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Challenges in cancer pain management–bone pain

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ABSTRACT

Whilst not strictly a neuropathic injury, cancer-induced bone pain (CIBP) is a unique state with features of neuropathy and inflammation. Recent work has demonstrated that osteoclasts damage peripheral nerves (peptidergic C fibres and SNS) within trabeculated bone leading to deafferentation. In addition, glia cell activation and neuronal hyperexcitability within the dorsal horn, are all similar to a neuropathy. Gabapentin and carbamazepine (both anti-convulsants that modulate neuropathy) are effective at attenuating dorsal horn neuronal excitability and normalizing pain-like behaviours in a rat model of CIBP. However alterations in neuroreceptors in the dorsal horn do not mimic neuropathy, rather only dynorphin is upregulated, glia cells are active and hypertrophic and c-fos expression is increased post-noxious behavioural stimulus. CIBP perhaps illustrates best the complexity of cancer pains. Rarely are they purely neuropathic, inflammatory, ischaemic or visceral but rather a combination. Management is multimodal with radiotherapy, analgesics (opioids, NSAIDs), bisphosphonates, radioisotopes and tumouricidal therapies. The difficulty with opioids relates to efficacy on spontaneous pain at rest and movement-related pain. Potential adjuvants to standard analgesic therapies for CIBP are being explored in clinical trials and include inhibitors of glutamate release.

1. Basic science

Cancer-induced bone pain (CIBP) remains a clinically challenging problem to treat rapidly and effectively. Our current pharmacological treatments are based on our understanding of their mechanisms of action in non-cancer pain syndromes and have not been developed in a logical way to target the specific neurobiological changes of CIBP. In order to evaluate properly our current therapies and direct the development of new therapies, it is important to understand the underlying mechanisms of CIBP logically.

1.1. *Animal models of CIBP*

Until relatively recently it was difficult to study the pain associated with bone metastases, as the systemic models of cancer have much more widespread effects, making the underlying CIBP difficult to evaluate. The emergence of focal bone metastases models, displaying behavioural signs compatible with the clinical syndrome, has meant that our understanding of the underlying mechanism of this chronic pain syndrome has advanced significantly in the last decade.

Most of these models use direct inoculation of tumour cells into the medullary cavity of bone (eg femur, humerus and calcaneus). A variety of cancer cell lines have been used, including those from breast, prostate, fibrosarcoma and melanoma.

What has emerged from study of these models is that the underlying neurobiological changes in CIBP are quite distinct from those seen with either inflammatory or neuropathic pain states, with some evidence that the tumour type may influence the mechanisms of CIBP.[1,2] This highlights the

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complex nature of the neurobiology and the multi-factorial components that will define the exact nature of CIBP in any one individual.[3] This may help to explain, for instance, why some individuals respond well to current standard treatments such as palliative radiotherapy and why others do not. It is also likely that a combination of analgesic approaches may be required to obtain optimum analgesia.

1.2. *Pain pathways*

Before going on to consider the neurobiological changes that occur in CIBP, it is worth remembering the IASP definition of pain as 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage' (IASP, 1986). Thus any formulation of the processes involved in the pain experienced in CIBP must take account not only of sensory input, but also the affective and cognitive aspects and how they interact. There is increasing evidence from brain imaging studies that there is the potential for modulation of sensory input by cortical processes and vice versa.[4]

In order to understand the changes occurring in CIBP, it is important to remember the basic sensory pathways involved in pain processing, as outlined briefly in the following section:

Sensory neurones, or primary afferents, can be classified according to size and conduction velocity, with large myelinated A- beta fibres responding to innocuous mechanical stimuli such as light touch and small unmyelinated C fibres transducing noxious and thermal sensation. Intermediate sized A-delta fibres are also involved in processing of noxious stimuli. Fig. 1 provides a basic outline of nociceptive pathways, showing the neuraxis (the peripheral and central nervous system) involved in sensory processing and giving a framework for understanding the changes occurring this as a result of tissue injury.[5–8] It is important to remember that this is a dynamic system, with significant modifications occurring in the neuraxis in response to tissue damage and also treatment (Fig. 2).

