ABSTRACT

Skeletal complications from bone metastases are associated with many consequences, including increased medical costs, impaired mobility, a negative impact on survival, and, most importantly in this context, diminished quality of life (QOL). This article focuses on the available treatment modalities for bone pain, one of the most disabling and QOL-impeding symptoms of skeletal metastases. Specific options reviewed in detail include kyphoplasty, a minimally invasive procedure used to treat vertebral compression fractures, and nitrogen-containing bisphosphonates, which have been shown to have palliative effects in metastatic bone disease. An extensive discussion of the efficacy of bisphosphonates in bone pain and their side effects, including osteonecrosis of the jaw and renal dysfunction, is also covered in this article. Lastly, the article includes a review of the pathophysiology of osteolytic bone disease and investigational therapies that reduce bone resorption by targeting the function of osteoclasts.


keletal complications from bone metastases are associated with many consequences, including increased medical costs, impaired mobility, diminished quality of life (QOL), and a negative impact on survival. Complications such as fractures and spinal cord compression often lead to postural changes, height loss, and functional impairment. Resultant vertebral deformities may lead to sleeping and eating disturbances (eg, reflux esophagitis), in addition to reduced balance and mobility. Among patients who have a hip fracture, 50% will become disabled and 25% will require nursing home care. The survival of men with prostate cancer who do not experience skeletal fractures is 39 months longer than that of patients with fractures—a finding that demonstrates the influence of skeletal complications on mortality. For patients with bone complications from metastases, the costs of medical care are considerable because treatment requires surgery and hospitalization, which amounts to more than double that of the total treatment costs for patients without skeletal complications. Although current treatment options for skeletal complications are limited in their ability to affect mortality, they can impact the QOL of patients with bone metastases.

ADDRESSING BONE PAIN

One of the most disabling and QOL-impeding symptoms of skeletal metastases is bone pain, which results from several processes, including expanding tumor mass, skeletal instability, formation of microfractures, development of pathologic fractures, or chemical stimulation of pain receptors following the release of cytokines from tumors. This latter nociceptive process causes sensitization to pain, which leads patients with metastatic disease to respond painfully to normally non-noxious stimuli. When bone pain initially develops, patients often describe it as a deep-boring ache with intermittent stabbing discomfort. Over time, bone pain becomes continuous and unrelenting, and may be aggravated by movement or changes in body position or posture.

Several tools are available to assess pain, including the Brief Pain Inventory (BPI), which is a 10-point scale that evaluates severity, quality, and location of the pain; interference with activities of daily living; and the
perceived cause of pain. The visual analogue scale is a scoring system (0–10 mm or 0–100 mm) that correlates points with amount of pain, and the Radiation Therapy Oncology Group scale utilizes a scoring system that incorporates the severity and frequency of pain.

Current treatment options for bone pain are similar to those that are generally used to manage metastatic bone disease. They include radiotherapy, radioisotopes, surgery, nerve ablation, analgesics, and bisphosphonates. Most of these treatments are discussed in more detail by Walter J. Curran Jr, MD, in his article.

Kyphoplasty is a minimally invasive surgical procedure that has been found to be effective for vertebral compression fractures. The technique involves injecting a needle with an attached deflated balloon into the vertebral body, which allows precise vertebral access and provides a working channel. Inflation of the balloon reduces the fracture, compacts the bone, and may elevate endplates. After the instrument is removed, a defined cavity and trabecular dam is left, which can be filled with an approved bone void filler. Kyphoplasty has mostly been studied in patients with bone metastases from myeloma. In one of these studies, which examined the effects of 55 kyphoplasties in 18 patients, the procedure was found to improve body pain, physical and social function, and vitality, with no major complications.5

