Bone metastases are a major cause of morbidity in patients with solid tumours, particularly those with breast, prostate, lung, kidney and thyroid cancers. Common bone related complications include pain, pathological fractures, hypercalcaemia, spinal cord compression and reduced mobility. The pathophysiology of bone metastases is multi-factorial resulting in osteolytic metastasis (when increased bone destruction predominates), sclerotic metastases (when increased osteoblastic activity predominates) or mixed osteolytic and osteoblastic metastases.

Bisphosphonates are chemical compounds known to inhibit osteoclast function and bone resorption. They are effective in conditions characterised by osteoclast-mediated bone resorption such as Paget’s disease and osteoporosis, and, since the 1990s they have become the treatment of choice for tumour-induced hypercalcaemia. Many studies have investigated the use of bisphosphonates in reducing skeletal complications (hypercalcaemia, bone pain, fractures, need for surgery or radiotherapy) associated with bone metastases, particularly in patients with multiple myeloma (MM) and breast cancer.

Pharmacology

Bisphosphonates, analogues of naturally occurring endogenous pyrophosphate, are drugs that have a high affinity for bone mineral. This is determined by their common chemical motif (P-C-P), whilst their potency and side effects is determined by the structure of their side chains. The precise mechanism(s) of bisphosphonate inhibition of bone resorption is not known but osteoclast inhibition (through a variety of mechanisms), macrophage inhibition and possibly direct anti-tumour effects have been proposed.

Bisphosphonates are available in both oral and intravenous forms. Of the oral formulations approved for use in malignancy, clodronate is the oldest. Whilst there have been published studies indicating some benefit from oral pamidronate, its poor oral bioavailability, gastrointestinal toxicity and the superiority of intravenous pamidronate have kept the oral form out of the clinic. In Australia there are currently two bisphosphonates commercially available: clodronate (Bonefos®; oral) and pamidronate (Aredia®, intravenous).

The recommended dose of sodium clodronate is 1,600mg p.o. daily, 1/2 hour before a meal or two hours after a meal, whilst that of disodium pamidronate is 90mg i.v. over one to two hours every three to four weeks. Toxicity with oral clodronate is usually mild and in the form of gastrointestinal disturbance that can be alleviated with divided dosing. Common adverse reactions with disodium pamidronate are asymptomatic hypercalcaemia, influenza-like symptoms and mild fever. These are usually mild and transient. Monitoring of electrolytes, calcium, magnesium and phosphate is nonetheless recommended.

More potent bisphosphonates under clinical evaluation or approved overseas for use in malignant states include ibandronate (1,000 times as potent than clodronate) and zolendronate (10,000 times as potent as clodronate). However the oral bioavailability of these new agents remains poor. Apart from the greater potency of these new agents, advances in the administration of the intravenous forms have permitted shorter infusion times without complications.

Bisphosphonates in multiple myeloma

Multiple myeloma is a plasma cell disorder characterised by lytic bone lesions, abnormal bone marrow plasmacytosis or paraproteinaemia. In patients with MM, skeletal complications are inevitable and hypercalcaemia is common. In fact, 95-100% of patients with MM develop lytic bone lesions during the course of their illness. Randomised controlled trial evidence has shown that in MM, bisphosphonates reduce bone pain, increase quality of life, and reduce the number of skeletal events. Subgroup analyses in two oral clodronate studies have suggested that oral clodronate may prolong survival in MM patients without overt skeletal disease at diagnosis. This observation is now the subject of ongoing study. In Australia, pamidronate 90mg i.v. every four weeks is the most commonly used bisphosphonate strategy in multiple myeloma. Use in this setting is supported by the Pharmaceutical Benefits Scheme (Highly Specialised Drugs Programme).

Bisphosphonates in advanced breast cancer

Sixty to 75% of women with advanced breast cancer suffer from bone metastases, which are a significant cause of cancer-related morbidity in these patients. Since the 1980s there have been numerous studies investigating the role of bisphosphonates in women with advanced breast cancer. These include oral clodronate and pamidronate, as well as intravenous pamidronate, clodronate, ibandronate and recently zolendronate. Several reviews have summarised the current status of the literature and Guidelines were published in 2000 by the American Society of Clinical Oncology (ASCO). A Cochrane systematic review is currently in progress. Interim results from this review were presented at the 2001 Annual Scientific Meeting of the Australian and New Zealand Breast Cancer Trials Group and will be referred to here.

