

ROLE OF OSTEOCLASTS AND NOCICEPTIVE SENSORY NEURONS IN BONE CANCER PAIN - A REVIEW

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Abstract

At late stages, many common malignancies, such as breast, prostate, and lung cancer spread to the bones, causing significant discomfort and functional impairment. Currently existing pharmacotherapies for bone cancer pain are insufficient to offer pain relief that is both safe and effective. The methods employed by cancer cells inside the bone tumour microenvironment (TME) to cause bone cancer pain are discussed in this narrative review.

We focus on the reciprocal interactions that generate bone cancer pain between tumour cells, bone-resorbing osteoclasts, and pain-sensing sensory neurons (nociceptors). We also discuss about how tumour cells in the bone TME speed up osteoclastogenesis and change osteoclast activity and function. Furthermore, we discuss how osteoclast's over-activation contributes to bone cancer pain via -

(1) Direct mechanisms, such as the production of pronociceptive factors that act directly on sensory afferents, and (2) Indirect mechanisms, such as osteoclast-driven bone resorption that weakens tumor-bearing bones and predisposes them to skeletal-related events, resulting in bone cancer pain and functional impairment.

Finally, we address the impact of possible therapeutic drugs such as denosumab, bisphosphonates, and nivolumab on bone cancer pain, osteoclast overactivity, and tumour development inside the bone TME.

1. Introduction

Cancer is the second biggest cause of mortality in the United States, and it affects millions of people worldwide each year [25]. Cancer typically presents with multiple neurological comorbidities, such as pain, sadness, and anxiety, in addition to being a life-threatening condition in and of itself, all of which result in a significantly diminished quality of life. Approximately 75% of patients with late-stage cancer feel moderate or severe pain, [21, 23, 31], and at least half of all patients with metastatic cancer indicate that present pharmacotherapies do not provide adequate pain relief [82]. Despite these staggering figures, the treatment choices for cancer pain remain restricted, with considerable effectiveness and long-term safety concerns [31, 82]. Given the current opioid crisis, healthcare practitioners are cautious to administer opioid analgesics because of the risk of addiction, abuse, and misuse, especially when cancer patients' long-term prognosis improves [71].

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Breast, prostate, and lung cancers are not only among the most frequent malignancies, but they also have a significant risk of metastasizing to the bones, resulting in severe bone cancer pain and other complications [22, 84]. Furthermore, bone metastases are difficult to treat and have a bad prognosis in the long run [84, 92, 93]. Because of its sluggish blood flow and high vascularization, the bone marrow is a good place for cancer to spread [22, 60]. Furthermore, the bone marrow is thought to be an immunosuppressive tumour microenvironment (TME), [67] potentially providing a haven for cancer cells to hide from immune monitoring and antitumor response. Locally invasive cancer cells penetrate and fill the bone marrow, producing mediators that modify the phenotypic and function of resident cells in this niche, such as bone-forming osteoblasts (OBs), bone-resorbing osteoclasts (OCLs), and nerve fibres from pain-sensing sensory neurons (nociceptors). [58] Skeletal-related events (SREs) are consequences that might include skeletal fractures, spinal cord compression/instability, and systemic hypercalcemia and anaemia as the bone malignancy advances. SREs have been linked to discomfort, functional impairment, decreased mobility, a worse quality of life, and a lower overall survival rate. [84, 92, 93] Importantly, sensory neurons whose cell bodies are situated in the dorsal root ganglion (DRG) or trigeminal ganglion extend central projections to the spinal cord or brainstem to send this sensory information to the central nervous system innervate bones widely. DRG nociceptors, in particular, are highly innervated on both the exterior and interior surfaces of long bones, allowing them to detect potentially dangerous stimuli such as fractures or neoplasms. Bone cancer pain is commonly described as a polymodal pain disease, presenting with features of inflammatory, neuropathic, compressive, and ischemia pain, and is thus often treated as a separate entity. [31]

We explore the molecular pathways through which cancer cells, osteoclasts, and sensory nerve fibres interact inside the bone marrow TME to cause bone cancer pain in this narrative review.

