UNDERGRADUATE RESEARCH IN NATURAL AND CLINICAL SCIENCE AND TECHNOLOGY (URNCST) JOURNAL
Read more URNCST Journal articles and submit your own today at: https://www.urncst.com

REVIEW OPEN ACCESS

Evaluating Route of Administration for Bisphosphonates in Patients with Metastatic Breast Cancer to the Bone: A Literature Review

Christine P. King, BS Student [1]*^, Jennifer P. Huynh, BS Student [1]^

[1] Department of Psychology, University of California-Los Angeles (UCLA), Los Angeles, California 90095

*Corresponding Author: cpking278@g.ucla.edu
^Both authors were equal contributors to this review.

Abstract

Introduction: Metastatic bone disease, the condition where tumor cells spread from their origin tissue to bone, is common for breast and prostate cancer. Two main hypotheses, referred to as Paget's "seed and soil" theory and Ewing's anatomical theory, describe the homing of cancer cells to the bone. When breast cancer becomes metastatic and the tumor spreads to the bone, skeletal-related events can occur. Many patients use bone-modifying agents such as bisphosphonates (BPs) to manage skeletal deterioration. Given the longstanding history of BPs, this review aims to evaluate the efficacy and side effects of oral versus intravenous BPs as adjuvant treatment options for patients with metastatic breast cancer.

Methods: Relevant literature was sourced through a search of the PubMed and Google Scholar databases, using established inclusion criteria for screening papers published between 1889 and the present.

Results: Currently, there are three generations of BPs. Literature on the different generations reports that studies mainly use first-generation BPs for Paget's disease and there is no significant effect of first-generation BPs on breast cancer survival rate. Second-generation BPs showed effectiveness in prolonging the progression of bone metastasis and decreasing distant recurrences to the bone in breast cancer patients. In attempts to improve the health outcomes of BPs, researchers examined third-generation BPs and found that they decreased skeletal-related events and pain levels.

Discussion: Comparing oral to intravenous administration of BPs, both had overall similar effects in reducing skeletal complications; however, the side effects resulting from BP use vary depending on the route of administration. Patients administered intravenous BPs exhibit an acute phase response and renal complications, while oral BPs cause disruptions in the gastrointestinal tract. Cost-effectiveness varied by study depending on assumptions made in the analytic models.

Conclusion: This novel review investigates the development of each generation of BPs to compare the implications of oral and intravenous administration. By accounting for differences across the three generations, healthcare providers can make informed decisions about BPs and create treatment plans tailored to the individual patient. Future research may explore how preexisting risk factors contribute to the occurrence of adverse effects of BP use.

Keywords: Breast cancer; bisphosphonates; intravenous; oral; skeletal-related events; bone metastasis

Introduction

Breast cancer is the most prevalent form of cancer, with the National Institutes of Health predicting 300,590 new breast cancer cases in 2023 [1]. Late-stage breast cancer is often metastatic, with metastasis to the lung and liver being very common [2]. However, bone is the primary site for tumor migration, with 75% of breast cancer metastasis spreading to the bone [3, 4].

To further understand the patterns and mechanisms of breast cancer metastasis, theories such as Paget's 1889 "seed and soil" hypothesis and Ewing's anatomical hypothesis provide valuable insight into the complex processes of tumor migration. The "seed and soil" theory posits that specific organs are predisposed to tumor development upon exposure to certain tumor cells due to the favorable microenvironment. According to Paget, the target of metastasis is not dictated by chance but rather arises preferentially due to specific traits of the organ to which the seed migrates [5]. Ewing's hypothesis posits that metastasis occurs when components on the surface of primary tumor cells attach to the lymphatic system and travel in a chain until the cells reach a secondary location for tumor growth. When an event causes the chain to break, the establishment of a secondary tumor growth occurs [6]. Ewing argues Paget's hypothesis on the discussion of secondary growth locations, suggesting that the exact site is not predetermined but rather depends on the anatomical lymphatic routes available [6]. Regardless, both methods address the process of cancer migration from the primary tumor to a distant site.

Metastasis to the bone is a common problem for breast cancer patients. Once the tumor spreads to the bone, it can cause skeletal-related events, which consist of skeletal complications such as bone pain, fractures, and hypercalcemia (SREs) [7]. Alongside chemotherapy and endocrine therapy, patients use bone-modifying agents (BMAs) such as bisphosphonates (BPs) and the monoclonal antibody denosumab to manage the symptoms of SREs [7]. Breast tumor subtypes, categorized based on gene expression patterns and the origin of the breast tumor cell, influence the extent of SRE symptoms and determine the treatment options [8]. There is a strong correlation between SREs in patients with breast cancer linked to bone metastasis and an increased risk of mortality [9]. As such, it is necessary to further investigate the various types of BMAs used as treatments for bone metastasis to better understand how we can reduce mortality in patients with SREs.

BPs can be administered either orally or intravenously, depending on the drug. When considering the efficacy of different routes of administration, factoring in both cost and outcome is important to evaluate the impact and feasibility of the implementation of a drug on the healthcare system. In this review, we seek to investigate the development of BPs in terms of both efficacy and patient experience to elucidate how their method of administration impacts disease progression.

Methods

A search for relevant articles was conducted through PubMed and Google Scholar, using the following key terms: “bisphosphonates,” “bone metastasis,” “breast cancer,” “intravenous,” “oral.” A total of 87 references were evaluated in this review. Additional sources were found by consulting the references of relevant articles. The abstracts of the results were screened to include only articles written in English, and filtered according to the following selection criteria:

- Articles were published from 1889 to the present day.
- Articles were published in a scholarly journal.

Results

Patients with bone metastatic breast cancer commonly use BPs to minimize SREs. BPs act as osteoclast inhibitors, reducing resorption by binding to hydroxyapatite crystals found in bone [10, 11]. Bone metastasis or lesions cause increases in bone turnover, resulting in the enhanced localization of BPs to these bone regions [12]. Many factors can affect the binding of BPs on hydroxyapatite of bone, including BP structure, method of delivery, absorption into bone, and drug retention [22, 23, 24, 25, 26]. The drug can influence the bone microenvironment in different ways depending on whether the BP contains nitrogen. The body metabolizes non-nitrogen-containing BPs into adenosine triphosphate analogs, which induce osteoclast apoptosis [13, 14]. Nitrogen-containing BPs, or aminobisphosphonates, reduce osteoclast function by disrupting the production of two critical biomolecules in osteoclasts, farnesyl pyrophosphate and geranylgeraniol pyrophosphate [16, 17]. Consequently, nitrogen-containing BPs affect signaling proteins that interfere with osteoclast attachment to bone, the organization of the osteoclast cytoskeleton, and osteoclast survival [15, 16, 17, 18]. Other effects of BPs on bone metastasis involve their anti-tumor effects and decreasing osteoblast and osteocyte apoptosis [19, 20, 21].

First-Generation Bisphosphonates

The first generation of BPs include etidronate, clodronate, and tiludronate, and they are all non-nitrogen-containing BPs.

Etidronate

Etidronate, the earliest clinically available BP, was initially established as an effective treatment for bone conditions such as Paget’s disease and osteoporosis [27]. A 1999 study investigating etidronate as a palliative measure for bone metastasis found a 58% response rate in pain reduction for patients experiencing pain due to bone metastasis from breast cancer [28]. Another study from 2002 evaluated the use of etidronate on metastatic bone pain and discovered that an oral dose of 400mg/day for two weeks significantly reduced bone pain and suppressed bone resorption within 2 to 12 weeks after administration [29]. However, case studies have suggested potential complications such as osteomalacia due to longer exposure to etidronate in combination with other treatments [30, 31].

