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CLINICAL REVIEW

Cancer induced bone pain

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Bone pain is the most common type of pain from cancer and is present in around one third of patients with bone metastases.^{1 2} Based on postmortem studies of patients with advanced cancer and clinical knowledge of how often bone metastases result in pain, the incidence of cancer induced bone pain is estimated at 30 000 patients in the United Kingdom each year.^{3 w1} Currently, improvements in cancer treatments mean that many patients are living with metastatic cancer for several years. The prevalence of cancer induced bone pain is therefore likely to be much greater than the annual incidence.^{w1} Cancer induced bone pain is considered one of the most difficult pain conditions to treat because of its frequent association with weight bearing and movement. Not surprisingly, it has a major impact on patients' daily functioning and mood and can result in admission to hospital.^{w2 w3}

Given the prevalence of cancer induced bone pain, it is likely that clinicians in primary or secondary care will be confronted by patients in pain crises. Recognising and initiating management of this specific pain state, as well as an awareness of the specialist treatments, is important for all clinicians.

What is cancer induced bone pain?

Cancer induced bone pain is a specific pain state with overlapping but distinct features of both inflammatory and neuropathic pain.⁴ The most important changes are in bone homeostasis, with corresponding events in the peripheral and central nervous system.⁵ In healthy bone, osteoclasts and osteoblasts are highly regulated to maintain balanced resorption and formation of bone respectively, through RANK-ligand (receptor activator of nuclear factor κ). In the presence of a bone metastasis, increased expression of RANK-ligand disrupts this relation leading to increased osteoclast activity and bone destruction. Cancer cells also stimulate local inflammatory mediators and create a highly acidic environment, which sensitises peripheral nerve endings within the bone marrow and bone matrix. When combined with the destruction of nerve endings through cancer invasion, the resulting pain is a mixture of ongoing inflammatory and neuropathic processes, which lead

to a hyperexcitability state within the spinal cord. Patients experience this as constant pain, with high sensitivity to movement.⁴

Who gets cancer induced bone pain?

Cancer induced bone pain can occur anywhere that cancer has metastasised to bone. Cancers most often involved are those of the prostate, breast, and lung, as well as myeloma.³ The most common sites of metastases are vertebrae, pelvis, long bones, and ribs.³ At postmortem examination, up to 70% of patients who died of cancer will have bone metastases.³ Bone metastases can be found in a wide range of places (figure 1). However, not all patients with bone metastases get pain; bone pain was identified in only a third of patients with bone metastases in one large prospective study.¹ It is not yet clear why some bone metastases cause pain and others do not.

What are the clinical features of cancer induced bone pain?

In a cross sectional survey in 2011 patients described their cancer induced bone pain as annoying, gnawing, aching, and nagging.^{w4} The pain is commonly a mixture of steady background pain, as well as pain that is exacerbated by weight bearing or movement, called incident or episodic pain.⁴ In a recent well conducted European-wide observational study of 1000 patients with cancer, 85.5% reported some form of incident pain episodes.⁶ The presence of movement related pain has most impact on function and daily activity.^{w4}

Cancer induced bone pain is most commonly experienced in the lower back, pelvis, long bones, and ribs. This can be the presenting feature of the cancer or highlight a recurrence in those previously treated. Therefore in patients with or without active cancer, persistent pain in these areas should alert clinicians to the possibility of bone metastases. Findings on examination are often non-specific with only some tenderness

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Additional references

The bottom line

Cancer induced bone pain is a common problem, which can be extremely debilitating to patients with an already limited life expectancy

When treating cancer induced bone pain, maintenance of function should be given high priority alongside pain relief

Early recognition, intervention with functional aids, and behaviour modification, combined with initial titration with analgesia (commonly, strong opioids) are important first steps for non-specialists

The evidence for early referral for radiotherapy is strong, although bisphosphonates will have an important role for some patients

