ABSTRACT

Skeletal complications of malignancy cause considerable morbidity, including pain, impaired mobility, pathologic fracture, spinal cord or nerve root compression, bone marrow infiltration, and hypercalcemia of malignancy. This article reviews new developments associated with the available treatment modalities, including radiation therapy, radiopharmaceuticals, surgery, and bisphosphonates. Fractionated external beam radiotherapy remains the standard of care in patients with symptomatic bone metastases, but one current area of debate is the utility of multiple versus single radiotherapy fractions. Also reviewed in this article are the indications, precautions, and response rates for radiopharmaceuticals. These agents are typically used in patients who have bony pain related to skeletal metastases and should only be considered in those who have a positive bone scan and reasonable hematologic reserve. This article offers a discussion of the recent changes made to the decision-making process surrounding surgical interventions, new and less-invasive surgical techniques, and innovative ways of mapping out surgical pathways. Also included is an overview of the commonly used bisphosphonates in oncology and recent studies examining the effects of these agents on skeletal-related events in patients with bone metastases from solid tumors.


B one metastases are a common result of many cancers, particularly multiple myeloma and solid tumors originating in the breast, prostate, or lung. Skeletal complications arising from bone metastases cause considerable morbidity, including pain, impaired mobility, pathologic fracture, spinal cord or nerve root compression, bone marrow infiltration, and hypercalcemia of malignancy. Fortunately, there is an increasing array of treatment options available for skeletal complications, such as radiation therapy, radiopharmaceuticals, surgery, and bisphosphonates. The goals of treatment include pain reduction, skeletal fracture avoidance, and maintenance of an active quality of life.

EXTERNAL-BEAM RADIATION FOR BONE METASTASES

In patients with symptomatic bone metastases, fractionated external beam radiotherapy (RT) has been the historically dominant nonoperative approach. Relatively low in cost and toxicity, this form of RT has been shown to produce partial and complete pain relief in 90% and 54% of patients with osseous metastases, respectively. One area that has been debated is the utility of multiple versus single RT fractions, particularly in patients with appendicular metastases. Thus far, studies have found the palliative benefits and toxicity profile to be similar between single-fraction and multiple-fraction RT. In one older trial that evaluated several different fractionation regimens ranging from 1 week to 3 weeks of treatment, the incidence of patients experiencing partial and complete pain relief was the same, regardless of whether patients received higher radiation doses for multiple bone metastases or lower radiation doses for solitary bone involvement. Critics of the study pointed out that: (1) pain assessment was performed by the caregiver rather than the patient; (2) narcotic-related relief was not taken into account; and (3) a higher incidence of reirradiation was observed in the lower radiation dose group.

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In an attempt to overcome these shortcomings, the Radiation Therapy Oncology Group (RTOG) randomized 900 patients with painful bone metastases to single 8 Gy radiation fraction or the more standard 2-week regimen of 30 Gy in 10 fractions of 3 Gy each. Patients were stratified according to solitary versus multiple painful sites, bisphosphonate usage, initial worst pain score, and weight-bearing versus non-weight-bearing symptoms. Treatment was allowed for patients with an increase of 2 or more points on the worst pain score, provided that at least 4 weeks had elapsed since completion of treatment.12 Researchers found that both regimens produced effective and equivalent pain relief, either partial or complete, in two thirds of patients. Post-treatment narcotic requirements were similar in both groups and responses to the regimens did not vary based on initial pain scores and symptoms, prior use of bisphosphonates, solitary versus multiple bony involvement, or prior use of bisphosphonates. Treatment was well tolerated with few side effects in either arm.13 Although this trial established the cost effectiveness of single-fraction 8 Gy RT, further analysis of fracture rate and health utilities would provide more insight into the relative value of single-fraction RT.

