Minimizing cancer's impact on bone with denosumab: current and future perspectives

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Bone metastasis is a serious complication of advanced cancer. It is most commonly observed in patients with metastatic breast and prostate cancers, but also occurs in most other metastatic solid cancers. Without treatment, patients may experience complications including intractable bone pain, hypercalcemia, fracture, spinal cord compression and/or a requirement for surgical or radiotherapeutic intervention. In 2010, denosumab, a fully human monoclonal antibody that inhibits RANK ligand (RANKL) and subsequent osteoclast-mediated bone destruction, was approved by the Food and Drug Administration for the prevention of skeletal-related events (SREs) in patients with bone metastases from solid tumors. This article reviews the role of denosumab in preventing SREs due to bone metastases, treating bone loss due to hormone-ablative cancer therapies, and describes denosumab's safety profile and potential future indications under investigation.

Improvements in cancer treatment have allowed patients with common cancers, such as breast and prostate cancers, to live longer with their disease.[1-3] In addition to extending life, an important goal of therapy is to minimize cancer's impact on functional status. Bone metastasis is a common complication of advanced cancer, occurring in a majority of patients with solid tumors, particularly breast and prostate cancers.[4] Bone metastases often impact quality of life, causing pain, fractures, cord compression, and secondary hypercalcemia. These complications may require therapeutic interventions such as radiation and surgery, which can further impact the patient's functional status.[4] Recognizing the importance of maintaining skeletal integrity in these populations, the National Comprehensive Cancer Network (NCCN) and the American Society of Clinical Oncology (ASCO) recommend bone-modifying agents such as denosumab or bisphosphonates as standard treatment for patients with bone metastases secondary to breast and prostate cancers.[5-7] This review discusses the burden of bone metastases and the role of denosumab in preventing complications of bone metastases in patients with advanced cancer and bone loss in patients receiving hormone ablative therapies. The safety profile of denosumab and current trials are also described.

Bone metastases

Bone metastases develop via a multistep process that begins with primary tumor cells entering systemic circulation, avoiding detection by the immune system, adhering to the vascular endothelium, and invading the skeletal stroma.[8] Under normal conditions, skeletal integrity is maintained through a continuous process of bone remodeling, in which old bone is resorbed by osteoclasts and replaced by new bone formed by osteoblasts.[9] These bone remodeling processes and the anatomic features of bone render it a favorable environment for tumor cell survival and growth.[10] Growth factors, cytokines, and calcium released by bone during the resorption process support the survival and proliferation of infiltrating cancer cells.[11,12] Cancer cells, in turn, secrete growth factors and cytokines that increase the synthesis and maturation of osteoblasts, leading to an increase in RANK ligand (RANKL). Increases in

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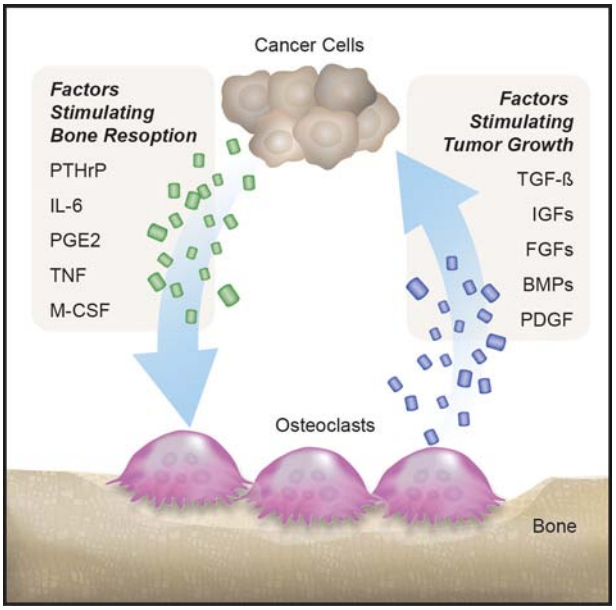

FIGURE 1 Cycle of cancer-induced osteolytic bone disease. Tumor-induced bone resorption leads to the release of growth factors and cytokines that support tumor survival and growth.
Abbreviations: BMP, bone morphogenetic protein; FGF, fibroblast growth factor; IGF, insulin-like growth factor; IL-6, interleukin-6; M-CSF, macrophage colony-stimulating factor; PDGF, platelet-derived growth factor; PGE2, prostaglandin E2; PTHrP, parathyroid hormone-related peptide; TGF-β, transforming growth factor-β; TNF, tumor necrosis factor.