Nociceptors are non-specialised free nerve endings (on unmyelinated C and small myelinated A-delta fibres) activated by high intensity noxious stimuli. The cell bodies of all sensory fibres are situated in the dorsal root ganglia, close to the spinal cord. The cell nucleus lies here, and this is where all neurotransmitters necessary for chemical transmission at the synapses are synthesized, before peripheral and central transport to axon terminals.[9]

A range of receptors has been identified on primary afferents and nociceptors in particular, that allow transduction of noxious mechanical, thermal and chemical stimuli. These include mechanically gated channels and purinergic receptors, that have a role in mechanical transduction and the transient receptor potential (TRP) family of ion channels, involved in noxious heat processing, in particular the vanilloid receptor VR1.[10–14] There are also several different types of receptor which detect noxious chemical stimuli (e.g. prostaglandins, endothelins, Nerve Growth Factor (NGF) and bradykinin) as is found in inflammation and also CIBP.[15–18] The majority of C fibres and A-delta fibres synapse in laminae I and II of the superficial dorsal horn, in the substantia gelatinosa, with some A-delta fibres terminating in lamina V. Complex modulation of dorsal horn neurones can occur both via intrinsic spinal mechanisms and descending systems. The second order projection neurones ascend to the brain in specific tracts.[9]

Within the spinal cord, the main neurotransmitter involved in fast synaptic transmission is glutamate, acting at the ionotropic receptor, the a-amino-3-hydroxyl-5-methyl-4-isoxazole propionic acid (AMPA) receptor. Neuropeptides, such as substance P are also released in response to noxious stimulation.[19,20]

At the level of the thalamus, multiple areas of the brain can be activated, reflecting the complex nature of pain perception. This has been studied in the clinical setting, using

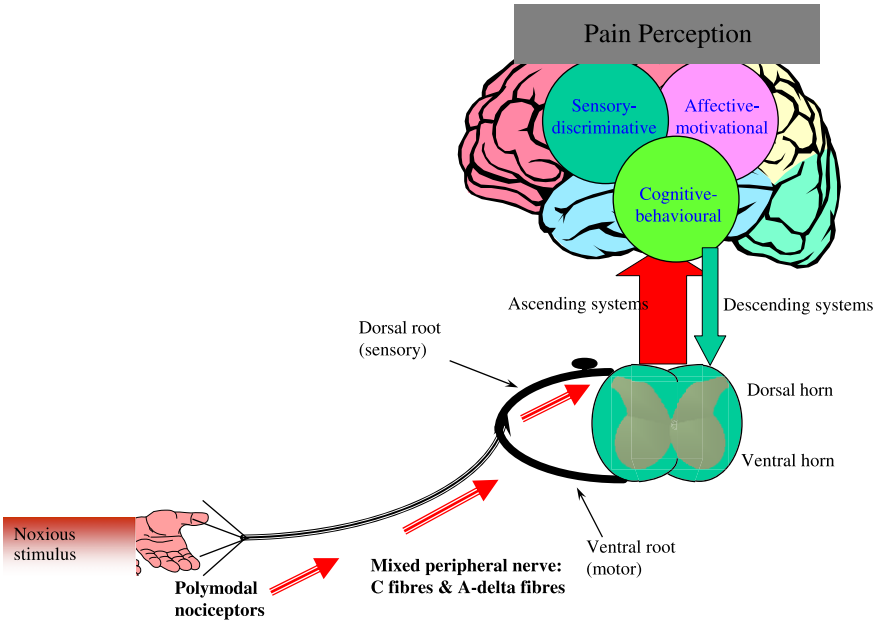

Fig. 1 – Spinal cord and brain communication.

