Tumor bone disease is responsible for considerable morbidity and markedly decreases the quality of life of breast cancer patients. The skeleton is the most common site of metastatic disease and the most common site of first distant relapse in breast cancer. Moreover, patients with skeletal involvement have a longer survival (median time of close to 2 years) after the diagnosis of bone metastases compared with patients with visceral metastases (1). The term skeletal-related events (SRE) refers to the major complications of tumor bone disease (i.e., pathologic fractures, need for radiotherapy, need for bone surgery, spinal cord compression, and hypercalcemia). Hypercalcemia classically occurs in 10% to 15% of the cases, spinal cord compression in ~10%, and, when long bones are invaded, fractures in 10% to 20% (2). Taken from data in placebo groups of randomized bisphosphonates trials, the mean skeletal morbidity rate (SMR; i.e., the mean number of SREs yearly) varies between 2.2 and 4.0 (2–5). Patients who only have bone metastases have a higher rate of SREs than patients with bone and visceral metastases. Moreover, debilitating bone pain will significantly complicate the life of most patients.

The osteotropism of breast cancer remains incompletely understood. Deposits into the skeleton can be due to the attraction of tumor cells by chemotactic factors released by the normal remodeling of bone matrix. However, the propensity of breast cancer cells to proliferate in bone is best explained by a “seed and soil” concept (6, 7). Breast cancer cells (the “seed”) appear to secrete factors, such as parathyroid hormone–related protein, 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. Local production of parathyroid hormone–related protein and of other osteolytic factors by cancer cells in bone stimulate osteoclastic bone resorption essentially through the osteoblasts. Tumor factors thus alter the ratio between osteoprotegerin, whose production is decreased, and receptor activator for nuclear factor-κB (RANK) ligand, whose production is increased (8). The net result of this imbalance in these key regulatory factors of osteoclast-mediated bone resorption is an increase in osteoclast proliferation and activity. This results in local foci of osteolysis with an enhanced release of growth factors, leading to a further stimulation of cancer cells proliferation (6, 7, 9).

Bisphosphonates inhibit bone resorption by inducing osteoclast apoptosis. Clodronate is metabolized to an ATP analogue, which is toxic for macrophages and osteoclasts. On the other hand, nitrogen-containing bisphosphonates, notably pamidronate, ibandronate, and zoledronic acid, interfere with the mevalonate pathway, which is essential to maintain cell membrane integrity. Pamidronate, ibandronate, and zoledronic acid are thus nanomolar inhibitors of farnesyl pyrophosphate synthase. This leads to an inhibition of the post-translational prenylation of proteins with farnesyl or geranylglycerol isoprenoid groups. Various cellular proteins have to be anchored to the 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 (10). The net result is osteoclast apoptosis. It has also been found that
Bisphosphonates can directly inhibit the growth of breast cancer cells by a combination of necrotic and apoptotic processes and inhibit the stimulatory effects of bone-derived growth factors (11). However, the relevance of these in vitro observations to the clinical beneficial effects of bisphosphonates remains to be shown.

