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REVIEW ARTICLE

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Bisphosphonates for cancer patients: why, how, and when?

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Abstract Bisphosphonates (BPs) are potent inhibitors of osteoclast-mediated bone resorption, and it is well accepted that tumor cells in bone, especially breast cancer and myeloma cells, can stimulate osteoclast formation and activity leading to the release of growth factors or cytokines, which will further stimulate cancer cells' growth and their secretion of osteolytic factors. BPs are now the standard treatment for cancer hypercalcemia, for which a dose of 90 mg of pamidronate or 1500 mg of clodronate is recommended; the former compound is more potent and has a longer lasting effect. Repeated pamidronate infusions exert clinically relevant analgesic effects in more than half of patients with metastatic bone pain. Recent data suggest that non-responding patients should perhaps be treated with higher doses. The optimal dose actually remains to be defined, especially as it is thought that it is probably a function of the disease stage. Regular pamidronate infusions can also achieve a partial objective response according to conventional UICC criteria and they can almost double the objective response rate to chemotherapy. Lifelong administration of oral clodronate to patients with breast cancer metastatic to bone reduces the frequency of morbid skeletal events by more than one-fourth. Two double-blind randomized placebo-controlled trials comparing monthly 90 mg pamidronate infusions to placebo infusions for 1–2 years in addition to hormone or chemotherapy in patients with at least one lytic bone metastasis have shown that the mean skeletal morbidity rate could be reduced by 30–40%. The results obtained with intravenous BPs are generally viewed as better than those obtained with oral clodronate. However, preference can be given to the oral route when BPs are started early in the process of metastatic bone disease in a patient receiving hormone therapy. According to the recently published ASCO guidelines, pamidronate 90 mg i.v. delivered over 2 h every 3–4 weeks can be recommended in patients with metastatic breast cancer who have imaging evidence of lytic destruction of bone and who are concurrently receiving systemic therapy with hormonal therapy or chemotherapy. Furthermore, the ASCO Panel considered it "reasonable" to start i.v. BPs in women with localized pain whose bone scans were abnormal and plain radiographs normal, but not when an abnormal bone scan is asymptomatic. The pertinence of these criteria is discussed below. Because BPs 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 classic antineoplastic drugs, and they should

not be stopped when metastatic bone disease is progressing. However, criteria to determine whether and for how long an individual patient benefits from their administration are lacking. New biochemical markers of bone resorption might help identify those patients continuing to benefit from therapy. Even better results have been achieved in patients with multiple myeloma, and the general consensus is that BPs should be started as soon as the diagnosis of lytic disease is made in myeloma patients. On the other hand, data are scanty in prostate cancer, but large-scale trials with potent BPs are ongoing or planned in such patients. Similar results to those achieved with pamidronate have been obtained with monthly 6-mg infusions of the newer BP ibandronate in patients with breast cancer metastatic to bone. The tolerance of ibandronate could be better, and the drug has the potential to be administered as a 15- to 30-min infusion. Zoledronate can also be administered safely as a 15-min 4-mg infusion, and large scale phase III trials have just been completed. These newer BPs will simplify the current therapeutic schemes and improve the cost-effectiveness ratio; they also have the potential to improve the therapeutic efficacy, at least in patients with an aggressive osteolytic disease or when given as adjuvant therapy. For that matter, initial data with clodronate indicate that they have the potential to prevent the development of bone metastases, but the use of BPs in the adjuvant setting must still be viewed as experimental.

Keywords Bone metastases · Osteolysis · Bisphosphonates · Breast cancer · Myeloma

Introduction

Tumor bone disease essentially complicates metastatic breast cancer, multiple myeloma and prostate cancer. Essential clinical aspects, respective pathophysiological key points and the indications for using bisphosphonates (BPs) will be briefly and systematically reviewed for each of these three neoplasms. Bone metastases can evidently complicate other tumors, especially lung cancer, but there are virtually no data on the usefulness of BPs for these advanced neoplasms.

