Review

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Bisphosphonates and Cancer

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Bisphosphonates form a family of drugs characterized pharmacologically by their ability to inhibit bone resorption and pharmacokinetically by similar intestinal absorption, skeletal distribution, and renal elimination. Two groups of bisphosphonates exist chemically, non–amino-bisphosphates and amino-bisphosphonates. The amino-bisphosphonates have greater antiresorptive capabilities and represent a newer generation of bisphosphonates. The primary mechanism of action of bisphosphonates is inhibition of osteoclastic activity. Non–amino-bisphosphonates are incorporated into the energy pathways of the osteoclast, resulting in disrupted cellular energy metabolism leading to apoptosis. Amino-bisphosphonates exert their effect on osteoclasts via their inhibition of the mevalonate pathways, resulting in disruption of intracellular signaling and induction of apoptosis. Bisphosphonates also inhibit cancer cell proliferation, induce apoptosis in in vitro cultures, inhibit angiogenesis, inhibit matrix metalloproteinase, have effects on cytokine and growth factors, and are immunomodulatory. Clinical applications in oncology could include therapy for hypercalcemia of malignancy, inhibition of bone metastasis, and therapy for bone pain. Although bisphosphonates are regarded as metabolically inert in the body, adverse effects do occur and include esophagitis, gastritis, suppression of bone repair, and allergic reactions. Little is published on the effects of bisphosphonates in dogs with cancer. Further research into the role of bisphosphonates in veterinary oncology is needed to identify clinical efficacy and safety of these potentially beneficial drugs.

Key words: Adverse effects; Alendronate; Etidronate; Hypercalcemia of malignancy; Multiple myeloma; Osteosarcoma; Pamidronate; Zoledronate.

Bisphosphonates form a family of drugs characterized pharmacologically by their ability to inhibit bone resorption, and pharmacokinetically by similar absorption, distribution and elimination.[1] The ability to inhibit bone resorption makes them useful drugs in the control of bone metabolism. The development of bisphosphonates was prompted by studies that showed that inorganic pyrophosphate binds strongly with calcium phosphate, thereby inhibiting crystal formation and dissolution in vitro.[2,3] However, no in vivo effect occurred because of the hydrolysis of pyrophosphate before it reached the bone.[2,3] Bisphosphonates were developed in an effort to circumvent this hydrolysis and are characterized by the presence of a geminal carbon (Fig 1). Bisphosphonates have been used for some time in human medicine as therapeutic agents for osteoporosis, bone pain associated with metastatic disease, Paget's disease of bone, and hypercalcemia of malignancy and in diagnostic nuclear medicine and targeted radiotherapy.[1,4–6] Numerous reports exist on the experimental use of bisphosphates in dogs, primarily as a model of human bone disease.[7–27] The reported use of bisphosphonates in veterinary oncology is limited to a single peer-reviewed publication,[28] although a number of conference proceedings and continuing education articles also report their use.[29–31] These early reports indicate that bisphosphonate use in veterinary oncology may include treatment of primary and metastatic bone cancers, therapy for hypercalcemia of malignancy, and possible antimetastatic and antitumor effects.[28–31] Based on these reports, the use of bisphosphonates in veterinary medicine likely will increase. In light of this, we review the human and veterinary literature for reports of experimental and clinical use of bisphosphonates in dogs, with emphasis on pharmacodynamics, pharmacokinetics, dosing schemes, adverse effects, efficacy, and anticancer effect.

