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CLINICAL REVIEW

Managing skeletal related events resulting from bone metastases

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Pain is one of the most common symptoms managed in a palliative setting, and over half of all metastatic cancers will be associated with pain originating from bone metastases. Breast, lung, and prostate cancers account for about 80% of all bone metastases.[1] Management of bone pain is especially important in patients with prostate or breast cancer as these patients may survive for many years with metastatic disease. Primary care physicians are well suited to provide palliative care as their long term relationships with patients and their families can result in a more satisfactory experience for all involved.

All too often the management of bone pain from cancer metastases stops at opioids and non-steroidal anti-inflammatory drugs. Although specialists administer treatments such as radiation therapy and radiopharmaceuticals, family physicians must be aware of their role if they are to make appropriate referrals.

What problems can bone metastases cause?

Bone formation is a finely balanced process involving the continuous remodelling of bone through the activity of osteoclasts and osteoblasts. This dynamic process may be disrupted by the migration of cancer cells into bone, creating bone metastases. Metastatic lesions are intrinsically weaker than normal bone and can lead to multiple sequelae termed "skeletal related events" (box 1), which greatly affect quality of life.[2] This review will outline the diagnosis and management of skeletal related events, with the exception of hypercalcaemia.

Bone pain

Although up to half of bone metastases are clinically silent,[1] a history of severe or progressive bone pain without an identifiable cause should prompt careful evaluation. Occasionally, metastatic bone pain can be the first symptom prompting a cancer diagnosis, but bone pain in the context of a previous, even remote, cancer history should be carefully evaluated. History should elicit pain characteristics: location, severity, timing, and exacerbating and relieving factors. Pain from bone metastases will commonly be well localised, although it can be radicular or referred. Patients may also describe their pain as constant, dull or aching, exacerbated by weight bearing, or worse at night.[3] A reproducible scale, such as a numerical rating from 0 to 10, where 0 is no pain and 10 is the worst pain imaginable, is useful to determine severity. Clinical examination often finds tenderness with percussion of the affected site.

Pathological fractures

A diagnosis of pathological fracture must be considered in those patients with bone pain in the setting of metastatic disease (fig 1). According to a functional system developed at Memorial Sloan-Kettering Cancer Center in New York, patients are at a higher risk of pathological fractures if they have painful medullary lytic lesions resulting in endosteal resorption of ≥50% of the cortical thickness; painful lytic lesions involving the cortex that are greater than the cross sectional diameter of the bone; painful cortical lesions more than 2.5 cm in length; or lesions producing functional pain after radiation.[4]

Spinal cord compression

Compression of the spinal cord is an oncological emergency requiring timely diagnosis and treatment to avoid irreversible paraplegia or incontinence, or both. Damage to the spinal cord is a result of infarction secondary to compression of the dural sac by metastases within the vertebrae and most commonly occurs in breast, lung, prostate, and renal cancers. Patients typically present with new or worsening back pain, faecal incontinence, urinary retention, weakness,

Fig 1 | X ray film showing a pathological fracture through an osteolytic lesion (arrowed)

Box 1 Skeletal related events resulting from bone metastases

- Bone pain
- Pathological fractures
- Nerve root compression
- Spinal cord compression
- Hypercalcaemia

Fig 2 | Bone scan showing diffuse bone metastases

spasticity, hyper-reflexia, and paraesthesia. Clinical diagnosis is confirmed by magnetic resonance imaging.[5]

Nerve root compression

Impingement of a nerve root by vertebral (or, less commonly, soft tissue) metastases can result in neuropathic pain. Patients generally describe this pain as stabbing, shooting, or burning, radiating in a dermatomal distribution.[6]

How should suspicious bone pain be investigated?

Blood tests

Raised serum concentrations of calcium and alkaline phosphatase can highlight increased osteoblastic activity. In the context of previously undiagnosed cancer or a known "marker positive" diagnosis, tumour markers (that is, prostate specific antigen, carcinoembryonic antigen, CA15-3, erythrocyte sedimentation rate, α fetoprotein, β human chorionic gonadotrophin, and lactase dehydrogenase), and serum protein electrophoresis may be useful. Such biochemical tests may point towards the type of cancer present and can be especially helpful if imaging results are equivocal (for example, a raised level of CA15-3 confirms metastatic disease in marker positive patients).[3] Tumour markers also provide a mechanism with which to monitor the efficacy of treatment.

Imaging

Imaging techniques are important in diagnosing bone metastases, but they have important limitations. Usually more than half of the bone must be involved for a lesion to be visible on plain radiography (fig 1).[7] The low sensitivity and specificity (46% and 32% respectively)[8] of radiography necessitates continued investigation if bone metastases are strongly suspected.

