

PALLIATIVE PEARLS

BY ENCLARA PHARMACIA

Symptom Management in Prostate Cancer Case March 2017

Patient Case

RF, a 75 y/o male, who lives at home with his wife, was admitted to hospice today with a primary diagnosis of prostate cancer metastatic to the bone. Additional diagnoses include hypertension, depression and hyperlipidemia. On assessment, his PPS is 50% and he is noted to have symptoms of fatigue and a severe level of pain (8/10). He is recently homebound due to overall weakness and discomfort. He has no known drug allergies.

Current medications for pain management:

- Morphine extended-release 100mg tab; 1 tablet PO BID
- Morphine 20mg/mL; 0.5mL (10mg) PO/SL every 4 hours as needed (average 4 doses/day)
- Naproxen 500mg; 1 tablet PO TID with meals

According to his medical history, RF's hormone-refractory prostate cancer was diagnosed 14 months ago. At that time, he was symptomatic of metastatic disease¹⁻³ including pain in his lower back and hips. He received external beam radiation therapy to his prostate, pelvic lymph nodes and spine initially achieving adequate pain relief.⁴⁻⁷ He also received androgen deprivation therapy (ADT) (hormonal therapy) and two courses of chemotherapy. Despite these treatments, his PSA continued to rise and he had evidence of worsening metastatic disease on a recent bone scan.

The benefits and the problems (side effects, cost and time) associated with undergoing additional palliative radiation were reviewed with RF and his wife. They opted to stop all treatment and focus on supportive care and comfort instead. His goals are to maintain his level of activity and be as pain free as possible. He continues to have pain in his lower back and hips that is partially relieved with morphine breakthrough doses. He tells you that his daughter is a nurse and recently read an article about bisphosphonate therapy for bone pain. He asks if there would be any benefit to starting this therapy.

How does bone metastasis affect the bone?

Cancer cells can travel to the bones through the blood stream and are thought to be attracted to the bone marrow by cytokines. There are 2 types of bone cells- osteoblasts and osteoclasts. Osteoblasts form new bone while osteoclasts dissolve old bone. When the bone cells are healthy, new bone is always forming while old bone is dissolving, keeping bones strong. Cancer cells weaken the bone structure by interfering with these actions, thus, creating risk for pain and/or fractures.⁸ Bone metastasis occurs in 70-90% of patients with prostate cancer.

What complications are caused by bone metastases?

Complications from bone metastases, commonly referred to as skeletal-related events (SREs), include:

- Pain: Bone pain may initially come and go and get better with movement. As metastases progress, pain often worsens with movement and is usually described as sharp and localized to the site of metastases.

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- Fractures: Fractures can occur more frequently with a fall or injury, as well as during everyday activities, most commonly in the bones of the arms and legs.
- Spinal cord compression: Metastases that travel to the spine can form tumors that place pressure on the spinal cord and cause nerve damage that may lead to paralysis if not treated. The spinal cord nerves are what allow the body to move and feel, including maintaining control of functions like bowel and bladder control. Trouble urinating and/or constipation often result.
- Hypercalcemia: Damage to the bones releases calcium in the blood stream and increases serum calcium levels. High serum calcium can cause constipation, nausea, loss of appetite and extreme thirst and is associated with fatigue, weakness and confusion if left untreated.

What are bisphosphonates?

Bisphosphonates are medications used for a number of indications including: treating and preventing bone fractures in patients with or at risk for osteoporosis, preventing SREs in patients with bone metastases and multiple myeloma, and treating Paget's disease and hypercalcemia of malignancy. Bisphosphonates work by inhibiting osteoclast-mediated bone resorption (less bone breakdown) without directly inhibiting bone formation.⁹

First generation class (These are not used to treat bone metastasis)

- Structure is non-nitrogen containing; less potent and less selective for osteoclasts vs. higher generation class
- Products/available dosage forms:
 - Etidronate (Didronel®) – Oral tablet
 - Tiludronate (Skelid®) - Oral tablet

Second and third generation classes

- Addition of nitrogen or amino group to structure increases potency for osteoclast inhibition
- Products, in ascending order of relative potency/available dosage forms:
 - Pamidronate (Aredia®) – Solution for injection
 - Alendronate (Fosamax®, Binosto®) – Oral tablet, effervescent tablet, and solution
 - Ibandronate (Boniva®) – Oral tablet and solution for injection
 - Risedronate (Actonel®, Atelvia®) – Oral tablet
 - Zoledronic acid (Reclast®, Zometa®) – Solution for injection

Pamidronate and zoledronic acid are the only bisphosphonates indicated for the treatment of SREs related to bone metastases. Zoledronic acid is administered every 3 to 4 weeks as a 4mg IV infusion over 15 min. Pamidronate is also administered monthly as a 90mg IV infusion over 4 hours. Intravenous pamidronate and zoledronic acid are considered equally effective in reducing SREs in patients with bone metastases.⁹ Zoledronic acid is the more costly of the two agents, however, the shorter infusion time may offset the higher medication cost with less nursing time, less outpatient facility time, and associated improved quality of life.