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Bisphosphonate Chemistry

Bisphosphonates have a structure similar to that of inorganic pyrophosphate, but with a carbon atom (geminal) substitution for the central oxygen atom (Fig 1).[32] Two additional covalent bonds (side chains) to the geminal carbon can be formed and are referred to as R_1 and R_2.[33] The ability of these side chains to bind carbon, oxygen, halogen, sulfur, or nitrogen atoms gives rise to numerous possibilities for the development of unique molecules.[33] As with inorganic pyrophosphate, bisphosphonates form a 3-dimensional structure that is capable of binding divalent metal ions such as Ca^{2+}, Mg^{2+}, and Fe^{2+} in a bi- or tridentate manner. Binding occurs by coordination of oxygen from the phosphonate group with the divalent cation. Affinity for Ca^{2+} can be increased by manipulating the R_1 side chain, such as by the addition of a hydroxyl group, which is common to most bisphosphonates. The addition of a hydroxyl or primary amine group on the R_2 side chain allows for the formation of a tridentate conformation with more effective binding to hydroxyapatite.[33]

The aliphatic carbon chain (R_2) length appears to be an important factor affecting the antiresorptive capability of bisphosphonates.[1] For example, alendronate has 100–1,000 times greater antiresorptive capacity than does etidronate. Table 1 compares the relative in vivo potency of the most

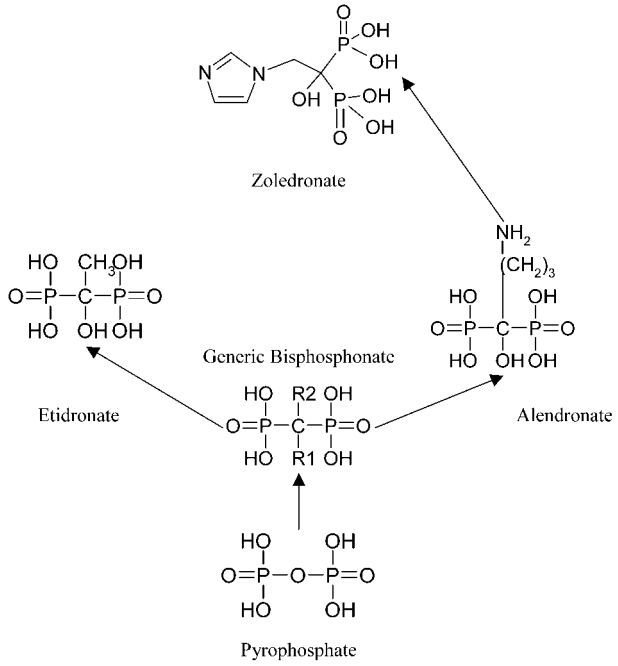

Fig 1. The development of bisphosphonates from pyrophosphate by the substitution of the central oxygen by a carbon (geminal) atom is shown. The 2 main classes of bisphosphonates are represented by alendronate (amino-bisphosphonates) and etidronate (non–amino-bisphosphonates). The presence of a primary amine group on the R_2 side chain offers significant improvement in therapeutic activity. Zoledronate is an example of a 3rd-generation amino-bisphosphonate with a tertiary amine in a ring structure on the R_2 side chain. The addition of an OH group on the R_1 side chain enhances binding to hydroxyapatite.

common bisphosphonates.[34] Further manipulation of this primary R_2 chain amine to form a tertiary amine increases its potency.[35] The most potent bisphosphonates to date appear to be those that contain a tertiary amine in a ring structure, for example, zoledronate, which has >10,000 times the potency of etidronate.[35]

Pharmacokinetics of Bisphosphonates

Bisphosphonates are administered PO or IV.[1] Routes of administration in experimental animals include intraperitoneal and SC injection.[36] Absorption is complete from these sites but tissue damage and pain at SC injection sites make this route of administration undesirable.

A number of important therapeutic bisphosphonates that can be given PO, such as alendronate, are poorly absorbed from the gastrointestinal tract for many reasons including the size of bisphosphonates (>0.150 kd), low lipophilicity, and ionization state (negatively charged).[1] These factors prevent transcellular transport and significantly reduce intercellular transport from the gastrointestinal tract. Absorption can be reduced further when bisphosphonates form complexes with calcium or other divalent cations.[1] Similarly, the presence of food in the stomach profoundly reduces absorption for etidronate from an already low rate of 3–7% to 0%.[37] Oral absorption of bisphosphonates can be improved marginally (5–10%) by increasing the dose because absorption is dose-dependent.[1,36] The increased absorption

Table 1. Antiresorptive potency of bisphosphonates.

