Pharmacologic Prevention of Skeletal-related Events in Cancer Patients

Sal Bottiglieri, PharmD; Val Adams, PharmD, BCOP, FCCP

Intravenous bisphosphonates are a standard therapeutic option in the prevention of skeletal-related events in metastatic breast and prostate cancer as well as multiple myeloma with bone involvement. Denosumab represents a new class of medications that inhibits the RANK ligand and is currently being evaluated to prevent skeletal-related events.

Skeletal-related events are a common complication of malignancy and can increase overall morbidity and mortality.1 Bone metastases are closely linked to skeletal-related events and are common in patients with metastatic disease. Nearly 70% of patients with breast or prostate cancer develop bone metastases.2 Cooperberg et al3 assessed the incidence of bone metastases over a 6-month period after primary treatment for localized prostate cancer, where the number of bone metastases was nearly 3% in just 6 months. Multiple myeloma is another condition that commonly affects bone, where patients characteristically develop lytic bone lesions due to an alteration in the bone remodeling process.4 Bone metastases are thought to develop through hematogenous spread from the primary tumor, where the cancer cells adhere to the bone and then grow. Adhesive molecules, growth factors, and nutrients make the bone an ideal environment for cancer cells to grow; however, the presentation of the metastatic lesions vary. Bone metastases are typically classified as osteolytic lesions or osteoblastic lesions.

In osteolytic bone metastases, osteoclasts are predominantly performing bone resorption near malignant cells while osteoblasts are suppressed, which is evident in multiple myeloma. In osteoblastic bone metastasis, an increase in osteoblast activity leads to irregular bone trabeculae, which is common in prostate cancer.5 Bone metastases of osteoblastic and osteolytic nature can lead to different skeletal effects, but most studies do not differentiate; instead they use a composite endpoint termed skeletal complications or skeletal-related events.

Skeletal-related events are commonly defined by pathologic fractures, spinal cord compression, surgery for the prevention and treatment of pathologic fractures or spinal cord compression, or radiation for bone pain. Hypercalcemia is an additional complication commonly seen in patients with bone metastases, where pharmacologic options have also been used.

Hypercalcemia can occur from both direct osteolytic affects on the bone and indirect humoral effects. In breast cancer, 92% of metastatic bone disease patients secrete parathyroid hormone-related peptide that stimulates bone resorption and subsequent hypercalcemia. The risk of developing a pathologic fracture with metastatic bone disease is nearly 4 times more likely to occur within 5 years than in a patient without metastatic bone disease.6 Additionally, metastatic bone disease can be painful, and the onset and severity of pain may be related to the direct resorption effects of the tumor, which may be relieved with pharmacologic treatment or radiation therapy.7

Fractures have a true effect on the morbidity and mortality of the patient. Saad et al8 performed a retrospective review of zoledronic acid and pamidronate to assess the effect of...
fractures on overall survival. Three thousand forty-nine patients with multiple myeloma or breast, prostate, or other solid tumors received zoledronic acid, pamidronate, or placebo every 3 to 4 weeks. The risk of fracture was highest in the multiple myeloma group (43%), followed by breast (35%), prostate (19%), and lung (17%). Breast cancer patients who developed pathologic fractures had the highest increased risk of death (32%; \( P < .01 \)), while multiple myeloma and prostate cancer had a trend for an increased risk (20%) after adjusting baseline characteristics and prior skeletal-related events.

**Prostate Cancer**

Bisphosphonates are a pharmacologic option in bone metastases that inhibit osteoclast-mediated bone resorption by decreasing osteoclast activity and interfering with attachment, differentiation, and survival. Zoledronic acid 4 mg every 3 weeks is currently approved in metastatic bone disease for the prevention of skeletal-related events, which include pathologic fractures, radiation or surgery on the bone, spinal cord compression, or hypercalcemia.