RANKL contribute to increased osteoclast formation, function, and survival that ultimately enhance bone resorption, causing a vicious cycle of cancer-induced bone destruction and tumor cell growth (Figure 1).[11,12]

Burden of bone metastases

Bone metastases are the most common cause of chronic pain in cancer patients. However, the pathophysiological mechanisms underlying bone pain are unclear. Possible mechanisms include stretching of the periosteum or nerve entrapment due to the growing tumor, fractures caused by osteolytic bone destruction, and acidification of the local microenvironment, which may activate nociceptive signaling pathways.[13-16] Approximately 35%-70% of patients with stage IV solid tumors eventually develop bone metastases depending upon the tumor type. In addition to pain medications, radiation therapy and/or surgical procedures may be required to relieve pain, preserve function and/or maintain skeletal integrity. Potentially the most catastrophic outcome for patients with metastatic bone cancer is spinal cord compression due to collapse of vertebrae or extension of bone metastases into the epidural space which can lead to incontinence, paralysis, and long-term care requirements. An estimated 12,700 cancer patients in the United States develop spinal cord compression each year, with breast, prostate, and lung cancer each accounting for 15%-20% of cases.[17]

Clinical trials evaluating bone metastases have used skeletal-related events (SREs) to specify study endpoints, defined as a composite of cord compression, fracture, radiation therapy to the bone, and surgical stabilization of bone. Other bone-related events such as pain are not included in the definition of SRE. The rate of SREs varies according to tumor type. For example, prior to the advent of bone-targeted treatments, breast cancer patients with bone metastases experienced a mean 3.7 SREs per patient per year, or 1 every 3-4 months.[18] As patients with bone-only metastatic breast cancer now have an expected median overall survival (OS) of about 5 years,[19] the prevention of SREs becomes greatly important. Furthermore, both breast and prostate cancer patients who experience 1 SRE are at higher risk for developing subsequent SREs.[20,21]

All SREs can impact patients beyond the acute event. In a recent evaluation of more than 2,000 patients with breast and prostate cancers admitted to the hospital for an SRE, 41.6% of prostate cancer patients and 34.4% of breast cancer patients were not discharged to their homes after acute hospitalization, but rather went to a skilled nursing or other facility, or died.[22] The impact of bone metastases and its complications can reduce quality of life and be devastating to patients who are already facing a limited life expectancy.

Bisphosphonates

Bisphosphonates have been used to treat bone metastases since the initial approval of pamidronate for breast cancer and multiple myeloma in 1998. They bind with high affinity to bone minerals such as calcium and reduce osteoclast-mediated bone resorption (Table 1). Zoledronic acid (ZA) was approved in the US in 2002 based on randomized clinical trials showing that over a median duration of 10.5 months, fewer metastatic prostate cancer patients who received the 4 mg dose of ZA had an SRE compared with placebo (33% vs 44%, respectively; P = .021; 422 patients) and over a median 3.8 months, fewer patients with metastatic solid tumors other than breast and prostate cancer had an SRE (38% with ZA vs 44% with placebo; P = not statistically significant; 507 patients).[23-25] Also, in a secondary analysis, the 4 mg ZA dosing group demonstrated an improvement in the time to first SRE for prostate cancer (HR, 0.67; 95% CI, 0.49-0.91; P = .011; and for other solid tumors (HR, 0.73; 95% CI, 0.55-0.96; P = .023; P-values not adjusted for multiple significance testing).[25] In a study of patients

