Pain Relief in Metastatic Cancer

88

Odette Spruyt and Natasha Michael

Competent Management of Pain in Patients

> Any man's death diminishes me, because I am involved in Mankinde [1].

Not only death, but the suffering of unrelieved pain diminishes man and involves us all. The relief of pain is cited as a human right because it is now possible to manage pain well and because of the terrible impact of unrelieved pain on individuals and society and the need to challenge the indifference which leads to inadequate pain management [2].

Prostate cancer is the most frequently diagnosed cancer in men, the majority of whom live with the disease for many years. The symptoms and sequelae of prostate cancer and its treatment are therefore chronic, with physical and psychosocial implications for the patient and his family. Chronic pain, when it occurs, is a distinct disease entity in itself, with mechanisms which differ from acute or short-term pain [3].

The following case report represents the story of many men with advanced metastatic prostate cancer in whom pain management occurs within an array of other clinical challenges. These include managing disease progression, psychosocial distress, and multiple comorbidities which influence the choice and modality of analgesia, contribute to the side effect profiles, compliance, and capacity to undertake optimal analgesic strategies.

Case Report

Mr. TR was a 77-year-old with a 13-year history of hormone-refractory prostate cancer. A recent diagnosis of metastatic bone disease heralded the beginning of severe pain. Multiple comorbidities included depression, atrial flutter, emphysema, and renal impairment. A previous laminectomy for benign disc prolapse led to continuous L5 sciatica associated with numbness in the left buttock. Recent disease staging with CT chest, abdomen, and pelvis revealed incidental findings of thrombus in the right pulmonary artery and widespread metastatic bony disease. He received palliative radiotherapy to his lumbar spine, right hip, and base of skull. The administration of zoledronic acid resulted in marked toxicity with nausea, bone aches, sweats, and weakness.

He presented with multiple symptoms of pain, dyspnea, nausea, low mood, drowsiness, and myoclonus. His main pains were bone ache following bisphosphonate administration, movement-related pain in the right rib and proximal right femur, and left buttock pain on walking. His pain remained well controlled at rest. Medications included transdermal fentanyl 50 mcg/h, gabapentin 300 mg nocte, diclofenac 50 mg bid, and oxycodone 5 mg as required and venlafaxine 150 mg daily.

Defining Pain

Pain may be defined as a "sensory and emotional experience characterized by actual or potential tissue damage or described in terms of such damage" [4]. Pain is what the patient says it is and is a multidimensional experience not limited to a physical abnormality [5,6]. This subjective, multidimensional nature of pain contributes greatly to the clinical challenge of pain management, which calls for empathy, relationship, and attention to detail – components of clinical care which are often lacking in modern medicine.

Coping with pain in the context of advanced cancer differs from chronic pain of nonmalignant nature and also appears to vary with types of cancer. Pain intensity and quality are significantly worse in lung cancer compared to head and neck and prostate cancer. Depression levels are also greatest for individuals with lung cancer and correlate with

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Table 88.1 Examples of cancer related pain in Prostate Cancer

Neuropathic pain
Radiculopathy from tumor compression
Spinal cord compression
Secondary to chemo, radiotherapy, and surgery
Related to cancer and its treatment, e.g., herpes zoster
Nociceptive pain
Visceral metastases
Ureteric obstruction
Lymphedema
Pressure areas
Dysuria secondary to bladder spasm and infection
Mucositis related to chemo or radiotherapy
Constipation
Steroid myopathy
Gynecomastia
Bone pain
Metastases
Fractures
Hypercalcemia
Bisphosphonate causing acute treatment-related pain and osteonecrosis
Total pain
Demoralization
Depression
Social isolation
Emasculation

catastrophizing that influences the overall pain experience [7]. Recognizing such differences assists with developing therapeutic strategies and programs that are best suited to the characteristics of specific patient groups.