Specialist support will be required if pain persists despite initial treatment with behaviour modification, commencement of a non-steroidal anti-inflammatory drug, and initial titration of a strong opioid

Sources and selection criteria

We searched Medline, Clinical Evidence, and the Cochrane Library using the terms "bone metastases", "pain", and "bone pain" and then combined these with the specific treatment terms individually. Where possible we have used systematic reviews but not referenced trials included in these reviews. We limited our search from 1990 to December 2014. We also searched the National Institute for Health and Care Excellence and the Scottish Intercollegiate Guidelines Network. In calculating the numbers needed to treat, we have assumed a conservative placebo response of 25%.

over the site of metastasis or pain specifically related to movement.

A bony metastasis can weaken bone sufficiently such that an innocuous movement, bump, or fall may result in a pathological fracture. Vertebral pain should always alert clinicians to the risk of spinal cord compression, especially in the presence of sensory disturbance, generalised leg weakness, or changes in bladder or bowel function. Even without "red flag" signs, a full neurological examination should be done in these patients, with a low threshold for a spinal magnetic resonance scan.⁷ Even if suspicion is low, advice should be sought from the patient's oncologist; retrospective cohort studies have shown that being able to walk at the time of diagnosis of spinal cord compression is correlated with overall survival and the ability to walk after treatment. Early diagnosis and treatment of impending spinal cord compression can drastically improve quality of life for patients.^{8,9}

Table 1 outlines the advantages and disadvantages of the various investigations for suspected cancer induced bone pain. Generalists may consider plain film radiography or computed tomography as initial investigations; other investigations are usually undertaken by specialists.

How is cancer induced bone pain initially managed?

The first steps in management are simple measures that can be initiated in non-specialist care, while referral for specialist treatments such as radiotherapy or bisphosphonates is awaited. In the following section we describe the evidence for each treatment that is commonly used for cancer induced bone pain. Consider specialist referral in any patient where pain persists despite these initial steps, those with rapidly increasing pain despite treatment or evidence of toxicity from opioids, and where pathological fracture or spinal cord compression are suspected.

Non-drug interventions

Important aspects of managing cancer induced bone pain are to support patient self management and encourage the use of non-drug measures. An observational study of 1000 European patients with cancer showed that in those who had pain on movement, many of whom had bone metastasis, 43% found consistent pain relief with non-drug measures, often reported as either rest or sleep.⁶ Discussing behaviour modifications, such as avoiding strenuous movement, and referring patients for any appropriate movement aids (walking stick, Zimmer

frame) or home adaptations (bath rails) can make important contributions to the maintenance of function and quality of life.

World Health Organization pain ladder

For cancer pain in general, the mainstay of treatment has been the World Health Organization's method for the relief of cancer pain, commonly known as the analgesic ladder.¹⁰ Observational studies have shown that about 73% of patients achieved adequate analgesia by following these guidelines, leaving an important minority of patients with inadequately controlled pain despite receiving strong opioids.^{11,12}

The first step of the WHO ladder is non-opioid analgesics, such as paracetamol and non-steroidal anti-inflammatory drugs. Although some patients find over the counter analgesics helpful, several systematic reviews that have examined the effectiveness of paracetamol for cancer pain showed that although it was well tolerated there was no significant benefit particularly when added to strong opioids.^{13,14} Non-steroidal anti-inflammatory drugs are often perceived to be more efficacious in cancer induced bone pain than in other pain states, and this is a reasonable assumption given the major inflammatory component. However, a well conducted systematic review in 2012 showed some benefit from adding non-steroidal anti-inflammatory drugs to strong opioids for cancer pain, although this evidence is limited and weak.¹³ There are well reported concerns regarding adverse effects of non-steroidal anti-inflammatory drugs; however, this systematic review failed to show any additional harm of adding a non-steroidal anti-inflammatory drug to a strong opioid.¹³ The studies did not perform subgroup analysis on cancer induced bone pain. Therefore the assertion that non-steroidal anti-inflammatory drugs are specifically beneficial in cancer induced bone pain cannot be supported.

