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Toxicities Following Treatment with Bisphosphonates and Receptor Activator of Nuclear Factor- κ B Ligand Inhibitors in Patients with Advanced Prostate Cancer

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Abstract

Context—Advanced prostate cancer (PCa) is associated with skeletal complications, both as a result of bone metastases and because of fractures associated with fragility due to androgen-

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deprivation therapy (ADT). Osteoclast inhibitors are commonly used to reduce skeletal complications but are associated with a number of potential adverse events.

Objective—To review clinical trials of osteoclast inhibitors in advanced PCa, to discuss the adverse event profile of these agents, and to discuss strategies to address specific adverse events.

Evidence acquisition—PubMed was searched for reports of clinical trials of osteoclast inhibitors in advanced PCa. As zoledronic acid and denosumab are used most commonly in this disease, these trials were the focus. The literature was reviewed to identify key publications addressing the prevention and management of adverse events associated with these drugs.

Evidence synthesis—The major findings of the trials and the adverse events are discussed. Prevention and management of common adverse events are addressed.

Conclusions—Zoledronic acid prevents loss of bone mineral density associated with ADT and delays skeletal-related events in metastatic castration-resistant PCa (mCRPC). Denosumab reduces the incidence of fragility fractures associated with ADT, delays the onset of bone metastases in nonmetastatic castration-resistant disease, and is superior to zoledronic acid in the prevention of skeletal complications in mCRPC. Adverse events associated with both agents include osteonecrosis of the jaw and hypocalcemia. Hypocalcemia is more common with denosumab. Zoledronic acid requires dose modifications for renal insufficiency, is contraindicated in severe renal insufficiency, and has been associated with deterioration of renal function. Appropriate patient selection with close attention to dental health, supplementation with calcium and vitamin D, and monitoring of laboratory values are effective strategies to minimize the impact of adverse events associated with osteoclast inhibitors in advanced PCa.

Keywords

Prostate cancer; Systematic review; Bone-targeted agents; Bisphosphonates; Denosumab; Adverse events

1. Introduction

Prostate cancer (PCa) is the most common noncutaneous malignancy in men and ranks second and third as the cause of cancer death in men in North America and Europe, respectively [1,2]. Bone metastases are common in advanced disease [3]. The consequences of bone metastases include skeletal-related events (SREs), defined as pathologic fractures, spinal cord compression, or the need for palliative irradiation or orthopedic surgery. These complications result in poor quality of life, decreased survival, and a significant economic burden [4,5]. Beyond the morbidity and mortality associated with bone metastases, treatment of nonmetastatic PCa with androgen-deprivation therapy (ADT) leads to loss of bone mineral density (BMD) and increases the risk of sustaining fragility fractures [6].

The use of osteoclast inhibitors has led to significant advances both in the prevention of fragility fractures in patients with PCa treated with ADT and in the prevention of SREs in patients with metastatic disease. Two classes of pharmaceutical agents, the bisphosphonates and the receptor activator of nuclear factor- κ B (RANK) ligand inhibitor denosumab, have received approval by regulatory agencies for treatment of patients with PCa.

Bisphosphonates are analogs of inorganic pyrophosphate and are preferentially deposited in bone, as they are adsorbed onto hydroxyapatite crystals in the extracellular matrix of bone. Bisphosphonates with nitrogen-containing side chains, such as the third-generation bisphosphonate zoledronic acid, are much more potent than earlier molecules [7]. Zoledronic acid has gained regulatory approval for use in advanced PCa.

Denosumab is a fully human monoclonal immunoglobulin G2 antibody that is delivered subcutaneously. Denosumab binds to the RANK ligand with high affinity. RANK is expressed on the osteoclast cell surface, and signaling through this receptor is critical to osteoclast differentiation, survival, and activation [8]. Denosumab has been evaluated in multiple advanced PCa clinical disease states and has gained regulatory approval in this disease.

