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Chapter

Bone Cancer Pain, Mechanism and Treatment

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Abstract

The world health organization (WHO) has predicted a global amount of 19 million cancer cases by 2025. Breast, prostate and lung cancer are common cancer types and show metastasis in 60 to 84% of the cases, with 75 to 90% experiencing life-altering cancer-induced bone pain (CIBP), characterized by continuous, dull progressive pain with movement-induced incident peaks and random breakthrough spikes. Therefore, it is the most difficult pain condition to treat. CIBP is a unique type of pain with neuropathic and nociceptive components. Briefly, an invading tumor cell disturbs the healthy balance of the bone resulting in an acidic microenvironment, activating sensory fibers in the bone. The invaded tumor cell and adjacent stromal cells secrete mediators initiating an immune response with transcriptional signaling, resulting in increased cytokines and growth factors. Sensory nerve fibers are damaged and start to sprout, causing ectopic firing, and as tumors grow in size they activate mechanoreceptors. Aside from bisphosphonates and antibody therapy, CIBP is treated by a range of NSAIDs to strong opioids, but remains undertreated in one-third of cases. This chapter discusses the accompanying CIBP of bone tumors, the mechanism of action and current treatments.

Keywords: CIBP, NOP receptor, RANK/RANKL, NGF/TrkA, IL-6

1. Introduction

Cancer induced bone pain (CIBP) is a big accompanying clinical problem of bone tumors with a high unmet medical need [1]. It is a debilitating form of different pain components that severely affects a patients' quality of life. The complex mechanism of CIBP largely involves the nervous system with transmembrane receptors and channels on the nerve fibers. Briefly, the nervous system consists of the central nervous system, i.e. the brain and the spinal cord, and the peripheral nervous system, i.e. the autonomic (unconscious, the para- and sympathetic nervous system) and somatic (conscious/voluntary) nervous system. A neuron is a nerve cell consisting of a cell body (soma), projections receiving input signals (the dendrites) and a single long arm away from the soma (the axon/fiber) that ends with the axon terminal (synapse). Axons contain a sheath of myelin that serves as isolation in a similar way as plastic around an electrical wire. Regarding the somatic nervous system, neurons with projections towards the spinal cord (afferent) respond to stimuli and are the sensory neurons. The neurons that respond to the brain and the signals from the spinal cord (efferent) are the motor neurons [2].

Pain is the defense mechanism against external factors that could cause tissue damage (a noxious stimuli) and nociception is detecting such stimulus. The

somatosensory nervous system contains the sensory neurons that respond to noxious stimuli (nociceptors). There are three types of nociceptors, receptors that sense 1) thermal, 2) mechanical and 3) chemical stimulants. When a threshold of either one of those three properties is exceeded, the nociceptor is activated – *the neuron depolarizes and an action potential occurs* – and an electrical signal follows through the nociceptive pathway. Two major nociceptive fibers are reasonably fast-conducting A-δ fibers, containing a thin layer of myelin and the unmyelinated slow-conducting C-fibers. Finally, there are thickly myelinated fast conducting A-β fibers, faster than A-δ fibers, primarily for the normal sensation of touch [2].

Pain can be acute, serving a biological purpose, e.g. protection, and chronic, without a biological purpose, becoming an own medical disease more than a symptom [3]. A workgroup from the international association for the study of pain (IASP) has defined chronic pain as a pain that persists for more than 3 months. They defined a subgroup in 2018 where it has been considered that pain can be the primary disease, i.e. in low-back pain. Moreover, they have made subgroups and considered conditions with chronic secondary pain, such as chronic cancer-related pain [4]. The transition to chronic pain involves neuronal plasticity – *the ability of the nervous system to adapt the composition, signaling and structure* – represented by the enhancement of neurons and pain pathways, entitled as central and peripheral sensitization [3]. A very detailed elaboration on the molecular mechanism of sensitization is described by Latremoliere and Woolf (2009). Here, it is important to know that central and peripheral sensitization is a mechanistic explanation for mechanical allodynia (*non-noxious stimuli become painful*), hyperalgesia (*painful, noxious stimuli are prolonged in response and exaggerated*) and secondary hyperalgesia (*pain spreads beyond the site of injury*) [3]. The definition of pain by IASP is: *"An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage"* and for nociception: "*The neural processes of encoding noxious stimuli*" [5]. Pain can be distinguished between injury to the peripheral tissue, nociceptive pain – *Immunologic response* – and pain directly to the nervous system, neuropathic pain. IASP has defined neuropathic pain as: "*Pain caused by a lesion or disease of the somatosensory nervous system*". No specific definition is mentioned for nociceptive pain, however, chronic inflammation is a particular pain-related event, recognized by chemical and inflammatory mediators, affecting nociceptive axons and resulting in lowered thresholds of neuronal excitation [6]. CIBP is a unique type of pain with nociceptive and neuropathic components but the exact mechanism remains unclear.