The next step in the WHO ladder is the use of weak opioids, although a systematic review has only shown marginal benefits of tramadol and codeine in cancer pain, with significant nausea and vomiting associated with tramadol compared with placebo or when added to fentanyl. The authors in these studies did not report the specific proportion of patients with bone metastases.¹⁵ Therefore it is common to miss this step and start low dose strong opioids if non-opioid analgesia is ineffective.

Strong opioids

Strong opioids are the mainstay of treatment for background pain in patients with cancer induced bone pain. In the United Kingdom, the National Institute for Health and Care Excellence

has published extensive guidance on initiating and managing strong opioids in palliative care.¹⁵ This guidance is not specific to cancer induced bone pain, but the principles are directly relevant. Several relatively small randomised controlled trials found no difference between immediate release and sustained release morphine in terms of efficacy or side effects when treatment with opioids was initiated. Therefore this decision should be based on patient and clinician consensus.^{16 w6-7}

Several different preparations and types of strong opioid are available. A network meta-analysis showed no important differences in efficacy between morphine and other strong opioids.¹⁷ Based on one well conducted randomised controlled trial, about 75% of patients will achieve good pain control with strong opioids, resulting in a number needed to treat of 2.¹⁸ Within this study, however, there was no subgroup analysis for cancer induced bone pain. Table 2⇓ provides a summary of the numbers needed to treat for various treatments for cancer induced bone pain.

In the United Kingdom, morphine is recommended by NICE as the preferred opioid treatment in patients who can take oral drugs. When morphine was compared with oxycodone no difference was found in pain intensity or adverse effects.^{17 18}

Transdermal opioids (fentanyl or buprenorphine) are likely to be less constipating than morphine or oxycodone.¹⁷ Specialist advice should be sought if pain control is inadequate after the initial titration of opioid analgesia, or treatment fails.¹⁷

Management of incident pain is less satisfactory. This is because pain manifests within five minutes, is often movement related, and subsides within 15 minutes in about half of patients with cancer induced bone pain.^{w4} Timing drug treatment to coincide with this pain profile is challenging.

A meta-analysis of fast acting fentanyl preparations found them to be statistically superior over oral morphine in the treatment of incident pain.¹⁹ When compared with oral morphine, however, the numbers needed to treat at 10 and 15 minutes after the drugs have been administered are 18 and 12, respectively.²⁰ This means that of 12 patients treated with fast acting fentanyl, only one would have gained benefit after 15 minutes of treatment that would not have done so had they been treated with morphine.²⁰ Given the additional cost of these preparations, current advice is to use immediate release morphine preparations as the preferred treatment and to try a fast acting fentanyl preparation if this treatment fails. Adverse events are difficult to quantify in these studies as patients are already taking regular background opioids. Constipation is a common side effect of opioid treatment and a laxative should be prescribed at the time treatment is started.¹⁷

Other drug interventions

Adjuvant drugs such as antidepressants and anticonvulsants may enhance analgesia from strong opioids and can target neuropathic pain mechanisms. A systematic review in 2011 examined the efficacy of these drugs for the treatment of cancer pain when added to opioids. A modest reduction in pain scores was found in patients with a neuropathic element to their pain, but more adverse effects were reported. Benefit was seen within 4-8 days and did not improve beyond this. These conclusions are limited owing to the quality of the studies included in the review.²¹ Although animal studies have suggested that gabapentin can have an important analgesic effect in cancer induced bone pain, there is no evidence confirming the efficacy of this class of drugs in humans.^{w8}

Currently there is no evidence to support the use of steroids for cancer induced bone pain; two randomised controlled studies have shown no sustained benefit for cancer pain.^{22 23}

Lidocaine (lignocaine) patches are not absorbed systemically and evidence to support their use for cancer induced bone pain is lacking.^{w9 w10}

What further treatment options are available?

