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INVITED REVIEW

Prostate Cancer

Bone targeted therapies for the prevention of skeletal morbidity in men with prostate cancer

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Men with prostate cancer suffer substantially from bone-related complications. Androgen deprivation therapy itself is a cause of loss of bone mineral density and is associated with an increased incidence of osteoporotic fractures. In advanced disease, bone is by far the most common site of metastasis. Complications of bone metastases prominently include pain and the potential for skeletal events such as spinal cord compression and pathologic fractures. Elevated osteoclast activity is an important aspect of the pathophysiology of both treatment-related osteoporosis and skeletal complications due to metastases. The osteoclast is therefore a therapeutic target. Denosumab is a fully human monoclonal antibody to receptor activator of nuclear factor-κ-B ligand that was designed to potently inhibit osteoclast activity and is the central focus of this review. Bisphosphonates, radiopharmaceuticals and systemically-active hormonal agents such as abiraterone acetate and enzalutamide have each been shown to improve skeletal morbidity in specific clinical situations. Denosumab is the only agent that has been shown to prevent osteoporotic fractures in men receiving androgen deprivation therapy and at elevated risk for fracture. It has also demonstrated superiority to the potent bisphosphonate zoledronic acid for the prevention of skeletal-related events in men with castration-resistant prostate cancer metastatic to bone. Efficacy and toxicity data will be discussed.

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INTRODUCTION

Skeletal complications are a potential direct or treatment-related hazard of prostate cancer. Men without bone metastases can be burdened by therapy itself as androgen deprivation leads to loss of bone mineral density (BMD) and an increased risk for osteoporotic fractures. Men with castration-resistant prostate cancer (CRPC) that does not yet involve bone are known to have substantial risk for the development of bone metastases at some point in the disease process. Those who do have bone metastases have an increased risk for pain or for skeletal events such as pathologic fractures or spinal cord compression due to epidural extension of tumor. Each of these clinical situations represents a potential point of therapeutic intervention for the prevention of skeletal morbidity and mortality.

These prominent and clinically-burdensome risks have led to considerable research related to the pharmacologic prevention of skeletal complications in men with prostate cancer. Given the important role that osteoclasts play in the pathogenesis of these processes, osteoclast inhibition is a rational strategy for bone targeted therapies in prostate cancer. The two approved classes of agents include the bisphosphonates and more recently, denosumab the monoclonal antibody to receptor activator of nuclear factor-kappa B (RANKL). Other molecular targets for bone-related systemic therapies under past or ongoing study have included cathepsin K,[1] endothelin A,[2,3] SRC[4–6] and hepatocyte growth factor (MET).[7,8] Anticancer agents not specifically targeted to bone such as abiraterone acetate and enzalutamide have also recently been shown to prevent skeletal complications, arguing that disease control is important to the prevention of skeletal events. Further, the radiopharmaceutical radium-223 represents a hybrid of anticancer therapy and bone-targeted therapy.

The role of denosumab in the prevention of skeletal morbidity in men with prostate cancer is a central focus of this review.

DENOSUMAB MECHANISM AND PHARMACOLOGY

Osteoclasts are tissue-specific macrophages that are responsible for bone resorption.[9] In physiologic bone remodeling, osteoclast-mediated bone resorption is in balance with new bone formation by osteoblasts. Osteoporosis can be the result of an excess of osteoclast activity relative to osteoblast activity. Distinct from their role in osteoporosis, osteoclasts can contribute to the pathophysiology of bone metastases through the resorption-mediated liberation of growth factors[10] that may stimulate tumor growth within the bone microenvironment. Bone turnover and osteoclast activity in particular are elevated in the presence of bone metastases.[11–13] The role of osteoclasts in these processes forms a basis for osteoclast inhibition as a therapeutic strategy.

