Analysis of Denosumab on Skeletal-Related Events in Patients With Advanced Breast Cancer

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Background: Bisphosphonates, which are also known as osteoclast modifiers, are the standard of care in the treatment of skeletal-related events (SREs) in patients with breast cancer with metastatic bone disease. SREs are frequently a complication of advanced breast cancer, and they greatly increase morbidity and mortality in these patients. Unfortunately, even while undergoing bisphosphonate therapy, many patients experience SREs. In 2010, a fully human monoclonal antibody, denosumab (Xgeva®), was approved by the U.S. Food and Drug Administration as another option to treat SREs.

Objectives: This article analyzes four primary human research studies looking at the effectiveness and safety of denosumab as compared to bisphosphonates in the prevention of SREs in this vulnerable population.

Methods: Articles published from 2006–2012 were located and reviewed through online database searches (CINAHL®, MEDLINE®, PubMed Plus) using the key words denosumab, skeletal-related event, breast cancer, metastases, and bisphosphonates.

Findings: Studies reviewed showed comparative adverse events and safety profile between denosumab and bisphosphonates. However, denosumab was shown to have increased effectiveness in the prevention of SREs. This knowledge can influence the preventive measures taken by physicians and advanced practice nurses to improve the prevention of SREs in patients with metastatic breast cancer. It can also increase staff nurse knowledge and implementation of evidence-based practice.

According to American Cancer Society (ACS), 2015a estimates, 231,840 new cases of invasive breast cancer are expected to be diagnosed among women in the United States during 2015, and more than 40,000 women will die from breast cancer in the same year. Breast cancer is the second leading cause of cancer death in women in the United States (ACS, 2015b). About 20% of patients diagnosed with breast cancer develop metastatic disease (Eckhardt, Francis, Parker, & Anderson, 2012), and, of those patients with metastatic breast cancer, as many as 80% will have metastatic disease present in the bone (Kennedy & Patel, 2011).

The formation of bone metastases indicates an increase of osteoclast activity, leading to bone destruction and potential skeletal complications (e.g., severe pain, hypercalcemia, skeletal-related events [SREs]) (Stopeck et al., 2010). SRE is an umbrella term used to refer to a pathologic fracture, spinal cord compression, the use of radiation therapy to improve pain or prevent fracture, and/or the use of surgery to treat or prevent fracture (Kennedy & Patel, 2011). SREs greatly increase morbidity and mortality in patients with advanced breast cancer (Kennedy & Patel, 2011). In addition, SREs can decrease patients' functionality and ability to maintain independence in activities of daily living. They may also contribute to pain, requiring additional medications used to control SRE-related symptoms. The purpose of this article is to analyze published primary sources that have evaluated denosumab (Xgeva®) and bisphosphonates, also known as osteoclast modifiers, in the prevention of SREs, specifically in the population of patients diagnosed with metastatic breast cancer.

Skeletal-Related Events

SREs may cause paresthesias, incontinence, paralysis, pain, and functional dependence, and they may lead to the inability to
carry out activities of daily living (Stopeck et al., 2010). Because of the debilitating sequelae of SREs, increased demand to prevent their development exists. The most common presenting symptom indicating an SRE is pain, which has a huge impact on nursing care provided to patients in this population. Nurses must be aware of SREs and their potential to cause severe, debilitating pain. As such, nurses play a significant role in adequate pain assessment, treatment, and evaluation of interventions. Nurses also frequently assess patients’ ability to partake in activities of daily living, and they collaborate with oncologists in taking measures to promote patients’ independence. One tangible way of potentially improving the quality of life (QOL) of those at high risk for developing SREs is administering medication to prevent SREs and related pain. New pain is often suggestive of SREs, but radiographic scans are needed for diagnosis and confirmation. The four studies examined in the current article used the same criteria to define an SRE: a fracture, the need for radiation or surgery to the bone, and spinal cord compression (Body et al., 2006; Fizazi et al., 2009; Lipton et al., 2007; Stopeck et al., 2010). Two additional studies (Cleeland et al., 2013; Martin et al., 2012) reviewed by the current authors provided further analysis of Stopeck et al. (2010).