Once initial treatment has been started, further treatment options are available to maintain function and quality of life.

Radiotherapy

Radiotherapy has been shown to reduce pain significantly and is the most effective treatment that is specific for cancer induced bone pain. Therefore patients with confirmed cancer induced bone pain should be referred to a clinical oncologist as soon as possible. A well conducted systematic review comparing single dose radiotherapy with multiple doses found no important differences between treatments. Both approaches resulted in a meaningful improvement in pain for about 60% of patients (number needed to treat 2.8).^{24 25} Within this group it was reported that approximately 25% would be pain-free. This means that a single dose of radiotherapy can be effective and without major burden for even very frail patients.

In a well conducted randomised trial of 850 patients, where most had had an initial response to radiotherapy but recurrence of pain, 28% experienced a further overall pain response at two months after re-irradiation. This was also associated with improved quality of life.^{26 27}

Radioisotopes

Referral to oncology also provides the opportunity to review hormonal treatment and chemotherapy, as well as to consider radioisotope treatment. Some evidence, largely from studies in prostate cancer, indicates that radioisotopes may provide complete reduction in pain over one to six months, with no increase in analgesic use, but severe adverse effects (leucocytopenia and thrombocytopenia) are common.^{w11}

Bisphosphonates

Bisphosphonates such as pamidronate and zoledronate are used to reduce both pain and skeletal events in patients with bone metastases. They act by inhibiting osteoclast function. Globally they are used to prevent skeletal related events and reduce pain in breast, prostate, and lung cancer as well as multiple myeloma. In the United Kingdom NICE only recommends early treatment with bisphosphonates for bone pain associated with breast cancer.²⁸ NICE advise it can be used in lung and prostate cancer once palliative measures and radiotherapy have been given. Several well conducted randomised controlled trials have shown a persistent reduction in pain scores over years with bisphosphonates in patients with breast cancer, and although pain scores increase over time in studies in prostate cancer there is still a significant difference in favour of bisphosphonate compared with placebo.²⁹ In a large well conducted randomised controlled trial in which patients with bone pain from prostate cancer were randomised to a single infusion of 6 mg of the bisphosphonate ibandronate or a single 8Gy fraction of radiotherapy, overall response rates at four weeks were 49% and 53%, respectively. This non-significant difference was also similar at 12 weeks.³⁰ This suggests that radiotherapy and

What to discuss with patients who are starting strong opioids

- Address concerns about addiction, tolerance, and side effects, being clear that prescription of strong opioids does not mean patients are in the last stage of life
- Give verbal and written advice on when and how to take opioids for both background and breakthrough pain
- Explain how long the pain relief should last and that patients' ability to drive may be impaired during initiation of treatment or when doses are increased
- Give advice on signs of toxicity, such as drowsiness, twitching, and hallucinations, and who to contact if any occur out of hours
- Provide drugs at the start of treatment, to deal with side effects such as constipation
- Offer regular review

Adapted from NICE clinical guideline 140 (<http://guidance.nice.org.uk/CG140>)

bisphosphonates are equally appropriate and effective interventions.

A Cochrane review from 2002 examined the effects of bisphosphonates on cancer induced bone pain and calculated numbers needed to treat of 11 at four weeks after infusion and 7 at 12 weeks after infusion.³¹ This review concluded that although evidence supports the use of bisphosphonates they should not be considered as first line management, which is in keeping with the advice from NICE.³¹ In patients with cancer induced bone pain from myeloma, a Cochrane review showed benefit from bisphosphonates in pain management.³²

Denosumab

Denosumab is a novel agent that specifically inhibits RANK-ligand. Clinical trials have shown important benefits in reducing skeletal related events. One randomised controlled trial recruited patients with breast cancer with mild levels of pain. The median time for moderate or severe pain to develop in those receiving denosumab was significantly delayed when compared with bisphosphonate zoledronic acid, although there was no difference in the use of strong analgesics at the end of the study.³³