	In vivo Potency
Non–amino-bisphosphonates	
Etidronate	1×
Clodronate	10×
Amino-bisphosphonates	
Pamidronate	100×
Alendronate	>100–<1,000×
Risedronate	>1,000–<10,000
Ibandronate	>1,000–<10,000
Zoledronate	>10,000

is thought to be due to binding of the bisphosphonates with cations at the epithelial tight junctions in a dose-dependent manner, this results in a widening of the tight junctions allowing more drug to pass through.[1]

After absorption into the blood stream, bisphosphonates can bind to plasma proteins because of complete ionization at physiologic pH (7.4). Factors that affect binding include drug concentration, species variation, pH, and calcium concentration. The concentration of protein-bound bisphosphonate is lower in dogs and humans than in rats. A change in pH from 6.6 to 8.6 results in a corresponding increase in binding from 50% to 98% for alendronate. Hypocalcemia leads to lower bisphosphonate binding to albumin, although paradoxically, hypercalcemia does not to lead to an increase in binding in experimental studies. It is also unclear whether bisphosphonates bind directly to albumin or to calcium, which in turn binds to albumin.[1]

After IV administration, bisphosphonates are rapidly cleared from the plasma with a half-life of 1–2 hours. Bone shows an increase in uptake over time (1 hour) consistent with movement of bisphosphonates from noncalcified tissue to bone.[1] Any areas in the bone that are metabolically active such as trabecular bone, growing bone, areas of osteolysis, or bone repair will receive more blood and have a larger amount of exposed hydroxyapatite crystals, and will therefore accumulate more bisphosphonate.[5] Importantly, with increasing dose, the uptake of bisphosphonates in bone is saturable because of competitive binding of exposed hydroxyapatite crystals.[1,38] However, if the dose is fractionated and given over time, this effect seems to be attenuated.[1] Elimination from bone is prolonged with release occurring only when the bone undergoes resorption. Accordingly, the half-life of bisphosphonates in bone depends upon the individual's rate of bone turnover. For example, the half-life for alendronate is estimated to be 300 days in dogs (adults) and 10 years in humans (adults).[23,39] Renal elimination of bisphosphonates is thought to occur through a concentration-dependent saturable active transport mechanism.[1] The process of excretion is not via the typical anion or cation renal transport systems, because inhibitors (eg, probenecid) of these systems do not inhibit renal bisphosphonate excretion in rats. In addition, bisphosphonates competitively inhibit renal excretion of each other.

Dosing rates have been reported for dogs in experimental and clinical oncology (Table 2). Many dosages are higher than is clinically relevant but these data represent a starting point for canine clinical trials. Dosing frequencies are var-

Table 2. Bisphosphonate dosages reported for dogs.

	Trade Name	Route	Dosage Range	Frequency
Non–amino-bisphosphonates				
Etidronate[7,8]	Didronel	SC	0.5 mg/kg	Daily
Clodronate[11]	Bonefos	PO	20–40 mg/kg	Daily
Amino-bisphosphonates				
Pamidronate[12,13,31]	Aredia	IV	1.3 mg/kg in 150 ml of 0.9% saline, given over 2 hours	Can be repeated in 7 days
Alendronate[17,22,28]	Fosamax	PO	0.5–1 mg/kg	Daily
Risedronate[25,26]	Actonel	PO	0.5–1 mg/kg	Undetermined
Zoledronate	Zometa	IV	Undetermined	Undetermined

iable depending on the bisphosphonate. Commonly, PO preparations are given daily, whereas IV formulations are given every 3 weeks. Recently, daily versus intermittent PO dosing regimes have been debated in the human literature. Intermittent regimes may reduce the incidence of drug complications such as esophagitis and inhibition of microdamage bone repair.[40–42] Cost versus benefit of dosing regimes also is being debated in the human literature because of the chronic nature of the diseases being treated with bisphosphonates and cost-benefit factors are likely to be significant in the use of bisphosphonates in veterinary oncology.[43]

Pharmacodynamics of Bisphosphonates (Mechanism of Action)