THE ROLE OF BISPHOSPHONATES IN RELIEVING BONE PAIN

Bisphosphonates have been demonstrated in numerous studies to reduce the incidence of and the time to skeletal-related events in patients with multiple myeloma and solid tumors. More recently, these agents were found to be effective for palliative treatment of metastatic bone disease. Although the non-nitrogen containing bisphosphonates (ie, etidronate and clodronate) have been shown in earlier studies to have little benefit for pain relief, the nitrogen-containing bisphosphonate, pamidronate, was shown in phase III trials of patients with myeloma and breast cancer to be effective in reducing pain, but it was found ineffective in patients with prostate cancer. Zoledronic acid, however, has been found to alleviate pain in patients with skeletal metastases from prostate cancer, maintaining relief (as assessed by the BPI scoring system) at 3, 9, 21, and 24 months of therapy.6 Unlike prior studies with pamidronate and clodronate, this study demonstrated the long-term palliative effects of a bisphosphonate on bone pain among patients with prostate cancer.7 Other studies are examining the prophylactic role of bisphosphonates in prevention of bone metastases in patients with solid tumors. Zoledronic acid, for example, is currently being evaluated as prophylactic therapy in stage IIIIB/IV non–small-cell lung cancer.

SIDE EFFECTS OF BISPHOSPHONATES

Oral bisphosphonates are generally associated with gastrointestinal intolerance, especially esophagitis and esophageal ulcers, in approximately one third of patients. Intravenous agents may cause flu-like symptoms (eg, fever, myalgias, and arthralgias) in 10% to 20% of patients, which usually arise 12 to 48 hours following infusion and last 6 to 24 hours. These symptoms occur at a similar frequency with different bisphosphonates and usually subside with ongoing dosing. Corticosteroids may help reduce the risk and intensity of this reaction. Ocular effects, including uveitis, are rare and anemia can occur with chronic use, but it has not increased requirements for erythropoietin or transfusions. The most worrisome complications of bisphosphonates are osteonecrosis of the jaw (ONJ) and renal dysfunction.

ONJ is a disorder characterized by temporary or permanent loss of blood supply to the jaw, resulting in the development of necrotic bone in the mandible or maxilla. Symptoms may include pain, swelling, or infection of the gums; loosening of teeth; and poor healing of the gums. Cases of ONJ have been reported in cancer patients receiving bisphosphonates (eg, pamidronate and zoledronic acid), mostly in those who have undergone dental procedures. However, it is important to recognize that, in many of these cases, the diagnosis was not confirmed by an expert and many of these patients simply had jaw pain from other causes and nonspecific symptoms. Factors that contribute to ONJ include use of bisphosphonates, cancer, radiation therapy, corticosteroids, poor dental hygiene, poor diet, dental work, trauma, alcohol and tobacco use, coagulopathy, chemotherapy, and infection. Patients with multiple myeloma appear to be at a higher risk, which may be related to the use of thalidomide or other drugs in this population.

To minimize the risk of ONJ, physicians should encourage patients to maintain excellent oral hygiene, limit alcohol and tobacco use, obtain dental assessments prior to starting intravenous bisphosphonates, and, most importantly, avoid dental procedures while
being treated with bisphosphonates. In patients who require invasive dental procedures, the bisphosphonate should be discontinued for 3 months prior to undergoing the procedure and restarted after healing is complete or after 1 to 3 months of delay.

In managing ONJ, the correct diagnosis is critical. Many patients who have other dental conditions are mistakenly diagnosed with ONJ, or, because the severity of ONJ can vary greatly, many patients are improperly managed. Although there is no standard treatment for ONJ, certain measures can be taken, including avoiding and/or treating secondary infections of the oral cavity (eg, actinomycosis and bacterial sources) and ensuring that patients are seen a dentist on a regular basis. There is no evidence suggesting that bisphosphonates should be discontinued once patients develop ONJ.

Although renal dysfunction is a class effect of bisphosphonates, the types of kidney problems that arise tend to vary among the different agents. Whereas pamidronate mostly causes a focal collapsing segment glomerulosclerosis (preceded by albuminuria), zoledronic acid usually causes interstitial nephritis, which presents initially as a rise in serum creatinine. Studies have shown that bisphosphonates induce deleterious effects on the kidneys at similar rates of infusion (mg/min). Therefore, more potent agents such as zoledronic acid can be infused more rapidly, yet safely, compared with weaker drugs such as pamidronate (90 mg over 2 hours vs 4 mg over 15 minutes). The American Society of Clinical Oncology does not recommend any changes in bisphosphonate dosing, infusion time, or time interval between doses in patients with pre-existing renal dysfunction, as long as the serum creatinine is less than 3 mg/dL. However, recent recommendations from Novartis (manufacturer of Zometa [zoledronic acid]) suggest that for patients with creatinine clearance between 30 mL/min and 60 mL/min, an adjustment in dose should be made, so that the calculated dose of the bisphosphonate be adjusted to achieve the same area under curve (0.66 mg hr/L) as that of patients with creatinine clearance of 75 mL/min. Patients on dialysis can be safely treated with pamidronate or zoledronic acid.