A number of new anticancer agents (abiraterone, cabazitaxel, enzalutamide, radium 223, sipuleucel-T) have recently been shown to extend survival in metastatic castration-resistant PCa (mCRPC). Given the predilection of advanced PCa to metastasize to bone, osteoclast inhibitors remain an indispensable component of therapy in these patients. While osteoclast inhibitors represent a major advance in reducing the morbidity associated with PCa and PCa treatment, like any medications, these therapies are not without adverse effects. Using these therapies requires a complete understanding of risks and benefits to facilitate shared decision making. In this paper, we review key clinical trials of zoledronic acid and denosumab in advanced PCa and discuss the adverse event profile of these two agents in this disease.

2. Evidence acquisition

PubMed was searched in November 2012 to identify major prospective trials exploring osteoclast inhibitors in PCa. Search terms included *clinical trial*, *prostate cancer*, *bisphosphonate*, and *denosumab*. The search was limited to English language publications.

3. Evidence synthesis

3.1. Key trials evaluating osteoclast inhibitors in advanced prostate cancer

Osteoclast inhibitors have been evaluated in a variety of scenarios typical of advanced PCa (Table 1). Trials have evaluated the ability of such drugs to prevent loss of BMD [9–15] and to prevent fragility fractures in patients requiring ADT [16]. Other trials have evaluated the ability of these agents to prevent bone metastases in patients with nonmetastatic castration-resistant PCa (CRPC) [17,18]. Osteoclast inhibitors have also been evaluated in metastatic PCa, most often with castration-resistant disease [19,20] but also in castration-sensitive metastatic disease [21].

The Medical Research Council performed a placebo-controlled trial of oral clodronate in 311 men with metastatic bone disease from PCa [22]. A slight reduction in the proportion of patients receiving clodronate experienced an SRE, and an improvement in time to progression and increased median survival was observed; however, none of these differences was statistically significant. Pamidronate has been studied in a placebo-controlled trial of 236 patients with advanced PCa and bone metastases. This trial assessed bone pain as the primary end point and included an assessment of SREs as a secondary end

point. In this population, pamidronate did not reduce the incidence of SREs and had only a slight effect on bone pain [23].

3.1.1. Zoledronic acid in metastatic castration-resistant prostate cancer—

Zoledronic acid has been evaluated in mCRPC with metastases to bone in the 039 trial (Table 1) [19]. This trial included 643 patients who were randomized to 4 or 8 mg of intravenous zoledronic acid or to placebo every 3 wk for 15 mo. The primary outcome was the proportion of patients with an SRE. High rates of renal toxicity occurred in the 8-mg treatment arm, necessitating a protocol amendment reassigning these patients to treatment at the 4-mg dose. In addition, zoledronic acid was initially given as a 5-min infusion, but the time of infusion was increased to 15 min, given concerns that the more rapid infusion contributed to renal toxicity. Treatment with zoledronic acid at the 4-mg dose was associated with a statistically significant decrease in the incidence of SREs compared with placebo (33.2% and 44.2%, $p = 0.021$). In addition, patients receiving zoledronic acid were more likely to have improvements in bone pain [24].

Fatigue, anemia, pyrexia, myalgia, and lower extremity edema occurred more commonly on the zoledronic acid arm. Grade 3–4 hypocalcemia and grade 3–4 renal failure were rare. However, renal deterioration was seen in 15.2% of the 4-mg arm, 20.7% of the 8/4-mg arm, and 11.5% of the placebo arm. Following the protocol amendment eliminating the 8-mg dose and increasing the time of infusion to 15 min, the rates of renal dysfunction were similar in the treatment and placebo arms. No cases of osteonecrosis of the jaw (ONJ) were reported in this study. However, it should be noted that the first cases of bisphosphonate-related ONJ were not reported until the year following publication of the 039 trial [25].

Zoledronic acid received regulatory approval in both the United States and Europe in 2001. In the United States, zoledronic acid is approved for use in cancer patients with bone metastases, multiple myeloma, and hypercalcemia of malignancy. With regard to PCa, approval stipulates that patients must have failed at least one hormonal therapy. In Europe, zoledronic acid is approved for use in advanced malignancies with bone involvement and in hypercalcemia of malignancy.