**Bisphosphonates Reduce Skeletal Morbidity in Metastatic Breast Cancer**

Placebo-controlled trials with oral or i.v. bisphosphonates have shown that their prolonged administration can reduce the frequency of SREs in patients with bone metastases from breast cancer by 30% to 40%. Three large-scale studies, one with clodronate and two with pamidronate, first proved that the prolonged administration of bisphosphonates can reduce the frequency of SREs in metastatic breast cancer. The clodronate trial was randomized, double blind, and placebo-controlled and included 173 patients with breast cancer metastatic to bone. Clodronate significantly reduced the incidence of hypercalcemic episodes and the number of vertebral fractures. The combined rate of all morbid skeletal events was reduced by 28% (12). Clodronate is now considered to be less effective than other bisphosphonates for the prevention of skeletal events (13). This has notably been shown in a limited comparative trial between clodronate and pamidronate (14). Two double-blind, placebo-controlled studies comparing 90-mg pamidronate infusions every 4 weeks to placebo infusions for up to 2 years in addition to chemotherapy or hormonotherapy in large series of breast cancer patients with at least one lytic bone metastasis showed that pamidronate can reduce the SMR by more than one third, increase the median time to the occurrence of the first SRE by ~50%, and reduce the proportion of patients having any SRE (5, 15). The results were more impressive in the chemotherapy trial (5) than in the hormone therapy trial (15) probably because the rate of progression of bone disease was greater in patients undergoing chemotherapy than in patients undergoing hormone therapy, who often have less advanced disease. In both trials, there was a significant reduction in the incidence of hypercalcemia and in the need for radiotherapy. In the chemotherapy trial, pamidronate also reduced the incidence of nonvertebral pathologic fractures and the requirement for surgery. It is worth noting that the median time to objective progression in bone (external review) was only slightly prolonged in the chemotherapy trial. Progression of metastatic disease in bone is currently not effectively prevented by monthly bisphosphonate therapy.

The value of newer more potent bisphosphonates has been studied extensively. The largest multicenter trial with zoledronic acid was randomized and double blind and compared 4 or 8 mg zoledronic acid to 90 mg pamidronate every 3 to 4 weeks for up to 2 years in the treatment of osteolytic lesions in breast cancer (n = 1,130) and in multiple myeloma (n = 510). The primary efficacy end point was the proportion of patients with at least one SRE, defined as pathologic fracture, spinal cord compression, radiation therapy to bone, and surgery to bone (16). Zoledronic acid (8 mg) was not more effective than the 4-mg dose level but was associated with an increased frequency of renal adverse events, explaining why all patients in that treatment arm were switched to the lower dose of 4 mg during the trial. The proportion of patients with at least one SRE was similar (46% for zoledronic acid and 49% for pamidronate). The pre-established criterion for noninferiority of zoledronic acid to pamidronate was thus met. Median time to first SRE was ~1 year in all treatment groups, and SMRs were also not significantly different. A preplanned multiple-event analysis, according to the Andersen-Gill model, nevertheless showed that zoledronic acid (4 mg) reduced the overall risk of experiencing an SRE by an additional 20% compared with pamidronate (hazard ratio, 0.799; P = 0.025; ref. 17; Fig. 1, **top**). Multiple event analyses factor into the number and the timing of all SREs during the trial, whereas the classically used SMR captures all of the SRE data but ignores the timing of these SREs. Even if the time to the first SRE is similar between two treatment groups, a multiple-event analysis can show a difference because it takes into account all the SREs that have occurred as well as the timing of these events (18). From the same study, patients were retrospectively stratified based on whether they had an SRE before study entry, which was the case for 68% of the patients. Zoledronic acid was significantly more effective than pamidronate at reducing the occurrence of on-study SREs. Also in this subgroup, fewer patients treated with zoledronic acid had an event and the SMR was lower (1.23 versus 1.70; P < 0.05; ref. 19). The short infusion time (15 minutes compared with 2 hours for pamidronate) is another evident advantage of zoledronic acid compared with pamidronate (4). Lastly, zoledronic acid has been compared recently with placebo infusions in a double-blind study in 227 Japanese patients with breast cancer and bone metastases. The primary end point was the ratio of the SRE rate (ratio of number of SREs yearly of zoledronic acid–treated patients over that of placebo). After 1 year, this SRE rate ratio was 0.61 (P = 0.016), indicating that the SRE rate was reduced by 39%. Using a multiple-event analysis according to the Andersen-Gill model, the hazard ratio was reduced to 0.59 with zoledronic acid (Fig. 1, **middle**; ref. 20).

