# Rational Use of Bisphosphonates for the Management of Patients with Breast and Prostate Cancer

*a report by*
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The skeleton is the most common site of metastatic disease and the most common site of first distant relapse in breast and prostate cancers. The term 'skeletal-related events' (SREs) refers to the major complications of tumour bone disease, namely pathologic fractures, the need for radiotherapy and bone surgery, spinal cord compression and hypercalcaemia. Patients with bone metastases from breast carcinoma have the highest frequency of SREs.[1] Taken from data in placebo groups of randomised bisphosphonates trials, the mean skeletal morbidity rate (i.e. the mean number of SREs per year) varies between 2.2 and 4 in breast cancer and close to 1.5 in prostate cancer metastatic to bone.

The propensity of breast and prostate cancer cells to proliferate in bone is best explained by a 'seed and soil' concept.[2,3] Cancer cells (the 'seed') appear to secrete 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 cell growth and their production of osteolytic factors. Osteoblasts targeted by cancer cell secretory products induce a marked increase in osteoclast proliferation and activity. In prostate cancer, enhanced bone formation in osteosclerotic lesions is also accompanied by a marked increase in bone resorption. Bisphosphonates inhibit bone resorption, essentially by inducing osteoclast apoptosis. Clodronate is metabolised to an adenosine triphosphate (ATP) analogue, which is toxic for osteoclasts. Nitrogen-containing bisphosphonates (pamidronate, ibandronate and zoledronic acid) interfere with the mevalonate pathway, which is essential to maintain cell membrane integrity and cell function.[4]

## Breast Cancer

### *Bisphosphonates Reduce Skeletal Morbidity in Metastatic Bone Disease*

Placebo-controlled trials with oral or intravenous (IV) bisphosphonates have shown that their prolonged administration can reduce the frequency of SREs by 30–40% in patients with bone metastases from breast cancer.

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.[5] Clodronate is now considered to be less effective than other bisphosphonates for the prevention of skeletal events.[6] Two double-blind, placebo-controlled studies comparing 90mg pamidronate infusions every four weeks to placebo infusions for up to two years in addition to chemo- or hormonotherapy in large series of breast cancer patients with at least one lytic bone metastasis demonstrated that pamidronate 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 any SRE.[7,8]

The value of newer, more potent, bisphosphonates has been studied extensively. The largest multicentre trial with zoledronic acid was randomised, double-blind and compared 4mg or 8mg of zoledronic acid to 90mg of pamidronate every 3–4 weeks for up to two years in the treatment of osteolytic lesions in breast cancer (n=1130) and in multiple myeloma (n=510). The primary efficacy end-point was the proportion of patients with at least one SRE.[9] Zoledronic acid 8mg was not more effective than 4mg, 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 4mg during the trial. The proportion of patients with at least one SRE was similar (46% for zoledronic acid and 49% for pamidronate). A pre-planned multiple-event analysis, according to the Andersen-Gill model, showed that zoledronic acid 4mg reduced the overall risk of experiencing an SRE by an additional 20% compared with pamidronate in the breast cancer subgroup. The short infusion time (15 minutes compared with two hours for pamidronate) is another evident advantage of zoledronic acid compared with pamidronate.[10]

Repeated 6mg monthly ibandronate infusions or oral ibandronate 50mg once daily also constitute efficient strategies to significantly reduce the morbidity rate of bone metastases from breast cancer.[11,12] In these trials, the primary efficacy end-point was the skeletal morbidity period rate (SMPR), defined as the number of 12-week periods with skeletal complications divided by the total observation time. Both forms of ibandronate significantly reduced SMPR and the number of new bone events compared with the placebo group. Bone pain was significantly reduced and maintained below baseline for the two years of evaluation. A pre-planned multivariate Poisson regression analysis showed that intravenous (IV) and oral ibandronate 6mg led to a statistically significant reduction in the risk of SREs compared with placebo by 40% and 38%, respectively.