We focus on how tumour cells disrupt and hijack the bone marrow microenvironment, as well as how osteoclasts use direct (e.g., production of pronociceptive mediators that act directly on nearby sensory nerve fibres) and indirect (e.g., bone resorption leading to increased SREs) mechanisms to drive bone cancer pain. The discussion of potential treatment targets for bone cancer pain comes to a close.

2. Osteoclasts: specialized bone-resident phagocytes with many functions

OCLs are specialised myeloid-derived phagocytes that live on the surface of bones and are responsible for bone resorption. They help maintain homeostatic bone turnover under steady-state settings. [94] OCLs

are huge multinucleated cells with a diameter of more than 100 μ m. Macrophage-colony stimulating factor (M-CSF) and receptor activator of nuclear factor kappa-ligand (RANKL) signalling are both important in the differentiation of OCLs from monocyte/macrophage cells. [7,54,64] Nearby stromal cells and OBs generate receptor activator of nuclear factor kappa-ligand and M-CSF, which are required for osteoclastogenesis by stimulating the overexpression of osteoclast-specific genes and the fusing of precursor cells to become mature, multinucleated osteoclasts. [7, 87] RANKL signalling enhances the survival and activation states of mature osteoclasts even after they have been produced, making it a significant target for controlling osteoclast activity. [7,39,87] Under steady-state conditions, skeletal maintenance and homeostasis necessitate a delicate balance between OB-mediated bone production and OCL-mediated bone resorption. Bone diseases can result from pathological overactivation or underactivation of either component. [32] OCLs establish a local acidic and lytic environment at the bone-OCL interface within resorption lacunae (Howship lacunae) to execute bone resorption, resulting to the collapse of the bone mineral structure. [59] The proton pump vacuolar-ATPase (V-ATPase) on the osteoclast boundary, in conjunction with a chloride ion/HCO₃ exchanger, provides a proton and hydrochloric acid-rich milieu in which the inorganic bone matrix is dissolved. The collagen fibres are broken down by lysosomal enzymes such as acid hydrolases released into the lacuna by the osteoclast, and the degraded components are phagocytosed by OCLs. [13] Given their origins in the monocyte/macrophage innate immune cell lineage, it's not unexpected that OCLs are now recognised as highly malleable cells that play crucial roles in immunosuppression or immunoactivation, depending on the cellular environment. OCLs release immunosuppressive cytokines such as interleukin-10 (IL-10) and transforming growth factor- β , which activate immunosuppressive regulatory T-cells (Treg), which also limit OCL development under steady-state circumstances. Osteoclasts, like macrophages, can detect and respond to infection, tissue injury, and local inflammation, and they have comparable phagocytic and antigen-presenting capacities. Pathological inflammation causes macrophages to release proinflammatory cytokines such as interleukin-1, interleukin-6, and tumour necrosis factor, both directly and indirectly through the activation of proinflammatory T lymphocytes. [26,49,54,62] As a result, OCLs are uniquely positioned, both physically and functionally, to participate in both bone resorption and immunoregulation depending on the state of the surrounding microenvironment, and they use both of these capabilities simultaneously in a variety of bone diseases, including bone cancer. [59]