Interventional procedures

If patients have ongoing complex cancer induced bone pain despite receiving opioids, radiotherapy, or bisphosphonates, referral to pain services should be considered. There is good evidence from a randomised controlled trial that implantable intrathecal devices lead to a reduction in pain and increased survival in patients taking high dose opiates for refractory pain.^{w12}

Surgery

In patients with a good performance status, prophylactic surgery may be considered for relief of cancer induced bone pain. One randomised controlled trial showed that percutaneous stabilisation in the long bones of leg can significantly reduce pain.^{w13} Once a pathological fracture has occurred, however, orthopaedic intervention can stabilise the fracture.

Complementary therapies

Complementary therapies may be considered, but as yet they are supported by weak evidence. A Cochrane systematic review of acupuncture acknowledged that there were studies showing benefit in cancer pain, but that evidence was insufficient to recommend this as a treatment.^{w14} Evidence was also insufficient to support TENS (transcutaneous electrical nerve stimulation), but one small feasibility randomised controlled trial in patients with cancer induced bone pain suggests that verbal rating scores of pain on movement are reduced with active TENS compared with sham TENS.^{w15} Patients may appreciate non-drug

measures that they can manage themselves and so TENS may be of value.

Contributors: CK conceived, drafted, and revised the paper and interviewed a patient to develop the patient's story. PH revised the paper and provided tables and images for inclusion. MIB conceived and revised the paper and calculated the numbers needed to treat. All authors approved the final manuscript. MIB is the guarantor.

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Questions for future research

- Why do some bone metastases cause pain and others do not?
- What are the disease processes that are responsible for some bone metastases causing pain and others not, and are there any associations with cancer type?
- Are there specific phenotypes of cancer bone pain that might predict response to analgesia?
- What is the contribution of spinal hyperexcitability in the experience of bone pain, and how best can this be identified and managed?
- What non-drug treatments may offer patients benefit in managing movement related pain?

Tips for non-specialists

- The focus of management should be maintenance of function
- Non-steroidal anti-inflammatory drugs may be helpful for some patients but most will require strong opioids
- Early referral for single fraction radiotherapy should be sought, even in relatively frail patients
- Referral for treatment with bisphosphonates can be helpful for some patients
- Consider early referral to specialist services in patients with refractory pain despite initial measures

A patient's perspective

I was diagnosed with cancer on my wedding anniversary a year ago. I developed back pain, which felt exactly the same as sciatica; however, it wasn't getting any better. One Saturday it became so unbearable that I went to A and E and they diagnosed a water infection and sent me home with antibiotics. I saw my general practitioner and he sent me back to A and E where they did a scan and told me my kidney looked slightly inflamed. They said it would settle down in a few days with antibiotics. They called me back a few days later to tell me they'd found cancer in the bones in my back and my pelvis on the scan I'd had.

Since then the pain has been bad but it's the things that it stops me from doing that I get upset about. I can't swim or walk anymore and it really wears you down. It's affected my marriage so we now sleep in separate beds.

I've really appreciated the doctors' help but they don't understand that I don't just want to lie in bed all day, because the tablets have made me sleepy. I want to be able to do things and this is so important to me. I'd really like doctors to think about trying to make sure I'm able to do things still rather than just giving me tablets.

