Chapter 7
Cancer-Induced Pain

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Abstract Most commonly, but not exclusively, cancer pain is a result of late-stage metastatic cancers and primary and metastatic cancers that grow in the bone. Cancer pain, like the disease itself, is widely diverse in its quality and extent, and can result from many different causative factors. Many factors have been implicated in the causation and maintenance of cancer pain. Neuropathic pain results from damaged peripheral or central neuronal tissue and from chronically altered neuronal signalling resulting from central and peripheral sensitization. Neuronal tissue can be damaged by direct invasion by tumour cells, as is the case of tumours of the central nervous system (CNS) or by invasion of peripheral neurons in peripheral host tissues. Cancer cells and associated cells also secrete a large number of chemical factors, some of which can directly damage or simulate neurons. Direct physical interaction between the tumour mass and the altered host tissues with neuronal tissue can also cause neuropathic damage through nerve disruption and destruction. Cancer cells and associated cells including stromal and immune cells also secrete a host of chemical signalling molecules that can directly and indirectly stimulate nociceptors. Thermal stimuli of sensory neurons can become pathological following peripheral and central sensitization, which decreases the threshold temperature at which thermally sensitive neurons will respond. Pain is also often a side effect of many treatments of cancer, although the mechanisms of these treatment-induced conditions are beyond the scope of this review. Treatment of cancer pain itself

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largely relies on analgesics and therapies directed against the cancers themselves, although specific treatments for cancer pain are more recently becoming available. It is often the case, however, that cancer pain conditions become intractable, or are poorly controlled. Breakthrough pain which is prevalent in cancer pain is defined by its relationship to treatment where it is an episodic painful event that occurs during a routine of normally effective pain control. Cancer pain is a serious and prevalent oncodynamic effect that arises from a highly variable array of stimuli. The study of cancer pain as a distinct phenomenon is still in its infancy.

Keywords Pain · Cancer-Induced bone pain · Nociception · Neuropathy · Breakthrough pain · Glutamate

Introduction

The ability to sense physiological pain is an essential self-preservational quality of an organism that allows the avoidance of tissue damage and the recognition of damaging pathological states. However, the physiological systems that allow us to perceive pain in a useful manner can also become pathological themselves, either seemingly independently as is the case with some chronic pain conditions, or as the result of an unrelated disease state, such as cancer. The pain produced by cancer can range from mild discomfort to severe, intractable, and self-propagating states of chronic pain.

Some type of cancer-induced pain is estimated to be experienced by 30–50 % of all cancer patients, and by 75–90 % of those with late-stage metastatic cancer [1]. Metastatic cancer-induced bone pain is the most common source of cancer pain reported by patients [2], and has also been the well-studied. Cancer pain can be debilitating and intractable and is a major impediment to the maintenance of quality of life and functional status in cancer patients [3, 4]. And yet, many barriers to the effective management of cancer pain still remain. These include significant sociological and regulatory barriers, but also a deficit of knowledge regarding the mechanisms and control of chronic pain itself, and of cancer pain in particular. It has been recently determined by systematic review that approximately 1/3 of patients undergoing treatment for cancer pain are undertreated, although this number is highly variable globally [5]. This chapter will summarize the molecular mechanisms of cancer-induced pain as an oncodynamic effect of great importance to people living with cancer.

Pain

Pain is defined by the International Association for the Study of Pain as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage [6]. The human experience of

pain is multifaceted and subjective and difficult to quantitatively study. Mechanistically, pain is subcategorized into three physiological sources; nociceptive, inflammatory and neuropathic pain. In many painful conditions, including many conditions of cancer pain, all three of these pain types will play a contributory role in the overall mechanisms and quality of the experience of pain.