Bone scans pick up reactive osteoblastic activity but do not differentiate metastatic disease from increased activity resulting from benign conditions, such as osteoarthritis or healing fractures (fig 2). Additionally, bone scans can be negative when metastases are lytic, such as those produced by multiple myeloma, thyroid, and kidney cancers.[9] Sensitivity and specificity increase to 63% and 64% respectively when plain radiography is coupled with bone scanning.

Hairline, undisplaced fractures or impending fractures may be difficult to diagnose. Computed tomography with bone windows or magnetic resonance imaging can be useful in locating such fractures when they do not show up on plain x ray films (fig 3).[7] Magnetic resonance imaging of axial skeleton is seen as the ideal imaging technique for detecting metastases, and it has a sensitivity of 100% and a specificity of 88%.[8]

Biopsy

Biopsy of bone metastases is appropriate if a patient presents without a known primary cancer; to confirm or restage a disease in a patient with a known primary cancer, but no previous bone metastases; or to obtain tissue for hormonal or immunohistochemical analysis.[10]

What can be used to treat metastatic bone pain?

Analgesics and non-steroidal anti-inflammatory drugs

Pain from bone metastases should be treated according to the World Health Organization's analgesic ladder. This ladder is a three step algorithm for cancer pain, which encourages prompt oral administration of pain medications, starting with non-opioids (paracetamol (acetaminophen) and non-steroidal anti-inflammatory drugs) and graduating to mild then strong opioids as the need arises.[11] Adjuvant medications may be added at any step of the ladder.

A meta-analysis of 25 randomised controlled trials related to use of non-steroidal anti-inflammatory drugs in cancer pain in humans found that non-steroidal anti-inflammatory drugs reduce cancer related pain 1.5 to 2.0 times more than placebo, but a lack of comparable studies precluded testing the hypothesis that non-steroidal anti-inflammatory drugs are specifically effective for malignant bone pain.[12] A more recent Cochrane systematic review included 42 randomised

Box 2 How radiation therapy works

- Radiation kills tumour cells by delivering high amounts of energy, which damages DNA and prevents further cell division
- The total desired radiation dose is divided into fractions, which are given over a period of time so that normal tissue has time to repair
- Symptomatic relief is achieved more quickly when a higher daily dose is used
- Palliative radiotherapy tends to use higher doses in fewer fractions as there is less concern about long term damage to tissues and more focus on timely symptom relief

Box 3 Doses for palliative radiation therapy

- Bone pain, single site—8 Gy, single fraction, or 20 Gy in five fractions*
- Half body, upper body—6 Gy, single fraction
- Half body, lower body—8 Gy, single fraction

*Overviews of randomised controlled trials show that single treatment is as effective as a longer treatment regimen[20]

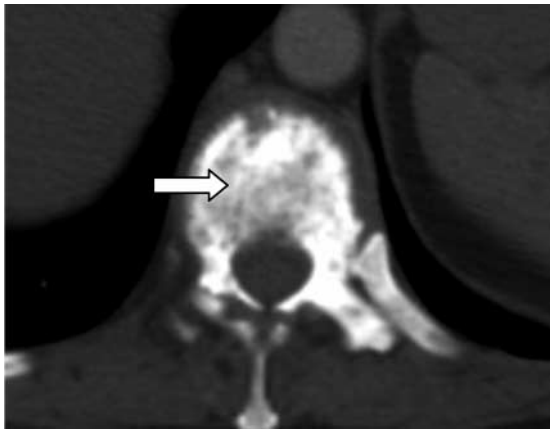

Fig 3 | Computed tomogram showing bone metastases in a thoracic vertebral body (arrowed)

control trials that compared various non-steroidal anti-inflammatory and opioid combinations in the treatment of cancer pain in a total of 3084 patients. Unfortunately, heterogeneity and short duration of studies precluded a full meta-analysis and limited generalisability of the findings, but a qualitative assessment found that non-steroidal anti-inflammatory drugs alone, or in combination with opioids, were effective for short term treatment of cancer pain.[13]

Neuropathic pain may respond to anticonvulsants or tricylic antidepressants; randomised controlled trials have shown that the number needed to treat for one patient to obtain a moderate (50%) improvement in pain for both categories of adjuvant drugs is between 2 and 4.[14] Calcitonin is proposed to be uniquely effective for bone pain; however, a Cochrane review found that the evidence is too limited to make any recommendations for its use in this setting.[15]

Bisphosphonates

Bisphosphonates inhibit osteoclast mediated bone resorption and thereby increase bone stability. A systematic review has found that when bisphosphonates are given in the setting of bone metastases, the rate of fractures, need for radiotherapy, and hypercalcaemia are significantly reduced.[16] However, rates of spinal cord compression are not significantly altered with the use of bisphosphonates, and the need for orthopaedic intervention becomes significantly decreased only after one year of treatment.[17]