According to the series, 30–90% of patients with advanced cancer will develop skeletal metastases. Carcinomas of the breast (47–85%) and of the prostate (33–85%) are the tumors most commonly associated with skeletal metastases [1]. The skeleton is in fact the most common site of metastatic disease in breast cancer, and the most common site of first distant relapse [2]. The patients thus affected have a relatively long survival after the diagnosis of bone metastases compared with patients with extraosseous metastases only. Their median survival is usually beyond 20 months, and about 10% of them are still alive 5–10 years after the first diagnosis of bone metastases [2].

Osteolytic bone disease is responsible for a considerable morbidity and markedly decreases the quality of life. Because of the long clinical course breast cancer may follow, morbidity from bone metastases also makes major demands on resources for health care provision. Besides the complications of bone marrow invasion, pain and functional disability occur in 45–75% of cases [1, 3], whereas major complications will be observed in up to one-third of the patients whose first relapse is in bone [2, 4]. Hypercalcemia occurs in 10–15% of cases and fractures will occur in 10–20% of the cases in which long bones are invaded [5]. Pathologic fractures constitute a major cause of prolonged disability in breast cancer, whereas they are relatively unusual in prostate cancer, with its predominantly sclerotic picture. However, severe bone pain is a classic and often devastating complication in advanced prostate cancer patients [5].

Bone pain is a presenting feature in three-fourths of the patients with multiple myeloma. Back pain correlates with the presence of vertebral fractures, which are present in more than half the patients at diagnosis. Extensive osteolytic lesions are frequent in this aggressive bone disease and typically do not heal despite successful antineoplastic treatment [6].

Why use bisphosphonates in cancer patients?

The pathophysiology of tumor-induced osteolysis (TIO) explains why the introduction of osteoclast inhibitors into the therapeutic armamentarium for bone metastases has met with such success. Once cancer cells colonize the bone marrow, they are attracted to bone surfaces by the products of resorbing bone and destroy bone via osteoclast stimulation. The importance of direct osteolytic effects of metastatic cancer cells, including the effects of collagenases, remains unknown. We and others have shown a marked increase in bone resorption markers in normocalcemic women with breast cancer and bone metastases [7]. Cancer cells essentially increase osteoclast differentiation of hematopoietic stem cells. An increased osteoclast number has been demonstrated in bone biopsies of women with breast cancer and predominantly lytic bone metastases, whether in bone adjacent to tumor cells or directly in the invaded bone [8]. Osteoblasts could also be important target cells for tumor secretory products. We have thus observed that breast cancer cells secrete factors that can inhibit the proliferation of human osteoblasts and increase their second-messenger response to osteolytic agents and their production of osteolytic cytokines and of enzymes degrading the collagen

matrix [9, 10]. In the process of TIO, osteoblasts could thus still have the central role that they have in the physiological regulation of osteoclast resorption activity.

The propensity of breast cancer cells to metastasize and proliferate in bone is best explained by the "seed and soil" concept [11]. Breast cancer cells (the "seed") appear to secrete osteolytic factors, such as parathyroid hormone-related peptide (PTHrP), potentiating the development of metastases in the skeleton, which constitutes a fertile "soil" rich in cytokines and growth factors that stimulate cancer cells growth. Local production of PTHrP and/or of other osteolytic factors by cancer cells in bone stimulates osteoclastic bone resorption, partly through the osteoblasts and the immune cells. Such factors probably induce osteoclast differentiation from hematopoietic stem cells and could also activate mature osteoclasts already present in bone. Increased osteoclast number and activity then cause local foci of osteolysis, an enhanced release of growth factors, and a further stimulation of cancer cell proliferation. Moreover, TGF-β, one of the most abundant growth factors in bone, which is released during bone resorption, can further increase PTHrP secretion from breast cancer cells. PTHrP also alters the ratio between osteoprotegerin (OPG), whose production is decreased, and RANKL, whose production is increased [12, 13]. The net result of this imbalance in these newly discovered and essential regulatory factors of osteoclast-mediated bone resorption evidently induces an increase in osteoclast proliferation and activity. We are thus typically dealing with a vicious circle, as the bone resorption-induced release of growth factors from the bone matrix will stimulate growth of breast cancer cells and the production of osteolytic factors, essentially PTHrP.