The primary effect of bisphosphonates is to inhibit bone resorption.[1] The osteoclast, the cell responsible for bone resorption, is the main target of bisphosphonates; it arises from hematopoietic stem cells of monocytic-macrophage lineage.[44] Therefore, it is not surprising that cytokines that stimulate hematopoietic tissue, such as interleukin (IL)-1, IL-3, IL-6, and IL-11, tumor necrosis factor, granulocyte-macrophage colony-simulating factor, macrophage colony-simulating factor, and c-kit ligand, also stimulate osteoclastic differentiation. Inhibiting cytokines include IL-4, IL-10, IL-18, and γ-interferon (γ-INF). Parathyroid hormone and vitamin D_3 are potent initiators of osteoclastogenesis. Calcitonin inhibits osteoclast development and promotes osteoclast apoptosis. Other hormones affecting bone include sex hormones, glucocorticoids, and thyroid hormone.[44–46] Glucocorticoids negatively affect bone mass via osteoblast inhibition and osteoclast stimulation. Interestingly, glucocorticoids have been shown to inhibit bisphosphonate-induced osteoclastic apoptosis.[46] Bisphosphonates are released from hydroxyapatite during the osteoclastic-mediated resorption process and are taken up by the osteoclast cell. This results in disruption of intracellular metabolism, which may lead to apoptosis.[33]

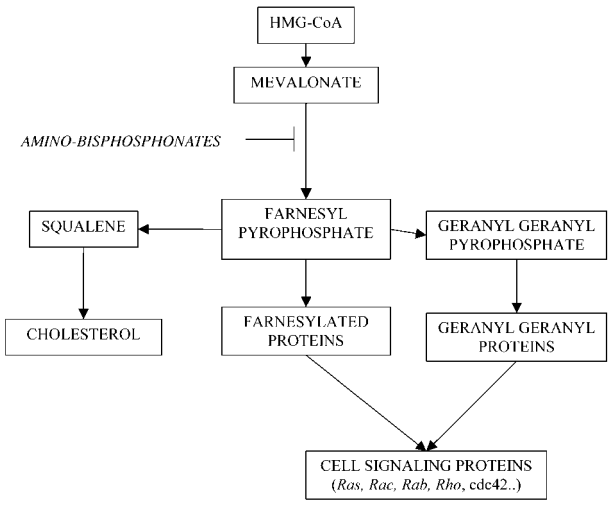

Fig 2. Mevalonate pathway inhibition by amino-bisphosphonates via the key regulatory enzyme farnesyl pyrophosphate synthase. Inhibition of this pathway prevents the biosynthesis of isoprenoid compounds that are essential for the posttranslational farnesylation and geranylgeranylation of small guanosine triphosphatases. Guanosine triphosphatases are important signaling proteins that regulate cell processes such as cell morphology, integrin signaling, membrane ruffling, trafficking of endosomes, and apoptosis.[33]

Two distinct mechanisms of action are proposed depending on the bisphosphonate group, whether amino-bisphosphonates or non–amino-bisphosphonates.[33] Because some non–amino-bisphosphonates (etidronate and clodronate) resemble inorganic pyrophosphate, they are incorporated into nonhydrolyzable analogues of adenosine triphosphate, thereby denying the osteoclast energy. It is likely that accumulations of these analogues would inhibit osteoclast function and cause apoptosis. The more potent amino-bisphosphonates (alendronate, pamidronate, risedronate, and zoledronate) are not metabolized but act as transition-state analogues of isoprenoid diphosphates, thereby inhibiting farnesyldiphosphate synthase and perhaps additional enzymes of the mevalonate pathway (Fig 2).[33]

The process of apoptosis in osteoclasts can be recognized by early morphological changes such as detachment from bone with the loss of ruffled borders, degradation of Golgi apparatus, fusion of nuclear envelope, appearance of ladder structures, nuclear pyknosis associated with condensation and margination of chromatin, and formation of apoptotic bodies.[47] Interestingly, osteoclastic apoptosis is required for inhibition of bone resorption in non–amino-bisphosphonates such as etidronate, but not in amino-bisphosphonates.[48] Bisphosphonates also are postulated to exert an effect because of the inhibition of IL-6 release from osteoblasts.[1,33,49,50]