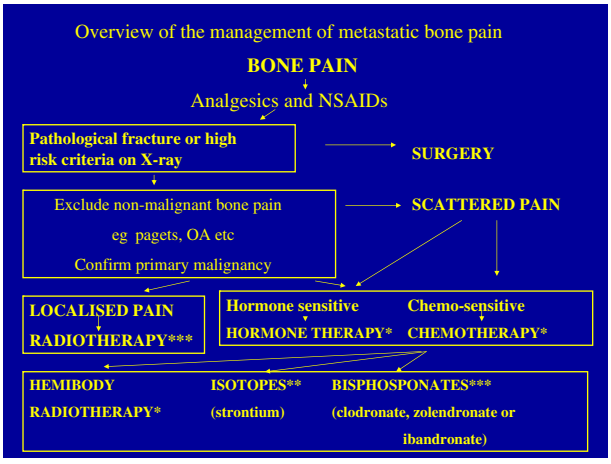

Fig. 2 – Overview of the management of metastatic bone pain (attribute to P. Hoskin). *, Systematic review or meta-analysis; **, One or more well-designed randomized controlled trials; *, Non-randomized controlled trials, cohort study etc.**

brain imaging techniques such as functional magnetic resonance imaging (fMRI) to study the cortical response to nociceptive stimuli, with the most consistently activated areas including the insular and the anterior cingulate regions.[21,22] There is increasing evidence of the complex interaction between the brain and the spinal cord in pain processing.[23,24] The descending brainstem systems modulate nociceptive input – this may either be inhibitory or excitatory.[25,26]

1.3. *Mechanisms of CIBP*

1.3.1. *Peripheral factors*

A key factor in CIBP is the relationship of the sensory nerves to the tumour itself and also to the bone.

Considering firstly the tumour itself, there is a complex relationship between the underlying disease and the presentation of CIBP that may be modulated by tumour type, site and extent of bony destruction. Even with a single tumour type, such as breast cancer, it has been shown that specific subtypes may be more likely to develop bone metastases, although the relationship to CIBP has not been clearly defined.[27] In animal models it has been shown that bony destruction is not necessary for pain behaviours to develop[28] and other factors, both local and central must be considered.

Direct effects of the tumour itself may include pressure and compression of surrounding structures, including the sensory nerves innervating the bone and periosteum. There is evidence that both myelinated and unmyelinated primary afferent neurons innervating the marrow and mineralised bone are injured and sensitised in CIBP.[29] The periosteum is densely innervated by a meshwork of Calcitonin Gene-Related Peptide (CGRP) containing fibres. CGRP sensory neurons form a subgroup of C fibres that are likely to be involved in nociceptive transmission and could contribute to the marked movement-related pain that is such a challenging component of CIBP.[30]

The tumour and associated immune system cells, including macrophages, neutrophils and T cells, release a range of pro-hyperalgesic mediators. These may act by sensitising peripheral nociceptors to subsequent stimuli, or by a direct activation of specific receptors on the primary afferent neurons themselves. Thus prostaglandins, endothelins, bradykinin, Tumour Necrosis Factor-alpha and a range of growth factors, such as transforming growth factor beta (TGF-β), may all have a role in CIBP.[31–35]

TGF-beta may promote proliferation of prostate cancer cells, activate osteoclasts and has been implicated in the development of bone metastases.[36,37]

Thus a combination of a neuropathic type nerve injury, either due to direct tumour compression or ischaemia, plus peripheral sensitisation secondary to release of cytokines and other mediators may both contribute to the chronic pain syndrome of CIBP.

It is also important to consider factors in the bone and its microenvironment that may affect tumour growth and CIBP, such as low oxygen levels, acidic pH, and high extracellular calcium concentrations.[38] Alterations in normal bone turnover with increased bone resorption and abnormal bone matrix formation occur, with the balance between osteoclast and osteoblast activity disrupted, such that the normal regulatory mechanisms are lost. Osteoclasts are derived from a monocyte/macrophage lineage. They degrade bone matrix, by secretion of acid and lytic enzymes resulting in bone resorption. The RANK signaling pathway plays a key role in this process. The TNF-related cytokine, RANK ligand (RANK-L), expressed on osteoblasts, and Colony Stimulating Factor (CSF)-1 combine to stimulate production of activated osteoclasts. Osteoprotegerin (OPG), a secreted soluble receptor that is also a member of the TNF family, has a negative feedback effect on this process by sequestering RANK-L, preventing osteoclast activation and reducing bone resorption.[39] In CIBP an osteoblast inflammatory response occurs with increased secretion of a range of cytokines that increases osteoclast activity and increases the ratio of RANK-L to OPG.[40]