Zoledronic acid was evaluated in androgen-independent prostate cancer with bone metastases, where it was demonstrated to decrease the risk of skeletal-related events by 11% compared to placebo at 15 months. Additionally, pamidronate was evaluated in androgen-independent prostate cancer and symptomatic bone metastases, where patients received pamidronate 90 mg every 3 weeks or placebo for 27 weeks. At 27 weeks, no difference was found in pain scores, analgesic use, or skeletal-related events. These data suggest that zoledronic acid is effective in androgen-independent prostate cancer with bone metastases in the prevention of skeletal-related events, while other bisphosphonates may lag in efficacy.

**Breast Cancer**

Bisphosphonates have also been evaluated in the prevention of skeletal-related events in metastatic breast cancer patients with osteolytic lesions, where pamidronate was one of the first bisphosphonates approved in this setting. Hortobagyi et al evaluated 380 metastatic breast cancer patients with lytic bone lesions on current chemotherapy treatment with either 90 mg of pamidronate monthly or placebo. At 12 months, skeletal-related events decreased significantly by 13% with pamidronate therapy, with an overall incidence of 43% and 56% in the pamidronate and placebo groups, respectively. Subsequently zoledronic acid was evaluated in a phase III noninferiority study evaluating metastatic breast cancer and multiple myeloma patients with osteolytic bone metastases. Patients were given zoledronic acid or pamidronate every 3 to 4 weeks for 1 year. Patients in the zoledronic acid and pamidronate groups had similar rates of skeletal-related events, with 44% and 43% of patients at 12 months, respectively, in the breast cancer patient cohort on chemotherapy. More recently, a post hoc analysis of this trial analyzed clinical skeletal complications, where the authors demonstrated a decreased risk of fractures by 20% with zoledronic acid when compared to pamidronate.

**Multiple Myeloma**

Bisphosphonates are also a therapeutic option in the management of multiple myeloma, as these patients traditionally develop lytic lesions. Rosen et al evaluated the incidence of skeletal-related events in a combined population of multiple myeloma and metastatic breast cancer patients with bone metastases as described previously. After 1 year of treatment, zoledronic acid reduced the risk of developing skeletal complications by an additional 16% \( (P = .030) \) in the combined population at 25 months when compared to pamidronate. However, when comparing the risk of skeletal complications in the multiple myeloma group, no difference was demonstrated. This study demonstrates that bisphosphonates are effective at reducing skeletal-related events in patients with lytic lesions in multiple myeloma; however, one bisphosphonate has not been shown to be superior to the other in this setting.

**Adverse Events of Bisphosphonates**

A common toxicity with bisphosphonate use is nephrotoxicity, which is cited to occur in 6% and 8% of patients given pamidronate and zoledronic acid, respectively. Dose adjustments are warranted for patients with impaired renal function at baseline, as well as temporary interruption of therapy for significant increases in serum creatinine for both pamidronate and zoledronic acid. The practice guidelines in multiple myeloma recommend regular monitoring of serum creatinine as well as monitoring electrolytes and hemoglobin/hematocrit.

A commonly discussed adverse event of bisphosphonates is osteonecrosis of the jaw. The estimated risk of osteonecrosis of the jaw is approximately 3.5% to 11%. The current update committee on bisphosphonates in multiple myeloma has recommended that all patients receive a comprehensive dental examination and preventive dentistry prior to initiating treatment.

Data regarding the use of bisphosphonates in multiple myeloma suggest that not all bisphosphonates are equal in risk of developing osteonecrosis of the jaw. A retrospective analysis conducted by Zervas et al reported that 11.02% of multiple myeloma patients receiving a bisphosphonate developed osteonecrosis of the jaw. A Cox regression analysis revealed a 9.5-fold greater risk of osteonecrosis of the jaw with zoledronic acid compared to pamidronate alone \( (P = .042) \). Additional toxicities may include myalgia, arthralgia, and flu-like symptoms (Table).

