Denosumab for the Prevention of Skeletal-Related Events in Patients with Bone Metastasis from Solid Tumor

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Most patients with advanced malignancy develop bone metastases during the course of their disease. For the remainder of the patient's life, these bone metastases lead to skeletal-related events such as pathologic fractures and spinal cord compression, as well as bone pain or lesions requiring palliative radiation therapy or surgery to prevent or treat fractures. Skeletal-related events result in increased morbidity, mortality and health care costs. For the past decade, intravenous bisphosphonates (zoledronic acid, pamidronate) have been recognized as the primary pharmacologic options in the prevention or treatment of skeletal-related events in patients with bone metastasis. Recently, the United States Food and Drug Administration approved denosumab, a fully human monoclonal antibody, for the prevention of skeletal-related events in patients with bone metastases from solid tumors. Three prominent clinical trials were conducted to establish the efficacy of denosumab. In two of three trials, denosumab was found to delay the time to first skeletal-related event significantly more than zoledronic acid in patients with breast or castration-resistant prostate cancer with bone metastasis. The third trial found denosumab to be noninferior to zoledronic acid in patients with metastases from solid tumors, excluding breast and prostate solid tumors. Overall survival and progression-free survival were similar between zoledronic acid and denosumab. Thus, evidence is insufficient to prove a greater efficacy of one agent over the other. According to the American Society of Clinical Oncology and the National Comprehensive Cancer Network, patients with bone metastasis should have zoledronic acid, pamidronate, or denosumab (with calcium and vitamin D supplementation) added to their chemotherapy regimen if they have an expected survival of 3 months or longer and have adequate renal function.

Key Words: denosumab, RANK ligand inhibitor, skeletal-related event, bone metastases.

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OUTLINE

Cancer is the second leading cause of mortality in the United States.[1] Skeletal-related events due to bone metastasis are a common cause of complications in patients with malignancies and increase morbidity and mortality in these patients.[2] Bone metastasis is frequently seen in patients with many advanced cancers, particularly breast, prostate, kidney, bladder, and lung malignancies.[3] Despite improvements in the treatment of these cancers, skeletal-related events significantly decrease the quality of life of patients with advanced disease. These events include pathologic fractures, spinal cord compression, hypercalcemia due to malignancy, and bone pain or lesions requiring palliative radiation therapy or surgery to prevent or treat fractures.[4, 5] The goal for treatment of bone metastasis is to prevent, or at least reduce the frequency of, complications from skeletal-related events, thus improving quality of life and functional independence of patients.

For the past decade, the National Comprehensive Cancer Network (NCCN) and the American Society of Clinical Oncology (ASCO) have recognized intravenous bisphosphonates such as zoledronic acid and pamidronate disodium as pharmacologic options for the prevention or treatment of skeletal-related events in patients with bone metastasis.[6, 7] Bisphosphonates are antiresorptive agents that inhibit osteoclast-mediated bone resorption by decreasing their activity and interfering with attachment.[2] This reduces tumor-induced osteolysis in patients with bone malignancies. The U.S. Food and Drug Administration (FDA) has approved intravenous zoledronic acid and pamidronate for the treatment of skeletal-related events in patients with bone metastasis. These two drugs have been shown to be efficacious in the treatment of skeletal-related events related to malignancies in numerous clinical trials.

Recently, denosumab, a fully human monoclonal antibody, was added to practice guidelines as a therapeutic option to help prevent skeletal-related events in patients with bone metastasis.[6, 7] Denosumab binds to the receptor activator of nuclear factor κ B (RANK) ligand (RANKL), which is a protein responsible for formation, function, and survival of osteoclasts. Denosumab prevents RANKL from activating its receptor, RANK, on the surface of osteoclasts. Therefore, denosumab reduces bone resorption, tumor-induced bone destruction, and skeletal-related events.[8, 9]

According to the NCCN and ASCO, denosumab, zoledronic acid, or pamidronate (in combination with calcium and vitamin D supplements) should be given to patients in addition to chemotherapy or endocrine therapy when there is evidence of bone metastases. Dental examination should be performed before initiation of these therapies, with monitoring of oral health during treatment because of the risk of developing osteonecrosis of the jaw.[6, 7]

Pathophysiology of Bone Metastases

Bone is the preferred site of metastasis for certain solid tumors. The basis for localization to the bone is not completely understood, but it involves communication between the tumor and the molecular components of the bone microenvironment.[10] Multiple cytokines and other signaling molecules normally involved in bone remodeling can be manipulated by tumor cells to facilitate their localization and proliferation. Bone remodeling involves the interaction between diverse cell types, including osteoclasts and osteoblasts, and an array of hormones and cytokines. During normal bone remodeling, bone osteoclast-mediated bone resorption is tightly coupled to osteoblast-mediated bone formation.[11] Alterations to this coupling can have dramatic effects on the bone microarchitecture.