3.1.2. Denosumab to improve bone health in patients with prostate cancer on androgen-deprivation therapy—

Denosumab has been compared with placebo in patients on ADT for nonmetastatic PCa in the Hormone Ablation Bone Loss (HALT 138) trial (Table 1) [16]. This study included 1468 patients at high risk for fragility fractures who received denosumab 60 mg or placebo subcutaneously every 6 mo. The primary outcome was change in BMD at the lumbar spine after 24 mo of treatment. At 24 mo, BMD in the lumbar spine had increased by 5.6% in the denosumab group and had decreased by 1.0% in the placebo group ($p < 0.001$). The incidence of new vertebral fractures was 1.5% with denosumab and 3.9% with placebo ($p = 0.006$).

No adverse events were clearly more common with denosumab except for an unexplained increase in cataracts. This finding was not seen in any of the other denosumab trials and is the focus of an ongoing safety study. There was no significant change in kidney function,

and no cases of ONJ were reported. Hypocalcemia was a rare event, with grade 2 hypocalcemia occurring in <1% of both the treatment and placebo groups.

Denosumab received regulatory approval in the United States and Europe for use in men with nonmetastatic PCa who are on ADT and at high risk for fracture. The approved dose is 60 mg delivered subcutaneously every 6 mo.

3.1.3. Denosumab to prevent bone metastases in nonmetastatic castration-resistant prostate cancer—Denosumab has been evaluated to delay bone metastases in patients with nonmetastatic CRPC who are at high risk for developing metastatic disease (Table 1) [18]. This trial included 1432 patients randomized to denosumab 120 mg or placebo delivered subcutaneously every 4 wk. The primary outcome was time until the development of bone metastases or death. The bone metastases-free survival was 29.5 mo in the treatment arm and 25.2 mo in the placebo arm ($p = 0.028$). The overall survival was similar in the treatment arms.

ONJ occurred in 5% of patients with denosumab and was not seen in the placebo group. The incidence of ONJ was 1% at 1 yr, 3% at 2 yr, and 4% after 3 yr. Risk factors for development of ONJ, including tooth extraction (70%), poor oral hygiene (55%), and dental appliance use (48%), were noted in 91% of patients who developed ONJ. Of patients who developed ONJ, 61% required limited dental intervention such as curettage and debridement, 6% required bone resection, and 30% required noninvasive therapies such as oral rinses or antibiotics. Hypocalcemia occurred in 12 patients (1.7%) with denosumab and in 2 patients (0.3%) with placebo. Grade 3 or 4 hypocalcemia was seen in 1.3% of the denosumab group. Only one patient on denosumab had symptomatic hypocalcemia. No impact on renal function was observed with denosumab.

In 2012, the US Food and Drug Administration (FDA) rejected extending the labeling of denosumab to include the prevention of bone metastases in men with nonmetastatic PCa, deeming the improvement in time to bone metastasis insufficient to justify the toxicity of treatment, notably ONJ.

3.1.4. Zoledronic acid compared with denosumab in metastatic castration-resistant prostate cancer—In a randomized phase 2 study of patients with malignancies, including PCa, who had elevated urine N-telopeptide despite bisphosphonate therapy, denosumab was shown to normalize this marker of osteoclast-mediated bone resorption more frequently than continuation of bisphosphonate therapy [26,27]. Zoledronic acid has been compared with denosumab for the prevention of SREs in men with CRPC metastatic to the bone (Table 1) [20]. In the 103 phase 3 trial, 950 patients were treated with subcutaneous denosumab 120 mg and intravenous placebo every 4 wk, and 951 patients received intravenous zoledronic acid 4 mg and subcutaneous placebo every 4 wk. The primary end point was time from randomization to first SRE, defined as a pathologic fracture, irradiation or surgery to bone, or spinal cord compression. Median time to first SRE was 20.7 mo with denosumab and 17.1 mo with zoledronic acid ($p = 0.0002$ for noninferiority and $p = 0.008$ for superiority).

The most common adverse events were anemia, back pain, decreased appetite, nausea, fatigue, constipation, and bone pain, and these events occurred at similar rates in both treatment arms. Hypocalcemia developed in 13% of patients on denosumab and 6% of patients on zoledronic acid ($p < 0.0001$). Hypocalcemia grade 3 occurred in 5% of patients on denosumab and 1% of patients on zoledronic acid. Most cases of hypocalcemia were asymptomatic, occurred during the first 6 mo of treatment, and did not recur.