Repeated 6-mg monthly ibandronate infusions or oral ibandronate (50 mg once daily) also constitutes efficient strategies to significantly reduce the morbidity rate of bone metastases from breast cancer (21, 22). In these trials, the primary efficacy end point was the skeletal morbidity period rate, defined as the number of 12-week periods with skeletal complications (vertebral fractures, nonvertebral fractures, radiotherapy to bone, and surgery to bone) divided by the total observation time. Both forms of ibandronate significantly reduced skeletal morbidity period rate and the number of new bone events compared with the placebo group. Bone pain was significantly reduced and maintained below baseline for the 2 years of evaluation. Physical functioning and performance status were significantly better with oral ibandronate than in the placebo group (P = 0.008; ref. 23). Preplanned multivariate Poisson regression analysis showed that i.v. ibandronate (6 mg) led to a statistically significant 40% reduction in the risk of SREs compared with placebo (hazard ratio, 0.60; 95% confidence interval, 0.43-0.85; P = 0.003). The effect of oral ibandronate (50 mg) on the risk of SREs was similar (38% reduction versus placebo; hazard ratio, 0.62; 95% confidence interval, 0.48-0.79; P < 0.0001; ref. 22; Fig. 1, **bottom**). Treatment with ibandronate was well tolerated (21, 22).

**Controversial issues and perspectives.** Criteria for when in the course of metastatic bone disease from breast cancer...
Bisphosphonate therapy should be started and stopped remain to be clarified. In an exploratory analysis of the breast cancer subset in the phase 3 trial comparing zoledronic acid to pamidronate, patients were stratified based on whether they had experienced an SRE before study entry. In the 68% of the patients who had experienced at least one SRE, the risk for the development of an on-study SRE was ~2-fold higher than it was in the patients with no prior SREs (58% versus 32%; ref. 19). This implies that one should not wait for the first SRE to start bisphosphonate therapy in breast cancer metastatic to bone. The American Society of Clinical Oncology guidelines indeed recommend the routine use of i.v. pamidronate or zoledronic acid in patients with breast cancer and radiographic evidence of bone destruction (23). Furthermore, the panel considered it reasonable to start i.v. bisphosphonates in women with abnormal bone scan with localized pain and normal imaging techniques but not if the abnormal bone scan is asymptomatic. They also suggested that, once initiated, i.v. bisphosphonates should be continued until evidence of substantial decline in a patient’s general performance status (i.e., until patients are in a preterminal condition; ref. 24).

These recommendations can be endorsed in view of the available data, but they can also be challenged with at least three types of arguments. First, the cost effectiveness of an extensive, early, and prolonged use of bisphosphonates has not been established. Second, measures to reduce morbidity from skeletal involvement by breast cancer are evidently essential for optimizing a patient’s quality of life, but monthly bisphosphonate infusions in a patient receiving a first-line endocrine therapy for one or a few asymptomatic bone lesion(s) might actually alter her quality of life because of this relatively intense and time-consuming therapeutic approach. Detailed prospective assessments of quality of life under bisphosphonate therapy are lacking. The situation could be more favorable in such a case if using oral ibandronate whose tolerance is good in placebo-controlled phase 3 trials (22) and that has been shown to improve quality of life (23). However, this compound is not approved in the United States. Lastly, the risk of an excessive antiosteolytic therapy is more and more evoked. The possibility of a “frozen bone” with the prolonged use of potent bisphosphonates is a matter of debate in the bone community. Mashiba et al. (25) reported that the administration for 1 year of high doses of oral alendronate (1 mg/kg daily) or oral risedronate (0.5 mg/kg daily) in dogs significantly increased microdamage accumulation due to lack of repair of microcracks. Bone toughness (i.e., its ability to absorb energy or sustain deformation without breaking) declined significantly. Both microdamage accumulation and reduced toughness were significantly related to the suppression of bone turnover. Such doses are high when compared with doses used to treat osteoporotic patients, but this is no longer true when considering doses of these products that could have been used in metastatic disease. Thus far, this remains a theoretical concern, but the recently described cases of osteonecrosis of the jaw (ONJ), which are essentially reported after prolonged bisphosphonate
therapy, could be partly due to an excessive inhibition of bone turnover.