TABLE 1 Mechanisms of action for antiresorptive agents

Agent	Name (administration)	Mechanism of action
Bisphosphonates (non–nitrogen-containing)	Clodronate (oral)[a]	Metabolized inside of osteoclasts into nonhydrolyzable ATP causing apoptosis[72,73]
Bisphosphonates (nitrogen-containing)	Zoledronic acid (IV) Pamidronate (IV) Ibandronate (IV or PO) Alendronate (PO) Risedronate (PO)	Bind to bone mineral and are incorporated into bone, then internalized by osteoclasts to cause apoptosis by inhibiting farnesyl pyrophosphate synthase (FPP) in the mevalonate pathway, preventing the formation of two metabolites (farnesol and geranylgeraniol) that are involved in protein attachment to cell membranes and protein-protein interactions that are essential for osteoclast function and survival[73,74]
RANKL inhibitor	Denosumab (SC)	Selectively inhibits RANKL which is necessary for osteoclast formation, function and survival[11]

Abbreviations: PO, oral; IV, intravenous; SC, subcutaneous.
[a] Not approved for use in the US.

with multiple myeloma or metastatic breast cancer (1,648 patients) ZA was noninferior to pamidronate.[26] ZA is administered by intravenous (IV) infusion every 3-4 weeks and is excreted by the kidney. Dosing is adjusted by renal function based upon calculated creatinine clearance. Side effects include renal toxicity, acute phase reactions such as occasional fever or flu-like syndrome, electrolyte abnormalities, and osteonecrosis of the jaw (ONJ).[25] Based on the design of the ZA clinical trials, it is unknown whether more than 1 year's administration of ZA is beneficial.[25] The optimal duration of bisphosphonate therapy remains unknown. In summary, bisphosphonates are effective at decreasing the risk of first SRE. Acute phase reactions and the potential for renal toxicity are important side effects that may occur. Furthermore, approximately one third of patients remain at risk for SREs.

Development of denosumab

In the 1990s, transgenic mice were generated to investigate the biological function of osteoprotegerin (OPG). Mice that overexpressed OPG exhibited increased bone density and a decreased number of osteoclasts. This discovery led to the identification of RANKL, which binds to OPG, and eventually to the development of denosumab, a fully human IgG2 monoclonal antibody that selectively inhibits RANKL. Although denosumab and naturally occurring OPG are alike in that both inhibit RANKL, denosumab has a significantly longer half-life.[27] It interrupts the interaction between RANKL and its receptor RANK on osteoclasts and osteoclast precursors, leading to osteoclast inhibition and thereby prevents osteoclast-mediated bone destruction.[11] Denosumab's novel mechanism of action and unique pharmacology make it a potent anti-resorptive agent. Additionally, being a fully human monoclonal antibody, it is cleared by the reticuloendothelial system, minimizing potential interactions with other therapeutic agents. There have been no reported cases of neutralizing antibodies.

Phase 2 trials of denosumab demonstrated a rapid decline in serum and urine markers of bone turnover within the first week following a single subcutaneous (SC) dose of denosumab, and the effects are reversed after stopping treatment. Denosumab given at dosing intervals of 120 mg every 4 weeks (Q4W), was determined to be the optimal dose for the prevention of SREs based upon a reduction in bone turnover markers such as urine N-terminal telopeptide (NTx).[28,29] The half-life of denosumab is approximately 25-30 days.[30] The pharmacokinetics of denosumab are not influenced by race, age, sex, or weight.[30] Because denosumab is not cleared through the kidney, dose adjustments based on renal function are not required.

Patients with advanced cancer

The phase 3 SRE trials enrolled > 5,700 patients in 3 identically designed international, double-blinded, double-dummy trials, comparing the safety and efficacy of denosumab 120 mg SC to ZA 4 mg IV Q4W. SREs were collected according to the standard definition: fracture, surgery, radiation, or cord compression. Skeletal surveys were performed every 12 weeks, and other standard radiographic assessments (eg, CT, MRI, bone scan, PET scan) were performed according to standard care. Independent central radiological review was blinded.

