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REVIEW

Bisphosphonates as antimyeloma drugs

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In patients with symptomatic multiple myeloma (MM), bisphosphonate (BP) treatment has been widely used to prevent bone loss and preserve skeletal health because of its proven effects on inhibiting osteoclast-mediated bone resorption. In addition to their effects on osteoclasts, it is becoming increasingly evident that BPs may have additional effects on the bone microenvironment and cells other than osteoclasts that may potentially inhibit the development and progression of MM. This review focuses on the pathophysiology of MM with an emphasis on the events that drive MM progression within the bone and the mechanisms by which BPs may inhibit specific processes. The underlying molecular mechanisms that drive the modulation of cellular fate and function and consequent physiological outcomes are described. Direct effects on myeloma cell growth and survival and the interactions between myeloma cells and the bone microenvironment are discussed. Clinical evidence of the antimyeloma effects of BPs is emerging and is also reviewed.
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Introduction

Monoclonal gammopathy of unknown significance is an asymptomatic condition characterized by the clonal expansion of plasma cells. In a small proportion of patients, monoclonal gammopathy of unknown significance progresses through a multistage process to symptomatic and malignant multiple myeloma (MM). There are few somatic genetic differences between the asymptomatic monoclonal gammopathy of unknown significance and malignant MM.[1] Interactions between myeloma cells and bone cells and the extracellular matrix proteins within the bone microenvironment underlie this progression and are mediated through cell surface receptors—for example, integrins, cadherins, selectins, syndecans and the immunoglobulin superfamily of cell adhesion molecules.[2] These interactions trigger a self-amplifying cascade of events that result in the secretion of cytokines and growth factors (such as vascular endothelial growth factor (VEGF), insulin-like growth factor-1, interleukin-6 (IL-6) and IL-1β) and members of the tumor necrosis factor superfamily (TGFβ1, CCL3, hepatocyte growth factor and IL-10) that promote the growth and proliferation of myeloma cells, increase bone resorption and enhance drug resistance by inducing antiapoptotic pathways.[1,2] The underlying mechanisms and pathways driving this vicious cycle of tumor growth and bone destruction have been extensively reviewed.[1,3–5]

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Bisphosphonates (BPs) are degradation-resistant analogs of inorganic pyrophosphate that can inhibit bone resorption. This effect is of particular clinical relevance in patients with symptomatic MM who, as a consequence of the physiological changes induced by malignant bone disease, undergo profound bone loss. Newer generation, nitrogen-containing BPs (N-BPs) prevent bone loss because of cellular effects involving both apoptosis of the osteoclasts and the destruction of the osteoclastic cytoskeleton, resulting in decreased osteoclast activity. The biochemical basis of these effects for N-BPs (for example, alendronate, risedronate, ibandronate, pamidronate and zoledronic acid) is the inhibition of farnesyl pyrophosphate synthase (FPPS), a key branch-point enzyme in the mevalonate pathway.[6,7] Consequently, cellular availability of isoprenoid lipids such as farnesyl pyrophosphate and geranylgeranyl pyrophosphate is decreased and the post-translational modification and function of small GTP-binding proteins that modulate key signaling events involved in cell survival, differentiation and proliferation are impaired.[8–10] Experiments in several *in-vitro* and *in-vivo* experimental model systems of cancer in general and MM in particular suggest that BPs may negatively modulate promyeloma signaling events and thereby provide clinical benefits that extend beyond bone conservation. This review examines the mechanisms by which BPs may interfere with progression of MM.