3. Cancer cells drive osteoclast overactivation, leading to “the vicious cycle” of bone destruction

Many studies have found that osteoclasts play an important role in the growth of bone cancer and the pain associated with it. Bone is turned over in a balanced cycle of bone resorption and bone production under steady-state circumstances, thanks to the reciprocal activities of OCLs and OBs. However, when tumour cells proliferate in the bone marrow microenvironment, they disrupt the normal bone remodelling cycle, shifting the balance toward osteoclast-mediated bone resorption and thereby allowing additional cancer cell invasion of bone tissue, a paradigm known as the “vicious cycle.” [1, 59, 75] Proinflammatory cytokines including IL-1, IL-6, and TNF, as well as chemokines like chemokine C-C motif ligand 2 (CCL2), which act directly on osteoclasts, boost osteoclast activity in osteolytic tumour cells (those that induce bone degradation). Furthermore, tumour cells promote osteoclastogenesis by secreting parathyroid hormone-related protein, a paracrine regulator of osteoclastogenesis that triggers the production of RANKL, a key regulator of osteoclast differentiation. [10,50,61,89,98] In fact, osteolytic cancer cells imitate OBs, the typical positive regulator of OCLs under homeostatic settings, in a variety of ways. [4,45,68] In turn, increasing numbers and activation of osteoclasts damage the bone matrix and encourage local invasion of cancer cells into bone tissue, while simultaneously releasing growth factors, chemokines, and cytokines that promote tumour development, completing “the vicious cycle.” [4, 10, 59] At the bone-tumor interface, osteolytic cancer cells drive a self-serving loop of osteoclast proliferation and hypertrophy, resulting in increased bone degradation. [43, 59] In contrast to direct engagement of nociceptive nerve fibres by osteoclasts through the production of pronociceptive mediator, this accelerated bone destruction leads to decreased bone mass and increased fragility, increasing the likelihood of subsequent nerve compression and SREs like fractures, thereby indirectly producing bone cancer pain [1,22,44,56,97] OCL dysregulation has also been reported in osteoblastic tumours (eg, those involving ectopic or excessive bone formation). Osteoblastic cancer cells, in contrast to osteolytic malignancies, enhance OB activity while decreasing OCL production and/or activity. [90] Endothelin-1 (ET-1) is a 21-amino-acid peptide that is produced by endothelial cells under steady-state settings and hypersecreted by tumour cells. It is a well-known regulator of OB function and a significant contributor to cancer-induced nociception. [33,66,99] Osteoclastic bone resorption is dramatically reduced in cocultures of human osteoblastic prostate cancer cells with bone slices, a result that can be reversed with the administration of an ET-1 neutralising antibody. ET-1 has also been demonstrated to have a concentration-dependent effect on osteoclast motility and bone

resorption. [2,19,96] ET-1 may thus adversely control osteoclast function while directly contributing to cancer-induced nociceptor sensitization in predominantly osteoblastic malignancies, such as metastatic prostate cancer. [90]

4. Osteoclasts produce pronociceptive mediators to drive bone cancer pain

4.1. Extracellular acidity as an activator of nociceptors

Osteoclasts actively contact nerve fibres from nociceptive sensory neurons to cause pain through several pathways, in addition to indirectly creating bone cancer pain through faster bone breakdown and higher risk of painful SREs. Overactivation of osteoclasts and local tumour growth produce a highly acidic extracellular TME that extends far beyond the resorbing lacunae, activating acid-sensing channels such as transient receptor potential channel-vanilloid subfamily-1 (TRPV1) and acid-sensing ion channels (ASICs), including ASIC1a, 1b, and 3. [31,31,53,97] In mice, blocking the osteoclast proton pump (V-ATPase) with bafilomycin A1, an inhibitor of H⁺ secretion, decreased pain behaviours in animals injected with intratibial multiple myeloma cells or Lewis lung cancer (LLC) cells, indicating that the V-ATPase plays a role in bone cancer pain. [36,88] Furthermore, as compared to WT mice, animals missing TRPV1, a nonselective cation channel expressed in nociceptive neurons and triggered by heat, capsaicin, and protons [80], showed less LLC-induced bone cancer pain. [88] Acid-sensing ion channels are proton-gated cation channels found in neurons that have been linked to the detection of extracellular acidosis in bone cancer patients. [101] The ASIC1a and ASIC2 subunits are typically found in the central nervous system, but ASIC1b and ASIC3 are abundant in peripheral sensory neurons, including nociceptors. [97] ASIC3 is located in peripheral nociceptive nerve fibres in the bone TME and is activated in bone malignancy. [3,97] ASIC1a, 1b, and 3 subunit mRNA and protein expression were all elevated in mouse bone cancer models [63,97,104] indicating a role in bone cancer pain. ASIC3 antagonist APETx2 was able to significantly diminish bone pain in a mouse intratibial multiple myeloma model and lowered excitability of DRG neurons cocultured with human multiple myeloma cells, giving functional evidence for ASIC3's participation [36].

