New developments of aminobisphosphonates: the double face of Janus

D. Santini*, S. Galluzzo, B. Vincenzi, G. Schiavon, E. Fratto, F. Pantano & G. Tonini

Department of Medical Oncology, University Campus Bio-Medico, Rome, Italy

**Background:** Bisphosphonate (BP) therapy has become a standard of therapy for patients with malignant bone disease. In vivo preclinical and preliminary clinical data indicate that BPs may prevent cancer treatment-induced bone loss and the onset of malignant bone disease in patients with early-stage cancer.

**Design:** This review will describe the preclinical evidences of action of BPs on osteoclasts and tumor cells. In addition, the effects of principal BPs on skeletal disease progression in patients with breast cancer, prostate cancer, non-small-cell lung cancer and other cancers will be reported. The preliminary clinical data from retrospective trials on the effect of zoledronic acid (ZA) on survival will be described and the ongoing adjuvant phase III trial will be analyzed.

**Conclusions:** This review will describe the preliminary clinical evidences from prospective studies on the effect of ZA treatment on the prevention of bone metastasis.

**Key words:** bisphosphonates, bone loss, bone metastases, survival, zoledronic acid

**Introduction**

Bisphosphonates (BPs) are a class of chemicals that share a basic phosphate-carbon-phosphate core and bind avidly to the bone mineral at sites of active bone metabolism. Over the past two decades, these drugs have assumed a significant role in the treatment of metabolic bone disorders related to bone resorption such as postmenopausal osteoporosis, Paget’s disease, tumor-associated osteolysis and hypercalcemia. These compounds have high affinity for calcium ions and therefore target bone mineral, where they are internalized by bone-resorbing osteoclasts and inhibit osteoclast function [1, 2]. They can be segregated into two distinct pharmacological classes: nitrogen-containing (N-BPs) and nonnitrogen-containing BPs (non-N-BPs) based on their molecular mechanism of action [3]. Nitrogen-containing BPs such as zoledronic acid (ZA), pamidronate (PA), alendronate, ibandronate and risedronate act intracellularly by inhibiting farnesyl diprophosphate synthase, an enzyme of the mevalonate pathway. Several intermediates in this pathway, including farnesyl diphosphate synthase, an enzyme of the mevalonate pathway. Several intermediates in this pathway, including farnesyl pyrophosphate and geranylgeranyl pyrophosphate, are required for the posttranslational modification (i.e., prenylation) of guanosine triphosphate-binding proteins such as Ras, Rho and Rac [4]. These signaling molecules are involved in the regulation of cell proliferation, cell survival and cytoskeletal organization [5–8]. Nonnitrogen-containing BPs such as clodronate and etidronate do not inhibit protein prenylation and have a different mechanism of action that seems to involve primarily the formation of cytotoxic metabolites in osteoclasts, thereby leading to loss of the mitochondrial membrane potential and to direct induction of apoptosis [9, 10]. Of the available BPs, i.v. ZA has demonstrated the broadest clinical activity (prevention or delay onset of skeletal complications) and it is actually approved for the treatment of bone metastases from any solid tumor in many countries. ZA is the only BP with activity evidence for the prevention of skeletal complications in patients with bone metastases secondary to solid tumors other than breast or prostate cancer, as in lung and renal cancer [11].

**Antitumor activity: preclinical results**

Growing *in vitro* and *in vivo* evidences pointed out that BPs act on cell types different from osteoclasts such as tumor cells (TCs) and endothelial cells (ECs) [12]. In fact, extensive *in vitro* and *in vivo* preclinical evidences support that N-BPs display an antitumor activity, including direct antitumor effects (*in vitro* and animal models) such as induction of TC apoptosis. Both N-BPs and non-N-BPs induce apoptosis of osteoclasts as well as TCs by activation of caspases [13–20]. These events may be
precipitated by the inhibition of Ras activation which in turn requires protein prenylation, specifically farnesylation [25].