This chapter elaborates on the mechanism of action of bone cancer pain. Next, a brief subsection of the bone anatomy & physiology. Finally, treatment options used for CIBP and bone metastases are described, including CIBP models to assess novel compounds and the mechanism of action.

2. Bone cancer pain

2.1 Bone anatomy, physiology and innervation

Bones can be classified by their shapes, i.e. flat, short, long and irregular bones [7]. The most common bones that encounter metastasis of tumor cells are long bones [8, 9], i.e. the tibia, femur and humerus, characterized by an extended tubular diaphysis and round-shaped distal and proximal epiphyses [10]. The outer part is covered with a fibrous layer and an inner osteogenic layer, the periosteum and cambium layer, respectively [11]. The latter contains progenitor cells for the bone building cells, osteoblasts [11]. Briefly, mesenchymal-derived cells are the progenitors which are stimulated by the transcription factors core binding factor

α1 (Cbfa1), Osterix (Osx) and activating transcription factor 4 (ATF4) to initiate osteoblastogenesis [12]. Matured osteoblasts secrete bone matrix until they become resting osteoblastic cells (bone-lining cells) [7, 12, 13]. Behind the periosteum are densely packed tube-like structures called osteons (Haversian system). One osteon consists of several layers (lamella) with small gaps (lacunae) in between, containing nutrient transportation cells, osteocytes, constituting 90 to 95% of the bone cells present in the mature human skeleton [7, 13]. Osteocytes originate from differentiated bone-linings cells after they are encapsulated by secreted bone matrix and are suggested to coordinate the location of bone formation or resorption [12]. The packed osteons is the bone matrix, surrounding and protecting the medullary cavity of the diaphysis, containing bone marrow, with a thin connective tissue membrane separating both. The hematopoietic lineage in the bone marrow is responsible for pre-osteoclastogenesis [14, 15]. The macrophage colony-stimulating factor (M-CSF) stimulates the progenitor bone marrow cell for differentiation into a pre-osteoclast, initiating the expression of the receptor activator of NF-κB (RANK) receptor [16, 17]. The osteoblasts express the opposite part of the RANK receptor, necessary for activation, the RANK ligand (RANKL). Upon activation of RANK by RANKL the osteoblasts ensure that several activated pre-osteoclasts fuse together, forming a larger multinucleated mature osteoclast [16]. A mature osteoclast is a specialized macrophage with multiple mitochondria and lysosomes, prepared for bone degradation [14, 15]. In addition, the cell–cell fusion process of pre-osteoclasts forming a mature osteoclast has a checkpoint, the stromal cells, which have the ability to interfere by secretion of Osteoprotegerin (OPG). This is a decoy receptor able to bind excessive levels of RANKL, preventing over-population of osteoclasts [9, 16, 18, 19]. Subsequently, the degradation of bone is initiated after maturation of osteoclasts and their allocation to the site-of-destruction, where they form a closed space, the resorption lacuna. Activation of H^+-ATPase proton pump and Cl/HCO_3 exchanger by osteoclasts follows, in combination with the secretion of lysosomal enzymes and active protease Cathepsin K into the lacuna [15]. The net effect of this cascade is an acidic environment of pH ± 4.5 to degrade the nearby bone cells [9, 15]. This triad of RANK/RANKL/OPG that regulates osteoclast activation is an important process in healthy bone physiology and plays an important role during bone cancer pain development [16–20]. Finally, At the level where the diaphysis reaches the proximal epiphysis, the medullary cavity is more spongy-like and is called trabecular or cancellous bone. Both epiphyses are composed primarily of spongy bone and a small quantity of compact bone, surrounded by cartilage [7].