4.2 Nociceptor sensitization in bone cancer pain

CCL2, a chemokine released by osteoclasts, stimulates C-C chemokine receptor type 2 (CCR2) receptors on peripheral nociceptor terminals. [89] Tumour cells also emit a number of proinflammatory cytokines, such as interleukin 1 (IL-1) and tumour necrosis factor (TNF), which bind to receptors on peripheral nociceptor terminals. [5] Continuous activation of nociceptor afferents within the bone TME causes spontaneous pain and sensitization of both peripheral and central nociceptors (termed peripheral sensitization and central sensitization,

respectively), resulting in increased sensitivity to sensory stimuli and neuropathic pain hallmarks like mechanical allodynia (eg, pain evoked by a normally innocuous stimulus such as light touch). [24,46,56] In the early phases of fibrosarcoma cell implantation into and around the calcaneus bone in mice, a subpopulation of C-nociceptors develops spontaneous activity and enhanced firing in response to heat stimuli. [11] This study also found a time-dependent change in nerve fibre sprouting, with increasing epidermal nerve fibre density in the skin overlaying the implanted tumour in the early stages but a sudden loss of epidermal nerve fibres in the later stages, indicating neuropathy. [11]

ET-1 has been found in several human malignancies with a high risk of bone metastasis, such as prostate, lung, and breast tumours, and has been shown to contribute to C-nociceptor sensitization. ET-1 is increased in animal models of cancer-induced hyperalgesia and allodynia [65,72,86], and ETA antagonists have been demonstrated to reduce cancer pain in mice [66,72,86] and humans. [14]

In mouse bone cancer models, ET-1 has also been demonstrated to contribute to peripheral sensitization. ET-1 injected into the receptive fields of C-nociceptors innervating the hind paw increased firing rate in both control and tumor-bearing animals, but the ETA receptor antagonist BQ-123 decreased tumor-evoked spontaneous activity and sensitization to heat in tumor-bearing mice. [33]

As a result, ET-1 appears to have a role in peripheral sensitization in a wide range of malignancies, including bone cancer. Activation of the ETB receptor has also been found to have a local analgesic effect. [47]

VEGF-A, VEGF-B, and PLGF-2, as well as other ligands of the vascular endothelial growth factor (VEGF) receptor 1 (VEGFR1), have been found to be released by osteolytic tumour cells. Intraosseous implantation of osteolytic sarcoma cells in mice resulted in significant discomfort, peripheral nerve remodelling, and nociceptor sensitization, as well as enhanced TRPV1 expression in the sciatic nerve's distal branches. This was related to cancer cells secreting VEGF ligands that bind to VEGFR1 on sensory afferent fibres, since sensory neuron-specific VEGFR1 deletion and pharmacological blockage of VEGFR1/VEGF signalling lowered cancer pain and decreased peripheral nerve sprouting into the tumour stroma. [74] Furthermore, bone cancer cells secrete granulocyte-colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF), both of which have receptors on local peripheral nociceptor afferents, which sensitise nerve fibres and cause peripheral sprouting. The activation of receptors for granulocyte-colony-stimulating factor and GM-CSF resulted in peripheral sensitization and pain behaviours, as well as enhanced nerve sprouting and tumour development. Loss of this signalling axis in mice was caused by pharmacologic suppression of G-CSF or GM-CSF signalling, which resulted in decreased bone cancer