Adverse Effects of Bisphosphonates

Reports suggest that most bisphosphonates are relatively nontoxic because they are inert substances that do not un-

dergo significant metabolism.[1,51] However, adverse effects have been reported and include esophageal and gastrointestinal tract irritation, bone and renal toxicity, electrolyte abnormalities, and acute-phase reactions. Oral bisphosphonates can be irritating to the esophagus if the drug is allowed prolonged contact with the tissue either due to acid reflux or to retention of the tablet in the esophagus.[19,52,53] The resulting esophagitis is attributed to inhibition of keratinocytes secondary to continuous bisphosphonate exposure and subsequent inhibition of tissue repair.[19,52] Additional evidence for mucosal toxicity comes from experimentation with Caco-2 cells, which mimic mucosal surfaces when differentiated.[54] Bisphosphonates demonstrated in vitro cytotoxicity in these cell lines.

As expected, bone, the target organ of bisphosphonates, can be adversely affected by high doses of these drugs.[51] One potential adverse effect is referred to as ''frozen bone.'' In this syndrome, bone remodeling and repair are inhibited to such an extent that the bone is weakened and fractures occur.[17,51] The syndrome has been reported in the dog and occurs more frequently when moderately high doses of non–amino-bisphosphonates such as etidronate are used.[7] Non–amino-bisphosphonates are implicated because of their narrow therapeutic index, which is the difference in dose between inhibition of bone resorption and inhibition of normal bone repair and mineralization.[22] Newer amino-bisphosphonates are safer because they inhibit osteoclastic activity at lower doses and have a wider antiresorption to antimineralization ratio.[22]

Renal toxicity occurs with bisphosphonate use.[51,55–57] Factors that appear to affect renal toxicity include infusion rate and type of bisphosphonate. One report[51] indicated that a too rapid infusion of a bisphosphonate leads to acute renal failure and this could be prevented by slowing the infusion rate to $<$200 mg/h. However, other clinical studies have not demonstrated renal toxicity in humans receiving IV infusion of pamidronate.[57,58] No reports of renal toxicity have been found for dogs in the experimental or clinical literature.[22] In experimental dogs poisoned with vitamin D_3 and treated with pamidronate IV infusions for hypercalcemia, no renal toxicity was observed.[12,13] In a rat model, zoledronate was shown to be less nephrotoxic than pamidronate.[55] Although not reported as occurring in experimental dogs, adverse effects (human) should be mentioned. These include inflammatory or acute-phase response,[51] various ophthalmic syndromes such as scleritis,[57] transient bone pain,[57] and hypocalcemia.[51]

Bisphosphonates and Cancer

In addition to their inhibitory effect on osteoclasts, which would be beneficial in controlling osteolysis and hypercalcemia in the cancer patient, bisphosphonates also exert direct effects on cancer cells. These effects are thought to be due to induction of apoptosis,[59,60] inhibition of angiogenesis,[61–63] reduction of tumor cell adhesion to bone matrix,[63] γ- and δ-T-cell stimulation,[63] and inhibition of matrix metalloproteinases.[64,65] These effects have resulted in the clinical use and investigation of bisphosphonates in humans to control hypercalcemia of malignancy, reduce pathologic fractures in metastatic bone disease, control bone pain, and possibly prevent metastatic events.[66]