Preclinical evidence and molecular basis of antimyeloma effects of BPs

Several preclinical studies have provided strong evidence for the antimyeloma potential of BPs (Figure 1).[2,11–18] In a study by Baulch-Brown *et al*,[19] the authors showed that myeloma cells treated with zoledronic acid, or other mevalonate pathway antagonists such as fluvastatin (an HMG-CoA reductase inhibitor) or SCH66336 (a farnesyl transferase inhibitor) suppressed the proliferation of myeloma cells (RPMI 8226, U266, OMP2, LP1 and NCI-H929) and that combinations of zoledronic acid and fluvastatin, but not zoledronic acid and SCH66336 acted synergistically. The study also showed that the antiproliferative effect of mevalonate pathway inhibitors is mediated principally by prevention of geranylgeranylation and is the result of both cell-cycle arrest and apoptosis induction. Indeed, microarray and quantitative real-time PCR analyses further demonstrated that genes related to apoptosis, cell-cycle control and the mevalonate pathway were particularly affected by zoledronic acid and fluvastatin, and that some of these transcriptional effects were synergistic. Similarly, incadronate and mevastatin (a known inhibitor of the mevalonate pathway) caused apoptosis in JJN-3 myeloma cells and inhibited cell proliferation.[20] Moreover, mevalonate pathway intermediates such as geranylgeraniol and farnesol prevented incadronate-induced apoptosis of JJN-3 myeloma cells and had a partial

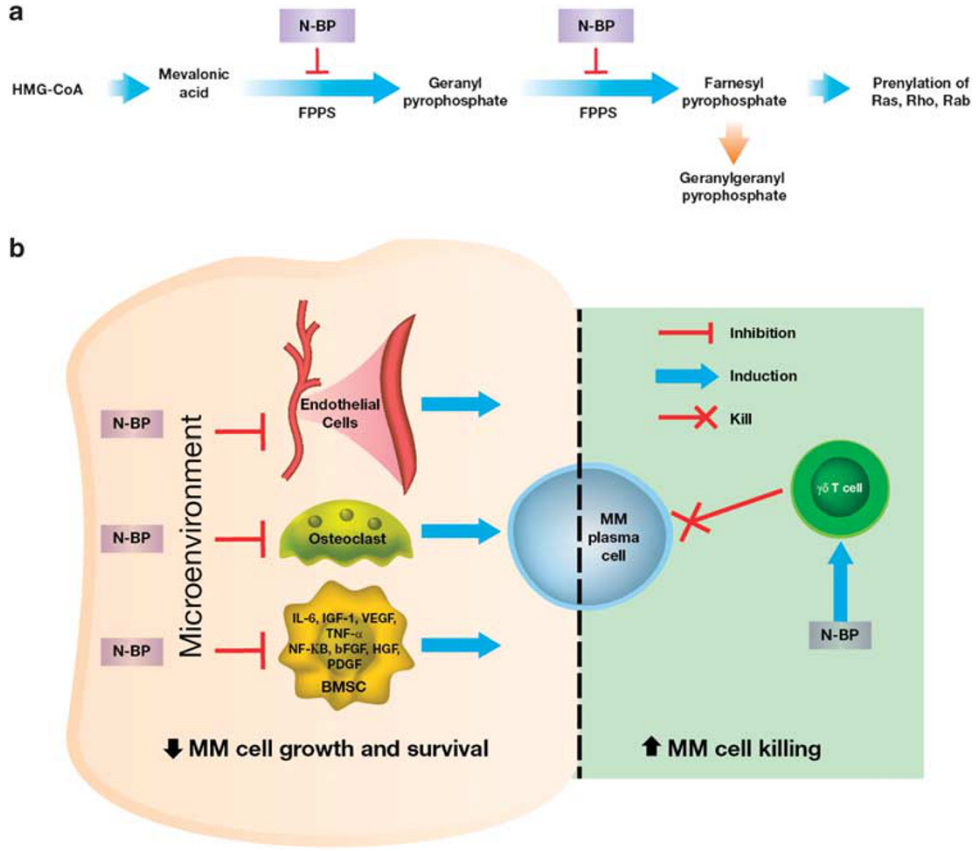

Figure 1 N-BPs may modulate myeloma progression through their effects on the mevalonate pathway and directly on MM plasma cells, bone marrow cells and immune cells in the bone marrow. (**a**) N-BPs affect cell survival by blocking the key enzyme (that is, FPPS) in the mevalonate pathway required for prenylation of proteins.[11,12,14] (**b**) N-BPs prevent proliferation of MM plasma cells directly via inhibition of growth factors that promote cell growth and survival within the bone microenvironment and indirectly via inhibition of angiogenesis (left).[2,14–18] N-BPs enhance host antitumor immune response (right).[13] The dotted line depicts the boundary between the bone microenvironment and the extraskeletal vasculature. bFGF, fibroblast growth factor; FPPS, farnesyl pyrophosphate synthase; HGF, hepatocyte growth factor; IGF-1, insulin-like growth factor-1; N-BP, nitrogen-containing bisphosphonate/aminobisphosphonate; NF-κB, nuclear factor-κB; PDGF, platelet-derived growth factor; TNF-α, tumor necrosis factor-α.