ONJ occurred in 2.3% of patients on denosumab and 1.3% of patients on zoledronic acid ($p = 0.09$). Most patients who developed ONJ (79%) had a risk factor for its development, such as history of tooth extraction, poor oral hygiene, or the use of a dental appliance. Of the 22 patients who developed ONJ on denosumab, 10 patients required limited surgery, and 2 patients required bone resection. Of the 12 patients on zoledronic acid who developed ONJ, 3 patients required limited surgery and 1 patient required bone resection. Resolution of ONJ was noted in 5 of the 34 cases. Adverse events potentially related to renal impairment occurred in 15% of patients on denosumab and in 16% of patients on zoledronic acid. Acute-phase reactions were identified from a predefined list of terms from the Medical Dictionary for Regulatory Activities. During the first three days of therapy, acute-phase reactions were reported in 8% of patients on denosumab and in 18% of patients on zoledronic acid.

Denosumab for use with solid tumors with bone metastases gained regulatory approval in the United States in 2010 and in Europe in 2011.

3.2. Specific adverse events

3.2.1. Osteonecrosis of the jaw—ONJ is a well-recognized adverse event associated with the use of bisphosphonates and denosumab. The American Association of Maxillofacial Surgeons (AAOMS) has defined *ONJ* as the presence of exposed bone in the oral cavity despite appropriate management for 8 wk occurring in patients who have not received irradiation to the jaw [28]. ONJ associated with the use of bisphosphonates was first reported in 2003 in a case series of 36 patients (35 with cancer) treated with zoledronic acid or pamidronate [25].

The incidence of this complication has varied considerably in different reports. A retrospective review of 4019 cancer patients from a single center treated with intravenous bisphosphonates reported an incidence of ONJ of 0.72% [29]. In another single-institution retrospective study of 1621 cancer patients treated with intravenous bisphosphonates, the incidence of ONJ was found to be 8.5% in multiple myeloma patients, 4.9% in PCa patients, and 3.1% in breast cancer patients [30]. In a prospective single-center study, 6.7% of 252 cancer patients treated with pamidronate or zoledronic acid developed ONJ [31]. In another small prospective study of cancer patients treated with intravenous bisphosphonates, 18.6% of 43 patients developed ONJ [32].

No cases of ONJ were reported in the 039 trial, though at the time of the report, an association between osteoclast inhibitors and ONJ had not yet been made. In HALT 138, no cases of ONJ occurred with subcutaneous delivery of denosumab 60 mg every 6 mo. In the bone metastases prevention trial of denosumab, ONJ occurred in 5% of patients. In the 103

phase 3 trial comparing zoledronic acid with denosumab in mCRPC, the incidence of ONJ with zoledronic acid was 1.3% and with denosumab was 2.3% ($p = 0.09$). Perhaps the most comprehensive data with regard to incidence and outcome of ONJ in cancer patients come from a pooled analysis of the three phase 3 trials that compared zoledronic acid with denosumab in cancer patients [33]. A total of 5723 patients were included in these three studies, and 89 patients (1.6%) developed ONJ.

The incidence of ONJ with denosumab and zoledronic acid was 1.8% and 1.3%, respectively. As in other reports, ONJ most commonly involved the mandible. Jaw pain, tooth extractions, and oral infections were common in patients with ONJ. Many patients (54%) required only conservative measures for treatment, such as oral rinses, antibiotics, or monitoring alone; 41% of the patients required limited surgical intervention; and only 4.5% of the patients required resection of bone. Resolution of ONJ was reported in 36% of the patients.

Risk factors for the development of ONJ in cancer patients treated with antiresorptive therapies have been identified. An association between tooth extraction and ONJ was noted in the initial report [25]. Other investigators have also reported an association of local factors such as tooth extraction, dentures, and poor oral hygiene with the development of ONJ [29,33–36]. Systemic factors such as smoking, diabetes, anemia, renal insufficiency, glucocorticoid use, chemotherapeutic agents, and the use of antiangiogenic agents have also been implicated [28,37–39]. Longer duration of therapy appears to increase the risk of ONJ [31]. There may be a higher risk of ONJ with zoledronic acid compared with pamidronate [40]. There is also a higher incidence of ONJ with increased doses or frequency of drug given for metastatic disease (ie, subcutaneous denosumab 120 mg monthly or intravenous zoledronic acid 4 mg monthly).

