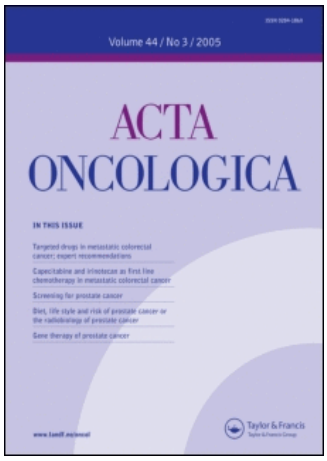

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REVIEW ARTICLE

The use of bisphosphonates in cancer patients

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Abstract
Skeletal-related events resulting from bone metastases or osteoporosis can significantly contribute to morbidity and mortality in cancer patients. Expert opinion on the effectiveness of bisphosphonates in this setting is evolving. Here we review current evidence on the risks and benefits of bisphosphonate therapy for a wide variety of cancers, as well as clinical management of its adverse effects. A MEDLINE search of English-language literature (1966 through May 2006) was conducted using the terms bisphosphonate, cancer, multiple myeloma, malignancy, and randomized controlled clinical studies. Studies were selected based on clinical pertinence, with an emphasis on phase III clinical trials. We reviewed bibliographies for other relevant articles. Accumulating evidence reveals that bisphosphonate therapy has a significant effect in preventing skeletal complications in multiple myeloma, breast cancers, and prostate cancer, and in reducing skeletal complications in other metastatic bone malignancies. Emerging data indicate that bisphosphonates are useful for preventing bone loss resulting from cancer or its therapy. The efficacy of bisphosphonates for early-stage breast cancers remains controversial. Significant risks of bisphosphonate therapy include nephrotoxicity, electrolyte abnormalities, and osteonecrosis of the jaw. Bisphosphonate therapy has a clear role in the management of skeletal metastases associated with a variety of cancers. However, significant side effects require ongoing monitoring and treatment.

Bone metastases lead to significant morbidity and mortality in cancer patients. They are associated with almost every type of malignant tumor, but most frequently with prostate, breast, and lung cancers (Table I) [1]. Even though bone metastases are often categorized into osteoblastic (prostate cancer), osteolytic (myeloma), and mixed types (breast cancer) according to radiographic appearances, the underlying pathogenesis regularly involves both osteoblastic and osteolytic processes [2]. In addition, primary or secondary osteoporosis is often comorbid in cancer patients, leading to significantly increased risk of fracture. Numerous factors contribute to cancer-related osteoporosis, including radiation, cytotoxic agents, gonadotropin-releasing hormone analogs, and aromatase inhibitors [3]. While the mechanism for bone metastasis and osteoporosis is different, osteoclastic activity is known to play an important role in both processes.

Bisphosphonates, which are analogs of endogenous pyrophosphates with the common structural element of a phosphorus-carbon-phosphorus (P-C-P) bond [4], have been used extensively to treat and prevent osteoporosis, and to treat Paget's disease and hypercalcemia of malignancy (Table II) [5,6]. Bisphosphonates have high affinity for bone. They bind to hydroxyapatite crystals on bone surfaces, where they are resorbed by osteoclasts. After they are internalized by osteoclasts through endocytosis, they reduce the activity of those osteoclasts and thus inhibit bone resorption. Each bisphosphonate has unique side chains (R1 and R2) attached to the central carbon atom. The R1 chain and the P-C-P backbone determine its binding to bone minerals, while the R2 side chain determines the antiresorptive potency, side effects, probably the mechanism of action, and possibly antineoplastic activity. Bisphosphonates with R2 side chains containing a primary nitrogen are more potent than nonnitrogen counterparts (Table II) [7] and can inhibit prenylation of GTP-binding proteins by farnesyl diphosphonate synthetase, which is critical for osteoclast function and

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Table I. Incidence of bone metastases in cancer patients with metastatic disease [1,78,79].