pain, peripheral nerve sprouting, and tumour development. Furthermore, RNA interference-mediated suppression of GM-CSFR in sensory neurons reduced bone cancer pain and intratumoral nerve sprouting, demonstrating a tumor-nerve signalling pathway. [73] Although it was not investigated if this affected osteoclast numbers, activity, or bone degradation, it is probable that G-CSF or GM-CSF affects osteoclastogenesis, as proven in a noncancer mouse model. [48] It's worth noting that nociceptive sensory neurons have been demonstrated to contribute to tumour development and progression in a number of preclinical cancer models, in addition to understanding nerve sprouting in the context of cancer pain. [55,69,70,103] As a result, nerve sprouting has significant consequences for cancer pain and progression. Cancer-induced sensory nerve sprouting has been seen in a range of preclinical models [6,41,42,51] and is regulated by a number of variables, including bradykinins, endothelins, and growth factors, which also contribute to peripheral sensitization and pain. [42,57] Neuron growth factor (NGF) generated by macrophages and cancer cells, in particular, appears to play a key role in nerve sprouting by binding to the tropomyosin receptor kinase A receptor found on sympathetic and nociceptive sensory nerve fibres. [41,42] In a mouse model of prostate cancer-induced bone discomfort, preemptive (before nerve sprouting) or late-stage injection of an anti-NGF neutralising antibody reduced nerve sprouting and cancer pain. [42] In patients with metastatic cancer who were also taking daily opioids, phase 2 clinical trials with intravenous administration of tanezumab, an anti-NGF monoclonal antibody, resulted in significantly improved pain scores over a 16-week period, validating efforts to further develop anti-NGF therapies. [77]

Surprisingly, central sensitization caused by peripheral bone cancer also results in the activation of spinal microglia and astrocytes, which maintain central sensitization and aid in the pathogenesis of bone cancer pain [91,95,102], as well as chronic pain in a range of other injury situations. [17,40] The receptive field size and ratio of wide dynamic range (WDR) and nociceptive-specific neurons were significantly increased in a rat model of CIPB in which MRMT-1 mammary tumour cells were administered via intratibial injection, a change that reflects local plasticity indicative of central sensitization. [81]

Tumor-bearing rats had more WDR neurons in the superficial dorsal horn (SDH), which enhanced the likelihood of responding to low-threshold peripheral inputs and likely contributed to allodynia's clinical characteristics. [81] The onset of cancer-induced behavioural hypersensitivity in rats is tightly linked to changes in surface SDH plasticity. [27,95] Sustained treatment with gabapentin, a potent modulator of spinal calcium channel activity that leads to decreased neurotransmitter release from afferents, was shown to reverse these pathological

changes in plasticity, implying that gabapentin could be useful in the treatment of cancer-induced bone pain. [28]

Therapeutics that target osteoclasts, nociceptors, cancer cells, or any other cell type that reduces peripheral afferent input are likely to help attenuate pathological alterations in central sensitization, such as glial cell activation and neuronal plasticity in the superficial SDH. Intrafemoral injection of 2472 osteolytic sarcoma cells into mice resulted in significant bone loss, spontaneous discomfort, and astrocyte activation. Osteoclastogenesis, bone degradation, cancer-induced pain behaviours, and spinal astrocyte activation were all significantly decreased when osteoprotegerin (OPG), a soluble decoy receptor of RANKL, was given. [37]

This study also shows how difficult it is to distinguish between the relative contributions of tumour cells, osteoclasts, and activated spinal glial cells to nociceptor activation and pain in bone cancer because each of these components is intricately linked, making it difficult to change one without affecting the others.

Microglia and macrophages, both members of the myeloid cell lineage, have been shown in preclinical investigations to have a role in pain aetiology, albeit in a sexually dimorphic way (eg, differently in males and females). [17,18,52,78]

