James Logan Prize Essay

The Challenges of Managing Bone Pain in Cancer

Carenza Glithero

Accepted: 9th September 2019

INTRODUCTION

With advances in cancer treatment significantly improving survival, it is increasingly vital to consider the impacts on the quality of life experienced by cancer patients. One factor is pain, with bone pain the most common cause among cancer patients. Bone pain typically results from metastases, especially from lung, breast, kidney and prostate cancer. Up to 70% of patients with advanced cancer have bone metastases, however only a third will be symptomatic. The presence of bone metastases confers a poor prognosis with median survival of several months.

Bone cancer typically results in a constant baseline pain punctuated by intermittent episodes of severe pain. While the pain may be non-specific, occurrence at night, at rest, or on movement should raise the index of suspicion and provoke further investigation. Episodic or incident pain may occur spontaneously or be provoked by moving or bearing weight on the affected bone. In up to 55% of cancer patients bone pain is undertreated, resulting in additional suffering for patients with a limited life-expectancy.

This essay will review the challenges of managing bone pain in cancer, reviewing the mechanisms involved, current available therapies and ongoing issues in management.

BONE PAIN IN CANCER

The underlying mechanisms behind the generation and maintenance of cancer-associated bone pain are complex, and a lack of understanding has long hindered the management of affected patients. Bone pain in cancer has both an inflammatory nociceptive and a neuropathic element. Metastases to bone alter the normal balance between resorption and formation, causing subsequent changes in the peripheral and central nervous systems.

Cancer cells promote bone destruction through the expression of κ-B ligand (RANKL) which binds to RANK receptors on osteoclasts, promoting their differentiation into mature osteoclasts. The osteoclasts then resorb bone via an acidic resorption zone, resulting in pathological fractures, hypercalcaemia and severe pain to the patient via the stimulation of TRPV1 and ASIC3 channels expressed by nerve fibres.

Continuous peripheral stimulation promotes neuroplastic change in the dorsal root ganglion neurones, increasing sensitivity and lowering the pain threshold, resulting in hyperalgesia. Inflammatory mediator release stimulated by the tumour cells further contributes to sensitisation of peripheral nerve endings. Direct damage to nerve endings by cancer invasion compounds the neuropathic component of cancer bone pain.

Bone metastases weaken bone and leave patients prone to fractures. These result in sudden and severe pain and may significantly impair patients’ mobility. Patients may also experience stress fractures, which are commonly missed clinically and difficult to control pharmacologically.

ASSESSMENT

Inadequate assessment is one of the most commonly reported factors in the undertreatment of cancer pain. The assessment of a patient with cancer bone pain should include a detailed pain history and the use of a structured pain assessment tool, such as the visual analogue scale or numerical rating scale. The impact on the patient’s life of the pain should also be explored, in addition to previous analgesic use and the patient’s choice. Where appropriate, an examination may be carried out to identify areas of tenderness indicative of the source of pain. Investigations must be considered in the context of the patient’s condition; only those which are likely to alter management should be performed and, in patients nearing the end of life, only if the pain may be due to a reversible cause.

Correspondence to: Carenza Glithero, 4th-year QUB medical student
E-mail: cglithero01@qub.ac.uk
MANAGEMENT

The World Health Organisation recommends a three-step ladder to treat cancer pain, according to the intensity of the pain. Firstly non-opioids (aspirin, non-steroidal anti-inflammatory drugs (NSAIDS), paracetamol), then mild opioids (codeine), followed by strong opioids (morphine) if required. The ladder also promotes the use of adjuvants at all stages where indicated for neuropathic pain or other symptoms, and a ‘step up, step down’ approach to changes in pain intensity. Despite being generally efficacious, pain in many bone cancer patients cannot be adequately controlled using this approach.

Several systematic reviews have found that while paracetamol is well tolerated, it does not provide any significant analgesic relief in cancer pain, especially when added to strong opioids. However, no subgroup analysis on cancer induced bone pain was performed in these studies.

Given the major role of inflammation in cancer induced bone pain, it is reasonable to assume that NSAIDs would be particularly efficacious compared with other pain syndromes, however to date the evidence for this is limited. Side effects including gastric ulcers and nephrotoxicity limit the clinical use of NSAIDs.

Systematic reviews of the use of Tramadol and Codeine in cancer pain found minimal if any benefit, with significant nausea and vomiting associated with tramadol. Again, there was no subgroup analysis for bone pain, and it is common to miss this step in the analgesic ladder with cancer induced bone pain and to progress directly to low dose strong opioids.