Results showed that denosumab was superior to ZA in decreasing time to first SRE in patients with breast cancer by 18% (HR, 0.82; 95% CI, 0.71-0.95; $P = .01$; 2,046 patients) and prostate cancer by 18% (HR, 0.82;

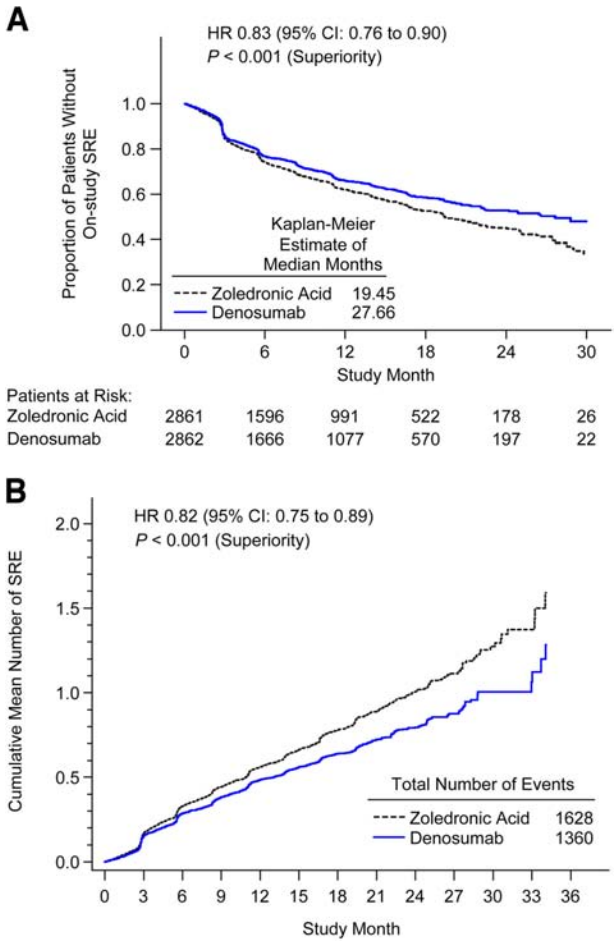

FIGURE 2 Time to skeletal-related event (SRE). Panel A, the estimated time to first on study SRE. Panel B, the time to first and subsequent on study SRE for events occurring at least 21 days apart (*P* adjusted for multiplicity). Both panels show the combined analyses of 3 identically designed phase 3 studies of patients with bone metastases secondary to advanced breast cancer, prostate cancer, and other solid tumors who were treated with denosumab (120 mg Q4W) or zoledronic acid.[34]
Abbreviations: CI, confidence interval; HR, hazard ratio; SRE, skeletal-related event; Q4W, every 4 weeks. Reprinted from Eur J Cancer. (2012) A. Lipton, K. Fizazi, A.T. Stopeck, et al. Superiority of denosumab to zoledronic acid for prevention of skeletal-related events: A combined analysis of 3 pivotal, randomized, phase 3 trials, Copyright (2012) with permission from Elsevier.

95% CI, 0.71-0.95; $P = .008$; 1,901 patients). In the third study, denosumab was noninferior to ZA in other solid tumors and multiple myeloma, reducing the risk of a first SRE by 16% (HR, 0.84; 95% CI, 0.71-0.98; noninferiority $P = .0007$; superiority $P = .03$ unadjusted, and .06 adjusted for multiplicity; 1,776 patients).[31-33] A prespecified, combined analysis of all 3 trials demonstrated a 17% reduction in the risk of first on-study SRE (HR, 0.83; 95% CI, 0.76-0.90; $P < .001$; Figure 2) and a delay in the time to first on study SRE of 8.2 months in patients receiving denosumab compared with ZA.[34]

Pain and analgesic use were also evaluated in these trials. A pooled analysis of all 3 trials demonstrated a significant delay in the median time to pain progression in denosumab-treated patients with no or mild pain at baseline (1.8 months, $P = .0002$) and a significant delay in clinically meaningful increase in pain in this group of patients (1.5 months, $P = .002$). Also, a significantly lower proportion of denosumab-treated patients required strong opioid analgesia across study visits.[35]