Inhibition of Tumor Cell Proliferation and Induction of Apoptosis In Vitro

Initial in vitro studies with human cancer cell lines (breast, myeloma, prostate, bone, and pancreas) have shown that bisphosphonates exert cytostatic and pro-apoptotic effects in a time- and dose-dependent manner. Concentrations used are high but are similar to those found in bone after IV administration.[66] Zoledronate, a new-generation amino-bisphosphonate, induces apoptosis in human breast cancer cells. It is associated with mitochondrial cytochrome *c* release into the cytosol and resultant activation of the caspase (caspase-3) cascade leading to apoptosis. This effect can be blocked by the forced expression of *BCL2*.[60] *BCL2* (tumor suppressor genes) and other homologues are potent inhibitors of apoptosis caused by cytotoxic insults.[60,67] These researchers also demonstrated a role for prenylation via the mevalonate pathway leading to impaired *RAS* membrane localization in apoptosis (Fig 2). *RAS*, a proto-oncogene, and its proteins play pivotal roles in the control of normal and transformed cell growth.[60] Numerous malignancies express mutations of the *RAS* oncogene.[68] Some researchers have examined the effects of bisphosphonates on osteosarcoma cell lines.[28,49,69–74] Some indication exists that the amino-bisphosphonate pamidronate may be more effective than clodronate in inhibiting cell growth in these cell lines.[69] Research also has shown that marked synergy exists when bisphosphonates are combined with chemotherapy drugs such as taxanes, doxorubicin, dexamethasone, and cyclooxygenase 2 inhibitors.[35,66]

Inhibition of Angiogenesis

Wood et al[62] reported that zoledronate had significant antiangiogenic properties in several different in vitro and in vivo models. Angiogenesis stimulated by human basic fibroblast growth factor was inhibited at lower dosages than angiogenesis induced by human vascular endothelial growth factor (VEGF), on the order of a 33-fold difference in dosage. The mechanism by which this occurs is not known.[62] In the clinical setting, Santini et al[63] treated 25 patients having various solid tumors with a single dose of pamidronate and measured blood concentrations of VEGF, γ-INF, IL-6, and IL-8 on days 1, 2, and 7. Pamidronate depressed VEGF concentrations for the full 7 days. VEGF has been shown to be an independent prognostic factor in several malignancies and is useful in predicting the response to treatment. IL-6 and γ-INF concentrations were increased on day 1 but rapidly decreased 2 days after infusion. IL-6 is an acute-phase cytokine and could be responsible for the some of the adverse effects of bisphosphonate.[51] Pamidronate has been linked with a transient IL-6-mediated acute-phase reaction that is thought to be due the production of IL-6 from macrophage monocytic cells. γ-INF is a cytokine endowed with potent immunostimulatory effects and is secreted by activated CD4 and CD8 T-cells.[63] In addition, γ-INF inhibits osteoclast differentiation.[44]

Inhibition of Matrix Metalloproteinase

Bisphosphonates are now recognized as having anti–matrix metalloproteinase (MMP) effects.[64,65] Teronen et al[65] observed in vitro inhibition and down-regulation of MMP-1, MMP-2, MMP-3, MMP-7, MMP-8, MMP-9, MMP-12, and MMP-13 by various bisphosphonates. Also, several bisphosphonates were shown to decrease the invasiveness of malignant melanoma and fibrosarcoma cell lines through an artificial basement membrane.[65] More recently, Heikkila et al[64] found that bisphosphonates can achieve therapeutic concentrations in vivo to inhibit MMPs and they concluded that bisphosphonates are broad-spectrum MMP inhibitors and that this inhibition involves cation chelation. Importantly, they also found that bisphosphonates have antimetastatic, anti-invasive, and cell adhesion–promoting properties, which may be helpful in preventing metastases not only into hard tissues but also into soft tissues.[64] Conversely, in a large open-labeled clodronate trial, no effect was seen on the rate of bone metastases; however, a deleterious influence on nonbony metastases was found.[75] A possible explanation could be that clodronate is not an amino-bisphosphonate and therefore it would lack the expected inhibition of mevalonate pathway. Derenne et al[76] reported that although amino-bisphosphonates and more specifically zoledronate are effective MMP inhibitors, the up-regulation of MMP-2 from bone marrow stromal cells by amino-bisphosphonates is cause for concern. MMP-2 is involved in bone resorption and the metastatic process.[76] Possible combination of bisphosphonates with an MMP-2 inhibitor may prevent up-regulation of the MMP.[35]