RANK is a cell surface receptor on osteoclasts and is a central regulator of their maturation, activation and survival.[9] Denosumab is a fully human monoclonal antibody that is conceptually similar to osteoprotegerin, an endogenous decoy receptor for RANKL.[14] Denosumab potently (Kd 3×10^{-12} M) and specifically binds to

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RANKL, thereby competitively inhibiting RANK binding and downstream signaling. It is highly bioavailable at typical doses when given by subcutaneous injection. It suppresses markers of bone turnover (N-telopeptide) within hours, an effect that can persist for over 6 months in some clinical situations.[15] Typical of a monoclonal antibody, its plasma half-life is approximately 1 month with clearance rates similar to those of endogenous IgG.[16,17]

Denosumab has been the subject of broad study for both benign and malignant indications. In the non-cancer population, it has been shown to improve osteoporotic fracture risk in postmenopausal women with osteoporosis[18] and to improve BMD in men.[19] In the cancer population, it has been shown to improve BMD in women receiving aromatase inhibitor therapy for breast cancer[20,21] and to reduce fracture risk in men at high risk of fracture receiving androgen deprivation therapy (ADT) for prostate cancer. It has also been shown to reduce skeletal-related events (SREs; a composite endpoint that includes pathological fracture, spinal cord compression and surgery or radiation therapy to bone) in patients with a broad range of solid tumors metastatic to bone.[22–24] Finally, it has been shown to reduce or eliminate RANK-positive tumor cells in patients with giant cell tumor of the bone.[25,26] Cancer-related indications for denosumab are summarized in **Table 1**. Dose and frequency vary considerably by clinical indication (e.g. 60 mg every 6 months for osteoporosis, 120 mg every 4 weeks for cancer metastatic to bone).

In notable contrast to denosumab, bisphosphonates are pyrophosphate analogs that feature a central carbon bonded to two phosphate groups and two organic side chains. They adsorb to calcium phosphate (hydroxyapatite) crystals within new bone matrix and exhibit inhibitory effects on osteoclasts within the bone microenvironment. The relative potency of a given bisphosphonate is determined by the structure of the two organic side chains bonded to the central carbon atom. Zoledronic acid is the most potent available bisphosphonate. Its serum half-life is 146 h with renal elimination, but once incorporated in bone it persists there and can durably suppress markers of osteoclast activity and bone turnover in some clinical situations.

OSTEOPOROSIS

Osteoporosis is a prevalent comorbid condition among men in the age range typical for prostate cancer. In the general population, osteoporotic fractures cause considerable morbidity and mortality. One-fourth of all hip fractures occur in men,[27] with incidence rising steeply with age. It is within this context that ADT causes deleterious effects on bone health.

ADT for prostate cancer causes marked changes in the hormonal environment most notable for a drop in circulating androgens. As male estrogen production takes place through the aromatization of testosterone, ADT-induced severe hypogonadism reduces circulating estrogen levels as well. This leads to a loss of BMD[28] and is associated with an increased risk for clinical fractures.[29,30] For comparison, men in the general population gain BMD with age.[31] Selective estrogen receptor modulators raloxifene and toremifene has been shown to improve BMD in men receiving ADT,[32,33] an effect that can reasonably be taken to serve as proof of principle of the importance of estrogen to bone health in men.

BMD is an important marker of fracture risk, but is just one among a number of well-described risk factors. Meta-analyses have demonstrated the importance of a number of clinical factors including tobacco smoking,[34] personal history of fracture,[35] alcohol intake,[36] chronic glucocorticoid use,[37] parental history of fracture,[38] and rheumatoid arthritis.[39] Each of those factors is associated with elevated fracture risk independent of its effect on BMD. Risk of osteoporotic fracture in men rises markedly with age in the general population even as BMD rises modestly, arguing for the importance of clinical factors. Some, such as smoking status and history of glucocorticoid use can be easily assessed. Others such as frailty are more difficult to quantitate.