Tiludronate

Tiludronate is a sulfured BP administered orally. In pre-clinical trials on animal models, tiludronate demonstrated a dose-dependent ability to inhibit bone resorption [32]. It is effective in treating conditions such as Paget’s disease. However, further clinical trials are necessary to ascertain its effectiveness for contending with the effect of SREs as a result of bone metastasis from breast cancer [33].

Clodronate

Clodronate, a non-nitrogen-containing BP, has been used orally to treat hypercalcemia and bone pain [34]. In a 1996 study evaluating clodronate’s effectiveness in reducing metastatic bone lesions from breast cancer, researchers observed a decrease in the number of skeletal metastases developed and a decrease in skeletal complications among women with no initial skeletal metastases, following oral administration of clodronate [34]. This further supports previous research indicating that clodronate reduces the number of bone metastases experienced by breast cancer patients over the course of two years [35]. However, a meta-analysis of oral clodronate treatment found no significant difference between the 5-

year survival rates of groups who received clodronate therapy and those who did not [36].

Second-Generation Bisphosphonates

Alendronate, ibandronate, and pamidronate make up the second generation of BPs, and they are all nitrogen-containing BPs.

Alendronate

First used as a pharmaceutical drug in 1988, alendronate is administered orally [37]. Previous studies with postmenopausal osteoporotic women showed that patients using alendronate had a decreased risk of breast cancer after controlling for differences in sex hormones [38, 39, 40, 41]. A 2018 study went further to evaluate the risk of bone metastasis in breast cancer patients receiving BP therapy. The study included postmenopausal women with early breast cancer and found a negative correlation between the use of oral alendronate and bone metastasis progression [42].

Postmenopausal women with breast cancer commonly receive aromatase inhibitors (AIs) as a drug treatment option. However, AIs are known to cause damage to bone mass [43]. When breast cancer patients who are treated with AIs receive alendronate and calcitriol, they show diminished bone loss compared to individuals treated with AI and a placebo, indicating alendronate's role as an effective adjuvant treatment option [44].

Ibandronate

Clinical studies show that ibandronate is less toxic to the renal system when compared to other BPs, making it a safer option when a BP treatment requires higher doses [45, 46, 47, 48]. Patients with stage I-III breast cancer administered 50 mg daily of oral ibandronate for three years have an 87.4% disease-free survival (DFS) rate after a 5-year follow-up [23]. Among all cancer recurrences that developed among this group of patients treated with ibandronate, 39.2% showed a distant recurrence at the bone. Further studies investigated the effectiveness of ibandronate on cancer recurrence and found that ibandronate cleared dormant disseminated tumor cells, which cause recurrence in cancer patients [49]. Administration of ibandronate also showed a decreased skeletal morbidity rate in patients with breast cancer and bone metastasis with 6 mg being most effective in decreasing SREs and delaying bone events [45, 50, 51, 52, 53].

Pamidronate

Pamidronate is a second-generation intravenous BP a recommended treatment option for breast cancer-associated bone metastasis [54]. A randomized controlled trial studied the effects of pamidronate in conjunction with chemotherapy in bone metastatic patients with breast cancer, concluding that time to the progression of bone metastasis was greater by 48% in patients who received pamidronate in addition to chemotherapy [55]. Additionally, other studies showed that stage IV breast cancer patients with bone metastasis who received 90 mg of pamidronate experienced a significant decrease in the skeletal morbidity rate, pain levels, and SREs [56]. However, the reported side effects of the drug include fatigue, fever, muscle pain, and hypocalcemia [57, 56].

Third Generation Bisphosphonates

The third generation of BPs includes risedronate and zoledronate, both of which are nitrogen-containing BPs [58]. This generation exercises greater inhibition of osteoclast activity compared to the second generation, a trait attributed to their chemical structure [59].

Risedronate

Risedronate, or risedronic acid, is an orally administered aminobisphosphonate effective for conditions such as Paget's disease and postmenopausal osteoporosis [60]. Risedronate has been shown to slow the development and inhibit further progression of bone metastasis while also increasing survival duration [61]. In a 1995 study, researchers injected mice with a human cancer cell line (MDA-231) and then administered either phosphate-buffered saline or risedronate. Using radiography, they found that the administration of risedronate resulted in the slowing or inhibition of bone metastases and decreased bone loss, overall tumor volume in the bone, and the number of osteoclasts compared to the control condition [61].

Risedronate also helps preserve the integrity of the bone itself after the development of breast cancer. A double-blind 1997 study explored risedronate's effect on bone mineral density (BMD) for human female patients with breast cancer and chemotherapy-induced menopause. Comparing the experimental group, treated with a dosage of 30 mg/d, with the placebo group, researchers found that the risedronate group had increased BMD values in the lumbar and hip regions, while the placebo group had decreased values [62].

Zoledronate

Zoledronate, the most potent BP, is an intravenously administered antiresorptive aminobisphosphonate, making it a viable option for patients who experience adverse effects, such as gastrointestinal issues, or contraindications to the oral route of administration [63, 64]. It is one of two BPs approved by the American Society of Clinical Oncology for the treatment of bone metastases resulting from breast cancer in women, the other being pamidronate [54]. A study on Japanese women with bone metastases resulting from breast cancer found that zoledronic acid reduced skeletal complications in comparison to the placebo group when administered every 4 weeks over the course of a year [65]. Zoledronic acid also reduced bone pain from baseline levels, and it was well tolerated by

patients [65]. A phase II trial further supported this finding, evaluating zoledronate as a second-line therapy after the first-line treatment of a less potent BP [66]. This study found that there were additional palliative benefits to switching to zoledronic acid, including significantly reduced pain scores and a reduced number of pain sites compared to baseline [66]. Overall, zoledronic acid is currently considered the standard of care for treating breast cancer-associated bone metastasis [67, 68, 69].

Discussion

Efficacy

Prior research shows that BP use reduces skeletal complications in breast cancer-associated bone metastasis with minimal differences in efficacy across generations. There were many experimental measures for SREs, one of which was the pain response rate, where multiple studies found an estimate of 41.9%-58% of participants experiencing pain reduction from BP treatment with variations depending on study guidelines. Additionally, when researchers evaluated pain score comparisons across intravenous (IV) pamidronate, IV clodronate, and oral clodronate administration, there was no significant difference in the efficacy of oral compared to IV and pamidronate compared to clodronate [70]. However, oral BP administration increased the incidence of new skeletal fractures [70].

Given the rise of second and third-generation BPs, many studies focus on direct comparisons between these two nitrogen-containing drug groups. In one study where participants received oral ibandronate or IV zoledronate, there was a significant difference in the number of SREs, whereby patients receiving zoledronate exhibited fewer SREs [71]. Another trial demonstrated that 4 mg of IV zoledronate reduced the progression of SREs by 20% compared to 90 mg IV pamidronate at 25 months [72]. With the decreased infusion time and increased efficacy of zoledronate, researchers recommend zoledronate as a viable treatment option for patients with metastatic breast cancer.

The American Society of Clinical Oncology and Cancer Care Ontario recommend IV zoledronic acid (4 mg every 12 weeks or 3 to 4 weeks) and pamidronate (90 mg every 3 to 4 weeks) for patients with metastatic breast cancer [73]. Ongoing research is evaluating the use of oral BPs as a potential additional treatment option offered clinically (see Table 1).