Several small randomised trials found no difference in either the efficacy nor side effects between intermediate and standard release morphine. Opioids commonly cause constipation, so co-prescription of a laxative should be considered. Alternatively, transdermal opioids may be used which are less likely to cause constipation. Around 75% of patients with cancer pain achieve good analgesia with strong opioids.

Incident pain is more difficult to control. The timing of analgesia is challenging since the pain manifests within 5 minutes and in around half of patients resolves within 15 minutes. Fast acting fentanyl preparations provided statistically superior analgesia when compared with oral morphine in a meta-analysis of the management incident pain. However, due to the higher number needed to treat (18 compared with 12) and greater cost they are currently recommended as a second line treatment, if intermediate release morphine fails.

The use of adjuvant drugs including anti-depressants and anti-convulsants may enhance analgesia with strong opioids, especially in patients with an element of neuropathic pain. However the current evidence is of poor quality and provides insufficient evidence on the efficacy and associated side effects. Two randomised controlled studies have found no sustained analgesic benefit from the use of steroids in cancer pain. There is currently insufficient evidence to support the use of lidocaine patches in bone pain in cancer.

Radiotherapy is the gold standard for pain relief in symptomatic bone metastases. A systematic review found 60% of patients experienced a meaningful reduction in bone cancer pain, with 25% being pain free. These results were achieved with both single and multiple dose radiotherapy, meaning that a single dose can provide effective pain relief with minimal side effects in frail patients.

Studies investigating metastasises to bone, especially from prostate cancer, have found that radioisotopes may be beneficial in palliation of diffuse bone cancer pain. However, severe adverse effects including leukocytopenia and thrombocytopenia were common.

Bisphosphonates reduce cancer-related bone pain and complications by inhibiting the function of osteoclasts. A 2002 Cochrane review examined the evidence for the use of bisphosphonates in bone secondary to bone metastases. While bisphosphonates provided some analgesic benefit, it was inferior to that of strong analgesics or radiotherapy, and as such the report recommended the use of bisphosphonates only where palliation and radiotherapy were insufficient to control a patient’s pain.

Novel agents including Osteoprotegrin and Denosumab inhibit osteoclast function by preventing the binding of RANK to its ligand, the stimulus necessary for osteoclast proliferation and maturation. Multiple studies have demonstrated reduced osteoclast function, tumour-related fractures and bone cancer pain with both bisphosphonates and RANK targeting therapies.

Prophylactic fixation of metastatic bone lesions can provide good long-term palliation of pain and maintenance of function in patients with a good performance status. Functional outcomes are superior with prophylactic fixation compared with stabilisation after fracture, and patients who may benefit can be identified with either the Mirel’s criteria. Furthermore, some bone primary tumours and metastases may be excised with curative intent.

A Cochrane review of acupuncture in cancer pain identified some studies demonstrating pain reduction, however none were large enough nor sufficiently well-designed and the report concluded there was insufficient evidence to assess efficacy. There was also insufficient evidence to recommend the use of TENS (transcutaneous electrical nerve stimulation), although one small feasibility study
demonstrated reduced verbal pain scores in cancer bone pain with TENS compared with placebo.4,46

CONCLUSION

The range of subtypes of bone pain in cancer patients, its changing nature and varied incidence complicate pain management. With limited understanding of the nature of bone pain, the lack of high quality evidence on the efficacy of many treatments and difficulty of balancing analgesic benefit with the side-effects of such therapies, treatment decisions are challenging. However, with adequate assessment and a multifaceted approach, pain management can be optimised to improve the quality of life of cancer patients.