Nociceptors are necessary to let the brain perceive CIBP, however, very little is known regarding the innervation of bone with sensory nerve fibers. Immunoreactivity studies have shown that sensory neurons are present in periosteum, cambium, bone matrix, Haversian canals and in bone marrow in the medullary cavity, and no detection was found in the articular cartilage of the epiphysis [21–29]. The density (nerves per unit area) of sensory fibers is largest in the periosteum, followed by bone marrow, mineralized bone and articular cartilage consisting in a ratio of 100:2:0.1:0, respectively [9, 10, 28]. Up to 80% of the nerve fibers innervating the bone have been shown TrkA positive [22], suggesting innervation of mostly thin myelinated Aδ-fibers and unmyelinated C-fibers [9, 10, 29, 30]. It seems that the fast conducting, highly myelinated Aβ-fibers do not contribute, or very scarcely, to the innervation of sensory neurons in the bone [29].

2.2 Epidemiology and primary vs. secondary tumors

The world health organization (WHO) report from 2014 predicted that a total of 19 million cancer cases exist globally in 2025 [18] and in 2018 a WHO press release

announced that lung (2.09 million cases), breast (2.09 million cases), colorectal (1.08 million cases) and prostate (1.28 million cases) are the most common [31]. All of these, except for colorectal, follow a high pattern of bone metastasis in 60 to 84% of the cases [9, 32]. In breast and prostate cancer patients particularly, it is expected that 90% develop bone metastases [33, 34]. Additionally, there are primary bone tumors that have their origin within the bone and the most common type is an osteosarcoma with a worldwide incidence of 3.4 cases per million people per year [35]. In pediatrics it accounts for 3 to 5% of the cancers and in adults less than 1% [8]. Tumors can affect osteoblasts, resulting in osteoblastic lesions and in contrast affect osteoclasts, causing osteolytic lesions [36]. Primary bone tumors, e.g. osteosarcoma, are more osteolytic [37], prostate cancer seems more osteoblastic and breast cancer osteolytic [38]. The latter two have been observed in 1/4th of the cases to be mixed [39]. A specific group of well-known signaling proteins, the Wnt pathway, is suggested to shift tumors towards an osteoblastic phenotype as blockage showed a highly osteolytic tumor [40]. This pathway has been observed to directly enhance osteoblast differentiation and bone formation, whereas indirectly inhibits osteoclast differentiation and bone resorption by OPG production from osteoblasts and osteocytes [41].

Some cancer patients encounter bone tumors without the presence of pain. Unfortunately, 30 to 50% of the patients will experience mild to moderate pain and in advanced cancer patients 75 to 90% have life-altering pain [37, 42]. The most prevalent type of pain experienced is bone cancer pain [9, 17, 33], which patients describe as a persistent presence of a dull ache that increases in intensity over time [32]. They start noticing mechanical allodynia during normal activities, such as coughing, turning in bed or gentle limb movements [43]. Furthermore, there is incident pain, that occurs when the pain spontaneously intensifies as a result of weight-bearing or during movement. Finally, there are breakthrough events of very sharp intense pain that can happen during rest [9, 32]. These breakthrough pain episodes occur in 40 to 80% of the patients with a median of 4 episodes per day, lasting up to 30 minutes [44]. Particularly the incident and breakthrough pain events are devastating for the quality of life and are considered as most difficult pain conditions to treat [9, 33].

2.3 Mechanism of action of bone cancer pain

The Aδ-fibers are recognized to be important in acute pain, whereas C-fibers are the slower conducting sensors that account for physiological changes such as "second pain" [9]. It has been observed during chronic pain that these start sprouting and show enhanced spontaneous activity, ectopic firing, resulting in allodynia and hyperalgesia [45–48]. Important surface channels and receptors of Aδ- and C-fibers involved in nociceptive signaling are TrkA, acid sensing ion channels (ASIC), Transient receptor vanilloid-1 (TRPV1), P2X receptors, endothelin receptor (ET-1), bradykinin receptor (B_2R), prostaglandin (PGE_2) receptor, the voltage-gated sodium channels Na.v1.7–1.9 and cytokine receptors [9, 18, 29, 49].