Additional educational resources

Resources for healthcare professionals

- National Comprehensive Cancer Network (www.nccn.org)—Provides guidelines for the management of adult cancer pain and treatment of specific cancers (free with registration)
- European Society for Medical oncology (www.esmo.org)—Guidelines for pain management in cancer with access to a smartphone app
- National Institute for Health and Care Excellence (www.nice.org.uk)—Evidence based guidance for specific treatments and an online treatment algorithm for initiating strong opioids and managing side effects

Resources for patients

- Macmillan Cancer Support (www.macmillan.org.uk)—Provides information and help on cancer and the management of symptoms, including bone pain; provides links to local support groups in the United Kingdom
- Cancer Research UK (www.cancerresearchuk.org)—Contains information about cancer and the management of specific symptoms such as pain and includes a forum for patients to discuss their illness
- American Cancer Society (www.cancer.org)—Has general information about bone metastases, and enables patients to search for local support services in the United States

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Tables

Table 1 | Advantages and disadvantages of investigations for bone metastases

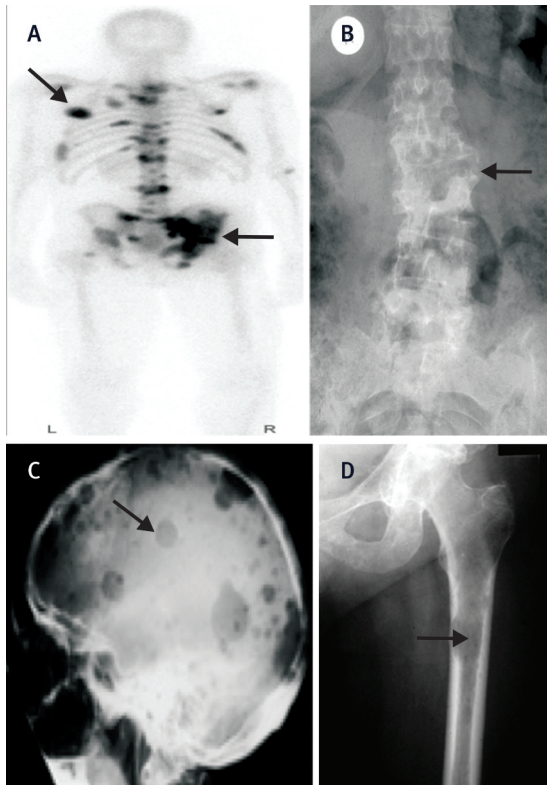
Investigation	Advantages	Disadvantages
Plain film radiography	Universal availability; portable films possible, low cost	Low sensitivity: requires >50% cortical destruction to be visible
Computed tomography	More sensitive than plain radiography; best for ribs and pelvic and shoulder girdles; gives information about soft tissue; can be reconstructed in three planes	Access variable outside large hospitals; high cost
Technetium 99m bone scan	Available widely; whole skeleton assessed; intermediate cost	Relatively low sensitivity; reflects osteoblastic activity: non-specific
Magnetic resonance imaging	Optimal images of bone; high sensitivity; detects small metastases before bone damage occurs; optimal for cord compression; gives soft tissue and nerve images; whole body magnetic resonance imaging screens entire skeleton	Access limited; high cost
Fluorodeoxyglucose positron emission tomography	Similar sensitivity to technetium 99m for bone metastases; additional information about other organs	Access limited; high cost; limited specificity: false positives can occur
Fluorine positron emission tomography	Most sensitive detection of bone metastases	Limited experience, evidence, and access; high cost
Choline positron emission tomography	Sensitive for prostate cancer metastases	Access limited but increasing; high cost

Table 2| Numbers needed to treat values for a meaningful clinical response* for various treatments in cancer induced bone pain

Intervention	Numbers needed to treat
Strong opioids for background pain	2
Fast acting fentanyl for incident pain (at 15 mins)	12
Radiotherapy (meaningful response)	2.8
Bisphosphonates (at 12 weeks)	7

*Defined as either 30% or 50% reduction in pain scores or an outcome of partial or complete response.

Figure



Radiological investigations showing bone metastases. A) Bone scan showing metastatic deposits throughout the skeleton. B) Plain radiography of spine showing lytic vertebral metastasis. C) Plain radiography of a skull showing multiple metastatic deposits. D) Plain radiography showing a lytic lesion of the upper shaft of the left femur