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REVIEW

Denosumab as Bone Modifying Therapy in Solid Tumors

Joanne E. Mortimer[1] and Sumanta Kumar Pal[2]

[1]Director Womens Cancers Program, Department of Medical Oncology and Experimental Therapeutics, City of Hope Comprehensive Cancer Center, Duarte, CA 91010, USA. [2]Division of Genitourinary Malignancies, Department of Medical Oncology and Experimental Therapeutics, City of Hope Comprehensive Cancer Center, Duarte, CA 91010, USA. Corresponding author email: jmortimer@coh.org

Abstract: For many solid tumors, bone is a common site of spread and one that compromises the quality of life of patients. The routine use of adjunctive intravenous bisphosphonates (IVBs) decreases skeletal related events such as fracture, hypercalcemia, spinal cord compression, and the need for palliative radiation therapy or orthopaedic stabilization. Denosumab has recently been approved as a bone modifying agent in oncology. This monoclonal antibody inhibits the receptor activator of nuclear factor kB ligand (RANKL), which mediates osteoclast differentiation, function and survival. In patient with bone metastases, Denosumab is at least equivalent to the IVBs. While the incidence of osteonecrosis of the jaw is similar to what has been reported with the IVBs, fever and pyrexia are not observed, and hypocalcemia and renal impairment are less frequent. We review the data leading to approval of denosumab as a bone-directed therapy in oncology and compare and contrast the efficacy and toxicity with intravenous bisphosphonates.

Keywords: denosumab, solid tumors

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Introduction

The development of bone-modifying agents in oncology is an example of how the successful partnership between clinician and laboratory scientists can enhance both our understanding of pathophysiology and improve patient care. The term "vicious cycle" has been used to describe the permissive environment in bone whereby tumor cells in the marrow secrete chemicals that stimulate osteoclast activity and osteoclasts in turn secrete chemicals that promotes cancer cell growth.[1] Cancer cells release substances such as PTHrP, IL1,6,8, PGE2, M-CSF and TNF which facilitate osteolysis and osteoclasts secrete BMP (bone morphogenic proteins), PDGF, FGFs, IGFs, and TFG-β which facilitate cancer cell growth.[2–4] Bone modifying agents can disrupt the vicious cycle. In cancer patients, the use of these agents has produced improvement in bone-specific and possibly cancer outcomes.

Bone metastases are common in advanced cancers and produce pain, spinal cord compression, hypercalcemia and the need for palliative radiation therapy and/or orthopedic surgery; complications categorized as skeletal related events (SREs). In patients with bone metastases, elevated markers of bone turnover, such as urinary N-telopeptide (NTx) predict for subsequent SREs and disease progression.[5,6] Agents that interrupt osteoclast function, such as the aminobisphosphonates, have successfully been used to decrease the incidence of skeletal related events and NTx may be a biomarker of the efficacy of such interventions.

Clodronate was one of the first aminobisphosphonates studied as a bone modifying agent in oncology.[7,8] However, clodronate has generally been replaced by pamidronate and zoledronate whose bone resorptive potency is significantly higher. In September, 1998 pamidronate was first approved as an adjunctive therapy for women with metastatic breast cancer to bone. The monthly administration of pamidronate for 1 year resulted in fewer "skeletal complications."[9] Over the subsequent decade zoledronic acid was added to the armamentarium of bone-modifying agents and the use of these therapies has expanded to include bone metastases from other primary cancer sites.[8,10] With the identification of effective therapies to maintain bone health, the potential use of these agents to minimize bone loss in postmenopausal women receiving adjuvant aromatase inhibitors and men undergoing androgen-deprivation therapy for prostate cancer is being explored.[11–14] Currently approved indications for the IVBs in Oncology include: malignant hypercalcemia, bone metastasis, and multiple myeloma.