Epidemiology of Pain

The prevalence of pain in cancer varies greatly with site, stage, and type of cancer and no single aggregate statement of prevalence can be made [8]. Up to 43 % of patients with non-metastatic prostate cancer and 66 % of patients with advanced disease have been reported to have pain, with 41 % suffering severe pain in the latter group [9,10]. A recent systematic review of the literature over the past 40 years found a prevalence of 64 % in patients with advanced cancer. Notably, this review found that pain was also prevalent in 33 % of patients following curative treatment [11]. Therefore, not all patients with advanced cancer suffer pain and much pain can be avoided.

While most cancer pain is due to direct cancer effects, not all pain is directly due to active disease [12,13] (Table 88.1). Many patients suffer multiple pains, as in prostate cancer where bone metastases are a prominent feature of disease spread [14]. Pain intensity varies greatly, does not correlate with radiological abnormality or tumor size, and shows a tendency to increase with progression of cancer.

Pain is generally of nociceptive (somatic or visceral) or neuropathic (central, peripheral, or sympathetic) mechanism or a combination of both, known as mixed pain. Nociceptive pain involves stimulation of a free nerve ending or nociceptor by physical or chemical stimuli such as tissue injury. Stimulation leads to the passage of impulses along the peripheral nerve to the dorsal horn of the spinal cord, synapsing there with spinothalamic tract neurons and on through to the brain stem, the thalamus, and terminating in various regions of the cerebral cortex. Neuropathic pain, however, results from damage of either the peripheral or central nervous system. Such damage is frequent in patients with advanced cancer. Damage may occur directly through erosive growth, compression, infiltration along neural tissue, or by cancer therapies. Chemotherapeutic agents such as vincristine and taxols may cause painful peripheral neuropathies and surgical and radiotherapy-related damage to nerves is not uncommon. A range of other cancer-related pain syndromes have been well described and are the cause of significant morbidity [15–17].

Pain Assessment and Classification

Good pain control depends on competent assessment of pain, which is directed at diagnosis of etiology, understanding of the experience for the patient, and developing a relationship within which pain management can most successfully take place. Careful assessment includes a narrative history of pain onset, quality, and intensity; impact on function; and alleviating and aggravating factors. Characteristics of the pain assist with diagnosis. For example, visceral pain is often described as aching, dull, constant pain and neuropathic pain as burning, numb, shooting, or other terms indicative of dysesthesias.

Investigations of etiology may include diagnostic imaging, with nuclear imaging of bone of particular value in assessing the extent of bone metastases. In general, there is poor correlation between complaints of bone pain and radiological evidence, though this correlation is stronger in prostate cancer than breast cancer [18]. Urgent magnetic resonance imaging should be performed if spinal cord compression is suspected.

There is a lack of consistent validated assessment and measurement tools which hampers the evaluation of treatment effectiveness and comparative research studies [19]. The Edmonton Classification System of Cancer Pain (ECS-CP) is a validated classification tool that helps identify patients with complex pain who would benefit from early referral to specialist pain/palliative care services as well as better describe pain populations recruited to analgesic studies [20–22]. The ECS-CP identifies that patients with neuropathic pain, incident pain, history of addiction, and

psychological distress were found to be more challenging to palliate, requiring higher opioid doses, more adjuvants, and a longer time to achieve stable pain control.

Undertreatment of Pain

There is evidence of continued undertreatment of pain in 40–50 % of patients despite the plethora of guidelines and evidence of availability of effective therapies dating back over the past 20 years [23–25]. Inadequate pain relief is not limited to resource poor countries, but the reasons for inadequate pain relief appear to vary between developed and developing countries. In the developed world, reasons include the lack of knowledge about pain relief among treating physicians, poor coordination of services across settings of care, physician indifference or poor assessment [23], and a focus on disease-based (rather than symptom-based) care. In the resource-poor world, the lack of health-care resources and infrastructure, opioid unavailability, and geography contribute greatly to undertreatment of pain [14]. Patient factors include fear of opioids and concerns about side effects and addiction leading to underreporting of pain and poor compliance with treatment [26].

Principles of Pain Management

In general, cancer pain management approaches fall into two major categories, those which are tumor specific and those which are pain specific [19].