Given the comorbid hazards of osteoporosis and treatment-induced adverse effects, several classes of pharmacologic agents have been tested in men receiving ADT for prostate cancer. Bisphosphonate treatment of men receiving ADT has clearly and reproducibly been shown to improve BMD, a surrogate for fracture risk. BMD benefits have been demonstrated with alendronate,[39] pamidronate,[28,41] zoledronic acid,[42,43] and neridronate[44] Denosumab was studied in a trial that enrolled over 1400 men and is the only approved agent that has been shown to improve both BMD and fracture risk for men receiving ADT for prostate cancer.[45] The trials involving bisphosphonates each enrolled 21–112 participants and were not powered to study effects on the rate of fractures. The effect of bisphosphonates on fracture risk is therefore simply not known. It is notable that the BMD effects of osteoporosis-treatment doses of zoledronic acid and denosumab are similar (approximately 4% gain in lumbar spine BMD at 12 months[43,45,46]).

Denosumab was studied in a double-blind trial that randomized 1468 men receiving ADT for nonmetastatic prostate cancer to denosumab treatment (60 mg subcutaneously every 6 months) or to placebo.[45] Inclusion criteria required at least one of the following two risk factors for fracture: (i) age ≥70 years and (ii) low BMD (T score ≤1.0 at the lumbar spine, total hip or femoral neck). The primary endpoint was percent change in BMD at the lumbar spine at 24 months. Key secondary endpoints included incidence of new vertebral fractures and change in BMD at other sites. The trial was positive as the denosumab treatment group was found to have significantly improved 24 month

Table 1: Cancer-related indications and dose schedules for denosumab

FDA indication	*Dose (mg)*	*Frequency*	*Comments*
Prevention of SREs in patients with Bone metastases from solid tumors	120	Every 4 weeks	Note that benefit in men with metastatic prostate cancer has only been demonstrated after the development of castration resistance.[23] Denosumab is not indicated for the prevention of SREs in patients with multiple myeloma[22]
Treatment to increase Bone mass in men at high risk for fracture receiving ADT for nonmetastatic prostate cancer	60	Every 6 months	Enrolled men were at high risk due to age ≥70 years or low BMD (T-score <−1.0 at lumbar spine, total hip or femoral neck) or history of an osteoporotic fracture[45]
Treatment to increase Bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer	60	Every 6 months	Enrolled women had measured low Bone mass (T-score <−1.0 at lumbar spine, total hip or femoral neck).[21] The study was not powered to examine fracture prevention
Treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity	120	Every 4 weeks, with additional 120 mg doses on days 8 and 15 of the first month of therapy	

ADT: Androgen Deprivation Therapy; BMD: Bone Mineral Density; FDA: Food and Drug Administration; SRE: Skeletal-Related Events

BMD of the lumbar spine (5.6% gain *vs* 1.0% loss; $P < 0.001$) and a lower incidence of new vertebral fractures at 36 months (1.5% *vs* 3.9%; relative risk 0.38; 95% CI 0.19–0.78; $P = 0.006$).

Toremifene and raloxifene are selective estrogen receptor modulators that have been studied in men receiving ADT for prostate cancer. Each has been shown to improve BMD,[32,33] and toremifene has been shown in a large phase III study to reduce fracture risk.[47] One prominent adverse effect of toremifene was the observation of more frequent venous thromboembolic events (2.6% with toremifene *vs* 1.1% with placebo). Neither agent is approved for use in men with prostate cancer.

Given the availability of these agents and the data supporting their use in men with prostate cancer, screening and selection of treatment candidates is essential. Supplementation of calcium and vitamin D in all men receiving ADT is recommended by current National Comprehensive Cancer Network guidelines. A subset of those men will have risk sufficient to justify pharmacologic therapy. Appropriate candidates for therapy should be identified by predictive models that take clinical factors beyond BMD into account. The World Health Organization fracture risk assessment model FRAX (http://www.shef.ac.uk/FRAX/) is one such model. Clinical inputs include gender, age, height, weight, history of fracture, parental history of hip fracture, smoking status, use of glucocorticoids, daily consumption of at least 3 units of alcohol, rheumatoid arthritis and other causes of secondary osteoporosis. National Osteoporosis Foundation guidelines recommend the use of drug therapy to reduce fracture risk if 10 year risk exceeds either of two thresholds (>20% risk of major osteoporotic fracture or > 3% risk of hip fracture).[48]

