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The Role of Bisphosphonates In The Management of Bone Metastasis

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Abstract

Metastasis to the bone indicates late and mostly incurable stage of cancer with an associated reduction in the quality of life of the subjects. Bone is a frequent site for distant metastasis, most especially from cancers of the prostate, breast, thyroid, and kidneys. It is associated with increased morbidity resulting from bone pain, spinal cord compression, and pathological fracture. Bisphosphonates are stable analogs of pyrophosphates, and they have been shown to effectively inhibit bone resorption, thereby improving mineral bone density and minimizing the risk of pathological fracture and other skeletal-related events while providing relief of pain in patients with bone metastasis and patients with prostate cancer on androgen deprivation therapy. There are better pain control and less requirement of analgesics in patients treated with bisphosphonates. Severe toxicity to bisphosphonates is uncommon but can arise with osteonecrosis of the jaw been one of the most serious complications. In this article, we review the Mechanism of bone metastasis, the pharmacology and Mechanism of action of bisphosphonates, and their role in the management of patients with bone metastasis supporting it with clinical studies that support their efficacy. We finally review the literature for their possible toxicity

Keywords: *Bisphosphonates, breast cancer, osteonecrosis of the jaw, prostate cancer.*

Introduction

Cancer is a major public health problem affecting people of all races, creeds, ages, and social strata in both developed and developing countries.[1-3] Many patients with cancers, especially in developing countries, present to the clinician with advanced and metastatic disease.[4] One of the inherent natures of malignant diseases is their ability to metastasize. Bone is one of the frequent sites of metastasis in patients with cancer, especially for cancers of the prostate, breast, thyroid, and kidney.[5] Bony metastasis usually indicates a short-term prognosis as the cure is rarely achieved, and the treatment of the patient aims at slowing tumor growth, improving quality of life (QOL), and life expectancy.[6] More than 80% of bone metastasis probably arises from prostate and breast cancers.[7] Bone formation is a finely regulated process that involves the continuous remodeling of bone through the activity of osteoclasts and osteoblasts, and this dynamic process may be disrupted by the migration of cancer cells into the bone, thus creating bone metastasis.[8] These lesions are intrinsically weaker than the normal bone leading to multiple sequelae termed "skeletal-related events" (SRE).[8] These result in increased morbidity, bone pain, decreased quality of life, increased cost of management, and greater mortality.[9, 10] Metastasis to the bone can cause suppression of bone marrow leading to the frequent requirement for blood transfusions.[11] Bone metastasis can either be osteolytic or osteoblastic based on their appearance on radiologic imaging.[10] The majority of bone metastasis in cancers is osteolytic, but most bone metastasis from prostate cancer are osteoblastic.[12] However, some patients may have mixed osteolytic (bone destruction) and osteoblastic (bone-forming) lesions.[12, 13] In osteoblastic metastasis, there is a marked increase in osteoblastic activity, which is reflected by an increase in the serum levels of total and bone-specific alkaline phosphatase.[14]

Bone loss from any type of cancer with the consequent SRE results from a variety of mechanisms depending on the clinical course of cancer, and the therapy is administered, or by the anti-cancer treatment.[15] These therapies include hormone deprivation therapies in prostate and breast cancers, the effect of chemotherapeutic agents on the bone, and the induction of bone loss due to the use of corticosteroids in the treatment of lymphoma.[16-19] Management of bone metastasis and preventing SRE requires a multi-disciplinary involvement of the radiologist, orthopedic surgeon, urologist, general surgeon, pain specialist, physical medicine specialist, and palliative care specialist.[20] The therapeutic strategies for the bone metastasis rely on first, the treatment of the cancer cells, the initiators of the bone insult using cytotoxic drugs, hormonal deprivation therapies as well as targeted agents that inhibit cancer signaling pathways.[21] Secondly, the modification of bone microenvironment and this involves disrupting the cancer cells - resident cells interaction and thirdly, palliative therapies aimed at the symptoms thus improving patient QOL.[21]

Because of increased bone resorption in bone metastasis, there is a need for therapies targeted at inhibiting bone resorption and hence minimizing the risk of skeletal complications. In patients with prostate cancer, androgen deprivation therapy is also associated with the increased osteoclastic activity.[22] Over the years, bisphosphonates have gained prominence as an effective therapy in the management of the metastatic bone disease. They have been shown to effectively inhibit bone resorption and significantly reduce skeletal complications while providing an analgesic effect for bone pain.[7]