Recurrence

Following cancer treatment, one area of concern is the potential recurrence of breast cancer. Researchers have identified factors, such as lymph node enlargement, primary tumor size, treatment type, weight, and bone microenvironment, as risks for recurrence [74]. Comparing the effects of BP treatments across generations, specifically oral clodronate from the first-generation BPs, oral ibandronate from the second-generation BPs, and IV zoledronic acid from the third-generation BPs, a clinical study investigated the DFS percentage of each drug. Overall, the study reported an 87-88% DFS rate for all drugs tested, and there was no significant difference in DFS rates across BP generation. Recurrence to the bone had the highest percentage compared to recurrence in other distant areas such as the liver, lungs, and central nervous system, but clodronate, ibandronate, and zoledronic acid did not show significant differences in recurrence to bone [23]. It was further discovered that reduced bone and breast cancer recurrence was found only in low-estrogen environments during post-menopause [75]. Thus, additional studies are necessary to elucidate specific interactions between the bone microenvironment, reproductive hormones, bone formation, and tumor growth.

Adverse Effects

Though BPs have been approved for conditions such as Paget's disease, osteoporosis, and bone metastasis, usage of BPs has also been associated with adverse effects depending on the route of administration. The most common BPs administered intravenously are pamidronate, zoledronic acid, and ibandronate [76, 72]. These BPs are associated with acute systemic inflammatory reactions (such as fever, nausea, and myalgia) following IV administration [76]. Due to their significant levels of nephrotoxicity, both pamidronate and zoledronic acid are associated with renal failure [76]. Patterns such as toxic acute tubular necrosis have occurred in some patients who use zoledronic acid [77, 78]. Other case studies found that some patients treated with pamidronate developed nephrotic syndrome, which results in a poor prognosis if it develops alongside impaired renal function [79]. However, the likelihood of severe renal failure from BP use is low if the BP is administered with the correct dosing regimen [80].

Although oral BPs are not a common clinical treatment for bone metastasis, they have been clinically approved for Paget's disease and osteoporosis, including postmenopausal osteoporosis. The most commonly researched oral BPs include clodronate, alendronate, ibandronate, and risedronate. Studies report that oral BPs for bone metastasis increase the risk of complications due to their low bioavailability. Symptoms of oral BPs include gastrointestinal lesions and esophagus inflammation, with severity levels determined by dosage [81, 82]. Gastrointestinal symptoms are specific to oral BPs because many have recommendations to take the drug on an empty stomach. Following gastrointestinal irritation, symptoms such as vomiting, diarrhea, and heartburn may result from BP use.

Table 1. Clinical Trials on the Efficacy of Bisphosphonates.

Reference	Interventions	Route of Administration	Treatment Duration	Subject Background	Subjects Analyzed	Efficacy	Outcome Measures
Han et al. 1999 [28]	(186)Re-etidronate (35-80 mCi)	IV	1 dose; 24 hour hospitalization	Patients with breast cancer and metastatic bone lesions	24	58% response rate	Pain assessment
Iwamoto et al. 2002 [29]	Etidronate (400 mg/d); Control	Oral	2 weeks	10 patients with cancer-associated bone metastasis; 20 with primary cancer with no skeletal-related events	10 intervention/20 placebo	Significant reduction in face scale score 2 weeks after treatment in intervention group ($p<0.001$); face scale score at 12 weeks significantly higher than at 2 weeks ($p<0.05$) but reduced compared to start of treatment ($p<0.01$)	Pain assessment using a facial expression scale
Reginster et al. 1994 [33]	Tiludronate (400 mg/d)	Oral	6 months	Patients with Paget's disease	128	58.3 ± 2.3% reduction in SAP activity	Pain assessment, Serum alkaline phosphatase (SAP) activity
Kanis et al. 1996 [34]	Clodronate (1600 mg/d); Placebo (daily)	Oral	3 years	Women with recurrent breast cancer but no skeletal metastases	133 (66 intervention/67 placebo)	32 skeletal metastases in intervention group vs. 63 skeletal metastases in placebo group ($p<0.005$); 26% reduction in skeletal complications	Incidence of skeletal metastasis
Diel et al. 1998 [35]	Clodronate (1600 mg/d); Control	Oral	2 years	Patients with primary breast cancer and bone marrow secondary tumors	302 (157 intervention/145 control)	21 patients with distant metastases in intervention group vs. 42 patients with distant metastases in control group ($p<0.001$)	Incidence of metastasis
Hue et al. 2014 [41] - FIT	Alendronate Sodium (5 mg/d for 2 years, 10 mg/d after); Placebo	Oral	mean follow-up of 3.8 years	Postmenopausal women	6194	1.8% (n=57) incidence of breast cancer in alendronate group vs. 1.5% (n=46) incidence of breast cancer in placebo group	Incidence of breast cancer

Reference	Interventions	Route of Administration	Treatment Duration	Subject Background	Subjects Analyzed	Efficacy	Outcome Measures
Rhee et al. 2013 [44]	Alendronate (5 mg/d); Placebo	Oral	24 weeks	Korean postmenopausal women with early breast cancer	98 (49 intervention/49 placebo)	-0.5 ± 0.6% change in lumbar BMD for intervention group during treatment vs. -3.5 ± 0.6% change for placebo group ($p<0.05$)	Lumbar BMD
Body et al. 2003 [45]	Ibandronate (2 mg for 154 patients, 6 mg for 154 patients every 3-4 weeks); Placebo	IV	60-96 weeks, maximum of 24 total treatments per participant	Women with breast cancer and bone metastases	466 (308 intervention/158 placebo)	20% reduction in SMPR with 6 mg ibandronate (1.19 vs. 1.48 periods with events per patient year; $p=0.004$); 11% non-significant reduction in SMPR with 2 mg ibandronate (1.31 vs. 1.48; $p=0.152$)	SMPR
Mancini et al. 2004 [48]	Ibandronate (4 mg/d for 4 days, 2-hour infusion)	IV	4 days (patients remained hospitalized for a range of 4-25 days)	Patients with bone metastases and opioid-resistant bone pain	18	Treatment significantly improved bone pain within 7 days ($p<0.001$)	Bone pain assessment
Hoffmann et al. 2011 [49]	Ibandronate (50 mg/d)	Oral	6 months	Previously diagnosed breast cancer patients with disseminated tumor cells (DTCs) 2-10 years after first diagnosis	18	3 out of 17 patients were still DTC-positive following 6 months of treatment. After 12 months of treatment, those patients no longer had DTCs	DTC detection
Body et al. 2004 [51]	Ibandronate (50 mg/d); Placebo	Oral	up to 96 weeks	Women with breast cancer and bone metastases	564 (287 intervention/277 placebo)	Mean SMPR of intervention was 0.95 vs 1.18 for placebo group ($p=0.004$)	SMPR
Diel et al. 2004 [52]	Ibandronate (2 mg/every 3-4 weeks); Ibandronate (6 mg/every 3-4 weeks); Placebo	IV	60-96 weeks	Patients with breast cancer and bone metastases	466 (158 placebo/154 2 mg ibandronate/ 154 6 mg ibandronate)	Bone pain scores increased in mean scores from baseline to final assessment in the 2 mg ibandronate (0.21 ± 0.09) and the placebo (0.19 ± 0.11) groups. The 6 mg	Bone pain score