Three factors which are important for osteoclastogenesis include: receptor activator of nuclear factor kB (RANK) which expressed on the surface of osteoclasts, and RANK ligand (RANKL), and osteoprotogerin (OPG) which are expressed by osteoblasts and marrow stroma. In normal healthy bone the ratio of RANKL/OPG detemines to the balance between new bone formation and bone resorption. The production of PTHrP, IL6 and IL11 increase the expression of RANKL in osteblasts and promote bone resorption. Denosumab is a humanized antibody that inhibits the receptor activator of nuclear factor kB ligand (RANKL), an important mediator of osteoclast differentiation, function and survival.[15] In the United States, denosumab is approved for the management of osteoporosis and bone metastases secondary to solid tumors. In Europe, denosumab is also approved for the maintenance of bone health in men with prostate cancer treated with androgen deprivation therapy. As we develop experience using this new bone modifying agent with a mechanism of action unique from the bisphosphonates, we are likely to continue to unravel the complex biology of bone metastases. This paper reviews the data leading to the approval of denosumab in the management of solid tumors and compares those results with those of the IVBs. A summary of the randomized trials that compared denosumab with zoledronic acid are summarized in Table 1.

Breast Cancer

Metastatic disease to bone

The use of intravenous bisphosphonates to decrease SREs in women with metastatic disease involving at least one bone site is well established.[9] Controlled trials demonstrate that 2 years of IVBs are superior to 1 year. The potential benefit of administering IVBs at longer intervals is currently being tested in controlled trials.[16] Because the half-life of zoledronic acid is 10 days and the terminal half-life is 10 years, alternatives to monthly administration are also under study.[16,17] Meanwhile the current ASCO guidelines

Table 1. Controlled trials of denosumab in solid tumors.

Population	Endpoints	Design	Findings
Bone metastases breast cancer STOPECK[1]	1. T to 1st SRE (non-inferiority) 2. T to 1st SRE (superiority) T to 1st and subsequent SRE (superiority)	Randomized Phase III double blind, double dummy Zoledronate 4 mg IV q4wk (n = 1020) vs. Denosumab 120 mg q4wk (n = 1026)	Denosumab equivalent to ZA And was more efficacious than zoledronic acid in delaying 1st or subsequent SRE on study.
Bone metastases castrate resistant prostate cancer FIZAZI[2]	1. T to 1st SRE (non-inferiority) 2. T to 1st SRE (superiority) T to 1st and subsequent SRE (superiority)	Randomized Phase III Zoledronate 4 mg IV q4wk (n = 951) vs. Denosumab 120 mg q4wk (n = 950)	Denosumab equivalent to ZA And was more efficacious than zoledronic acid in delaying 1st or subsequent SRE on study.
Treatment and prevention of bone loss with hormone ablation in prostate cancer GnRH agonist (90%) or orchiectomy (10%) SMITH[3]	1. % change in LS BMD at 2 yr 2. % change in femoral neck and hip BMD at 24 mo.,% change in femoral neck and hip BMD, new fx at 36 mo.	Randomized Phase II double blind Placebo (n = 734) vs. Denosumab 60 mg q 6 mo × 3 yr (n = 734)	↑ LS BMD at 24 mo (+5.5% vs. −1.0%) Dec vertebra fractures at 36 mos.1.5% with denosumab vs. 3.9% placebo
Bone metastases non-breast, prostate or myeloma (7% of pts) HENRY[4]	1. T to 1st SRE (non-inferiority) 2. T to 1st SRE (superiority) T to 1st and subsequent SRE (superiority)	Randomized Phase III double blind, double dummy Zoledronate 4 mg IV q4wk (n = 951) vs. Denosumab 120 mg q4wk (n = 950) *Zometa dose adjusted for renal function	Denosumab equivalent to ZA

Notes: [1]Stopeck AT, Lipton A, Body J-J, et al. Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: a randomized, double-blind study. *Journal of Clinical Oncology*. Dec 10, 2010;28(35):5132–9.
[2]Fizazi K, Carducci M, Smith M, et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. *The Lancet*. 2011;377(9768):813–22.
[3]Smith MR, McGovern FJ, Zietman AL, et al. Pamidronate to prevent bone loss during androgen-deprivation therapy for prostate cancer. *N Engl J Med*. Sep 27, 2001;345(13):948–55.
[4]Henry DH, Costa L, Goldwasser F, et al. Randomized, double-blind study of denosumab versus zoledronic acid in the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma. *Journal of Clinical Oncology*. Mar 20, 2011;29(9):1125–32.