Mechanism of Cancer Metastasis to the Bone

Metastasis is a term used to label the presence of tumor sites distant to the site of the primary tumor. Cancer metastasis has been an intriguing focus of research for researchers. The Mechanism of cancer metastasis has undergone much evolution starting from the landmark 'soil and seed' hypothesis espoused by Stephen Paget in 1889.[23]. The seed refers to the tumor cells, while the soil is the site of metastatic deposit, which provides a congenial environment for tumor growth and development.[24] The spread of cancer cells from the primary site to a remote location is a complex multi-step process.[25, 26] These multi-step processes are termed invasion-metastasis cascade and begin with the tumor growing beyond the basement membrane and invading the peripheral extracellular matrix.[25] The basement membrane plays an important role in maintaining the architectural integrity of epithelial tissues, partially by separating the stromal and the epithelial compartments.[27] Growth factor molecules are also stored within the basement membrane, which can be released by the action of carcinoma-secreted proteases.[27] Similarly, the basement membrane has a critical role in signal transduction within the carcinoma cells through integrin-mediated cell-matrix adhesions initiated pathways, leading to alterations in cell polarity, proliferation, invasiveness, and survival.[27] Following the invasion of the basement membrane, there is the development of neo-vasculature to sustain the primary tumor growth, and there is a subsequent invasion of the tumor into the neo-vasculature.[25] The tumor must then survive in the bloodstream or lymphatics and then get arrested at the target organ.[25] Then finally, there is metastatic colonization, a term used to describe the adaptation to thrive within the target organ tissue.[25]

The propensity of some tumors to metastasize to the bone while others cannot, despite having similar circulatory patterns and tumor-cell deposition in the bone matrix, suggest that either the cell of origin or stromal influence at the primary tumor is essential for bone metastasis. There is also enough evidence to support the idea that inducers of cellular plasticity, cancer stemness, and the epithelial-to-mesenchymal transition (EMT) primes certain cells for bone metastasis.[28]

Epithelial-mesenchymal transition is a biologic process that occurs when a polarized epithelial cell progress through multiple biochemical alterations that enables it to assume mesenchymal cell phenotypes such as migratory capacity invasiveness, increased resistance to apoptosis, and increased production of the extracellular matrix.[29]

Epithelial-to-mesenchymal transition refers to the loss of epithelial features and the acquisition of mesenchymal properties, which is paramount in preparing cancer cells to invade surrounding parenchyma and intravasate to enter the bloodstream.[24] Distinct molecular processes involved in initiating and completing the EMT include activation of transcription factors, expression of specific cell surface proteins, reorganization and expression of cytoskeletal proteins, production of extracellular matrix-degrading enzymes, and changes in the expression of specific micro RNAs.[30]

To buttress the role of the cell of origin is that healthy kidney tissue has a high expression of calcium-sensing receptor (CSR) to regulate calcium homeostasis. It has been shown that there is a strong correlation between CSR and bone metastasis in patients with renal cell carcinoma (RCC). Furthermore, the addition of calcium to RCC cells was mitogenic in cells from patients with bone metastasis.[28] Similarly, to support the idea that stromal influences precede bone metastasis, it has been shown that cancer-associated fibroblasts secrete CXCL-12, which primes the tumor cells for metastasis to organs rich in CXL12 through selection for high SRC activity.[28] Then, to support the need for stemness/EMT is the finding that embryonic miR409 correlated with higher Gleason score and EMT/stemness gene signatures in prostate cancer tumors or that a gain of RAS/MAPK (mitogen-activated protein kinase) signaling and a loss of PTEN in prostate cancer-induced an EMT that resulted in bone metastasis with 100% penetrance.[28]

Bone metastasis is a complex process that involves cooperative reciprocal interactions between tumor cells and bone marrow stromal cells.[31] The fenestrated structure of the bone marrow sinusoid capillaries, high volume flow of blood in the areas of red marrow, sluggish blood flow, and the presence of adhesive molecules on tumor cells that bind to the bone marrow stromal cells facilitate metastasis to the bone.[5] The bone marrow stromal cells include osteoblast, osteoclast as well as a bone matrix, which all have an important role in bone remodeling and niche structure.[5] There is a homeostatic imbalance between resorption and bone formation in bone metastasis.[31]

