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REVIEW

Importance of antiresorptive therapies for patients with bone metastases from solid tumors

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Abstract: Patients with bone metastases are at risk of skeletal-related events such as pathologic fractures, spinal cord compression, the need for orthopedic surgery to bone, and palliative radiotherapy for severe bone pain. Antiresorptive therapies have demonstrated efficacy for reducing the risk of skeletal-related events and ameliorating bone pain. Despite the well documented clinical benefits of antiresorptive therapies, patient benefits can be limited or compromised by nonadherence with scheduled therapy. Potential reasons for poor compliance include lack of understanding of how antiresorptive therapies work, neglecting the importance of bone health in maintaining quality of life, and being unaware of the potentially debilitating effects of skeletal-related events caused by bone metastases. Indeed, patients may stop therapy after bone pain subsides or discontinue due to generally mild and usually manageable adverse events, leaving them at an increased risk of developing skeletal-related events. In addition, the cost of antiresorptive therapy can be a concern for many patients with cancer. Medical care for patients with cancer requires a coordinated effort between primary care physicians and oncologists. Patients' medical care teams can be leveraged to help educate them about the importance of adherence to antiresorptive therapy when cancer has metastasized to bone. Because primary care physicians generally have more contact with their patients than oncologists, they are in a unique position to understand patient perceptions and habits that may lead to noncompliance and to help educate patients about the benefits and risks of various antiresorptive therapies in the advanced cancer setting. Therefore, primary care physicians need to be aware of various mechanistic and clinical considerations regarding antiresorptive treatment options.

Keywords: antiresorptive therapy, bisphosphonates, bone metastases, cancer, denosumab, zoledronic acid

Introduction

Antiresorptive therapies are important for maintaining bone health in patients with cancer metastatic to bone. Bone metastases can have a markedly negative impact on skeletal health by disrupting normal bone metabolism and weakening the skeleton. Consequently, patients with bone metastases are at risk of skeletal-related events such as pathologic fractures, spinal cord compression, the need for orthopedic surgery to bone, and palliative radiotherapy for severe bone pain.[1] Moreover, pathologic fractures in particular are associated with decreased survival.[2,3] Fortunately, antiresorptive therapies have demonstrated efficacy for reducing the risk of skeletal-related events and ameliorating bone pain.[4–10]

Despite the well documented clinical benefits of antiresorptive therapies, patients may often limit the benefits they derive by not adhering to the planned

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treatment schedule. There are several potential causes of poor compliance. For example, many patients focus on primary anticancer therapy and may fail to realize the importance of bone health in maintaining quality of life. These patients have limited awareness of the frequency and potentially debilitating effects of skeletal-related events caused by bone metastases. Typically, this patient group may not realize the extent to which skeletal health may deteriorate and may not be driven to educate themselves about the mechanisms of action of antiresorptive therapies. This could potentially lead to patients stopping therapy after bone pain subsides, leaving them at an increased risk of developing skeletal-related events. Additionally, unpleasant, but usually manageable, adverse events can cause patients to discontinue therapy. For example, the acute-phase response (APR) associated with some antiresorptive therapies can cause flu-like symptoms. Although these symptoms can often be managed with prophylactic acetaminophen, without appropriate advice, they may discourage patients from continuing therapy. Finally, the cost of therapy can be a major concern for many patients with cancer.

The medical care team can play an important role in educating the patient regarding the importance of antiresorptive therapy when cancer has metastasized to bone. Medical care for patients with cancer requires coordinated effort between primary care physicians and oncologists. Patients usually have frequent contact with their primary care physicians, especially once their disease stabilizes. Therefore, primary care physicians are in a unique position to help educate their patients and should be educated on issues related to the mechanisms of action, costs, benefits, and safety considerations associated with antiresorptive therapy options (particularly denosumab and zoledronic acid, which have the broadest indications across several tumor types for patients with bone metastases).[11,12] The purpose of this review is to bring the importance of bone health in patients with cancer to the forefront for physicians.

Literature search methods and limitations

Articles indexed on PubMed during the last 5 years were searched using the search terms zoledronic acid and denosumab in combination with bone metastases, cancer, cost, and compliance. Important studies were identified from the literature search, and were limited to bone metastasis studies. Publications or presentations regarding postmenopausal osteoporosis, aromatase-inhibitor induced bone loss, or cancer therapy-induced bone loss were not included. Older relevant studies were also included. Relevant presentations at large oncology congresses (eg, ASCO and ECCO/ESMO) during the last 5 years were included. However, smaller congresses and abstracts for congress presentations not readily available online were not included. Major limitations to these literature search methods are that some congress activity may have been missed and that relevant articles may not have been identified during the literature search.