REFERENCES

1. Mantyh PW. Bone cancer pain: from mechanism to therapy. Curr Opin Support Palliat Care. 2014;8(2):83-90.
2. Zhu XC, Zhang JL, Ge CT, Yu YY, Wang P, Yuan TF, et al. Advances in cancer pain from bone metastasis. Drug Des Devel Ther. 2015;9:4239-45.
3. Coleman RE. Clinical features of metastatic bone disease and risk of skeletal morbidity. Clin Cancer Res. 2006;12(20 Pt 2):6243S-9S.
4. Kane CM, Hoskin P, Bennett MI. Cancer induced bone pain. BMJ. 2015 Jan 29;350:h315.
5. Grond S, Zech D, Diefenbach C, Radbruch L, Lehmann KA. Assessment of cancer pain: a prospective evaluation in 2266 cancer patients referred to a pain service. Pain. 1996;64(1):107-14.
6. De Felice F, Piccioli A, Musio D, Tombolini V. The role of radiation therapy in bone metastases management. Oncotarget. 2017;8(15):25691-9.
7. Soeharno H, Povegliano L, Choong PF. Multimodal treatment of bone metastasis—a surgical perspective. Front Endocrinol. 2018;9:518.
8. Patrick DL, Cleeland CS, von Moos R, Fallowsfield L, Wei R, Öhrling K, et al. Pain outcomes in patients with bone metastases from advanced cancer: assessment and management with bone-targeting agents. Support Care Cancer. 2015;23(4):1157-68.
9. Honore P, Mantyh PW. Bone cancer pain: from mechanism to model to therapy. Pain Med. 2000;1(4):303-9.
10. Middlemiss T, Laird BJ, Fallon MT. Mechanisms of cancer-induced bone pain. Clin Oncol (R Coll Radiol). 2011;23(6):387-92.
11. Clohisy DR, Perkins SL, Rammarine ML. Review of cellular mechanisms of tumor osteolysis. Clin Orthop Relat Res. 2000;373(3):104-14.
12. Stjernsward J, Teoh N. The scope of the cancer pain problem. In: Foley KM, Banica JJ, Ventafridda V, Collaway MV eds. 3rd ed. Advances in pain research and therapy. Vol 16. New York: Raven. 1990. p. 7-12.
13. Gonzales GR, Elliott KJ, Porteny RK, Foley KM. The impact of a comprehensive evaluation in the management of cancer pain. Pain. 1991;47(2):141-4.
14. NICE Clinical Knowledge Summaries. Palliative cancer care - pain. London: National Institute for Health and Care Excellence; 2016. Available from: https://cks.nice.org.uk/palliative-cancer-care-pain#scenario1. Last accessed October 2019.
15. World Health Organisation Mondiale de le Sante. Traitement de la douleur cancéreuse. Geneva:WHO. 1987.
16. Vargas-Schaffer G. Is the WHO analgesic ladder still valid? Twenty-four years of experience. Can Fam Physician. 2010;56(6):514-7, e202-5.
17. Nabal M, Librada S, Redondo MJ, Pigni A, Brunelli C, Caraceni A. The role of paracetamol and nonsteroidal anti-inflammatory drugs in addition to WHO Step III opioids in the control of pain in advanced cancer. A systematic review of the literature. Palliat Med. 2012;26(4):305-12.
18. McNicoll ED, Strassels SA, Goudas L, Lau J, Carr DB. NSAIDS or paracetamol, alone or combined with opioids, for cancer pain. Cochrane Database Syst Rev 2005(1):CD005180.
19. Liu Z, Xu Y, Liu Z, Tian Y, Shen XH. Combined application of diclofenac and celecoxib with an opioid yields superior efficacy in metastatic bone cancer pain: a randomized controlled trial. Int J Clin Oncol. 2017;22(5):980-5.
20. Straube C, Derry S, Jackson KC, Wiffen PJ, Bell RF, Strassels S, et al. Codeine, alone and with paracetamol (acetaminophen), for cancer pain. Cochrane Database Syst Rev. 2014(9): CD006601.
21. Wiffen PJ, Derry S, Moore RA. Tranadol with or without paracetamol (acetaminophen) for cancer pain. Cochrane Database Syst Rev. 2017;5:CD003726.
22. Klepadl P, Kaasa S, Jystad Å, Hval B, Borghgreivkn PC. Immediate- or sustained-release morphine for dose finding during start of morphine to cancer patients: a randomized, double-blind trial. Pain. 2003;101(1-2):193-8.
23. Riley J, Branford R, Droney J, Gretton S, Sato H, Kennett A, et al. Morphine or oxycodone for cancer-related pain? A randomized, open-label, controlled trial. J Pain Symptom Manage. 2015;49(2):161-72.
24. Davis MP. Efficacy of rapid-onset oral fentanyl: what does it mean? J Pain Symptom Manage. 2014;48(1):e2-3.
25. Bennett MI. Effectiveness of antiepileptic or antidepressant drugs when added to opioids for cancer pain: systematic review. Palliat Med. 2011;25(5):553-9.
26. Marras F, Leali PT. The role of drugs in bone pain. Clin Cases Miner Bone Metab. 2016;13(2):93-6.
27. Yennurajalingam S, Frisbee-Hume S, Palmer JL, Delgado-Guay MO, Bull J, Phan AT, et al. Reduction of cancer-related fatigue with dexamethasone: a double-blind, randomized, placebo-controlled trial in patients with advanced cancer. J Clin Oncol. 2013;31(25):3076-82.
28. Paulsen O, Klepadl P, Rosland JH, Asss N, Albert E, Fayers P, et al. Efficacy of methylprednisolone on pain, fatigue, and appetite loss in patients with advanced cancer using opioids: a randomized, placebo-controlled, double-blind trial. J Clin Oncol. 2014;32(29):3221-8.
29. Schneider G, Voltz R, Gaertner J. Cancer Pain Management and Bone Metastases: An Update for the Clinician. Breast Care (Basel). 2012 Apr;7(2):113-20.
30. Dennis K, Makhani L, Zeng L, Lam H, Chow E. Single fraction conventional external beam radiation therapy for bone metastases: a systematic review of randomised controlled trials. Radiother Oncol. 2013;106(1):5-14.
31. Chow E, Zeng L, Salvo N, Dennis K, Tsao M, Lutz S. Update on the systematic review of palliative radiotherapy trials for bone metastases. Clin Oncol (R Coll Radiol). 2012;24(2):112-24.
32. Raval A, Dan TD, Williams NL, Pridjian A, Den RB. Radioisotopes in management of metastatic prostate cancer. Indian J Urol. 2016;32(4):277-81.
33. Zacho HD, Karthigasee NN, Fonager RF, Petersen LJ. Treatment with bone-seeking radionuclides for painful bone metastases in patients with lung cancer: a systematic review. BMJ Support Palliat Care. 2017;7(3):230-7.
34. Hendriks LE, Hermans BC, van den Beuken—van, Mariehe JH, Hochstenbag MM, Dingemans AC. Effect of bisphosphonates, denosumab, and radioisotopes on bone pain and quality of life in
patients with non–small cell lung cancer and bone metastases: A systematic review. J Thorac Oncol. 2016;11(2):155-73.