Acute nociceptive pain arises from the stimulation of specialized sensory nerve fibres called nociceptors. This includes the myelinated and rapidly conducting Aβ- and Aδ-fibres, and the unmyelinated, slow-conducting C-fibres. Nociceptors innervate most somatic tissues at differing densities, and exhibit receptors that allow sensitivity to a range of inputs including noxious thermal, mechanical, and chemical stimuli. Most nociceptors in the body remain constitutively inactive until activated with unusual stimuli, as is the case when the distortion of a broken bone stimulates dormant mechanically sensitive nociceptors. The cell bodies of nociceptors that innervate the body lie in the dorsal root ganglia (DRG), lateral to the spinal cord at the vertebral column, or in the trigeminal ganglion for facial nociceptive innervation. The central terminals of nociceptors synapse with second-order neurons in the CNS, usually at the dorsal horn of the spinal cord. Here, these connections are subject to inhibitory, facilitory and other modulatory influence by central descending neurons and by glial cells [7]. Ascending neurons generally pass along the spinothalamic or spinoreticulothalamic tracts to the thalamus and brainstem, and further to the cortex [8]. Multiple brain regions are involved in the perception and processing of pain signalling, including primarily the primary and secondary somatosensory cortex, as well as the insular cortex, anterior cingulate cortex and prefrontal cortex [9]. Nociceptors are widely variable in their structures and functions, including their activating stimuli and thresholds, the extent of their receptive fields, and their speed and frequency of signalling. This heterogeneity allows the sensation of a wide variety and quality of painful sensations at the CNS [10].

Inflammatory pain is pain produced by nociceptors activated by the mediators and molecular products of inflammation. Nociceptors express many receptors for individual products of inflammation, including but not limited to substance P, bradykinin, prostaglandins, adenosine triphosphate (ATP), nerve growth factor (NGF), tumour necrosis factor-α (TNF-α), and protons. These are secreted by the peripheral terminals of nociceptors, and by cells associated with inflammatory states including mast cells, macrophages, and fibroblasts, to the extracellular "inflammatory soup" of pro-inflammatory and algesic signalling molecules that is characteristic of inflammatory sites [11].

Neuropathic pain is pain that arises as a direct consequence of damage or disease affecting the somatosensory system [6]. This can arise from a number of conditions including surgical or traumatic damage, chronic inflammation, and invasive cancer. There is increasing evidence that despite the phenotypic similarities of many conditions of pain, the mechanisms that contribute to the production and maintenance of pain can be significantly divergent. There are peripheral and central mechanistic differences between painful conditions, and between sexes experiencing the same condition that are relevant to treatment [12].

Despite their etiological differences, all pain regardless of the source or any modulation must be transmitted by neuronal cells to the brain in order for perception to occur. This is as true for cancer pain as it is for the pain of any other condition. Also at play, regardless of the source of the pain, is that chronic nociceptive signalling and pathological conditions can produce dramatic reorganization of the structures that transmit and regulate pain signalling. This reorganization includes physiological changes in neurons and glial cells that are associated not only as indicators of a state of chronic pain, but as factors implicit in the maintenance of that pain. Ultimately these pain pathways can transition from acute activation to chronic ongoing activation through the processes of peripheral and central sensitization. Sensitization results in the conditions of hyperalgesia and allodynia, whereby a lower stimulus threshold triggers a nociceptive response and a normally non-nociceptive stimulus becomes painful, respectively. These processes are essential to the physiology of chronic pain conditions, including cancer pain.

Cancer Pain

As befitting such a diverse pathological condition as cancer, pain resulting from cancer can arise from many physical, chemical, and thermal stimuli. Cancer pain can be nociceptive, inflammatory and neuropathic, and is commonly a result of situations such as physical pressure from the tumour itself, damage to or remodelling of tissues in close proximity to the tumour, and peritumoural inflammation. Central and peripheral sensitization renders cancer pain into a chronic condition that can become constant and intractable. Treatments of cancer also often cause pain as a side effect, most notably, chemotherapy-induced peripheral neuropathy (CIPN), and opioid-induced hyperalgesia; however these conditions are not directly oncodynamic, and as such, will not be addressed in this review.

Conditions of cancer pain are defined by the source tissue of the primary cancer, and the host tissue from which the pain emanates. A list of common clinical cancer-associated pain syndromes and their treatment can be found in this review by Portenoy [13]. The quality and intensity of these pain conditions are widely variable, for example the pain emanating from a primary tumour in the breast, if any, presents very differently than the pain of a metastatic breast cancer growing in the spine. One of the challenges of cancer pain management, however, is the inconsistency of the influence of location or tumour type in the generation of pain. One patient's tumour may not cause pain until late stages, whereas a similar tumour in another patient may generate severe pain before the lesion is detectable by other means [14]. This is due to widely differing primary cancers, but also the structures and functions of host tissues in the body, which play a defining role not only in the progression of the invading cancer, but also in the nature and extent of the oncodynamic consequences of that invasion. Despite this, regardless of the host tissue, cancers can cause pain by similar mechanisms. Many cancers secrete a host of algesic chemicals capable of stimulating and sensitizing nociceptors. In innervated

tissue, these chemicals would be expected to be independently capable of nociceptive stimulation, as has been shown to be the case with endothelin-1 (ET-1) which can cause pain following secretion from several different types of cancer cells in multiple tissues [15–18].