Tumor type	Incidence of bone metastases (%)
Myeloma	70–95
Prostate	65–90
Breast	65–75
Lung	30–40
Bladder	40
Renal	20–25
Thyroid	60
Melanoma	14–45
Colorectal	7–24

survival [8]. Nonnitrogen-containing bisphosphonates are incorporated into nonhydrolysable cytotoxic analogues of ATP [9]. In cancer patients, bisphosphonates may affect bone microenvironment to reduce the invasion of tumor cells [10], thus delaying bone metastases in high-risk early-stage cancers. They may also have direct tumor cytotoxicity [11–13] and antiangiogenic activity [14–16]. However, the biological diversity of cancers and their bone metastases may result in different responses to bisphosphonate therapy. Furthermore, bisphosphonate treatment may expose patients to serious side effects that primary care physicians should recognize. We here review existing evidence regarding the benefits and risks of bisphosphonate use in the contemporary care of patients with various cancers.

Methods

We performed MEDLINE searches of the English-language literature (1966 through May 2006) using the terms bisphosphonate, cancer, multiple myeloma, malignancy, and randomized controlled clinical studies. We manually reviewed relevant bibliographies for additional material. We obtained further information from presentations at the 2006 American Society of Clinical Oncology (ASCO) Meeting and 2006 Prostate Cancer Symposium, and reviewed published guidelines from the National Comprehensive Cancer Network and ASCO. In evaluating the benefits of bisphosphonate therapy, we focused on phase III randomized controlled trials. On review of clinical trials, endpoints were prevention or delay of skeletal complications and palliation of bone pain. No studies have been designed to evaluate survival as a primary endpoint for bisphosphonate therapy.

Efficacy of bisphosphonate therapy

Bisphosphonate therapy was initially evaluated in 1996 in large randomized controlled phase III clinical trials for multiple myeloma and breast cancer [17,18], then in 2002 and 2003 for prostate and many other malignancies [19,20]. To date, the use of bisphosphonates has been demonstrated to reduce skeletal-related events (SREs) in many malignancies, including multiple myeloma, breast, prostate, and other solid tumors (Table III); however, the impact of bisphosphonate treatment on overall survival has been very limited for patients with metastatic cancers in these clinical trials [17–20]. Thus, the main focus of this review is the role of bisphosphonates in reducing skeletal complications of malignancies, as well as potential toxicities of bisphosphonates.

Multiple myeloma

Multiple myeloma is the third most common hematologic malignancy in the United States. At the time of diagnosis, nearly 80% of patients have osteolytic lesions, osteoporosis, or fractures [21]. Pamidronate,

Table II. Bisphosphonates in clinical use [7].

Generic name	Feature of side chain (generation)	Dose	Route	Schedule	FDA-approved indications
Etidronate	Nonnitrogen-containing (1^{st})	20 mg/kg/d	po	Daily	Paget's disease; heterotropic ossification; HCM
Clodronate	Nonnitrogen-containing (1^{st})	300 mg 800–3200 mg	iv po	Daily × 5d	NA
Tiludronate	Nonnitrogen-containing (1^{st})	400 mg	po	3 months	Paget's disease
Pamidronate	Containing a nitrogen atom (2^{nd})	60–90 mg	iv	3–4 weeks	HCM; multiple myeloma; bone metastases; Paget's disease
Alendronate	Containing a nitrogen atom (2^{nd})	10 mg 70 mg	po po	Daily Weekly	Osteoporosis; Paget's disease
Ibandronate	Containing a nitrogen atom (3^{rd})	2 mg 2.5 mg	iv po	Daily	Osteoporosis
Risedronate	Heterocyclic ring containing a nitrogen atom (3^{rd})	5 mg 35 mg	po po	Daily Weekly	Osteoporosis; Paget's disease
Zoledronic acid	Imidazole ring containing 2 nitrogen atoms (3^{rd})	4 mg	iv	3–4 weeks	HCM; multiple myeloma; bone metastases; Paget's disease

HCM: hypercalcemia of malignancy, NA: not available.

Table III. Major randomized double-blind placebo-controlled clinical studies of bisphosphonate therapy in metastatic bone disease, selected based on their importance in the clinical development of bisphosphonate therapy.