BPs have also been shown to inhibit adhesion of TCs to extracellular matrix (ECM) proteins and to promote invasion and metastasis. Inhibition of the mevalonate pathway and induction of caspase activity are important mechanisms in explaining the inhibitory effects of N-BPs on TC adhesion to the ECM and on invasiveness [26–29]. In vitro and in vivo findings have demonstrated that N-BPs, particularly ZA, can affect ECs exerting a suppressive effect on angiogenesis [30]. In fact, N-BPs inhibit the expression of vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) that induce the proliferation of ECs and enhance the formation of capillary-like tubes. Clinical data indicate that N-BPs can also reduce in humans the circulating levels of both PDGF and VEGF [31–33]. Interestingly, this potential antiangiogenetic effect could expand N-BPs' efficacy in the treatment of malignant bone diseases and it could extend their potential clinical use to other diseases with an angiogenic component.

BPs have demonstrated antitumor activity in preclinical models and clinical evidence indicates that this class of drugs may slow the progression of bone lesions or prevent breast metastasis [21]. Preclinical evidences of antineoplastic effects on different animal models provide convincing evidence of the potential of ZA to induce TC apoptosis in bone lesions, reduce tumor burden in bone, reduce the number of osteolytic lesions in tumor-bearing mice, prevent formation and progression of bone metastases in a variety of tumor models and reduce serum levels of tumor markers [22, 34, 35]. Moreover, preclinical evidences in animal models support the role of ZA in the prevention of visceral metastases [36]. Finally, evidences from in vitro and in preclinical in vivo models indicate a synergistic antitumor activity of BPs when used in combination with cytotoxic drugs, targeted molecular and biological therapies and radiotherapy [37–40]. All these findings allowed the translation from preclinical studies to clinical trials.

**Prevention of cancer treatment-induced bone loss: first clinical evidences**

With the development of new-generation BPs, such as ZA, the role of BPs in the treatment of malignant bone disease continues to expand and new opportunities are being explored.

Preclinical and preliminary clinical data indicate that BPs may prevent cancer treatment-induced bone loss (CTIBL) [11]. Patients receiving adjuvant hormonal therapy for breast cancer or androgen deprivation therapy for prostate cancer are at a high risk for CTIBL because of reduced estrogenic signaling. Oral clodronate, oral risedronate and i.v. ZA have demonstrated efficacy in preventing CTIBL in patients receiving hormonal therapy for breast cancer [41, 42].

Recently, Brufsky et al. [43] reported a first study (Z-FAST, Zometa-Femara Adjuvant Synergy Trial) on ZA therapy in the prevention of adjuvant letrozole-induced bone loss in postmenopausal women with early breast cancer. Patients were randomly stratified to receive either upfront or delayed start ZA (4 mg every 6 months). The delayed group received ZA when lumbar spine (LS) T score decreased to less than −2 or when a nontraumatic fracture occurred. The primary objective was the evaluation of percent change in LS BMD at 12 months. With 1 year of follow-up, results of the primary end point of the ZA–letrozole adjuvant synergy trial indicate that upfront ZA therapy prevents (LS BMD higher 4.4% and 3.3% in the upfront than in the delayed group, \( P < 0.0001 \)) bone loss in the LS in postmenopausal women with early breast cancer. Interestingly, among patients with normal baseline, BMD LS measurement at 12 months 3.4% versus 12.6% of upfront and delayed group, respectively, showed mild to moderate osteopenia (T score ≤ −1 to ≥2), whereas among those with basal osteopenia 1.4% versus 14.8% (upfront and delayed group, respectively) developed severe osteopenia (T score < −2).

Twenty-four month follow-up (Z-FAST 24 month) BMD data presented by Brufsky et al. (personal communication data presented at the 2006 San Antonio Breast Cancer Symposium) indicate that the overall difference in the percentage change in BMD, at both LS and total hip measurements, is greater respect to 12-month BMD change, when the two groups are compared. These data demonstrate that the anticancer efficacy of letrozole can be combined safely and effectively with the bone-protective effect of ZA. Moreover, bone loss can be easily managed/prevented with concomitant use of ZA and upfront ZA therapy provides the greatest benefit to breast cancer patients at risk of bone loss and fracture. On the other hand, in patients receiving androgen deprivation therapy for prostate cancer, ZA has produced significant increases in bone mineral density compared with baseline values [44].