Collagen cross-link metabolites are also increased in patients with bone metastases from prostate cancer, underlining an increase in bone resorption even in blastic disease. Prostate cancer cells stimulate osteoclast activity, probably also through the osteoblasts [14]. They have been shown to produce factors that stimulate osteoblast growth and activity, such as fibroblast growth factors (FGFs), bone morphogenic proteins (BMPs), urokinase (uPA) and, especially, endothelin-1. As in bone disease induced by breast cancer or myeloma, a vicious circle also appears to be likely, since prostate cancer cells can secrete various proteases, such as PSA and uPA, which can dissociate IGF-1 from its binding proteins and activate latent TGF-β. Such factors would then stimulate the growth of prostate cancer cells [14].

Multiple myeloma is characterized by a marked increase in osteoclast activity and proliferation. Various factors have been implicated in the genesis of myeloma-induced bone disease, notably IL-6, macrophage inflammatory protein-1α (MIP-1 α), and very recently RANKL [15]. MIP-1 α is produced by myeloma cells and can stimulate osteoclast-mediated bone resorption in vivo (demonstrated by inoculation of CHO cells transfected with MIP-1 α). This cytokine could play a key role in the pathogenesis of myeloma bone disease [16]. Other authors postulate, however, that the production of RANKL by myeloma cells and/or its induction by stromal cells could be essential too. The excessive resorption of bone probably stimulates the growth of myeloma cells in bone, through the release of growth factors from resorbed bone matrix and the secretion of interleukin-6 (IL-6) by the bone microenvironment. Using established cell lines, it has been shown that through direct cell-to-cell contact, myeloma cells can down-regulate osteocalcin production but up-regulate IL-6 secretion, supporting the concept of the importance of the bone microenvironment in the genesis of myeloma-induced osteolysis [15].

There are far fewer data on bone metastases from other cancers, but the findings summarized here indicate that bone-resorbing cells are a logical target for the treatment and perhaps the prevention of TIO. Currently, 'osteoclast inhibitors' essentially means the BPs.

BPs localize preferentially to sites of active bone remodeling. They act directly on mature osteoclasts, decreasing their bone resorption activity, notably by lowering H^+ and Ca^{2+} extrusion and modifying the activity of various enzymes [17]. Moreover, BPs can induce osteoclast apoptosis. Clodronate, but not the amino-BPs, can be metabolized to an ATP analogue that is toxic for macrophages and for osteoclasts [18]. On the other hand, nitrogen-containing BPs, but not clodronate, interfere with the mevalonate pathway, which is important for the maintenance of cell membrane integrity. Amino-BPs, such as pamidronate, are nanomolar inhibitors of farnesyl-pyrophosphate (PP) synthase. This leads to an inhibition of post-translational prenylation of proteins with farnesyl or geranylgeranyl isoprenoid groups. Various cellular proteins have to be anchored to cell membrane by a prenyl group to become active. Most of these proteins are GTP-binding proteins, including the protein ras, and prenylated proteins are essential for osteoclast function, notably cell activity and attachment [19]. The net result, regardless of the mechanism (clodronate vs amino-BPs), is osteoclast apoptosis, notably through the induction of caspase-3 [20].

It has also been found that BPs can directly inhibit the growth of breast cancer and of myeloma cells by a combination of necrotic and apoptotic processes [21, 22]. The relevance of these in vitro observations to the clinical beneficial effects of BPs remains to be demonstrated, however [20].

When and how can bisphosphonates be used in cancer patients?

Tumor-induced hypercalcemia

BPs are indicated for hypercalcemia complicating all tumor types even though, in some instances, other com-

pounds can be quite active, such as glucocorticoids for hypercalcemia complicating multiple myeloma and most lymphomas. Rehydration has generally mild and transient effects on calcium levels, effecting a median decrease of only 1 mg/dl, but it improves the clinical status and interrupts the vicious circle of tumor-induced hypercalcemia (TIH) by inhibiting the increased tubular reabsorption of calcium. Rehydration should be combined with BP therapy and administered according to the hydration status of the patient [23].