For bone metastasis to occur, there is detachment of tumor cells from the primary tumor and entrance of such cells into the systemic circulation, as well as evasion of the immune system and adherence to the bone marrow capillaries, which eventually leads to extravasation of the tumor cells into the bone marrow space.[10] The attachment of the tumor cells to the bone marrow capillaries is facilitated by chemoattractants and adhesion molecules such as vascular cell adhesion molecules (VCAM) and E-selectin.[6] Another adhesion molecule expressed by the cancer cells is the cluster of differentiation 44 (CD44), which also promotes invasion and adhesion, directly inducing bone metastasis.[12] The C-X-C receptor type 4 (CXCR-4) through interaction with C-X-C motif ligand 12 (CXCL12) on osteoblasts induces migration and bone metastasis.[12] Once the tumor cells are within the bone marrow space, and they begin to colonize the space with some adapting to the local environment.[12] These tumors cells may grow instantly or upon interaction with the local environment though they may remain dormant for several years.[10, 12] The dormant cells may be reactivated at any point leading to the formation of micrometastasis.[12] Within the bone microenvironment, the tumor cells secrete factors such as parathyroid hormone-related peptide (PTHrP), that stimulate osteoblast.[31, 32] These activated osteoblasts increase the expression of receptor activator of nuclear kB ligand (RANKL).[5, 31] The RANKL then activates the osteoclast through interaction with the osteoclast precursors displaying RANKL receptor on their surface

which results in the eventual maturation of the osteoclast precursors into functional osteoclast.[5] Osteoprotegerin (OPG), a soluble decoy receptor, is also produced by the osteoblast, which can block RANK/RANKL signaling via scavenging RANKL.[5] therefore, the balance between RANKL and ODG is the trigger for osteoclasts activation.[5] The activated osteoclasts lead to the destruction of the bone marrow matrix through the production of proteinases and acids, such as the matrix metalloproteinases (MMPs) and cathepsins.[31] Tumor cells enrich the premetastatic niche (local microenvironment) for further tumor cell colonization and growth through priming the stroma by producing factors that trigger responses within the bone microenvironment.[10] This is evident by the increased release of transforming growth factor-beta (TGF-β), insulin-like growth factors (IGFs), and other growth factors stored in the bone matrix into the bone microenvironment.[31] [32] These growth factors stimulate further growth of the tumor with resultant increased levels of tumor-derived PTHrP establishing a vicious cycle that accelerates tumor-stromal interaction in the bone microenvironment which provides a fertile ground to promote the aggressive behavior of the cancer cells that reach the bone microenvironment.[31, 32]

Pharmacology and Mechanism of action of Bisphosphonates

Bisphosphonates are stable analogs of pyrophosphates.[33, 34] The structure of pyrophosphates (PPi) consists of two phosphate groups that are linked by an oxygen atom, P-O-P (Fig 1a).[33] On the other hand, the structure of bisphosphonate consist of a geminal central carbon atom which replaces the central oxygen, P-C-P (Fig 1b).[33, 35] R_1 and R_2 are attached to the carbon atom as side chains and influence the ability of bisphosphonate to bind to bone and their anti-resorptive properties.[33] Generally, R_1 is a hydroxyl group that maximizes bone affinity, while the R_2 side chain structure is a major determinant of the anti-resorptive property of the biphosphonate.[36-38] Bisphosphonates that contain a primary nitrogen atom (amino group) such as pamidronate and alendronate (Fig 2) are more potent than those without a primary nitrogen atom in the R_2 side chain such as clodronate or etidronate (Fig 2).[33, 36] Again, modification of the primary amine to a tertiary amine (methylation) such as in ibandronate (Fig 3) gives an even more potent drug.[33, 36] Bisphosphonates with a tertiary amine within a ring structure such as zoledronate appear to be the most potent of all (Fig 1c).[33, 36]

Bisphosphonates are known to inhibit osteoclastic bone resorption.[39] They are used in the treatment of complications associated with malignant disease such as hypercalcemia, skeletal morbidity related to metastatic bone disease and less often, in the adjuvant setting to delay the onset of bone metastasis.[39]

Bisphosphonates can inhibit bone resorption because of two features of the molecule.[36] One is the high affinity for a bone mineral, which allows rapid and selective targeting of bisphosphonates to bone mineral surfaces in vivo.[33, 36] The affinity of bisphosphonate to hydroxyapatite is due to the P-C-P motif.[36] The second feature is the structure of the R_1 and R_2 side chains, which determines the affinity of the molecule to the bone and its resorptive potency.[36]