Breakthrough cancer pain is a separate condition that is defined by its relationship to pain treatment. It is a transitory exacerbation of pain in excess of the otherwise effective analgesic regimen of the patient [19]. This pain can arise spontaneously or as a result of an action or movement committed by the patient in which case it is labelled as incident pain. The rapid onset and occasional unpredictability of breakthrough pain makes it particularly difficult to control and burdensome for the patient.

Secreted Factors

Many algogenic factors that contribute to cancer pain are secreted from cancer cells and associated stromal cells. Several of these are also mediators of inflammation and inflammatory pain secreted from immune cells recruited to the tumour site. Other classes of secreted factors include neurotrophins, neurotransmitters and cell-signalling molecules including hormones and cytokines. There have been several lines of research focussed on pursuing the importance of particular secreted factors to cancer pain, some of which have shown more potential for treatment than others. It is appearing more evident that targeting a single factor is unlikely to emerge as a valid treatment of cancer pain in isolation. Many secreted factors play complex and intertwined roles in inducing and maintaining cancer pain, and determining their physiological roles and respective importance to cancer pain is an important pursuit.

Nerve Growth Factor

Nerve growth factor (NGF) has recently been found to be an important compound in the development and treatment of multiple pain states including cancer pain, and particularly cancer-induced bone pain. Targeting NGF in cancer pain has accumulated much primary basic and clinical evidence of efficacy, and is emerging as a promising therapeutic avenue. NGF can directly activate nociceptors that bear either the tropomyosin receptor kinase-A (TrkA) receptor or the low-affinity neurotrophin receptor p75. NGF is known to be upregulated in inflammatory pain states, and NGF-TrkA signalling is a mediator of sensitization through action at the spinal cord and DRG [20]. In mouse models of osteosarcoma, NGF promotes the rapid neurogenesis of TrkA positive sensory and sympathetic fibres that eventually reach a pathologic density in the periosteum of tumour-bearing bone [21]. Antibody sequestration of tumour-generated NGF reduces pain and pathological neurogenesis

in animal models of osteosarcoma, prostate cancer, and breast cancer in bone [21–23]. NGF also promotes the development of sensitization through transcriptional upregulation of neuropeptides and ion channels at the DRG in nociceptors, including substance P, calcitonin gene-related peptide (CGRP), and brain-derived neurotrophic factor (BDNF) [21]. BDNF is a neurotrophin that binds the TrkB receptor, and, like NGF, also to p75. The overexpression of BDNF at the spinal cord is likewise involved in the generation of central sensitization in both inflammatory and neuropathic pain states [24]. Microglial production of BDNF is also involved in the development of central sensitization in an animal model of metastatic breast cancer-induced bone pain. Treatment of these animals with a tetracycline inhibitor of microglial activation, minocycline, reduced BDNF at the dorsal horn simultaneously with behavioural evidence of pain [25].

Endothelin-1

Endothelins are vasoactive and nociceptive peptides usually secreted from endothelial cells but also important in the regulation of angiogenesis, bone turnover, and tumour growth. Endothelin-1 (ET-1) can directly stimulate and sensitize nociceptors, and has been found to be secreted by breast and prostate cancer cells [26], fibrosarcoma [15, 16] and oral squamous cell carcinoma [17]. Much research has been focussed on the role of endothelins in cancer pain and they continue to pose a promising, if complex, target for treatment. Inhibition of the endothelin-A receptor (ET_AR) which is expressed by sensory neurons and sensitive to ET-1, has successfully reduced cancer pain in multiple animal models [15–17], however these findings have not yet been validated at clinical trial [27]. Interestingly, inhibition of the endothelin-B receptor (ET_BR) can have the opposing effect of increasing cancer pain in animal models [28].

Acidic Environment

Acidic microenvironments are characteristic of tumours and can directly stimulate nociceptors and induce downstream mediators of pain through several signalling cascades. Acid is a well-characterized mediator of pain. In cancer pain, particularly cancer-induced bone pain, it has been proposed that this acidic microenvironment in bone following tumour growth and osteoclast upregulation may produce sufficient acid to activate the low pH receptors acid-sensing ion channel (ASIC) and transient receptor potential channel-vanilloid subfamily member 1/capsaicin receptors (TRPV1) that are present on nociceptors [29]. In addition, expression of both of these receptors at the DRG is elevated in animal models of cancer-induced bone pain [30, 31], and TRPV1 inhibition has reliably decreased cancer pain in animal models [32].