Synthesis

ADT causes loss of BMD and is associated with an increased incidence of osteoporotic fracture. Osteoporosis therefore merits screening and management among men who receive ADT for prostate cancer. Measurement of BMD can aid risk assessment, but is not adequately sensitive in the absence of clinical factors. The online World Health Organization/FRAX fracture risk assessment tool is one method of more comprehensive risk assessment and is recommended by National Comprehensive Cancer Network guidelines. For those who merit treatment, denosumab is the only approved agent that is supported by level 1 evidence of fracture prevention. Several bisphosphonates have been shown to improve BMD and are also reasonable choices among treatment candidates.

CASTRATION-RESISTANT NONMETASTATIC PROSTATE CANCER

The natural history of advanced prostate cancer strongly features risk for metastases to bone. Recent phase III trials of systemic agents in men with metastatic CRPC have enrolled populations with 80%–90% baseline prevalence of bone metastases.[49-51] This propensity for the disease to metastasize to bone has led to efforts to prevent bone metastases in men who have not yet developed. Denosumab is the only agent that has been shown to delay the onset of bone metastases. No bone-targeted agent has been approved for the prevention of bone metastases. See **Table 2** for a summary of data related to osteoclast inhibition in men with prostate cancer.

Bisphosphonates have failed to demonstrate benefit for the prevention of bone metastases. Clodronate is a relatively weak bisphosphonate that was studied in a well-designed phase III trial that did not demonstrate a significant difference relative to placebo in time to first bone metastasis.[52,53] Zoledronic acid is more potent and was the subject of a phase III trial that closed early due to poor accrual and a lower than expected rate of bone metastases.[54] Analysis of the placebo group of that trial revealed that time to first metastasis was shorter in men with prostate-specific antigen (PSA) > 10 ng ml^{-1} (relative risk (RR) 3.18) and elevated PSA velocity (RR 4.34 for each 0.01 increase in PSA velocity).[54]

Denosumab was then examined in a randomized phase III trial that met its primary endpoint, but did not led to approval of the agent for this indication. The trial enrolled 1432 men with CRPC not metastatic to bone who were at elevated risk for bone metastases as indicated by short PSA doubling time (≤10.0 months) and/or an absolute PSA value ≥8.0 ng dl^{-1}. They were randomized 1: 1 to receive denosumab (120 mg) or placebo every 4 weeks. The primary endpoint was bone-metastasis-free survival. The trial was positive as denosumab significantly increased bone-metastasis-free survival by 4.2 months (29.5 *vs* 25.2 months; hazard ratio (HR) 0.85; 95% CI 0.73–0.98; $P = 0.028$). Overall survival (OS) did not differ between the study arms. To date, it is the only positive trial of an osteoclast targeted agent for this indication.

Regulatory review by the United States Food and Drug Administration Oncology Drug Advisory Committee led to a recommendation against approval of denosumab for metastasis prevention. According to the briefing document, the recommendation was based on several factors including the absence of an effect on OS, an uncertain effect on symptoms and quality of life and treatment-related risk for osteonecrosis of the jaw (ONJ).

CASTRATION-SENSITIVE PROSTATE CANCER METASTATIC TO BONE

Cancer control is important to the prevention of skeletal morbidity in men with prostate cancer. First-line ADT for metastatic prostate cancer produces responses commonly and often for durations measured in years. In this context, no bone-targeted agent has improved skeletal

Table 2: Osteoclast-targeted therapy for men with prostate cancer

Clinical setting	*Goal of treatment*	*Evidence*
Men who are receiving androgen deprivation therapy for prostate cancer and are at elevated risk for fractures	Decrease risk for osteoporotic (e.g. vertebral body or hip) fractures	Denosumab[45] improves bone mineral density and reduces fracture risk. Multiple bisphosphonates improve bone mineral density
Castration-resistant nonmetastatic prostate cancer	Prevent or delay the onset of bone metastases	Denosumab significantly delayed metastasis free survival,[79] but was not approved for this indication. Bisphosphonate trials were negative or closed early
Castration-sensitive prostate cancer metastatic to bone	Prevent or delay skeletal disease progression and/or skeletal-related events (SRE; compared to standard use starting at the time of castration-resistance)	Clodronate ineffective for primary endpoint, but found to improve overall survival. Zoledronic acid did not demonstrate benefit in a study that was closed early for administrative reasons. Denosumab not studied
Metastatic castration-resistant prostate cancer	Prevent or delay SREs	Zoledronic acid lengthens time to first SRE compared to placebo.[71] Denosumab lengthens time to first SRE compared to zoledronic acid.[23] Each is approved monthly for this indication