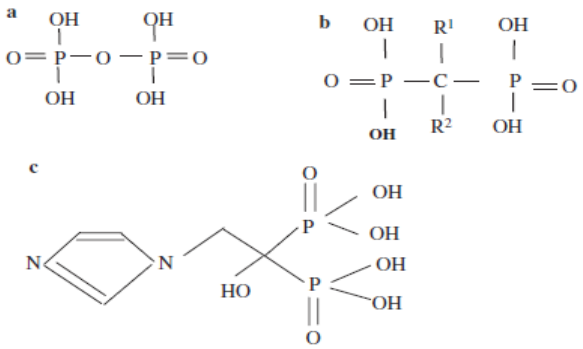

Fig 1: (a) Structure of PPi, (b) General structure of bisphosphonate (c) Zoledronic acid

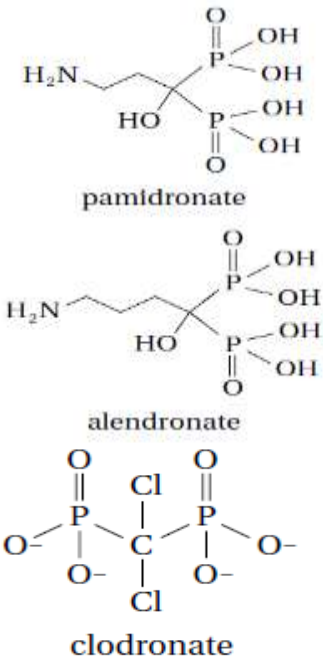

Fig 2: Structure of pamidronate, alendronate and clodronate

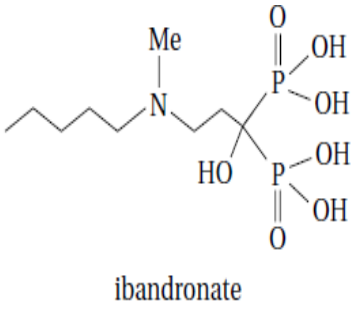

Fig 4: Structure of Ibandronate

Because of the strong binding of bisphosphonates to exposed hydroxyapatite crystals of bone, they rapidly disappear from the circulation.[35] Once these compounds are bound to the bone, and they are only released when the bone is damaged during turnover or metastatic erosion.[35]

The Mechanism of action of Bisphosphonates was initially ascribed to their ability to strongly adsorb to hydroxyapatite crystals and to inhibit their growth as well as dissolution.[36] It has now become clear that this alone is not enough to explain all their effects.[36] It is thought that bisphosphonates are internalized by osteoclast and interfere with certain biochemical processes.[36] The Mechanism of action of nitrogen-containing and non-nitrogen containing biphosphates differs. Inhibition of osteoclast activity through inhibition of ATP-dependent enzymes by the formation of non-hydrolyzable analogs of ATP is the primary mode by which the nitrogen-containing agents work.[40] The non-nitrogen containing agents, in contrast, exert their action through both intracellular and extracellular mechanisms.[40] They act as calcium chelators in the extracellular space by binding to calcium, thereby stabilizing calcium phosphate within the bone matrix and preventing dissolution.[40] However, the intracellular effects are multiple; most important is the inhibition of the mevalonate pathway, which is required for post-translational lipid modification and anchoring of small GTPases in cell membranes.[35, 40] Several cellular processes, including integrin signaling, endosomal trafficking, membrane ruffling, and apoptosis require the function of GTPases.[40] Another mechanism by which bisphosphonates act is through their ability to disrupt cell energetics by inhibiting ATP-dependent metabolic pathways and to damage the cytoskeleton of the osteoclast through inhibition of actin assembly.[40] Therefore, they can induce osteoclast apoptosis and hence the number of osteoclast on the bone surface, which leads to a reduction in bone resorption.[35] There is also evidence to suggest that bisphosphonates can directly affect tumor cells, and the potency of their anti-tumor activity in vitro also depends on the anti-resorptive property of the agent.[33] Hence, Zoledronic acid is the most potent in this respect.[33] Corey E et al.,[41] reported that Zoledronic acid decreased prostate cancer cell proliferation and induced G1 arrest and apoptosis of prostate cancer cells in vitro.[41] However, the growth of prostate cancer was not affected by zoledronic acid in vivo.[41] In contrast, there was significant inhibition of the growth of both osteoblastic and osteolytic metastases of prostate cancer in vivo.[41]

Role of Bisphosphonates in the Management of Cancer Patients

Over the years, several studies have been done to assess the efficacy of bisphosphonates as an adjunctive drug in the management of patients with various malignancies and especially among those with bone metastasis. They have been found to have the following roles:

Inhibition of metastasis

Some studies in rodent models have shown that bisphosphonates can prevent tumor-induced osteolysis and delay the progression of metastasis.[35]

Prevention of osteoporosis associated with androgen deprivation therapy (ADT) in prostate cancer

The bones are the commonest sites of metastasis from prostate cancer, and skeletal complications in these patients result not only from metastasis to the bones but also from androgen deprivation therapy.[42] Bisphosphonates can decrease osteoporosis in prostate cancer patients treated with ADT. Androgen deprivation therapy (ADT) usually leads to low bone mineral density (BMD).[43] The concomitant use of bisphosphonate, such as alendronate, has been shown to increase BMD in such patients. Bruder et al.,[43] reported that there was a statistically significant difference ($P<0.05$) in the percentage change of BMD per year in patients not treated with alendronate compared to patients receiving 70mg of alendronate weekly. This was especially evident in the spine, total hip, femoral neck, and trochanter, but the difference was not statistically significant at the radius.[43] Similarly, Planas et al.,[44] reported that patients treated with alendronate had a significant increase in BMD at the lumbar spine and femoral neck after one year of follow-up. Smith et al.,[45] also reported that pamidronate, when given 60mg intravenously for two hours every twelve weeks prevented bone loss in the hip and lumbar spine in patients with prostate cancer receiving ADT. Zoledronic acid has been reported to be effective in reducing skeletal events (SRE) in patients with castrate-resistant prostate cancer and bone metastasis.[46] Saad et al. .[47] in their study reported that 4mg of zoledronic acid administered by intravenous infusion over 15 minutes at 3-month intervals prevented SRE more than placebo and had less renal toxicity than a regimen of 8mg of zoledronic acid. The former regimen was also reported to be well tolerated and is an effective therapy in patients with bone metastasis from prostate cancer.[48, 49] Therefore, bisphosphonates may be used to prevent bone loss in patients on ADT and therefore reduce the risk of pathologic fractures.

Treatment of bone pain and other skeletal-related events associated with bone metastasis

Metastasis of cancer to the bone may cause bone pain and severe discomfort for the patient. The treatment of choice for localized bone pain from metastatic bone disease has been radiotherapy; however, the use of bisphosphonates can provide additional benefit, particularly in those patients with diffuse bone pain or recurrence of pain after initial irradiation.[33, 50] Pain control appears to be independent of the nature of the radiographic appearance of the metastasis, with both osteolytic and osteoblastic lesions having a similar response.[33] For more than two decades, bisphosphonates have been the standard of care in the management and prevention of skeletal morbidity related to bone metastasis from several types of cancers.[50] Zoledronic acid appears to be the bisphosphonate that is most effective in preventing skeletal-related events in patients with prostate cancer. Placebo-controlled trials have shown Zoledronic acid given monthly reduces the overall risk of SRE by 27% to 41% while also extending the time to first and subsequent SREs.[51] Zoledronic acid is the only bisphosphonate that has been proven to reduce SRE in patients with androgen-independent metastatic prostate cancer.[22] Heidenreich et al.,[52] reported that the use of 6mg of Ibandronate every four weeks resulted in a

significant reduction in pain score from 6.5 (5-10) to 2.0 (0-4) with P-value <0.001 in 92% of patients with 39% of the patients completely free of pain. It also resulted in a significant decrease in pain and analgesic requirement in 92% of patients with hormone-refractory prostate cancer.[52]

There is substantial evidence that supports the role of bisphosphonates in the management of advanced breast cancer.[53] A Cochrane Collaboration systematic review and meta-analysis of 9 studies with 2,806 patients showed that bisphosphonates reduced the rate of SRE by 15% compared with placebo in breast cancer women with bone metastasis.[53] All bisphosphonates were found to be effective and produced a reduction in SRE by 20% to 40% depending on the agent used. There was no significant difference between the oral and the intravenous agents.[53] However, the role of bisphosphonates as adjuvant therapy in early breast cancer has been rather controversial even though there are several studies that have proposed that bisphosphonates can alter the local tissue microenvironment and produce anti-cancer effects that may prevent or delay the onset of bone metastasis.[53] These agents can reduce the rate of bone loss associated with breast cancer therapy.[53] The adjuvant use of bisphosphonate therapy has been shown to decrease the development of bone metastasis, distant recurrence, and mortality from breast cancer among women in their post-menopausal period.[53]

The use of bisphosphonates in patients with bone metastasis from renal cell carcinoma is somewhat conflicting. Mckay et al. .[54] reported that the use of bisphosphonates in patients with RCC and bone metastasis did not produce a decrease rate of skeletal-related events compared to non-users and is not associated with improved overall survival. Eduard et al. .[55,] on the other hand, reported that bisphosphonates might have delayed early disease progression for prognostically worse patients treated with sunitinib/bisphosphonate.