In patients who experience a rise in serum creatinine while being treated with a bisphosphonate, other causes of renal dysfunction (eg, myeloma and diabetic or hypertensive nephropathy) should be ruled out. If a bisphosphonate is the suspected cause, therapy should be interrupted until serum creatinine decreases to 10% of baseline levels and then reinitiated at a slower infusion (1 hour for zoledronic acid and over 4 hours for pamidronate). If renal problems persist, switching to a different agent is a rational approach because individual bisphosphonates affect the kidney differently. If a patient still experiences renal problems, he can be switched to oral alendronate.

**NEW TARGETS FOR METASTATIC BONE DISEASE**

In examining potential therapeutic targets for metastatic bone disease, it is important to recognize that most patients with lung cancer have osteolytic lesions; therefore, inhibition of osteolytic bone disease is a major focus with this particular cancer. To understand the nature of current research and development efforts, a review of the pathophysiology of osteolytic bone disease is pertinent. In this process, bone destruction is primarily mediated through osteoclasts rather than by the tumor cells themselves. Tumor-derived factors that cause activation of osteoclasts vary by tumor type and may include interleukins, tumor necrosis factor, macrophage colony-stimulating factor, and parathyroid hormone-related protein. These factors increase expression of receptor activator of nuclear factor κB ligand (RANKL), which acts on osteoclast precursors to induce the formation of osteoclasts, consequently causing bone resorption. The process of bone resorption results in the release of growth factors from the bone matrix, which in turn stimulate further tumor growth. Growth factors released from the bone matrix include transforming growth factor β, insulin-like growth factors, fibroblast growth factors, platelet-derived growth factor, and bone morphogenic proteins. This reciprocal relationship between tumor cells and osteoclasts results in a vicious cycle of tumor growth and bone destruction (see Figure). In developing potential agents for the treatment of bone metastases, researchers attempt to target any one of these aforementioned substances, including growth factors and tumor-derived factors. One potential agent under investigation is a humanized monoclonal antibody that binds to RANKL, inhibiting further activation and maturation of osteoclasts. The agent, called denosumab, was recently evaluated in a phase I study of patients with breast cancer and myeloma who had osteolytic bone disease. Denosumab was found to suppress markers of bone resorption (N-telopeptide) to an extent similar to that of pamidronate. Other agents, already on the market, that have been shown to inhibit osteoclast function by blocking RANK
signaling include bortezomib, thalidomide, and arsenic trioxide. Bortezomib is also the strongest inducer of osteoblasts of any drug known today. In patients with multiple myeloma, the agent has been shown to increase markers of bone formation (bone alkaline phosphatase) and reduce bone resorption.15-16 The combination of radiopharmaceutical agents with bisphosphonates or bortezomib is another area of interest. In one study of patients with symptomatic chemorefractory myeloma, samarium-153 combined with zoledronic acid produced responses in 4 of 8 patients.17 Another study found positive results from combining samarium with bortezomib in patients with refractory and relapsed multiple myeloma.18

CONCLUSIONS

Although skeletal complications of metastatic bone disease are associated with a high mortality rate, there are various options that physicians can turn to in improving the QOL of patients. Kyphoplasty is a minimally invasive procedure that has been shown to improve body pain, physical function, vitality, and social function. Bisphosphonates have been shown to reduce skeletal-related events and produce pain relief in patients with bone metastases from various tumors. Researchers are investigating several agents that target bone resorption, including denosumab, bortezomib, thalidomide, and arsenic trioxide. Novel combination regimens of radiopharmaceuticals, monoclonal antibodies, and bisphosphonates also bring promise of a better life for patients with bone metastases.

