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Bisphosphonates and RANK ligand inhibitors for the treatment and prevention of metastatic bone disease

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ABSTRACT

Bisphosphonates (BPs) are potent inhibitors of osteoclast-mediated bone resorption, which is increased when cancer cells invade bone. BPs are an established treatment for cancer that has spread to bone, and effectively reduce pain and other skeletal-related events. New directions in metastatic bone disease (MBD) include personalised BP therapy, such as using bone markers to guide frequency of BP administration and bone targeting agents such as denosumab (AMG 162). Clinical trials strongly suggest that denosumab might play a defined role in the future management of MBD. In terms of potential anti-cancer activity, early data tentatively suggest that zoledronic acid might have a role to play in the prevention of metastatic disease, though whether this is a direct effect on cancer cells, or indirect via the bone marrow micro-environment, or both, is as yet undiscovered. The definitive answer as to the role of adjuvant BP in early cancer is being addressed, with over 20,000 patients with breast, prostate or lung cancer currently participating in adjuvant BP randomised trials. The results of these trials should be available in the next few years, and this will establish whether BPs given early in the course of cancer will be able to prevent the formation of metastases, bone or otherwise.

1. Introduction

In advanced cancer, approximately 50% of patients with bone metastases develop a skeletal-related event (SRE), such as bone pain requiring radiotherapy, fractures, bone surgery, spinal cord compression, hypercalcaemia and bone demineralisation. Bisphosphonates (BPs) are an established treatment for metastatic bone disease (MBD), as they are potent inhibitors of osteoclast-mediated bone resorption, which is increased when tumour cells invade bone. This review focuses on new insights into BP mechanism of action in bone, the use of marker-directed BP therapy in MBD, the role of BPs in early cancers and new bone targeting agents such as denosumab (AMG 162).

1.1. *Structure and molecular pathways*

BPs are stable analogues of pyrophosphate, with a P–C–P structure in which a central carbon atom replaces the oxygen found in pyrophosphate (P–O–P). Side chains R^1 and R^2 are attached to the carbon atom (Fig. 1). R^1 is known as the bone hook and influences the ability to bind to bone. R^2 influences the anti-resorptive ability[1] with nitrogen (N)-BPs, such as ZA (Fig. 2) being the most potent bone resorption inhibitors.[2] BPs bind avidly to hydroxyapatite bone mineral surfaces and are selectively internalised by osteoclasts,[3] leading to loss of the ruffled border[4] and disturbance of the cytoskeleton,[5] which in turn causes loss of actin rings, and inhibition of bone resorption.[4] Within the osteoclast, N-BPs inhibit the

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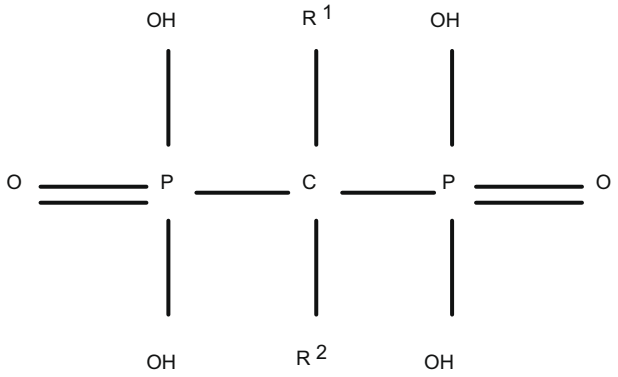

Fig. 1 – P–C–P structure of bisphosphonates. R^1 influences ability to bind to bone, whilst the R^2 side chain influences anti-resorptive ability.

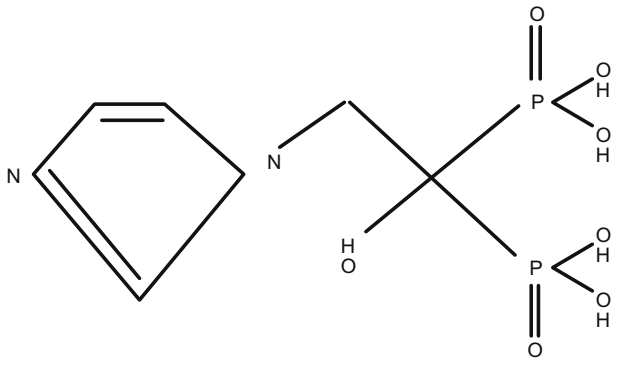

Fig. 2 – Structure of zoledronic acid, which contains two nitrogen atoms within an imidazole ring structure.

mevalonate pathway[6] (Fig. 3), the main target being farnesyl pyrophosphate synthase (FPPS).[7,8] FPPS inhibition causes loss of farnesyl, and geranylgeranyl, pyrophosphate, required for prenylation (i.e. post-translational lipid modification), of signalling GTPases, such as Ras, Rho and Rac.[9] This leads to defective intracellular vesicle transport,[10] and loss of prenylated proteins, ultimately leading to induction of apoptosis, via activation of the caspase cascade,[11] and interference of processes, as seen in Table 1.