The mechanism of CIBP in osteoblastic lesions is poorly understood and the most influential factors described are bone morphogenetic factors and endothelin-1. The mechanisms in osteolytic lesions have been better elucidated [36]. First, the infiltrating tumor cells start an interaction with the stromal cells, resulting in a cascade of different pathways, shown in **Figure 1**. A primary effect on sensory nerve fibers occurs as the secreted mediators, e.g. NGF, PGE_2, transforming growth factor-β (TGF-β), bradykinin, endothelin, cytokines (e.g. IL-1, IL-6, IL-8, IL-11 and IL-17) are ligands for the receptors and cause excitation of the nerve fibers [17, 22, 29, 50–53]. It has been shown in a rat CIBP model that IL-6 plays a pivotal

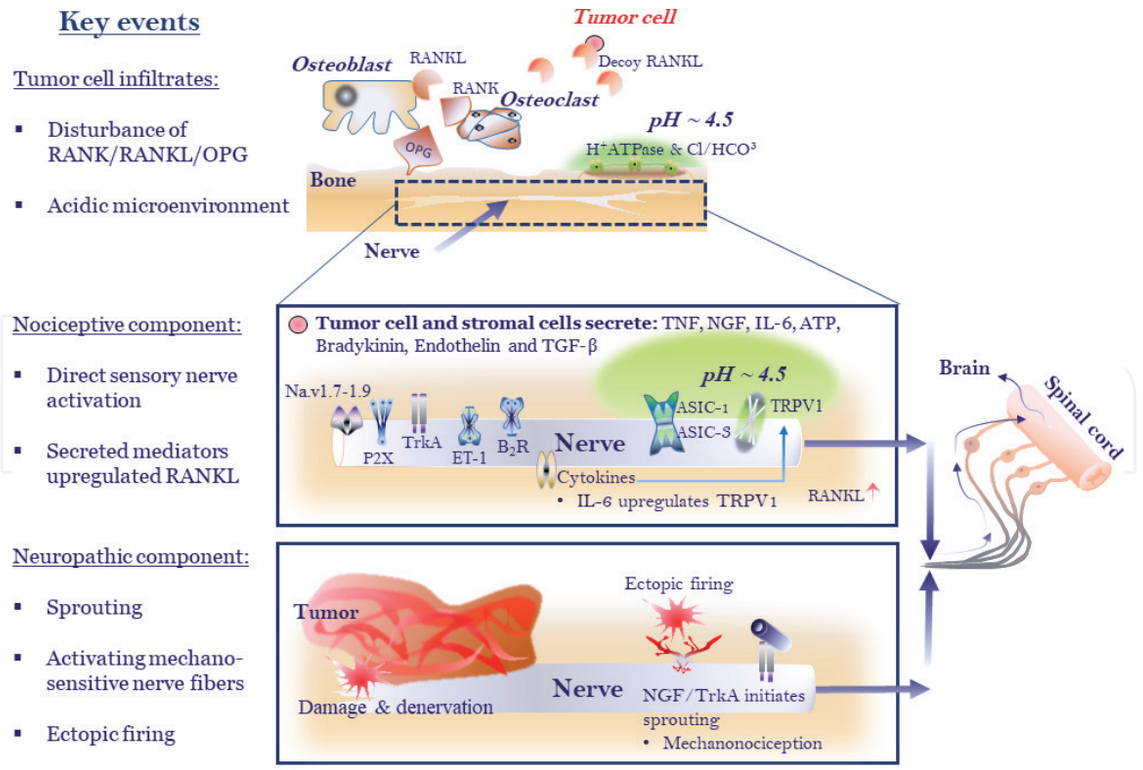


Figure 1.
The cascade of events responsible after infiltration of a tumor cell, resulting in CIBP with a nociceptive and neuropathic component. First, disturbance of the RANK/RANKL/OPG triad. Next, the nociceptive component; an acidic environment occurs, directly activating sensory nerve fibers and secreted mediators contribute to the upregulation of RANKL. In addition, the neuro-inflammatory mediator upregulates TRPV1 channels. The neuropathic component; nerves are damaged and denervate, resulting in ectopic firing and sprouting and an enlarged tumor activates mechano-sensitive nociceptors. The NGF/TrkA is pivotal in the process of sprouting and thereby for hypersensitivity. RANK = receptor activator of NF-κB, RANKL = RANK ligand, OPG = osteoprotegerin, Na.v1.7–1.9 = sodium channels, P2X = purinergic receptor, TrkA = Tromomyocin receptor kinase a, NGF = nerve growth factor, ET1 = endothelin receptor, B_2R = bradykinin receptor, ATP = Adenosinetriphosphate, IL-6 = interleukin-6, ASIC = acid-sensing ion channel, TRPV1 = transient receptor vanilloid-1, TGF-β = transforming growth factor-β, TNF = tumor growth factor.