Tumor-Specific Measures

To date, tumor-specific measures remain poorly evaluated in clinical trials, where the outcomes commonly focus on impact on survival rather than improvements in symptoms. Palliative radiotherapy and surgical interventions including placement of stents, relief of obstruction, and orthopedic maneuvers play an important role in optimizing pain management for many cancer patients including those with advanced disease. The benefit of radiotherapy for bone metastases is well established. External beam radiotherapy has been shown to provide at least 50 % pain relief in over 40 % of patients with just under a third experiencing complete relief after 1 month. Single fractions are as effective as multiple fractions administered for palliation [27,28]. The use of radioisotopes such as strontium-89 can reduce the number of new sites of metastases [27] and are effective for those with multiple painful metastases.

Bisphosphonates are a class of agent that act primarily by inhibiting osteoclast function and as such were assumed to have no role in prostate cancer where osteoblastic metastases predominate. However, recent studies have demonstrated high bone resorption in metastatic prostate cancer reflecting substantial osteoclastic activity [29]. The biologic rationale for its use relates both to the management of metastasis and ongoing bone loss secondary to androgen deprivation arising from treatment. Studies have shown benefit by way of reduction in bone pain and skeletal-related events particularly with the use of the more potent, new generation bisphosphonates such as zoledronic acid [30,31]. There is no evidence of influence on disease progression or survival. The reduction in pain and skeletal events with the use of bisphosphonates must be weighed against potential adverse events such as nephrotoxicity and osteonecrosis of the jaw which has a reported incidence of approximately 3 per 100 patients in prostate cancer [32].

There is little data comparing the effectiveness of differing palliative options for pain such as radiotherapy, surgery, analgesia, or interventional approaches. The burden/benefit ratio of more intensive palliative interventions must be carefully considered, ideally through a multidisciplinary approach, which is the standard for best care in oncology practice. Pain and palliative care providers experienced in cancer care bring particular expertise in the judicious selection of optimum maneuvers in the patient with advanced illness. Prognostic expertise is of particular importance. Prognostic overoptimism and reticence in truth telling lead to poor selection of palliative procedures. Developing care systems in which the experience of the whole multidisciplinary team including nursing, physiotherapists, occupational therapists, pastoral care, and psychological therapists is brought to bear, improves the quality of therapeutic decision making in advanced disease, and broadens the options available beyond the pharmaceutical or medical intervention.

Pain-Specific Approaches

The World Health Organization cancer pain relief guidelines (1986) and analgesic ladder (Fig. 88.1) continue to provide the framework for cancer pain management today and are supported by several validation studies [33,34]. Evidence showed that significant pain reduction was achieved within the first week of treatment ($P<0.001$), strong opioids (WHO step III) were prescribed on 49 % of treatment days, administration was via the enteral route on 82 % of treatment days, good or satisfactory pain relief was reported in 88 % of patients and inadequate pain relief occurred in 12 % of patients [33]. The essential elements of this guideline can be summarized as follows: “by the mouth, by the clock, by the ladder,” that is, cancer pain is ideally treated by administration of analgesics by the oral route, at regular intervals in an