Reference	Interventions	Route of Administration	Treatment Duration	Subject Background	Subjects Analyzed	Efficacy	Outcome Measures
						ibandronate group experienced a decrease in bone pain score from baseline to final assessment (mean change of -0.28 ± 1.11), which is statistically significant compared to the placebo group (p<0.001)	
Tripathy et al. 2004 [53]	Ibandronate (20 mg/d); Ibandronate (50 mg/d); Placebo	Oral	96 weeks	Women with breast cancer and bone metastases	435 (143 placebo/144 ibandronate 20 mg/148 ibandronate 50 mg)	Mean SMPR of placebo was 1.20 compared to ibandronate 20 mg (0.97) and ibandroante 50 mg (0.98) (p=0.044)	SMPR
Conte et al. 1996 [55]	Chemotherapy and pamidronate (45 mg in 250 mL saline for 1 hr/3 weeks); Chemotherapy only	IV	until evidence of disease progression in bone	Patients with metastatic breast cancer to the bone receiving chemotherapy	295 (143 chemotherapy and pamidronate/152 chemotherapy only)	48% increase in median time to disease progression in bone (249 days in intervention group vs. 168 days in chemotherapy only group, p=0.02)	Time to disease progression in bone
Lipton et al. 2000 [56]	Pamidronate (90 mg every 3-4 weeks for 24 cycles); Placebo	IV	up to 24 months	Women with stage IV breast carcinoma and bone metastases	215 (115 intervention/100 placebo)	2.5±5.6 mean skeletal morbidity rate (skeletal complications) per year for the pamidronate group vs. 4.0 ±6.1 in the placebo group (p<0.001).	Skeletal morbidity rate
Delmas et al. 1997 [62]	Risedronate (30 mg/d); Placebo	Oral	8 cycles (2 weeks with drug, 10 weeks without drug)	White female patients 36-55 years old with breast cancer and chemotherapy-induced menopause. 36 patients took tamoxifen (20mg/d).	53 (27 intervention/26 placebo)	Mean difference in BMD was 2.5% ± 1.2% at lumbar spine (p=0.041) and 2.6% ± 1.1% at the neck of the femur (p=0.029) with intervention group exhibiting increased BMD	BMD of lumbar spine and proximal femur

Reference	Interventions	Route of Administration	Treatment Duration	Subject Background	Subjects Analyzed	Efficacy	Outcome Measures
Hue et al. 2014 [41] - HORIZON-PFT	Zoledronic acid (5 mg/year); Placebo	IV	3 years	Postmenopausal women	7580	Higher incidence of breast cancer in the zoledronic acid group (0.9%, n=33) vs. placebo group (0.8%, n=29)	Incidence of breast cancer
Himelstein et al. 2017 [64]	Zoledronic acid (dosage calculated based on creatinine clearance for patients' body weight, every 12 or every 4 weeks for 2 years, 15+ minute infusion time)	IV	2 years	Patients with bone metastasis and breast cancer/prostate cancer/multiple myeloma	1822 (911 zoledronic acid every 4 weeks/911 zoledronic acid every 12 weeks)	The every 4-week dosing regimen was noninferior to the every 12-week dosing regimen ($p<0.001$) in terms of SRE occurrence under the assumption that dropouts had at least 1 SRE	SRE occurrence
Kohno et al. 2005 [65]	Zoledronic acid (4 mg/4 weeks); Placebo	IV	1 year	Female patients with bone metastases	228 (114 intervention/114 placebo)	39% reduction in SRE rate ratio by intervention compared to placebo ($p=0.027$)	SRE rate ratio
Clemons et al. 2006 [66]	Zoledronic acid (4mg/month for 3 months, 15 minute infusion time)	IV	3 months	Breast cancer patients with bone metastases and an SRE or progression of bone metastases. Patients had received first-line treatment with bisphosphonates before start of trial	31	41.9% of patients experienced significant reduction in pain scores (both average pain and worst pain) by week 8 ($p<0.001$)	Pain scores
Black et al. 2007 [69]	Zoledronic acid (5 mg/single dose); Placebo	IV	Single doses at start of study, 12 months, and 24 months	Postmenopausal women 65-89 years old with specific evidence of skeletal complications	7736 (3875 intervention/3861 placebo)	70% reduction in morphometric vertebral fracture in intervention group (92 in intervention group vs. 310 in placebo group, $p<0.001$); 41% reduction in hip fracture in intervention group (n=52 in intervention group vs.	Incidence of fractures

Reference	Interventions	Route of Administration	Treatment Duration	Subject Background	Subjects Analyzed	Efficacy	Outcome Measures
						n=88 in placebo group, p=0.002)	
von Au A et al. 2016 [70]	Pamidronate (60 mg/3 weeks); Clodronate (900 mg/3 weeks, IV); Clodronate (2,400 mg/d oral)	IV pamidronate, Oral clodronate, IV clodronate	24 months	Female breast cancer patients with bone metastases	321 (109 pamidronate/105 IV clodronate/107 oral clodronate)	No significant difference between pain development of the three groups based on baseline and final examinations.	Pain development
Barrett-Lee et al. 2014 [71]	Zoledronic acid (4 mg/4 weeks, 15+ min infusion time); Ibandronic acid (50 mg/d); Placebo	IV zoledronic acid, Oral ibandronic acid	96 weeks	Breast cancer patients with bone metastases		41% of patients in the zoledronic acid group had SREs of any kind, while 42% of the ibandronic acid group had SREs	SRE occurrence
Rouach et al. 2018 [42]	BP Intervention group (90% alendronate, 10% risedronate); Control (62% calcium and vitamin supplements, 38% unknown non-BP)	Oral	1-5 years	Osteoporotic women	297 (145 BP intervention/152 control)	0.7% (n=1) incidence of bone metastasis in intervention group vs. 9.9% (n=8) incidence of bone metastasis in control	Incidence of bone metastasis
Gralow et al. 2020 [23]	Zoledronic acid (4 mg reduced to 3 mg over time, monthly for 6 months, then every 3 months after); Clodronate (1600 mg/d); Ibandronate (50 mg/d)	IV zoledronic acid, Oral clodronate, Oral ibandronate	3 years	Female patients with breast cancer	5400 (2000 zoledronic acid/2000 clodronate/1400 ibandronate)	5-year DFS was 88.3% for zoledronic acid, 87.6% for clodronate, 87.4% for ibandronate with no significant difference across groups (p=0.49)	DFS

Sharing the BP classification, both IV and oral BPs have similar side effects involving areas of bone remodeling. Central to BP activity is altering osteoclast cell function, so prevalent symptoms of BP use are osteonecrosis of the jaw (ONJ) and hypocalcemia. ONJ from IV medication occurs more frequently than in oral delivery of the medication [83, 84]. One study found that among 9,482 participants receiving zoledronic acid for cancer treatment, 40 (0.42%) developed osteonecrosis [85]. Among 8,572 female participants administered oral alendronate, risedronate, or ibandronate, 25% reported developing dental complications with 0.10% diagnosed with ONJ and many others experiencing symptoms similar to ONJ [86]. Studies addressing the safety of BP use also found an increased rate of hypocalcemia in patients treated with BP administered orally or intravenously with no significant difference in incidence between the two treatment groups [71].