Since 1983, there have been 16 published randomised controlled studies comparing therapy with a bisphosphonate to therapy without a bisphosphonate in women with early or advanced breast cancer. Of these, 10 studies have been in women with established bone metastases and three studies in women with advanced breast cancer but no bone metastases. Eight of these studies have been with oral bisphosphonates (six with oral clodronate and two oral pamidronate), three with i.v. pamidronate and one study with i.v. clodronate and ibandronate respectively. The largest studies in advanced breast cancer were the combined Aredia Study Group studies 18 and 19, with 751 patients included, an ibandronate study (462 patients) and two other pamidronate studies (404 and 295 patients respectively). The oral bisphosphonate studies in advanced breast cancer were all relatively small studies, with a range of 10 to 173 patients included in each.
The primary study endpoints varied across the studies but included at least one of the following outcomes: skeletal events (defined as any or all of the following: new bone metastases, pathological fractures, spinal cord compression, irradiation of or surgery to bone or the development or progression of bone pain); Quality of life (QoL); bone pain; survival. A pooled comparison of efficacy across these studies is difficult because of differences in patient selection, concomitant therapies and outcome measures. Nonetheless, one can still consider the global effect of bisphosphonates on skeletal events, where the observed clinical benefits include reduced hypercaemic episodes, pathological fractures, the need for surgery and bone pain. Only six studies adequately evaluated QoL.

With regards to skeletal events in women with established bone metastases the strongest evidence for benefit is seen with the use of pamidronate i.v. (90mg every three to four weeks for two years) which reduced skeletal morbidity by 35% (p<0.001, in Aredia Study Group Studies 18 and 19). There was a significant reduction in the cumulative number of skeletal events observed with 60mg pamidronate every three to four weeks for two years (p<0.01), whilst a significant delay in progression of bone metastases and reduction in bone pain was observed with 45mg pamidronate i.v. every four weeks (increase median time to progression by 48%, p = 0.02). There was a 44% reduction in the skeletal event rate observed with the use of ibandronate 6mg i.v. monthly (p = 0.025). There was a trend for improved overall QoL and significantly reduced bone pain with 90mg pamidronate i.v. and significantly improved QoL and reduced bone pain with high dose ibandronate 6mg i.v monthly). No study showed an effect of therapy on survival.

The use of oral bisphosphonates is associated with a 36-60% reduction in skeletal events in women with advanced breast cancer. This evidence comes from the two largest clodronate studies (N= 133 and p < 0.01, and N = 173 and p = 0.001 respectively) and a single oral pamidronate study (N = 161, p < 0.001). In women with advanced breast cancer but no bony metastases, one of three studies showed that oral clodronate compared to placebo significantly reduced the incidence of bone metastases (32 vs 63, p<0.005) however the number of patients affected was not significantly different (15 vs 19 respectively). From this evidence the American Society of Clinical Oncology Bisphosphonates Expert Panel recommended in 2000 the use of i.v. pamidronate over one to two hours every three to four weeks in women with metastatic breast cancer and radiographic evidence of bony metastases who are concurrently receiving hormonal therapy or chemotherapy. In Australia, i.v. pamidronate has been approved for several years by the Pharmaceutical Benefits Scheme (Highly Specialised Drugs Programme) for patients with lytic bone disease from breast cancer, whilst the indication for oral clodronate has recently been extended to permit its use in this setting.

The optimum timing and duration of bisphosphonate treatment for women with advanced breast cancer is not known. Safety data is available beyond three years for oral clodronate and up to six years for i.v. pamidronate and zolendronate. This data suggests that women with advanced breast cancer could be treated indefinitely.

**Bisphosphonates in early breast cancer**

In the adjuvant setting three studies have been presented of results to date. Two published studies compared adjuvant oral clodronate (up to three years) in addition to standard adjuvant chemotherapy or hormonal therapy with an open control in women with high-risk early breast cancer. These two studies showed contradictory results. The third and largest study compared the addition of oral clodronate to placebo for two years in over 1,000 women. Results from this study are only available in abstract form with final study results in preparation. Interim pooled analysis of these studies shows a 37% reduction in the risk of developing bone metastases with the use of adjuvant oral clodronate (Relative risk of developing bone metastases 0.73 (95% CI 0.55-0.98), unpublished results). Whilst the use of bisphosphonates as adjuvant therapy to reduce bone metastases remains open, there is some evidence indicating reduced decline in bone mineral density with the use of adjuvant oral clodronate. The NSABP-34 study, a double blind randomised placebo-controlled study of oral clodronate in women with early breast cancer, has recently commenced.

**References**