Tumor	Study	N	Arms	Outcome (SRE)
Multiple myeloma	Berenson et al. [17,22]	392	Pamidronate vs. placebo	Significant decrease
Multiple myeloma or breast cancer	Rosen et al. [23,52]	1 648	Zoledronic acid vs. pamidronate	Significant decrease
Breast	Hortobagyi et al. [18,28]	382	Pamidronate vs. placebo	Significant decrease
Breast	Theriault et al. [29]	372	Pamidronate vs. placebo	Significant decrease
Breast	Hultborn et al. [80]	404	Pamidronate vs. placebo	Significant decrease
Breast	Kohno et al. [30]	227	Zoledronate vs. placebo	Significant decrease
Breast	Body et al. [81]	312	Ibandronate vs. placebo	Significant decrease
Prostate	Saad et al. [19,43]	643	Zoledronic acid vs. placebo	Significant decrease
Prostate	Small et al. [44]	350	Pamidronate vs. placebo	No significant difference
Prostate	Dearnaley et al. [45]	311	Clodronate vs. placebo	No significant difference. Trend toward improved bone progression-free survival.
Prostate	Ernst et al. [46]	204	Mitoxantrone and prednisone with or without clodronate	No significant difference
Lung and other solid tumors	Rosen et al. [20]	773	Zoledronic acid vs. placebo	Significant decrease

SRE: skeletal-related event.

zoledronic acid, clodronate, and ibandronate have been evaluated in the treatment of myeloma. In a trial performed by Myeloma Aredia Study Group, 392 patients with advanced multiple myeloma were randomized to placebo or pamidronate (90 mg as a 4-hour iv infusion) every 4 weeks for 21 cycles [17,22]. The primary endpoints were reduction of SREs and evaluation of safety and survival after 9 and 21 cycles of therapy. SREs were defined as pathologic fractures, irradiation of or surgery to bone, and spinal cord compression. At the 9-month follow-up, the mean number of SREs per year was reduced from 2.1 in the placebo group to 1.1 in the pamidronate group ($p = 0.0006$). At the 21-month follow-up, the number of SREs remained stable at 2.2 per year in the placebo group and 1.3 per year in the pamidronate group ($p = 0.008$). In addition, median time to the first SRE was 10 months in the placebo group and 21 months in the pamidronate group ($p < 0.001$).

A large phase III randomized trial reported by Rosen et al. compared 4 or 8 mg of zoledronic acid to 90 mg of pamidronate iv every 3–4 weeks [23]. The trial included 1 648 eligible patients, of whom 513 had multiple myeloma. As increases in creatinine occurred more often among patients randomized to 8 mg zoledronic acid, the dose was reduced to 4 mg. Median time to first SRE was not statistically different between the 4 mg zoledronic acid and pamidronate treatment groups (380 days vs. 286 days, $p = 0.538$). Thus, this trial met its primary endpoint of demonstrating non-inferiority of zoledronic acid to pamidronate.

An MRC study evaluated clodronate in 536 patients with newly diagnosed multiple myeloma who received either oral clodronate (1 600 mg/day) ($n = 264$) or placebo ($n = 272$) [24]. Clodronate was associated with significantly lower incidence of vertebral (38% vs. 55%, $p = 0.01$) and nonvertebral fractures (6.8% vs. 13.2%, $p = 0.04$). A smaller benefit was noted in an earlier Finnish multicenter trial ($n = 350$) in which clodronate was associated with a significantly lower rate of radiological skeletal progression at 24 months, but no improvement in fracture incidence or pain relief [25].

Ibandronate has not been demonstrated to be effective in reducing SREs in advanced myeloma. Stage II or III myeloma patients ($n = 214$) receiving chemotherapy were randomly assigned to receive monthly iv ibandronate at 2 mg or placebo for 24 months in a study performed by Menssen et al. [26]. Neither incidence nor time to first SRE differed significantly between the 2 groups.

As there have been no direct comparisons between clodronate and pamidronate or clodronate and zoledronic acid, it is unclear which bisphosphonate is more effective in multiple myeloma. ASCO guidelines recommend only pamidronate and zoledronic acid because studies have more thoroughly assessed skeletal complications with their use. Clodronate is not available in the USA [27].