Glutamate

Many cancer cells secrete the neurotransmitter and cell-signalling amino acid glutamate, including breast, prostate, melanoma and glioma cells. In these cell types, the mechanism of glutamate secretion has been found to be the cystine/glutamate antiporter system x_C^- [33, 34]. Depending on the host tissue or metastatic site, this glutamate release can be a severely a disruptive influence on normal host tissue cell signalling, and can directly activate and sensitize primary afferent nociceptors [35]. In glioma in the CNS, this glutamate release provides a functional advantage to the tumour, promoting malignancy, causing the excitotoxic cell death of neurons, and inducing detrimental oncodynamic side effects including seizures, and possibly headache [33, 36, 37]. In peripheral tissues, glutamate secretion and pain have been investigated in the context of cancer-induced bone pain. Reducing glutamate release from cancer cells by inhibiting the system x_C^- transporter can reduce cancer pain in animal models of breast cancer metastasized to the bone [38]. This outcome may be due to the direct effects of secreted glutamate on the glutamate-sensitive nociceptors in the bone and peritumoural space, or due to differential changes in bone physiology that are susceptible to glutamatergic interference.

There are many other relevant secreted factors to cancer pain. These include but are not limited to: proteases, prostaglandins, bradykinin, TNF-α, interleukins-1 and 6, epidermal growth factor, transforming growth factor-β (TGF-β), and platelet-derived growth factor (Fig. 7.1). These many factors have been detailed in a number of comprehensive reviews [14, 39, 40].

Physical Factors

Visceral pain syndromes often result from physical interference with one or more visceral organs by a tumour mass. Commonly, this pain results from obstructions or distension of the visceral organs due to tumour growth or associated edema, including hepatic distension and intestinal obstructions [13]. The bulk of a growing tumour also poses a risk of physically encountering a sensory neuron that varies with the characteristics and innervation of the host tissue. Physical contact between a tumour and neuron can cause nerve entrapment and injury and induce neuropathic pain states including plexopathies and radiculopathies. In animal models, the leading edge of tumours in bone were found to come into contact, injure and then destroy the distal processes of sensory fibres in conjunction with the development of neuropathic cancer pain states [41]. In addition to stimulating and sensitizing sensory neurons, some of the secreted factors described above, including proteases, can also directly damage neurons, given certain conditions.

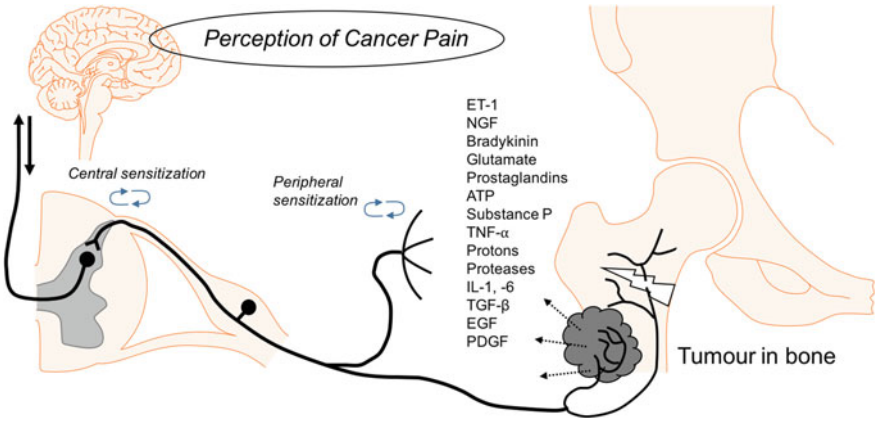

Fig. 7.1 Pain is perceived by transmission through sensory neurons to the central nervous system. Cancer pain is initially stimulated through many mechanisms. This figure illustrates several mechanisms of cancer-induced bone pain, including bone fracture due to weak or degraded bone structures proximal to the tumour, and multiple secreted factors from tumour cells and other cells including immune cells recruited to the tumour site. These secreted factors can modify the tumour itself, the host tissue environment, and can directly stimulate nociceptors. Pain signalling is initiated by sensory neurons in and around in the bone and tumour, and transmitted through the dorsal horn and spinothalamic or spinoreticulothalamic tracts of the spinal cord to the brain. Descending controls from the brain and spinal cord can alter pain signalling and initiate features of central and peripheral sensitization which serve to maintain and amplify pain, leading to intractable chronic cancer pain