A common pathway involved in osteoclast activation involves the receptor activator for RANK, RANKL, and osteoprotegerin.[12] The RANKL protein is a member of the tumor necrosis factor family of cytokines that is abundantly expressed in bone and lymphoid tissues. In the bone, it is produced by osteoblasts, bone marrow stromal cells, and certain cells of the immune system. The RANKL and macrophage colony-stimulating factor binding to their cognate receptors on preosteoclasts are vital for osteoclastogenesis and osteoclast activation. Osteoblasts can also be stimulated to secrete osteoprotegerin, which is a decoy RANK receptor. Osteoprotegerin binds RANKL and decreases the RANKL available to activate RANK, thereby decreasing bone resorption. Whether osteoblasts produce RANKL or osteoprotegerin depends on

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the presence of hormones, cytokines, and other factors that influence osteoblast activity.[11]

Tumor metastasis to bone leads to an imbalance in osteoblast and osteoclast activities and frequently results in skeletal-related events. The metastases are classified as either osteolytic or osteoblastic, although many cancers display both components to varying degrees.[13] Osteolytic metastases are the most common and involve abnormal osteoclast activity resulting in dysregulated bone destruction. Decreased osteoblast activity can also be present. Osteoblastic metastases are believed to be primarily caused by factors produced by cancer cells that lead to dysregulated osteoblast activity and abnormal bone formation.[14]

Osteolytic metastases generally involve tumor cell upregulation of RANK-RANKL signaling, either directly or indirectly. A tumor-derived osteolytic factor that is crucial for the metastasis of many tumors to bone is parathyroid hormone-related peptide.[15] This peptide stimulates osteoblasts to produce RANKL. The bone microenvironment contains a number of immobilized growth factors such as transforming growth factor (TGF)-β, platelet-derived growth factor, cytokines, and ionized calcium that are released upon bone resorption. These factors have a major impact on osteoclast and tumor cell activity. For example, the TGF-β that is released upon bone resorption increases parathyroid hormone-related peptide secretion by the tumor cells.[16] This type of complex interplay between tumor cells and the bone microenvironment sets up a vicious cycle that leads to further osteolysis and to a selective growth advantage for the tumor cells.

Osteoblastic metastases involve tumor cell–derived factors that lead to osteoblast formation such as endothelin-1.[17] Endothelin-1 suppresses a negative regulator of the Wnt/β-catenin signaling pathway, leading to osteoblast activation.[18] Although dysregulated osteoblastic activity is dominant in this type of metastasis, there is some evidence to suggest an osteolytic component in these tumors, hence, the use of antiresorptive drugs in the treatment of some tumors that are primarily osteoblastic in nature.[19]

Bisphosphonate Pharmacology

Bisphosphonates are approved in combination with antineoplastic therapy for the treatment of bone metastases from solid tumors and multiple myeloma.[20] They are effective in reducing the occurrence of skeletal-related events. Bisphosphonates are negatively charged analogs of pyrophosphate that are capable of chelating calcium, and therefore bind avidly to bone.[21] Once bound, bisphosphonates are incorporated into the bone matrix until they are released in the acidic environment of the osteoclast resorption lacunae during remodeling. After release they are internalized by osteoclasts where they inhibit osteolysis.

Bisphosphonates may or may not contain nitrogen, which affects the mechanism by which they inhibit osteoclast activity.[21] Those that contain nitrogen—pamidronate and zoledronic acid—are used in the treatment of bone metastases. Their major mechanism is inhibition of a key regulatory enzyme of the mevalonate pathway, farnesyl diphosphonate synthase.[22] This pathway produces isoprenoid groups that are needed for the posttranslational modification of small guanosine triphosphatases (GTPases), a class of signaling proteins including Ras and Rho. The function of these GTPases requires the isoprenoid (prenyl) group to anchor them to the cell membrane. By disrupting these signaling pathways, the nitrogen-containing bisphosphonates lead to loss of osteoclast activity.