effect on cell-cycle arrest, suggesting that the anticancer effects of incadronate are a direct consequence of its known mechanism of action (that is, mevalonate pathway inhibition).

In a study by Shipman *et al*[21] in the human myeloma cell line JJN-3 and the EBV transformed Burkitt lymphoma cell line HS-Sultan,[22] pamidronate and the more potent BP, YM175, induced apoptosis and significantly decreased cell number ($P<0.001$). Both pamidronate and YM175 increased in the proportion of cells with altered nuclear morphology ($P<0.05$) and fragmented DNA, in both JJN-3 and HS-Sultan cells. In contrast, clodronate, a BP that does not contain any nitrogen and does not inhibit the mevalonate pathway, had little effect on cell number and did not cause apoptosis at the concentrations examined. In another study, risedronate dose dependently inhibited prenylation of (*ras* in *b*rain) RAB GTPases (for example, Rap1A and Rab6), eliciting a dose-dependent apoptotic response in human myeloma cells and arresting these cells in the S phase.[23] This study also showed that geranylgeraniol prevented inhibition of prenylation, induction of apoptosis and cell-cycle arrest in response to risedronate. These data support the critical role of mevalonate pathway inhibition by N-BPs and the consequent impairment of function of small GTPases in mediating the observed anticancer effects (Figure 1a).

The role of isoprenylation of proteins in mediating these events is also supported by data from a more recent study in the 5T2MM model of MM that showed that 3-PEHPC (2-[3-pyridinyl]-1-hydroxyethylidene-1,1-phosphonocarboxylic acid), a novel geranylgeranyl-transferase II inhibitor, prevented bone loss, inhibited the development of osteolytic bone lesions and reduced myeloma burden in bone.[24] In contrast to other agents that inhibit the mevalonate pathway or post-translational prenylation, BPs have a natural affinity toward bone mineral that limits the effects of mevalonate pathway inhibition to select cellular components (mainly osteoclasts, and non-osteoclast cells including tumor cells and lymphocytes) within the bone microenvironment. This is particularly desirable in a disease such as MM, a disease whose progression is primarily driven within the bone.

In addition to data from cell-culture experiments, *in-vivo* experiments in animal models of MM provide additional evidence of the antimyeloma activity of BPs. For example, zoledronic acid significantly prolonged survival in severe combined immunodeficiency mice inoculated with human INA-6 plasma cells.[12] Importantly, this study used clinically relevant doses of zoledronic acid, and histological analysis of INA-6 tumors from the peritoneal cavity revealed extensive areas of apoptosis associated with poly (ADP ribose) polymerase cleavage. Furthermore, western blot analysis of tumor homogenates demonstrated the accumulation of unprenylated Rap1A, which is indicative of the uptake of zoledronic acid by non-skeletal tumors and inhibition of the mevalonate pathway.

Similarly, in another *in-vivo* study, zoledronic acid prevented the formation of skeletal lesions, prevented cancellous bone loss and loss of bone mineral density, and reduced osteoclast perimeter in mice injected with 5T2MM murine myeloma cells.[25] Zoledronic acid also decreased paraprotein concentration, decreased tumor burden and reduced angiogenesis. In separate experiments, Kaplan–Meier analysis demonstrated a significant increase in disease-free survival after treatment with zoledronic acid when compared with control ($P<0.005$). Thus, these data are consistent with the antimyeloma effects observed with other mevalonate pathway inhibitors.