Breast cancer

Bone metastases from breast cancer encompass both osteolytic and osteoblastic lesions. Bisphosphonates have been studied extensively in metastatic breast cancer. In women with osteolytic metastatic breast cancer on systemic chemotherapy ($n = 382$), iv pamidronate (90 mg) monthly for 2

years delayed the appearance of clinical skeletal complications, with a median time to first SRE of 14 months vs. 7 months with placebo ($p < 0.001$), as reported by Protocol 19 Aredia Breast Cancer Study Group [18,28]. In women with metastatic osteolytic breast cancer ($n = 372$) on concurrent hormonal therapy, pamidronate was associated with prolonged time to first SRE (median 10.4 months vs. 6.9 months, $p = 0.049$) and reduced skeletal complications at 24 months (56% vs. 67%, $p = 0.027$) [29]. Kohno et al. observed a similar effect of zoledronic acid on reducing skeletal complications in Japanese women with metastatic breast cancer [30]. Finally, Body et al. found that ibandronate at 6 mg every 3–4 weeks reduced the risk of SREs by 38% over a 12-week period in breast cancer patients with bone metastases [31].

A phase III double-blind study by Rosen et al. compared zoledronic acid to pamidronate in the treatment of metastatic bone disease of breast cancer ($n = 1\ 130$) [23]. The proportion of patients who experienced SREs was similar between zoledronic acid and pamidronate in the breast cancer chemotherapy stratum (RR = 0.945, $p = 0.745$); however, it was associated with 30% additional risk reduction of SREs in the breast cancer hormonal therapy stratum in comparison with pamidronate (RR = 0.693, $p = 0.009$) [32].

A pooled analysis by Cochrane Database of Systematic Reviews showed that oral bisphosphonates, including pamidronate and clodronate or ibandronate, reduced the risk of SREs by 16% ($p = 0.001$) in breast cancer patients with metastatic bone disease [33].

Three studies have evaluated the use of clodronate and pamidronate in advanced breast cancer without clinically evident bone metastases [34–36]. There was no significant reduction in incidence of SREs (RR 0.99, $p = 0.97$) by meta-analyses [33].

The utility of bisphosphonates as an adjuvant treatment for breast cancer remains controversial. In 3 studies of oral clodronate that included 1 653 women with early-stage breast cancer but high risk for metastatic disease, there was no significant reduction in the risk of developing skeletal metastases (RR 0.82, $p = 0.07$) [33]. However, there was evidence of improved survival (RR 0.82, $p = 0.02$), a finding that has prompted a phase III National Surgical Adjuvant Breast and Bowel Project (NSABP) trial comparing clodronate with zoledronate or ibandronate as adjuvants for women with resected stage I–III breast cancer.

Women undergoing treatment for breast cancer are at greater risk of bone loss as a result of decreased estrogen levels associated with therapy or postmenopausal status. Aromatase inhibitors including anastrozole, letrozole, and exemestane have a pronounced effect on bone mineral density, and are associated with a higher incidence of osteoporosis/osteopenia as demonstrated in several breast cancer adjuvant trials [37–39]. Early results from several large randomized trials indicate that zoledronic acid may reduce bone loss associated with aromatase inhibitors [40]. Adjuvant chemotherapy may be associated with premature menopause and early bone loss in premenopausal women. Short-term intermittent use of clodronate has not been shown to prevent bone loss in this setting [41].

Bisphosphonates may have an analgesic effect in women with painful bone metastases secondary to breast cancer. Seven of 12 placebo-controlled trials showed a modest reduction in metastatic bone pain with bisphosphonates. The effect of bisphosphonates on patient-rated quality of life is not evident [33].

In summary, bisphosphonates reduce the risk of skeletal complications and may also reduce pain in patients with breast cancer metastatic to the bone. ASCO guidelines recommend iv pamidronate or zoledronic acid for women with radiographic evidence of lytic metastatic bone disease [42]. The utility of bisphosphonates in early breast cancer requires further study.

Prostate cancer

Bone metastases from prostate cancer are predominantly osteoblastic; however, there is increased osteoclastic activity associated with metastasis or androgen-deprivation therapy (ADT). Saad et al. evaluated zoledronic acid in a randomized placebo-controlled trial that enrolled 643 men with hormone-refractory prostate cancer and metastatic bone lesions [19]. Patients received placebo or iv zoledronic acid at 4 mg or 8 mg (8 mg was subsequently reduced to 4 mg due to a high incidence of renal function deterioration) every 3 weeks for 15 months. A significant reduction in the frequency of SREs was found in men receiving zoledronic acid 4 mg compared with placebo (33% vs. 44%). Moreover, there was a 41% decrease in pathologic fractures seen with 4 mg zoledronic acid compared to placebo (13.1% vs. 22.1%, $p = 0.015$). At 24 months follow-up, reduction of SREs was stable (38% vs. 49%) and median time to develop an SRE was significantly longer in the treated group (488 days vs. 321 days). However, the therapy had little impact on pain, quality of life, or survival [43]. In contrast, pamidronate and clodronate have shown no significant clinical benefit in men with metastatic prostate cancer [44–46].