35. Ross JR, Saunders Y, Edmonds PM, Patel S, Broadley KE, Johnston SR. Systematic review of role of bisphosphonates on skeletal morbidity in metastatic cancer. BMJ. 2003 327(7413):469.

36. Wong RK, Wiffen PJ. Bisphosphonates for the relief of pain secondary to bone metastases. Cochrane Database Syst. Rev; 2002(2):CD002068

37. Lipton A, Jun S. RANKL inhibition in the treatment of bone metastases. Curr Opin Support Palliat Care. 2008;2(3):197-203.

38. Henry DH, Costa L, Goldwasser F, Hirsh V, Hungria V, Prausova J, et al. Randomized, double-blind study of denosumab versus zoledronic acid in the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma. J Clin Oncol. 2011;29(9):1125-32.

39. Stopeck AT, Lipton A, Body J, Steger GG, Tonkin K, de Boer RH, et al. Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: a randomized, double-blind study. J Clin Oncol. 2010;28(35):5132-9.

40. Von Moos R, Strasser F, Gillessen S, Zaugg K. Metastatic bone pain: treatment options with an emphasis on bisphosphonates. Support Care Cancer. 2008;16(10):1105-15.

41. Soeharno H, Povegliano L, Choong PF. Multimodal Treatment of Bone Metastasis–A Surgical Perspective. Front Endocrinol. 2018;9:2-518.

42. Tomita K, Kawahara N, Kobayashi T, Yoshida A, Murakami H, Akamaru T. Surgical strategy for spinal metastases. Spine. 2001;26(3):298-306.

43. Mirels H. Metastatic disease in long bones. A proposed scoring system for diagnosing impending pathologic fractures. Clin Orthop Relat Res. 1989;249:256-64.

44. Shaerf DA. Cancer induced bone pain...What about the role of the orthopaedic surgeon? BMJ. 2015;350:h315. Available from: https://www.bmj.com/content/350/bmj.h315/rr. Last accessed October 2018.

45. Paley CA, Johnson MI, Tashani OA, Bagnall A. Acupuncture for cancer pain in adults. Cochrane Database Syst Rev. 2015(10);CD007753

46. Hurlow A, Bennett MI, Robb KA, Johnson MI, Simpson KH, Oxberry SG. Transcutaneous electric nerve stimulation (TENS) for cancer pain in adults. Cochrane Database Syst Rev. 2012(3);CD006276