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James Logan Prize Essay

The Challenges of Managing Bone Pain in Cancer

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PREFACE

James Alexander Logan, a second-year medical student at the Barts and The London School of Medicine and Dentistry, died in February 2001 after a painful illness. A Trust was set up in his name in 2003 to promote education in the recognition and treatment of cancer pain and it provided funds for an annual essay prize, open to those undergraduate medical students of Queen's University, Belfast, who had completed their fourth year palliative care teaching. The first competition took place in 2010 and the winning entry appeared in the Ulster Medical Journal in 2011.

The Trust itself was dissolved in 2014 but the essay prize continues and the Trust's website can still be accessed at http://www.jameslogantrust.org.uk/

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.[1,2] Bone pain typically results from metastases, especially from lung, breast, kidney and prostate cancer.[1] Up to 70% of patients with advanced cancer have bone metastases, however only a third will be symptomatic.[3-5] The presence of bone metastases confers a poor prognosis with median survival of several months.[6]

Bone cancer typically results in a constant baseline pain punctuated by intermittent episodes of severe pain.[1,4] 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.[7] Episodic or incident pain may occur spontaneously or be provoked by moving or bearing weight on the affected bone.[1,4] In up to 55% of cancer patients bone pain is undertreated, resulting in additional suffering for patients with a limited life-expectancy.[8]

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.[9] Bone pain in cancer has both an inflammatory nociceptive and a neuropathic element.[1,4] Metastases to bone alter the normal balance between resorption and formation, causing subsequent changes in the peripheral and central nervous systems.[4,10]

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.[1,2] 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.[1,9,11]

Continuous peripheral stimulation promotes neuroplastic change in the dorsal root ganglion neurones, increasing sensitivity and lowering the pain threshold, resulting in hyperalgesia.[2] Inflammatory mediator release stimulated by the tumour cells further contributes to sensitisation of peripheral nerve endings.[2,4] Direct damage to nerve endings by cancer invasion compounds the neuropathic component of cancer bone pain.[4]

Bone metastases weaken bone and leave patients prone to fractures.[2] 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.[2]

ASSESSMENT

Inadequate assessment is one of the most commonly reported factors in the undertreatment of cancer pain.[5,12,13] 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.[14] 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.[14] Where appropriate, an examination may be carried out to identify areas of tenderness indicative of the source of pain.[14] 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.[14]

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MANAGEMENT

The World Health Organisation recommends a three-step ladder to treat cancer pain, according to the intensity of the pain.[15] Firstly non-opioids (aspirin, non-steroidal anti-inflammatory drugs (NSAIDS), paracetamol), then mild opioids (codeine), followed by strong opioids (morphine) if required.[15,16] 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.[16] Despite being generally efficacious, pain in many bone cancer patients cannot be adequately controlled using this approach.[2]

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.[4,17,18] However, no subgroup analysis on cancer induced bone pain was performed in these studies.[4]

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.[4,17,19] Side effects including gastric ulcers and nephrotoxicity limit the clinical use of NSAIDS.[2]

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.[20,21] 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.[4]

Several small randomised trials found no difference in either the efficacy nor side effects between intermediate and standard release morphine.[22] Opioids commonly cause constipation, so co-prescription of a laxative should be considered.[4] Alternatively, transdermal opioids may be used which are less likely to cause constipation.[4] Around 75% of patients with cancer pain achieve good analgesia with strong opioids.[4,23]

Incident pain is more difficult to control.[4] The timing of analgesia is challenging since the pain manifests within 5 minutes and in around half of patients resolves within 15 minutes.[4] Fast acting fentanyl preparations provided statistically superior analgesia when compared with oral morphine in a meta-analysis of the management incident pain.[4,23] 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.[4,24]

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.[4] However the current evidence is of poor quality and provides insufficient evidence on the efficacy and associated side effects.[4,25,26] Two randomised controlled studies have found no sustained analgesic benefit from the use of steroids in cancer pain.[4,27,28] There is currently insufficient evidence to support the use of lidocaine patches in bone pain in cancer.[4]

Radiotherapy is the gold standard for pain relief in symptomatic bone metastases.[29] A systematic review found 60% of patients experienced a meaningful reduction in bone cancer pain, with 25% being pain free.[30,31] 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.[4]

Studies investigating metastasises to bone, especially from prostate cancer, have found that radioisotopes may be beneficial in palliation of diffuse bone cancer pain.[4] However, severe adverse effects including leukocytopenia and thrombocytopenia were common.[4,32-34]

Bisphosphonates reduce cancer-related bone pain and complications by inhibiting the function of osteoclasts.[1,4,35] A 2002 Cochrane review examined the evidence for the use of bisphosphonates in pain secondary to bone metastases.[36] 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.[36]

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.[1,37] Multiple studies have demonstrated reduced osteoclast function, tumour-related fractures and bone cancer pain with both bisphosphonates and RANK targeting therapies.[1,9,37-40]

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.[4,41] 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.[4,42-44] Furthermore, some bone primary tumours and metastases may be excised with curative intent.[44]

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.[4,45] 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.

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