Bisphosphonate therapy is generally not stopped when metastatic bone disease is progressing. Criteria for stopping bisphosphonates should indeed be different from the ones used to modify antineoplastic therapies. Continuing bisphosphonates in this setting is thus common practice but this attitude is not scientifically proved. We actually lack criteria to determine if and how long an individual patient benefits from their administration, and the decision to continue therapy remains essentially empiric. Promoting lifelong treatment contradicts the extreme paucity of data about the usefulness and safety of treatment durations beyond 2 years. New biochemical markers of bone resorption may help identify those patients continuing to benefit from therapy. One such marker, the collagen telopeptide urinary NTX, seems to be an excellent predictor of disease progression in bone, whether patients are receiving bisphosphonates or not (26). Baseline and on-treatment NTX levels have also been shown to correlate with the number of SREs (27). A high rate of bone resorption is one of the factors underlying a poor response to bisphosphonates and is a good predictor of the likelihood of future skeletal events (28). However, the routine use of bone turnover markers is not currently recommended by the American Society of Clinical Oncology. It is nevertheless reasonable to assume that therapeutic schemes ought to be individualized and their intensity be a function of the number and severity of bone lesions and of bone turnover markers levels. On the other hand, if bone turnover markers are suppressed well into the reference range in a patient whose bone disease is well controlled, it is probably reasonable to consider a temporary arrest of therapy or a switch to intermittent treatments after a prolonged therapy (e.g., an infusion every 3 months). The value of treatment frequency as a function of marker values is currently tested in the BISMARK prospective trial.

Lastly, the fact that the efficacy of the highest 8-mg zoledronic acid dose was not superior to the 4-mg dosage (16) suggests that we have reached a ceiling effect at least with classic therapeutic schemes. Along the same line, the SMR is reduced by only approximately 35% to 40% even when bisphosphonate therapy is started early, and this is probably true whatever the compound. Increasing the dose in patients who would seem to respond poorly to standard doses of zoledronic acid would certainly be risky because of the potential renal toxicity, and caution is anyway mandatory with all bisphosphonates used on a long-term basis. Patients seem to be treated very early in their metastatic process, but are we nevertheless acting too late? Do we need to envisage other molecular targets on bone cells? In this context, exciting results are awaited with the use of substances blocking the RANK/RANK ligand system, which plays a key role in osteoclast activation and tumor bone disease (8). Initial trials with a human antiserum against RANK ligand, called denosumab, have shown a much longer inhibitory activity on bone resorption than standard doses of pamidronate (29). The compound is easy to administer by the s.c. route, but it is unknown if denosumab will lead to better clinical results than potent bisphosphonates. Its prolonged inhibitory activity on bone resorption is promising, but it is also possible that we have underestimated the probable role of cancer cells in the process of bone destruction.

**Analgesic Effects**

Pain is the most frequent symptom of bone metastases and can significantly alter the quality of life of cancer patients. Bisphosphonates are useful for localized bone pain that can no longer be treated by radiotherapy or in case of widespread painful metastatic lesions. The current opinion is that the i.v. route has to be selected in such cases because of the relative inability of first-generation oral bisphosphonates to reduce metastatic bone pain, but this statement is now challenged by the demonstrated analgesic effects of oral ibandronate (22).

Short-term placebo-controlled trials have established that both clodronate and pamidronate given i.v. can exert significant and rapid analgesic effects (30). Clinically meaningful bone pain relief seems to occur in approximately half of the patients treated with pamidronate infusions, and most of the analgesic effect is obtained after only two infusions (31). The analgesic effect of a single pamidronate infusion has been best shown by Purohit et al. (32), who showed that a single infusion of 120 mg pamidronate induced a reduction of 20% or more in a pain questionnaire score recording a composite of pain intensity, analgesic consumption, and performance status in 20 (59%) of 34 normocalcemic patients with painful bone metastases, mostly from breast cancer. The response rate was 68% in patients with breast cancer. The median duration of symptomatic response was 12 weeks, and a comparable response was seen after the second infusion only in previous responders. However, other recent data suggest that nonresponding patients should perhaps be treated with higher doses. The optimal dose actually remains to be defined, especially that it is probably a function of the disease stage. The administration of high doses of ibandronate (4 mg/d i.v. for 4 consecutive days) in patients with "opioid-resistant" metastatic bone pain is successful in an open trial in 18 patients with various tumors, including 10 with breast cancer (33). Such intensive regimens could thus lead to better results in patients with severe and uncontrolled bone pain, but their efficacy has to be confirmed in prospective and blinded studies.