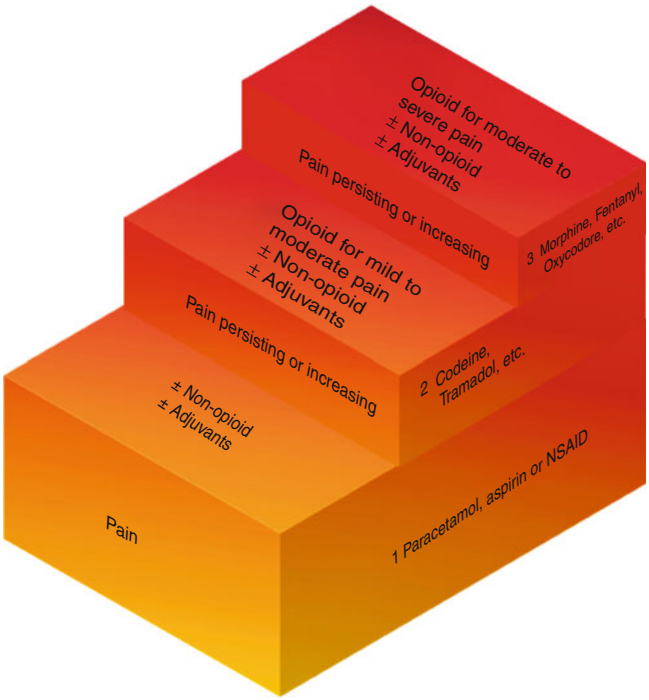

Fig. 88.1 World Health Organization analgesic ladder

incremental manner. Frequent review and recognition of detail and difference lead to a tailored analgesic approach for each patient and avoidance of complications of analgesics used inappropriately or without due regard to their many adverse effects.

Analgesia

The WHO Analgesic Ladder

The WHO pain ladder is still widely utilized due to its simplicity and transferability to a variety of settings. Its three-step approach allows for the stepwise titration of opioids in an incremental manner with the concomitant use of co-analgesics and adjuvant. Mild pain requires nonsteroidal anti-inflammatory analgesics or acetaminophen/paracetamol [33–36]. Moderate pain requires commencement of so-called weak opioids. In recent years, low doses of more potent opioids have been introduced at this step in recognition of the need to titrate most patients with cancer pain onto more potent opioids in a shorter timeframe [37]. Many patients though have a resistance to commencing morphine or related potent opioids making it useful to maintain step two of the ladder.

Strong opioids are available in a range of preparations suited to chronic administration for the patient with severe pain. Initial commencement is best achieved using a short-acting formulation, replacing this with a long-acting formulation of the same opioid once acceptable pain relief and toxicity profile has been achieved [69]. When spontaneous or movement-related pain is a major component of the pain experience, potent, rapid, and short-acting opioids such as transmucosal or intranasal fentanyl and sufentanil are effective [38–40].

Adjuvant use throughout the ladder is determined by the underlying mechanism of pain. For example, anticonvulsants are used for neuropathic pain or antispasmodics for colic. Commencement of any opioid must be accompanied by the use of regular stimulant and softening laxatives as the majority of patients will develop constipation without these. The availability of new therapies for opioid-induced constipation such as methylnaltrexone or combination opioid-opioid antagonist preparations such as oxycodone-naloxone is now available for the improved management of opioid-induced constipation [41–43].

Problems with prolonged opioid use may lead to the development of opioid tolerance and opioid-induced hyperalgesia (OIH), with glial cells implicated in the development of opioid tolerance [44]. OIH is a clinical entity separate to tolerance, in which patients experience worsening of pain and abnormal symptoms such as allodynia despite increasing opioid doses. The N-methyl-d-aspartic receptor (NMDAR), a glutamate receptor, is key to the development of OIH, assisted by spinal dynorphins and descending pathway facilitators [45]. Therapeutic strategies include opioid switching which usually allows a decrease in mean equivalent daily dose of opioid and/or the addition of agents such as ketamine, an NMDAR antagonist [46].

Cancer-Induced Bone Pain (CIBP)

Bone metastases are reported to be present in over 90 % of patients who die of prostate carcinoma [47], with the main symptom of bone pain occurring in approximately 85 % of patients [48]. Bone pain can be difficult to control and exhibit features that involve nociceptive inflammatory, neuropathic, and tumorigenic mechanisms [49]. The pattern of pain may be variable and unpredictable with both aching, dull, constant background pain and spontaneous or movement-related breakthrough pain. Breakthrough pain in particular has a profound effect on daily functioning and quality of life [50] and is associated with a poor prognosis for achieving effective pain control [22] due in part to its rapid onset, intensity, and brevity. Efforts to achieve pain control for these breakthrough episodes are often hampered by opioid toxicity that is unacceptable to the patient and reflective of the poor responsiveness of this pain to opioid analgesia.