Agents that interfere with osteolysis may have therapeutic potential in the treatment of CIBP. This includes not only currently available agents such as bisphosphonates, but also indicates there is potential for the development of novel agents that would alter the balance of bone metabolism to reduce CIBP. These include OPG type drugs, anti- NGF and other agents that interfere with intracellular pathways in osteoclasts.[41–45]

1.3.2. *Central effects*

While it has long been acknowledged that changes within the central nervous system contribute to the maintenance of other chronic pain states, such as neuropathic pain, this has not been studied in any detail until the recently described animal models of CIBP were developed, allowing correlation of pain behaviours with changes in the spinal cord.

These changes appear to be distinct for CIBP and include alterations both in neurochemistry and functional responses.[1]

Changes in the endogenous opioid systems have been noted in animal models of CIBP. A decrease in mu opioid receptors (MOR) in specific subpopulations of primary afferent neurons in the dorsal root ganglia has been found.

These neurons were predominantly CGRP or TRPV1 containing neurons, known to be involved in CIBP. This reduction in MOR expression seemed to correlate to a reduced analgesic response to intrathecal morphine and was not seen either in control animals or an inflammatory model.[46] There is also evidence that the doses of morphine required to reduce pain behaviour in CIBP are much greater than those for inflammatory pain, suggesting fundamental differences in the underlying mechanisms.[47] Another recent study found that prolonged treatment with morphine increased pain behaviour with an associated increase in CGRP neurons in the dorsal root ganglia and increased osteoclast activity.[48] A marked increase in the pro-nociceptive opioid peptide, dynorphin, in the dorsal horn of the spinal cord has been reported.[49] This may contribute to an increase in the activity of descending facilitatory systems from the brain.[50,51]

In addition to changes in the opioid systems, there is very marked astrogliosis in the spinal cord in CIBP models.[1] The significance of this is unclear, but interventions that reduce pain behaviours also seem to reduce astrocyte changes.[52] There is increasing interest in the role of glial cells in modulating a variety of chronic pain states, with some evidence that the glutamate systems, which are known to be involved in central sensitisation are modulated by glial cells.[53,54]

As well as changes in neurochemistry there are several studies that have shown sensitisation of Wide Dynamic Range (WDR) neurons in the spinal cord in CIBP, with increased responsiveness to mechanical and thermal stimuli in addition to ongoing spontaneous activity. This activity and related pain behaviour was also shown to be sensitive to gabapentin, which acts through reducing glutamate release and thus alters central sensitisation.[55–57]

2. Relationship to clinical progress

Our understanding of the mechanisms underlying CIBP has been advanced significantly by development of appropriate animal models. The complex interactions between tumour, bone and sensory nerves require further study, but there is potential for developing new targeted therapies that should improve the quality of life for patients with this distressing condition.

2.1. *Clinical aspects of CIBP*

2.1.1. *Assessment and management*

Careful clinical observation has demonstrated that CIBP has several components: a tonic background pain at rest, spontaneous pain at rest and pain associated with movement.[58] While the tonic background pain is usually controlled with opioid analgesia, the other two components are problematic because of three factors:

- Temporal onset of pain in relation to temporal onset of analgesia from opioids (50% of movement-related pain is sudden and all spontaneous pain is by definition, sudden)
- Resolution of pain in relation to duration of opioid analgesia (50% of sudden pain has resolved by 15 mins)
- Evidence of poor opioid-responsiveness of some aspects of the underlying neurophysiology of the spontaneous and movement-related pain components[30,46]

The combination of above factors mean that opioid adverse effects, especially sedation, are more likely to dominate over analgesia.[58] In any pain syndrome where there are sudden, short-lived, peaks of pain over and above a stable background pain, the opioid adverse effects are more likely to be problematic.