The urine measurement of N-telopeptide of type 1 collagen (uNTx) is a marker of bone resorption, or bone loss. Many studies have used this measurement to analyze inhibition of osteoclast function and predict the risk of SRE formation (Body et al., 2006; Fizazi et al., 2009; Lipton et al., 2007; Stopeck et al., 2010). Studies consistently use uNTx levels as an indicator of medication effectiveness in reducing the risk of SREs. However, the values used vary among studies; some measure the overall percentage reduction of uNTx (Lipton et al., 2007), whereas others use absolute value points (Body et al., 2006; Fizazi et al., 2009) or median levels (Stopeck et al., 2010).

**Bisphosphonates**

Bisphosphonates, particularly zoledronic acid (Zometa®), have been used for the prevention of SREs from metastatic solid tumors since their approval by the U.S. Food and Drug Administration (FDA) in 2002 (Ibrahim et al., 2003). Because they cause osteoclast apoptosis and interfere with osteoclast activity, bisphosphonates prevent the loss of bone mass (Kennedy & Patel, 2011). Wong, Stockler, and Pavlakis (2012) completed a meta-analysis comparing bisphosphonates to a placebo. In all eight studies evaluated by Wong et al. (2012), bisphosphonates significantly reduced SRE rate and delayed median time to first SRE compared to the control. One bisphosphate, zoledronic acid, was shown to be the most effective bisphosphonate in preventing SREs and was 20% more effective than the next most effective bisphosphonate, pamidronate (Aredia®) (Wong et al., 2012).

Although zoledronic acid is shown to be effective, several factors limit its use. In particular, it is available only for IV administration, and caution must be used in patients with renal impairment. Zoledronic acid is contraindicated in patients with creatinine clearance levels of less than 30 ml per minute and requires a dose adjustment for creatinine clearance of less than 60 ml per minute (Novartis Pharmaceuticals Corporation, 2015). Healthcare providers should discuss the potential side effects of zoledronic acid (e.g., nephrotoxicity, osteonecrosis of the jaw, postinfusion flu-like symptoms) with patients prior to prescribing (Kennedy & Patel, 2011).

**Denosumab**

Many growth factors and cytokines affect the homeostasis of the bone marrow environment. Receptor activator of nuclear factor-kB ligand (RANKL) is stimulated by cancerous cells and is a key component of osteoclast survival (Wong et al., 2012). Excess RANKL in the bone marrow increases formation, function, and survival of osteoclasts, leading to unwarranted bone resorption (Kurata & Nakagawa, 2012). Developed by Amgen Inc., denosumab is a fully human monoclonal antibody. Its mechanism of action inhibits osteoclast activity by binding to RANKL, decreasing bone resorption, and protecting against bone degradation (National Cancer Institute [NCI], 2012). Denosumab was approved by the FDA in 2010 for the prevention of SREs in bone metastases from solid tumors (FDA, 2011; NCI, 2012).

In addition to being effective in reducing SREs, denosumab is a subcutaneous injection, whereas zoledronic acid is administered via IV. Subcutaneous injection may be the preferred route of administration for some patients (Wong et al., 2012). Zoledronic acid has been the standard of treatment in the prevention of SREs in patients with bone metastases from advanced breast cancer (Stopeck et al., 2012). However, denosumab is a newer option that has been demonstrated to be more effective (Stopeck et al., 2012).

Denosumab has been compared to bisphosphonates, particularly zoledronic acid, in many studies (Body et al., 2006; Fizazi et al., 2009; Lipton et al., 2007; Stopeck et al., 2010). It has been shown to be effective in prolonging the suppression of uNTx levels (Body et al., 2006; Fizazi et al., 2009), as well as delaying the time to SRE and the number of SREs (Martin et al., 2012; Stopeck et al., 2010). However, Stopeck et al. (2010) found no difference between the two study cohorts of denosumab and placebo or zoledronic acid and placebo when analyzing overall survival, disease progression, and rates of adverse events (AEs) and serious AEs.

**Methods**

A comprehensive literature review was conducted by searching CINAHL®, MEDLINE®, and PubMed Plus using the following key words: denosumab, skeletal-related event, breast cancer, metastases, and bisphosphonates. Search limits included randomized, controlled trials; publication dates from 2006–2012; English language; and human participants. By searching the titles and abstracts, four primary sources of human research were chosen for further analysis. Each study primarily analyzed patients with breast cancer and compared denosumab to bisphosphonate therapy in relation to SREs. To better compare and choose the most appropriate therapy, study results, study designs, and patient populations will be discussed in more detail later in the current article.