A Cochrane review suggested that bisphosphonates should not be used as first line agents for treating bone pain but that when used in conjunction with radiotherapy and analgesics they can provide analgesia (number needed to treat 6, for pain relief within 12 weeks[18]). Patients must be treated with bisphosphonates for an average of six months before a beneficial effect is evident.[18] The optimal duration of treatment is not currently known, and a randomised controlled trial has shown that benefits are not maintained when the drugs are discontinued.[19] Pooled data for intravenous versus oral bisphosphonates show that intravenous preparations have a more significant reduction in skeletal related events.[18]

Bisphosphonates are not without side effects and can cause fever, phlebitis, transient myalgias, arthralgias, osteonecrosis, hypocalcaemia, and renal impairment. Hence, practice guidelines may fall short of recommending their routine use.

Radiation therapy

Radiation therapy is perhaps the most effective, but least known, tool for management of painful bone metastases. A systematic review found a number needed to treat of 4.2 for complete relief (pain score of zero at treated site and no concomitant increase in analgesic intake) one month after radiation (box 2).[20] Radiation treatment therefore presents a means to resolve bone pain and obviate or substantially decrease the need for opioids, particularly for patients who develop dose limiting opioid toxicities without complete pain relief. The result is an increase in three components of quality of life: decreased pain, fewer side effects from opioids, and improved functionality. The onset of pain relief can be rapid, and 71% of patients will have at least partial, but significant, pain improvement with a single radiation treatment (box 3, table).[21]

Side effects with palliative radiation doses are generally mild (table).[1] A systematic review has shown that there is no increased risk of fractures with treatment and no increased risk of cord compression with treatment.[22] About a third of patients will experience a brief flare-up of pain in the first few days after radiotherapy, for which dexamethasone may be an effective treatment.[23] Patients with widespread

SOURCES AND SELECTION CRITERIA

We did Embase and Medline searches from 1980 to 2008 (week 22) using the medical subject headings "bone metastases or bone metastases.mp", "palliative therapy or palliative care.mp", and "cancer pain or bone pain or pain or pain.mp". We selected only those in English and involving humans. We used the same terms to search the Cochrane Library for systematic reviews.

UNANSWERED QUESTIONS AND ONGOING RESEARCH

- What is the role of non-steroidal anti-inflammatory drugs specifically for pain from bone metastases?
- What is the optimal duration of treatment with a bisphosphonate?
- Do bisphosphonates have a role in the primary prevention of bone metastases?
- Are corticosteroids effective for managing pain from bone metastases?
- Can pain prompted by radiotherapy for bone metastases be prevented with anti-inflammatory agents?
- How useful are biochemical markers of bone turnover in predicting tumour activity and guiding treatment?
- How lasting will the pain relief from radiofrequency ablation prove to be, and what are the long term side effects of this treatment?

Efficacy, regimens, and side effects of radiotherapy and radiopharmaceuticals for metastatic bone pain

Type of treatment	Dose	Efficacy		Median onset of pain relief	Duration of pain relief	No of treatments possible	Side effects
		Pain relief (% of cases)	Complete response (% of cases)				
Radiotherapy	8 Gy in one fraction or 20 Gy in five fractions	58	23[21]	1-3 weeks	13-24 weeks; 50% pain-free at six months	Many, depending on normal tissue tolerances	Fatigue, pain flare-up, nausea, vomiting, enteritis (depending on anatomical location)
Half body treatment	6 or 8 Gy in one fraction	70-90	15-40[1]	1-3 days	Until death in most patients	Many	As above, with possible myelosupression
Radiopharmaceuticals	Variable	65[24]		<15 days	3-12 months	Up to 10 treatments, three months apart	Myelosupression

TIPS FOR NON-SPECIALISTS

- Patients with new bone metastases or bone metastases not consistent with pre-existing neoplasm should be investigated to identify the reason for these lesions
- Patients with painful bone metastases should be treated with analgesics according to the World Health Organization's analgesic ladder
- Pathological fracture, spinal cord compression, and hypercalcaemia should be ruled out. Patients with proved spinal cord compression should be treated with dexamethasone 4 mg four times a day and immediately referred for neurosurgical and/or radiation oncology assessment
- All patients with poorly controlled pain from bone metastases should be referred for radiation oncology assessment

symptomatic bone metastases may be candidates for half body irradiation, rather than several single treatments.[24]

Radiopharmaceuticals

When bone metastases are widespread and present on both sides of the diaphragm, radiation treatment is no longer feasible. Radionuclides can be used in these cases.[25] Systemic radiotherapeutic agents are calcium analogues that are intravenously administered and preferentially taken up by bone at diseased sites. A Cochrane review of the use of radioisotopes for metastatic bone pain found a number needed to treat of 4 for complete pain relief in the short and medium term (one to six months).[26] However, there is a corresponding number needed to harm of 11 for leucocytopenia in this same population. Other adverse effects include thrombocytopenia and temporary flare-up of pain in 15% of patients.[26] Radionuclides are not effective in the treatment of soft tissue masses or spinal cord compression as their uptake is primarily by bone. They can be used when symptoms recur at a previously irradiated site, and they have been shown to lessen development of new bone pain.[25]