Prospective studies have shown that preventive strategies may reduce the incidence of bisphosphonate-associated ONJ [41,42]. These strategies include an oral examination prior to treatment, completion of any invasive dental procedures prior to initiation of therapy, and optimizing and maintaining dental health [28,43]. Although there is no clear recommendation, it is strongly suggested that if invasive dental surgery is required while a patient is taking an antiresorptive agent, it is prudent to stop therapy prior to the procedure and consider restarting it only when complete healing has occurred.

The AAOMS has proposed a staging system and treatment recommendations for ONJ (Table 2). Treatment generally includes pain control that often requires opioid pain medications, antibacterial mouth rinses such as chlorhexidine, and systemic antibiotics. While infection is not the inciting event in ONJ, advanced-stage ONJ is complicated by infection, and systemic antibiotics are indicated. Generally, a penicillin is used, with alternatives considered for patients with allergies to penicillin. If the case is refractory to initial management, antibiotics are adjusted and may be given intravenously. Long-term antibiotics are sometimes required. Superficial or surgical debridement with resection of bone may be necessary in stage 3 ONJ. There are no clear data to support a benefit of discontinuation of antiresorptive agents on diagnosis of ONJ, but discontinuation is generally advised, particularly for advanced-stage ONJ.

3.2.2. Renal insufficiency—While denosumab has no recognized impact on renal function, bisphosphonates have been associated with renal insufficiency. In the 039 phase 3 study, either 4 or 8 mg of zoledronic acid was initially delivered intravenously every 3 wk. A protocol amendment was required to reduce the 8-mg dose to 4 mg and to increase the time of infusion from 5 to 15 min, given concerns for higher renal toxicity at the higher dose and with more rapid infusion [19]. Following the amendment, renal deterioration was noted in 15.2% of patients given zoledronic acid compared with 11.5% of patients given placebo, a difference that did not reach statistical significance. In the 103 phase 3 study comparing zoledronic acid with denosumab in mCRPC, adverse events possibly related to renal insufficiency occurred in 16% and 15% of patients given zoledronic acid and denosumab, respectively, though it was noted that patients receiving zoledronic acid required more frequent dose holding and dose modification for increased creatinine than patients receiving denosumab [20]. Postmarketing surveillance has revealed a number of cases of renal failure with bisphosphonates. In 2003, the US FDA reported that 72 cases of renal failure had been associated with zoledronic acid [44]. Of these cases, 27 required dialysis. Renal failure developed, on average, 56 d after initiation of zoledronic acid.

Based on the association of bisphosphonates with renal toxicity, the US FDA and the European Regulatory Agency have warned of the risk of nephrotoxicity and added restrictions to the prescribing of intravenous bisphosphonates to patients with abnormal renal function. In the United States, determination of a serum creatinine level is required prior to each dose of zoledronic acid, and it is suggested that the drug be held if the creatinine level increases by 0.5 mg/dl in patients with normal baseline renal function and if creatinine level increases by 1.0 mg/dl in patients with abnormal baseline renal function. The drug may be resumed if the creatinine level returns to $\pm 10\%$ of baseline values. Zoledronic acid requires dose adjustment for a glomerular filtration rate (GFR) of 30–60 ml/min and is not recommended in patients with a GFR <30 ml/min.