As a consequence of the inhibition of the mevalonate pathway in cells, N-BPs can induce formation of a novel ATP analog, triphosphoric acid 1-adenosin-5′-yl ester 3-(3-methyl-but-3-enyl) ester or ApppI.[26] Accumulation of ApppI correlated with the capacity of N-BPs to inhibit the mevalonate pathway in macrophages. ApppI inhibited the mitochondrial ADP/ATP translocase in isolated rat liver mitochondria and caused apoptosis in osteoclasts. These data broaden the mechanistic basis of N-BPs' action (beyond inhibition of post-translational modification of small GTPases involved in cell signaling) to include ApppI formation. In contrast to mevalonate pathway inhibition that results in impaired function of small GTPases, ApppI functions through the blockade of mitochondrial ADP/ATP translocase, thereby inducing apoptosis. In addition to its effects on mitochondrial function, ApppI and another intermediate, isopentenyl pyrophosphate (IPP), are phosphoantigens that can enhance host anticancer activity.

Raikkonen *et al*[27] reported that zoledronic acid-induced IPP/ApppI accumulation in MCF-7 breast cancer cells was decreased by farnesol and almost completely blocked by geranylgeraniol and geranyl pyrophosphate. The functionality of the regulatory enzymes of IPP and ApppI, IPP isomerase and aminoacyl-tRNA synthase, respectively, or protein levels of FPPS were not affected by the treatments. However, protein levels of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (the rate-controlling enzyme of the mevalonate pathway) and unprenylated Rap1A were decreased, thereby suggesting that mevalonate pathway intermediates may also rescue N-BP effects by inhibiting IPP/ApppI accumulation.[27] Thus, the anticancer effects of mevalonate pathway inhibition result from multiple outcomes including impairment of function of small GTPases, inhibition of ATP/ADP translocase and stimulation of host antitumor activity.

Synergistic activity of BPs with other agents and antimyeloma therapies

Sequential blockage of the mevalonate pathway by zoledronic acid and simvastatin resulted in the synergistic induction of apoptosis and reversal of cell adhesion-mediated drug resistance.[28] Treatment of myeloma cell lines with the combination of zoledronic acid and dexamethasone also demonstrated synergistic induction of apoptosis *in vitro*, providing a rationale for potential applications *in vivo*.[29,30] In another study, bortezomib and zoledronic acid showed distinct and synergistic inhibitory effects on cell proliferation, adhesion, migration and expression of angiogenic cytokines (for example, VEGF, bFGF, hepatocyte growth factor and platelet-derived growth factor).[14] Similar effects were observed on capillarogenic organization and expression of vascular markers in cells that became vasculogenic. Activation of VEGFR2, ERK1/2 and NF-κB activity was also inhibited. Overall, these data provide evidence that the exposure of bone marrow macrophages in MM during treatment with zoledronic acid impacts their angiogenic and vasculogenic properties (Figure 1b).

BPs as immunomodulators

In addition to their direct effects on cancer and bone cells, BPs may also repress cancer progression by stimulating the host anticancer response and/or by inhibiting proangiogenic signaling by immune cells. Newer generation BPs appear to induce or activate Vγ9Vδ2 subset T cells by mimicking phosphoantigens and/or by increasing circulating phosphoantigen levels.[31] The Vγ9Vδ2 T cells have antitumor activity and appropriate cell surface antigens to target secondary lymphoid organs and exert costimulatory activity.[32] BP treatment has been shown to induce the accumulation of IPP and dimethylallyl bisphosphonate, phosphoantigens that activate Vγ9Vδ2 T cells.[13] Several studies have demonstrated that zoledronic acid treatment causes the expansion of Vγ9Vδ2 T-cell populations and increases sensitivity of cancer cells to the cytotoxic effects of Vγ9Vδ2 T cells.[33,34] In a small clinical study, patients infused with zoledronic acid-activated Vγ9Vδ2 T cells generated from the culture of peripheral blood mononuclear cells maintained their M-protein levels in the serum at baseline, demonstrating that activation of the innate host antitumor response by N-BPs can successfully control the expansion of myeloma cells.[35]