### *Controversial Issues*

Criteria for when, in the course of metastatic bone disease from breast cancer, bisphosphonates should be started and stopped remain unclear. In patients who have experienced an SRE, the risk of developing another SRE is almost two-fold higher than in patients with no prior SRE. This implies that one should not wait for the first SRE to start bisphosphonate therapy. American Society for Clinical Oncology (ASCO) guidelines recommend the routine use of IV pamidronate or zoledronic acid in patients with breast cancer and radiographic evidence of bone destruction.[13] The ASCO panel considered it 'reasonable' to start IV bisphosphonates in women with an abnormal bone scan with localised pain and normal imaging techniques, but not if the abnormal bone scan is asymptomatic. They also advised that, once initiated, IV bisphosphonates should be continued until evidence of a substantial decline in the patient's general performance status (until patients are in a pre-terminal condition).

The cost-effectiveness of an extensive, early and prolonged use of bisphosphonates has not been established. The impact of monthly infusions on quality of life is unclear. The situation could be more favourable in patients receiving hormonal therapy when using oral bisphosphonates, especially ibandronate whose tolerance has been shown to be good in placebo-controlled phase III trials.[12] This compound is not approved in the US. Lastly, and most importantly, the risk of excessive anti-osteolytic therapy is more and more evoked. The recently described cases of osteonecrosis of the jaw, essentially reported after prolonged bisphosphonate therapy, could be partly due to an excessive inhibition of bone turnover.

Criteria are also lacking to determine if and how long an individual patient benefits from bisphosphonate administration, and the decision to continue therapy remains essentially empiric.

Promoting lifelong treatment is definitely in contradiction with the extreme paucity of data regarding the usefulness and the safety of treatment durations beyond two years. New biochemical markers of bone resorption may help identify those patients continuing to benefit from therapy. One such marker, urinary NTX (N-terminal type 1 collagen telopeptide), appears to be an excellent predictor of bone events, whether patients are receiving bisphosphonates or not.[14] The value of treatment frequency as a function of marker values is currently being tested and the routine use of bone turnover markers cannot be currently recommended.

Lastly, the fact that the efficacy of the highest 8mg zoledronic acid dose was not superior to the 4mg dosage suggests that we have reached a ceiling effect, at least with classical therapeutic schemes.[9] The event rate is reduced by 'only' 35–40%, even when bisphosphonates are started early, and this appears to be true whatever the compound. Maybe better results will be obtained with the use of substances blocking the RANK/RANK Ligand system, which plays a key role in osteoclast activation in tumour bone disease. Initial trials with a human anti-serum against RANK Ligand, named denosumab, have shown a much longer inhibitory activity on bone resorption than standard dose of pamidronate.[15] The prolonged inhibitory activity of denosumab on bone resorption is promising, but it is also possible that we have underestimated the role of cancer cells in the process of bone destruction.

### *Analgesic Effects of Bisphosphonates*

Pain is the most frequent symptom of bone metastases. The current opinion is that the IV route has to be selected for the treatment of bone pain. The demonstrated analgesic effects of oral ibandronate challenge this opinion.[12] Clinically meaningful bone pain relief seems to occur in about one half of the patients treated with pamidronate infusions and most of the analgesic effect is obtained after 1–2 infusions.

Placebo-controlled trials have established that all IV bisphosphonates can exert significant and rapid analgesic effects.[16] The optimal dose remains to be defined, especially since it is probably a function of the disease stage. The administration of high doses of ibandronate (4mg/day IV for four consecutive days) in patients with 'opioid-resistant' metastatic bone pain has been shown to be quite successful in an open trial in 18 patients with various tumours, including 10

with breast cancer.[17] Such intensive regimens could 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. Over the long term, randomised, placebo-controlled trials have shown that pamidronate, zoledronic acid and ibandronate exert useful pain relief.

### *Use of Bisphosphonates in the Adjuvant Setting and for Cancer Treatment-induced Bone Loss*

Bisphosphonates have the potential to reduce tumour burden in bone, whether indirectly by decreasing bone turnover or directly by one or several anti-tumour effects.[18] Published trials in the adjuvant setting have only used clodronate so far. The only placebo-controlled trial involving more than 1,000 unselected breast cancer patients after surgery treated for two years with 1,600mg clodronate or placebo, indicates that clodronate can indeed reduce the incidence of bone metastases by 31% at five years ($p=0.043$) and apparently prolong survival ($p=0.048$).[19] Newer aminobisphosphonates, such as ibandronate and zoledronic acid, are expected to inhibit bone metastases more effectively and they are currently being tested. Use of bisphosphonates in the adjuvant setting has to be considered experimental.

