The Role of Bisphosphonates in Medical Oncology and Their Association with Jaw Bone Necrosis

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KEYWORDS

• Bisphosphonates • Bisphosphonate-related osteonecrosis of the jaw • Cancer • Jaw bone necrosis • Multiple myeloma • Oncology

KEY POINTS

- Bisphosphonates can be used to treat patients with multiple myeloma or solid tumors with metastatic lesions to the bones.
- They can also be used to combat malignancy-associated metabolic disorders, such as hypercalcemia, and hormonal- and chemotherapy-induced osteoporosis.
- Bisphosphonate side effects include acute-phase infusion reactions, kidney impairment, and bisphosphonate-related osteonecrosis of the jaw (BRONJ).
- The pathogenesis of BRONJ is multifactorial, involving remodeling suppression, osteoclast depression, angiogenesis disruption, and infection.
- The effect of oral pH may influence the propagation of BRONJ.
- Drugs that affect bone remodeling or angiogenesis may result in BRONJ-like symptoms.

Bisphosphonates, synthetic analogues to inorganic pyrophosphates found in the bone matrix, inhibit bone resorption. Bisphosphonates and their related effects on the jaw have been established since 2001.

THE ROLE OF BISPHOSPHONATES IN MEDICAL ONCOLOGY

Bisphosphonates are used in many clinical situations to treat conditions causing bone resorption, such as metastatic bone disease (particularly seen with multiple myeloma, breast cancer, and prostate cancer), osteoporosis, hypercalcemia, and Paget disease.

Mechanism of Action

Bisphosphonates, synthetic analogues to inorganic pyrophosphates found in the bone matrix, work by inhibiting bone resorption.[1] They do not repair existing bone damage, but help prevent formation of new lytic lesions. They do so through several mechanisms of action, including attaching to hydroxyapatite-binding sites on bony surfaces to impair osteoclast activity, decreasing the development of osteoclast progenitor cells, and promoting apoptosis of osteoclasts.[2–4]

Normal bone growth and maintenance involve a tightly coupled process of bone resorption by osteoclasts and deposition by osteoblasts.

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Bisphosphonates inhibit the resorption of bone by accumulating in resorption lacunae located near osteoclasts. At the time of bone resorption, bisphosphonates are released locally and absorbed by osteoclasts; this inhibits osteoclasts maturation and leads to apoptosis.[3]

Types of Bisphosphonates

There are three different groups of bisphosphonates: those without nitrogen substitution (eg, etidronate, clodronate), aminobisphosphonates (eg, pamidronate, alendronate), and bisphosphonates substituted at nitrogen (eg, ibandronate, risedronate, zoledronate). The bisphosphonates substituted at nitrogen are the more potent inhibitors of bone resorption and act by inhibiting farnesyl pyrophosphate synthase, which causes cytoskeletal abnormalities in the osteoclast and an accumulation of bisphosphonates substituted at nitrogen farnesyl pyrophosphate precursor, isopentenyl pyrophosphate. Isopentenyl pyrophosphate binds to a receptor that allows the release of tumor necrosis factor-α, which may be responsible for the acute-phase reaction seen with bisphosphonates.[5–8] The non–nitrogen-containing bisphosphonates act by causing apoptosis of osteoclasts when metabolites from the bisphosphonates are exchanged with the terminal pyrophosphate moiety of ATP, which prevents the ATP from being used as an energy source.[7]

Administration and Side Effects

Route of administration

Bisphosphonates can be administered either orally or intravenously. Because bisphosphonates have poor oral absorption (approximately 1%), they are absorbed best on an empty stomach. Two advantages of intravenous bisphosphonate administration are that it has a short infusion time and greater bioavailability than oral bisphosphonates, and that intravenous bisphosphonates are often given monthly, which increases patient compliance. Not all bisphosphonates have the same potency. Intravenous bisphosphonates, which are used in patients with multiple myeloma, are more potent than oral bisphosphonates, which are used in patients with osteoporosis.

Side effects

The side effects that can be seen with intravenous or oral bisphosphonate use include acute-phase infusion reactions, kidney impairment, and osteonecrosis of the jaw.[9] During therapy with bisphosphonates, patients should maintain good oral hygiene, have regular dental examinations, and avoid dental procedures. Side effects can be seen with either oral or intravenous bisphosphonate use, but are more common with intravenous administration because of the greater potency of the drugs. Bisphosphonates do not repair existing bone damage, but help prevent formation of new lytic lesions. Oral bisphosphonates can cause gastrointestinal side effects, such as gastritis and diarrhea.[10]

Absorption and half-life

Regardless of route of administration, approximately 70% of the absorbed bisphosphonate is cleared by the kidneys, and the other 30% is absorbed by the bone.[2] The exact half-lives of bisphosphonates are unknown, but they are thought to remain in the bone for years.[11]

Bisphosphonates in Multiple Myeloma

Based on several prospective, randomized controlled trials and two systematic reviews, bisphosphonates are used to treat patients with multiple myeloma to reduce pain and the risk of skeletal-related events.[12–16] Approximately 60% of patients with multiple myeloma have lytic lesions at the time of diagnosis.

Bisphosphonate treatment is generally well tolerated, but patients require periodic monitoring for complications, such as renal insufficiency, nephrotic syndrome, electrolyte abnormalities, and osteonecrosis of the jaw.[17] Laboratory tests that should be followed include serum creatinine, calcium, and magnesium levels. Patients undergoing treatment with bisphosphonates for multiple myeloma should have a 24-hour urine assessment every 3 to 6 months to screen for albuminuria.[17] If the albuminuria is greater than 500 mg in 24 hours, the bisphosphonate should be temporarily stopped.[17,18] This side effect occurs more frequently with pamidronate because it causes glomerular damage; in contrast, zoledronic acid damages the renal tubules.[19–21]

Steroids are routinely used as part of the treatment regimen in multiple myeloma and as an antiemetic given with chemotherapy, which also increases the risk of osteonecrosis of the jaw, as described later, and steroid-induced osteoporotic bone density loss. Before initiating therapy, patients should be evaluated for comorbidities that would require bisphosphonate dosing adjustments.

There are limited data concerning the optimal duration of treatment with bisphosphonates for multiple myeloma. In the absence of evidence from randomized clinical trials, the suggested dosing of bisphosphonates is monthly for a 2-year period; consideration is then given to stopping bisphosphonates in those with responsive or stable disease.[12,17,22–24] Therapy should be