Radiofrequency ablation

Radiofrequency ablation is a new treatment method in which a tumour is destroyed by local application of a high frequency alternating current guided by imaging. Radiofrequency ablation seems to be fast, effective (95% of patients experienced a clinically significant decrease in pain in one study[27]), and safe in small case-control studies. It may be contraindicated in the spine owing to proximity of the spinal cord and nerve roots. The duration of treatment effect is not yet known.[28]

Other treatments

Hormonal therapy, systemic chemotherapies, and biological agents (such as trastuzumab) may play a role in the treatment of bone metastases but will not be discussed here. Anaesthetic techniques and orthopaedic interventions, including osteosynthetic devices and prosthetic reconstructions, can also be useful but are outside the scope of this review.

How are pathological fractures and spinal cord compression treated?

Unstable pathological fractures should be treated with surgery when possible, and postoperative radiation therapy considered. Postoperative radiation has been shown in two retrospective trials to improve outcomes significantly, primarily by improving mobility.[1]

Spinal cord compression should be treated as an emergency at the first sign of symptom onset to prevent permanent neurological impairment.[29] Patients should receive high dose steroids together with referral to either neurosurgery or radiation oncology for surgical decompression or radiation therapy.[30]

ADDITIONAL EDUCATIONAL RESOURCES

For healthcare professionals

- National Comprehensive Cancer Network. *Clinical practice guidelines in oncology. Adult cancer pain*. Version 1.2008. www.nccn.org/professionals/physician_gls/PDF/pain.pdf
- Eisenberg E, Berkey CS, Carr DB, Mosteller F, Chalmers TC. Efficacy and safety of nonsteroidal antiinflamatory drugs for cancer pain: a meta-analysis. *J Clin Oncol* 1994;12:2756-65.
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- Cancer Care Ontario. Therapeutic Radiopharmaceuticals Guidelines Development Group. *Radiopharmaceuticals for the palliation of painful bone metastases. Practice guideline report #14-1*. 2004. www.cancercare.on.ca/pdf/pebc14-1f.pdf

For patients

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- National Cancer Institute. *Pain*. 2008. www.cancer.gov/cancertopics/pdq/supportivecare/pain/patient

SUMMARY POINTS

Bone is an extremely common site of cancer metastases, and bone metastases frequently results in pain

Bone metastases can be detected on a bone scan, computed tomogram, and magnetic resonance imaging; plain x ray films will show abnormalities only when at least half of the bone is involved

Pathological fracture and spinal cord compression should always be ruled out

Treatment of metastatic bone pain should comprise analgesics, non-steroidal anti-inflammatory drugs, and bisphosphonates. Systemic chemotherapy, hormonal therapy, and surgery can play a role in some cases

Radiation therapy, as a single fraction, half body treatment, or as a systemic radiopharmaceutical, can provide effective pain relief with minimal side effects

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A memorable patient

Crisis

My patient lives alone. She has had a long string of compulsory admissions for psychosis and has been insisting on reducing her neuroleptic against advice. On a routine visit, her community psychiatric nurse finds her distressed and distracted. She denies any problems, declines a suggestion that she increase her medication, and insists that the nurse leave. Later that day a member of our crisis team goes to her flat, but she refuses to let him in.

This is typical of her pattern of relapse, with terrifying psychotic experiences and compulsory detention in a psychiatric hospital expected to follow. Of course, community treatment or voluntary admission would be preferable, but previous experience suggests that neither will be possible. So next day I arrange to be joined outside her flat by the social worker and a second doctor, whose agreement will be necessary for me to admit the patient against her will.

We don't expect her to let us in, and we talk about the likelihood of needing to get a court order allowing the police to force an entry. This is not usually as bad as it sounds, with persuasion succeeding in the end, but it can be a dreadful experience for the person involved: how would you feel if several police officers, a psychiatrist, and a social worker broke into your home while your neighbours looked on? But she has been so ill in the past that doing nothing is not a humane option.

I knock on her door, and she asks who it is. I tell her, and to our surprise she sounds pleased and cheerfully lets us in. She apologises for her behaviour the previous day, saying that her daughter had just had an emergency caesarean and the baby had been on a ventilator when her nurse called. She had thought that the nurse might be upset if she told her what was troubling her, and it might put her off having children herself. As for the crisis team member, she wasn't going to let a stranger into her home was she?

The baby, her mother, and my patient are all fine now, and she thanks us for our visit and shows us out.

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