role by sensitizing nociceptive fibers, mediating peripheral and spinal sensitization [54] by upregulation of TRPV1 receptors via JAK/PI3K signaling in dorsal root ganglia neurons [55]. In addition, PGE_2, TGF-β, IL-1, IL-6, IL-8, IL-11 and IL-17 showed to be involved in a secondary effect, namely the ability to increase the expression of RANKL and decrease OPG [17, 19, 52, 56]. TGF-β is also released by the bone matrix and stimulates osteolytic bone destruction of cells close to the tumor cells [56]. The normally present OPG that serves as a peace-keeper between osteoclasts and osteoblasts is overwhelmed by the excessive amounts of RANKL, resulting in exaggerated activity of osteoclasts [19]. Consequently, osteoclastogenesis is initiated resulting in many resorption lacunae creating an acidic environment [20]. Additional pro-inflammatory cells become active, secreted cytokines bind their designated receptors and proton (H^+ & Na^+) amounts increase, lowering the pH and thereby triggering P2X7 and TRPV1 receptors, and ASICs [1, 20, 49]. The rapid Na^+ influx is associated with ASICs and a second slow current activated at pH < 6.2 is typical for TRPV1 [20]. Subsequently, tumor cells release NGF, tumor necrosis factor (TNF), IL-1 and IL-6, chemokines and endothelins which contribute to further develop an acidic environment [32]. This could be the explanation regarding the difficulty of treating CIBP [29].

Next to the nociceptive component of CIBP is the neuropathic component, caused by damage or denervation of nerves, pressure of tumors on the nerves

and sprouting. The degradation of bone and the damage that occurs can activate mechanosensitive ion channels, e.g. TRPV, ASIC and P2X7 [29, 57, 58]. Activated NGF regulates the maintenance of the peripheral sensory neuron system and initiates sprouting of adjacent non-injured afferents upon injury or denervation, resulting in collateral sprouting [59, 60]. Random sprouting of sensory neurons co-expressing TrkA was shown in prostate cancer metastases [9, 48] and similar in breast cancer metastases [47]. Hypersensitivity occurs as a result of sprouting, causing sensitization of sensory nerves, which in its turn induces mechanonociception (by Aδ-fibers) [59]. Changes also have been shown to occur in the central nervous system in the spinal cord where the excitatory synaptic transmission mediated through A-δ and C-fibers was enhanced [61].

On the one hand, it is suggested that the increase in activated osteoclasts causes the development of CIBP while on the other hand the secreted mediators directly exciting sensory nerve fibers is suggested to be the primary explanation [17, 51]. Nevertheless, all these multidisciplinary factors – *neurological, oncological and immunological* – contribute to CIBP and while they are described extensively, the exact mechanism remains to be elucidated.

3. Treatment of bone cancer pain

When a patient experiences bone cancer pain, the first step of therapy is tumor eradication, i.e. via chemotherapy and radiation, unfortunately in <50% of the patients the pain levels will return to pre-treatment levels [62]. Radiotherapy, described as the golden standard palliative therapy, shows full pain relief in 25% of treated patients, however, only after a month [29]. Different radiotherapy protocols showed a single radiotherapy fraction (8Gy) provides equal pain palliation compared to multiple fractions (30 or 20 Gy in 10 or 5 fractions, respectively) [63]. Low fractionated radiotherapy also caused a higher incidence of pathological fractions at site of irradiation [1]. Chemotherapy is an option for the treatment of CIBP when the tumor histology is more nociceptive, the patient did not previously receive chemotherapy and when the tumor is chemosensitive [64]. However, oxaliplatin and paclitaxel are used for animal models of induced-neuropathy to investigate hypersensitivity [65, 66].