By affecting the activity of small GTPases, bisphosphonates impact a wide variety of processes in the cell including growth, cellular differentiation, and cell movement. Emerging evidence from in vitro and in vivo preclinical studies in several tumor types indicate that bisphosphonates can reduce tumor burden in bone and soft tissue, inhibit angiogenesis, prevent tumor cell invasion and adhesion in bone, induce tumor cell apoptosis, and affect angiogenesis.[23] There is further evidence to suggest that combining bisphosphonates with cytotoxic chemotherapy may provide synergistic antitumor activities.[24]

Both zoledronic acid and pamidronate are administered by intravenous infusion.[20] Pamidronate is infused over at least 2 hours every 3–4 weeks, whereas zoledronic acid is infused over at least 15 minutes every 3–4 weeks. Zoledronic acid is a 100–850-fold more potent inhibitor of bone resorption than pamidronate and has a prolonged response time in comparison to other bisphosphonates.[20] It distributes mainly to bone in a triphasic process. The early distribution half-life is 0.23 hour, early elimination half-life is 1.75 hours, and terminal elimination half-life is 167 hours, with low plasma concentrations observed up to 28 days after administration. Elimination from the bone appears to be considerably longer, as markers of bone turnover

continue to be decreased 3 years after administration of a single dose.[25] Pamidronate also preferably distributes to bone. The plasma half-life is 28 ± 7 hours, and the terminal phase elimination half-life in bone is approximately 300 days.[20]

Both zoledronic acid and pamidronate are eliminated unchanged in the urine, and both can cause renal impairment. Monitoring of serum creatinine concentration is recommended during therapy.[20] If renal function deteriorates during pamidronate therapy, treatment may need to be withheld until the serum creatinine concentration is within 10% of the baseline value, but no quantitative recommendations for dosage adjustments with renal impairment are available.[20] Zoledronic acid can be used to treat hypercalcemia of malignancy without dosage adjustments in patients with mild-to-moderate renal impairment, but in patients with a serum creatinine concentration greater than 4.5 mg/dl, the drug should be used only if the benefit of treatment outweighs the risk of further renal damage.[20] In patients with multiple myeloma or bone metastases, dosage adjustments of zoledronic acid are recommended for patients with mild-to-moderate renal impairment, but the drug is not recommended for patients with a serum creatinine concentration greater than 3 mg/dl.[20]

Bisphosphonate therapy for bone metastasis is usually started as soon as there is radiographic evidence of bone disease and is continued indefinitely, although trials assessing treatment duration are ongoing.[26]

Denosumab Pharmacology

Denosumab is a fully human monoclonal antibody that binds to RANKL and prevents its interaction with the RANK receptor on preosteoclasts, as well as the receptor on activated T and B lymphocytes.[27] Because of the key role of RANK activation in osteoclast formation and activation, denosumab decreases bone resorption and increases mass and strength in both cortical and trabecular bone. The beneficial effects of denosumab may extend beyond its indication for bone metastasis management. Expression of RANK has been detected in a wide percentage of bone metastases deriving from several different primary histotypes including breast and prostate, and there appears to be high concordance in RANK expression between bone metastasis and corresponding primary tumors.[28] Preliminary evidence suggests that RANK expression status of cancer cells directs tumor migration to bone where RANKL is abundantly expressed.[29] Several studies have concluded that blocking the RANKL-RANK interaction may prevent progression of both breast and prostate cancer in bone.[30–32] Denosumab is being evaluated as adjuvant therapy in women with early-stage breast cancer who are at a high risk for disease recurrence.[33]

Denosumab is given as a 120-mg dose by subcutaneous injection every 4 weeks.[20] The mean terminal half-life is approximately 28 days. Unlike the bisphosphonates, denosumab is primarily a circulating soluble protein that does not bind to bone surfaces.[34] Clearance of denosumab occurs through the reticulendothelial system and is independent of renal clearance.[35] Although dose adjustment is not required with renal impairment, patients with a creatinine clearance of less than 30 ml/minute are at a greater risk for developing hypocalcemia with denosumab therapy.[9] Measurements of bone mineral density decrease to baseline values within 12 months of therapy discontinuation.[36]

Clinical Efficacy

To our knowledge, no studies have directly compared denosumab with pamidronate for the prevention of skeletal-related events in patients with bone metastases. Three studies have been published that compared denosumab with zoledronic acid.

A phase III, randomized, double-dummy, noninferiority trial compared denosumab with zoledronic acid for bone metastases in men aged 18 years or older with castration-resistant prostate cancer.[37] Those enrolled in the trial had confirmed prostate cancer, with bone metastasis at one or more sites and with at least one failed hormonal therapy. Those who had previous treatment with bisphosphonates for metastases or planned radiation were excluded. Patients were randomly assigned to denosumab 120 mg (950 patients) or zoledronic acid 4 mg (951 patients) and were stratified according to previous skeletal events, prostate-specific antigen (PSA) concentration, and receipt of chemotherapy within 6 weeks of enrollment. Approximately 85% of patients were Caucasian and had a PSA level greater than 10 μg/l. Twenty-four percent of patients had experienced a previous skeletal-related event.