Pain is essentially viewed as an SRE in long-term bisphosphonate trials, and the marked decrease in radiotherapy needs is a surrogate marker for clinically significant pain relief. In the long-term, randomized, placebo controlled trials have shown that pamidronate, zoledronic acid, and ibandronate exert useful pain relief. The role of bisphosphonates as an alternative or an adjunct to radiotherapy requires further study. The optimal combination or sequencing of radiotherapy or radioisotopes with bisphosphonates has not been studied.

**Safety Issues**

Although generally well tolerated, bisphosphonates are associated with adverse events. Characteristic adverse effects with oral bisphosphonates are gastrointestinal, such as epigastric pain and esophagitis (34). Intravenous infusions can be associated with renal safety issues, injection site reactions, and flu-like syndromes. The reported incidence of renal function deterioration in clinical trials of zoledronic acid was 10.7% in patients with multiple myeloma or breast cancer, not significantly different than the pamidronate figures (17). Although most cases of renal deterioration were mild and reversible, the Food and Drug Administration thereafter reported 72 cases of...
renal failure with zoledronic acid observed in clinical practice (35). Renal safety data from a study of i.v. ibandronate in patients with breast cancer and metastatic bone disease (22) show a low incidence of renal adverse events with i.v. ibandronate (6 mg) that is comparable with placebo (4.0% versus 4.5%). If the safety of prolonged ibandronate therapy administered as a 1- to 2-hour infusion is well shown, ongoing clinical trials are investigating the safety of repeated shorter 15-minute infusions. Conversely, it is unknown if prolonging the infusion time for zoledronic acid would reduce the risk of renal adverse effects. Renal safety issues also affect patient management. For example, serum creatinine should be monitored before each dose of zoledronic acid, and its use is not recommended in patients with severe renal deterioration and those taking nephrotoxic medications (24). Renal safety monitoring with i.v. ibandronate is not mandatory because no cases of renal failure have been reported at the time of this writing, but the renal safety of ibandronate also has to be confirmed in routine clinical practice outside clinical trials.

Recently, ONJ was reported to occur with the use of some bisphosphonates (36). The relationship with bisphosphonates seems to be more evident even if the exact pathogenesis needs further investigation. Although sometimes devastating, it was believed to be a rare complication with an estimated frequency below 1% and essentially seen after dental extraction and concomitant corticosteroid therapy. Recent series suggest the incidence has been underevaluated. In a prospective evaluation of 252 cancer patients treated with bisphosphonates for 6 years, Bamias et al. (37) reported that the incidence of ONJ was 6.7% overall (17 patients), 9.9% in myeloma, 6.5% in prostate cancer, and 2.9% in breast cancer. The median number of infusions was 35 in the patients who developed ONJ compared with 15 for patients without ONJ ($P < 0.001$). In all patients, pain was the presenting symptom. All cases occurred in patients who were treated with zoledronic acid either alone or after pamidronate therapy. Length of exposure seems to be the most important risk factor for ONJ, and caution is required for use of bisphosphonates beyond 2 years. Clinicians have to be vigilant and able to detect subtle changes that can precede ONJ, such as changes in the health of periodontal tissues, nonhealing mucosal ulcers, loose teeth, and unexplained soft tissue infection (38). A dentist aware of this complication should probably examine all patients before bisphosphonate treatment is started to avoid later dental procedures after prolonged therapy.