Radiopharmaceuticals

The currently available radiopharmaceutical products include strontium-89, samarium-153, and phosphorus-32. Phosphorus-32 is rarely used for bone metastases. Following intravenous (IV) administration, these agents concentrate at skeletal metastatic sites and provide selective systemic irradiation with minimum exposure to distant soft tissue. Strontium-89 is a long-acting beta emitter, which, because of lack of gamma emission, has modest tissue penetration (approximately 7 mm). The agent is indicated for patients who have bony pain related to skeletal metastases and should only be considered in those who have a positive bone scan and reasonable hematologic reserve. Because thrombocytopenia is the main side effect associated with strontium-89, in addition to other radiopharmaceutical agents, the product should only be used in patients who have a platelet count of at least 60,000/mm³ and a white blood cell count of at least 2400/mm³. Another issue associated with radiopharmaceutical agents is the possibility of a “flare” reaction, in which the pain can actually become more severe before a symptomatic response.

Strontium-89 has historically been used in patients with osseous metastases from prostate cancer and the symptomatic response rate is reported to be between 40% and 70%.14 In some of the pivotal trials, strontium-89 has been shown to relieve pain in patients with multiple bone metastases and, when used concomitantly with radiation, the agent was shown to significantly reduce the appearance of new painful metastases, analgesic requirements, and serum levels of tumor markers.15

Samarium-153 is an intermediate beta and gamma emitter that, compared to strontium-89, has a much shorter half-life (2 days vs 50 days) and, therefore, has greater dosing requirements (1 MCi/kg vs 3 MCi to 4 MCi). However, samarium also has greater tissue penetration and is associated with higher response rates (60%–80%), compared with strontium-89. Several phase II trials reported the benefits of samarium-153 and strontium-89 in patients with osseous metastases, but just recently, a phase III study was undertaken to systematically evaluate concomitant use of radiopharmaceuticals and zoledronic acid in the palliation of osteoblastic metastases in patients with carcinoma of the breast, lung, and prostate.14

Orthopedic Surgical Intervention

The goals of surgery for any spinal metastases are centered around achieving oncologic control of the region, spinal stabilization, neurologic palliation, pain relief, and histologic diagnosis. Of the several available surgical approaches, decompressive laminectomy, followed by RT, has historically been the most common procedure performed in patients with epidural spinal cord compression from epidural metastases. With recent changes made to the decision pathway used to determine whether surgical or nonsurgical intervention is warranted for spinal metastases, the use of laminectomy procedures has increased. This turn in practice has been largely influenced by a study in which researchers randomized patients with symptomatic epidural metastases to RT or decompressive laminectomy followed by RT. Patients assigned to surgery had a statistically significant superior outcome, with particular improvement in neurologic function.15 In selecting patients with spinal metastases for aggressive surgery, several surgical groups have implemented a systematic approach, based on the patient’s primary tumor type, neurologic status, general physi-
cal condition, number of bone lesions, number of visceral metastases, and number of spinal lesions. There are also unique new ways of mapping out surgical pathways. Figure 1 depicts a surgical staging system with the vertebral region represented by 12 zones. This system helps orient surgeons to what type of resection may or may not be appropriate. Looking from right to left at examples of tumor involvement in Figure 2, one can see that performing an unblocked resection of the tumor while still preserving the spinal canal requires resection of zones 3-10, 2-6, and 4-7.

**Stereotactic Radiosurgery**

Of the new approaches being considered, stereotactic radiosurgery appears promising and is the subject of ongoing research. This is a technique of employing a nonoperative approach with high-dose single-fraction radiation delivered precisely to the target location. In a study of 125 patients with spinal lesions, this frameless image-guided spinal radiosurgery system was found to be feasible, safe, and effective. The major potential benefits of radiosurgical ablation of spinal lesions are short treatment time in an outpatient setting with rapid recovery and symptomatic response. This technique can be used in medically inoperable patients, in those with lesions located in previously irradiated sites, or as an adjunct to surgery.

Another phase I-II study is evaluating the impact of the procedure on pain relief, neurologic improvement, and radiologic tumor response in 49 patients with 61 lesions. Because some of these patients already had maximum spinal cord radiation, radiation oncologists performing this procedure attempt to place the radiation dose in the vertebral body while sparing the spinal canal. So far, researchers have observed some healing and less extrusion into the epidural space at 2 months following surgery. Another novel approach involves delivery of a single-fraction extracranial stereotactic radiosurgery dose using a multileaf collimator and the helical technology of computed tomography. There are many other techniques and devices in use that permit high-dose radiation to be delivered with a small margin around the tumor.