SRE: Skeletal-Related Event

outcomes for men with castration-sensitive prostate cancer metastatic to bone.

The comparably weak bisphosphonate clodronate was studied in 311 men starting or responding to first-line ADT. Clodronate produced no significant benefit in skeletal disease progression or prostate cancer death relative to placebo.[55] Long-term follow-up, however, revealed a significant OS benefit (8-year OS 22 vs 14%; HR for death 0.77, 95% CI 0.60–0.98, $P = 0.03$),[53] suggesting the potential for benefit with a more potent bone targeted agent.

The subsequent randomized placebo-controlled cooperative group trial CALGB 90202 was designed to assess early use of zoledronic acid for men with prostate cancer metastatic to bone. It enrolled men with castration-sensitive disease metastatic to bone and within 6 months of initiation of ADT and randomized them to zoledronic acid (4 mg every 4 weeks) or placebo until progression to CRPC. The trial was halted early due to withdrawal of drug supply by the corporate supporter. At the time it was halted, the trial had enrolled 645 of 680 planned participants and observed 284 of 470 anticipated SRE events. Primary analysis of this truncated study did not demonstrate significant delay in time to first SRE with early use of zoledronic acid (32.5 months with zoledronic acid vs 29.8 months with placebo; HR 0.96, 95% CI 0.76–1.22).[56]

Zoledronic acid is under study for men in this population in an additional phase III trial that has not yet reported its results (NCT00242567). The primary endpoint is skeletal-event-free survival at 18 months. Secondary endpoints include OS, SRE-free survival and multiple-event analysis of SREs over 3 years. Estimated enrollment is 550.

Synthesis

No bone-targeted agent has been convincingly shown to improve outcomes among men with prostate cancer metastatic to bone that is responding to first-line ADT. Clodronate significantly improved survival in a study that was negative for its primary endpoint. Early zoledronic acid was then studied in a large cooperative group trial that was halted early for administrative reasons and did not demonstrate benefit. Disease control is clearly a central aspect of the prevention of skeletal morbidity. Robust initial responses to first-line ADT make SREs less common and therapeutic benefit more difficult to demonstrate in this population. Denosumab has not been studied for the prevention of SREs in castration-sensitive disease.

It is important to note that United States and European regulatory approvals of zoledronic acid and denosumab are worded broadly enough to include the use of either agent in castration-sensitive prostate cancer metastatic to bone. These approvals were granted on the strength of the accumulated data from a number of clinical trials that together demonstrated benefits in patients with metastatic CRPC (detailed below) as well as with breast cancer or other solid tumors metastatic to bone. Despite this broadly-worded approval, current evidence does not support the use of either agent in men with prostate cancer metastatic to bone prior to the development of castration resistance.

METASTATIC CASTRATION-RESISTANT PROSTATE CANCER

CRPC metastatic to bone is clinically hazardous. Without osteoclast inhibition, the median time to first SRE is in the range of 11 months and approximately half of patients experience an event within 2 years.[57] CRPC metastatic to bone is an approved indication for monthly potent osteoclast inhibition, specifically with denosumab or zoledronic acid. After failures of less potent bisphosphonates clodronate[58] and pamidronate[59] in this population, zoledronic acid was the first agent to demonstrate evidence of benefit. When the denosumab and zoledronic acid were later compared directly, denosumab produced a significantly superior time to first SRE. Data from the positive trials will be reviewed.