Overall survival (OS) was similar in all 3 trials. In the solid tumor and multiple myeloma study, when patients were stratified by tumor type, a post hoc analysis demonstrated decreased OS in denosumab-treated patients with multiple myeloma. As this was a retrospective analysis in a small subset of patients, it is unclear if the observed imbalance in known predictive factors could explain this difference. A randomized, controlled trial is underway to determine the efficacy and safety of denosumab for patients with multiple myeloma.[36] Currently, denosumab is not approved in patients with multiple myeloma in the United States. Conversely, this post-hoc analysis demonstrated a prolonged OS with denosumab in the large subset of patients with non-small-cell lung cancer (HR, 0.78; 95% CI, 0.65-0.94; $P = .01$; 702 patients), in the context of balanced prognostic factors.[37] No conclusions can be made here regarding OS, but this finding has sparked interest in further investigation of denosumab to prolong survival for patients with lung cancer in prospective clinical trials.

Safety

Hypocalcemia

Combined data from the 3 head-to-head clinical trials showed that adverse events of hypocalcemia were reported in 9.6% of patients receiving denosumab and 5.0% receiving ZA. Hypocalcemia was more common in the first 6 months of denosumab treatment than in subsequent time periods.[38] Severe hypocalcemia (albumin-corrected serum calcium < 7 mg/dL or < 1.75 mmol/L) occurred in 3.1% of patients treated with denosumab compared with 1.3% of patients treated with ZA.[39] There were no fatalities in the controlled situation of a clinical trial, but severe hypocalcemia has been reported in the post-marketing setting, in some cases with symptoms, including rare fatal cases.[39] As with any bone-targeted therapy, preexisting hypocalcemia should be corrected prior to denosumab treatment.[39]

The importance of adhering to recommended calcium and vitamin D supplementation was demonstrated by an ad hoc analysis of combined data from the 3 denosumab

TABLE 2 Supplementing calcium and vitamin D: selected pearls

1. Inquire about other dietary supplements.
2. Recommendations for calcium usually refer to elemental calcium, consult label (eg, 1,000 mg of calcium carbonate is ~400 mg of elemental calcium).
3. Oral calcium doses over ~2,000 mg/day may not be tolerated due to nausea and constipation.[75]
4. If giving > 500 mg calcium/day, divide doses to increase absorption.
5. Calcium carbonate is
   Better absorbed on a full stomach;
   Poorly absorbed with proton pump inhibitors or H2 blockers;
   Less expensive than calcium citrate.
6. Calcium citrate is
   Absorbed with or without food;
   More expensive than calcium carbonate.
7. An 8 oz glass of fortified milk has approximately 300 mg of calcium and 100 IU of vitamin D.
8. Vitamin D dosing frequency may not be important – 1,500 IU daily = 10,500 weekly = 45,000 IU monthly
9. Vitamin D deficiency is common and should be corrected for good calcium homeostasis: 50,000 IU QW x 8 wks or 6,000IU/day (of vitamin D2 or D3), then maintenance therapy of 1,500–2,000 IU/day.[76]
10. Common vitamin D formulations
    Cholecalciferol is vitamin D_3 400 IU, 800 IU, 1000 IU, 2000 IU, 5000 IU, 10,000 IU, 50,000 IU;
    Ergocalciferol is vitamin D_2 (often plant derived); doses are 400 IU, 5000 IU or 8000 IU/mL (liquid);
    Calcitriol is the vitamin D formulation to consider with renal disease;
    Calcidiol is the vitamin D formulation to consider with hepatic dysfunction.

SRE trials comparing denosumab-treated patients who received the recommended calcium and vitamin D supplementation with those who did not. Hypocalcemia was reported in 8.7% (213) of patients who reported taking the recommended supplementation compared with 15.8% (60) of patients who did not report taking supplemental calcium and vitamin D.[38] While post hoc analyses must be interpreted with caution, these results suggest that some risk of severe hypocalcemia may be mitigated by adherence to recommended calcium and vitamin D supplementation (Table 2).