3.2.3. Hypocalcemia—Hypocalcemia is seen with bisphosphonates and denosumab. In the 039 trial, grade 3 or 4 hypocalcemia was seen in 1.9% of patients treated with zoledronic acid compared with none of the patients in the placebo group [19]. With denosumab delivered subcutaneously at a dose of 60 mg every 6 mo, hypocalcemia was seen in only 1 of 731 PCa patients. In the metastases prevention trial in PCa, hypocalcemia occurred in 1.7% of patients on denosumab and in 0.3% of patients on placebo. Only one patient on denosumab developed symptomatic hypocalcemia [18]. In a randomized phase 2 study of denosumab (180 mg every 4 or 12 wk) or bisphosphonate (pamidronate or zoledronic acid every 4 wk) in patients with multiple malignancies with bone involvement, 6 of 74 patients treated with denosumab developed grade 3 hypocalcemia and 1 patient developed grade 4 hypocalcemia, compared with 1 patient with grade 3 hypocalcemia in 37 patients treated with a bisphosphonate [27]. In the 103 phase 3 trial comparing denosumab with zoledronic acid, hypocalcemia developed in 13% of patients on denosumab and in 6% of patients on zoledronic acid ($p < 0.0001$). Hypocalcemia grade 3 occurred in 5% and 1% of the denosumab and zoledronic acid groups, respectively [20]. In each of these trials, patients were given supplemental calcium and vitamin D. Although most cases of hypocalcemia associated with denosumab have been asymptomatic, fatal cases of denosumab-induced

hypocalcemia have been reported, highlighting the critical need for adequate supplementation [45].

The risk of hypocalcemia with denosumab appears to be higher in patients with renal insufficiency. In one report, 55 patients with varying degrees of renal function were given a single 60-mg dose of denosumab. None of 12 patients with normal renal function developed hypocalcemia, whereas 4 of 17 patients who had a GFR <30 ml/min or were on dialysis developed hypocalcemia, defined as a corrected calcium of <7.5 mg/dl. The protocol did not originally require supplementation with calcium and vitamin D. After supplementation was required, no further hypocalcemia was seen [46]. It should be noted that subcutaneous denosumab 120 mg given monthly has not been evaluated in patients with a GFR <30 ml/min, and concern exists that rates of hypocalcemia may be higher in these patients. The conversion of vitamin D to the active form (25-hydroxycholecalciferol to 1,25-hydroxycholecalciferol [calcitriol]) occurs in the kidneys, and this process is impaired in the setting of significant renal dysfunction. Thus, it has been suggested that supplementation with calcitriol may be useful in the prevention or treatment of denosumab-induced hypocalcemia [47].

Cancer patients treated with intravenous bisphosphonates or denosumab should be treated with supplemental calcium and vitamin D, as long as they do not have hypercalcemia. Additionally, patients should have normal calcium levels at initiation of therapy and should have calcium levels monitored during therapy. Should hypocalcemia develop, the osteoclast inhibitor should be held, and calcium and vitamin D should be provided.

3.2.4. Acute-phase reactions—Acute-phase reactions are a recognized adverse event associated with the use of bisphosphonates [48]. In the 039 study, fever was reported in 20.1% (4 mg dose) and 13% of patients on zoledronic acid and placebo, respectively. Myalgia occurred in 24.8% (4 mg dose) of patients on zoledronic acid and in 17.8% of patients on placebo [19].

In the 103 phase 3 study comparing zoledronic acid with denosumab in mCRPC, acute-phase reactions during the first 3 d after treatment were seen in 18% and 8% of patients with zoledronic acid and denosumab, respectively [20].

Severe episodes of musculoskeletal pain have been reported with bisphosphonates. Regulatory agencies have dictated that package inserts warn of the risk of severe bone, joint, or muscle pain with zoledronic acid. Most acute-phase reactions occur in the first several days after treatment, and the reactions are more common at initiation of treatment than with subsequent treatments. Specific treatment is not required, though analgesics or antipyretics may provide symptomatic relief [49].

3.2.5. Atypical femur fractures—Atypical femur fractures have been associated with bisphosphonate therapy [50]. Decreased bone turnover has been postulated to play a key role in the pathogenesis. These fractures can occur with no trauma and may be bilateral. Although not described in clinical trials of osteoclast inhibitors in PCa, the labels for zoledronic acid and denosumab (60 mg delivered subcutaneously every 6 mo) warn of the

risk of this complication. Atypical femur fractures have been seen in an open label extension study of denosumab 60 mg delivered subcutaneously every 6 mo. Patients may have a prodrome of pain in the hip or groin, and such reports from patients on antiresorptive therapy may warrant imaging.