In male but not female mice, intrathecal (spinal) treatment of microglial inhibitors such as minocycline and propentofylline, or microglial ablation with MAC-1-saporin toxin, is sufficient to reduce nerve injury-induced pain. [78] Female mice adopt an adaptive immune cell-driven strategy in the absence of microglia. [78] Microglia have been discovered to contribute to bone cancer pain, hence sex dimorphism may be depending on the pathological pain state in issue. Intra-tibial injection of Walker 256 mammary gland cancer cells in female rats resulted in strong mechanical and thermal hypersensitivity as well as spontaneous pain, which was associated by strong spinal microglia activation. Microglia suppression with intrathecal minocycline dramatically reduced mechanical and thermal hypersensitivity in this paradigm, suggesting that microglia may play a role in bone cancer pain in both males and females. [95] Similarly, macrophages appear to play a role in the development of pathological pain in numerous animals [18], although males and females may use different signalling systems. [52] At this time, no evidence of sexual dimorphism in osteoclast contribution to cancer pain has been found, and no male- or female-specific pronociceptive osteoclast signalling pathways have been revealed. As a result, it will be fascinating to observe if osteoclasts, like microglia and macrophages, contribute to bone cancer pain or other chronic pain syndromes in a sexually dimorphic manner.

5. Therapeutic targets for bone cancer pain: effects on cancer pain, bone destruction, and tumor growth

5.1. Food and drug administration (FDA) FDA-approved treatments for bone cancer pain

To prevent bone deterioration and alleviate bone cancer pain, a small number of treatment options directly targeting osteoclasts have been developed for primary or metastatic bone cancer. The clinical gold-standard therapy for metastatic bone cancer pain is bisphosphonates such as pamidronate, clodronate, and zoledronic acid. [22,29] Bisphosphonates are taken up selectively by active osteoclasts and interfere with cellular metabolism, resulting in osteoclast death and a decrease in osteoclast-mediated bone resorption and tissue acidosis. [29]

Bisphosphonates diminish both bone cancer-induced SREs and pain when they are successful, although efficacy varies greatly between tumour types [85], with only 50% of patients displaying reduced SREs. Bisphosphonates also have limited anticancer effects, with 30 to 50 percent of patients who take them developing further metastases. [92,100] Long-term use of bisphosphonates has been linked to major consequences such as renal insufficiency and bisphosphonate-related osteonecrosis of the jaw, hence it is suggested that they not be taken for more than 2 years. [83,100]

Apart from bisphosphonates, denosumab is the only other clinically licenced biological therapy for bone cancer metastases and pain that targets osteoclasts. [100] Denosumab is a monoclonal antibody that prevents osteoclastogenesis and subsequent bone resorption by decreasing RANKL signalling, which is needed for osteoclastogenesis and maintaining osteoclast activity. [35]

In compared to zoledronic acid, denosumab delayed the beginning of SREs and the development of moderate/severe pain by roughly 1 month in phase III clinical trials of patients with bone metastases (regarded as the most effective bisphosphonate). [20,76] These results were accompanied by improved quality of life and a decrease in the usage of opioids for pain relief. Denosumab will likely continue to gain appeal as an osteoclast-targeting therapy for metastatic bone cancer because it has been shown to have superior results in pain and SREs when compared to bisphosphonates.

5.2. Prospective bone cancer pain therapeutics emerging from preclinical studies

Several intriguing ways to manage bone cancer pain and/or SREs have emerged from preclinical investigations in addition to the already utilised medicines with shown clinical effectiveness. Some potential therapeutic targets have focused on targeting nociceptors as a step toward providing palliative care (e.g., pain reduction) for patients with a poor long-term prognosis. Intrathecal injection of the TRPV1 super agonist resiniferatoxin (RTX) decreased pain, lameness, and needed treatment unblinding and/or analgesic protocol adjustment substantially later in dogs with bone cancer than in control animals. [8,9] Intra-articular injections of RTX have also been proven to reduce