Time to first skeletal-related event during the study period was the primary end point.[37] Additional end points included overall survival, disease progression, PSA concentration, and

change in bone turnover markers. Patients were evaluated at baseline and every 12 weeks for skeletal-related events with radiographs of the skull, spine, chest, pelvis, upper arm, and thigh. An event was defined as a pathologic fracture (except those from trauma), radiation therapy to the bone, surgery to the bone, or spinal cord compression. This trial estimated at 90% power to detect noninferiority, which was defined as denosumab preserving at least half of the effect of zoledronic acid; if noninferiority was reached, there was a 90% power to detect superiority. Data were analyzed by using an intent-to-treat approach.

Skeletal-related events occurred in 38% of patients, 341 patients treated with denosumab and 386 treated with zoledronic acid. Compared with zoledronic acid, denosumab delayed the time to skeletal-related event by 18% (hazard ratio [HR] 0.82, 95% confidence interval [CI] 0.71–0.95, p=0.008 for superiority). The between-group difference was 3.6 months. Overall survival, disease progression, and PSA concentrations did not differ significantly between denosumab and zoledronic acid groups. The most common adverse effects reported for denosumab and zoledronic acid, respectively, included anemia (36% in each group), back pain (32% and 30%), and various gastrointestinal effects. Infectious events occurred in 43% and 40% of patients receiving denosumab and zoledronic acid, respectively. Osteonecrosis of the jaw occurred in a small number of patients—32 in the denosumab group and 13 in the zoledronic acid group; many had a history of tooth extraction, poor dental hygiene, or use of a dental appliance. Hypocalcemia occurred significantly more frequently in patients treated with denosumab (13% vs 6%, p<0.0001).

A second randomized, double-dummy, double-blind, noninferiority, phase III study compared denosumab 120 mg with zoledronic acid 4 mg for delaying skeletal-related events in patients aged 18 years or older with breast cancer and at least one confirmed site of bone metastasis.[8] Patients were excluded if they had received previous bisphosphonate therapy for treatment of bone metastases, had unhealed dental or oral surgery, or had a malignancy within the 3 years before randomization. Patients were randomly assigned to denosumab (1026 patients) or zoledronic acid (1020 patients) and stratified according to previous skeletal-related event, prior oral bisphosphonate use, current chemotherapy, and geographic location. Skeletal events were defined and determined as in the previous trial.[37]

The primary efficacy end point of the trial was time to first skeletal-related event during the study period.[8] Additional end points included overall survival, disease progression, and biochemical markers of bone turnover. This study had a 97% power to detect noninferiority. Noninferiority was assumed to demonstrate that denosumab preserves more than 50% of the treatment effect of zoledronic acid. If noninferiority was achieved, the study had a 90% power to determine superiority of denosumab. Data were analyzed by using an intent-to-treat approach.

Twenty-four percent of patients in each treatment group had more than two metastatic bone lesions; 37% of patients in each group had a previous skeletal-related event. Time to first skeletal-related event was delayed by 18% with denosumab compared with zoledronic acid (HR 0.82, 95% CI 0.71–0.95, p=0.01 for superiority). Overall survival and disease progression were not significantly different between groups. Denosumab significantly lowered markers of bone turnover more than zoledronic acid. Bone-specific alkaline phosphatase levels decreased a median of 44% with denosumab versus 37% with zoledronic acid (p<0.001), and urinary *N*-telopeptide:creatinine ratio decreased a median of 80% versus 68% (p<0.001). Common adverse events experienced by patients receiving denosumab versus zoledronic acid included gastrointestinal events (17.3–34.9% vs 20.2–37.9%), fatigue (29.5% vs 32%), back pain (23.6% vs 26.1%), bone pain (18.2% vs 23.5%), and anemia (18.8% vs 22.9%). Serious infection events occurred in 7% and 8% of patients, respectively. Occurrence of osteonecrosis of the jaw was low, with 2% of the denosumab group and 1.4% the zoledronic acid group experiencing this event.

A third phase III, noninferiority study evaluated denosumab in patients with solid tumor and bone metastases or patients with myeloma and osteolytic lesions.[38] Patients were aged 18 years or older with confirmed solid tumor or myelomoa and at least one site of bone metastasis or lesion. Patients with breast or prostate solid tumors were excluded. Others excluded from the trial included those who received intravenous bisphosphonate therapy, had planned radiation or surgery to the bone, or had unhealed dental or oral surgery. Patients were randomly assigned to denosumab 120 mg (886 patients) or zoledronic acid 4 mg (890 patients) and stratified by tumor type, previous skeletal-related event, and systemic anticancer therapy at

enrollment. Approximately 40% of patients in each treatment group had non–small cell lung cancer as their primary tumor type. Skeletal events were defined and assessed as in the previous two trials.[8, 37]

The primary efficacy end point was time to first skeletal-related event during the study period.[38] Additional end points included overall survival, disease progression, and biochemical markers of bone turnover. Power of the study was stated to be sufficient to determine noninferiority. This would assume that denosumab preserved 50% or more of the effect of zoledronic acid. Data were analyzed by using an intent-to-treat approach.