**Use of Bisphosphonates in Bone Metastases**

As presented by Corey J. Langer, MD, in his article, bisphosphonates are synthetic analogues of the naturally occurring pyrophosphate molecule, in which the unstable P–O–P moiety has been replaced by a nonhydrolyzable P–C–P. The addition of various side chains to the central carbon atom has produced a range of bisphosphonate drugs that strongly bind to mineralized bone and inhibit osteoclast-mediated bone resorption. First-generation bisphosphonates (etidronate and clodronate) were introduced almost 3 decades ago and are relatively weak inhibitors of bone resorption. Incorporation of a single nitrogen atom into the molecular structure has led to development of
more potent second-generation bisphosphonates (pamidronate, alendronate, andibandronate), and the addition of a second nitrogen atom has led to the development of zoledronic acid, an agent that is considered to be a very potent inhibitor of osteoclasts.\textsuperscript{19}

In recent years, bisphosphonates have become more widely used for skeletal metastases because of their ability to reduce bone resorption, which leads to decreases in hypercalcemia, new osteolytic lesions, and fractures. The 2 most commonly used bisphosphonates in oncology are zoledronic acid and pamidronate, which were initially indicated for skeletal metastases from breast and prostate cancer. Both agents are now indicated for osteolysis related to multiple myeloma and various solid tumors of malignancy. Pamidronate is given monthly as a 2- to 4-hour infusion and has been in clinical use for many years, especially for the management of hypercalcemia of malignancy. Compared with pamidronate, zoledronic acid requires a shorter monthly IV infusion (15 minutes), has a longer duration of effect on osteoclasts, and has been shown to be superior in the treatment of hypercalcemia of malignancy.\textsuperscript{20} Both of these bisphosphonates have been found in several breast cancer studies to reduce progression to skeletal-related events (SREs) and the number of SREs.\textsuperscript{21-23} One study directly compared the effects of pamidronate and zoledronic acid on SREs in patients with breast cancer and in those with multiple myeloma. Approximately 50% of all the patients in each treatment group experienced 1 or more SRE during the 25-month study, and the percentage was similar between treatment groups. Zoledronic acid (4 mg every 3–4 weeks) was found to be more effective than pamidronate (90 mg every 3–4 weeks) in reducing the overall incidence of SREs and the individual types of SREs (including pathologic fractures, spinal cord compression, surgery to bone, and radiation therapy to bone), in addition to the skeletal morbidity rate.

Zoledronic acid was further evaluated in several studies of patients with skeletal metastases from numerous solid tumors including lung cancer. In one of these trials, more than 700 patients were randomized to zoledronic acid 8 mg (with an eventual reduction to 4 mg), zoledronic acid 4 mg, or placebo.\textsuperscript{24} The endpoint was the time to and frequency of SREs, which included fracture, need for RT, need for surgery for bony metastases, and spinal cord compression. Compared to placebo, there was a statistically significant reduction in SREs in both of the zoledronic acid groups (44% for placebo vs 38% for 4 mg and 35% for 8 mg). There was also a statistical difference in the time to the first SRE between the placebo group (163 days) and the zoledronic acid 8 mg (219 days) and 4 mg (230 days) groups. This study was the first to demonstrate benefit of a bisphosphonate in non–small-cell lung cancer and tumors other than those of the breast and prostate. The most common adverse events associated with zoledronic acid include bone pain, nausea, anemia, vomiting, and constipation. Nausea, vomiting, pyrexia, and dyspnea are all known symptoms of the acute-phase reaction associated with IV bisphosphonates. Cases of osteonecrosis of the jaw have been reported among cancer patients receiving pamidronate or zoledronic acid. Many of these patients were also receiving chemotherapy, corticosteroids, and had dental procedures, which may have exacerbated the condition.

**CONCLUSIONS**

Skeletal complications cause considerable morbidity but, fortunately, there are increasing treatment options available, such as RT, radiopharmaceuticals, orthopedic surgery, stereotactic radiosurgery, and bisphosphonates. In patients with symptomatic bone metastases, fractionated external-beam RT has been the standard of care in achieving partial or complete pain relief in most patients. Many strides are being made in surgical and nonsurgical interventions, including unique ways of mapping out surgical pathways and innovative procedures such as stereotactic radiosurgery. Bisphosphonates are being used more frequently because of their ability to decrease hypercalcemia, new osteolytic lesions, and fractures. In the future, it is likely that the therapies summarized will be combined into synergistic regimens that will produce better results in the many patients affected with osseous metastases.