Cost Effectiveness

When comparing treatment options within the BP family, considering cost-effectiveness is crucial. Studies show that adding BPs to the treatment regimen improves quality of life and reduces later expenses by decreasing the likelihood of SREs [87]. The pharmacoeconomic implications of each drug vary based on factors such as dosage, spacing of hospital visits, and route of administration. In a 2008 study, researchers created a cost-effectiveness analysis using Germany and United Kingdom (UK) health data to compare oral clodronate, oral ibandronate, IV zoledronate, and IV pamidronate as adjuvant treatments, alongside chemotherapy, for metastatic breast cancer [88]. Considering the frequency of hospital visits, drug acquisition costs, cost of transportation, the likelihood of adverse events based on BP, and improvement of quality of life, researchers found that in both countries, oral clodronate had the lowest cost per patient, followed by oral ibandronate. Both IV pamidronate and IV zoledronate incurred the highest costs (88). This finding is supported by results from De Cock et al., whose study excluded clodronate and found oral ibandronate to be the most cost-effective, followed by pamidronate and zoledronic acid [89].

Another study found conflicting results on the cost-effectiveness of variance BPs for breast cancer metastasis to bone using data from the UK's National Health Services. The study compared various IV and oral BPs over 10 years [87]. IV zoledronic acid was identified as the most cost-effective BP, considering cost per quality-adjusted life expectancy gained and net monetary benefit. However, all BPs were found to be cost-effective compared to no therapy [87]. Differences in results between studies may be due to variations in the assumptions regarding factors such as median survival, efficacy of BP, and economic cost related to adverse events.

Conclusions

This literature review presents an overview of the three generations of BPs in clinical use and evaluates the implications of the drug properties and routes of administration on outcomes for patients with breast cancer-associated bone metastasis. There are a variety of factors to take into consideration when comparing IV and oral BPs, including efficacy, recurrence, adverse effects, and cost-effectiveness. It is essential to address these factors to determine the most suitable treatment for the patient. To continue to expand research on BP use among breast cancer patients, future research should aim to explore the impact of age and disease-associated hormonal changes in the bone microenvironment on clinical outcomes of BP treatment and how compounding comorbidities may exacerbate the adverse effects of BPs. Nevertheless, the use of BPs for the treatment of SREs continues to be a crucial component in improving the quality of life for patients with breast cancer-associated bone metastasis.

List of Abbreviations Used

SRE: skeletal-related event
BMA: bone-modifying agent
BP: bisphosphonate
AI: aromatase inhibitor
BMD: bone mineral density
DFS: disease-free survival
ONJ: osteonecrosis of the jaw
IV: intravenous
NHS: National Health Services
UK: United Kingdom
SMPR: skeletal morbidity period rate

Conflicts of Interest

The authors declare that they have no conflict of interest.

Ethics Approval and/or Participant Consent

Ethics approval and participant consent were not required for this study due to its nature as a literature review.

Authors' Contributions

CPK: Contributed equally to conducting the literature search, drafting the review, and finalizing the completed version.
JPH: Contributed equally to conducting the literature search, drafting the review, and finalizing the completed version.

Acknowledgements

We would like to acknowledge the valuable support and contributions of our mentor, Amel Sassi, who guided us through the process of creating this review and contributed critically to the planning and revision of this article.

Funding

This study was not funded.

References

[1] Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. CA Cancer J Clin. 2023 Jan;73(1):17-48. https:///doi.org/10.3322/caac.21763

[2] Liang Y, Zhang H, Song X, Yang Q. Metastatic heterogeneity of breast cancer: Molecular mechanism and potential therapeutic targets. Semin Cancer Biol. 2020 Feb;60:14-27. https://doi.org/10.1016/j.semcancer.2019.08.012

[3] Tulotta C, Ottewell P. The role of IL-1B in breast cancer bone metastasis. Endocr Relat Cancer. 2018 Jul;25(7):R421-R434. https://doi.org/10.1530/ERC-17-0309

[4] Gerratana L, Fanotto V, Bonotto, M et al. Pattern of metastasis and outcome in patients with breast cancer. Clin Exp Metastasis. 2015 Jan 29; 32, 125–133. https://doi.org/10.1007/s10585-015-9697-2

[5] Paget S. The distribution of secondary growths in cancer of the breast. The Lancet. 1889 March 23; 133(3421):571-573. https://doi.org/10.1016/S0140-6736(00)49915-0

[6] Ewing J. Neoplastic Diseases: A Treatise on Tumors. 2nd ed. Philadelphia, Pennsylvania: W.B. Saunders Company; 1919. Chapter IV, Metastasis; [Revised 1922]; 76-88. Available from: https://books.google.com/books?id=zFM11IvIbxcC&lr&pg=PA88#v=onepage&q&f=false

[7] Clemons M, Gelmon KA, Pritchard KI, Paterson AH. Bone-targeted agents and skeletal-related events in breast cancer patients with bone metastases: the state of the art. Curr Oncol. 2012 Oct;19(5):259-68. https://doi.org/10.3747/co.19.1011

[8] Perou C, Sørlie T, Eisen M et al. Molecular portraits of human breast tumours. Nature. 2000 Aug 17; 406:747–752. https://doi.org/10.1038/35021093

[9] Yong M, Jensen A, Jacobsen J et al. Survival in breast cancer patients with bone metastases and skeletal-related events: a population-based cohort study in Denmark (1999-2007). Breast Cancer Research and Treatment. 2011 Apr 2; 129:495–503. https://doi.org/10.1007/s10549-011-1475-5

[10] Fleisch H, Graham R, Russel G, Francis M. Diphosphonates inhibit hydroxyapatite dissolution in vitro and bone resorption in tissue culture and in vivo. Science. 1969 Sep 19; 165(3899):1262-1264. https://doi.org/10.1126/science.165.3899.1262

[11] Fleisch H, Russel R, Straumann. Effect of pyrophosphate on hydroxyapatite and its implications in calcium homeostasis. Nature. 1966 Nov 26; 212:901-903. https://doi.org/10.1038/212901a0

[12] Naylor K, Jacques R, Paggiosi M et al. Response of bone turnover markers to three oral bisphosphonate therapies in postmenopausal osteoporosis: the TRIO study. Osteoporosis International. 2015 May 20; 27(1):21-31. https://doi.org/10.1007/s00198-015-3145-7

[13] Rogers M, Ji X, Russel R et al. Incorporation of bisphosphonates into adenine nucleotides by amoebae of the cellular slime mould Dictyostelium discoideum. Biochemical Journal. 1994 Oct 1; 303(1):303–311. https://doi.org/10.1042/bj3030303

[14] Frith J, Mönkkönen J, Auriola S et al. The molecular mechanism of action of the antiresorptive and antiinflammatory drug clodronate: evidence for the formation in vivo of a metabolite that inhibits bone resorption and causes osteoclast and macrophage apoptosis. Arthritis & Rheumatism. 2001 Sep; 44(9):2201-2210. https://doi.org/10.1002/1529-0131(200109)44:9<2201::aid-art374>3.0.co;2-e

[15] Luckman S, Hughes D, Coxon F et al. Nitrogen-containing bisphosphonates inhibit the mevalonate pathway and prevent post-translational prenylation of GTP-binding proteins, including Ras. Journal of Bone and Mineral Research. 2009 Dec 4; 13(4):581-9. https://doi.org/10.1359/jbmr.1998.13.4.581

[16] van Beek E, Pieterman E, Cohen L et al. Farnesyl pyrophosphate synthase is the molecular target of nitrogen-containing bisphosphonates. Biochemical and Biophysical Research Communications. 1999 Oct 14; 264(1):108-111. https://doi.org/10.1006/bbrc.1999.1499