In MM, cells belonging to the monocyte-macrophage lineage form part of an inflammatory circuit that promotes tumor progression, invasion and metastasis mainly through their proangiogenic activity.[16,18] These cells express a broad array of matrix metalloproteases, proangiogenic cytokines and growth factors. The combination of factors facilitates matrix breakdown and tunneling that promote neovascularization and invasion. A recent study evaluating the effect of clinically relevant doses of zoledronic acid on bone metastasis in a constitutionally active ErbB-2 transgenic mouse model reported that zoledronic acid treatment resulted in M2 (anti-inflammatory and proangiogenic) to M1 (antitumor) reversion of tumor-associated macrophages.[36] This study also reported that zoledronic acid treatment resulted in a profound reduction in $CD11^+$ macrophages infiltrating mammary lesions and was accompanied by reduced vascularization of the tumor and decreased VEGF levels in the tumor microenvironment. Moreover, this study also showed that Ras prenylation and Ras-GTP levels were suppressed by treatment with zoledronic acid. Overall, the study demonstrated that zoledronic acid improved disease-free and overall survival (OS). These data are consistent with decreases in VEGF levels observed in cancer patients treated with repeated low-dose therapy with zoledronic acid.[17] These results show that N-BPs affect the immune system by both increasing host antitumor activity and reducing tumor-associated neovascularization.

BP effects on the bone marrow microenvironment

In MM, bone marrow stromal cells increase the concentration of angiogenic factors and matrix degrading enzymes in the bone marrow microenvironment by direct secretion or by the stimulation of myeloma cells or endocrine cells through paracrine interactions.[15,16] *In-vitro* studies have demonstrated the anticancer potential of zoledronic acid on myeloma cell lines, but few data are available on its effects on bone marrow stromal cells.[37] In a study by Corso *et al*,[37] treatment of bone marrow stromal cells derived from the bone marrow of myeloma patients with zoledronic acid reduced proliferation; increased apoptosis; decreased IL-6, tumor necrosis factor-α and IL-1β production; and modified the pattern of expression of adhesion molecules, especially those involved in plasma cell binding. These effects on bone marrow stromal cells suggest that the anticancer activity of zoledronic acid may in part result from its

ability to disrupt the vicious cycle of signaling that promotes myeloma growth and progression (Figure 1b).

Taken together, the data available suggest that BPs inhibit MM growth directly (Figure 1a) and indirectly via the bone marrow microenvironment or by stimulating the immune system (Figure 1b). The final mechanism responsible for a possible antimyeloma effect is not fully understood, but it seems that indirect effects via modulation of the microenvironment mediate a broader antimyeloma effect.

Clinical evidence of the antimyeloma effect of BPs

Data from clinical trials of BPs in patients with MM[38–40] provided the first clinical evidence of antimyeloma activity of BPs. For example, in a long-term follow-up (8.6 years) of a placebo-controlled trial ($N=619$), the subset of clodronate-treated patients who did not have vertebral fractures at baseline had significantly longer OS vs patients who received placebo (median OS, 59 months vs 37 months, respectively; $P=0.006$).[40] Similarly, in patients with newly diagnosed or relapsed/refractory MM ($N=392$), long-term treatment with pamidronate significantly increased survival in the subset of patients with MM receiving second-line antimyeloma therapy 14 months vs 21 months; $P=0.041$ compared with placebo.[39] In a retrospective analysis of patients with MM who had bone marker assessments ($N=353$) in a phase III trial comparing zoledronic acid (4 mg) with pamidronate (90 mg), patients with high baseline bone-specific alkaline phosphatase ($\geqslant$146 IU/l) levels had significantly better 25-month survival with zoledronic acid than with pamidronate (82 vs 53%, respectively; $P=0.041$).[38]

Small clinical studies have also provided insight into the antimyeloma potential of zoledronic acid. In 2007, Aviles *et al* conducted a clinical trial in which 94 patients (treated with cyclophosphamide, vincristine, melphalan and prednisone) were randomized to receive either zoledronic acid (4 mg intravenous infusion every 28 days) or not (control group). After 49.6 months median follow-up, assessment of the primary end points of 5-year event-free survival and 5-year OS showed significantly greater benefit for the zoledronic acid-treated group vs the control group (5-year event-free survival was 80% in the zoledronic acid group vs 52% in the control group ($P<0.01$); 5-year OS was 80% in the zoledronic acid group vs 46% in the control group ($P<0.01$)).[41]