The superiority of pamidronate over clodronate in patients with TIH has been demonstrated in a randomized trial involving 41 patients; it was not significantly superior in terms of success rate, but led to a longer duration of normocalcemia. Indeed, the median duration of action of clodronate was 14 days, compared with 28 days for pamidronate [24]. Large studies indicate that a dose of 90 mg achieves normocalcemia in more than 90% of patients [25]. The response to lower doses of pamidronate will, however, be less pronounced in patients with humoral hypercalcemia of malignancy than in patients with bone metastases, as the importance of PTHrP for increased renal calcium reabsorption will be more evident [26]. Pamidronate is well tolerated, the only clinically detectable side-effect being transient fever and a flu-like syndrome in about one-fourth of cases. Oral clodronate is often prescribed after successful i.v. therapy, but the efficacy of this strategy has not been systematically examined.

The recommended dose of pamidronate for the treatment of TIH is now 90 mg for all patients, which is actually also the recommended dose for the treatment and prevention of the complications of bone metastases. The median duration of normocalcemia after adequate doses of pamidronate therapy varies from 8–12 days to 3–4 weeks [23]. When hypercalcemia recurs, the efficacy of subsequent pamidronate infusions becomes progressively less, especially in tumors other than breast cancer and in patients who do not have bone metastases [27].

More potent BPs have recently been studied, especially ibandronate and zoledronate. In a randomized phase II trial in a large series of patients with moderate to severe hypercalcemia, the success rate was 50% in the 2-mg dose group, which was significantly lower than the response rates in the 4- and 6-mg dose groups, which were 76% and 77%, respectively [28]. A phase I dose-finding study in 30 hypercalcemic cancer patients has shown that very low doses of zoledronate (0.02 and 0.04 mg/kg, i.e. 1.2 and 2.4 mg for a 60-kg individual) administered in a short-time infusion (30 min) constitutes quite an effective treatment for TIH [29]. Recent data suggest that ibandronate and zoledronate achieve even better results than pamidronate in patients with severe hypercalcemia.

Metastatic bone pain

BPs are useful for localized bone pain that can no longer be treated by radiotherapy or in the case of widespread painful metastatic lesions. The i.v. route has to be used in such cases, and the relative inability of oral BPs to reduce metastatic bone pain has been confirmed in a placebo-controlled study of oral clodronate after a median time on study of almost 2 months in patients with progressive bone metastases [30]. To obtain optimal analgesic effects, the i.v. route is the route of choice, at least until more potent and well-tolerated oral BPs are developed [31].

Bone pain relief seems to occur in about one-half of patients treated with repeated pamidronate infusions [32]. Short-term placebo-controlled trials have confirmed that both clodronate and pamidronate given i.v. can exert significant and rapid analgesic effects [33]. In 62 evaluable patients, most of whom had breast cancer or myeloma, there was no difference in the analgesic response between the doses of 60 and 90 mg of pamidronate [34]. The response was essentially observed in patients with moderate or severe bone pain, and most of the effect was obtained after only two infusions, which suggests that further administrations are useless in non-responders, at least for that purpose [35]. However, other recent data suggest that such non-responding patients should perhaps be treated with higher doses. The optimal dose remains to be defined, especially since it is probably a function of the disease stage. Some data indicate that specific markers of bone matrix resorption, such as NTx, correlate with the analgesic effects of pamidronate and follow a similar time-course [36]. However, we were not able to confirm such a relationship in an open "high-dose" (4×4 mg) study of i.v. ibandronate in patients with severe metastatic bone pain [37]. A high rate of bone resorption could nevertheless be one of the factors underlying "resistance" to BPs, at least from the viewpoint of their analgesic effects. It is probable that a high-dose "intensive" regimen could lead to better results, but the efficacy of such regimens has to be tested adequately and, for the time being, a dose of 90 mg pamidronate every 3–4 weeks must still be recommended for palliation of bone pain.