Clodronate was not effective in delaying bone metastasis in patients with nonmetastatic prostate cancers. In the MRC PR04 trial of 508 men with T2-4 prostate cancers on standard therapy, clodronate at 2 080 mg/day for up to 5 years was compared to placebo, with a primary endpoint of bone progression-free survival (BPFS), defined as the time to development of symptomatic bone metastasis or to death from prostate cancer [47]. There was a trend to decreased BPFS in the clodronate arm (HR = 1.29, p = 0.13).

Bisphosphonates are also effective in preventing bone loss associated with ADT. In patients with metastatic and nonmetastatic prostate cancer, both pamidronate and zoledronic acid showed clear benefit in maintaining or improving bone mineral density compared with placebo, as reported by Smith et al. [48,49]. Recent reports at the 2006 Prostate Cancer Symposium and ASCO Annual Meeting showed that weekly oral alendronate or annual zoledronic acid can prevent bone loss in men with nonmetastatic prostate cancer on ADT [50,51].

In short, zoledronic acid is the only bisphosphonate that has been shown to reduce SREs in men with androgen-independent metastatic prostate cancer, and the only bisphosphonate approved for this use by the FDA. Pamidronate, zoledronic acid, and alendronate mitigate bone loss associated with ADT.

Other solid tumors

Few studies have been performed to evaluate the effect of bisphosphonates in metastatic cancers other than multiple myeloma and breast and prostate cancers. Zoledronic acid is the only bisphosphonate that has been evaluated in a wide variety of metastatic solid tumors. A randomized phase III double-blind placebo-controlled clinical trial (n = 733) by Rosen et al. evaluated zoledronic acid in various metastatic solid cancers other than breast and prostate cancers, including lung (50% non-small cell lung cancer and 8% small cell lung cancer), renal (10%), unknown primary (7%), thyroid (2%), and head and neck (2%) cancers [20,52]. In comparison with placebo, 4 mg iv zoledronic acid significantly decreased the risk of SREs (38% vs. 47%, p = 0.039). Zoledronic acid also prolonged median time to first SRE by more than 2 months (p = 0.007). However, when hypercalcemia of malignancy was excluded from the analysis, the primary endpoint of reducing SREs did not reach statistical significance.

Due to the diversity of tumor types in the above-mentioned trial, the actual benefit of zoledronic acid in reducing skeletal complications of metastatic bone disease in an individual malignancy is not clear. However, it might not be feasible to evaluate the efficacy of zoledronic acid in all of these individual tumors. Despite the absence of direct evidence, bisphosphonate therapy may still be appropriate for patients with metastatic bone disease from solid tumors other than breast and prostate cancers, considering the significant benefit of bisphosphonate therapy in breast and prostate cancers, which encompass a wide range of osteolytic and osteoblastic lesions.

Risks and adverse effects of bisphosphonates

Bisphosphonates are generally well tolerated. However, significant side effects such as acute-phase reactions, renal toxicity, electrolyte abnormalities, and osteonecrosis of the jaw should be monitored regularly and treated in a timely manner.

Acute-phase reactions

Acute-phase reactions are self-limiting flu-like symptoms, including low-grade fever, arthralgia/myalgia, nausea, and increased bone pain. This is the most common adverse event, occurring in up to 18% of patients treated with either zoledronic acid or pamidronate [23]. Symptoms occur within 24 hours after the first infusion, persist for less than 48 hours, and usually diminish or disappear by the second or third infusion. Management includes acetaminophen and fluids for flu-like symptoms and antiemetics for nausea.

