# E15. Treatment of metastatic bone disease

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## Introduction

Advanced cancers frequently metastasise to the skeleton, and the resulting bone destruction is associated with a variety of skeletal complications, including pathological fractures, bone pain, impaired mobility, spinal cord compression, and hypercalcaemia. It is estimated that more than 1.5 million patients worldwide have bone metastases. We now appreciate that the interaction between cancer and the bones is largely mediated by osteoclasts, irrespective of the underlying tumour type [1].

The treatment of metastatic bone disease requires high quality multi-disciplinary care. Rapid developments are occurring with improvements in reconstructive orthopaedic surgery, the development of bone-seeking radiopharmaceuticals, new endocrine, biologically-targeted and cytotoxic treatments, and, in particular, the development of bisphosphonates to prevent and treat skeletal complications.

## Clinical uses of bisphosphonates

Initially bisphosphonates were introduced into oncological practice to treat hypercalcaemia resulting from malignancy. Today, these agents have an increasing role in the management of metastatic bone disease and prevention of skeletal complications. The bisphosphonates are characterised by a P-C-P-containing central structure, referred to as a 'bone hook', and a variable side-chain that determines the relative potency and side-effects. On release from the bone surface, bisphosphonates are internalised by the osteoclast, where they cause disruption of the biochemical processes involved in bone resorption. Bisphosphonates may also have direct effects on cancer cells [2].

**Bisphosphonates for bone pain:** Radiotherapy remains the treatment of choice for localised bone pain, but many patients have widespread, poorly localised, non-mechanical bone pain, while others will experience recurrence of pain in previously irradiated skeletal sites. The bisphosphonates provide an alternative treatment approach to the management of these patients with clinically meaningful pain improvement in approximately 50% of patients. Until recently, it appeared that the intravenous (i.v.) route was necessary for a significant effect on metastatic bone pain. However, recent data with the oral formulation of ibandronate indicate that this agent also has beneficial effects on bone pain.

**Bisphosphonates to prevent skeletal morbidity in breast cancer:** The absorption of bisphosphonates from the gut is poor, variable, and dramatically inhibited by food intake. Nevertheless, several studies have been reported using oral therapies. Clodronate has some effect on skeletal morbidity, while ibandronate, a new, highly potent amino-bisphosphonate is active with a broadly similar impact on skeletal morbidity to that observed in earlier placebo-controlled trials with other bisphosphonates.

It was the results of two double-blind, placebo-controlled trials of pamidronate in addition to cytotoxic or endocrine treatments for breast cancer patients that established i.v. bisphosphonate treatment in breast cancer as the 'standard of care' in the mid-1990s. These two studies [3,4] had similar designs, with the exception of the systemic anticancer treatment at study entry. They clearly showed that pamidronate had clinically important effects on skeletal morbidity, with a reduction in the proportion of patients experiencing skeletal events, as well as the time to the first skeletal event, the skeletal morbidity rate and the total number of skeletal complications. Beneficial effects were also seen with regard to pain, analgesic use and quality of life. However, there were no significant effects on overall survival.

Subsequently, zoledronic acid has been compared with pamidronate in 1130 patients with advanced breast cancer and bone metastases. Although the proportion of patients experiencing one or more events was similar, the study did show overall superiority for 4mg zoledronic acid over pamidronate. Using a pre-planned multiple event analysis, which assesses both the number and time course of events, a reduction of 20% in the risk of developing a skeletal complication was observed (Hazard Ratio 0.799; 95% confidence intervals 0.68–0.98, P=0.025) [5]. This improved outcome can be attributed to the more complete inhibition of bone resorption seen with zoledronic acid. At all time points, urinary n-telopeptide (NTX) excretion, a marker of bone resorption, was significantly lower in the zoledronic acid group compared with the pamidronate group.

I.v. ibandronate has also been evaluated in advanced breast cancer. A recent report of a phase III placebo-controlled trial of monthly infusions in breast cancer has shown a significant reduction in skeletal-related morbidity with 6 mg ibandronate [6]. Additionally,

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improvements in pain and quality of life were clearly demonstrated at this dose.

**Optimum use of bisphosphonates in metastatic bone disease:** The optimum choice of bisphosphonates is confounded by varied and somewhat clinically-naïve assessments of clinical benefit, although zoledronic acid is the best agent currently available. Skeletal-related events (SREs) are important endpoints, but are of varying importance; the clinical relevance of an asymptomatic vertebral fracture is completely different from spinal cord compression causing paraplegia. Multiple event analysis techniques, such as the Andersen-Gill method, that evaluate both the number and time between individual events are most informative. Robust economic modelling based on multiple event analysis, and ideally incorporating clinical weighting of SREs would help define the value of bisphosphonate administration more precisely.

Questions persist as to the timing and duration of treatment, and whether patients at greatest need of treatment can be identified to improve the cost-effectiveness of bisphosphonate treatment. Health economic analyses have shown that bisphosphonates are a relatively expensive intervention. The use of specific bone resorption markers, such as type I collagen crosslinks, may enable better selection of patients and allow clinicians to tailor therapy to maintain a normal rate of bone resorption. This is an intense area of current investigation as it is perhaps both unrealistic and unaffordable to administer long-term bisphosphonate treatment to every cancer patient with bone metastases. Evidence is accruing that, as in benign bone diseases, the aim of bisphosphonate treatment in metastatic bone disease should be to normalise bone resorption. Bone resorption levels correlate with both subjective improvement and the incidence of SREs. Patients with accelerated bone resorption are at higher risk for SREs and are thus most likely to personally benefit from the use of a bisphosphonate.

In a study of 121 patients with metastatic bone disease, urinary NTX of type I collagen was assessed as a predictor of skeletal morbidity [7]. NTX was strongly correlated with the number of SREs and/or death ($P<0.001$). Patients with NTX values above 100 nmol/mmol creatinine were many times more likely to experience a SRE/death than those with NTX below this level ($P<0.01$). These observations suggest that a more cost-effective use of bisphosphonates might be to reserve them until patients have NTX levels above either 50 or 100 nmol/mmol creatinine, and adjust the dose and schedule to maintain a normal (<50 nmol/mmol creatinine) rate of bone resorption. Randomised trials to assess this approach are planned.

Because bisphosphonates are providing supportive care, reducing the rate of skeletal morbidity but not necessarily abolishing it, the criteria for stopping their administration are different from those used for classical antineoplastic drugs. They should not be stopped when a skeletal event occurs, or when there is progression in bone, but be continued for as long as bone disease is a clinically relevant problem. If bisphosphonate treatment is stopped, bone resorption rates will increase within a few weeks and this will leave the patient again at a high risk for skeletal complications. The pharmacodynamics of bisphosphonates in metastatic bone disease are very different (much shorter duration of action) than those observed in benign bone disease or post-menopausal osteoporosis.

## Conclusions

Bisphosphonates should now be part of 'standard care' for women with bone metastases from breast cancer. How can we improve further on the current situation? It is unlikely that other bisphosphonates in development are going to be more effective than the modern, potent agents now in clinical use. Attention now needs to turn to agents that target other aspects of the interaction between cancer and the bones. There are a number of promising compounds in development including endothelin-1 antagonists, antibodies to parathyroid-related hormone (PTHrP), and agents that interact with the receptor activator for NFkappaB (RANK)/RANK ligand/osteoprotegerin (OPG) cell signalling system between osteoclasts and osteoblasts, that may improve further on the results of bisphosphonate treatment.

## References

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