Effects on Cytokines and Growth Factors

Local growth of osteosarcoma involves destruction of bone by proteolytic mechanisms, host osteoclast activation, or both.[35,70] Osteoclast formation and activity are regulated by osteoblast-derived factors such as the osteoclast differentiating factor, receptor activator of nuclear factor-κ B ligand (RANKL), and the inhibitor osteoprotegerin (OPG) (Fig 3). Mackie et al[70] reported that expression of mRNA for osteopontin and RANKL was down-regulated by both clodronate and pamidronate, whereas the expression of mRNA for alkaline phosphatase, pro-alpha1(l) collagen, and OPG was unchanged.

Clinical Trials: Hypercalcemia of Malignancy

Bisphosphonates are now currently the standard therapy for cancer hypercalcemia in humans. The recommended IV dose is 90 mg pamidronate or 1,500 mg clodronate; the former compound is more potent and has a longer-lasting effect.[78] Pamidronate should be considered a viable option in veterinary medicine because it has been used for treating hypercalcemia due experimental cholecalciferol toxicity in the dog. Although not hypercalcemia of malignancy, the doses used would be a good starting point for clinical trials. Rumbeiha et al[12,13] showed that dosages of 1.3–2 mg/kg are needed to control hypercalcemia in these cases. However, a lower dosage of 0.65 mg/kg was not effective in controlling the hypercalcemia. A recent peer-reviewed continuing education article on the diagnosis and treatment of humoral hypercalcemia discusses pamidronate as a therapeutic option.[31] The authors reference Rumbeiha et al[12,13] as the source of the recommended dosage of 1.3 mg/kg (see Table 2 for more detail).

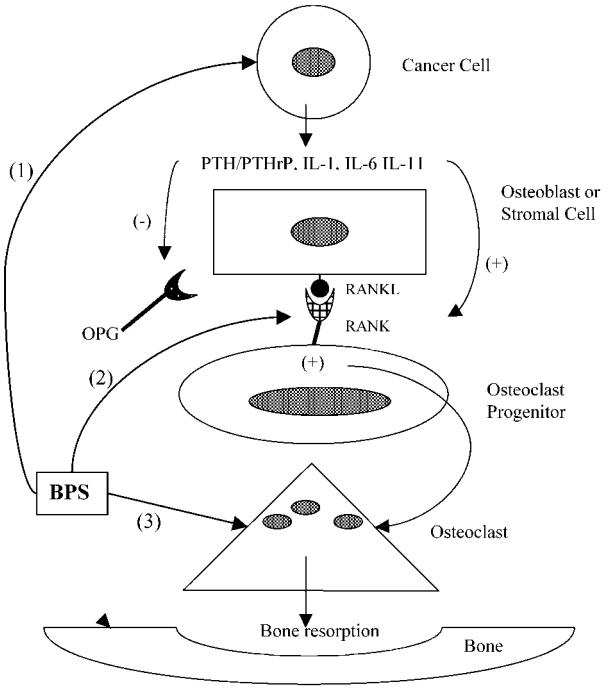

Fig 3. Graphic summary of hypothesized bisphosphonate (BPS) effect on osteosarcoma cells in bone showing the **(1)** direct effect on the cancer cell via caspase-3 activation; **(2)** inhibition of osteoclast differentiating factor ligand (receptor activator of nuclear factor-κ B ligand [RANKL],) mRNA allowing osteoprotegerin (OPG osteoclast inhibitory factor) to block RANK leading to decreased osteoclast progenitor cell differentiation to osteoclasts; and **(3)** direct osteoclast inhibition via mevalonate pathway leading to apoptosis.[70,77]