Renal toxicity

Elevation of serum creatinine during bisphosphonate therapy is uncommon but potentially serious. Approximately 10% of patients treated with 4 mg zoledronic acid or 90 mg pamidronate experience deterioration of renal function (defined as an increase of 0.5 mg/dL in patients with normal baseline serum creatinine $\leq$1.4 mg/dL or an increase of 1.0 mg/dL in patients with baseline serum creatinine >1.4 mg/dL) [23]. Prolonged use of bisphosphonates (>2 years) is associated with notable serum creatinine increase in 12.5% of patients [53]. Underlying risk factors for renal failure include multiple myeloma, diabetes mellitus, hypertension, advanced age (>65 years old), previous bisphosphonate exposure, and the use of NSAIDs. For zoledronic acid, renal impairment is also associated with 8-mg doses and infusion duration less than 15 minutes [23,52]. The underlying tumor type may also contribute to renal failure. Most cases (42/72) have been reported in patients with multiple myeloma, but many cases

(22/72) have been reported in patients with solid tumors [54]. The impact of hydration status on the development of acute renal failure needs further study. The mechanism for bisphosphonate-associated renal failure is not well understood, but some case reports have suggested a link with acute tubular necrosis [55].

Nephrotic syndrome was reported in 7 patients with multiple myeloma (n = 6) or breast cancer (n = 1) receiving pamidronate therapy [56,57]. These patients had been treated with pamidronate for 15–48 months; 5 had received more than the standard dose of 90 mg per month. Average peak urine protein excretion was 12.4 g/day. Renal biopsy revealed collapsing focal segmental glomerulosclerosis (FSGS). FSGS is rare, occurring most commonly in African Americans with HIV infection. The study patients were white and HIV-negative, suggesting a possible association between pamidronate and FSGS. Pamidronate was stopped in 5 patients, with 2 requiring dialysis and 3 having stable renal insufficiency. Pamidronate was continued in 2 patients, both of whom required maintenance dialysis.

During iv bisphosphonate therapy, patients may need to avoid agents with potential renal side effects, such as radiographic contrast reagents and NSAIDs, due to the risk of nephrotoxicity. If these agents must be used in conjunction with bisphosphonates, they should ideally be given on different days, and patients' renal function should be regularly assessed. Imaging studies with contrast could be carried out if renal function is adequate. In the presence of baseline renal insufficiency, the dose of bisphosphonates should be adjusted based on creatinine clearance, as per manufacturer recommendations (Table IV) [58]. However, for many bisphosphonates, optimal dosages in this situation have not been determined. In accordance with FDA labeling, ASCO guidelines recommend that creatinine be monitored prior to each dose of pamidronate or zoledronate [42]. Unexplained azotemia should prompt temporary discontinuation of the bisphosphonate. Patients should be reassessed every 3–4 weeks. If renal function returns to baseline, therapy may be cautiously reinstituted.

Electrolyte abnormalities

Serum ion fluctuations, including hypocalcemia, hypophosphatemia, and hypermagnesemia, may occur during bisphosphonate therapy. They are usually mild but may have serious consequences such as seizure and tetany. Hypophosphatemia is most common during treatment of hypercalcemia of malignancy and can be present in 12.3% of patients receiving zoledronic acid infusion [58]. Incidence of hypocalcemia varies according to malignancy. In studies of breast cancer patients, hypocalcemia was associated with 39% of patients treated with zoledronic acid, compared with 7% in the placebo arm [30]. Hypocalcemia develops as a result of a deficient compensatory mechanism, such as prior parathyroidectomy, hypomagnesemic hypoparathyroidism or low vitamin D levels, and parathyroid hormone (PTH) resistance. Loop diuretics may further worsen hypocalcemia. Hypocalcemia is rarely symptomatic. Classic presentations include perioral paraesthesia, carpopedal spasm, tetany, and QT prolongation. Vague symptoms such as weakness and tingling may occur [59]. Hypocalcemia may also promote PTH secretion and cause or aggravate secondary hyperparathyroidism [60].

Vitamin D and calcium supplements are strongly recommended to minimize the incidence of hypocalcemia during bisphosphonate therapy. Any preexisting electrolyte abnormalities should be corrected before starting bisphosphonate treatment, and serum magnesium, calcium, and phosphate should be monitored periodically. Treatment of electrolyte abnormalities varies with severity and may necessitate iv replacement.