Role of antiresorptive agents in cancer therapy

Bone remodeling occurs through the coordinated activity of bone formation and bone resorption. Bone metastases cause an imbalance in the activity of osteoclasts (bone-resorbing cells) and osteoblasts (bone-forming cells), thereby weakening the skeleton and resulting in a vicious cycle of bone destruction and tumor growth facilitated by growth factors released during osteolysis.[13] Therapies that inhibit osteoclast activity are used to prevent bone loss and delay skeletal-related events in patients with bone metastases from advanced cancer.

Antiresorptive therapies (ie, bisphosphonates and denosumab) are indicated for treating bone lesions and are effective for delaying onset of skeletal-related events (Table 1),[4–7,9,10,14–25] and ameliorating bone pain.[4–10] Bisphosphonates are a well established treatment option for maintaining bone health in patients with cancer and are a standard supplemental therapy for patients with advanced cancer. In the metastatic setting, the nitrogen-containing bisphosphonates, pamidronate and zoledronic acid, are approved for treating bone metastases from breast cancer.[11,26] However, zoledronic acid (4 mg intravenously every 3 to 4 weeks) is the only bisphosphonate indicated for reducing the risk of skeletal-related events in patients with bone metastases from other solid tumors. Furthermore, zoledronic acid has a well established safety profile and a wealth of real-world data documenting tolerability and efficacy. Denosumab (120 mg subcutaneously every month) is a newer antiresorptive agent indicated for preventing skeletal-related events in patients with bone metastases from solid tumors but is not indicated for patients with multiple myeloma or hypercalcemia of malignancy.[12]

Mechanisms of action of antiresorptive therapies

Bisphosphonates

All bisphosphonates accumulate in the mineral portion of the bone matrix and are released during bone resorption.

Table 1 Key antiresorptive therapy clinical trials for prevention of skeletal-related events in advanced cancer

Antiresorptive therapy	N	Dosing	Comparator	Results
Prostate cancer				
ZOL[14]	422[a]	4 mg IV q 3–4 wk	Placebo	↑ Median time to 1st on-study SRE (not reached ZOL vs 321 days placebo; $P = 0.011$) ↓ In proportion of patients with SREs (44.2% ZOL vs 33.2% placebo; $P = 0.021$)
Dmab[4]	1904	120 mg SC q 4 wk	ZOL 4 mg IV q 4 wk	Additional 18% ↑ in time to 1st on-study SRE ($P = 0.008$; superiority)
Breast cancer				
ZOL[15]	227	4 mg IV q 3–4 wk	Placebo	41% ↓ in SRE risk ($P = 0.019$)[b]; 13.5% ↓ in fractures
Dmab[9]	2046	120 mg SC q 4 wk	ZOL 4 mg IV q 4 wk	Additional 18% ↑ in time to 1st on-study SRE ($P = 0.01$)
PAM[10]	751	90 mg IV q 3–4 wk	Placebo	23% ↓ in SRE risk ($P < 0.001$)[b]; 12% ↓ in pathologic fractures ($P = 0.002$)
Ibandronate[16]	312	6 mg IV q 3–4 wk	Placebo	18% ↓ in SRE risk ($P = 0.03$)[b]; ↓ vertebral fractures ($P = 0.023$)
Ibandronate[17]	564	50 mg PO qd	Placebo	14% ↓ in SRE risk ($P = 0.08$)[b]; no significant difference in number of fractures
CLO[18–20]	422	1600 mg PO qd	Placebo	31%, 17%, 8% ↓ in SRE risk respectively ($P = 0.03$, pooled)[b]; ↑ time to 1st fracture ($P = 0.023$) (Kristensen et al[18]), ↓ vertebral fractures ($P < 0.025$) (Paterson et al[19])
Other solid tumors or multiple myeloma				
ZOL (BC or MM)[6,21]	1116[c]	4 mg IV q 3–4 wk	PAM 90 mg IV q 3–4 wk	Additional 20% ↓ in SRE risk ($P = 0.025$); 7% ↓ in pathologic fractures ($P \leq 0.05$)
ZOL (OST)[7,22]	507[a]	4 mg IV q 3–4 wk	Placebo	↑ Median time to 1st on-study SRE (236 days ZOL vs 155 days placebo; $P = 0.01$); 31% ↓ in SRE risk ($P = 0.003$)
ZOL (MM)[23,24]	1960	4 mg IV q 3–4 wk	CLO 1600 mg PO qd	↓ Proportion of patients with an SRE (27.0% ZOL vs 35.3% CLO; $P = 0.0004$) 16% ↓ in mortality ($P = 0.0118$), ↑ median OS 5.5 mo ($P = 0.04$), 12% ↑ in PFS ($P = 0.0179$)
Dmab (OST or MM)[5]	1776	120 mg SC q 4 wk	ZOL 4 mg IV q 4 wk	Additional 16% ↑ in time to 1st on-study SRE ($P = 0.0007$)