Aromatase inhibitors (AI) have become standard in the first-line endocrine treatment of breast cancer, as well as in the adjuvant setting. Cancer treatment-induced bone loss (CTIBL) is probably the most serious side effect of AI treatment. Increased bone loss and increased fracture rate have been reported. In the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial comparing anastrozole to tamoxifen in the adjuvant setting, at a median follow-up of three years, 7% of women assigned to anastrozole had experienced a fracture compared with 4.4% in the tamoxifen group.[20] Preliminary results indicate that the addition of zoledronic acid can effectively protect women against anastrozole- or letrozole-induced loss of bone mineral density in both the lumbar spine and hip.

## Prostate Cancer

### *Zoledronic Acid Reduces Skeletal Morbidity In Metastatic Disease*

There is only one prospective trial whose primary objective was to demonstrate a reduction in the frequency of objective SREs following bisphosphonate therapy. Hormone-refractory prostate cancer patients with bone metastases (n=643) were randomised to zoledronic acid 8mg, 4mg or placebo every three to four weeks.[21,22] As mentioned above for breast cancer, the group receiving 8mg was switched during the trial to 4mg because of renal toxicity.

At the end of the core trial, there was an absolute reduction of 11% corresponding to a relative reduction of 25% in the number of patients presenting with an objective bone complication. Although the number of patients became smaller, this difference was maintained at 24 months, as shown by a higher percentage of patients taking placebo who had SREs compared with those treated with zoledronic acid 4mg (49% versus 38%, $p<0.05$). In a multiple-event analysis, zoledronic acid 4mg significantly decreased the risk of developing skeletal complications by 36% compared with placebo ($p<0.005$). Although frequently used, there is no proof that bisphosphonates are beneficial in the earlier stages of the metastatic disease, i.e. before patients become hormone refractory.

### *Other Potential Indications*

In patients treated for bone pain due to metastatic bone disease from prostate cancer, uncontrolled trials have often been positive, while placebo-controlled studies were usually negative, whether for clodronate or pamidronate. Initial pamidronate uncontrolled trials reported impressive results but a more recent controlled trial suggests that pamidronate is no more effective than placebo in reducing bone pain or SREs over six months.[23] In a large-scale, placebo-controlled study of zoledronic acid, a favourable pain response, defined as a two-point difference on the 11-point scale of the Brief Pain Inventory (BPI) assessment, was observed in 33% of the zoledronic acid-treated patients compared with 25% for patients receiving placebo.[24] The effect on bone pain appears to be less marked when compared with the analgesic effects observed in breast cancer.

There is currently no indication for the use of bisphosphonates in the adjuvant setting in prostate cancer. Pamidronate and zoledronic acid can prevent castration-induced bone loss, but the effect on fracture rate is unknown.[25]

## Safety Aspects

Although generally well tolerated, bisphosphonates are associated with adverse events.[26] Characteristic side effects with oral bisphosphonates are gastrointestinal, such as dyspepsia, oesophagitis and

diarrhoea. IV 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 to the pamidronate figure.[9]

Although most cases of renal deterioration were mild and reversible, the US Food and Drug Administration (FDA) reported 72 cases of renal failure with zoledronic acid.[27] Renal safety data from a study of IV ibandronate in patients with breast cancer shows a low incidence of renal adverse events with ibandronate that is comparable to placebo (4% versus 4.5%).[11] The safety of prolonged ibandronate therapy administered as a 1–2 hour infusion is well demonstrated and on-going clinical trials are investigating the safety of repeated shorter 15-minute infusions. It is not known if prolonging the infusion time for zoledronic acid would reduce or eliminate the risk of renal adverse effects. Renal safety issues also affect patient management.

As an example, serum creatinine has to be monitored before each dose of zoledronic acid. Renal safety monitoring with IV ibandronate is not mandatory as no cases of renal failure have been reported. The renal safety of ibandronate has yet to be confirmed in routine clinical practice.

Osteonecrosis of the jaw (ONJ) was recently reported in patients receiving bisphosphonate therapy.[28] The estimated frequency of ONJ is around 1% per year of therapy in solid tumours and is seen after dental extraction and concomitant corticosteroid therapy. Length of exposure to bisphosphonates appears to be an essential risk factor for ONJ.[29] Caution is certainly required for the use of bisphosphonates beyond two years and it is advised that a dentist aware of this complication treats all patients before bisphosphonate treatment is started. ■

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