Osteonecrosis of the jaw

Osteonecrosis of the jaw (ONJ), also called avascular necrosis of the jaw, refers to the death of bone tissue in the jaw, probably due to impaired blood supply. The typical presenting lesion is a painful nonhealing ulcer, extraction socket, or exposed jawbone that has not responded to conservative debridement and antibiotic treatment. Prolonged use of bisphosphonates has been associated with ONJ in 5–6.7% of patients treated with bisphosphonates for bone metastases [53,61]. Actual incidence may vary depending on the underlying malignancy, duration of bisphosphonate treatment, and clinician awareness. One series included 36 ONJ patients who received pamidronate or zoledronate for myeloma or breast cancer [62]. A second series included 63 ONJ patients who received either iv bisphosphonates for at least one year (n = 56) or chronic oral bisphosphonates [63]. Other notable cases have also been reported [64–67]. ONJ may be a class effect of bisphosphonate therapy, occurring most commonly in second- and third-generation bisphosphonates. The FDA conducted a postmarketing safety review in 2004, and a search of the Adverse Event Reports database revealed 139 cases of bisphosphonate-associated ONJ: 47 patients taking pamidronate, 33 taking zoledronic acid, and 59 taking both drugs. Fewer cases were identified in patients taking alendronate or risedronate (n = 12 and 1

Table IV. Bisphosphonate dosing recommendations for patients with reduced baseline renal function.

Bisphosphonate	Dose adjustment per renal function
Alendronate	No dosage adjustment necessary for elderly or patients with CrCl* 35–60 mL/min. Not recommended for patients with CrCl <35 mL/min due to lack of experience.
Clodronate	For iv: CrCl 50–80 mL/min: 25% reduction in dose; CrCl 10–50 mL/min: 25–50% dose reduction; CrCl <10 mL/min: contraindicated. For oral: CrCl 10–30 mL/min: 50% dose reduction; CrCl <10 mL/min: contraindicated.
Etidronate	No experience to specifically guide treatment in patients with impaired renal function. Dosage should be reduced when glomerular filtration rates drop.
Ibandronate	No dose adjustment necessary for patients with CrCl ≥30 mL/min. Not recommended for use in patients with CrCl <30 mL/min.
Risedronate	Not recommended for use in patients with CrCl <30 mL/min. No dosage adjustment necessary in patients with CrCl ≥30 mL/min or in the elderly.
Pamidronate	Limited information available in patients with serum creatinine ≥3.0 mg/dL. Not recommended for patients with severe renal impairment. Resume treatment only when creatinine returns to within 10% of baseline value.
Tiludronate	Not recommended for patients with CrCl <30 mL/min.
Zoledronic acid	Reduced iv doses: 3.5 mg in patients with baseline CrCl 50–60 mL/min; 3.3 mg with CrCl of 40–49 mL/min; 3 mg with CrCl 30–39 mL/min. No clinical or pharmacokinetics data available to guide dose selection or safe use in patients with severe renal impairment.

*Creatinine clearance (CrCl) is calculated using the Cockcroft-Gault formula with a unit of mL/min. The above recommendations are derived from the manufacturers' prescribing information. For patients with reduced CrCl, zoledronate dosing is calculated to achieve the same AUC as in patients with CrCl of 75 mL/min, as per manufacturer [58].

respectively). Possible risk factors of ONJ include length of exposure to bisphosphonates [61], a diagnosis of cancer, concomitant therapies (*e.g.*, chemotherapy, radiotherapy, corticosteroids), and comorbid conditions such as anemia, coagulopathies, infection, and preexisting oral disease [68]. Previous dental procedures may be a precipitating factor. Possible mechanisms for bisphosphonate-associated ONJ include a compromised repair resulting from suppressed bone metabolism and angiogenesis secondary to bisphosphonates, and increased damage due to trauma or infection [69].