Sensitization

Cancer pain, like other enduring pain states, eventually becomes a state of chronic pain through the development of peripheral and central sensitization. Evidence of physiological changes indicative of sensitization in animal models of cancer pain are plentiful, including central sensitization at the dorsal horn [42–45], peripheral sensitization of local primary afferent C nociceptors [15, 46–48], and cellular and neurochemical changes in the DRG neurons and dorsal horn of the spinal cord [41, 45, 49].

Cancer-Induced Bone Pain

Bone pain from cancer is the most common type of cancer pain and despite the transition of several mechanistically targeted therapies into clinical practice, cancer-induced bone pain has remained extremely difficult to manage.

Cancer in bone can be a result of primary cancers of bone tissues and of metastases from distant sites. Bone metastases are extremely disruptive to normal

bone cell metabolism, often resulting in the development of lesions featuring the dysregulated destruction and formation of mineralized bone tissue and the release of pro-inflammatory and algogenic substances into the bone microenvironment. This disruption is responsible for a host of intertwined pathologic consequences including bone fractures and microfractures, spinal cord compression, hypercalcaemia, and severe pain. Cancers of the lung, prostate, kidney, thyroid and breast are the most likely to produce a bone metastasis, with lung, prostate and breast cancer accounting for the vast majority of these cases [50].

Pain in metastatic cancer afflicted bone can arise from a number of stimuli and from any location within the bone. Bones are densely but unevenly innervated with sympathetic and sensory nerve fibres. Aβ-, Aδ- and C-fibres have been identified in the periosteum, as well as throughout mineralized bone and the bone marrow [51, 52]. The densely innervated periosteum is highly sensitive to disruption, however many painful lesions have been found to entirely lack periosteal involvement [1].

Animal models have revealed that cancer-induced bone pain is a unique pain state exhibiting distinct neurochemical and cellular features in the spinal cord and DRG that are not shared with other inflammatory or neuropathic pain states. In particular, changes in the expression of both substance P and CGRP were observed in the dorsal horn of the spinal cord in both inflammatory and neuropathic animal models, but neither neuropeptide was altered in models of bone cancer pain. In addition, bone cancer pain resulted in a much greater increase in glial fibrillary acidic protein (GFAP), a marker of astrocyte proliferation and hypertrophy than other modelled pain states [53].

As discussed above, a number of factors involved in tumour metastasis, growth and lesion formation have the potential to cause pain both directly and indirectly. The confluence of multiple contributing algogenic substances and extensive physical disruption at the tumour site indicate that the mechanisms responsible for cancer-induced bone pain are heterogeneous and complex.

The growing tumour itself contributes to pain generation through pressure on the periosteum or sensory nerves in bone, and through the destruction of sensory neurons. Both osteolytic (net bone resorbing) and osteoblastic (net bone forming) lesions are characterized by weaker bone that is more prone to fracture, compression, and collapse [54]. Microfractures of the bone trabeculae and fractures of the whole bone compress sensory neurons and distort the periosteum, contributing significantly to pain [2].

The mechanisms of pathological bone cell turnover itself have also been linked to cancer-induced bone pain. Osteoblastic lesions commonly arise from prostate cancers and from ~25 % of breast cancers [55]. Their promotion of bone formation in the lesions associated with the metastatic tumour has been associated with the production by the tumour cells of a number of factors that are secreted into the bone microenvironment. The most well-characterized of these many associated factors is the aforementioned ET-1 which is released by typically osteoblastic prostate and breast cancer cell lines, and has been shown to act at ET_AR on osteoblast cells [56]. A number of other tumour associated factors are involved in the promotion of bone volume including osteoprogenetrin (OPG), TGF-β, urokinase, fibroblast growth

factors, and possibly also prostate-specific antigen, all of which are associated with osteoblast cell proliferation [55]. Pathological osteoblast activity associated with bone metastases is not just the overactive production of normal mineralized woven bone or osteons; rather cancerous osteoblastic lesions are typically dysregulated and osteosclerotic tissue that is of poor functional quality and conducive to pain [57].