pain and functional impairment in dogs with osteoarthritis, suggesting that delivery into the bone TME in dogs with bone cancer might be justified. [38] Although these studies focused on cancer pain and functional impairment as their endpoints, nociceptors have been shown to contribute to tumour progression in a variety of preclinical models [55,69,70,103], suggesting that RTX or other nociceptor ablation approaches could have antitumor properties as well. However, because it is currently uncertain whether RTX affects tumour development or osteoclast resorption, its efficacy must be considered in the context of palliative treatment. Selective techniques targeting peripheral terminals within the bone TME have been developed in addition to ablative treatments. In a mouse model of multiple myeloma bone pain, APETx2, a specific antagonist for the ASIC3 receptor, decreased bone pain, indicating that more research is needed. [36] Osteoclasts have also been shown to upregulate the checkpoint inhibitory molecule programmed cell death ligand-1 (PD-L1), which signals through its receptor programmed cell death protein-1, in the presence of a pro-osteoclastogenic milieu (PD-1). PD-L1/PD-1 signalling, in particular, promotes an immunosuppressive environment by inhibiting the activation of T-cell subsets necessary for anticancer immune responses. As a result, medicines that target checkpoint inhibitory pathways like the PD-L1/PD-1 signalling axis have emerged as the gold standard in cancer immunotherapy. [30,54] In a mouse model of bone cancer, anti-PD-1 treatment with the widely utilised monoclonal antibody nivolumab was recently shown to diminish bone cancer pain and osteoclast development. [89] After intrafemoral injection with LLC cells, animals missing PD-1 showed decreased bone cancer pain. Pd1/ mice had pain hypersensitivity and lower osteoclast levels at baseline, which is interesting. [16,89] Through JNK activation and CCL2 release inside the bone TME, PD-L1 increased RANKL-induced osteoclastogenesis. Furthermore, CCL2 directly stimulated CCR2-expressing DRG nociceptors, as indicated by the CCR2 antagonist RS504393's ability to reduce bone cancer pain. [89] Given that anti-PD-1 medicines are currently being utilised in clinical trials for a variety of tumours, this might be a promising new treatment option for patients with primary or metastatic bone cancer who are experiencing pain and bone degradation.

Inhibitors of CSF1 and its receptors have demonstrated therapeutic potential in the same way as denosumab targets OCL regulatory molecules. Pexidartinib (PX3397), a CSF1R inhibitor, has demonstrated clinical effectiveness in various soft tissue cancer clinical studies and has been proven to alleviate pain in mouse and rat cancer-induced bone pain models. There was a significant reduction in pain as well as tumour development, creation of new tumour colonies, and tumor-induced bone resorption by osteoclasts in the mouse and rat prostate cancer-induced bone pain paradigm. [79] Pexidartinib has

progressed to phase 2 clinical trials in patients with metastatic prostate cancer in the bone, although findings are still pending. [12] Given the promising outcomes of preclinical and early clinical studies, more study into the therapeutic potential of CSFR1 inhibitors for primary or metastatic bone cancer pain is needed.

Conclusions

As cancer treatments extend people's lives, providing increasingly safe and effective long-term cancer pain treatments becomes increasingly important. The capacity to give palliative care to patients suffering from severely painful bone cancer pain is crucial to improving their quality of life, even for patients with a poor long-term prognosis. Through indirect pathways involving bone degradation and SREs, as well as direct ones involving nociceptor activation by inflammatory mediators and extracellular acidosis, osteoclasts play a key role in the genesis and progression of bone cancer pain. Overactivation of osteoclasts not only contributes to the aetiology of bone cancer pain, but it also promotes tumour development. Thus, targeting osteoclasts in patients with bone cancer has the potential to give synergistic pain relief while also delaying tumour growth, and several treatments have shown promise in this regard. Bisphosphonates and denosumab are two popular biologics approved to target osteoclasts in the setting of bone cancer, although they're only used for palliative treatment. Other prospective treatments, such as resiniferatoxin and APETx2, directly target nociceptors and are in phase I clinical studies or have demonstrated effectiveness in animal models. Finally, PD-1 antagonists like nivolumab and CSFR1 inhibitors like pexidartinib are relatively new to the field of bone cancer pain, but preclinical models indicate encouraging outcomes that justify further exploration. Further studies aimed at understanding reciprocal interactions between cancer cells, osteoclasts, and nociceptors are likely to generate new therapeutic targets and mechanistic insights, and further studies aimed at understanding reciprocal interactions between cancer cells, osteoclasts, and nociceptors are likely to generate new therapeutic targets and mechanistic insights.

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