Molecular Biology of CIBP

In recent years, the neurobiology of CIBP has been better elucidated through the development of experimental models [48,51–54]. There is a "neurochemical signature" unique to

bone cancer pain, which is consistent with a hyperexcitable state, and which differs from persistent neuropathic or inflammatory pain [55]. Features of this include enhanced neuronal activity and enlargement of the receptive field size in lamina 1 neurons; increased responsiveness to mechanical, electrical, and thermal stimuli; and marked astrocyte hypertrophy in the spinal cord ipsilateral to the bone with cancer. These changes occur at the same time as behavioral signs of pain in rat models and do not occur in inflammatory or neuropathic pain states, making them a useful substrate for studies of new agents in CIBP [56].

Osteobiology of CIBP and Development of Novel Therapies

In prostate cancer, osteoblastic metastases predominate with disordered proliferation and incomplete bone calcification [57,58]. The pathway of proliferation involves several neurotransmitters and receptors and commences with upregulation of an adhesion molecule, alpha 6 integrin on tumor cells, allowing them to attach to bone matrix collagen. Prostate cancer cells then produce urokinase-type plasminogen activator (uPA) which stimulates mitosis and produces growth factors resulting in osteoblast migration and differentiation. Finally, prostate cancer cells express endothelin-1 which further promotes osteoblast proliferation and other growth factors.

Increased osteoclast activity also features in CIBP of prostate cancer. Markers of increased bone turnover such as interleukin-6 and parathyroid hormone-related protein (PTHrP) are high and are thought to mediate osteoclast proliferation by triggering the receptor activator of nuclear factor-κβ ligand (RANKL)-RANK interactions [59].

Murine studies have shown that blockade of RANKL which is an essential regulator of osteoclasts attenuates sarcoma-induced bone pain, bone remodeling, and tumor growth within the bone [42]. This final common pathway is a target for novel therapies such as monoclonal antibodies to RANKL (denosumab) [60] or interrupting the ligand through use of an analog of osteoprotegerin, a decoy RANK receptor [53].

Other Targets for Novel Therapies

In experimental models, antibodies to nerve growth factor (NGF) and antagonists to transient receptor potential vanilloid type 1 (TRPV-1) ion channel and endothelin-1 receptor have been shown to relieve CIBP [61,62] (Table 88.2). Cancer-affected bone undergoes marked sprouting and reorganization, implicating NGF activity. Nearly all nerve fibers that innervate bone also express tropomyosin kinase A and p75 receptors through which NGF sensitizes and activates nociceptors. Antibodies to NGF administered early in animal studies have shown reduction in pain-related behaviors greater than that achieved with morphine sulphate [49]. Early phase II clinical trials using tanezumab, a fully humanized monoclonal antibody to NGF, is currently underway to evaluate effects at reducing bone pain in advanced prostate and breast cancer [61].

Other strategies have included studying the action of a cannabinoid 2 receptor agonist, AM1241, on an osteolytic sarcoma murine bone cancer model. Bone loss and pain behaviors were both reduced following systemic administration both acutely and over 7 days of AM1241 [63]. Finally, increased understanding of the role of glial cells in the generation of chronic pain and hyperalgesia is leading to the exploration of their role in CIBP and the potential for human therapies in the future [3]. With the development of these and other such targeted therapies, the pursuit for better analgesia for bone metastases becomes one which is closely aligned with the pursuit for better disease therapies.

Interventional Therapies

Increasingly, a more mechanism-based approach to managing cancer pain is advocated as opposed to the traditional WHO approach. In approximately 3–14 % of patients, cancer pain proves unresponsive to analgesics given in the more standard ways and more interventional therapies may be considered [33,34]. This may include nerve blocks, spinal infusions, vertebroplasty, and neurosurgical ablative techniques. Typically, patients are referred when there is failure to respond to pharmacological means and the pain is anatomically amenable to an intervention. However, procedures such as intraspinal administration of analgesics carry significant risk and require specialist management which may lead to prolonged inpatient care. Integrated cancer pain management programs involving palliative, anesthetic teams, and neurosurgical teams among others are required and the infrequency of utilization of interventions makes the maintenance of expertise difficult. However, with careful and early patient selection, the right intervention may dramatically transform the distressing situation of a patient in unrelieved pain.