Zoledronic acid was compared to placebo in a phase III randomized trial of 643 men with CRPC and asymptomatic to minimally symptomatic bone metastases. The trial initially included two dose levels of zoledronic acid (4 or 8 mg given every 3 weeks), but the higher dose was reduced to 4 mg after the observation of nephrotoxicity. The primary endpoint was the proportion of men who experienced one or more SRE. After 15 months of follow-up, 44% of the placebo group and 33% of the treatment group had experienced an SRE ($P = 0.02$). Median time to first SRE was also significantly improved with treatment (>420 vs 321 days; $P = 0.01$). Zoledronic acid did not improve OS.

Denosumab was later compared to standard-of-care zoledronic acid a phase III trial for men with CRPC metastatic to bone. A total of 1904 men were randomized to every 4 weeks treatment with denosumab (120 mg subcutaneous) or zoledronic acid (4 mg intravenous). The primary endpoint was time to first on-study SRE and was assessed for non-inferiority. Assessment for superiority was a secondary endpoint. The trial was positive as median time to first SRE was significantly longer with denosumab (20.7 vs 17.1 months; HR 0.82; 95% CI 0.71–0.95; $P = 0.0002$ for non-inferiority; $P = 0.008$ for superiority). Survival was not significantly different between the two arms of the trial.

It is notable that two additional similarly-designed phase III trials compared the two agents in patients with non-prostate cancers metastatic to bone. In 2046 women with breast cancer metastatic to bone, median time to first SRE was superior with denosumab (HR 0.82; 95% CI 0.71–0.95; $P = 0.01$ for superiority).[24] In 1776 patients with non-breast, non-prostate solid tumors or multiple myeloma involving bone, median time to first SRE was non-inferior with denosumab (HR 0.84; 95% CI 0.71–0.98; $P = 0.0007$). Survival did not differ between the study arms of any of the phase III trials comparing zoledronic acid and denosumab for cancers metastatic to bone.

Several lines of evidence suggest that denosumab inhibits osteoclast activity more potently than zoledronic acid. First, it produces superior median time to first SRE in two of the three trials discussed above.[23,24] Second, hypocalcemia is an on-target side effect that occurs more frequently with denosumab than with zoledronic acid (e.g. 13% vs 6% in one trial[23] and 10.8% vs 5.8% in another[22]). Third, one biomarker-driven trial examined the use of denosumab among patients with cancer involving bone and with elevated bone turnover despite treatment with zoledronic acid or pamidronate. Participants were randomized to continue bisphosphonate therapy or to switch to denosumab (180 mg subcutaneous every 4 weeks). N-telopeptide, a marker of osteoclast activity, normalized more frequently with denosumab than with control therapy (71% vs 29%; $P < 0.001$).[60]

Synthesis

Zoledronic acid and denosumab are each approved for use in this population to prolong time to first SRE. The relevant phase III trials showed that zoledronic acid offers a 5.6 month advantage over placebo and that denosumab offers a 3.6 month advantage over zoledronic acid. Thus, either agent is reasonable, but denosumab is superior in time to first SRE. Cost and availability are largely beyond the scope of this review, but may be important factors in clinical practice. Clinical and cost effectiveness analyses comparing the two agents have yielded varied results. Some have suggested that denosumab is not cost effective[61–63] relative to zoledronic acid, while others have suggested that it is cost effective.[64] In addition, it is anticipated that cost for zoledronic acid will be reduced by its patent expiration in 2013.

The dosing schedule of either agent is also a subject of some scientific and practical uncertainty. Zoledronic acid has been studied on an every 3 weeks schedule and on an every 4 weeks schedule, giving some flexibility of evidence-based dosing. Denosumab has been studied only as frequently as every 4 weeks; more frequent dosing is therefore not known to be safe. It is therefore important to note that denosumab dosing schedule may not align well with every 3 weeks chemotherapy dosing for patients receiving docetaxel or cabazitaxel. Strict evidence-based use would require dys-synchronous dosing weeks. More relaxed dosing of either agent (taxane every 4 weeks or denosumab every 6 weeks) could promote convenience, but with unknown impact on efficacy.