**DISCUSSION**

**Dr Ettinger**: In the clinical trial RTOG 9714, palliative radiation therapy for osseous metastases, the outcome was similar for the treatment arms (single fraction vs the standard), with less toxicity in the single-fraction arm. Has that become the standard?

**Dr Curran**: I have not seen updated patterns of practice information.

**Dr Ettinger**: In your institution, when do you use...
the 10 fraction versus the single fraction?

Dr Curran: We use the single fraction for extremity lesions. We use the fractionated treatment for appendicular lesions where there is concern about toxicity from the single fraction. For the single-fraction arm of the study discussed, bear in mind that most of these metastases were in the extremities, hip, or shoulder. The number of spinal lesions in this trial was relatively small.

Dr Langer: Is there a concern about spinal cord damage?

Dr Curran: To randomize patients for this study, you had to be comfortable with a single 8 Gy fraction. There may have been some selection among those physicians enrolling patients.

Dr Langer: Was there any difference in subsequent retreatment rates?

Dr Curran: I do not think so, which differs with the results from some of the previous studies.

Dr Ettinger: What is the status of rhenium-186 as a radiopharmaceutical for palliative relief of bone pain from metastases?

Dr Curran: I have not seen any update.

Dr Langer: There has been a fear of cytopenia. Is that a legitimate concern?

Dr Curran: The big issue is whether it is used concomitantly with bisphosphonates. I think the risk of myelosuppression is manageable. The major concern is how well one can modulate cytotoxics with radiopharmaceuticals.

Dr Berenson: Many new agents are extremely radiosensitizing, and that has been underexploited. There is real potential to target the bone and the tumor, particularly for myeloma, and hopefully with bone metastases. These agents tend to target the regions of metastatic disease; I would, then, add a radiosensitizer.

Dr Curran: At our institution, Richard Valicenti, MD, has completed a phase II trial examining the use of samarium-123 along with androgen deprivation and pelvic RT as a preventative approach for men with prostate cancer who are thought to be at very high risk of osseous metastasis. If we could identify markers that could predict which lung cancer patients with locally advanced or high-risk resected disease were at a prohibitively high risk of developing bone metastases, that could be part of a regimen to consider.

Dr Berenson: As an example, bortezomib is beginning to show some value in lung cancer.

Dr Ettinger: We discussed surgery related to spinal metastases, which is the most difficult situation. What about a lytic lesion that is localized to the femur, and what if the patient is symptomatic or asymptomatic, which is obviously 2 different situations? If the surgeon is called first, the question becomes, “When do you do prophylactic pinning to prevent pathologic fracture?”

Dr Berenson: That is changing. Orthopedists are much less likely to do that than they were 10 to 20 years ago. They now recognize that many of these patients do not end up fracturing. There are certain rules regarding the percentage of the diameter that is involved.

Dr Langer: Is that because your systemic therapies are improving?

Dr Berenson: Yes, I think so, that would go for postoperative radiation too. I recently saw a patient who had cauda equina syndrome from a lesion at L4. In the past, following a decompression laminectomy, we would have radiated, but we have such good anti-tumor therapy that we are certainly hesitant to radiate the lumbar spine where the majority of marrow function resides. Therefore, we are not using that as much anymore.

Dr Brahmer: However, for lung cancer, our systemic therapy is not yet quite as good.

Dr Langer: I am unsure whether we share your optimism, particularly if patients are starting to have pain and we receive a radiographic report that states impending pathologic fracture.

Dr Ettinger: These patients are usually presented at our musculoskeletal tumor conference with the radiotherapist, the medical oncologist, and the orthopedic surgeon. The real issues become: (1) the amount of cortical destruction; and (2) how well the patient understands that it is necessary to convalesce, stay off of it, and give it time to let the radiation therapy take effect.

Dr Berenson: One of the problems arising with the new medications that are so clot-inducing, especially for myeloma, is that a patient can participate in a clinical trial with an excellent response, and then has a hip replacement and dies with pulmonary emboli. The power of these clot-inducing agents must be considered. There was interest in the bisphosphonates reducing the requirement for radiotherapy by their ability to palliate pain alone, so that dose would be reduced. There were some European groups looking at studies.
to evaluate whether less radiation therapy could be used in the presence of bisphosphonates.