Many cancers including multiple myeloma and most breast cancer metastases produce primarily osteolytic lesions which extensively degrade mineralized bone and are frequently severely painful. Other conditions including postmenopausal osteoporosis and hormone-ablative therapies in cancer treatment are also associated with pathological osteolysis [58]. Most of the osteolytic degradation associated with metastatic cancer is a result of the pathological activation of osteoclasts by the tumour; however, it has also been demonstrated that tumour cells can directly resorb bone even in the absence of osteoclast cells. Like osteoblastic metastases, osteoclastic bone resorption is stimulated by the tumour through the release of a number of stimulatory factors that upregulate osteoclast proliferation and activity. One released factor, parathyroid hormone related peptide (PTHrP) shares many structural and functional similarities with parathyroid hormone (PTH). At the bone, PTHrP stimulates osteoclast proliferation through osteoblastic production of the receptor activator of nuclear factor-κB ligand (RANKL) [59]. Treatment of animal models of metastatic bone cancer with neutralizing antibodies to PTHrP significantly reduces bone metastasis and resorption [60]. However, PTHrP may have a dual role in bone remodelling, as its expression by prostate cancer cells has conversely been associated with the extent of osteoblastic lesions [61]. Other osteolysis-inducing factors either released directly or induced to be released by tumour cells include macrophage colony-stimulating factor (M-CSF), TGF-β, TNF-α and β, interleukin-1, 6, and 11 [62], and Jagged1 of the Notch signalling pathway [63].

One of the roles of mineralized bone matrix is to act as a reservoir of minerals and growth factors that can be re- released into circulation by osteoclastic bone resorption. Bone resorption in the event of a lytic metastasis results in the pathologic release of these same reserved substances. Ca^{2+} release in this manner is partially responsible for the hypercalcaemia that is characteristic of bone metastases [64], and the release of both mineral and growth factor has been implicated in a positive feedback cycle of tumour growth and bone destruction commonly referred to as the vicious cycle hypothesis. The vicious cycle consists of the release of osteoclast stimulating factors including PTHrP from the metastatic tumour cells which promote osteoclast cells to increase bone resorption, resulting in the release of tumour cell-stimulating cytokines and growth factors from the bone matrix reserves that further stimulate tumour growth and perpetuate the “vicious” cycle. Factors released in this manner from mineralized bone that stimulate tumour cell growth include TGF-β, insulin-like growth factor 1, and Ca^{2+} itself [55].

Bone resorption can also occur independently of osteoclasts through the direct action of cancer cells. This ability has been demonstrated in vitro in several cancer types including breast [65], prostate [66], murine melanoma [67], and giant cell tumour of bone [68]. MMPs secreted from these cancer cells are thought to play a

significant role in this process, particularly MMP-2 and 9 [69], and MMP-13 [68]. Inhibition of MMPs reduced the ability of in vivo human breast cancer cells to degrade bone [69].

Inhibitors of osteoclast activity have reliably been demonstrated to limit bone pain, and the enhancement of resorption has conversely been demonstrated to increase pain, but this could be due to a number of factors [70]. Osteoclastic bone resorption is initiated through the acidification of the resorption compartment of the osteoclast cell at the mineralized bone surface by vacuolar-ATPase H^+ transporters. Due to this process and to the induction of an acidic microenvironment by cancer cells themselves, the extracellular environment of various human tumours becomes progressively acidic as tumours develop [71]. This acidic microenvironment in bone following tumour growth and osteoclast upregulation may produce sufficient acid to activate the ASIC and TRPV1 low pH receptors that are present on nociceptors in bone [29].