Prevention of the skeletal complications in patients with established tumor bone disease

Breast cancer

Most of the data have been obtained with clodronate or pamidronate, and new trials are being analyzed with ibandonate and zoledronate. Placebo-controlled trials with oral or i.v. BPs have shown that their prolonged administration can reduce the frequency of skeletal-related

events (SREs) by one-fourth to one-half in patients with bone metastases from breast cancer [31, 38].

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 BPs until death can reduce the frequency of SREs. The clodronate study was randomized, double-blind, and placebo-controlled, and involved 173 patients with breast cancer metastatic to bone. In the clodronate-treated group (1600 mg/day) there were significant reductions in the incidence of hypercalcemic episodes, the number of vertebral fractures, and the rate of vertebral deformities. The combined rate of all morbid skeletal events was reduced by 28% [39].

Three randomized studies of regular pamidronate infusions are available in patients with breast cancer and bone metastases [40, 41, 42]. An open trial comparing low doses of pamidronate (infusions of 45 mg every 3 weeks) plus standard first-line chemotherapy or chemotherapy alone showed that pamidronate increased the median time to progression in bone by almost 50% [40]. Two double-blind randomized placebo-controlled trials comparing 90 mg pamidronate infusions every 4 weeks with placebo infusions for up to 2 years in addition to chemotherapy or hormone therapy in large series of breast cancer patients with at least one lytic bone metastasis indicate that BPs can reduce the skeletal morbidity rate by more than one-third, increase the median time to the occurrence of the first SRE by almost 50%, and reduce the proportion of patients having serious SREs [41, 42]. There were also favorable effects on quality of life and, at the end of the evaluation, a significant decrease in the pain score. The results were more impressive in the chemotherapy trial than in the hormone therapy trial, probably because the skeletal disease was more aggressive at the beginning of the trial. Because the odds ratio of having an SRE while receiving pamidronate in the endocrine study was not significantly different from the odds ratio in the chemotherapy study, the data of the two studies have been pooled [43]. In this combined analysis of 751 patients, the proportion of patients having any SRE (not including TIH) was reduced from 64% to 51% by the end of the 24 monthly cycles, whereas the mean skeletal morbidity rate was reduced from 3.7 to 2.4 events/year and the time to the first SRE increased from 7 to 12.7 months (all $P<0.001$).

The combination of occasional poor tolerance reflected in gastrointestinal side effects and the low absorption of oral BPs, implying the need for high doses making it necessary for the patients to swallow large capsules, at least in the case of clodronate, remains an obstacle, especially in advanced cancer patients. As summarized above, the results obtained with i.v. administration are also more impressive than those obtained with oral compounds. However, the choice between the oral and the i.v. route depends on individual circumstances and remains controversial. For example, the oral route will be preferred for many patients on hormonal therapy, especially if the bone disease is not evolving rapidly and if BPs are started early in the course of the disease. The cost/benefit ratio of such an early intervention is unfortunately unknown and will certainly be much influenced by local factors.

Criteria for when in the course of metastatic bone disease from breast cancer BPs should be started and stopped remain poorly determined. According to the recently published ASCO guidelines, i.v. pamidronate 90 mg delivered over 1–2 h every 3–4 weeks should be recommended in patients with metastatic breast cancer who have imaging evidence of lytic destruction of bone and who are concurrently receiving systemic hormone therapy or chemotherapy [38]. Furthermore, the ASCO Panel considered it “reasonable” to start i.v. BPs in women with abnormal bone scan when they have localized pain and normal plain radiographs, but not in women who have abnormal bone scans and are asymptomatic. These recommendations are certainly valid in view of the available data and can be endorsed, but they can be criticized as well on the basis of at least three types of arguments. First, a post hoc evaluation of the cost-effectiveness of the two double-blind pamidronate trials led to the conclusion that the costs of pamidronate therapy were higher than the costs savings from prevented SREs [44]. This study actually essentially underlines the need for prospective cost-effectiveness assessments! Secondly, measures to reduce morbidity from skeletal involvement by breast cancer are evidently essential for optimizing a patient’s quality of life but, to take a common situation, monthly BP infusions given to a patient who is receiving a first-line endocrine therapy with at least a 50% chance of a lasting response will certainly alter her quality of life. Well-tolerated and potent oral BPs would certainly be preferable for such patients. Lastly, the risk involved in excessive anti-osteolytic therapy is real. The possibility of a “frozen bone” with the prolonged use of potent BPs is still a matter of debate in the “bone community.” High doses of alendronate or risedronate in dogs significantly increase microdamage accumulation and decrease bone toughness (i.e. its ability to absorb energy or sustain deformation without breaking). Both parameters are related to the suppression of bone turnover [45]. Low turnover could thus retard strain-related repair of microdamage, permit accumulation of microcracks and, theoretically at least, increase the risk of fractures. There are no data in cancer patients, but this theoretical concern should at least be kept in mind! BPs evidently constitute a major progress to reduce the skeletal morbidity rate in breast cancer metastatic to bone, but only prospective trials, probably conducted by cooperative groups, would allow scientific determination of the optimal timing to start BP therapy. For the time being, I would certainly recommend starting BPs when there is a