While it is accepted that radiotherapy is the gold standard treatment for pain relief in CIBP, there are a significant number of patients who fail to receive adequate analgesia. External beam radiotherapy, whether single or multiple fractions, produced 50% pain relief in 41% of patients and complete pain relief at one month in 24% of patients.[59] However, many patients are too frail to attend for palliative radiotherapy or it is too late to reasonably expect pain relief before death.

We know that the current therapeutic regimens leave up to 45% of patients with inadequate and undermanaged pain control.[60,61]

For such reasons, an improved understanding of the pathophysiological mechanisms underlying, in particular, spontaneous pain at rest and movement-related pain are important. The development of effective pharmacological interventions to act as adjuvants or synergists to palliative radiotherapy to improve the degree of pain relief, in addition to providing analgesia to those too unwell to benefit from palliative radiotherapy, is an important area of research.

2.2. *Pharmacological management*

2.2.1. *Current therapeutic options*

Current analgesic therapies for CIBP have not altered significantly in over a decade, since the introduction of bisphosphonates. Treatment is multimodal and includes systemic analgesics (opioids, non-steroidal anti-inflammatory drugs [NSAIDs]) bisphosphonates, anti-tumour chemotherapy, radiotherapy, systemic radio-isotopes, local surgery and anaesthetic techniques[59,62–64]

2.3. *Optimising opioid analgesia in CIBP*

Opioid-based therapy does remain the basis for most analgesia in CIBP. In theory, there are two aspects to the optimisation of opioid analgesia, firstly establishing the best opioid for an individual based on the pharmacogenomic principal of interindividual variation in balance between analgesia and side-effects and secondly, assessing the optimal pharmacokinetic: pharmacodynamic profile from the opioids available. There is more weight given to the first aspect in relation to chronic background pain, however more weight given to the second in relation to spontaneous pain at rest and movement-related pain. Clearly an opioid with a faster onset of action and faster peak analgesic response with more rapid fall in plasma concentration is preferred for pain of rapid onset and short duration. Unfortunately, apart from IV formulations which are rarely practical, the choice is limited to fentanyl in various formulations; lozenge, buccal, nasal and

sublingual sprays. Improvisation with the intravenous alfentanil preparation, used sublingually, has been the practice in some specialist units, however this is not useful for the majority of non-specialist use and rarely outside the inpatient setting.

The pharmaceutical industry has concentrated on fentanyl, therefore the evidence available is limited to fentanyl for faster onset of analgesia and quicker peak plasma analgesic levels.[65]

A group of patients exists who only get uncontrolled CIBP after considerable and predictable movement, such as a long walk. This group are often satisfied to use a standard opioid such as normal release morphine 30 minutes in advance of such activity.

It is not uncommon for patients to use a sustained release opioid preparation such as morphine for background bone pain and either normal release morphine or a fentanyl preparation for spontaneous pain and movement-related pain.

2.4. *Non-steroidal anti-inflammatory drugs (NSAIDS)*

The use of NSAIDs in CIBP has been questioned due to the lack of robust, clinical evidence. The three randomised trials of NSAIDs in cancer pain do not separate out bone metastases, and six non-randomised trials mention bone metastases but do not record incident pain.[66–74] The newer COX II specific inhibitors may in theory be of greater therapeutic potential due to their anti-tumour/antiangiogenesis properties.[75,76] In an animal model of CIBP, acute treatment with a highly selective COX II inhibitor attenuated both background and movement-induced pain, whilst chronic treatment in addition reduced tumour burden and osteoclast destruction.[77] Clearly the use and availability of COXII inhibitors has fluctuated since they were first available because of concerns with some drugs within this class. Most clinicians regard NSAIDs as an important part of CIBP management unless contraindications exist.