Recently, the Medical Research Council Myeloma IX trial, a large, randomized, controlled trial to evaluate the role of BPs in patients with newly diagnosed MM, was designed and conducted by the UK Medical Research Council.[42] This phase III trial ($N=1960$) compared the efficacy and safety of monthly intravenous zoledronic acid (4 mg) vs daily oral clodronate (1600 mg) used concurrently with the prevailing standard treatment. The primary end point of this trial was OS, and additional end points included progression-free survival, response rates and incidence of skeletal-related events. Patients were assigned to two main treatment pathways based on their age and performance status. Younger, transplant-eligible patients were assigned to the intensive pathway, which consisted of induction therapy (randomized between standard cytotoxic and thalidomide-based regimens) followed by autologous stem-cell transplantation. Non-transplant eligible patients were assigned to the non-intensive pathway, which consisted of systemic therapy only (randomized between melphalan/prednisone and a thalidomide-based regimen). Within each treatment pathway, patients were randomized to oral clodronate (1600 mg/day) or zoledronic acid (4 mg via 15 min intravenous infusion) and treated until disease progression or death.

Of 1960 evaluable patients, 981 received zoledronic acid and 979 received clodronate. At the median follow-up of 3.7 years, 24% and 19% of patients, respectively, discontinued study before disease progression. Median time on treatment was $\sim$1 year across all treatment groups. At the time of the database lock, 11–13% of patients (zoledronic acid and clodronate arms, respectively) were still receiving BP treatment. Zoledronic acid significantly prolonged both progression-free survival and OS ($P=0.0179$ and $P=0.0118$, respectively) vs clodronate. But it should be pointed out that the effect of zoledronic acid relative to clodronate on OS and progression-free survival occurred in the first 4 months, whereas OS and progression-free survival curves were essentially parallel during follow-up. This is probably due to the markedly higher relative activity of zoledronic acid vs clodronate also shown in a rat osteoclast model.[43] In addition, the better bioavailability of zoledronic acid due to intravenous application possibly results in a stronger inhibition of FPPS and subsequent protein prenylation.[44] Zoledronic acid also reduced the proportion of patients with a skeletal-related event vs clodronate (27.0 vs 35.3%, respectively; $P=0.0004$). Further, the improvement in OS was maintained after adjustment for time to first skeletal-related event in a Cox model ($P=0.0178$), suggesting that antimyeloma effects likely underlie the OS benefit. In addition, zoledronic acid halved the incidence of new osteolytic lesions, regardless of treatment pathway.[42] These data support an antimyeloma benefit from zoledronic acid treatment in patients with newly diagnosed MM.

In contrast to these studies demonstrating the antimyeloma benefits of BPs, there are also reports that suggest that BPs do not have any clinically meaningful effect on the progression of MM. For example, in an updated indirect meta-analysis of 17 trials with $\sim$3000 patients,[45] the authors concluded that BP treatment was not significantly associated with any survival benefit. However, it should be noted that this study included several different BPs, which in individual studies have shown differences in their antimyeloma activity. Overall, zoledronic acid and pamidronate have proven to be more effective than other BPs in terms of the clinical benefit they provide. Moreover, it should be noted that these analyses did not include the Medical Research Council Myeloma IX study[42] and that although it did include the study by Aviles *et al*[41] that showed survival benefit, it comprised only a small fraction of the pooled population and the effect might therefore be masked. Similarly, in a study by McCloskey *et al*,[40,46] survival benefit was not observed in the overall study population, but subgroup analysis showed significant survival benefit in the subset of patients without skeletal involvement at diagnosis. Finally, in the study by Musto *et al*,[47] zoledronic acid treatment did not have an effect on the progression of asymptomatic MM to symptomatic disease. Taken together, these data suggest that to gain clinically meaningful insight into the question of antimyeloma benefit, one may need to evaluate data not only in the context of a specific type of BP but also in the disease stage.