**Study Designs**

Body et al. (2006) investigated the safety and efficacy of denosumab in patients with breast cancer with radiologic
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<td>Body et al., 2006</td>
<td>To investigate the safety and efficacy of denosumab (Xgeva®) compared to pamidronate (Aredia®) in patients with multiple myeloma and breast cancer with bone metastases. Bisphosphonate and chemotherapy use was restricted for study participants. Double-blind, active-controlled, and multicenter study involving four centers and 54 participants (29 with breast cancer)</td>
<td>The 29 patients with breast cancer with radiologic evidence of lytic or mixed bone metastasis and the 25 patients with multiple myeloma with lytic bone disease were split into two treatment arms: (a) SC denosumab and IV placebo or (b) SC placebo with IV pamidronate. A dose escalation and parallel-dose phase occurred. Patients were randomly assigned in a 3:1 ratio to receive pamidronate or denosumab 0.1 mg/kg. After the safety was confirmed at 0.1 mg/kg, new patients were randomized with dose escalation in 0.3 mg/kg, 1 mg/kg, and 3 mg/kg cohorts.</td>
<td>A significant decrease in median uNTx was observed one day after single denosumab or pamidronate use. With denosumab, the duration of uNTx suppression was dose dependent. In the 0.1 mg/kg cohort, uNTx returned to baseline at 21 days, but at 3 mg/kg, uNTx remained suppressed through the 84-day follow-up. The pamidronate cohort had a median nadir of uNTx at three days and rose after 28 days.</td>
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<td>Cleeland et al., 2013</td>
<td>To evaluate the effect of denosumab versus ZOL (Zometa®) on pain in patients with advanced breast cancer and bone metastases. Pain assessment of study participants from Stopeck et al. (2010)</td>
<td>Pain severity and interference with daily functioning were assessed at baseline and monthly with the Brief Pain Inventory—Short Form. Pain ratings of 1–4 were considered mild pain, 5–6 were moderate, and 7–10 were severe. Analgesic use was measured using the Analgesic Quantification Algorithm. Responder analysis went through month 18.</td>
<td>The ZOL cohort had higher pain rankings reported earlier in treatment than the denosumab cohort. Pain was no or mild pain at baseline had a four-month delay in progression to moderate or severe pain with denosumab versus ZOL (9.7 months versus 5.8 months, p = 0.002). Denosumab delayed time to increased pain interference by about one month compared to ZOL (16 months versus 14.9 months, p = 0.09). Time to pain improvement (p = 0.72) and time to decreased pain interference (p = 0.92) were similar between groups.</td>
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<td>Fizazi et al., 2009</td>
<td>To evaluate the effect of denosumab in patients with bone metastases and elevated uNTx levels despite ongoing bisphosphonate therapy. Randomized, open-label, and multicenter phase II study involving 26 centers and 111 patients</td>
<td>Study participants were stratified into three treatment arms: (a) continued current bisphosphonate (86% ZOL) every 4 weeks, (b) added SC denosumab 180 mg every 12 weeks, or (c) added SC denosumab 180 mg every 4 weeks to current bisphosphonate therapy. Of those enrolled, 41% had breast cancer. uNTx levels were measured at week 13, with effectiveness noted if levels decreased to less than 50 nmol/L. Study lasted 25 weeks; continued follow-up extended for an additional 32 weeks.</td>
<td>SREs developed in 8% of patients on denosumab versus 17% of patients on bisphosphonates. In patients with elevated uNTx despite ongoing IV bisphosphonate therapy, denosumab normalized uNTx levels more frequently than the continuation of bisphosphonates. Denosumab normalized uNTx levels consistently across tumor types and screening uNTx levels. uNTx suppression escape was noted more in patients receiving bisphosphonates and denosumab every 12 weeks versus denosumab every 4 weeks. Less than 50 nmol/L uNTx was achieved by 71% of patients receiving denosumab versus 29% of patients receiving bisphosphonates. Less than 50 nmol/L uNTx was maintained for 25 weeks in 64% of patients receiving denosumab versus 37% of patients receiving bisphosphonates. Median time to reduction of uNTx to less than 50 nmol/L was 9 days with denosumab versus 65 days with bisphosphonate.</td>
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<td>Lipton et al., 2007</td>
<td>To evaluate the efficacy and safety of five dosing regimens of denosumab in patients with breast cancer-related bone metastases not previously treated with bisphosphonates. Randomized, active-controlled, international, multicenter, multidose, and parallel group phase II study involving 56 centers and 255 women with breast cancer</td>
<td>Patients were stratified into six treatment arms: (a) denosumab 30 mg every 4 weeks, (b) denosumab 120 mg every 4 weeks, (c) denosumab 180 mg every 4 weeks, (d) denosumab 60 mg every 12 weeks, (e) denosumab 180 mg every 12 weeks, or (f) IV bisphosphonates every 4 weeks at physician’s discretion: 91% of this group received ZOL. Effectiveness was measured by median percent change in uNTx/Cr from baseline to week 13; 65% reduction from baseline was noted as effective suppression. Study lasted 24 weeks; continued follow-up extended for an additional 32 weeks.</td>
<td>On-study SREs developed in 9% of patients treated with denosumab versus 16% of patients treated with IV bisphosphonates. A greater than 65% reduction in uNTx/Cr occurred in 74% of pooled patients treated with denosumab versus 63% of patients treated with IV bisphosphonates. Median time to greater than 65% reduction in uNTx/Cr was 13 days in patients treated with denosumab versus 29 days for patients treated with IV bisphosphonates. Denosumab 120 mg every 4 weeks showed the greatest overall median suppression at week 13 and resulted in a numerically greater extent of suppression of uNTx/Cr than denosumab every 12 weeks. No apparent dose-dependent increase in adverse events occurred.</td>
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SC—subcutaneous; SRE—skeletal-related event; uNTx/Cr—urine N-telopeptide of type I collagen adjusted for creatinine; ZOL—zoledronic acid