Notes: [a]n reflects patients in the 4 mg ZOL and placebo groups only; [b]percentage decrease in SRE risk and *P* value derived from the Cochrane database meta-analysis;[25] [c]n reflects patients in the 4 mg ZOL and 90 mg PAM groups only.

Abbreviations: BC, breast cancer; CLO, clodronate; Dmab, denosumab; IV, intravenous; MM, multiple myeloma; OST, other solid tumors; OS, overall survival; PAM, pamidronate; PFS, progression-free survival; PO, orally; q, every; SC, subcutaneously; SRE, skeletal-related event; ZOL, zoledronic acid; wk, week; vs, versus.

The relative efficacy of bisphosphonates to delay the onset and reduce the risk of potentially debilitating skeletal-related events depends primarily on their chemical structure. Non-nitrogen-containing bisphosphonates, such as clodronate, are metabolized by osteoclasts into nonhydrolyzable cytotoxic ATP analogs. In contrast, nitrogen-containing bisphosphonates inhibit the mevalonate pathway after internalization by osteoclasts.[27] Notably, zoledronic acid was the most potent bisphosphonate tested in preclinical model systems, with the greatest antiresorptive activity.[28,29]

All bisphosphonates are rapidly removed from the circulation by skeletal deposition or by renal filtration, after which they are excreted nonmetabolized within a few hours. The rate of bone turnover in a patient determines the proportion of bisphosphonates that becomes bound to the skeleton or is filtered through the kidneys.[30] Patients with higher rates of bone turnover (eg, patients with metastatic bone disease or receiving therapies that increase bone turnover) retain more of the initial bisphosphonate dose within the skeleton compared with patients with lower rates of bone turnover (eg, healthy individuals). Furthermore, once bound to the skeleton, bisphosphonates are released during active bone remodeling, at which time they inhibit osteoclast function and viability.[27,30] Therefore, bisphosphonates avidly bind the mineralized bone matrix and inhibit bone destruction in patients with bone metastases.

Originally considered supportive care, the role of nitrogen-containing bisphosphonates in therapy is evolving because of the growing body of evidence demonstrating their potential anticancer activity. Preclinical evidence supports the anticancer activity of bisphosphonates.[31–33] Furthermore, numerous clinical studies examining the potential anticancer activity of bisphosphonates have been completed (Table 2),[24,34–55] and several of them show that zoledronic acid influences the prevalence and persistence of disseminated tumor cells in bone. Indeed, one