[17] van Beek E, Pieterman E, Cohen L et al. Nitrogen-containing bisphosphonates inhibit isopentenyl pyrophosphate isomerase/farnesyl pyrophosphate synthase activity with relative potencies corresponding to their antiresorptive potencies in vitro and in vivo. Biochemical and Biophysical Research Communications. 1999 Feb 16; 255(2):491-494. https://doi.org/10.1006/bbrc.1999.0224

[18] Ory S, Brazier H, Pawlak G et al. Rho GTPases in osteoclasts: Orchestrators of podosome arrangement. European Journal of Cell Biology. 2008 Sep 4; 87(8-9):469-477. https://doi.org/10.1016/j.ejcb.2008.03.002

[19] Boissier S, Ferreras M, Peyruchaud O et al. Bisphosphonates inhibit breast and prostate carcinoma cell invasion, an early event in the formation of bone metastases. Cancer Research. 2000 Jun 1; 60(11):2949-54. https://pubmed.ncbi.nlm.nih.gov/10850442/

[20] Jagdev S, Coleman R, Shipman C et al. The bisphosphonate, zoledronic acid, induces apoptosis of breast cancer cells: evidence for synergy with paclitaxel. British Journal of Cancer. 2001 Apr; 84(8):1126-1134. https://doi.org/10.1054/bjoc.2001.1727

[21] Bellido T, Plotkin L. Novel actions of bisphosphonates in bone: Preservation of osteoblast and osteocyte viability. Bone. 2010 Aug 18; 49(1):50-55. https://doi.org/10.1016/j.bone.2010.08.008

[22] Puljula E, Turhanen P, Vepsäläinen J et al. Structural Requirements for Bisphosphonate Binding on Hydroxyapatite: NMR Study of Bisphosphonate Partial Esters. American Chemical Society Medicinal Chemistry Letters. 2015 Feb 2; 6(4): 397-401. https://doi.org/10.1021/ml5004603

[23] Gralow J, Barlow W, Paterson A et al. Phase III Randomized Trial of Bisphosphonates as Adjuvant Therapy in Breast Cancer: S0307. Journal of the National Cancer Institute. 2019 Nov 6; 112(7): 698-707. https://doi.org/10.1093/jnci/djz215

[24] Nancollas G, Tang R, Phipps R et al. Novel insights into actions of bisphosphonates on bone: Differences in interactions with hydroxyapatite. Bone. 2006 May; 38(5):617-627. https://doi.org/10.1016/j.bone.2005.05.003

[25] Cremers S, Papapoulos S, Gelderblom H. Skeletal retention of bisphosphonate (pamidronate) and its relation to the rate of bone resorption in patients with breast cancer and bone metastases. Journal of Bone and Mineral Research. 2005 May; 20(9):1543-7. https://doi.org/10.1359/JBMR.050522

[26] Pillai G, Gieschke R, Goggin T. A semimechanistic and mechanistic population PK–PD model for biomarker response to ibandronate, a new bisphosphonate for the treatment of osteoporosis. British Journal of Clinical Pharmacology. 2004 Dec; 58(6): 618-631. https://doi.org/10.1111/j.1365-2125.2004.02224.x

[27] Francis MD, Valent DJ. Historical perspectives on the clinical development of bisphosphonates in the treatment of bone diseases. J Musculoskelet Neuronal Interact. 2007 Jan-Mar; 7(1): 2-8. https://pubmed.ncbi.nlm.nih.gov/17396000/

[28] Han SH, Zonneberg BA, de Klerk JM, et al. (186)Re-etidronate in breast cancer patients with metastatic bone pain. J Nucl Med. 1999 Apr;40(4):639-42. https://pubmed.ncbi.nlm.nih.gov/10210223/

[29] Iwamoto J, Takeda T, Ichimura S. Transient relief of metastatic cancer bone pain by oral administration of etidronate. J Bone Miner Metab. 2002 July; 20:228-234. https://doi.org/10.1007/s007740200033

[30] Hatano M, Kitajima I, Yamamoto S, et al. Case report: Osteomalacia due to bisphosphonate treatment in a patient on hemodialysis. BMC Nephrol. 2021 Sep; 22(1): 298. https://doi.org/10.1186/s12882-021-02509-5

[31] Thomas T, Lafage MH, Alexandre C. Atypical osteomalacia after 2 year etidronate intermittent cyclic administration in osteoporosis. J Rheumatol. 1995 Nov; 22(11):2183-5. https://pubmed.ncbi.nlm.nih.gov/8596168/

[32] Bonjour JP, Ammann P, Barbier A, et al. Tiludronate: Bone Pharmacology and Safety. Bone. 1995 Nov; 17(5 Suppl): 473S-477S. https://doi.org/10.1016/8756-3282(95)00344-9

[33] Reginster JY, Treves R, Renier JC, Amor B, Sany J, Ethgen D, Picot C, Franchimont P. Efficacy and tolerability of a new formulation of oral tiludronate (tablet) in the treatment of Paget's disease of bone. J Bone Miner Res. 1994 May;9(5):615-9. https://doi.org/10.1002/jbmr.5650090505

[34] Kanis JA, Powles T, Paterson AH, McCloskey EV, Ashley S. Clodronate decreases the frequency of skeletal metastases in women with breast cancer. Bone. 1996 Dec;19(6):663-7. https://doi.org/10.1016/s8756-3282(96)00285-2

[35] Diel IJ, Solomayer E, Costa SD, et al. Reduction in new metastases in breast cancer with adjuvant clodronate treatment. N Engl J Med. 1998 Aug 6; 339:357-363. https://doi.org/10.1056/NEJM199808063390601

[36] Ha TC, Li H. Meta-analysis of clodronate and breast cancer. British Journal of Cancer. 2007 Feb 27; 96: 1796-1801. https://doi.org/10.1038/sj.bjc.6603661

[37] Cummings S, Santora A, Black D et al. History of alendronate. Bone. 2020 Aug; 137:115411. https://doi.org/10.1016/j.bone.2020.115411

[38] Vestergaard P, Fischer L, Mele M et al. Use of bisphosphonates and risk of breast cancer. Calcified Tissue International. 2011 Jan 21; 88:255-262. https://doi.org/10.1007/s00223-011-9463-7

[39] Chlebowski R, Chen Z, Cauley J et al. Oral bisphosphonate use and breast cancer incidence in postmenopausal women. Journal of Clinical Oncology. 2010 Aug 1; 28(22):3582-3590. https://doi.org/10.1200/JCO.2010.28.2095

[40] Cardwell C, Abnet C, Veal P et al. Exposure to oral bisphosphonates and risk of cancer. International Journal of Cancer. 2012 Sep 1; 131(5):E717–E725. https://doi.org/10.1002/ijc.27389

[41] Hue T, Cummings S, Cauley J et al. Effect of bisphosphonate use on risk of postmenopausal breast cancer. JAMA Internal Medicine. 2014 Oct; 174(10):1550-1557. https://doi.org/10.1001/jamainternmed.2014.3634

[42] Rouach V, Goldshtein I, Wolf I et al. Exposure to alendronate is associated with a lower risk of bone metastases in osteoporotic women with early breast cancer. Journal of Bone Oncology. 2018 Aug 8; 12:91-95. https://doi.org/10.1016/j.jbo.2018.07.011

[43] Perez EA, Weilbaecher K. Aromatase inhibitors and bone loss. Oncology (Williston Park). 2006 Aug;20(9):1029-48. https://pubmed.ncbi.nlm.nih.gov/16986348/