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Ibandronate and risedronate have been used off-label for bone metastases, however, they are less effective and considered suboptimal alternatives. Oral bisphosphonates like risedronate and alendronate are poorly absorbed (< 1%) from the gastrointestinal tract, and only about half of the absorbed drug is taken up in bone, with the rest being excreted unchanged in the urine.⁹

What is bisphosphonates' place in hospice therapy for palliating bone pain?

Commonly used medications to manage bone pain such as NSAIDs, corticosteroids, and opioids, focus on pain relief via the reduction of inflammatory mediators and/or inhibition at pain receptors. These analgesics are the mainstay of the management of bone pain in hospice and palliative care, however there is a subset of this population that may benefit from the use of other adjunct therapies:¹⁰

- Bisphosphonates may be useful for reducing both bone pain and high calcium levels and lowering the risk of broken bones.¹¹⁻¹⁴ Long-term treatment better manages pain therefore bisphosphonate therapy should be reserved as adjunctive therapy and not the primary method of pain control.¹¹ Their role in the management of acute malignant bone pain remains unclear. In general, single-dose treatments may be useful for patients with hypercalcemia of malignancy, however, regular monthly treatments are required to prevent SREs.
- Denosumab (Xgeva®) is a human monoclonal antibody with activity against receptor activator of nuclear factor kappa-beta ligand (RANKL) and indicated for the prevention of SREs in patients with bone metastases from solid tumors. It blocks osteoclast activation causing less bone resorption and is administered as a subcutaneous injection once every 4 weeks.⁹ Denosumab has been compared to zoledronic acid in patients with metastatic bone disease from a variety of solid tumors and found to have a slight benefit in preventing SREs. Several reports also note a “modest though significant advantage” for denosumab for level of analgesia.¹⁰
- Calcitonin (Miacalcin®) is used off-label for the management of bone pain due to bone metastases and is administered as a daily subcutaneous injection or intranasal spray. Small controlled trials have yielded conflicting information about the potential for calcitonin to reduce metastatic bone pain.^{10,15} Given the lack of evidence, this treatment generally is not recommended, although an empirical trial could be considered when other treatments are unavailable or ineffective.¹⁰

Pharmacist Assessment:

RF's pain is partially relieved with his scheduled long-acting morphine and maxed out on his dose of naproxen, causing him to seek breakthrough pain management with short-acting liquid morphine, averaging 4 doses a day. His medical history and description of pain indicate bone pain. Bone pain, being somatic in nature, is inflammatory and never fully relieved with opioid therapy alone, requiring the need to adjust his NSAID adjuvant therapy or replace with an oral steroid. It is also noted that the

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morphine breakthrough dose does not complement his scheduled morphine therapy and may be too low.

Recommendations

1. Discuss with RF that he is already prescribed the recommended therapy for the type of pain he is experiencing, however, he may not be on the right dose of morphine (we can adjust this) and naproxen is currently at the maximum dose allowed (we can try a medication that works similarly but in another drug class). Considering his prognosis, low functional status and reasons for foregoing further palliative radiation, he is not a good candidate for bisphosphonate therapy.
2. Adjust scheduled long-acting morphine based upon use of breakthrough morphine
 - Breakthrough dose = morphine 10mg x 4 doses = 40mg morphine/day
 - Increase morphine extended release to 120mg PO BID
3. Adjust morphine breakthrough dose
 - Breakthrough doses should be 10-20% of scheduled opioid dose/day (now 240mg morphine)
 - 10-20% of 240mg = 24-48mg/breakthrough dose
 - For ease in liquid measurement, increase morphine breakthrough to 2mL (40mg) PO every 4 hours as needed
4. Discontinue naproxen and start dexamethasone 4mg PO BID. This therapy will not only assist with bone pain, but may help short term with symptoms of fatigue. Long-term benefits of corticosteroids for fatigue have not been shown.¹⁶ After approximately 2 weeks, reassess his pain and fatigue and consider adjustment of therapy if needed.

For additional information on this topic, please review these references:

Enclara Pharmacia's On Demand Educational Webinar, "Cancer-related Syndromes in Hospice and Palliative Care". Click [here](#) to log in.

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