Table 2 Trials demonstrating anticancer benefits of bisphosphonates

Study (follow-up)	N	Tumor type	BP	Results
Neoadjuvant setting				
Neoadjuvant AZURE[34] (6 mo)	205	BC	ZOL 4 mg IV q 3–4 wk for 6 doses	↓ RITS by 44% (27.4 mm vs 15.5 mm; $P = 0.006$) ↑ pCR rate by nearly 2-fold ($P = 0.146$)
Adjuvant setting				
Powles et al[35] (5.6 y)	1069	BC	CLO 1600 mg/d for 2 y	↑ BMFS (HR = 0.692; $P = 0.043$) ↑ OS (HR = 0.768; $P = 0.048$)
Diel et al[36] (36 mo) (8.5 y)[37]	302	BC	CLO 1600 mg/d for 2 y	↑ BMFS (92% vs 83%; $P = 0.003$) ↑ OS (HR = 96% vs 85%; $P = 0.0001$) ↑ OS (79.6% vs 59.3%; $P = 0.049$)
Saarto et al (5 y)[38] (10 y)[39]	299	BC	CLO 1600 mg/day for 3 y	↓ OS (70% vs 83%; $P = 0.009$) ↓ DFS (56% vs 71%; $P = 0.007$) ↓ DFS (45% vs 58%; $P = 0.01$); Similar OS
NSABP-34[40] (8.4 y)	3323	BC	CLO 1600 mg/d for 3 yr	No effect on DFS (HR = 0.91; $P = 0.27$) ↑ BMFI (HR = 0.63; $P = 0.024$) and ↑ NBMFI (HR = 0.63; $P = 0.015$) in women ≥ 50 y
GAIN[41] (39 mo)	3023	BC	IBN 50 mg/d for 2 y	No effect on DFS (HR = 0.945; $P = 0.59$) or OS (HR = 1.04; $P = 0.80$)
Lin et al[42] (24 mo)	45	BC	ZOL 4 mg IV monthly for 2 y	↓ In persistent DTCs: ↓ In 66% of patients at 1 y ($P = 0.0018$) ↓ In 71% of patients at 2 y ($P = 0.01$)
Solomayer et al[43] (12 mo)	76	BC	ZOL 4 mg IV q 4 wk for 2 y	↓ In persistent DTCs ($P = 0.066$) ↑ DTC-free patients (67% vs 35%; $P = 0.009$)
Aft et al[44] (3 mo)	120	BC	ZOL 4 mg IV q 3 wk for 1 y	↓ In persistent DTCs (30% vs 47%; $P = 0.054$)
Rack et al[45] (39 mo)	172	BC	ZOL 4 mg IV q 4 wk for 6 mo	↓ Proportion with persistent DTCs after ZOL (13% vs 27%; $P = 0.099$)
ZO-FAST (36 mo)[46] (60 mo)[47]	1065	BC[a]	ZOL 4 mg IV q 6 mo for 5 y; immediate vs delayed	↑ DFS (HR = 0.588; $P = 0.0314$) with immediate vs delayed ZOL ↑ DFS (HR = 0.66; $P = 0.0375$)
ABCSG-12 (48 mo)[48] (84 mo)[49]	1803	BC[b]	ZOL 4 mg IV q 6 mo for 3 y	↑ DFS (HR = 0.64; $P = 0.01$) ↑ DFS (HR = 0.72; $P = 0.014$) ↑ OS (HR = 0.63; $P = 0.049$)
AZURE (59 mo)[50]	3360	BC	ZOL 4 mg IV q 3–4 wk × 6; 4 mg q 3 mo × 8; 4 mg q 6 mo × 5	No change in DFS in overall population (HR = 0.98; $P = 0.79$) Trend ↑ OS in the overall population (HR = 0.85; $P = 0.07$) ↑ IDFS (HR = 0.75; $P = 0.02$) and ↑ OS (HR = 0.74; $P = 0.04$) in women > 5 y postmenopause (n = 1041)
Metastatic setting				
Mystakidou et al[51] (18 mo)	40	Advanced solid tumors (no BM)	ZOL 4 mg IV monthly	↑ BMFS at 12 mo (60% vs 10%; $P < 0.0005$) ↑ BMFS at 18 mo (20% vs 5%; $P = 0.0002$)
Zaghloul et al[52] (24 wk)	40	Bladder cancer	ZOL 4 mg IV monthly for 6 mo	↑ 1-y OS (36.3% vs 0%; $P = 0.004$)
Zarogoulidis et al[53]	144	LC	ZOL 4 mg IV q 21 d	↑ OS by > 6 mo (578 d vs 384 d; $P < 0.001$)
Aviles et al[54] (49.6 mo)	94	MM	ZOL 4 mg IV q 28 d	↑ 5-y OS (80% vs 46%; $P < 0.01$) ↑ 5-y EFS (80% vs 52%; $P < 0.01$)
MRC Myeloma IX[24] (3.7 y)	1960	MM	ZOL 4 mg IV q 3–4 wk	↑ PFS (HR = 0.883; $P = 0.0179$) ↑ OS (HR = 0.842; $P = 0.0118$)