Open Discussion

**Dr. Coleman:** How would you design a proof-of-concept study to evaluate combination strategies with a new drug?

**Dr. Body:** We need to combine drugs that act differently. It was somewhat disappointing to note there were no differences between a bisphosphonate given orally daily at low doses and the same bisphosphonate given monthly at “high” doses. If we discover drugs that truly act on a different target and are safe, we should not combine them immediately, but first compare them with a potent bisphosphonate and then use them sequentially and/or in combination with a bisphosphonate.

**Dr. Roodman:** Do you think we need another drug? Would adding another antiresorptive or bone-targeted drug while we still don’t have something to control the tumor, change the rate of skeletal-related events? We can pile on more and more drugs or we can wipe out every osteoclast in the body and these patients will still have growing tumors. Somebody raised the idea of tumors reabsorbing bone, but that is a different question. We need to think about designing trials to add drugs to drugs that already have good efficacy in a lot of patients.

**Dr. Coleman:** You might be right. I think it’s unlikely that the combination strategy will improve survival, but it is reasonable to hope that a combination strategy may reduce events from 60% to 30% to 40%.

**Dr. Powles:** Have trials ever been done looking at chemotheraphy for treatment of bone metastases as opposed to across the board with or without a bisphosphonate?

**Dr. Weibachser:** The problem is it is hard to identify response rates with bone metastasis. Bone scans are not reasonable. PET imaging with FDG could be reasonable in selective patients, but it is very difficult.

**Dr. Powles:** In terms of crude objective response in bone, trials comparing endocrine therapy versus chemotherapy showed that the endocrine therapy worked about twice as well. We always thought that was because the endocrine therapy was having an effect not directly on the tumor but on the tumor-bone interaction.

**Dr. Pearse:** What’s wrong with eliminating all the osteoclasts in the body?

**Dr. Roodman:** I don’t think it’s healthy for people, unless all of your bone is full of tumor.

**Dr. Pearse:** We don’t have a good marker for true osteoclast activity in patients who are fully treated with bisphosphonates.

**Dr. Boyce:** One of the things that bisphosphonates do is stimulate osteoclAst formation. Part of the problem with bisphosphonates is that if osteoclasts are rapidly resorbing bone matrix, that is not where the bisphosphonates are going to go. They get deposited at sites of bone formation.

**Dr. Roodman:** I agree. It has to be intermittent; you can’t give it continuously. However, we keep talking about adding drugs onto drugs, and all of these trials take 4,000 patients and 5 billion dollars.

**Dr. Coleman:** We have to find a way that doesn’t take 4,000 patients. What is a reasonable surrogate for this concept?

**Dr. Roodman:** We need a more sensitive marker.

**Dr. Body:** Do we still see active osteoclasts in the bones of patients who have been treated with bisphosphonates for several years? This could explain the ceiling effect.

**Dr. Boyce:** I’ve seen biopsies of patients with Paget’s disease, and there are clearly areas of bone biopsy specimens where osteoclasts have been entirely wiped out. But when you review biopsy specimens, you can also see sites that are just as active as they ever would have been in the absence of bisphosphonate therapy.

**Dr. Body:** The situation for Paget’s disease is not the same than for breast cancer or even for prostate cancer. Also, it is clear now that bisphosphonate’s beneficial effects are less in prostate than in breast cancer.

**Dr. Guise:** Has anyone looked at bone that wasn’t involved with tumor and in patients who have been treated with bisphosphonates?

**Dr. Vessella:** We certainly have observed some sites where there’s no tumor. We don’t see much of an effect, and there
doesn’t appear to be a systemic osteoblastic effect at those particular sites where tumor isn’t present.

Dr. Lipton: One end point that hasn’t been discussed is time to progression in bone. Is it true that none of these drugs have affected time to progression in bone and, if so, why?

Dr. Body: There was an effect on time to progression in Conte’s trial. This was the primary end point of that particular study, and treatment was stopped at that time. I am not so sure it has been carefully examined in any of the other long-term trials.

References
Breast Cancer: Bisphosphonate Therapy for Metastatic Bone Disease

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