**New Pharmacologic Options**

Bisphosphonates are pyrophosphate compounds that...
the rate of multiple skeletal-related event and demonstrated superiority by bone metastases. Denosumab prostate cancer patients with androgen-independent travenously every 4 weeks in zoledronic acid 4 mg intravenously every 4 weeks in randomized, double-blind trial metastases. A phase III, randomized, double-blind study in 2046 bisphosphonate-naive breast cancer patients compared denosumab 120 mg subcutaneously to zoledronic acid 4 mg intravenously every 4 weeks. The median time to onset of first skeletal-related event was 26.5 months for zoledronic acid and undetermined for denosumab due to limited skeletal-related events. The overall rate of skeletal-related events was significantly lower with denosumab (hazard ratio, 0.77; 95% CI, 0.66-0.89). No large phase III trials have been conducted with denosumab in multiple myeloma; however, phase II data have led to ongoing phase III trials. Adverse effects with denosumab most commonly include nausea, bone pain, and anemia (Table). In clinical studies conducted by Fizazi et al, 8% and 3% of patients developed grade 3 and grade 4 hypocalcemia, respectively. Other less common side effects include upper respiratory infections, arthralgia, hypertension, and urinary tract infections. Long-term monitoring of this therapy will be required to determine if osteonecrosis of the jaw and other toxicities become a complication of this treatment.

**CONCLUSION**

Intravenous bisphosphonates are currently the standard treatment to prevent skeletal-related events in patients with bone metastases in breast cancer, prostate cancer, or multiple myeloma. Denosumab is a new monoclonal antibody that may have a future indication to prevent skeletal-related events. Phase III trials comparing denosumab to bisphosphonates in the prevention of skeletal-related events in patients with bone metastases and breast or prostate cancer are promising and may lead to a new standard of care.

**REFERENCES**

4. Kyle RA, Rajkumar SV. Mul-

---

### Treatment Options in Metastatic Bone Disease and Multiple Myeloma

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose</th>
<th>Route</th>
<th>Frequency</th>
<th>Monitoring</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zoledronic acid</td>
<td>4 mg over 15 min</td>
<td>Intravenously</td>
<td>Every 3-4 wk</td>
<td>Serum creatinine prior to each dose; regular dental examinations; electrolytes and hemoglobin/hematocrit</td>
<td>Myalgia; nephrotoxicity; osteonecrosis of the jaw; hypocalcemia</td>
</tr>
<tr>
<td>Pamidronate</td>
<td>90 mg over 2 h</td>
<td>Intravenously</td>
<td>Every 3-4 wk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Denosumab</td>
<td>120 mg</td>
<td>Subcutaneously</td>
<td>Every 4 wk</td>
<td>Electrolytes (calcium, phosphorous, magnesium); regular dental examinations; signs of infection or skin rash</td>
<td>Nausea; vomiting; anemia; hypocalcemia; bone pain</td>
</tr>
</tbody>
</table>

---

*Initial dose should be adjusted based on renal function, and subsequent doses should be held in light of renal deterioration.

*Consider dose reduction at initiation if renal function is poor, and subsequent doses should be held in light of renal deterioration.

*Not currently Food and Drug Administration approved for the above indications.
The Bottom Line

- Intravenous bisphosphonates are preferred treatment options in the prevention of skeletal-related events. Zoledronic acid may be preferred in metastatic prostate cancer patients with significant bone pain.
- Zoledronic acid appears to have a higher risk of osteonecrosis of the jaw in the multiple myeloma patient population; pamidronate may be preferred until further prospective data is available. Other common toxicities of bisphosphonates include myalgia, flu-like symptoms, hypocalcemia, and nephrotoxicity.
- Denosumab is a fully human monoclonal antibody that binds and inhibits RANKL. Phase III data have demonstrated decreased time to first skeletal-related event in prostate and breast cancer, while minimal data are currently available in multiple myeloma.
- Denosumab is well tolerated to date with a lower risk of nephrotoxicity and a similar or lower risk of osteonecrosis of the jaw or infections, with the most common reactions being bone pain, nausea, and anemia.

Denosumab is well tolerated to date with a lower risk of nephrotoxicity and a similar or lower risk of osteonecrosis of the jaw or infections, with the most common reactions being bone pain, nausea, and anemia.

Denosumab is well tolerated to date with a lower risk of nephrotoxicity and a similar or lower risk of osteonecrosis of the jaw or infections, with the most common reactions being bone pain, nausea, and anemia.