Notes: [a]Postmenopausal women with early-stage endocrine-responsive breast cancer; [b]premenopausal women with early stage endocrine-responsive BC. Hamilton E, Clay TM, Blackwell KL. New perspectives on zoledronic acid in breast cancer: potential augmentation of anticancer immune response. *Cancer Invest*. 2011;29(8):533–541. Copyright 2011, Informa Healthcare. Reproduced with permission of Informa Healthcare.[55]

Abbreviations: BC, breast cancer; BMFI, bone metastasis-free interval; BMFS, bone metastasis-free survival; DFS, disease-free survival; DTC, disseminated tumor cell; EFS, event-free survival; HR, hazard ratio; IBN, ibandronate; I IDFS, invasive disease-free survival; IV, intravenous; LC, lung cancer; MM, multiple myeloma; NBMFI, nonbone metastasis-free interval; OS, overall survival; pCR, pathologic complete response; PFS, progression-free survival; q, every; RITS, residual invasive tumor size; ZOL, zoledronic acid.

possible mechanism of nitrogen-containing bisphosphonate anticancer activity may be through rendering the bone marrow microenvironment less suitable for the growth of tumor cells. Some bisphosphonates may also target some steps involved in the metastatic process, including tumor cell growth, migration, adhesion to extracellular matrix, extravasation into distant tissues, angiogenesis, and avoidance of immune surveillance. Furthermore, nitrogen-containing bisphosphonates have demonstrated synergistic anticancer activity when used in combination with anticancer agents in the preclinical setting, and clinical studies to explore this effect further are ongoing. Knowledge and understanding of the potential anticancer effects of bisphosphonates could influence a patient's preference for one antiresorptive therapy over another.

Denosumab

Denosumab is a new antiresorptive therapeutic option for patients with bone metastases from solid tumors, but not for patients with multiple myeloma.[12] It is a fully human monoclonal antibody that specifically targets the receptor activator of nuclear factor kappa B ligand (RANKL), a key modulator of osteoclast-mediated bone resorption. Notably, in head-to-head clinical trials, denosumab was found to be superior to zoledronic acid for delaying skeletal-related events in patients with bone metastases from breast or prostate cancer and non-inferior to zoledronic acid for delaying SREs in patients with bone metastases from other solid tumors.[4,5,9] Denosumab is not incorporated into the mineralized bone matrix and does not selectively target bone.[56,57] Because RANKL is expressed systemically, blocking RANKL with denosumab may interfere with RANKL-mediated pathways outside of bone. Indeed, in addition to osteoclasts, RANKL is also expressed by cells of the immune system (eg, T cells, B cells, and dendritic cells), vascular endothelial cells, heart, brain, kidney, skeletal muscle, and skin.[58–60] Functions of RANKL in these cells include regulation of vascular integrity, lymph node organization, T cell and dendritic cell communication, and dendritic cell survival. Furthermore, in murine models, RANKL mRNA and protein have been detected throughout development, suggesting multiple other potential functions of the protein.[61]

Serum steady-state levels of denosumab are reached around 6 months after 120 mg dosing every 4 weeks, and the mean serum elimination half-life is 28 days.[12] Denosumab clearance is proportional to body weight, with steady-state exposure higher in lower weight individuals compared with higher weight individuals.[12] Although denosumab remains in serum for several weeks, studies suggest that regular dosing is required to maintain its antiresorptive effects.[30,62,63] Indeed, studies in patients with osteoporosis showed that the bone turnover marker levels increased above baseline levels within 3–6 months after discontinuation.[62,63] Furthermore, denosumab discontinuation was associated with decreased bone mineral density at the lumbar spine (6.6%) and total hip (5.3%) within 12 months of receiving the final dose.[63] These studies suggest that stopping denosumab therapy may be associated with a rebound effect, leading to subsequent decrease in bone mineral density.[30,62,63] It is important for clinicians to understand these issues when prescribing denosumab so that they can stress the importance of remaining on therapy. In addition, the rebound effect is of particular relevance in a real world setting as patients with advanced cancer are likely to experience events that may warrant discontinuation of therapy, thereby increasing their risk of skeletal-related events.