2.5. *Bisphosphonates*

A recent review (published 2000) indicated that regular use of bisphosphonates reduced the number of skeletal-related events in numerous cancers.[78] A Cochrane review of the clinical efficacy of bisphosphonates for pain relief in metastatic bone disease suggested that there was some evidence for their use as analgesics, although the effect was delayed. The number needed to treat to achieve 50% pain relief at 4 weeks was 11, falling to 7 at 12 weeks.[63]

While bisphosphonates form part of standard therapy for the prevention of skeletal events in some cancers, the role of bisphosphonates in pain relief is less well-defined. This highlights the problems in extracting evidence from studies where there are wide variations in quantifying quality of life and bone pain. Multiple different methods have been used to assess quality of life and pain, making it difficult to compare results between different studies. This has prevented the effective collation of evidence.

Analysis of the publications available to date has not revealed any great differences between individual bisphosphonates given at standard doses, but objective assessment is complicated by the differences in study design, measurement methods and statistical analyses. Comparative studies will help resolve this.

The Cochrane review in 2000 concluded that there is evidence to support the effectiveness of bisphosphonates in providing some pain relief for CIBP but that there is insufficient evidence to recommend bisphosphonates for immediate effect as first line therapy; to define the most effective bisphosphonates or their relative effectiveness for different primary neoplasms.[63] However, while a clearer evidence base for these areas is eagerly awaited, it is reasonable to consider bisphosphonates for pain relief in CIBP where analgesics and/or radiotherapy are inadequate.

2.6. *Topical lidocaine*

There is anecdotal evidence that topical lidocaine patches may be useful in CIBP, this is particularly the case with vertebral metastases where there may of course be a significant neuropathic pain component as well.

2.7. *Glutamate inhibitors and NMDA antagonists*

On the basis that CIBP has neuropathic and inflammatory components and clinical and laboratory evidence of central wind-up, it is not surprising that inhibitors of glutamate have been considered and investigated. We know that in animal studies, gabapentin reverses dorsal horn changes associated with CIBP resulting in relief of spontaneous and movement-related pain.[56] Clinical studies are currently underway with pregabalin, a more potent inhibitor of glutamate release and the hypothesis is that this class of drug may provide very useful adjuvant analgesia to standard care.

Inhibitors of the N-methyl-d-aspartate (NMDA) complex may also be of interest, especially as NMDA subtype inhibitors are developed. At present the non-specific NMDA antagonist, ketamine, is used in some difficult to manage cases.

2.8. *Osteoprotegerin*

Early clinical work with osteoprotegerin (OPG) is interesting and may hold future promise.[79] A single SC dose of AMGN-0007 suppressed bone resorption as indicated by a rapid, sustained and profound decrease of urinary N-telopeptide of collagen (NTX)/creatinine in multiple myeloma and breast carcinoma patients. Changes were comparable to those with pamidronate.

2.9. *Endothelin-1 antagonists*

Androgen refractory prostate cancer continues to evade effective treatment. The potent vasoconstrictor endothelin-1 is produced by prostate cancer and appears to have a role in prostate cancer progression and morbidity. Based on preclinical and clinical trial data, the endothelin axis is emerging as potentially important in the biology of prostate cancer progression and morbidity.[80] Drugs targeting the endothelin axis, such as the potent ET(A) receptor antagonists atrasentan, have been studies in large clinical trials and appear to have

an impact on disease progression and morbidity. The role of the endothelin axis in prostate cancer deserves further investigation in the laboratory and clinic.

3. Future concepts

3.1. *Alphavbeta3 integrin blocker*

The integrin alphavbeta3 mediates cell-matrix interactions.[81] Vitazin®, a humanised monoclonal antibody that blocks human and rabbit alphavebeta3 integrins, is in clinical trials for metastatic melanoma and prostate cancer. Vitaxin decreases bone resorption by impairing osteoclast attachment, without affecting osteoclast multinucleation. Data also show that Vitaxin's inhibitory effects on osteoclasts can be modulated by factors known to alter the conformation of alphavebeta3.

4. Conclusion

It is clear that CIBP is complex and that optimum treatment in the future is likely to be multimodal. Clarity of thought about CIBP future management depends on appropriate design of clinical trials, in particular in relation to patient and pain assessments and outcome measures. In addition, the basic science evidence base is increasing rapidly, with an excellent animal model of CIBP. Close basic science and clinical collaboration will help to inform the direction of clinical research.

Conflict of interest statement

None declared.

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