Denosumab delayed time to first skeletal-related event by 16% compared with zoledronic acid (HR 0.84, 95% CI 0.71–0.98, p=0.0007). However, denosumab failed testing for superiority (p=0.06). Survival and disease progression were not significantly different between groups. Markers of bone turnover were decreased significantly more at 13 weeks with denosumab compared with zoledronic acid (p<0.001 for urine *N*-telopeptide:creatinine ratio and bone-specific alkaline phosphatase concentration). Common adverse events with denosumab and zoledronic acid, respectively, included those related to gastrointestinal events (21.2–28.2% vs 20.8–30.3%), anemia (27.6% and 32.6%, p=0.03, unadjusted), fatigue (~25% for both), back pain (19.7% and 22.3%), and pyrexia (15.8% and 20.7%, p=0.01, unadjusted). Serious infectious adverse events occurred in approximately 14% of patients in both treatment groups. The rate of osteonecrosis of the jaw was low in both groups (1.1% and 1.3%, respectively). Of the 21 patients in the study to develop this event, 17 had risk factors known to be associated with osteonecrosis of the jaw (tooth extraction, poor oral hygiene, use of dental appliance).

Each of the three studies that evaluated denosumab for the prevention of skeletal-related events were well designed and used methods such as randomization and blinding to reduce bias. Also, outcomes across all studies were consistently defined and measured. Each study took the opportunity to explore the benefits of denosumab in specific situations[8, 37] in addition to a broader population.[38]

In light of these positive aspects, these studies are not without limitations. One could argue the use of a noninferiority design was not appropriate, especially since superiority testing was conducted as well. Also, with this design, one may question if the criteria for noninferiority were appropriate. Each study determined that as long as denosumab performed at 50% or more of the effect of zoledronic acid, then it could be considered noninferior. One would need to consider the clinical impact of that difference. A drug considered no worse than a regularly used therapy but potentially performs at only half the efficacy rate may not be ideal. As denosumab was considered superior in two of the three studies,[8, 37] this is likely not a major limitation to the trials.

One should consider the involvement of the study sponsor in the development and execution of the trials. Each trial was sponsored by Amgen Inc. (Thousand Oaks, CA), the manufacturer of denosumab. Also, lead investigators were commonly Amgen employees. Despite the heavy involvement of the study sponsor, appropriate measures appear to have been taken to reduce bias within the study methodology. Finally, one may question why denosumab was found to be superior in two trials, but not the third. The third study was well designed and had what appears to be an appropriate sample size.[38] Although the authors state that an appropriate power was included, we do not know the final power of the study. Perhaps the sample size was not large enough to detect a difference for superiority testing. All studies used similar methodologies, the same primary end point, and defined and assessed the end point the same way. The major difference was the patient population studied. Perhaps the exclusion of breast and prostate cancers from the third study played a part. Additional trials in those populations are needed to further determine the benefit of denosumab compared with zoledronic acid.

Safety and Tolerability

Zoledronic Acid and Pamidronate

Bisphosphonates are generally well tolerated at recommended doses if both prescribers and patients adhere to the monitoring guidelines. The most common adverse events with intravenous bisphosphonates (zoledronic acid and pamidronate) are transient early-phase reactions at the initial administration. They include hypocalcemia, hypophosphatemia, pyrexia, myalgia, arthralgia, and bone pain. However, these are not usually long-term events and usually resolve with ongoing monthly therapy. Daily oral calcium and vitamin D supplements are recommended in order to minimize the occurrence of hypocalcemia during therapy.

Renal toxicity and osteonecrosis of the jaw are the more serious adverse events that need to be monitored at baseline and during therapy with intravenous bisphosphonates. Recent trials have shown that nephrotoxicity may occur in 6% of patients receiving pamidronate and 8% of patients receiving zoledronic acid. In patients with impaired renal function, dosing adjustments need to be made to avoid nephrotoxicity. Also, temporary interruption of treatment is recommended if a patient's serum creatinine concentration significantly increases compared with the baseline level.[2] According to FDA-approved labeling, serum creatinine concentration monitoring at baseline and during treatment before administration of each dose is recommended. Practice guidelines dictate monitoring levels of serum calcium, electrolytes (magnesium, phosphate), and hemoglobin and hematocrit during intravenous bisphosphonate treatments; however, frequency of monitoring is not specified.