Recent work suggests that N-BP inhibition of FPPS might also cause an accumulation of isopentenyl diphosphate (IPP) (Fig. 3), which is metabolised to an intracellular ATP analogue, triphosphoric acid 1-adenosin-5′-yl ester-[3-methylbut-3-enyl] ester (Apppi).[12] Apppi inhibits mitochondrial ADP/ATP translocase, causing loss of mitochondrial membrane potential and direct apoptosis induction.

1.2. *Treatment of MBD*

Multiple, randomised controlled trials over the past two decades have clearly demonstrated that BPs are effective in reducing bone pain and skeletal morbidity from breast cancer and multiple myeloma (MM).[13] Zoledronic acid is the most potent BP, and reduces the risk of skeletal complications by 30–50%, not only in breast cancer, but across the range of solid tumours affecting bone. Quite appropriately, BPs are increasingly used alongside specific anti-cancer treatments to prevent skeletal complications.[13,14]

1.3. *Marker-directed therapy in MBD*

Within bone, tumour-induced osteolysis is associated with increased turnover of bone resorption markers, such as urinary (u)-N-telopeptide of type I collagen (NTX) and serum (s) bone formation marker bone-specific alkaline phosphatase. Patients with solid tumours and MBD, and high levels of u-NTX at baseline, are at an increased risk of SRE, disease progression and even death, compared with patients with normal levels of u-NTX.[15] Further work has investigated the association among BP treatment in MBD, u-NTX levels and clinical outcome. Patients with MBD secondary to breast ($n = 578$) and prostate cancer ($n = 472$), or non-small cell lung cancer/other solid tumours ($n = 291$) received ZA or control (pamidronate in breast cancer, placebo other groups) for up to 2 years. Patients were stratified by NTX (normal, or high, [< or >64 nmol/mmol, respectively]). Within the high NTX group, 81%, 70% and 81% of patients with breast, prostate and lung/other tumours, respectively, had normalisation of NTX levels after 3 months of ZA, and importantly, normalisation of NTX was correlated with reduced SREs and improved overall survival.[16]

Pamidronate also normalises NTX levels, but to a lesser extent than ZA (65%), especially in patients with high baseline NTX levels. Patients with NTX > 100 were nearly three times more likely to achieve a normal NTX level of <50 with zoledronic acid as opposed to pamidronate.[17] As ZA is not without toxicity, notably occasional renal dysfunction and jaw osteonecrosis, the ability to personalise therapy will likely benefit patient care. The recently closed 'BISMARK' trial is assessing whether patients can receive ZA based on u-NTX (4- to 16-weekly scheduling), instead of the current recommended 4-weekly scheduling for all. Results are anticipated in 2011. For patients who prefer oral therapy, oral ibandronate (50 mg/d) in women with breast cancer and MBD reduces bone resorption markers by a similar proportion to that of ZA,[18] and seems to be associated with fewer renal adverse events.[19]

2. The role of the RANK/OPG pathway

Regulation of normal bone remodelling occurs via the receptor activator of nuclear factor κB/RANK ligand/osteoprotegerin (RANK/RANKL/OPG) pathway, which is disrupted in MBD. Regardless of the tumour type causing MBD, this triad of molecules regulates osteoclast maturation, differentiation and survival. Osteoblasts and stromal cells express RANKL (a member of the tumour necrosis factor family), which binds to RANK present on pre-osteoclasts and mature osteoclasts. This induces differentiation and promotes the function of osteoclasts.[20,21] Excessive bone resorption is prevented by the decoy receptor OPG, produced by osteoblasts, that binds to RANKL, thus preventing interaction between RANKL and RANK.[22] This tightly controlled system is lost when cancer cells invade the bone micro-environment, as tumour cells induce excessive osteolysis, via the expression of RANK[23] or