TOXICITIES OF OSTEOCLAST INHIBITION

Potent osteoclast inhibition is associated with several adverse class effects. The most prominent are hypocalcemia and ONJ. Incidence and severity of these and other side effects vary by dose and schedule and are generally more common with treatment designed to prevent SREs due to bone metastases. For example, the incidence of hypocalcemia was 13% with monthly denosumab to prevent SREs but was less than 1% with every 6-months denosumab to treat osteoporosis.[23,45] Side effects of monthly dosing are summarized in **Table 3**.

Hypocalcemia is common in response to either agent, but is most common with denosumab (13% with monthly denosumab and 6% with monthly zoledronic acid; $P < 0.0001$).[23] Most cases are asymptomatic, but some are symptomatic and require hospitalization for intensive calcium repletion. Management of hypocalcemia is dependent on the clinical situation. First, it is likely important that all patients are vitamin D replete prior to initiation of therapy. Testing of serum 25-OH vitamin D is easily accomplished and can afford an opportunity to replete levels.

ONJ is an uncommon but potentially-morbid complication of osteoclast inhibition that was observed after the introduction of potent bisphosphonates such as pamidronate and zoledronic acid.[65,66] Clinically, it presents as an exposed, non-healing area of bone. Risk factors identified in retrospective analyses prominently include invasive dental procedures after initiation of therapy, use of more potent agents and long duration of treatment.[67] Published guidelines recommend preventive and management strategies that prominently include dental consultation and the completion of all anticipated procedures prior to initiation of potent osteoclast inhibition.[68,69]

Table 3: Notable adverse effects in phase III trials of monthly dosing in advanced cancer[22-24]

	Zoledronic acid (%)	*Denosumab (%)*	*Comments*
Any adverse event	96-97	96-97	
Adverse event leading to treatment discontinuation	12-15	10-17	
CTCAE grade ≥3 adverse events	63-80	60-77	
Infectious adverse events	40-49	41-46	
Cumulative ONJ	1.3-1.4	1.1-2	
Hypocalcemia	3.4-6	5.5-13	Significantly more common with denosumab
New primary malignant disease	0.3-1	0.6-2	
Acute phase reaction	14.5-27	7-10	Significantly more common with zoledronic acid
Renal toxicity, any	4.9-8.5	3.3-4.9	
Renal toxicity, grade ≥3	2.2-2.8	0.4-2.3	

CTCAE: Common Terminology Criteria for Adverse Events; ONJ: Osteonecrosis of the Jaw

ONJ risk related to the two agents may be different based on their differing serum and bone half-lives. Zoledronic acid has a serum half-life measured in days, but is present in bone for years. Denosumab has a serum half-life on the order of 1 month, but has been shown to suppress markers of bone turnover in some clinical settings for as long as 6 months in the wake of a single dose. Clinical trial evidence for a distinction in ONJ risk based on these pharmacologic differences is lacking. In the trio of phase III trials comparing monthly treatment with denosumab to zoledronic acid, the incidence was 1%–2% without significant difference between arms.[70]

An important distinction between denosumab and zoledronic acid is the potential for nephrotoxicity with zoledronic acid. All bisphosphonates are potentially nephrotoxic. Zoledronic acid in particular was found to cause acute kidney injury consistent with acute tubular necrosis[55] in participants in early clinical study.[71] Current guidelines for its use seek to minimize this risk by lengthening infusion time to ≥15 min, reducing doses for stable creatinine clearance 30 and 60 ml min^{-1} and holding dosing for creatinine clearance < 30 ml min^{-1} or acutely declining renal function.[72] Nephrotoxicity due to denosumab has not been described.

One safety and efficacy concern particular to denosumab is the possibility of treatment-related immune dysfunction. RANKL and RANK are expressed by T-lymphocytes, B-cells and dendritic cells.[73,74] Denosumab-mediated inhibition of RANK signaling may therefore inhibit dendritic cell function and has been associated with a small but measurable increase in the number of infectious serious adverse events.[75] Sipuleucel T improves survival in men with metastatic CRPC, a therapeutic effect that is thought to depend on dendritic cell mediated antitumor immune effects. It is possible that these effects are blunted by concurrent or subsequent treatment with denosumab. Data to support or refute that theoretical concern are presently lacking.