Osteonecrosis of the jaw is a rare but serious occurrence that has been reported in patients receiving intravenous bisphosphonates. Both ASCO and NCCN recommend completion of any dental work before the start of treatment and preventive oral care during treatment in order to minimize the risk of developing osteonecrosis of the jaw. Patients should avoid extensive dental work while receiving bisphosphonate therapy.[2, 7, 39]

Denosumab

In three randomized, double-blind studies (2841 patients), the most common adverse effects observed among 18% or greater of patients who were treated with denosumab were nausea (31%), diarrhea (20%), fatigue and asthenia (45%), hypocalcemia (18%), and hypophosphatemia (32%).[8, 9] Hypophosphatemia and hypocalcemia occurred more commonly with denosumab than with the intravenous bisphosphonate zoledronic acid.[9, 40] The most common serious reaction in patients receiving denosumab was dyspnea.[8] Early-phase reactions associated with flu-like syndrome were also reported in a small percentage of patients after starting treatment and then at the end of the 4-week trial.[8] However, these occurrences were 2.7 times more common in the zoledronic acid group than in the denosumab group. Severe hypocalcemia and hypophosphatemia were more common among patients using denosumab than zoledronic acid.[9]

The frequency of osteonecrosis of the jaw was similar between denosumab and zoledronic acid groups.[8, 37] The most common adverse effecs that led to discontinuation of denosumab were hypocalcemia and osteonecrosis of the jaw. The overall survival rate of patients were similar between patients using denosumab and those receiving zoledronic acid.[9]

Dosing and Administration

Pamidronate

Pamidronate is FDA approved for treatment of moderate or severe hypercalcemia with malignancy, with or without bone metastases in adults. The safety and efficacy data have not been established in the pediatric population.[41] The initial recommended dose of pamidronate for moderate hypercalcemia with malignancy is 60–90 mg as a single-dose intravenous infusion administered over 2–24 hours, in an attempt to reduce the renal toxicity associated with this product, particularly in patients with preexisting renal insufficiency. The initial recommended dose for severe hypercalcemia with malignancy is 90 mg as a single-dose infusion administered at the same infusion rate.

It is necessary to calculate the corrected serum calcium level of each patient planning to receive pamidronate in order to determine the appropriate category of hypercalcemia. A corrected serum calcium level of 12–13.5 mg/dl corresponds to moderate hypercalcemia, and greater than 13.5 mg/dl corresponds to severe hypercalcemia.[41] The following formula can be used to calculate albumin-corrected serum calcium level: observed serum calcium (mg/dl) + 0.8 (4.0 – observed serum albumin [g/dl]).

Pamidronate should always be used in conjunction with adequate hydration, typically in the form of normal saline, which should be started promptly to maintain urine output at approximately 2 l/day throughout the duration of treatment. Retreatment may be necessary for patients who achieve only a partial response with initial therapy, especially if serum calcium levels do not return to or remain in the normal range after treatment. It is recommended that a minimum of 7 days elapse before retreatment is started to allow the initial dose time to achieve full response.[41]

Pamidronate is also FDA-approved for treatment of osteolytic bone metastases of breast cancer, in conjunction with antineoplastic therapy.

The initial recommended dose for this indication is 90 mg administered as a 2-hour infusion given every 3–4 weeks. Common antineoplastic agents used with pamidronate include doxorubicin, vinblastine, methotrexate, and tamoxifen. Before starting each treatment, the patient's serum creatinine concentration should be assessed to determine if any renal deterioration has occurred as a result of pamidronate therapy, and if so, dosage adjustments should be made accordingly. The optimum duration of pamidronate therapy is not known, but studies demonstrated an overall benefit when therapy was administered for 24 months.[41]

Pamidronate is supplied as 30- and 90-mg intravenous powder for injectable solution. Reconstitution of the powder is performed by adding 10 ml of sterile water for injection to the vial, producing a final concentration of 30 mg/10 ml or 90 mg/10 ml. The drug powder should be completely dissolved before any of the solution is withdrawn. The reconstituted product can be stored for up to 24 hours in the refrigerator before dilution into 0.45% or 0.9% sodium chloride or 5% dextrose in water (D_5W). If treating hypercalcemia of malignancy, the recommended dose should be diluted into 1000 ml of either 0.45% or 0.9% normal saline or D_5W, which will remain stable at room temperature for up to 24 hours. The dose should be administered as a slow intravenous infusion over 2–24 hours to avoid renal toxicity, as mentioned earlier.[41, 42] If treating osteolytic bone metastases of breast cancer, the recommended dose should be diluted into 250 ml of either 0.45% or 0.9% normal saline or D_5W, which will remain stable at room temperature for up to 24 hours. The dose should be administered as a slow intravenous infusion over a 2-hour period every 3–4 weeks. The maximum dose for all indications in adults is 90 mg in each intravenous infusion.[41, 42]