recommend that clinic judgment should guide the continued administration of IVBs until the patient's medical condition declines.[18]

In patients with bone metastases, the magnitude of decline in NTxs with denosumab is similar or possibly greater than zoledronic acid. In women who have received zoledronic acid, further decrease in NTx has been observed when patients have been switched to denosumab, suggesting that some individuals may derive more benefit from denosumab than zoledronic acid.[19,20] Denosumab was compared to zoledronic acid in 2,046 women with metastatic disease and at least one site of bone metastases and no prior exposure to IV bisphosphonates. This double-blind study randomized women to either denosumab 120 mg subcutaneously or zoledronic acid 4 mg IV every 4 weeks. The primary endpoint of the study was the demonstration of non-inferiority in the time to first on study SRE. Secondary endpoints included superiority of time to first on study SRE, and time to first and subsequent on study SRE. The primary endpoint was achieved; denosumab was found to be non-inferior to zoledronic acid. For the secondary endpoints, denosumab was shown to be superior. Compared to zoledronic acid, denosumab significantly delayed the time to first SRE on study by 18% ($P = 0.01$) and reduced the risk of subsequent SREs by 23% ($P = 0.001$).[20]

ASCO has recently revised their recommendations for the use of bone modifying agents in breast cancer and the panel concluded that the currently available data are insufficient to recommend one agent over another.[18]

Bone loss from aromatase inhibitors in postmenopausal women

In postmenopausal women who have osteopenia prior to institution of an aromatase inhibitor, the addition of an intravenous bisphosphonate every 6 months has been show to improve bone density. The Z-FAST and ZO-FAST trials tested the use of zoledronic acid in postmenopausal women who were to receive adjuvant letrozole. Women whose pre-treated BMD was >–2.0 were randomized to receive zoledronic acid 4 mg every 6 months or no bone therapy unless their T-score fell below –2.0 after starting treatment. After 36 months, the women assigned "up front" zoledronic acid demonstrated an improvement in BMD without demonstrable difference in bone fractures was not. Of interest, a significant improvement in progression free survival was also observed with early institution of zoledronic acid.[21]

A randomized double-blind placebo control trial of denosumab was conducted in 252 women with early stage breast cancer who were treated with an adjuvant aromatase inhibitor. Denosumab 120 mg was administered subcutaneously for 4 doses. The primary endpoint of the trial was the percent change in bone mineral density at 12 months compared to baseline. Secondary endpoints were changes in BMD of the spine and 6 months and the change in total hip and femoral neck at 6 and 12 months. The primary and secondary endpoints were achieved, demonstrating improved BMD with denosumab at all time points. During the 24 month study period, vertebral fractures were not observed, but 8 patients in each arm developed a non-vertebral fracture. This study was not designed to address cancer-specific outcomes, but survival was comparable in both groups.[22]

Bone loss from LHRH agonists with tamoxifen or anastrozole in premenopausal women

Intravenous zoledronate has also been used to prevent bone loss in women with early stage breast cancer receiving adjuvant endocrine therapy. The Austrian Breast and Colorectal Cancer Study Group addressed the use of IVB in ABCSG 12. This trial employed a 2×2 factorial design to test the impact of anastrozole and zoledronic acid in premenopausal women with early stage hormone receptor positive cancers. Patients receiving an LHRH agonist were randomized to receive either tamoxifen or anastrozole with a second randomization to zoledronic acid 4 mg q 6 mo × 6 or placebo. Over 1800 women enrolled in this trial. The preliminary data analysis with a median follow-up of 47.8 months found no difference between anastrozole and tamoxifen. However, an improved disease free survival was observed for those treated with zoledronic acid, both in combination with tamoxifen and anastrozole.[14]

Studies using denosumab in the adjuvant setting are currently on-going.[23]