[44] Rhee Y, Song K, Park S et al. Efficacy of a combined alendronate and calcitriol agent (Maxmarvil) in Korean postmenopausal women with early breast cancer receiving aromatase inhibitor: a double-blind, randomized, placebo-controlled study. Endocrine Journal. 2013; 60(2):167-172. https://doi.org/10.1507/endocrj.EJ12-0283

[45] Body JJ, Diel IJ, Lichinitser MR, et al. Intravenous ibandronate reduces the incidence of skeletal complications in patients with breast cancer and bone metastases. Annals of Oncology. 2023 Sept;14(9):1399-1405. https://doi.org/10.1093/annonc/mdg367

[46] Lyubimova NV, Kushlinsky NE, Lichinitser MR et al. Renal Safety of Intravenous Ibandronic Acid in Breast Cancer Patients with Metastatic Bone Disease. Clin. Drug Investig. 2012 Aug 29; 23: 707–71. https://doi.org/10.2165/00044011-200323110-00003
[47] Pecherstorfer M, Rivkin S, Body JJ, Diel I, Bergström B. Long-term safety of intravenous ibandronic acid for up to 4 years in metastatic breast cancer: an open-label trial. Clin Drug Investig. 2006;26(6):315-22. https://doi.org/10.2165/00044011-200626060-00002
[48] Mancini I, Dumon JC, Body JJ. Efficacy and safety of ibandronate in the treatment of opioid-resistant bone pain associated with metastatic bone disease: a pilot study. J Clin Oncol. 2004 Sep 1;22(17):3587-92. https://doi.org/10.1200/JCO.2004.07.054
[49] Hoffman O, Aktas B, Goldnau C, et al. Effect of Ibandronate on Disseminated Tumor Cells in the Bone Marrow of Patients with Primary Breast Cancer: A Pilot Study. Anticancer Research. 2011 Oct; 31(10): 3623-3628. https://pubmed.ncbi.nlm.nih.gov/21965788/
[50] Tripathy D, Body JJ, Bergstr Bengt. Review of ibandronate in the treatment of metastatic bone disease: Experience from phase III trials. Clinical Therapeutics. 2004 Dec;26(12): 1947-1959. https://doi.org/10.1016/j.clinthera.2004.12.010
[51] Body JJ, Diel IJ, Lichinitzer M, et al. Oral ibandronate reduces the risk of skeletal complications in breast cancer patients with metastatic bone disease: results from two randomised, placebo-controlled phase III studies. Br J Cancer. 2004 Mar 22;90(6):1133-7. https://doi.org/10.1038/sj.bjc.6601663
[52] Diel IJ, Body JJ, Lichinitser MR, et al; MF 4265 Study Group. Improved quality of life after long-term treatment with the bisphosphonate ibandronate in patients with metastatic bone disease due to breast cancer. Eur J Cancer. 2004 Jul;40(11):1704-12. https://doi.org/10.1016/j.ejca.2004.03.025
[53] Tripathy D, Lichinitzer M, Lazarev A, et al; MF 4434 Study Group. Oral ibandronate for the treatment of metastatic bone disease in breast cancer: efficacy and safety results from a randomized, double-blind, placebo-controlled trial. Ann Oncol. 2004 May;15(5):743-50. https://doi.org/10.1093/annonc/mdh173
[54] Hillner BE, Ingle JN, Chlebowski RT, et al; American Society of Clinical Oncology. American Society of Clinical Oncology 2003 update on the role of bisphosphonates and bone health issues in women with breast cancer. J Clin Oncol. 2003 Nov 1;21(21):4042-57. https://doi.org/10.1200/JCO.2003.08.017
[55] Conte PF, Latreille J, Mauriac L, Calabresi F, Santos R, Campos D, Bonneterre J, Francini G, Ford JM. Delay in progression of bone metastases in breast cancer patients treated with intravenous pamidronate: results from a multinational randomized controlled trial. The Aredia Multinational Cooperative Group. J Clin Oncol. 1996 Sep;14(9):2552-9. https://doi.org/10.1200/JCO.1996.14.9.2552
[56] Lipton A, Theriault RL, Hortobagyi GN, et al. Pamidronate prevents skeletal complications and is effective palliative treatment in women with breast carcinoma and osteolytic bone metastases: long term follow-up of two randomized, placebo-controlled trials. Cancer. 2000 Mar 1;88(5):1082-90. https://doi.org/10.1002/(sici)1097-0142(20000301)88:5%3C1082::aid-cncr20%3E3.0.co;2-z
[57] Jackson C, Freeman ALJ, Szlamka Z, et al. The adverse effects of bisphosphonates in breast cancer: A systematic review and network meta-analysis. PLoS One. 2021 Feb 5;16(2):e0246441. https://doi.org/10.1371/journal.pone.0246441
[58] Young CM, Fahrholz, CN, Manikowski KJ, et al. Side Effects of Drugs Annual: A Worldwide Yearly Survey of New Data in Adverse Drug Reactions. Elsevier; 2022. Chapter 34, Drugs for metabolic bone disease; 471-481. https://doi.org/10.1016/bs.seda.2022.09.005
[59] Barbosa JS, Paz FAA, Braga SS. Bisphosphonates, Old Friends of Bones and New Trends in Clinics. Journal of Medicinal Chemistry. 2021 Feb 1; 64: 1260-1282. https://doi.org/10.1021/acs.jmedchem.0c01292
[60] Crandall C. Risedronate: A Clinical Review. Arch Intern Med. 2001 Feb 12; 161(3): 353-360. https://doi.org/10.1001/archinte.161.3.353
[61] Sasaki A, Boyce BF, Story B, et al. Bisphosphonate risedronate reduces metastatic human breast cancer burden in bone in nude mice. Cancer Res. 1995 Aug 15;55(16):3551-7. https://pubmed.ncbi.nlm.nih.gov/7627963/
[62] Delmas PD, Balena R, Confravreux E, Hardouin C, Hardy P, Bremond A. Bisphosphonate risedronate prevents bone loss in women with artificial menopause due to chemotherapy of breast cancer: a double-blind, placebo-controlled study. J Clin Oncol. 1997 Mar;15(3):955-62. https://doi.org/10.1200/JCO.1997.15.3.955
[63] Drake MT, Clarke BL, Khosla S. Bisphosphonates: mechanism of action and role in clinical practice. Mayo Clin Proc. 2008 Sep;83(9):1032-45. https://doi.org/10.4065/83.9.1032
[64] Himelstein AL, Foster JC, Khatcheressian JL, et al. Effect of Longer-Interval vs Standard Dosing of Zoledronic Acid on Skeletal Events in Patients With Bone Metastases: A Randomized Clinical Trial. JAMA. 2017 Jan 3;317(1):48-58. https://doi.org/10.1001/jama.2016.19425

[65] Kohno N, Aogi K, Minami H, et al. Zoledronic acid significantly reduces skeletal complications compared with placebo in Japanese women in bone metastases from breast cancer: A randomized, placebo-controlled trial. J Clin Oncol. 2005 May 20; 23(15): 3314-3321. https://doi.org/10.1200/JCO.2005.05.116

[66] Clemons MJ, Dranitsaris G, Ooi WS, et al. Phase II trial evaluating the palliative benefit of second-line zoledronic acid in breast cancer patients with either a skeletal-related event or progressive bone metastases despite first-line bisphosphonate therapy. J Clin Oncol. 2006 Oct 20;24(30):4895-900. https://doi.org/10.1200/JCO.2006.05.9212