Denosumab is newly approved in the US for use in patients with bone metastases from solid tumors. Although a 2-year open-label extension of the skeletal-related events study in patients with breast cancer confirmed the safety profile of denosumab established in the primary study,[64] it has not been reported how the efficacy and safety of denosumab therapy in clinical trials will translate to long-term use in clinical practice. No clinical anticancer effects of denosumab have been reported; however, a Phase III study in patients with nonmetastatic castration-resistant prostate cancer showed that it significantly increased bone metastasis-free survival by a median of 4.2 months versus placebo (hazard ratio [HR] = 0.85; $P = 0.028$). Despite this statistically significant finding, denosumab had no effect on overall disease progression (HR = 0.90; $P = 0.13$) or survival (HR = 1.01; $P = 0.91$). Moreover, this study reported a higher incidence of osteonecrosis of the jaw with denosumab compared with other denosumab trials in patients with advanced cancer (5% versus 2%).[65,66] Ongoing anticancer trials with denosumab include ABCSG-18 (n = 3400) and D-CARE (n = 4500), both in patients with breast cancer.[67,68]

Safety and managing adverse events with antiresorptive therapies

Acute-phase responses

Acute-phase responses have been reported in patients receiving antiresorptive therapy and consist of flu-like symptoms including fever, chills, flushing, bone pain and/or arthralgias, and myalgias. Approximately 15%–27% of patients with advanced cancer receiving nitrogen-containing bisphosphonate therapy have reported APR-related adverse events.[4,5,9] An integrated analysis of the three Phase III clinical trials for treating bone metastases in patients with advanced cancer shows that APR-related adverse events were reported less frequently with denosumab compared with zoledronic acid (9% versus 20%, respectively).[65]

It should be noted that APR-related adverse events are often easily managed,[69] and prophylactic use of acetaminophen or diphenhydramine before the first bisphosphonate dose can reduce the incidence and severity of these events.[70] Furthermore, APR-related adverse events are usually mild and reversible.[71] These events either do not manifest in subsequent cycles of nitrogen-containing bisphosphonate therapy or are of reduced severity. Therefore, APR-related adverse events need not be a contraindication to the long-term use of bisphosphonate therapy. The primary care physician must be aware of how to manage APR-related adverse events and should communicate this information to patients with cancer.

Osteonecrosis of the jaw

Osteonecrosis of the jaw is an uncommon but potentially serious adverse event of complex etiology, generally affecting 1%–2% of patients with advanced cancer receiving complex treatment regimens including chemotherapy and antiresorptive therapy (ie, nitrogen-containing bisphosphonates and denosumab).[4,5,9,65] A combined analysis of the three Phase III trials comparing denosumab with zoledronic acid in patients with bone metastases confirms these rates of osteonecrosis of the jaw and showed that, as of October 2010, osteonecrosis of the jaw resolved in 36% of patients (40% for denosumab versus 30% for zoledronic acid).[72] In contrast with the metastatic setting, the risk of osteonecrosis of the jaw with antiresorptive therapy (zoledronic acid or denosumab) in the adjuvant setting is extremely rare.[48,73,74] The infrequent dosing schedule for zoledronic acid or denosumab might be one factor contributing to the exceptionally low event rate for osteonecrosis of the jaw in this setting.

Despite the potential seriousness of this adverse event in the metastatic setting, the risk of developing osteonecrosis of the jaw can be minimized by preventive dental care before initiating bisphosphonate therapy.[75] The primary care physician can play a critical role in educating the patient on the importance of preventive dental care in this setting. Furthermore, conservative management often leads to resolution of osteonecrosis of the jaw[76] (Table 3).[77] Although not specifically examined with denosumab, these preventive techniques also would likely be useful for minimizing the risk of osteonecrosis of the jaw in patients receiving denosumab.

Renal impairment

The incidence of renal impairment is high in elderly patients (ie, age $\geq$ 65 years) even in the absence of comorbidities.[78–81] Renal impairment is also common among patients with cancer.[82] Moreover, this patient population often has pre-existing comorbidities or other risk factors that increase the risk of renal impairment. For example, patient age, pre-existing kidney disease, chronic comorbidities such as diabetes, hypertension, and cardiac insufficiency, and some long-term medications all increase the risk of renal impairment.[83] Thus, monitoring renal function in patients with cancer is crucial for safe administration of anticancer agents and antiresorptive therapies, which can be nephrotoxic.[84,85] Primary care providers can play a critical role in managing comorbidities and multiple medications.