Prostate Cancer

Metastatic disease to bone

The role of bisphosphonate therapy has been well established for metastatic castration-resistant prostate cancer (mCRPC). Saad et al reported a randomized study in which 643 patients with CRPC received either (1) zoledronic acid at 4 mg intravenous every 3 weeks, (2) 8 mg initially followed by 4 mg intravenous every three weeks, or (3) intravenous placebo every 3 weeks for a total duration of 3 months.[24] A total of 38%, 28% and 31% of patients completed a planned 15 months of therapy. Patients treated with zoledronic at 4 mg intravenous every 3 weeks had an improved time to first SRE (not reached vs. 321 days; $P = 0.011$); interestingly, no difference was seen in time to first SRE in those patients receiving the 8/4 schedule as compared to placebo (363 days vs. 321 days; $P = 0.491$). These results led to the incorporation of zoledronic acid as an adjunctive treatment in patients with mCRPC.[25]

Recently, denosumab has emerged as an alternative bone-directed therapy for patients with mCRPC. The potential utility of denosumab was first outlined in a randomized, phase II study enrolling 111 patients, amongst whom 50 patients had mCRPC.[26] Patients had 1 or more bone lesions and had urine N-telopeptide levels greater than 50 nM despite the use of intravenous bisphosphonate therapy. At the time of study entry, patients were randomized to either continue bisphoshonate therapy every 4 weeks, denosumab 180 mg subcutaneous every

4 weeks, or densoumab 180 mg every 12 weeks. At roughly 13 weeks after study initiation, more than 69% of patients receiving denosumab had a reduction in N-telopeptide to <50 nM, as compared to just 19% of the zoledronic acid treated population. These results provided the first indication of a potential benefit of denosumab as compared to zoledronic acid.

Data from a phase III study comparing these agents head-to-head has since been reported.[27] In this effort, 1,904 patients were randomized in a 1:1 fashion to receive either zoledronic acid 4 mg intravenous every 4 weeks (plus subcutaneous placebo) or denosumab 120 mg subcutaneous every 4 weeks (plus intravenous placebo). The primary endpoint of the study was time to first on-study SRE. Ultimately, the median duration of protocol therapy was 12.2 months with denosumab as compared to 11.2 months with zoledronic acid. Time to SRE was improved with denosumab therapy (20.7 months vs. 17.1 months, $P = 0.0002$ for non-inferiority, $P = 0.008$ for superiority.

Androgen deprivation therapy

In men undergoing androgen deprivation therapy for prostate cancer, the IVBs have been shown to prevent and even decrease bone loss.[13]

A double blind placebo controlled trial was conducted in 1,468 men undergoing androgen deprivation therapy for prostate cancer.[28] The primary endpoint of the trial was the percent change in lumbar spine BMD from baseline to 24 months. Secondary endpoints were the change in BMD of the femoral neck and total hip at 24 months and at all 3 sites at 36 months. Denosumab was administered at a dose of 60 mg every 6 months throughout the study period. Significant improvement in BMD was observed at 24 month and new vertebral fractures were significantly decreased in the treatment arm (1.5% vs. 3.9%; $P = 0.006$). It is of interest that radial fractures were decreased in men assigned denosumab. The radius is predominantly cortical bone and prior studies of IVB and SERMs in this population have not found a difference in radial fractures. This suggests that denosumab may have a unique advantage in this regard. This study was not designed to assess cancer-specific endpoints; all cause mortality in the treatment was identical to the control arm. In Europe, denosumab has been approved for treatment of bone loss associated with androgen deprivation.

Other Solid Tumors

The IVBs have an established role in preventing SREs in patients with a variety of solid tumors.[8,10]

A double blind, double dummy trial was conducted in 890 patients with bone metastases from cancers other than breast, prostate or myeloma. Identical to the aforementioned trial in breast cancer, the primary endpoint was to demonstrate non-inferiority in time to first SRE on study with secondary endpoints of superiority in time to development of first SRE while on study and time to first or subsequent SRE on study. Both drugs were administered monthly using denosumab 120 mg subcutaneously and zoledronic acid 4 mg IV. Denosumab was found to be non-inferior to zoledronic acid. Unlike the trials in advanced breast cancer and castrate resistant prostate cancer trials, superiority was not demonstrated.[29]