**BPs and survival: preliminary clinical data from retrospective trials**

The first preliminary retrospective analysis (Berenson et al., personal communication data presented at the 2006 American Society of Clinical Oncology) on survival rate has been carried out in patients with multiple myeloma included in a prospective phase III study comparing the effect of ZA with PA. Patients were stratified by baseline bone alkaline phosphatase (BALP) levels. Among patients with high BALP, ZA improved survival (survival rate 25 months) compared to PA. Moreover, ZA reduced risk of death by 42% and by 55% among patients with a baseline and high BALP level, respectively. It is interesting to observe that the highest impact on risk of death concerns a subset of patients (high BALP) with worse prognosis. This finding could indicate that tumors characterized by low sensibility to standard therapy are more responsive to ZA therapy. This represents the first evidence in literature demonstrating a positive impact on survival of BP therapy in cancer patients. Moreover, although preliminary, the positive effect on survival was confirmed in a retrospective analysis of a phase III trial of ZA in patients with bone metastasis from lung cancer and high baseline N-telopeptide levels (NTX) (Major et al., personal...
communication, data presented at the 2006 American Society of Clinical Oncology). The results showed a reduction of the relative risk ratio (0.650, risk reduction 35%) of death in patients with high urinary NTX levels at baseline who received ZA compared with those who received placebo. The relative risk ratios of death in patients with high urinary NTX levels at baseline stratified by serum bone-specific alkaline phosphatase levels showed a reduction (risk ratio 0.537, risk reduction 46%) into the subset with high BALP levels. No differences were detected comparing patients with normal BALP levels. Another, even if preliminary, retrospective analysis evaluated the reduced risk of disease progression in a subset of breast cancer patients with bone metastases treated with ZA and compared with PA (Lipton, personal communication data presented at the 2006 San Antonio Breast Cancer Symposium). The results support a reduced risk of overall disease progression (≈24%, hazard ratio (HR) = 0.760; P = 0.021) in patients who developed bone metastases ≤3 years from initial diagnosis and in those with a baseline BPI score >3.0 (28% HR = 0.719; P = 0.009).

**BPs and survival: prospective studies as adjuvant therapy**

Prospective studies were designed to evaluate the role of ZA as adjuvant therapy in different tumors. Among them, the AZURE study was designed on patients with breast cancer stage II/III (3300 patients), randomization criteria (standard therapy plus/minus ZA 4 mg every 15 min. Six doses once every 3–4 weeks, eight doses once every 3 months, five doses once every 6 months), follow-up 10 years for survival and recurrence of disease. The S0307 trial design on breast cancer patients is enrolling stage I, II, IIIa breast cancer patients receiving 'standard' systemic therapy. Randomized three arms: oral ibandronate 50 mg/day for 3 years; oral clodronate 1600 mg/day for 3 years, i.v. ZA 4 mg monthly for 6 months, then every 3 months for 2.5 years. The EAU-ZEUS study on prostate cancer patients is designed to evaluate if the early administration of ZA in high risk (Gleason score >8 a/o presence of positive lymph nodes and/or PSA >20 at diagnosis) can prevent or delay the appearance of bone metastases. Randomization ZA 4 mg every 3 months for 48 months compared to control group. The results of these trials on the impact of BPs as adjuvant therapy in tumor patients will be of enormous interest in defining the clinical benefit of BP’s adjuvant therapy.

**Preliminary clinical evidences from prospective studies on the effect of ZA treatment on the prevention of bone metastasis**

A randomized, open-label, prospective study that examined the effect of preventive ZA treatment on the development of bone metastases in patients with recurrent solid tumors, without bone metastases at the time of randomization, reported interesting results [45]. Forty patients were randomized into the trial to either receive ZA or no treatment. Bone metastases-free patients were 60% (ZA) versus 10% (control) (P < 0.0005) and 20% (ZA) versus 5% (control) (P < 0.0002) at 12 and 18 months, respectively. This study included a small sample of patients and the results are interesting but preliminary. Moreover, an integrated analysis of Z-FAST and ZO-FAST studies find out exciting data on disease recurrence (Brufsky et al., personal communication data presented at the 2006 San Antonio Breast Cancer Symposium). In fact, at 12-month follow-up, a difference was reported in term of disease recurrence (0.8 versus 2.2%) and median time to disease recurrence (8.6 versus 6.4 months) between the upfront and the delayed groups.

Although the 12-month follow-up is too short, these preliminary data are encouraging. Results at 2, 3 and 5 years as well as data on impact on skeletal events and on survival (time to disease progression) will be mandatory. The results of these clinical trials should further define the clinical benefit of BPs in the oncology setting.

**References**