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TABLE 1. Summary of the Included Studies (Continued)

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<td>Martin et al., 2012</td>
<td>To compare denosumab with ZOL for the prevention of SREs in patients with advanced breast cancer Further analysis of Stopeck et al. (2010)</td>
<td>A total of 2,046 patients with advanced breast cancer enrolled and were split into two treatment arms: (a) denosumab 120 mg with IV placebo or (b) SC placebo with ZOL 4 mg.</td>
<td>Denosumab reduced the risk of skeletal complications, including preventing or delaying SREs, radiation to bone, or hypercalcemia of malignancy. Regardless of SRE history, denosumab prolonged time to first radiation to bone by 26% versus ZOL (p = 0.012). Denosumab prolonged time to first SRE or hypercalcemia of malignancy by 18% compared to ZOL (p = 0.007). On-study SREs with denosumab were 31% versus 36% with ZOL (p = 0.006). Multiple on-study SREs were 33% with denosumab versus 38% with ZOL (p = 0.16).</td>
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<td>Stopeck et al., 2010</td>
<td>To compare denosumab with ZOL in delaying or preventing SREs in patients with breast cancer and bone metastases International, randomized, double-blind, and active-controlled phase III study involving 322 centers and 2,046 patients</td>
<td>Two treatment arms were involved: (a) denosumab 120 mg with IV placebo or (b) SC placebo with ZOL 4 mg. SREs were assessed by skeletal surveys every 12 weeks or radiographic assessments and identified independently by at least two radiologists. Bone turnover markers were measured at baseline and week 13. Median time on the study was 17 months.</td>
<td>Denosumab delayed time to first on-study SRE by 18% versus ZOL and reduced risk of multiple SREs by 23% (p = 0.001). Median time to first on-study SRE was not yet reached for denosumab versus 26.4 months ZOL (p = 0.01). Denosumab reduced the mean skeletal morbidity rate by 22% versus ZOL (p = 0.004). At week 13, median uNTx/Cr decreased by 80% in denosumab versus 68% in ZOL (p = 0.001). Overall survival (p = 0.49) and disease progression (p = 0.93) were similar between groups.</td>
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SC—subcutaneous; SRE—skeletal-related event; uNTx/Cr—urine N-telopeptide of type I collagen adjusted for creatinine; ZOL—zoledronic acid

Discussion

The analyzed studies support consideration of denosumab as part of the therapeutic regimen in the prevention of SREs in patients with metastatic breast cancer. Denosumab was shown to be at least as effective or more effective than current standard therapy with zoledronic acid. In all studies analyzed for the current article, no AEs that were considered to be dose dependent, severe, or life threatening were reported with denosumab therapy. No evidence of renal toxicity, liver...
failure, or antidenosumab antibodies was shown. The adverse reactions noted were comparable to those observed with standard bisphosphonate therapy.