Other electrolyte disturbances identified in the randomized clinical trials include severe hypophosphatemia (serum phosphorus < 2 mg/dL or < 0.6 mmol/L), which occurred in 15.4% of patients treated with denosumab and 7.4% of patient treated with ZA.[39]

Osteonecrosis of the jaw

ONJ was assessed in the denosumab clinical trials as an area of exposed bone in the jaw persisting for > 8 weeks in patients without prior craniofacial radiation to the jaw. This definition is consistent with guidelines issued by the American Association of Oral and Maxillofacial Surgeons.[40] Over the 2-year study period, ONJ in both denosumab and ZA treatment groups occurred after a median of 14 months (range, 4-30 months), and the rate of ONJ was not significantly different between treatment groups (denosumab 1.8%, ZA 1.3%; $P = .13$).[41] Resolution of ONJ occurred in 36.0% of patients (40.4% denosumab, 29.7% ZA). Tooth extraction was the predominant oral factor associated with the development of ONJ, reported in 61.8% of patients who developed ONJ on study, as was poor oral hygiene. This finding emphasizes the importance of assessing oral health and preventive dentistry prior to initiating therapy.

The incidence of ONJ was higher with longer duration of exposure, with a patient-year adjusted incidence of 1.1% during the first year of treatment and 4.1% thereafter (median overall exposure 14.9 months; range, 0.1-67.2). The median time to ONJ was 20.6 months (range, 4-53).[39] As ONJ was not identified as a risk factor in patients receiving bisphosphonates until the post-marketing setting, the estimated incidence of ONJ after longer exposure periods is based upon retrospective data with these drugs. A recent independent meta-analysis (10,380 patients) suggested a mean weighted prevalence of 8.6% (95% CI, 3.4-13.9) with ZA when used in the metastatic-cancer setting.[42]

In summary, denosumab appeared to be well tolerated regardless of tumor type with similar safety profiles across the 3 SRE trials.

Cost

The financial burden of SREs on the US medical system is significant. Based upon data from a Medicare/Commercial claims database, the mean 2009 inpatient estimated costs due to an SRE for bone surgery are $31,016-$42,094, costs for a pathological fracture are $22,390-$26,936 and costs for spinal cord compression are $43,691-$59,854.[22] Cost analyses of antiresorptive agents have yielded conflicting results due to differences in assumptions.[43-45] It should be noted that costs analyses may not reflect the true cost to society, such as lost productivity/wages for the patient and/or the caretaker.

Other patient populations

Cancer treatment-induced bone loss

Hormone-ablative cancer therapies are a mainstay of estrogen receptor-positive breast cancer and hormone-sensitive prostate cancer. Because estrogen plays a key role in main-

taining bone density, patients receiving hormone-ablative therapies may suffer bone loss and be more susceptible to fracture. Denosumab (60 mg Q6M) was evaluated in 2 placebo-controlled, phase 3, Hormone Ablation Bone Loss Trials (HALT) in patients with breast (252 patients) and prostate cancer (1,468 patients).[46-47] In patients with breast cancer who were receiving adjuvant aromatase inhibitor (AI) therapy, denosumab increased bone mineral density (BMD) at 12 and 24 months regardless of the duration of AI therapy.[46,48] It also increased BMD and reduced fracture risk in men with prostate cancer who were receiving androgen-deprivation therapy.[47] The drug is approved for increasing bone mass in women at high risk for fracture receiving adjuvant AI therapy for breast cancer and men at high risk for fracture receiving androgen deprivation therapy for non-metastatic prostate cancer.[49] There are several ways that "high risk" can be defined (eg, history of fracture, age, corticosteroid use).[50] Because no universal definition exists, it is at the discretion of the health care provider to ultimately determine who is considered at high risk for fracture.