It is notable that zoledronic acid is associated with a flu-like acute phase reaction that often features fever, malaise and myalgias. It is generally self-limited and resolves within 24–48 h.

Synthesis

Denosumab and zoledronic acid have similar but not identical toxicity profiles. Preventative dental work and vitamin D repletion are wise prior to the start of either therapy to avoid ONJ and hypocalcemia risks, respectively. Acute kidney injury and an acute phase reaction are each risks particular to zoledronic acid. The potential for suppression of dendritic cell function is a risk particular to denosumab. In patients with impaired renal function, denosumab is thought to be safe but has not been extensively studied.

OTHER AGENTS FOR THE PREVENTION OF SKELETAL MORBIDITY

The term SRE was created to refer to a group of bone-related clinical events (pathological fracture, spinal cord compression, surgery or radiation therapy to bone) that could be taken together as a composite endpoint for clinical trials of bone-targeted therapies. The pivotal trials that established zoledronic acid[71] and denosumab[23] for men with metastatic CRPC are among the important studies featured SRE-related primary endpoints. It is important to also note that any systemic agent that is active against prostate cancer likely has the potential to prevent skeletal morbidity. This realization has led to the recent inclusion of SREs as an endpoint for trials involving drugs such as hormonal agents that are not specifically targeted to bone. Active hormonal agents such as abiraterone and enzalutamide have been shown to prevent SREs.[50,76]

Radiopharmaceuticals have become a more prominent therapeutic consideration with the recent demonstration of a survival advantage

with the alpha-emitting radium-223. In general, radiopharmaceuticals are systemically delivered bone-seeking agents that either emit radiation themselves or are linked to a radioactive source. Beta-emitting radiopharmaceuticals have long been approved for the palliation of pain due to bone metastases, but are limited by prominent marrow suppression and the absence of a demonstrated effect on survival.[77] Radium-223 is a newer alpha emitting radiopharmaceutical that was shown in a randomized placebo controlled trial to improve OS and prevent SREs in men with CRPC metastatic to bone without visceral metastases.[78] At present, there is limited data with regard to the safety and efficacy of combining radium-223 with other systemic anticancer agents or bone-targeted agents.

One important unanswered question is the amount of added benefit of osteoclast inhibition in the context of newer systemic therapies that are active in the setting of CRPC. Given that disease control reduces the risk for SREs, it is possible that the benefits previously demonstrated with osteoclast inhibition are now blunted by the benefits produced by abiraterone, enzalutamide, radium-223 and other agents. In the absence of level 1 evidence to guide-related decisions, it is likely important to be mindful of individualized risk for SRE. Those at highest risk for events have historically been most likely to benefit from bone-targeted therapy. For example, benefits have been demonstrated in the setting of CRPC metastatic to bone but not with castration-sensitive metastatic disease. Rising PSA, short PSA doubling time and elevated markers of bone turnover are among the prognostic factors indicating highest risk for SREs and could rationally be taken as particularly strong indications for osteoclast inhibition in the setting of metastatic CRPC regardless of the concurrent systemic regimen.

CONCLUSIONS

Osteoclast inhibition is a validated strategy in the management of men with prostate cancer. In those at elevated risk for osteoporotic fractures, denosumab as well as several bisphosphonates have been shown to improve BMD, a surrogate for fracture risk. Denosumab is the only approved agent that has also been shown to prevent fractures. In men with CRPC metastatic to bone, monthly therapy with either denosumab or zoledronic acid has been shown to reduce risk for SREs. When the two agents were compared directly, denosumab was superior. Prominent potential adverse effects of potent osteoclast inhibition include hypocalcemia and rarely, ONJ. Finally, there are a number of new classes of agents under current study for the prevention of skeletal morbidity in men with prostate cancer.

COMPETING INTEREST

The author declares no relevant competing interests.

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