DISCUSSION

Dr Langer: Were those refractory patients in the phase I trial with samarium-123?

Dr Berenson: Multiple refractory, monthly zoledronic acid.

Dr Langer: They actually failed the bortezomib?

Dr Berenson: Some failed bortezomib, but not all. One responder was a bortezomib failure. Another patient was refractory but moved into minor response to this therapy. We were trying to assess the tumors, and it is clear from preclinical studies that you must go higher than 4 mg/dL. We had several phase I patients at 16 mg/dL who went into complete remission, with the drug administered over 30 to 60 seconds. This was in the late 1990s and we did not know about the renal toxicity issues; the patient's kidney went to the point of dialysis. One patient's creatinine is down to 1.8 mg/dL; he is off dialysis with a complete remission 7 years later. The antitumor story is anecdotal, but it should be explored.

Dr Ettinger: When you have a rise in creatinine at 4 mg/dL with zoledronic acid given over 15 minutes, do you respond next time by giving zoledronic acid over 30 minutes, or use another strategy?

Dr Berenson: I hold the dose, allow the creatinine to fall back to an acceptable range, and then I administer it much slower (an hour).

Dr Curran: How clear is the dose response to renal toxicity for zoledronic acid?

Dr Berenson: There is not enough data and experience to date. If you administer 16 mg/dL over 1 minute, it is not easy on the kidney, but I think it is acceptable. The key is the Cmax.

Dr Garvey: That has been observed with pamidronate, with the nephrotoxicity being associated with the rate of infusion, rather than total dose.

Dr Langer: There has been such push-back. If we are dosing the patient, our pharmacist will go to that nomogram, recalculate the creatinine clearance using the house staff formula, and change the dose, even though the creatinine has been fine.

Dr Berenson: The key here is that once you are on that dose, you do not adjust the dose. Do not adjust it based on the creatinine. Hold it and then come back with the same dose.
**Dr Langer**: We are talking about minor adjustments and minor changes in creatinine, such as in older, thin patients that have creatinine levels that are still in normal range. Therefore, a 75-year-old, 90-lb woman is going to have a creatinine clearance that falls into the range; with these patients, their creatinine has jumped from 0.9 to 1.1.

**Dr Berenson**: However, they should not adjust the dose. They should hold the dose and allow the creatinine to come back.

**Dr Ettinger**: For ONJ, do you instruct all patients to see a dentist before taking zoledronic acid?

**Dr Berenson**: Yes, without exception.

**Dr Langer**: I tell them to go to the dentist but I do not wait to begin treatment.

**Dr Berenson**: I think waiting 1 or 2 months in this case is not a big deal.

**Dr Ettinger**: I agree.

**Dr Berenson**: It is more of an issue with lung cancer patients because the median survival is 6 months; with myeloma, 6 years. If I have a patient with bad bone disease, I probably will just start treatment, but that is only approximately 2% of the cases I see.

**Dr Ettinger**: Let’s review the sequence of ONJ. There is a little osteonecrosis, it may be painful, the bone dies—does it heal itself?

**Dr Berenson**: Not often. It usually remains exposed as dead bone, and osteomyelitis can result. The key is to prevent secondary infection. Good dental hygiene and antibiotics become important.

**Dr Garey**: In my experience, the duration of treatment also has an impact on the development of ONJ, with the majority of patients who developed ONJ having been treated for longer durations.

**Dr Berenson**: It is true that there is a higher risk that correlates with a longer period since the first dose. However, we do not know whether the doses generate cumulative effects from 12 months, or from the first dose. I have seen patients who have developed ONJ within several months of diagnosis.

**Dr Langer**: If it is more likely to be recognized in people who have been on it for longer periods, then the lung cancer population may not be an issue.

**Dr Brahmer**: It will be interesting to see whether there will be more ONJ in lung cancer patients now that we are using more bevacizumab—especially for patients with adenocarcinoma, who tend to have more bone metastases. Anecdotally, I have not seen that.

**Dr Langer**: I have seen 1 case, but it was in a breast cancer patient.

**Dr Garey**: It will also be interesting to note whether incidence will increase if we begin to look at use of this for prevention of bone metastases. It will be a really important issue because patients will be on therapy much longer, and the potential for the incidence to increase will be there.