3.3. Rates of discontinuation because of adverse events

In the randomized studies of denosumab and zoledronic acid in advanced PCa, treatment discontinuation secondary to severe-grade adverse events was generally similar in treatment and placebo arms (Table 1). In the 039 trial, treatment discontinuation secondary to adverse events occurred in 9.8% of patients on 4 mg of zoledronic acid and in 10.1% of patients on placebo. In HALT 138, treatment discontinuation was required for 6.7% of patients on denosumab and 6.5% of patients on placebo. In the denosumab metastases prevention trial, 11% of patients on denosumab discontinued treatment compared with 10% of patients on placebo. In the 103 trial in mCRPC, 17% and 15% of patients on zoledronic acid and denosumab, respectively, discontinued treatment because of an adverse event.

3.4. Serious adverse events

In randomized studies of zoledronic acid and denosumab, serious (grade 3–4) adverse events have occurred with similar frequencies between treatment arms. The incidence of severe adverse events seen in HALT 138 was 34.6% with denosumab and 30.6% with placebo. In the metastases prevention study, 46% of patients receiving either denosumab or placebo had a severe-grade adverse event. In the 103 phase 3 trial on mCRPC, 60% of patients on zoledronic acid and 63% of patients on denosumab had a serious adverse event. The total incidence of severe-grade adverse events was not reported in the 039 trial.

3.5. Choosing between denosumab and zoledronic acid

With regard to the choice between zoledronic acid and denosumab in CRPC metastatic to bone, denosumab is superior to zoledronic acid in delaying SREs. Thus, if one is to select the most effective agent, denosumab would be the most logical drug choice. The toxicity profile of denosumab lacks nephrotoxicity and acute-phase reactions. However, hypocalcemia is more common with denosumab. Rates of ONJ are similar between these two agents. In patients with severe renal dysfunction (GFR <30 ml/min), zoledronic acid is contraindicated. While denosumab lacks nephrotoxicity and is not metabolized by the kidneys, there is concern that rates of hypocalcemia may be higher in the setting of severe renal dysfunction. In patients with more modest degrees of renal impairment, if potential nephrotoxicity is a concern, then denosumab may be favored. In terms of patient convenience, a subcutaneous route as opposed to an intravenous route may be preferable, again favoring the use of denosumab. However, in patients being treated with either docetaxel or cabazitaxel, both of which are given every 3 wk, treatment with denosumab (given every 4 wk) as opposed to zoledronic acid (given every 3–4 wk) will require additional visits.

4. Conclusions

Zoledronic acid reduces the incidence of SREs in mCRPC, and denosumab further extends the time until first SRE in these patients. Denosumab reduces the incidence of fragility fractures in men with nonmetastatic PCa on ADT who are at high risk for fracture. High-potency osteoclast inhibitors such as zoledronic acid and denosumab are associated with a number of adverse events. There is a clear association of the dose intensity and frequency of these agents with their adverse event profiles.

Appropriate management can mitigate adverse events associated with osteoclast inhibitors. To reduce the incidence of ONJ, oral examinations should be performed before and during ongoing therapy, and invasive dental work should be completed prior to initiation of treatment. Patients should be educated to report any oral concerns and to avoid invasive dental work while on therapy. If ONJ does develop, guidelines for staging and treatment should be referenced. With regard to renal function, a creatinine level should be checked prior to each dose of zoledronic acid, appropriate dosing modifications should follow accepted guidelines, and patients with severe renal dysfunction should not be treated with zoledronic acid. The risk for hypocalcemia appears to be greater with denosumab than with zoledronic acid. All patients treated with these agents should be given supplemental calcium and vitamin D unless they are hypercalcemic to minimize the risk of hypocalcemia. Acute-phase reactions have been associated with bisphosphonates. These reactions are generally transient and do not require specific therapy. Atypical femur fractures are uncommon, though treating physicians should be aware of this rare adverse event.

In general, osteoclast inhibitors are well-tolerated agents and provide significant benefit to patients with advanced PCa. However, a thorough discussion regarding the risks and benefits of these agents should be undertaken prior to their initiation, and appropriate steps should be taken to minimize the risk of adverse events.