lytic or a mixed metastatic bone disease in weight-bearing bones, when the bone disease appears to be "aggressive" or in the case of symptomatic or multiple metastases after failure of a first-line hormonal antineoplastic therapy. Patients who have dominant life-threatening visceral disease should probably not start BP therapy unless they have severe uncontrolled bone pain. In any case, whatever the recommendations, clinical judgment fortunately remains essential and therapy has to be adapted to the individual patient!

Because BPs 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 classic antineoplastic drugs and they should not be stopped when metastatic bone disease is progressing. The ASCO Panel suggested that, once initiated, i.v. BPs should be continued until evidence of substantial decline in a patient's general performance status [38]. However, criteria are lacking to determine whether and for how long an individual patient benefits from their administration, and the decision to continue or stop BP therapy or possibly increase their dosage remains essentially empirical and based on personal experience. New biochemical markers of bone resorption might help identify those patients continuing to benefit from therapy and those in whom BP dosage might have to be increased as the biochemical response seems to predict for the likelihood of SREs [46]. However benefits of such an attitude have not been demonstrated.

Newer, more potent, BPs, such as ibandronate and zoledronate, are being actively investigated. They will certainly simplify current therapeutic schemes. The remarkable potency of these new compounds, and hence the use of much lower doses, indeed allows their administration as rapid i.v. infusions, which will make therapy more convenient and less unpleasant for the patients, and probably increase compliance and decrease treatment costs. The long-term efficacy of ibandronate on the skeletal morbidity rate in patients with bone metastases from breast cancer has been evaluated in a multicenter double-blind placebo-controlled trial involving 462 patients who were treated for up to 2 years with monthly 2-mg injections of ibandronate or infusions of 6 mg over 1–2 h or placebo injections or infusions. The mean number of events per patient year during treatment was highest in the placebo group, at 2.18, ranging through 1.83 in the 2 mg ibandronate group to 1.61 in the 6-mg dose group ($P<0.05$). The event-free survival rate was similarly lower in the 6-mg dose group. There were also significant improvements in bone pain score ($P<0.001$) and in quality of life assessed by the EORTC QLQ-C30 scale [47]. It has recently been shown that ibandronate can be safely administered as a 30-min infusion, whereas at the currently tested dose of 4 mg zoledronate is infused over 15 min.

Multiple myeloma

Randomized placebo-controlled trials have demonstrated that BPs are of great benefit to myeloma patients [48]. A randomized placebo-controlled trial of 2400 mg clodronate daily for 2 years in 350 patients with newly diagnosed myeloma showed a significant reduction in the proportion of patients with progression of osteolytic bone lesions, 24% vs 12% in an intention-to-treat analysis, although the progression rate of vertebral fractures was not significantly different between the two groups [49]. Another randomized placebo-controlled trial in 548 myeloma patients evaluated the efficacy of 1600 mg clodronate daily given at the time of diagnosis. At the time of disease progression there were fewer patients with worsened back pain or deterioration in performance status, and there were fewer new vertebral fractures after the 1st year [50].