**Dr Berenson**: Absolutely. The big challenge is that you will have patients at risk for years, and we know there is a dramatic impact on these patients’ lives, whereas in the setting of benign disease, the reduction in fractures is minor.

**Dr Ettinger**: Remember that zoledronic acid was being considered for treatment of osteoporosis. In the cancer patient, it is risk versus the benefit and benefit is always going to outweigh the risk with a 1% incidence. However, you are right, it is a bigger issue with benign disease if the patient is going to live to be 90 years old.

**Dr Berenson**: Also, the risk is 0.2% of a fracture per year; it is not very high. I think it will be a real problem.

**Dr Brahmer**: For kyphoplasty or vertebroplasty in patients with lung cancer, rather than for multiple myeloma, would you recommend radiation therapy in that region afterward, or just watch and wait?

**Dr Berenson**: It depends on what is happening. In most of our patients, it is largely osteoporotic. I do not want to irradiate bone marrow, because that is what my patients need; 40% of marrow is in the low T and L spine and you will lose marrow function. By comparison, in lung cancer, if the patient has large metastases, you may want to irradiate, but you base judgment on the balance of osteoporosis simply from being older versus a fracture because of the combination of therapy. Women who become menopausal with adjuvant chemotherapy lose unbelievable amounts of bone. There is a recent controversial trial using androgen blockade, or rather, gonadotropin-releasing hormone treatment with aromatase inhibitors. The reduction in bone mass was approximately 17% with that combination.19

**Dr Ettinger**: Has kyphoplasty used in benign disease been approved?

**Dr Berenson**: Yes, for osteoporosis. It is not approved for cancer. I think it is a highly effective procedure. I often send myeloma patients for it because I do not want iridium, and it avoids irradiation. There has been some argument that contiguous vertebral bodies are at high risk for fracture.
Dr Ettinger: If we had good treatment for osteonecrosis, we would not have to spend so much time discussing a side effect that occurs in approximately 1% of patients. This reminds me of the interstitial fibrosis or the interstitial lung disease that we see with gefitinib or erlotinib. It is less than 1%, but when it occurs, it can be devastating.

Dr Garey: Returning to the nephrotoxicity issue, the major education point is that you can continue to administer the drug by slowing down the infusion. However, the dose should be held until creatinine returns to baseline.

Dr Langer: Creatinines are going to fluctuate. They are going to change from 0.9 to 1.0, to 1.1, back to 0.9.

Dr Garey: Small fluctuations month-to-month are not necessarily significant. The change from baseline determines the adjustment in management.

Dr Langer: So you would hold, then prolong the infusion, but not adjust the dosage?

Dr Berenson: You are not supposed to adjust the dosage. Once you are on that dose, you stay there. The only adjustment is in the infusion time.

Dr Garey: If a patient’s starting creatinine clearance is 40 mL/min, we will adjust the dose down.

Dr Berenson: Yes, based on what the US Food and Drug Administration recommends.

Typically, in my patient population, creatinine creeps up, but it is because of the myeloma. The rest of you see a fair number of hypercalcemia episodes if you have a patient in the emergency department with elevated creatinine. It has been clearly demonstrated that zoledronic acid (4-mg dose) is better at reversing hypercalcemia of malignancy, based on a pooled analysis of randomized, controlled clinical trials.

Dr Garey: Also, the renal adjustments do not apply as soundly to treatment of hypercalcemia.

Dr Ettinger: Part of the other problem is the polypharmacy that the patient is on. As in your service, we have a pharmacist that makes rounds with us to review the medications and you can frequently identify medications that can affect the creatinine level. This is a major problem with hospital shifts and the way we work now. Rather than remove a drug, someone will add another drug, further complicating the problem.

Dr Berenson: One of our myeloma patients had his creatinine increase; he was weak, dizzy, and short of breath. We discovered that he was taking pioglitazone, so we eliminated it and he recovered.

Dr Garey: The lung cancer population is also prone to coronary artery disease and diabetes. With so many other concomitant medications and morbidities, it is important to manage medication interactions because certain drugs will increase the risk of nephrotoxicity.

REFERENCES