.

Three randomised studies of regular intravenous pamidronate infusions have recently been completed [26, 29, 30]. There are no similar trials with clodronate and trials with newer bisphosphonates are ongoing.

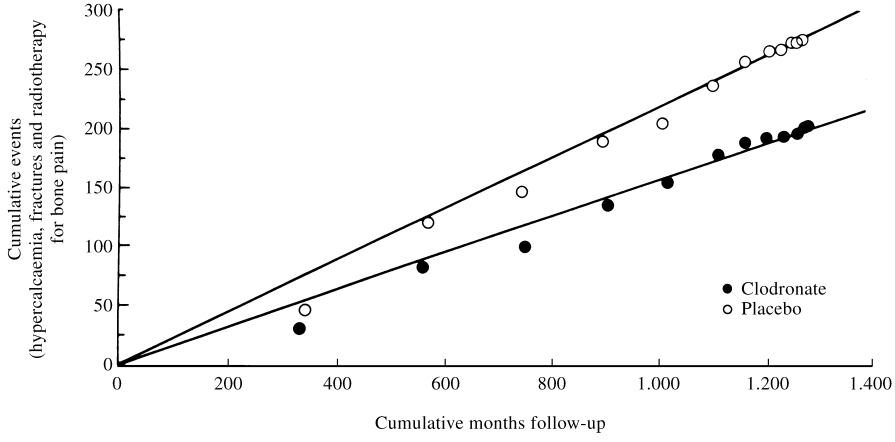

Figure 2. Cumulative skeletal events (episodes of hypercalcaemia, fractures, and radiotherapy treatments for bone-related pain) in patients receiving clodronate (●) compared with placebo (○). The reduction in cumulative skeletal events for clodronate is statistically significant ($P < 0.001$). Reproduced with permission of *J Clin Oncol* 1993, 11, 59–65.

Conte and collaborators randomised almost 300 patients in a multicentre open trial comparing infusions of 45 mg of pamidronate every 3 weeks plus standard first-line chemotherapy or chemotherapy alone in patients with breast cancer and bone metastases. The study was stopped when the disease progressed in the skeleton. In the 224 assessable patients, there was an increase of 48% in the median time to progression in bone. Improvement in bone pain was also seen more often in the pamidronate group, but the decrease in other skeletal-related events was not significant [29]. These somewhat disappointing results can be explained by the high activity of first-line chemotherapy in breast cancer; by the premature cessation of bisphosphonate administration; and by the choice of a low-dose of pamidronate.

The results of double-blind randomised placebo-controlled trials, comparing 90 mg pamidronate infusions every 4 weeks to placebo infusions for 1 year, in addition to chemo- or hormonotherapy, in large series of breast cancer patients with at least one lytic bone metastasis, have just been made available. The results were particularly impressive in the chemotherapy trial which included 382 patients [26]. Skeletal-related events were defined as pathological fractures, spinal cord compression, vertebral collapse, radiation for pain relief or for treatment of pathological fractures or of spinal cord compression, or surgery to bone. The median time to the occurrence of the first skeletal-related event was increased by 47% in the pamidronate group (Figure 3; 13.1 versus 7.0 months). There was a significant reduction in the proportion of patients having any skeletal-related event (43 versus 56%), in the number of non-vertebral pathological fractures (by 60%) and in the proportion of patients having radiation to bone (by 45%) or surgery on bone (by 52%). The follow-up of this trial indicates that the mean skeletal morbidity rate (number of skeletal-related events per year) has been 2.1 in the pamidronate group compared to 3.3 in the placebo group ($P < 0.005$). Corresponding figures in the hormone therapy trial were 2.4 and 3.6 ($P < 0.01$). In that latter trial, the median times to the occurrence of the first skeletal-related event significantly differed between the pamidronate and the placebo group only during the second year of the trial, probably due to the fact that the disease progressed more slowly in that group of patients [30]. There were also favourable effects on the quality of life and, at the end of the evaluation, there was a significant decrease in the pain score and in the analgesic requirement in both trials.

The optimal therapeutic schedule for pamidronate is not known with certainty, but monthly infusions are clearly effective and this schedule, while not ideal, is compatible with palliation of advanced malignancy. Criteria for when in the course of metastatic bone disease bisphosphonates should be started and stopped need to be determined. Because bisphosphonates are providing supportive care, reducing the rate of skeletal morbidity (but evidently not abolishing it), the criteria for stopping their administration have to be different from those used for classical antineoplastic drugs and they should not necessarily be stopped when metastatic bone disease is progressing. However, criteria are lacking to determine if and how long an individual patient benefits from their administration and the decision to continue or stop bisphosphonate therapy remains essentially empirical and based on personal experience. New biochemical markers of bone resorption may help identify those patients continuing to benefit from therapy. The cost-effectiveness of prolonged bisphosphonate therapy also is largely unknown. Bisphosphonates hold the potential for reducing the financial costs of treating metastatic breast cancer, especially as metastatic skeletal disease accounts for the largest component of hospital costs and totals almost two thirds of the expenses in advanced breast cancer [31, 32].