However, each study had specific AEs that should be noted. Stopeck et al. (2010) observed hypocalcemia occurring more often in the denosumab cohort than in the zoledronic acid cohort. Most instances occurred within the first six months of the initiation of therapy and were generally not related to clinical changes or increased monitoring (Stopeck et al., 2010). The grade 3 or 4 AEs of hypocalcemia were similar between groups: 1.6% denosumab versus 1.2% zoledronic acid (Stopeck et al., 2010). Lipton et al. (2007) found that 8% of patients receiving denosumab and 5% of patients receiving zoledronic acid had asymptomatic hypocalcemia. Calcium levels normalized without intervention in 63% of patients receiving denosumab and in 50% of patients receiving zoledronic acid. Fizazi et al. (2009) found that 11% of the denosumab cohort had severe hypocalcemia versus 3% of the bisphosphonate cohort. The absolute values used to define severe hypocalcemia were not reported in these studies. Because of the mechanism of action of denosumab, oral supplementation of calcium (at least 500 mg per day) and vitamin D (at least 400 IU per day) was recommended in all studies.

Body et al. (2006) determined fatigue to be the most common AE, reported in 25% of patients receiving denosumab and in 40% of patients receiving pamidronate. Denosumab injections caused injection-site reactions in 3% of participants in the Lipton et al. (2007) study. Fizazi et al. (2009) noted similar rates of AEs in denosumab and bisphosphonate groups and saw no difference between the two denosumab doses. More than 20% of patients in both groups reported bone pain, nausea, anemia, constipation, and asthenia (Fizazi et al., 2009).

In Stopeck et al. (2010), the largest study reviewed, 18 AEs were reported. Pyrexia, bone pain, arthralgia, and renal failure were more common in the zoledronic acid cohort, whereas toothache and hypocalcemia were seen more frequently in patients who received denosumab (Stopeck et al., 2010). Severe and serious renal AEs occurred in about 4% of participants in the zoledronic acid cohort and in about 1% of the denosumab group (Stopeck et al., 2010). In addition, Stopeck et al. (2010) determined that the overall number of severe and serious AEs were balanced between the two cohorts. In Cleeland et al. (2013), patients receiving denosumab reported less pain, less interference with activities of daily living by pain, and less opioid use when compared to patients receiving zoledronic acid.

Practice changes must take into consideration the effectiveness of new drugs compared to standard therapy, as well as the financial cost of new therapies. Stopeck et al. (2012) developed a Markov lifetime model looking at the cost effectiveness of denosumab versus zoledronic acid. The cost for each SRE avoided by bisphosphonate therapy was estimated to be about $13,500 (Stopeck et al., 2012). Using a Markov model, Xie, Diener, Sorg, Wu, and Namjoshi (2012) analyzed the cost of medication, an AE, and SRE treatment from the perspective of a third-party payer and found that the overall cost of denosumab therapy was $7,522 more than zoledronic acid therapy. When SREs occur, treatment options (e.g., radiation therapy and surgery for fractures) can be costly. In addition, patients’ QOL must be considered when making treatment decisions. Although denosumab has been shown to be effective in the treatment of SREs in patients with advanced breast cancer, financial concerns should be considered when prescribing this medication.

**Implications for Practice**

- Recognize skeletal-related events (SREs) as complications of metastatic breast cancer.
- Understand that SRE prevention is a goal for the management of metastatic breast cancer and that if SREs develop, they can decrease patient mobility and quality of life, as well as increase pain.
- Complete a thorough pain assessment at every patient visit because pain can be the first indication of an SRE, and use denosumab (Xgeva®) to reduce the risk of SRE development in patients with metastatic breast cancer.