As no effective treatments have been established in prospective studies, the best approach to bisphosphonate-associated ONJ is prevention. Before initiating bisphosphonate therapy, it is recommended that patients be referred to a dentist familiar with existing guidelines for the prevention of oral complications of cancer therapy [70]. Newly issued postmarketing guidelines for zoledronic acid and pamidronate also stress the importance of this regimen. Although the optimal waiting period for instituting bisphosphonate therapy following invasive dental procedures has not been determined, the standard of care prior to radiation therapy is a delay of at least 10 days to allow for healing. If possible, invasive dental procedures such as tooth extractions and bone biopsies should be postponed until after iv bisphosphonate therapy. Once ONJ develops, it is advisable to discontinue bisphosphonates until the lesions resolve, even though doing so may not actually promote healing of the lesions. Bisphosphonates should be reinstituted only if clinically indicated and after careful consideration of risks and benefits. Prompt referral to a dentist trained in oral medicine, a hospital dentist, or an oral/maxillofacial surgeon is recommended for patients with symptoms of ONJ. Conservative management includes culturing of any lesions, prescribing antibiotics as appropriate, and recommending an antiseptic oral rinse that contains chlorhexidine gluconate. Some patients will need hyperbaric treatments, debridement or resection of portions of the jaw, and subsequent reconstructive surgery.

Areas of controversy

Duration and frequency of bisphosphonate therapy

Data on the optimal duration of bisphosphonate therapy are limited. For multiple myeloma, the single randomized study was continued for 21 cycles. It has been recommended that therapy be continued even if the patient has an SRE such as compression fracture or pathologic fracture [43]. Current ASCO guidelines recommend that bisphosphonate therapy be continued as long as it is well tolerated, or until there is a significant decrease in performance status in patients with multiple myeloma or bone metastasis from breast cancer [27,42,71]. There are no consensus guidelines for the duration of bisphosphonate therapy in patients with prostate cancer. However, recommendations from a multidisciplinary panel suggest that bisphosphonate treatments should be indefinite in patients with androgen-independent prostate cancer and bone metastasis. This is supported by evidence that efficacy does not decrease during long-term bisphosphonate treatment [43]. No formal recommendations have been

published for patients with bone metastases from solid tumors other than breast or prostate cancer.

Pharmacoeconomic issues

The widespread use of bisphosphonates will have a major impact on pharmaceutical expenses. Costs will vary depending on the duration of bisphosphonate use, the specific bisphosphonate used, and how the bisphosphonate is delivered (oral vs. iv). Using Markov models, Ross et al. estimated that the overall cost of bisphosphonate therapy to prevent an SRE was GBP 250 and GBP 1 500 per event for patients with breast cancer and multiple myeloma respectively [72]. Hillner et al. found cost-effective ratios associated with adding pamidronate of USD 108 200 per quality-adjusted life year in women concurrently treated with chemotherapy, and USD 305 300 per quality-adjusted life year in women treated with hormonal therapy [73]. The cost of preventing one SRE was USD 9 350 in the chemotherapy cohort and USD 12 760 in the hormonal therapy cohort. These ratios are much higher than most routinely accepted medical therapies. However, a Canadian analysis concluded that pamidronate's incremental cost was USD 18 700 per quality-adjusted life year gained [74]. The major differences in these results are explained primarily by: 1) the fact that the cost of pamidronate per treatment is approximately 50% lower in Canada than in the United States, and 2) by an assumption that a nonvertebral fracture would require in-patient treatment. The cost of treatment could be reduced by introducing bisphosphonate home therapy as part of long-term therapy [75]. In a multicenter trial, patients with multiple myeloma ($n = 37$) were randomly allocated to receive 3 months of in-home treatment with iv pamidronate, followed by 3 months of in-hospital treatment with pamidronate or vice versa [76]. Home therapy with pamidronate appeared feasible and safe. Similar results have been demonstrated with iv zoledronic acid [77].

Conclusions

Accumulating evidence reveals that bisphosphonate therapy plays a significant role in preventing skeletal complications in patients with bone metastases from multiple myeloma, breast cancers, and hormone-refractory prostate cancers. In addition, zoledronic acid reduces skeletal complications in a wide variety of other metastatic malignancies, and emerging data suggest that bisphosphonates are useful for treatment-related bone loss in prostate cancer. The efficacy of bisphosphonates as adjuvants in the treatment of early-stage breast or prostate cancers has not been clarified. Significant side effects of long-term bisphosphonate therapy include renal toxicity, hypocalcemia, and osteonecrosis of the jaw. With proper vigilance, bisphosphonate therapy is safe and can have substantial benefits for cancer patients.

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