PREVENTION OF BONE METASTASES IN BREAST CANCER

Another potential role for bisphosphonate treatment is the prevention or at least a delay in the development of bone metastases. Trials in patients with established bone metastases suggest that long-term administration of bisphosphonates could indeed fulfil this major objective and studies in animal models of bone metastases support this exciting concept. Animal models of bone metastases have shown that when the bisphosphonate risedronate is injected at the same

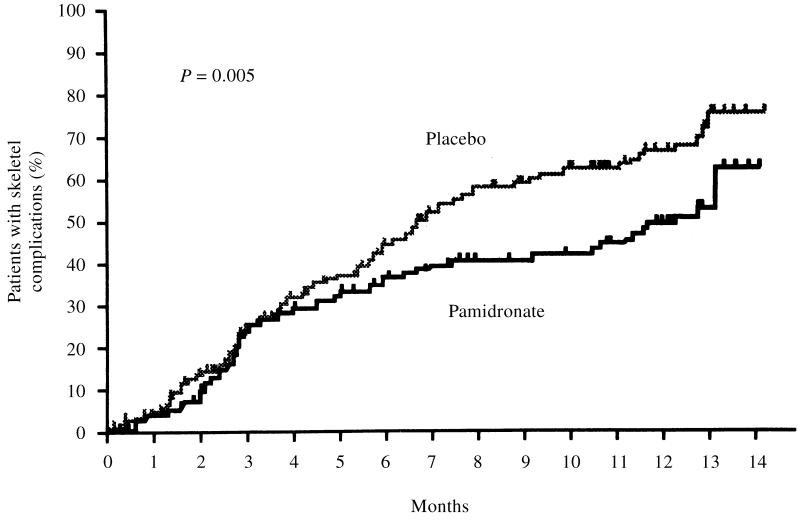

Figure 3. Kaplan–Meier estimates of the time to the first skeletal complication in 380 patients with breast cancer and bone metastases who were receiving cytotoxic chemotherapy and had at least one osteolytic lesion. Patients were given either placebo or pamidronate (90 mg) as 2 h i.v. infusions monthly for 12 cycles. Reproduced with permission of *N Eng J Med* 1996, 335, 1785–1791.

time as breast cancer cells, the development of bone metastases is inhibited [33]. The number of bone deposits is decreased and survival is prolonged, suggesting that the effects of osteolytic substances produced by the cancer cells can be interrupted by anti-osteoclastic drugs [33].

A secondary prevention double-blind trial continued for 3 years after extraskeletal recurrence in 133 women with breast cancer has shown a significant reduction in the number of bone metastases in the clodronate group [34]. However, the use of bisphosphonates to prevent the appearance of bone metastases must still be considered experimental. It will be important to determine the patients at high risk of developing bone metastases before recommending a general primary preventive use of bisphosphonates. Classical prognostic factors, such as tumour size, axillary node involvement, receptor status, but also PTHrP expression by the tumour cells and selected investigational prognostic markers will probably be relevant [12, 35]. Preventive therapy with bisphosphonates could also have the additional beneficial effect of preventing postmenopausal osteoporosis in a population of women for whom oestrogen replacement therapy is generally avoided.

MULTIPLE MYELOMA

Multiple myeloma is typically characterised by a marked increase in osteoclast activity and proliferation and an extensive osteolytic process is generally the hallmark of the disease. Moreover, this excessive resorption of bone could itself, notably through the release of interleukin-6 by the osteoclasts, play a contributory role to the growth of myeloma cells in bone (see Mundy, pp. 246–251). Recently performed trials support the notion that bisphosphonates could be of great benefit for the treatment of multiple myeloma.

In a randomised placebo-controlled trial in 350 patients with newly diagnosed myeloma, it has been demonstrated that 2400 mg of clodronate daily for 2 years resulted in a significant reduction in the proportion of patients developing progression of osteolytic bone lesions (24 versus 12%, $P < 0.05$). The proportion of patients without pain at the end of the trial was also higher in the clodronate group. Clodronate was well tolerated but the progression rate of vertebral fractures was not significantly different between the two groups and there was no effect on the occurrence of fractures or on survival [36]. A subgroup analysis of this trial has suggested that the efficacy of clodronate is dependent of the treatment response to cytotoxic drugs, as clodronate was effective only in patients who responded to melphalan-prednisolone [37].

Another randomised placebo-controlled trial in 548 patients evaluated the efficacy of 1600 mg of clodronate given daily at the time of diagnosis. The reduction in skeletal complication rate was not observed initially, but became apparent when the effects of chemotherapy wore off. At the time of disease progression, there were fewer patients with increased back pain or deterioration in performance status and less new vertebral fractures after the first year [38].