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Table 1

Key randomized studies of zoledronic acid and denosumab in advanced prostate cancer

Study	Patients, no.	Population	Arm 1	Arm 2	Primary outcome	Discontinued, %	Total grade 3–4 AEs, %	Notable AEs			
								ONJ, %	Renal, %	Hypocalcemia, %	APR, %
Zoledronic acid 039, Saad et al. [19]	643	mCRPC	Z 4 mg or Z 8/4 mg IV every 3 wk	P	Z decreased SREs: 44.2% vs 33.2% ($p = 0.021$)	Z 8/4 mg: 12.4 Z 4 mg: 9.8 P: 10.1	NR	NR	Renal deterioration: Z 8/4 mg: 20.7 Z 4 mg: 15.2 P: 11.5 Grade 3: Z 8/4 mg: 3.3 Z 4 mg: 2.3 P: 1.0	Grade 3–4: Z 8/4 mg: 1.9 Z 4 mg: 2.0 P: 0	Fever: Z 8/4 mg: 22.0 Z 4 mg: 20.1 P: 13.0 Myalgia: Z 8/4 mg: 24.3 Z 4 mg: 24.8 P: 17.8
Denosumab HALT 138, Smith et al. [16]	1468	Nonmetastatic CRPC on ADT	D 60 mg SC every 6 mo	P	D increased BMD at LS: +5.6% vs -1.0% ($p < 0.001$)	D: 6.7 P: 6.5	D: 34.6 P: 30.6	0	No change in creatinine	Any grade: D: 0.1 P: 0	NA
Denosumab phase 3 147, Smith et al. [18]	1432	Nonmetastatic CRPC at high risk for bone metastases	D 120 mg SC every 4 wk	P	D prolonged metastasis-free survival: 29.5 vs 25.2 mo ($p = 0.028$)	D: 11.0 P: 10.0	D: 46.0 P: 46.0	D: 5.0 P: 0	No difference in creatinine between treatment arms	Any grade: D: 1.7 P: 0.3 Grade 3–4: D: 1.3 P: 0	NA
Denosumab phase 3 103, Fizazi et al. [20]	1904	mCRPC	D 120 mg SC + P IV every 4 wk	Z 4 mg IV + P SC every 4 wk	D prolonged time to first SRE: 20.7 vs 17.1 mo ($p = 0.0002$) ^a	D: 15.0 Z: 17.0	D: 71.9 Z: 66.5	D: 2.3 Z: 1.3	AEs potentially related to renal dysfunction: D: 15.0 Z: 16.0	Any grade: D: 13 Z: 6 Grade 3–4: D: 5 Z: 1	AEs potentially related to APR: D: 8.0 Z: 18.0

ADT = androgen-deprivation therapy; AE = adverse event; APR = acute-phase reaction; BMD = bone mineral density; CRPC = castration-resistant prostate cancer; D = denosumab; HALT = Hormone Ablation Bone Loss trial; IV = intravenous; LS = lumbar spine; mCRPC = metastatic castration-resistant prostate cancer; NA = not applicable; NR = not reported; ONJ = osteonecrosis of the jaw; P = placebo; SC = subcutaneous; SRE = skeletal-related event; Z = zoledronic acid.

^aFor noninferiority.

Table 2

Staging and treatment strategies for osteonecrosis of the jaw

	Characteristics	Treatment
Stage 0	No visible bone, but nonspecific symptoms	Symptomatic treatment; conservative management of dental issues such as caries or periodontal disease; antibiotics if concern for infection
Stage 1	Exposed, necrotic bone without symptoms	Antimicrobial rinses
Stage 2	Exposed, necrotic bone with local signs or symptoms of infection	Symptomatic treatment; antimicrobial rinses and systemic antibiotics
Stage 3	Exposed, necrotic bone with pain, infection, and one or more of the following: necrosis beyond alveolar bone, pathologic fracture, extraoral fistula, abnormal communications, extensive osteolysis	Symptomatic treatment; systemic antibiotics; superficial or surgical debridement with possible resection of bone

Based on Ruggiero et al. [43].