The product labeling does not specify any quantitative renal dosing adjustments for pamidronate; however, it is recommended to modify the dose dependent on the patient's clinical response and degree of renal deterioration, as determined by the increase in serum creatinine concentration from baseline. An increase in serum creatinine concentration of 0.5 mg/dl in patients with normal baseline function, and an increase of 1.0 mg/dl in patients with abnormal baseline function, is considered grounds for withholding therapy. Pamidronate therapy is resumed only when serum creatinine concentrations return to within 10% of normal baseline values.[41, 42] It is recommended to therapeutically monitor serum levels of calcium, phosphorus, magnesium, and electrolytes, as well as serum creatinine and blood urea nitrogen, while patients are receiving pamidronate.

Pamidronate is contraindicated in patients with severe hypersensitivity to this agent or any of the excipients, including mannitol and phosphoric acid. Pamidronate is also contraindicated in patients with hypersensitivity to bisphosphonates, such as alendronate, ibandronate, or risendronate.[41–43] Caution should be used when administering pamidronate to patients with deteriorating renal function, due to the significant risk of renal toxicity progressing into renal failure. A baseline serum creatinine concentration should be obtained and reassessed before each subsequent intravenous infusion to minimize the risk of renal impairment. Leukocytes should be monitored during the first 2 weeks of pamidronate treatment because of reports of leukopenia, particularly in those patients with preexisting blood dyscrasias.[42, 43]

Zoledronic Acid

Zoledronic acid is FDA-approved for treatment of patients with multiple myeloma and with documented osteolytic metastases from solid tumors, in conjunction with standard antineoplastic therapy.[44] Two formulations are available: zoledronic acid 4 mg/5 ml reconstituted solution for injection[44] and zoledronic acid monohydrate 5 mg/100 ml ready-to-infuse solution for injection.[45] The initial recommended dose of zoledronic acid monohydrate is 5 mg/100 ml, but the optimal duration of therapy is not known.[45]

Zoledronic acid supplied as 5-mg/100-ml ready-to-infuse solution for intravenous infusion should be administered as a single intravenous solution through a vented infusion line, separate from other drugs, at a constant infusion rate for an infusion time of no less than 15 minutes.[45] Patients must be adequately hydrated before infusion of zoledronic acid, and acetaminophen should be administered after the infusion to reduce the occurrence of early-phase reaction symptoms. Zoledronic acid should not come into contact with calcium or any other divalent cation-containing solutions, such as Ringer's lactate solution.[44, 45] Once the solution has been opened, it is stable for 24 hours if refrigerated. If the solution was previously refrigerated, allow

the solution to warm to room temperature before administering to the patient.[45]

The product labeling specifies that zoledronic acid should not be used in patients with severe renal impairment, which is a creatinine clearance of less than 35 ml/minute, because of the lack of clinical experience in this patient population. No dosage adjustments are required in patients with a creatinine clearance 35 ml/minute or greater.[45] Insufficient data are available for patients receiving dialysis. Serum levels of calcium, magnesium, phosphorus, electrolytes, creatinine and blood urea nitrogen, as well as a complete blood count with differential, should be monitored, while receiving zoledronic acid.[44, 45] The drug is contraindicated in patients with hypersensitivity to the agent or any of its components, such as mannitol or sodium citrate. Zoledronic acid is also contraindicated in patients with severe hypocalcemia; calcium levels must be corrected before initiation of therapy.[45] Extreme caution is advised with concomitant administration of zoledronic acid with other nephrotoxic drugs, such as aminoglycosides or nonsteroidal antiinflammatory drugs, or drugs that increase the risk of hypocalcemia, such as loop diuretics, to avoid the additive hypocalcemic effects induced by these agents.[45]

Denosumab

Denosumab is FDA-approved for the prevention of skeletal-related events in adults with bone metastases from solid tumors. The drug's safety and efficacy have not been established in the pediatric population.[9] The initial recommended dosage is 120 mg administered as a subcutaneous injection every 4 weeks in the upper arm, upper thigh, or abdomen. The administration of calcium and vitamin D may be necessary when receiving denosumab because of the associated risk of severe hypocalcemia. Vitamin D supplementation will vary dependent on baseline serum 25-hydroxyvitamin-D levels. A baseline value greater than 20 ng/ml requires vitamin D 400 IU/day, 12–20 ng/ml requires 800 IU/day, and use is discouraged if serum 25-hydroxyvitamin-D levels are less than 12 ng/ml. Calcium supplementation should be 500–1000 mg/day for treatment and prevention of hypocalcemia during administration with denosumab.[9]