Nonmetastatic prostate cancer

Several cancer studies have evaluated whether the addition of bone-targeting agents to standard adjuvant therapy could prevent or delay bone metastases.[51] Recently, this antitumor hypothesis was tested in a study of men with castration-resistant prostate cancer with prostate-specific antigen (PSA) doubling time of ≤ 10 months and/or a PSA ≥ 8 ng/mL and no evidence of bone metastases at study entry. Denosumab (120 mg Q4W) was successful at delaying the time to bone metastasis or death by 4.2 months in the overall population (Figure 3)[52] and by 7.2 months in a post hoc analysis of patients at high risk of bone metastases based on PSA doubling time ≤ 6 months.[53] The study was not designed to detect a difference in OS, because once patients developed bone metastases they went off study and received various systemic therapies for their disease. The incidence of ONJ over time was similar to that seen in the 3 SRE pivotal trials. The drug is not approved in the US for this patient population.

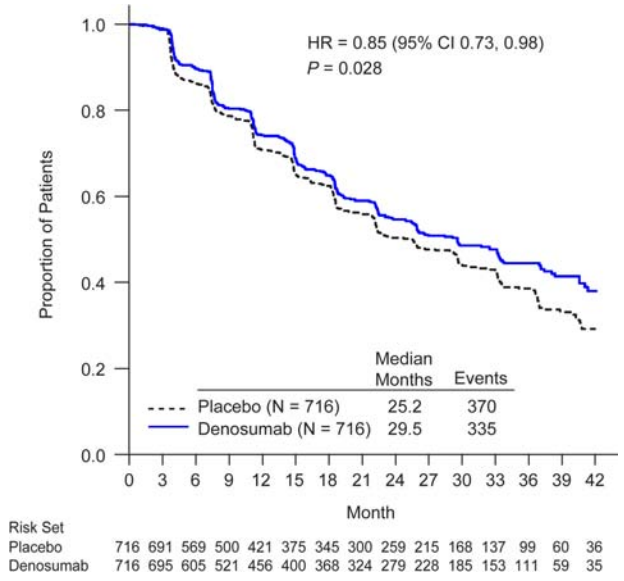

FIGURE 3 Prolongation of bone metastasis-free survival. The estimated time for the prolongation of bone-metastasis-free survival for denosumab (120 mg Q4W) compared with placebo in men with castration-resistant prostate cancer without bone metastasis at baseline.[52]
Abbreviations: CI, confidence interval; HR, hazard ratio; SRE, skeletal-related event; Q4W, every 4 weeks.
Reprinted from Lancet, Vol 379, M.R. Smith, F. Saad, R. Coleman, et al. Denosumab and bone-metastasis-free survival in men with castration-resistant prostate cancer: results of a phase 3, randomised, placebo-controlled trial, pages 39-46, Copyright (2012) with permission from Elsevier.

Trials in progress

Giant cell tumor of bone

GCTB is a rare, locally aggressive, primary osteolytic bone tumor occurring most commonly in the long bones of young adults. It represents 3%-5% of primary bone tumors in the US. Although considered benign, GCTB tends to recur after surgical resection and can metastasize in rare instances, most commonly to the lung. GCTB lesions are composed of osteoclast-like giant cells that express RANK and stromal cells that express RANKL, providing strong rationale for examining denosumab as a potential treatment option. In a phase 2, open-label proof-of-concept study, denosumab was associated with a tumor response in 86% of GCTB patients.[54] A second phase 2, multicenter, open-label study is underway to further evaluate the safety and efficacy of denosumab in patients with GCTB. Interim analysis results showed a safety profile consistent with that observed in the SRE trials and clinical benefit, both in preventing disease progression in patients with surgically unsalvageable disease, and in delaying, eliminating, or reducing the scope of planned surgery. ONJ was reported in 3 (1.9%) patients and hypocalcemia was reported in 7 (4.4%) patients.[55]

Hypercalcemia of malignancy

HCM is a potentially life-threatening complication of bone metastasis, most commonly caused by the release of humoral factors from the tumor, such as parathyroid hormone-related protein (PTHrP) and less commonly 1,25-dihydroxyvitamin D (calcitriol). Other causes of HCM are tumor-induced bone osteolysis, which can cause bone calcium release into the circulation.[56] Bisphosphonates are approved for this indication, but patients can relapse or become refractory.

