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Review

Improving quality of life in patients with advanced cancer: Targeting metastatic bone pain

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Abstract Metastatic bone disease in patients with advanced cancer is frequently associated with skeletal complications. These can be debilitating, causing pain, impaired functioning and decreased quality of life, as well as reduced survival. This review considers how the management of metastatic bone pain might be optimised, to limit the considerable burden it can impose on affected patients. Cancer-related pain is notoriously under-reported and under-treated, despite the availability of many therapeutic options. Non-opioid and opioid analgesics can be used; the latter are typically administered with radiotherapy, which forms the current standard of care for patients with metastatic bone pain. Surgery is appropriate for certain complicated cases of metastatic bone disease, and other options such as radiopharmaceuticals may provide additional relief. Treatments collectively referred to as bone-targeted agents (BTAs; bisphosphonates and denosumab) can offer further pain reduction. Initiation of therapy with BTAs is recommended for all patients with metastatic bone disease because these agents delay not only the onset of skeletal-related events but also the onset of bone pain. With evidence also emerging for pain control properties of new anticancer agents, the potential to individualise care for these patients is increased further. Optimisation of care depends on physicians' thorough appreciation of the complementary benefits that might be achieved with the

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various agents, as well as their limitations. Appropriate anti-tumour treatment combined with early initiation of BTAs and adequate analgesia plays a key role in the holistic approach to cancer pain management and may minimise the debilitating effects of metastatic bone pain.

1. Introduction

Managing patients with cancer requires a multidisciplinary approach, especially when the cancer has metastasised to bone. Bone metastases frequently cause complications known as skeletal-related events (SREs), which are associated with significant morbidity [1], impaired mobility and social functioning [2], reduced quality of life (QoL) [2], increased resource utilisation [3–7] and reduced survival [1,8]. Bone metastases are particularly common in advanced breast, prostate or lung cancer [9]; indeed, metastatic bone disease is evident *post mortem* in approximately 40–70% of these patients [1]. Renal cell carcinoma also metastasises to bone, and multiple myeloma invariably spreads to multiple sites within the bone [10,11]. Here, we review metastatic bone pain, its impact on patients, and how management can optimise QoL; implications for clinical practice are summarised in Table 1.

2. Incidence of metastatic bone pain

Approximately two-thirds of individuals with metastatic cancer experience pain, which is moderate to severe in almost half of the cases [12,13]. Often, this pain originates from primary cancers that have metastasised to bone. For example, 81.4% of patients with metastatic cancer reported bone pain, compared with only 23.3%, 10.9%, 7.8% and 0.8% of the same patients reporting pain that was deemed pleuritic, neural, visceral or attributable to headache, respectively [14]. Indeed, in bisphosphonate and denosumab studies in patients with bone metastases, significant pain was reported at study entry: mean Brief Pain Inventory (BPI) bone pain scores were 2.0–4.5 [15–18], mean BPI (Short Form; BPI-SF) worst pain scores were 4.1–6.3 [18–20], 21–24% of patients reported moderate bone pain (BPI-SF score 5–6) and 23–35% reported severe bone pain (BPI-SF score 7–10) [19–22].

3. Aetiology of metastatic bone pain

Metastatic bone pain is complex, originating via inflammatory and neuropathic pathways. Tumours may contain numerous inflammatory cells, and both inflammatory cells and tumour cells secrete various pain-mediating chemicals that activate sensory nerve endings in the bone. Increased osteoclast activity can destroy these endings and acidify the environment, causing neuropathic pain and stimulation of pH-sensitive nerve endings. Furthermore, osteoclastic bone loss destabilises bone, causing pain via mechanosensitive receptors. Bone distension or nerve damage caused by invading tumours may generate constant pain at rest and elevate sensitivity to pain during movement [23–28]. Although periosteal infiltration is rare, periosteum stretching may also cause bone distension [29]. SREs, including pathologic fracture, radiation or surgery to bone, and spinal cord compression, may also cause bone pain [30].

4. Impact of bone metastases and SREs on pain and QoL

Patients with metastatic breast cancer experiencing on-study SREs reported increased pain, and pain interference with daily functioning, compared with those with no on-study SREs [31]. Meta-analyses also show that SREs in patients with metastatic cancer significantly increase the risk of pain progression and the need for strong opioids (Fig. 1) [32]. Furthermore, SRE-associated pain may persist despite strong opioid use, such that patients might not recover fully [32]. Cancer-related pain can markedly reduce QoL [33], negatively affecting mood, work, relationships, the ability to walk [34,35] and sleep [34,36]. Sleep disturbance can further perturb pain tolerance thresholds, potentially leading to a vicious cycle of pain [37].

4.1. Assessing metastatic bone pain and related impact on QoL

There are many tools for evaluating metastatic bone pain and its impact on QoL [38] (Table 2). The value of routinely assessing patient-reported outcomes was demonstrated recently in patients with metastatic cancer [39]. One group reported their symptoms between clinic visits via a Symptom Tracking and Reporting system, which alerted nurses to severe or worsening symptoms. Treating physicians received symptom printouts at visits. Compared with the routine care group, more patients using Symptom Tracking and Reporting reported improved QoL and fewer reported worsening QoL; they were also less likely to visit the emergency room or to be hospitalised, more likely to survive 1