Denosumab is supplied as a 120-mg/1.7-ml solution for injection in a single-use vial, which should be refrigerated in the original carton and protected from direct light and heat.[1, 2] Before use, denosumab may be removed from the refrigerator and brought to room temperature by allowing it to stand in the original container, which generally takes 15–30 minutes. It is important not to vigorously shake this product, in order to avoid the disruption of the monoclonal antibody structure. Visually inspect the product to ensure the absence of particulate matter and to check that the color is appropriate, typically a clear, colorless to pale yellow that may contain trace amounts of translucent to white proteinacious particles. Once the solution is at room temperature, a 27-gauge needle is used to withdraw and subcutaneously inject the entire 1.7-ml content of the vial into the designated site of injection. The vial must be discarded after entry or single-use administration.[9]

The product labeling for denosumab states that patients with renal impairment are at greater risk of severe hypocalcemia than patients with normal renal function. At this time, no renal dosing adjustments are available for patients with a creatinine clearance less than 30 ml/minute or for those receiving dialysis because of the absence of clinical data in this patient population.[9, 41] Periodic therapeutic monitoring of serum levels of calcium, phosphorus, and magnesium should be done to assess for hypocalcemia risks.

There are currently no contraindications to denosumab; however, preexisting hypocalcemia should be corrected before using this product. In addition, a dental examination should be performed before starting denosumab because of the risk of osteonecrosis of the jaw, and invasive dental procedures should be avoided for the duration of treatment.[9]

Place in Therapy

Intravenous bisphosphonates have been the cornerstone of therapy for the prevention of skeletal-related events in patients with bone metastasis for many years. These drugs include intravenous pamidronate 90 mg given over 2 hours and intravenous zoledronic acid 4 mg given over 15 minutes, both given at 3–4-week intervals. Recently, the FDA approved subcutaneous denosumab, a new RANKL inhibitor, for the same indication. Denosumab 120 mg injected subcutaneously every 4 weeks was shown to be effective in delaying skeletal-related events for 5 months or longer when compared with zoledronic acid.

Several factors need to be considered when choosing a treatment for a patient with cancer.

These include route of administration, toxicity, patient preferences, and cost. Denosumab has a more desirable route of administration over the intravenous bisphosphonates. Subcutaneous administration eliminates the need for an infusion clinic or space. This means that denosumab can be given subcutaneously at any office visit and requires a shorter duration for administration. It also reduces the risk of an early-phase reaction seen with intravenous formulations, and it is suitable for patients with no intravenous access. In patients with renal impairment, dosing adjustments are needed with the intravenous bisphosphonates. Denosumab does not need any renal dosing adjustment; therefore, monitoring of renal function is not needed. Patients with hypersensitivity to bisphosphonates may benefit from using denosumab.

Denosumab therapy does have some disadvantages. Denosumab has been shown to cause more severe cases of hypocalcemia compared with intravenous bisphosphonates; thus, monitoring calcium levels are very important when using this agent. Also, denosumab therapy costs one to five times more than intravenous bisphosphonate therapy.[46]

The concern for development of osteonecrosis of the jaw remains the same with all the available agents. The FDA labeling recommends that all patients need to receive dental examinations and preventive dentistry before initiation of treatment with bone-modifying agents. Patients should avoid extensive dental work and monitor their oral health while being treated with these agents.

Conclusion

Denosumab presents a new option for prevention of skeletal-related events; however, data do not consistently support superiority to other available agents on the market. In clinical trials comparing denosumab with zoledronic acid, overall survival and progression-free survival were similar between the two groups. Therefore, NCCN and ASCO added denosumab to intravenous zoledronic acid and intravenous pamidronate as recommended agents for the prevention of skeletal-related events in patients with bone metastasis. However, they state that there is insufficient data supporting the efficacy of one bone-modifying agent over another.

Most oncology clinics are able to make the necessary accommodations for treating patients with intravenous bisphosphonates. Since these agents have been used for over a decade, most clinicians are familiar with them and can anticipate their adverse effects. In addition, a generic formulation of zoledronic acid is due to enter the market in early 2013. However, one can argue that in a busy oncology practice, time is very valuable and use of a more expensive drug may be appropriate in the interest of treating more patients at any given time. Also, some patients may prefer using a more expensive drug in the interest of saving time. Thus, whether treatment with denosumab provides a great advantage over its less costly available counterparts remains to be seen.

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