**Dr Curran:** That may be true in tumors that are very treatment sensitive. I doubt it is going to be true in non–small–cell lung cancer. I would be interested in seeing the data. There have not been many studies outside the key malignancies where any systemic therapy is allowed for a reduction in radiation dose without compromising tumor control. Once you get outside the key malignancies, there are just not many good examples.

**Dr Garey:** What is the role for radiopharmaceuticals in the treatment of lung cancer metastatic to bone?

**Dr Curran:** It involves an unusual case of lung cancer where that is a front–line approach. There are occasional examples of patients in which the dominant failure pattern in lung cancer is bone, and that is the type of patient we could consider. There is actually a patient, who visited all 3 of us years ago, who had a bone–dominant failure pattern of small–cell lung cancer. It is unusual, but that is the type of patient you might consider for this type of approach.

**Dr Langer:** It is my belief that radiation oncologists continue to get 10, even 14 fraction, and stretch it out. From the standpoint of patient care, and to expedite care, a single fraction makes sense. So, many of our studies mandate a 2–week, sometimes a 4–week, delay from last radiation. These patients are waiting 6 weeks from the time they started the radiation.

**Dr Curran:** One of the most important factors is to examine how many patients had which types of fields, such as how many patients had lumbar metastases with lumbar fields and still fared well with the 8 Gy. That is the kind of detail that really needs to get out there.

**Dr Garey:** How quickly did pain relief occur?

**Dr Curran:** The study endpoint was at 3 months. There are some people, including myself, who believe that there will be faster pain relief with the larger fractions.

**Dr Garey:** I would assume that as well.

**Dr Berenson:** One of the other considerations, in terms of the single fraction, is the delay in systemic therapy if you are giving agents that are radiosensitizing, such as conventional doxorubicin, liposome–complexed doxorubicin, bortezomib, or arsenic trioxide, because if you are giving a single fraction, you can get your systemic therapy in much quicker.

**Dr Ettinger:** Where does radiofrequency ablation fit into this setting?

**Dr Curran:** Radiofrequency ablation is a promising new approach for painful extremity lesions. It has not been thoroughly compared. The American College of Radiology Imaging Network has multicenter trials that are ongoing. One example is for ablation of lung tumors in non–small–cell lung cancer patients with pulmonary metastases.

**Dr Berenson:** Kyphoplasty and vertebroplasty are gaining wider use, especially in the myeloma population because many of our patients actually have osteoporotic fractures and not true bone metastasis fractures. This has been extremely beneficial with minimal morbidity and almost immediate pain relief.

**Dr Ettinger:** The single bone metastasis loop is an interesting issue because that is stage IV disease by definition. You cannot just resect one in the pelvis. Do you take care of a single bone metastasis with definitive therapy and then treat the lung cancer definitively for stage III disease, as an example? It is a fascinating problem that we increasingly face because our staging techniques are improving. At Johns Hopkins Hospital, we now detect approximately 1.2% of unexpected primary malignancies, based on positron emission tomography imaging when staging cancer. We are detecting more things and it is getting more complicated.

**Dr Garey:** It would be interesting to know if some of the tumor markers that were discussed earlier might impact that particular patient population as well.

**Dr Ettinger:** It is my understanding that in prostate cancer, bisphosphonates are associated with a survival advantage of approximately 2.5 months.

**Dr Langer:** At the American Society of Clinical Oncology 2006 meeting, Vera Hirsch et al reported preliminary data on parathyroid hormone levels related to lung cancer, in the context of a solid tumor trial. The group also reported that lung cancer patients with bone metastases who had high baseline levels of N–telopeptide had a relative risk of death that was significantly reduced by 35% in those who received 4–mg zoledronic acid, compared with placebo.

**Dr Berenson:** I also presented data at the American Society of Clinical Oncology 2006 meeting that showed myeloma patients with high bone alpha bisphosphatase levels who received zoledronic acid have a significant survival advantage (82%), compared with those who received pamidronate (55%).
REFERENCES