[67] Polascik TJ, Mouraviev V. Zoledronic acid in the management of metastatic bone disease. Ther Clin Risk Manag. 2008 Feb;4(1):261-8. https://doi.org/10.2147/tcrm.s2707

[69] Van Poznak CH, Unger JM, Darke AK, et al. Association of Osteonecrosis of the Jaw With Zoledronic Acid Treatment for Bone Metastases in Patients With Cancer. JAMA Oncol. 2021 Dec;7(2):246–254. https://doi.org/10.1001/jamaoncol.2020.6353

[68] Black DM, Delmas PD, Eastell R, et al. Once-Yearly Zoledronic Acid for Treatment of Postmenopausal Osteoporosis. N Engl J Med. 2007 May 3;356:1809-1822. https://doi.org/10.1056/NEJMoa067312

[70] von Au A, Milloth E, Diel I, et al. Intravenous pamidronate versus oral and intravenous clodronate in bone metastatic breast cancer: a randomized, open-label, non-inferiority Phase III trial. Onco Targets Ther. 2016 Jul 8;9:4173-80. https://doi.org/10.2147/OTT.S103130

[71] Barrett-Lee P, Casbard A, Abraham J, et al. Oral ibandronic acid versus intravenous zoledronic acid in treatment of bone metastases from breast cancer: a randomised, open label, non-inferiority phase 3 trial. Lancet Oncol. 2014 Jan;15(1):114-22. https://doi.org/10.1016/S1470-2045(13)70539-4

[72] Gordon DH. Efficacy and safety of intravenous bisphosphonates for patients with breast cancer metastatic to bone: a review of randomized, double-blind, phase III trials. Clin Breast Cancer. 2005 Jun;6(2):125-31. https://doi.org/10.3816/CBC.2005.n.014

[73] van Poznak C, Somerfield MR, Barlow WE. Role of Bone-Modifying Agents in Metastatic Breast Cancer: An American Society of Clinical Oncology—Cancer Care Ontario Focused Guideline Update. J Clin Oncol. 2017 Dec; 35(35): 3978-3986. https://doi.org/10.1200/JCO.2017.75.4614

[74] Mayo Clinic [Internet]. Rochester (MN): Mayo Foundation for Medical Education and Research. [Cited 2023 July 20]. Available from: https://www.mayoclinic.org/diseases-conditions/recurrent-breast-cancer/symptoms-causes/syc-20377135

[75] Ottewell PD, Wang N, Brown HK, Reeves KJ, Fowles CA, Croucher PI, Eaton CL, Holen I. Zoledronic acid has differential antitumor activity in the pre-and postmenopausal bone microenvironment in vivo. Clin Cancer Res. 2014 Jun 1;20(11):2922-32. https://doi.org/10.1158/1078-0432.CCR-13-1246

[76] Tanvetyanon T, Stiff PJ. Management of the adverse effects associated with intravenous bisphosphonates. Ann Oncol. 2006 Jun;17(6):897-907. https://doi.org/10.1093/annonc/mdj105

[77] Rahbari-Oskoui F, Fielder O, Ghasemzadeh N, et al. Prolonged recovery time from zoledronic Acid induced acute tubular necrosis: a case report and review of the literature. Case Rep Nephrol. 2013 July 29; 2013:651246. https://doi.org/10.1155/2013/651246

[78] Perazella MA, Markowitz GS. Bisphosphonate nephrotoxicity. Kidney Int. 2008 Dec;74(11):1385-93. https://doi.org/10.1038/ki.2008.356

[79] ten Dam MA, Hilbrands LB, Wetzels JF. Nephrotic syndrome induced by pamidronate. Med Oncol. 2011 Dec;28(4):1196-200. https://doi.org/10.1007/s12032-010-9628-7

[80] Conte P, Guarneri V. Safety of Intravenous and Oral Bisphosphonates and Compliance With Dosing Regimens. The Oncologist. 2004 Sept; 9(S4): 28-37. https://doi.org/10.1634/theoncologist.9-90004-28

[81] Lufkin EG, Argueta R, Whitaker MD, et al. Pamidronate: an unrecognized problem in gastrointestinal tolerability. Osteoporos Int. 1994 Nov;4(6):320-2. https://doi.org/10.1007/BF01622190

[82] Abraham SC, Cruz-Correa M, Lee LA, Yardley JH, Wu TT. Alendronate-associated esophageal injury: pathologic and endoscopic features. Mod Pathol. 1999 Dec;12(12):1152-7. https://pubmed.ncbi.nlm.nih.gov/10619269/

[83] Khosla S, Burr D, Cauley J, Dempster DW, et al; American Society for Bone and Mineral Research. Bisphosphonate-associated osteonecrosis of the jaw: report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res. 2007 Oct;22(10):1479-91. https://doi.org/10.1359/jbmr.0707onj

[84] Baim S, Miller PD. Assessing the clinical utility of serum CTX in postmenopausal osteoporosis and its use in predicting risk of osteonecrosis of the jaw. J Bone Miner Res. 2009 Apr;24(4):561-74. https://10.1359/jbmr.090203

[85] Goodwin JS, Zhou J, Kuo YF, Baillargeon J. Risk of Jaw Osteonecrosis After Intravenous Bisphosphonates in Cancer Patients and Patients Without Cancer. Mayo Clin Proc. 2017 Jan;92(1):106-113. https://doi.org/10.1016/j.mayocp.2016.09.015

[86] Lo JC, O'Ryan FS, Gordon NP, et al; Predicting Risk of Osteonecrosis of the Jaw with Oral Bisphosphonate Exposure (PROBE) Investigators. Prevalence of osteonecrosis of the jaw in patients with oral bisphosphonate exposure. J Oral Maxillofac Surg. 2010 Feb;68(2):243-53. https://10.1016/j.joms.2009.03.050

[87] Botteman M, Barghout V, Stephens J, et al. Cost effectiveness of bisphosphonates in the management of breast cancer patients with bone metastases. Ann Oncol. 2006 Jul;17(7):1072-82. https://doi.org/10.1093/annonc/mdl093

[88] Paterson A, McCloskey E, Redzepovic J, et al. Cost-effectiveness of oral clodronate compared with oral ibandronate, intravenous zoledronate or intravenous pamidronate in breast cancer patients. J Int Med Res. 2008 May-Jun;36(3):400-13. https://doi.org/10.1177/147323000803600304

[89] De Cock E, Hutton J, Canney P, et al. Cost-effectiveness of oral ibandronate compared with intravenous (i.v.) zoledronic acid or i.v. generic pamidronate in breast cancer patients with metastatic bone disease undergoing i.v. chemotherapy. Support Care Cancer. 2005 Dec;13(12):975-86. https://doi.org/10.1007/s00520-005-0828-1

Article Information
Managing Editor: Jeremy Y. Ng
Peer Reviewers: Amel Sassi, Siobhan O'Brien
Article Dates: Received Jul 28 23; Accepted Sep 05 23; Published Oct 13 23

Citation
Please cite this article as follows:
King CP, Huynh JP. Evaluating route of administration for bisphosphonates in patients with metastatic breast cancer to the bone: A literature review. URNCST Journal. 2023 Oct 13: 7(10). https://urncst.com/index.php/urncst/article/view/515
DOI Link: https://doi.org/10.26685/urncst.515