Toxicity of Denosumab

The toxicities reported from trails comparing denosumab to zoledronate are summarized in Table 2.[20,27,30,31] Pyrexia and fever are recognized toxicities of the IVBs. These symptoms generally occur with the first administration of an IVB and last 2–3 days. Often patients experience muscle and joint discomfort as well. This toxicity has been attributed to increased levels of TNF-α and IL-s and has not been observed with denosumab.[32] Hypocalcemia, elevations in serum creatinine and renal failure are also reported more often with IVBs than denosumab. Osteonecrosis of the jaw (ONJ) is reported in 0.8%–12% of patients on IVBS.[33] In the randomized trials, the incidence of ONJ observed with denosumab is comparable to what has been reported with IVBs. The infectious complications reported in the controlled trials of denosumab in osteoporosis have not observed in the solid tumor trials.[22]

Discussion

In recent years, the oncology community has witnessed many advances in supportive care modalities. A direct reflection of this are the datasets that have been amassed for both zoledronic acid and denosumab, as discussed herein. Despite the large investment in comparative trials to juxtapose the efficacy and safety of

Table 2. Toxicities reported in solid tumor trials.[20,31,35,36]

	Denosumab	IV bisphosphonates
Nausea	28%–34.9%	26%–37.9%
Anemia	18.8%–37.6%	22.9%–36%
Fatigue	24%–29.5%	23%–32.0%
Constipation	17.3%–25%	20.2%–27%
Vomiting	20.8%–21.1%	20.8%–23.5%
Back pain	18.2%–32%	22.3%–30%
Asthenia	19.6%–25%	20.2%–25%
Anorexia	18.8%–28%	22.2%–29%
Pyrexia	15.8%	20.7%
Arthralgias	21%–24.5%	21%–28.7%
Diarrhea	22.6%	20.4%
Dyspepsia	21.8%	18.8%
Pain in extremity	20.0%–21%	21.9%, 21%
Headache	19.3%	21.1%
ONJ	1.1%–2%	1%–1.4%
Increased creatinine	3%–3.3%	4%–4.9%
Renal failure	0.2%–2.3%	2.5%–2.8%
Hypocalcemia	6%	13%

the two agents, the optimal choice between them is not obvious by any means. For instance, in patients with mCPRC, the aforementioned phase III data clearly indicate an improvement in time to first SRE with denosumab as compared to zoledronic acid. However, the utility of this endpoint is somewhat contentious—with the improvement in time to first SRE, is there any peripheral benefit in quality of life or pain-response? Also, it is unclear whether the methodologies employed in studies of bone-directed therapies mimic real life utilization of the agents. For instance, in the comparison of denosumab and zoledronic acid in mCRPC, skeletal surveys were conducted on intervals of 12 weeks. This could certainly affect the frequency of SREs detected, and perhaps more importantly, does not reflect common clinical practice.

The bar for approval of antitumor systemic therapies for metastatic prostate and breast cancer has continually been raised. A delay in progression-free survival (PFS) no longer appears to be sufficient for approval; rather, an improvement in OS has almost universally been mandated. It is likely that the threshold will similarly be raised over time for supportive care modalities, especially as data emerges regarding the potential antitumor effect of these agents. Studies are currently underway to specifically assess the antitumor effect of both bisphosphonates and denosumab.

Both the IVBs and denosumab inhibit bone resorption though their mechanisms of action are slightly different. The IVBs have a long half-life, while denosumabs effects are of shorter duration. How these differences will impact the management of bone metastases in oncology is only being realized. Ultimately, what may dictate utilization of either intravenous bisphosphonates or denosumab is the cost associated with these therapies. With an increasing burden on health care systems globally, there is a demand for cost-effectiveness studies to aid in negotiating such decisions. It is estimated that the cost per skeletal complication avoided with zoledronic acid therapy is approximately US$12,300.[34] Similar projections for denosumab would offer a useful comparison for both patients and payers.

Disclosure

Author(s) have provided signed confirmations to the publisher of their compliance with all applicable legal and ethical obligations in respect to declaration of conflicts of interest, funding, authorship and contributorship, and compliance with ethical requirements in respect to treatment of human and animal test subjects. If this article contains identifiable human subject(s) author(s) were required to supply signed patient consent prior to publication. Author(s) have confirmed that the published article is unique and not under consideration nor published by any other publication and that they have consent to reproduce any copyrighted material. The peer reviewers declared no conflicts of interest.

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