Discussion

BPs have an important role in the treatment of MM bone disease. In addition to the established benefit to skeletal health, there are both *in-vitro* and *in-vivo* evidence that BPs have

potential antimyeloma effects. For example, Tassone *et al*[29] showed that combination of zoledronic acid and dexamethasone inhibits growth and induces apoptotic death synergistically in MM cell lines. Ural *et al*[30] extended the observation of zoledronic acid synergy with antimyeloma agents in their study demonstrating cytotoxic effects of zoledronic acid in combination with dexamethasone and thalidomide on myeloma cell lines ARH-77 (EBV transformed) and RPMI-8226. Croucher *et al*[25] used zoledronic acid on 5T2MM-bearing mice, and results showed that N-BPs decreased osteolysis, tumor burden, and angiogenesis and increased survival.

Bone resorption in MM releases several types of growth factors and cytokines including VEGF, tumor necrosis factor and interleukins; all of which further support the tumor growth. In addition to the direct effects of BPs on myeloma cells, BPs may indirectly affect tumor growth by preventing bone resorption and inhibiting further release of tumor stimulating factors. Corso *et al*[37] suggested that BPs inhibit the survival of stromal cells and block the interaction of plasma and stromal cells, thus interfering with bone microenvironment. In addition, inhibition of angiogenesis[17] and immunomodulatory effects of BPs including activation of Vγ9Vδ2 T cell-mediated innate immunity[13,35] may contribute to their negative effects on tumor progression.

The *in-vitro* evidence of the antimyeloma effects of BPs was further confirmed by several clinical studies that demonstrate the efficacy of BPs in reducing skeletal events in patients with MM with a concomitant antimyeloma effect.[38–42] Aviles *et al*[41] conducted a trial in 2007 and demonstrated that addition of zoledronic acid to conventional chemotherapy in treatment-naive patients improved 5-year event-free survival and 5-year OS compared with conventional therapy alone. It is of note that in this trial the event-free survival was high with 80% in the group treated with zoledronic acid. More recently, the randomized, controlled Medical Research Council Myeloma IX study demonstrated that in newly diagnosed patients with MM, combining conventional therapy with zoledronic acid provided a significant survival advantage compared with clodronate, across all treatment pathways.[41,42] However, the response rates within the intensive and non-intensive chemotherapy arms did not differ with zoledronic acid vs clodronate treatment, suggesting that the zoledronic acid-associated OS advantage occurred independently from the myeloma response. Further, in this trial thalidomide was the only novel agent used in the intensive or non-intensive cohorts. Novel agents such as bortezomib[48] and lenalidomide[49] target MM cells and bone marrow microenvironment cells mediating bone formation and resorption. Therefore, it is not surprising that antiresorptive agents that primarily target the bone (that is, BPs such as zoledronic acid and pamidronate) may also favorably impact MM.

Future trials need to incorporate novel agents to determine their optimal use as both antimyeloma therapy and their synergy with BPs in terms of controlling bone disease.[41,42] Ongoing studies such as DAZZLE ($N=53$) and a larger single-arm trial in Australia (MM6; $N=243$) are evaluating the effect of zoledronic acid on disease progression in patients with MM. Data from these studies may provide additional clinical insights into the therapeutic role of zoledronic acid in patients with MM.

Although other studies[45–47] suggest that BPs do not improve mortality in the overall study population after treatment with BP, the majority of data presented herein provides evidence for the antimyeloma effects of BPs. Further, several studies have proven the reduction of skeletal-related events in MM patients treated with either pamidronate or zoledronic acid.[50] Nevertheless, based on the fact that BPs increase the risk of osteonecrosis of jaw and are possibly associated with increased risk of atypical subtrochanteric fractures,[51] the use of BPs needs to be critically evaluated in the context of the clinical situation of each individual patient. Although the optimal duration of BP treatment in this patient population is unknown, the potential antimyeloma benefit warrants further evaluation of the risk: benefit ratio of BPs in conjunction with primary treatment for MM. Thus, further clinical studies that assess the efficacy of BPs in combination with the prevailing standards of care are warranted.

Conflict of interest

The authors declare no conflict of interest.

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