Toxicity Associated with Bisphosphonates

Even though bisphosphonates are generally well tolerated, their use is not without the risk of toxicity ranging from acute reactions, gastrointestinal and renal toxicity, electrolyte derangement, osteonecrosis of the jaw, among others. Therefore, patients on bisphosphonate therapy should be counseled and monitored for these side effects.

Acute reactions

These are the most frequent side effects and can occur in up to 18% of patients treated with bisphosphonates, especially zoledronic acid or pamidronate.[22] These symptoms are mostly self-limiting but may be ameliorated with Acetaminophen.[22, 56] These reactions include low-grade fever, arthralgia, myalgia, and increased bone pain.[22, 56] It generally occurs with the first infusion of the drug, but the incidence of the reaction progressively decreases with subsequent infusions.[56]

Nephrotoxicity

Renal toxicity is uncommon, and when it occurs, it can be potentially serious. Renal toxicity is commoner with the intravenous agents and is directly related to the dose and inversely related to the infusion time.[57] Long-term use of bisphosphonates is associated with a raised level of creatinine in 12.5% of patients receiving these agents, and the underlying tumor may also contribute to the development of renal impairment.[22] Most of the toxicity is seen in patients with multiple myeloma.[22] Potentially nephrotoxic drugs, such as radiographic contrast media and NSAIDs should be avoided in patients receiving intravenous bisphosphonate, and where such agents must be given, they should be administered on different days, and there should be monitoring of patients renal status.[22]

Gastrointestinal Toxicity

This is seen more often with oral bisphosphonates and may result from improper administration of the drug, which causes erosive esophagitis, especially in patients who fail to remain in an upright position for 30 minutes to 1 hour following ingestion of biphosphonates.[56] Non-specific side effects such as nausea, vomiting, diarrhea, dyspepsia, and abdominal pain can also occur, and they are among the reason for poor compliance and discontinuation of bisphosphonates in some patients.[56, 57]

Musculoskeletal complications

Studies have linked atypical fractures with bisphosphonate use and are thought to be due to prolong over-suppression of bone turnover, which results in impaired bone remodeling, accumulation of microdamage in the bone, and increased fragility of the bone.[58] This has led to discussions on how long should bisphosphonate be used. Muscolo-Skeletal pain has been reported as a potential side effect of bisphosphonate therapy. Babayan et al.,[59] reported that a patient developed severe aching muscle pain (10/10 on a visual analog scale) throughout the body 15 hours following admiration of one dose of Risedronate. Other possible muscle-skeletal side effects include arthralgia and incapacitating bone pain.[56] There is an improvement of symptoms in some patients following discontinuation of bisphosphonate therapy, but in others, the resolution appears to be slow or incomplete.[56]

Osteonecrosis of the jaw (ONJ)

This is the most widely reported bisphosphonate toxicity in literature. This condition is defined as exposed necrotic bone in the maxillofacial region, not healing after 6-8 weeks in patients with no previous craniofacial radiation.[58] The mandible is more commonly affected than the maxilla in a ratio of 2:1, and 60% of cases are preceded by a dental surgical procedure.[60] Other risk factors include poor oral hygiene, use of denture, and prolonged exposure to high doses of biphosphonates.[56] The elimination of all sites of potential jaw infection before initiation of bisphosphonate therapy can help minimize the necessity of subsequent dentoalveolar surgery.[60] The treatment of ONJ is largely supportive with antimicrobial mouth rinses, antibiotics, limited debridement of necrotic bone, and withdrawal of biphosphonate.[56, 60]

Other complications

Other potential complications include atrial fibrillation, oesophageal cancer, Ocular complications, among others.[56, 58]

Conclusion

Bisphosphonates are effective therapy for the treatment of skeletal-related events and osteoporosis associated with bone metastasis from cancers. In prostate and breast cancers, they have been found to be effective in these conditions of androgen and oestrogen deprivation. The intravenously administered Alendronic acid has been documented to be more effective than oral bisphosphonates. However, patients should be monitored for potential side effects, and in cases of severe toxicity, the agent should be discontinued.

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