Cancer-Induced Bone Pain Treatment

An impediment to the effective treatment of cancer-induced bone pain is that current standard treatments are largely based on principles developed from studies of non-cancer pain [1]. Standard treatment for progressive ongoing pain involves adherence to the World Health Organization (WHO) analgesic ladder following progression from non-opioid analgesics for mild pain through strong opioids in conjunction with non-opioids and adjuvant treatment for moderate to severe pain. Adjuvant treatments in this case are non-analgesics that modify analgesic outcomes. The use of adjuvant treatments in the management of pain is quite common, and standard treatments can include the use of antidepressants or anticonvulsants. In the treatment of cancer-induced bone pain the use of drugs that prevent osteoclastic bone resorption are widely used as adjuvants. Bisphosphonates are a class of antiresorptive compounds with a high affinity to bind Ca^{2+} and therefore to become sequestered in the Ca^{2+} rich bone matrix. When released and absorbed by osteoclasts, bisphosphonates inhibit the enzyme farnesyl diphosphate synthase which then limits the downstream ability of the cell to produce several essential GTP-binding proteins, inducing apoptotic cell death [72]. This limits the extent of osteoclastic resorption in the bone and therefore limits pain from mechanical stress and osteoclast-associated algogenic factors. Bisphosphonate treatment has also been tentatively shown to reduce metastasis to bone and increase survival in breast cancer patients without current bone metastases [73]. These results have fuelled the search for drugs that, like bisphosphonates, inhibit osteoclastic bone resorption. Treatments with OPG, the decoy receptor for RANKL has successfully limited bone pain and tumour growth in animal models [74]. A fully human monoclonal antibody to RANKL, denosumab, has also been developed as a more specific inhibitor of osteoclast activity than bisphosphonates. In multiple phase III clinical trials, denosumab was superior to several bisphosphonates in the prevention of

skeletal-related events including pain in both prostate and breast cancer patients [53]. The inhibition of osteoclasts appears to have several serious side effects that have limited treatment with these drugs. Bisphosphonates are associated with occasional atrial fibrillation, osteomyelitis, and more commonly, osteonecrosis of the jaw of which bisphosphonate treatment is involved in over 90 % of all cases [75]. Standard treatments for cancer in bone can also have an impact on pain including radiotherapy and surgery. Both are applied palliatively with pain control as the primary intention [76]. Recently, a fully humanized monoclonal antibody to NGF, tanezumab has demonstrated clinical efficacy in the treatment of cancer-induced bone pain [77].

Currently, μ-agonist opioids remain the gold standard for the treatment of moderate to severe cancer pain in adherence to the WHO pain ladder. Their efficacy is limited by the occurrence of severe side effects at the doses necessary for adequate analgesia and patient quality of life suffers as a result. Adjuvant treatments are successfully utilized in cancer-induced bone pain management, but reliable pain relief in a manner not independently detrimental to patient quality of life remains elusive.

Current Treatment

The effective management of cancer pain is largely performed in accordance with the principles of the WHO guidelines for cancer pain relief. The core of the guidelines is based upon adherence to the WHO Analgesic Ladder which stipulates a treatment progression from non-opioid analgesics through weak opioids to strong opioids as is necessary to treat progressively worsening pain. Adjuvant drug supplementation and other supplementary interventions including radiotherapy and alternative treatments are applicable throughout as necessary. Adherence to this treatment paradigm has been validated as effective for good or satisfactory pain relief in the majority of cancer patients; however, 24 % of treated patients do not experience complete pain control, with 12 % reporting inadequate pain control [78, 79]. It has also been reported that approximately two-thirds of patients undergoing treatment with opioids experience episodes of breakthrough pain [19]. Episodes of breakthrough pain are treated usually with a “rescue dose” of the patient’s current analgesic, or with a different fast-acting transmucosal μ-opioid agonist [80].

Current analgesic treatment practices are often effective at their priority of reducing the experience of pain for the cancer patient, but that pain relief often comes at the cost of otherwise impairing the patient’s quality of life through treatment side effects. Opioids in particular induce a number of serious dose-limiting side effects including nausea, constipation, vomiting, respiratory depression, sedation, somnolence, and cognitive impairment, and prolonged use can induce the development of physical dependence, tolerance and addiction [81, 82]. Non-steroidal anti-inflammatory drugs (NSAIDs) are most often the first analgesic treatment for cancer pain, and they too are associated with dose-dependent adverse

effects, most predominantly, gastrointestinal and renal side effects [83, 84]. Patient or caregiver concern about treatment-associated side effects or of the consequences of dependence on pain treatment with analgesics can often result in the insufficient control of otherwise manageable pain, as can layers of regulation governing access to controlled pain medications [85, 86]. For these patients who cannot or do not access adequate pain relief, in addition to those patients whose pain cannot be fully controlled with available analgesics, inadequate cancer pain management yet remains a global public health concern.

Conclusion

In conclusion, the oncodynamic effect of cancer pain is a common and severely detrimental consequence for patients living with cancer. As cancer treatments continue to improve, and cancer patients live longer with their disease, strategies of pain control that maintain patient quality of life become ever more valuable, and the understanding and high-quality management of chronic cancer pain becomes a more pressing priority.

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