This synthesis of research on denosumab is valuable for oncologists and oncology advanced practice providers. Providers must be aware of new medical advances that may improve patient care. New medications, such as denosumab, may prevent SREs in patients with metastatic bone disease. Translation of evidence into clinical practice is imperative to providing the best and safest patient care. As breast cancer advances, patients commonly develop bone metastases, which can dramatically decrease QOL and increase pain. Providers should be aware of available interventions that reduce this risk and maintain QOL. This article summarizes the findings of current literature to aid providers in making informed decisions about preventive measures. In addition, this information is important to oncology nurses because it allows them to recognize patients at risk for SREs and increases awareness of SREs as complications of advanced breast cancer.

The analysis of pain in patients receiving denosumab versus zoledronic acid by Cleeland et al. (2013) noted that patients receiving denosumab had less severe pain and longer pain-free intervals than those receiving zoledronic acid. Oncology nurses must be aware of preventive measures and additional nursing assessments required for patients taking denosumab. They must adequately assess pain and complete a medication review during every visit. Oncology nurses and other providers must encourage daily calcium and vitamin D supplements, as well as assess compliance while patients are receiving denosumab. Findings from these studies may inform providers and improve patient education regarding rationale for use and potential complications of therapies with osteoclast modifiers, such as denosumab.

**Future Research**

Denosumab may be added to current practice guidelines regarding the prevention of SREs in patients with breast cancer. More research is needed to understand how other
factors besides RANKL contribute to the development of bone metastases. This knowledge is necessary to further guide the pharmacological prevention of SREs in the population of patients with breast cancer. Another important research question is whether 120 mg of denosumab is the most effective and safest dose in this population. Monte Carlo simulations of Lipton et al.’s (2007) study involving 255 participants were used to identify the clinical dosing of Stopeck et al.’s (2010) study. Based on the results of Stopeck et al.’s (2010) study of more than 2,000 patients, the FDA approved denosumab 120 mg for prevention of SREs in patients with metastatic breast cancer. Future studies that examine dosing and frequency of administration may show increased effectiveness and patient safety.

Another area for future research is how study participants' current disease status may influence study results. For example, Body et al. (2006), Fizazi et al. (2009), Lipton et al. (2007), and Stopeck et al. (2010) all had inclusion criteria of known metastatic disease. However, Lipton et al. (2007) specifically excluded patients with evidence of an impending fracture in a weight-bearing bone. All participants in the Fizazi et al. (2009) study had had previous bisphosphonate therapy, whereas Lipton et al. (2007) and Stopeck et al. (2010) excluded patients who had undergone previous bisphosphonate therapy. In addition, the Fizazi et al. (2009) study had three treatment arms. One was a control arm in which patients continued previous bisphosphonate regimens (86% on zoledronic acid, 14% on pamidronate); the other two arm examined denosumab 180 mg given every 4 or 12 weeks. Results from the studies may not be solely indicative of the effects of bisphosphonates or denosumab but of later-stage disease. For example, because all patients in the Stopeck et al. (2010) study had radiographic evidence of at least one bone metastasis at study entry, the authors explored the prevention or delay in development of SREs in this population. Variability in study design, as well as in inclusion and exclusion criteria, makes synthesizing findings and making recommendations for practice a challenge. However, therapy with bisphosphonates is involved in preventing SREs in patients with cancer bone metastases. Further research will be beneficial in confirming dosing, assessing preventive treatment with calcium and vitamin D, and determining the role of bone-protective agents in preventing bone metastases in those at risk.

Conclusion

Four primary studies were analyzed with particular attention paid to the effectiveness of denosumab compared to zoledronic acid (Body et al., 2006; Fizazi et al., 2009; Lipton et al., 2007; Stopeck et al., 2010). Zoledronic acid has been the standard of care for prevention of SREs, but studies have shown denosumab to be just as or more effective. In all studies, uNTx levels, which are a predictor of bone loss and can accurately estimate a patient’s risk of developing SREs, were measured. Some studies also directly measured SREs with radiographic scans. In these studies, denosumab was shown to be superior to zoledronic acid in suppression of uNTx levels. However, because overall survival and disease progression were similar when comparing denosumab and zoledronic acid, further research is necessary to warrant the higher cost of denosumab.

References