The efficacy of monthly 90-mg pamidronate infusions in myeloma has been demonstrated in a double-blind placebo-controlled trial including almost 400 patients each with at least one osteolytic lesion. The proportion of patients developing an SRE was significantly smaller in the pamidronate than in the placebo group, 24% vs 41%. The mean morbidity rate was reduced by almost half (2.1 in the placebo group vs 1.1 in the pamidronate group). Quality of life score, performance status, pain score, incidence of pathologic fractures and need for radiotherapy were all favorably affected by BP therapy [51, 52].

These placebo-controlled trials indicate that BPs in addition to chemotherapy are superior to chemotherapy alone for multiple myeloma. The optimal therapeutic schemes remain unknown, and cost-benefit analyses should be performed. However, it can be stated that BP treatment should now be considered for all patients with multiple myeloma with at least one osteolytic lesion. BPs should probably be used very early in all patients, not only because of their beneficial skeletal effects, but also because they may slow tumor growth [53]. However, the optimal duration and doses of treatment are unknown.

Prostate cancer

Although skeletal metastases from prostate cancer are typically osteoblastic, histomorphometric and biochemical studies have shown unequivocal evidence for an increase in bone resorption [54]. The analgesic effect of BPs has been shown in several open trials with pamidronate or newer BPs [55]. However, there are no large-scale double-blind trials, and there are as yet too few systematic data to justify advising the regular use of BPs in metastatic prostate cancer [31]. Controlled trials are planned or already under way with the newer BPs, and

the place of these compounds in the management of metastatic prostate cancer will be more precise in the near future.

Prevention of bone metastases from breast cancer

Another potential major role for BPs 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 BPs could indeed fulfill this major objective. Animal models of bone metastases have shown that BPs can effectively inhibit the development of bone metastases and decrease the tumor burden in bone when the BP is injected at the same time as breast cancer cells, suggesting that the production of bone-destroying substances by the cancer cells can set up a vicious circle, which can be interrupted by antiosteoclastic drugs [56].

In a randomized open trial involving about 300 patients with primary breast cancer and tumor cells in the bone marrow, which is an adverse risk factor for the development of metastases, it was shown that 1600 mg clodronate daily for 2 years reduced the number of bone as well as non-bone metastases by about 50% after a median follow-up of 36 months [57]. Despite the enthusiasm this has generated, we must remain cautious, especially as two other trials have not confirmed these data [58, 59]. An open trial on a similar scale, in 299 women with node-positive tumors receiving adjuvant clodronate 1600 mg/day for 3 years with a minimum follow-up time of 5 years, has provided results indicating the opposite. The clodronate group had more non-bone metastases and a shorter survival [59]. The groups were apparently well balanced, but these two studies indicate that large-scale trials are definitely needed to avoid any possible unrecognized imbalance between the groups and to provide hopefully definitive results. A preliminary report of a double-blind trial involving 1079 breast cancer patients after surgery indicates that a 2-year treatment with 1600 mg clofronate daily could indeed reduce the incidence of bone metastases. The median follow-up was 4 years, and a significant reduction was observed in postmenopausal patients: 7.3% in the placebo group as opposed to 3.3% in the clodronate group (P=0.04) [58]. Some of these spectacular results could be due to a reduction in tumor burden in bone following an alteration of the microenvironment induced by BPs, which could interrupt the osteolytic cycle by reducing local production of growth factors, or by a direct cytotoxic effect of BPs on breast cancer cells in bone, which would make secondary metastasis less likely. It will be essential to filter out the patients who are at high risk of developing bone metastases before recommending a general primary preventive use of BPs. Not only classic prognostic factors, such as tumor size, axillary node involvement, and receptor status, but also expression of PTHrP or other factors by the tumor cells could be relevant in this matter.

Preventive therapy with BPs will also have the additional beneficial effect of preventing postmenopausal osteoporosis in a population of women for whom estrogen replacement therapy has to be avoided. However, the use of BPs in the adjuvant setting must still be considered experimental.

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