For patients receiving nitrogen-containing bisphosphonates, monitoring renal function (ie, serum creatinine

Table 3 American Association of Oral and Maxillofacial Surgeons recommendations for treatment of osteonecrosis of the jaw

Stage	Symptoms	Recommended treatment
At risk	No apparent necrotic bone in patients who have been treated with either oral or intravenous bisphosphonates	• No treatment indicated • Patient education
0	No clinical evidence of necrotic bone, but nonspecific clinical findings and symptoms	• Systemic management, including the use of pain medication and antibiotics
1	Exposed/necrotic bone in patients who are asymptomatic and have no evidence of infection	• Antibacterial mouth rinse • Quarterly clinical follow-up • Patient education
2	Exposed/necrotic bone associated with infection (ie, pain and erythema in the region of exposed bone)	• Symptomatic treatment with broad-spectrum antibiotics • Antibacterial mouth rinse • Pain control • Superficial debridements to relieve soft tissue irritation
3	Stage 2 symptoms + 1 or more of the following: exposed and necrotic bone extending beyond the region of alveolar bone (ie, inferior border and ramus in the mandible, maxillary sinus and zygoma in the maxilla) resulting in pathologic fracture, extraoral fistula, oral antral/oral nasal communication, or osteolysis extending to the inferior border of the mandible or sinus floor	• Antibacterial mouth rinse • Antibiotic therapy and pain control • Surgical debridement/resection for longer-term palliation

Note: Adapted from Ruggiero SL, Dodson TB, Assael LA, Landesberg R, Marx RE, Mehrotra B. American Association of Oral and Maxillofacial Surgeons. Position paper on bisphosphonate-related osteonecrosis of the jaw – 2009 update. *Aust Endod J*. 2009;35:119–130. Copyright 2009, with permission from Elsevier.[77]

assessment before each dose) is required because nitrogen-containing bisphosphonates not bound to the skeleton are cleared by renal filtration. Dose adjustment guidelines for nitrogen-containing bisphosphonates are available for patients with renal impairment (Table 4).[11,26,69,86–88] Monitoring renal function with denosumab is not required.[12] However, the rate of renal adverse events was similar for zoledronic acid compared with denosumab in patients with castration-resistant prostate cancer.[4] Moreover, an integrated analysis of the trials comparing zoledronic acid with denosumab for the treatment of bone metastasis also showed similar rates of renal adverse events (12% versus 9%, respectively).[65] It should also be noted that patients with renal impairment who receive denosumab are at increased risk of developing hypocalcemia, a potentially serious complication. Indeed, 10% of patients receiving denosumab experienced hypocalcemia compared with 5% of patients receiving zoledronic acid.[65] Therefore, it is prudent to assess renal function regularly in patients with cancer receiving antiresorptive therapy.

When determining the optimal choice of antiresorptive therapy for an individual patient, the safety profiles of antiresorptive therapies need to be considered within the context of individual clinical situations and preferences. Other tools that can be useful for evaluating the risk/benefit ratios of a therapy are number-needed-to-treat (NNT) and cost/benefit analyses. The NNT is a measure used to compare the relative efficacies of two therapies. It represents the number of patients who need to be treated with an agent to avoid one additional event. In addition to NNT analyses, cost/benefit analyses can help evaluate the cost-effectiveness of a therapy given the known efficacy and safety profiles.

Table 4 Modified bisphosphonate dosing schedules for renal impairment

Creatinine clearance, mL/min	Dose adjustment		
	Pamidronate, mg[a]	Zoledronic acid, mg[b]	Ibandronate, mg[c]
90–60	60–90	4	6
60–50	60–90	3.5	6
50–40	60–90	3.3	4
40–30	60–90	3.0	4
<30 or patients receiving hemodialysis	Not recommended	Not recommended	2 or not recommended[d]

Notes: [a]Pamidronate formulations: 90 mg/10 mL, 60 mg/10 mL, or 15 mg/5 mL;[26,86] [b]zoledronic acid formulation: 4 mg/5 mL;[11] [c]ibandronate formulations: 6 mg/6 mL, or 2 mg/2 mL;[87] [d]Swiss summary of product characteristics.[88] Updated from Launay-Vacher et al[86] and printed in Aapro M, Abrahamsson PA, Body JJ, et al. Guidance on the use of bisphosphonates in solid tumours: recommendations of an international expert panel. *Ann Oncol*. 2008;19(3):420–432, by permission of Oxford University Press.[69]