The efficacy of regular pamidronate infusions in myeloma has also been demonstrated in a double-blind placebo-controlled trial. The study comprised 392 patients with at least one osteolytic lesion who received either 90 mg pamidronate or placebo infusions monthly for 9 months in addition to their antimyeloma chemotherapy regimen. The proportion of patients developing a skeletal-related event was significantly smaller in the pamidronate than in the placebo group, 24 versus 41%. The therapeutic benefit was independent of the line of antimyeloma therapy. The mean morbidity rate was 2.1 in the placebo group versus 1.1 in the pamidronate group ($P < 0.02$). Quality of life score, performance status, pain score, incidence of pathological fractures and the need for radiotherapy were all favourably affected by bisphosphonate therapy [39]. These effects were maintained during the one-year extension period of the trial and preliminary follow-up data suggest a prolongation of survival in patients receiving second or subsequent lines of chemotherapy combined with pamidronate.

These placebo-controlled trials, with clodronate and even more with pamidronate, indicate that bisphosphonates in addition to chemotherapy are superior to chemotherapy alone for multiple myeloma. Confirmatory trials would be useful, and cost-benefit analyses should be performed, but it can probably already be stated that bisphosphonate treatment should now be considered for all patients with multiple myeloma and at least one osteolytic lesion. However, the optimal duration and doses of treatment are still to be determined.

WHAT CAN WE EXPECT FROM NEWER BISPHOSPHONATES?

Alendronate is another aminobisphosphonate that has been extensively tested in benign bone diseases, but its use in oncology is limited. Newer and even more potent bisphosphonates are currently being studied, such as ibandronate and zoledronate [40, 41].

In a first randomised phase II trial in 174 patients with TIH (Corrected calcium > 10.8 mg/dl), it was shown that doses of 0.6, 1.1 and 2.0 mg of intravenous ibandronate normalised calcium levels in 44, 52 and 67% of the patients, respectively [42]. The drug was well tolerated but because the success rate of 67% was still lower than that achieved with adequate doses of pamidronate, a further dose escalation trial was conducted in 147 patients with calcium levels $\geq$ 12 mg/dl after rehydration, 125 of whom were evaluable for response. The success rate was 50% in the 2 mg group, which was significantly lower than the responses in the 4 and 6 mg dose groups, 75.6 and 77.4%, respectively. A logistic regression analysis indicated that the response rate was also dependent on the initial calcium level and on the tumour type, as the group of patients with breast cancer or myeloma responded better than patients with other tumours [43]. This latter consideration is, however, open to criticism, as the pathogenesis of TIH complicating solid tumours with bone metastases is different to that of multiple myeloma [7–9].

In an open dose-finding trial, it was shown that doses of 0.02 to 0.04 mg of zoledronate/kg bodyweight normalised serum calcium in 93–100% of the patients. The fall in serum calcium appeared to be particularly rapid and the duration of the effect quite long. Preliminary data obtained in phase II trials in normocalcaemic patients with lytic bone metastases confirmed these effects on biochemical markers of bone resorption and showed that zoledronate doses up to 8 mg can be safely administered as a 5 min infusion [44]. Ibandronate at the dose of 3 mg has also been given as a bolus injection without real toxicity, but the safety of this procedure has to be confirmed in a larger number of patients [45].

The increased potency of these newer agents compared with pamidronate and clodronate will obviously allow the use of much lower doses and, of more clinical importance, their administration as rapid intravenous injections rather than

slow infusions. Several studies with repeated infusions of newer bisphosphonates in patients with bone metastases are ongoing. The development of oral, potent and well-tolerated compounds should also allow more convenient therapeutic schemes. Newer bisphosphonates will perhaps also allow more efficient therapeutic schedules, as preliminary data indicate that the effects of bisphosphonates on the complications of bone metastases are a function of the degree of the inhibition of bone resorption.

CONCLUSION

Bisphosphonates represent a major therapeutic advance in the area of supportive care in cancer. They reduce skeletal morbidity from breast cancer and multiple myeloma. Intravenous bisphosphonates successfully treat hypercalcaemic episodes, relieve bone pain and may lead to recalcification of lytic metastases. The favourable effects on the quality of life of prolonged bisphosphonate therapy appear to be particularly relevant, but they require further systematic studies, both for oral and for intravenous bisphosphonates.

Prolonged use of clodronate or pamidronate reduces the frequency of skeletal-related events in patients with metastatic bone disease. The mean skeletal morbidity rate can be reduced by 25 to 33% by adding bisphosphonates to chemotherapy or hormonal treatment for breast cancer metastatic to bone. Moreover, placebo-controlled trials, with clodronate and with pamidronate, indicate that bisphosphonates in addition to chemotherapy are superior to chemotherapy alone in patients with multiple myeloma. The reduction in skeletal morbidity rate can be reduced by almost 50%, strongly suggesting that bisphosphonate treatment should now be considered for all patients with multiple myeloma and at least one osteolytic lesion. Bisphosphonates could also reduce the financial burden of metastatic breast cancer and myeloma, but the cost–benefits of routine bisphosphonate usage are only beginning to be identified. In particular, the optimal therapeutic schedules and the selection of patients for treatment are still to be defined. The increased potency and safety of newer compounds will facilitate the use of bisphosphonates and permit their administration as direct intravenous injections, allowing more convenient and probably more efficient therapeutic schedules.

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Acknowledgements—Supported by a grant from 'Fondation Médic' and from 'Fonds National de la Recherche Scientifique no 3.4577.96'.