An ongoing phase 2, multicenter, open-label study is underway to evaluate the safety and efficacy of denosumab in patients with HCM who had not responded to recent IV bisphosphonates.[57] Interim analysis results showed that 12 of 15 patients (80%) achieved a response, defined as corrected serum calcium ≤ 11.5 mg/dL, and 10 of 15 patients (67%) had achieved a complete response, defined as corrected serum calcium ≤ 10.8 mg/dL.[58]

Nonmetastatic breast cancer

Breast cancer trials that have evaluated whether the addition of bone-targeted agents to standard adjuvant therapy could prevent or delay bone metastases have shown inconsistent results.[7,59] With regard to oral bisphosphonates, 2 randomized trials of oral clodronate in breast cancer patients showed a reduction in the occurrence of bone metastasis,[60,61] and another did not demonstrate a difference relative to the control group.[62] Also, three-year interim analysis results of the German Adjuvant Intergroup Node Positive (GAIN) study found no differences in disease-free survival (DFS) or OS in patients who received oral ibandronate relative to placebo.[63] Clinical trials of IV bisphosphonates are also somewhat inconsistent. The Austrian Breast Cancer and Colorectal Cancer Study Group Trial 12 (ABCSG-12) demonstrated a reduction in the risk of DFS in ovarian-suppressed premenopausal women with breast cancer who received ZA compared with patients who did not.[64] Yet in the Adjuvant ZA to Reduce Recurrence (AZURE) trial, a phase 3 open-label trial of 3,360 patient with early stage breast cancer, no significant differences in DFS, OS, or invasive DFS were detected between those who received ZA and standard (neo)adjuvant therapy and those who received standard adjuvant systemic therapy alone.[65] One subgroup analysis demonstrated improvements in invasive DFS ($P = .02$) and increased OS ($P = .04$, P values not adjusted for multiple significance testing) in women who were at least 5 years post-menopausal. However, ZA had no effect on distant skeletal recurrence, regardless of menopausal status.[65]

Preclinical evidence suggests that inhibition of RANKL may be a rational strategy to prevent bone and visceral metastases. In a preclinical mouse model, inhibition of RANK/RANKL signaling reduced skeletal tumor burden and improved survival.[66] It also reduced carcinogen- and hormone-induced tumor formation.[67,68] Recently, RANKL was shown to be potentially important for the mitogenic, paracrine effects of progesterone in the mammary gland.[69] Progesterone-receptor positive cells release RANKL in the presence of progesterone, which then activates, its receptor RANK on adjacent mammary epithelial cells, which can expand the normal mammary stem cell pool.[67,69] The same may occur with breast cancer stem cells, suggesting that RANKL inhibition could reduce the breast cancer stem cell pool, thereby reducing breast cancer risk.[70] A large phase 3, placebo-controlled study of denosumab as adjuvant treatment for women with high risk early breast cancer receiving neoadjuvant or adjuvant therapy (D-CARE), with an anticipated enrollment of 4,500 patients, is being conducted to evaluate whether denosumab can delay or prevent skeletal metastases and improve DFS and OS in women with early stage breast cancer.[71]

Conclusions

The goal for patients with metastatic cancer is, unfortunately, rarely cure. Extending life, while preserving quality of life is the goal of therapy. In patients with bone metastases, an integral part of preserving functional status is preventing SREs. Both denosumab and bisphosphonates delay and prevent SREs in patients with bone metastases. Denosumab is the stronger bone protective agent, which has been demonstrated in an integrated analysis of 3 large head-to-head trials. Its unique mechanism of action allows administration to patients regardless of renal and hepatic function. Prescribers need to be aware of the risks of hypocalcemia and ONJ and manage patients appropriately. Preclinical and clinical data are suggestive of antitumor effects, and ongoing new studies will evaluate the role of denosumab in other patient populations who may benefit from RANKL inhibition.

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