

Management of bone metastases

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Peter, a 77-year-old engineer, has nonresectable lung cancer that has metastasized to his bones. Palliative radiotherapy to his pelvis and spine helped the pain for some time, but now he is in the last stages of his disease. He is bedridden because of weakness, fatigue, and pain. Peter wants to leave this world in the house he built with his own hands, so he receives frequent home visits.

Pain from bone metastases in his left pelvis has recurred and has not responded to increases in his opioid. Peter has had maximum radiotherapy to his pelvis. He is taking 3 80-mg oxycodone SR tablets every 12 hours and, on average, 5 20-mg oxycodone IR tablets for breakthrough pain daily. He is now having trouble swallowing his pills because of a stubborn esophageal candidiasis, which is being treated with 100 mg of fluconazole daily. He reports hip pain at 10 on a 10-point scale.

Bone metastases are a frequent complication of cancer and the most frequent type of pain related to cancer. In advanced breast and prostate cancer, they occur in up to 70% of cases.^{1,2} In lung, colon, stomach, bladder, uterus, rectum, or kidney cancer, the prevalence is between 15% to 30%. While most patients with bone metastases present with pain in the bones, some patients present with complications of the bone metastases, such as neurological impairment secondary to compression of nerves in the spine or base of the skull. The extent of investigation of neurological impairment or bone pain depends upon the stage of the disease, the goals of care, and the potential effect of investigation on management or outcome.

Figure 1. Algorithm for switching opioids

1. Calculate the total 24-hour dose of each opioid received. (Do not forget the breakthrough doses.)
2. Convert every opioid received to a morphine-equivalent dose. Morphine is used as the converting opioid for all others. This equals total dose of morphine per 24 hours of morphine-equivalent dose.
3. Decide on the new opioid, depending on the mechanism of pain, available formulations, side-effect profile, and interindividual variation.
4. After converting to the new opioid, reduce the dosage by 25% to take into account individual variations in opioid sensitivity.
5. Make your calculations at least twice to avoid any mistakes.
6. If you use the subcutaneous approach, divide the dose in half to convert from oral to parenteral:
 - if intermittently, every 4 hours—a maximum 2-mL dose; or
 - if continuously, the ideal volume equals 0.4 mL/h, up to 2 mg/h.
7. Include breakthrough doses:
 - Every opioid prescription must include a provision for breakthrough pain.
 - Use the same opioid (exception is fentanyl transdermal).
 - The oral dose is 10% of the daily dose. If continuous infusion, the dosage is the hourly dose.
 - Breakthrough doses must be available at the request of the patient: every 60 minutes by mouth or every 20 minutes subcutaneously.
 - If your patient requires more than 3 breakthrough doses per 24 hours, the pain is not controlled adequately and the regular dose should be increased, taking into account the total breakthrough dosage given over 24 hours.

Adapted from Hallenbeck³ and Harlos and MacDonald.⁴

Opioids

The first step is to optimize the opioid dosage. Because Peter is experiencing dysphagia, his medication must be administered parenterally to get his pain under control. Dysphagia can happen in the final stage of illness with loss of consciousness or general weakness. Various conditions can cause dysphagia to temporarily occur, including esophageal candidiasis.

Figure 1^{3,4} provides an overall guide to switching from one opioid to another. Careful calculations are needed to determine the exact dose of the new medication. By applying the guidelines in **Figure 1**, the calculations for Peter are as follows:

1. Six 80-mg tablets of oxycodone SR every 24 hours equals 480 mg. Add 5 20-mg oxycodone IR tablets every 24 hours, which equals 100 mg. The opioid total is 580 mg of oxycodone every 24 hours.
2. The morphine-equivalent dose of 580 mg of oxycodone every 24 hours is 1160 mg of morphine every 24 hours.
3. Hydromorphone is chosen to minimize the subcutaneous (SC) volume. Calculation is as follows: $1160 \div 5 = 232$. Conversion of 1160 mg of morphine is, therefore, 232 mg of hydromorphone.
4. The hydromorphone dose is decreased by 25%, as Peter can be more sensitive to this opioid. The total is 174 mg of hydromorphone every 24 hours, rounded off to 180 mg every 24 hours.
5. Calculation is revisited to ensure accuracy.
6. The SC approach is used to administer the hydromorphone; therefore, the 180-mg dose is halved, equaling 90 mg of hydromorphone every 24 hours. It is delivered continuously, which represents 4 mg/h of SC hydromorphone (rounded up from 3.75 mg).
7. Peter's breakthrough doses will be 4 mg of hydromorphone subcutaneously every 20 minutes as needed.

Over the next 24 hours, Peter's pain is reduced to a 5 on a 10-point scale with the switch to SC hydromorphone; however, his optimal pain level is 1 to 2 on a 10-point scale, and he is not able to sit comfortably at this point. Radiotherapy is not an option, as further dosage can result in neurological damage. Peter needs a good adjuvant to manage the refractory pain. He is given 16 mg/d of dexamethasone subcutaneously.