Non-pharmacological Methods of Cancer Pain Control

These have been defined as actions or behaviors which are not drug-based and which "come between" the pathophysiological mechanism of the cancer pain and the patient's perception of that pain [64]. Examples are summarized in Fig. 88.2. A meta-analysis of the efficacy of CBT, including pain coping skills training, suggests that systematic training in cognitive and behavioral strategies for reducing cancer

Table 88.2 Mechanism-based therapies for the treatment of bone cancer pain

Drug class	Target	Action	Indication	Potential complications
Tumor/inflammatory products				
Selective COX-2 inhibitors	Prostaglandin synthesis	Peripheral and central sensitization	Prostaglandin-dependent cancers	Cardiotoxicity
				Nephrotoxicity
				Bone formation
Endothelin-receptor antagonists	Nerve fibers	Sensitization of nerve fibers	Endothelin-sensitive cancers	Hypotension
	Smooth muscle cells			Teratogenicity
Anti-NGF antibody	NGF receptor blocker	Analgesia	Cancers with inflammatory	?
			Component	
Acid sensitive ion channels(TRPV-1; ASIC)	pH-sensitive nerve fibers	Blockade of H+through channels	Proton- or acid-producing cancers	Delayed wound healing
				Altered taste
Purinergic receptor antagonists	ATP-sensitive nerve fibers	Blockade of P2Xreceptors	Cancers that invade mechanically sensitive	Altered touch perception
Bone remodeling				
Osteoprotegerin	Osteoclast activation	Osteolysis inhibition	Lytic bone pain	Autoimmune response
Bisphosphonates	Osteoclast apoptosis	Analgesia	Lytic and blastic bone pain	GI toxicity
		Tumor shrinkage		Fever
		Osteoclast activity		Electrolyte abnormality
		Suppression		
Nerve injury				
Anticonvulsants (gabapentin)	Calcium channel subunit	Aberrant neuronal discharge suppression	Neuropathic pain	Bone marrow suppression
				Ataxia
				Drowsiness
Antidepressants	NE serotonin uptake inhibition	Analgesia	Neuropathic pain	Sedation
		Anxiolysis	Musculoskeletal pain	Hypotension
			Opioid enhancement	Cardiotoxicity
				Seizures
GDNF-like therapy (artemin)	Growth factor receptor stimulation	Analgesia	Neuropathic pain	Stimulated tumor growth

Adapted from Sabino and Mantyh [68]
COX-2 cyclooxygenase-2, *NGF* nerve growth factor, *TRPV-1* transient receptor potential V-1, *ASIC* acid sensing ion channel, *P2X* purinergic receptor, *NE* norepinephrine, *GDNF* glial cell line derived neurotrophic factor

pain is effective [65]. In recognition of the psychological distress experienced by partners of patients in pain, coping skills training involving partners is being studied to evaluate benefits on both patient's pain levels and caregiver strain and self-efficacy with regard to helping patients cope with pain [66]. Much research on cancer pain and coping has focused on catastrophizing which is an overly negative appraisal of pain. Catastrophizing relates to an increased level of psychological distress which generates higher levels of concern in caregivers who report higher levels of stress and lower quality of life.

Conclusion

"The quantity and quality of scientific evidence on cancer pain relief compare unfavorably with evidence related to treatment of other high-impact conditions, including cancer itself" [67]. From the experience over the past 20 years, there is reason to speculate that improvements in pain management in advanced cancer will need to be closely linked to improvements in disease management before real progress is to be made. This viewpoint is taken because without investment of much greater economic, scientific, and clinician resources, efforts to improve pain management will remain the concern of the few who work in the fields of palliative and anesthetic pain management rather than occupy the efforts of the many involved in the treatment of cancer. The development of new molecular targets with a translational approach in CIBP is an important link with the disease-targeted therapies which also target pain mechanisms. In the light of these developments, the pharmacological management of cancer pain, particularly CIBP, is likely to dramatically change over the coming decades. However, effective pain management will always require multimodal approaches that recognize the subjective unique experience of each patient.

Fig. 88.2 Non-pharmacological management of pain

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