Clinical Trials: Inhibition of Bone Metastasis and Bone Pain

Numerous articles exist indicating the benefits of these drugs in metastatic bone pain in humans.[79–83] Repeated pamidronate infusions exert clinically relevant analgesic effects in more than one half of patients. Regular pamidronate infusions also can achieve a partial objective response according to conventional Union Internationale Contre le Cancer criteria, and they can almost double the objective response rate to chemotherapy. Lifelong administration of PO clodronate to patients with breast cancer metastatic to bone reduces the frequency of morbid skeletal events by more than one-fourth. Two double-blind randomized placebo-controlled trials comparing monthly 90-mg pamidronate infusions to placebo infusions for 1–2 years in addition to hormone or chemotherapy in patients with at least 1 lytic bone metastasis have shown that the mean skeletal morbidity rate could be reduced by 30–40%. The results obtained with IV bisphosphonates are generally viewed as better than those obtained with PO clodronate. However, preference can be given to the PO route when bisphosphonates are started early in the process of metastatic bone disease in a

patient receiving hormone therapy. Because bisphosphonates provided supportive care, reducing the rate of skeletal morbidity but not abolishing it, the criteria for stopping their administration have to be different from those used for classic antineoplastic drugs, and they should not be stopped when metastatic bone disease is progressing.[78] Good results have been achieved in patients with multiple myeloma, and the general consensus is that bisphosphonates should be started as soon as the diagnosis of lytic disease is made in myeloma patients.[80] Clodronate and pamidronate have shown efficacy in reducing pain and hypercalcemic episodes and in slowing progression of osteolytic bone lesions.[80,84] Unfortunately, data are scarce for prostate cancer, but large-scale trials with potent bisphosphonates are ongoing or planned in such patients.[78]

Newer bisphosphonates have shown similar results to those achieved with pamidronate when using monthly 6-mg infusions of ibandronate in patients with breast cancer metastases to bone. The tolerance to ibandronate could be better when compared to earlier bisphosphonates, and the drug has the potential to be administered as a 15- to 30-minute infusion. Zoledronate is also administered safely as a 15-minute 4-mg infusion, and large-scale phase III trials have just been completed. These newer bisphosphonates will simplify the current therapeutic schemes and improve the cost-effectiveness ratio. They also have the potential to improve the therapeutic efficacy, at least in patients with an aggressive osteolytic disease or when given as adjuvant therapy. Examination of initial data for clodronate indicates that it has the potential to prevent the development of bone metastases, but the use of bisphosphonates in the adjuvant setting must still be viewed as experimental.[78]

Only a single case report has been published in the veterinary literature on the use of alendronate in dogs with osteosarcoma.[28] Alendronate was administered at doses between 10 and 20 mg. Results from 2 dogs were reported, 1 with a distal tibial osteosarcoma associated with a spiral fracture, and the other with a zygomatic arch osteosarcoma. The primary tumors were not removed, and in the case of the tibial osteosarcoma, the fracture was repaired surgically with an external fixator. This dog received alendronate at 10 mg once a day, starting 40 days after surgery. The dog survived 12 months and was euthanized because of tumor progression. The original fracture did heal and there was an improvement in lameness. The dog with the zygomatic arch osteosarcoma received cisplatin chemotherapy in addition to alendronate. Alendronate was started 30 days after diagnosis and continued until euthanasia 9 months later. The dog improved as regards pain on opening the mouth and ate and drank normally, but the cancer progressed in size. Tomlin et al[28] concluded that further investigation was called for, because both dogs survived a significant time without tumor removal when compared to published survival times, and improvement in pain control was evident.

In summary, bisphosphonates, specifically amino-bisphosphonates, are being developed that are safer and may exert inhibitory effects on cancer. The predominant mechanism of action of amino-bisphosphonates on osteoclasts and cancer cells appears to be via the mevalonate pathway with inhibitory action on bone resorption and many procancerous cellular functions. Administration includes PO and IV routes. With PO formulations, absorption from the gastrointestinal tract is poor and if dosed inappropriately, significant esophageal complications can occur. Intravenous preparations appear to be the route of choice with conditions such as hypercalcemia of malignancy but may be implicated in nephrotoxicity if given too rapidly. From this review it is clear that bisphosphonates can be important drugs in veterinary oncology, but require clinical trials to evaluate possible adverse effects, pain control, and antimetastatic and primary tumor effects in dogs and cats.

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