Pain medications

Adjuvant pain medications are indicated at this point, as they will improve pain management and reduce toxicity from only steadily increasing the opioid. A variety of adjuvant classes of medications can be helpful in bone metastases, including nonsteroidal anti-inflammatory drugs, steroids, bisphosphonates, and cannabinoids.⁵

Nonsteroidal anti-inflammatory drugs. Nonsteroidal anti-inflammatory drugs are most useful in a patient

with moderate bone pain who is able to tolerate oral medications. They should not be used by frail elderly, patients with renal failure or previous peptic ulcer disease, or those who were unable to tolerate them in the past.

Steroids. Steroids are the choice for treatment of short-term relief from bone pain, as they can be given parenterally and act within 24 to 48 hours. A dose of 4 to 16 mg of dexamethasone is typically used in palliative pain management. Because dexamethasone has a long half-life, a daily dose given in the morning is less likely to cause insomnia. If rapid pain control is needed, start with the highest dose and see if it has the desired effect. When pain is controlled, the dose can be titrated down to the lowest effective dose. The dose should be substantially reduced in older adults because of potential side effects, such as psychosis.

Bisphosphonates. If Peter had been in a palliative care unit in hospital, intravenous bisphosphonates could be considered. All oral bisphosphonates are poorly absorbed by the intestines and have little effect on established bone metastases.

Bisphosphonates form a 3-dimensional structure that chelates calcium (Ca⁺⁺). Consequently, they have a strong affinity for bone and are used extensively in conditions of osteoclast bone resorption, such as tumour-associated osteolysis. Bisphosphonates are concentrated at sites of active remodeling; their antiresorptive action is due to direct inhibitory effects on osteoclasts rather than strictly physiochemical effects. The antiresorptive activity is thought to involve 2 primary mechanisms: osteoclast apoptosis and inhibition of the components of the cholesterol biosynthetic pathway.

Bisphosphonates can be divided into 3 generations; the third-generation bisphosphonate (eg, zoledronic acid) is 10 000 times more potent than first-generation etidronate. Sixty to 90 mg of pamidronate (a second-generation bisphosphonate) intravenously, in 500-mL infusion solution of 5% dextrose in water (D₅W) over 2 hours, can give up to 4 weeks of adjuvant pain relief. Four mg of Zoledronate intravenously in 100-mL infusion solution of D₅W over 15 minutes can give pain relief for up to 4 to 8 weeks. Bisphosphonates are best used in patients who will live at least 2 weeks to benefit from the more expensive but longer-lasting relief.

BOTTOM LINE

- Bone metastases are frequent in many cancers and devastating. They can be a challenge to treat.
- Use adjuvant analgesics and do not concentrate solely on opioids.
- Knowing how to switch to another route of opioid administration is a key skill in providing palliative care.
- Remember orthopedic surgeons; involve them early in case you need to treat a potential pathologic fracture ahead of time to keep a limb functional.

POINTS SAILLANTS

- Les métastases aux os sont fréquentes dans de nombreux cancers et sont dévastatrices. Elles peuvent être difficiles à traiter.
- Utilisez des analgésiques adjuvants et ne vous concentrez pas seulement sur les opioïdes.
- Savoir comment passer à un autre mode d'administration des opioïdes est une habileté importante en soins palliatifs.
- N'oubliez pas les chirurgiens orthopédiques; faites appel à eux tôt dans la bataille au cas où vous auriez besoin de traiter d'avance une éventuelle fracture pathologique pour pouvoir préserver le fonctionnement d'un membre.

Bisphosphonates are excreted by the kidneys, and modifications need to be made in cases of renal failure. In particular, zoledronate is known to be toxic to the kidneys, and their function should be monitored if this medication is given on a regular basis. When pamidronate is given for the first time, it can be accompanied by a release of cytokines, which might explain a flulike syndrome associated with mild fever and muscular aches and pains.

Cannabinoids. There are 3 cannabinoids available on the market. Only 1 has the official indication to treat pain in cancer—Sativex.⁶ This is a combination of 2 cannabinoids from the *Cannabis sativa* plant: delta-9-tetrahydrocannabinol and cannabidiol. Sativex has recently received approval as an adjuvant medication for the treatment of cancer pain in Canada. It is initiated at 3 to 4 sprays daily and titrated up to the most effective dose.

Radiotherapy for bone metastases

Radiotherapy is used for bone metastases to relieve pain, prevent impending pathological fractures, and promote healing of pathological fractures.⁷ Radiotherapy is successful in pain relief in 60% to 70% of patients, but it takes up to 3 weeks for the full effect to be seen. Single-fraction treatments have the same response rate as multiple fractions in the management of bone metastases.

It is indicated for use in cancer pain with a neuropathic component not adequately treated with opioids.

Within 48 hours, the dexamethasone and titration of the opioid result in good pain relief for Peter. The dexamethasone is titrated to 12 mg subcutaneously once a day. Two weeks after these adjustments, Peter passes away peacefully and free of pain. ✿

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Competing interests

None declared

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