NNT and cost/benefit analyses for zoledronic acid versus denosumab

The NNT analysis can be used to make sense of numerical results from clinical trials, and is useful in evaluating the real-world clinical benefit of one agent relative to another. Recently, NNT analyses were performed using skeletal-related event data from two Phase III clinical trials comparing denosumab with zoledronic acid for treating bone metastases in patients with castration-resistant prostate cancer or other solid tumors (excluding breast cancer).[89] These analyses determined the NNT required to avoid a single skeletal-related event during continuous, long-term denosumab therapy in patients with castration-resistant prostate cancer or other solid tumors. For patients with castration-resistant prostate cancer, 22 patients would need to be treated with denosumab for 41 months to prevent any skeletal-related event versus zoledronic acid.[89] Similarly, in patients with other solid tumors, 21 patients would need to be treated with denosumab for 34 months to prevent any one skeletal-related event compared with zoledronic acid.[89] Furthermore, the NNT required to prevent radiation to bone, fractures, or surgery to bone was notably high for patients with castration-resistant prostate cancer (37, 163, and 317, respectively) or other solid tumors (36, 56, and 167, respectively).[89] These analyses show that the potential incremental benefit of denosumab compared with zoledronic acid for preventing any one skeletal-related event would be realized only after 21–22 patients received long-term (34–41 months) denosumab therapy. Moreover, the higher NNTs for more debilitating and costly skeletal-related events (eg, fracture, surgery to bone) suggest a low incremental benefit with denosumab compared with zoledronic acid. Indeed, these marginal benefits need to be considered in conjunction with the safety profiles and costs of denosumab and zoledronic acid when choosing an antiresorptive therapy for patients with metastatic bone disease from advanced cancer.

In addition to the safety and efficacy of antiresorptive therapies, cost also must be taken into consideration, because drug costs will influence the out-of-pocket expenses incurred by patients. Cost/benefit analyses can be useful for evaluating the cost, efficacy, and safety considerations of a therapy. Such analyses utilizing a literature-based Markov model of denosumab compared with zoledronic acid were based on data from 27 months of therapy in Phase III clinical trials in patients with bone metastases from castration-resistant prostate cancer or breast cancer. These analyses show that denosumab is not cost-effective compared with zoledronic acid.[90,91] Indeed, the cost per quality-adjusted life-year (QALY) for patients with breast cancer is approximately $697,000,[91] and the cost per QALY for patients with castration-resistant prostate cancer is approximately $1.25 million.[90] Both of these figures are far above what is considered a good medical value in the US (ie, $50,000 to $100,000 per QALY).[90,91] In both analyses, the high cost per QALY with denosumab is due to higher drug acquisition costs, combined with the limited improvement in prevention of skeletal-related events with denosumab versus zoledronic acid. These high costs per QALY for denosumab suggest that the cost/benefit ratio of denosumab may be prohibitive for many patients. However, a third analysis using a literature-based lifetime Markov model showed smaller values for the increase costs per QALY gained with denosumab ($78,915 for breast cancer, $49,405 for castration-resistant prostate cancer, and $67,931 for non-small-cell lung cancer).[92] The increased cost per QALY gained with denosumab compared with zoledronic acid in this analysis is within what is considered good medical value in the US. Overall, the cost-effectiveness of denosumab remains open to interpretation at this time, and may influence treatment decisions differently in each geographic area/practice setting.

Conclusion

Clinical data indicate that the antiresorptive therapies, zoledronic acid and denosumab, are generally well tolerated in patients with bone metastases from advanced cancer. It should be noted that bisphosphonates are a well established treatment option with a long history of clinical use in this patient population and have a well characterized and manageable safety profile. Denosumab is a newly approved antiresorptive therapy option for patients with bone metastases from solid tumors. Although the long-term safety profile of denosumab in clinical practice remains to be determined, it provides an alternative antiresorptive therapy option for this patient population. However, cost/benefit analyses do not favor denosumab over zoledronic acid for treating bone metastases from solid tumors.

Patient compliance with antiresorptive therapy is critical for maintaining bone health and quality of life. Understanding the benefits of antiresorptive therapies and the risks associated with skeletal-related events may improve patient compliance. Because primary care physicians generally have more contact with their patients than oncologists, they are in an excellent position to monitor compliance and help educate patients on the benefits and risks of various antiresorptive therapies. Therefore, primary care physicians need to be aware of the risks and benefits of various antiresorptive therapy options for patients with advanced cancer.

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