3.1 Bisphosphonates

Bisphosphonates are agents that are often used to treat pain as a symptom [67]. They act by inhibiting farnesyl diphosphate synthase in phagocytic cells, e.g. osteoclasts, macrophages and microglia, thereby decrease extracellular acidification and consequently reduce ASIC- and TRPV1-mediated activation of nociceptive primary afferents located in bone [67]. Other effects of bisphosphonates unrelated to farnesyl diphosphate synthase inhibition that have been suggested are interactions with purinergic receptors, e.g. P2X7. The bisphosphonate zoledronate exerted an analgesic effects in rat CIBP models [68]. It is the most widely used bisphosphonate, also observed to significantly reduce CIBP in clinical practice for breast cancer metastases [69], being 100 to 1000 times more effective than pamidronate [70]. Furthermore, anti-inflammatory effects have been indicated where alendronate inhibited TNF-α, IL-1, IL-6 and NGF [67].

3.2 Monoclonal antibody therapy

Monoclonal antibody therapies have the ability to interfere with tumor-induced processes, e.g. RANK/RANKL, NGF/TrkA, and inhibit or avoid cytotoxic T

lymphocyte [71]. A hand full of these therapies have been FDA approved for cancer therapy and a small amount has been tested in breast, prostate or lung cancer metastases [71]. Tanezumab is a monoclonal antibody interfering with NGF/TrkA and has been described unbeneficial in one CIBP study [72], however, has also been shown to attenuate late stage cancer pain [73]. Denosumab is another monoclonal antibody and acts by interfering with the interaction between RANK/RANKL, capturing RANKL, resulting in osteoclast inactivation [74]. Denosumab has been tested as treatment in breast cancer metastases and while it showed a good activity profile for delaying or preventing skeletal related events, no direct relief of pain has been described. Nevertheless, the delay and/or prevention of skeletal related events would have an indirect pain-impairing potential as such events are associated with pain and increased morbidity [75]. Denosumab did show superiority concerning first on-study skeletal-related events compared to zoledronate [76]. Similar outcomes were found by a meta-analysis of 4 RCTs between denosumab and zoledronate [77]. Regarding the dosing, a study showed no difference between 4-weekly and 12-weekly administration for denosumab and the two bisphosphonates zoledronate and pamidronate, suggesting that incorporating 12-weekly dosing could benefit patients [78]. Denosumab seems to be the only antibody therapy so far that is approved for direct treatment of skeletal-related events with bone metastases from solid tumors and giant cell tumors of the bone [71]. Ipilimumab is an antibody that activates the immune system, specifically, inhibits an inhibitory mechanism of cytotoxic T lymphocytes. It was tested in metastatic prostate cancer in combination with radiotherapy and suggested clinical antitumor activity [79]. Nivolumab therapy was recently tested in lung cancer metastases into the bone and showed that 40% of the treated patients had osteosclerotic change on CT scans, indicating successful treatment of bone lesions [80]. The small amount of monoclonal antibodies used for bone metastases often have skeletal related events as indication of efficacy but lack bone cancer pain as direct outcome measure. Currently there are no recorded monoclonal antibodies specifically targeting CIBP.

3.3 Analgesics: NSAIDs and opioids

Available options for the direct treatment of CIBP are analgesics. The WHO has established a 3-step ladder as a guideline for analgesic prescription in 1986 and revised the version in 1996 with a quick guide to opioid availability [81]. Afterwards, the stigma on opioid prescription was broken and received acceptance as treatment for (chronic) pain conditions [82–84]. The 3-step ladder starts with non-opioids (Step 1) for mild pain, weak opioids ± non-opioids and adjuvants for mild to moderate pain (Step 2), and strong opioids ± non-opioids and adjuvants for moderate to severe pain (Step 3) [85].

First in line are NSAIDs that inhibit the enzyme cyclooxygenase-2 (COX-2), responsible for PGE synthesis [64]. A challenge with NSAIDs is that they reach a ceiling effect in analgesic efficacy [81, 86]. Increasing the doses does not result in increased efficacy, conversely, side effects worsen, further impairing the quality of life of patients [86, 87]. Second in line are weak opioids, e.g. codeine, tapentadol or tramadol, in combination with adjuvants, indicating proven analgesic efficacy in bone cancer pain [88]. There are three classical opioid receptors, e.g. the μ-, δ- and κ-opioid receptors (MOP, DOP and KOP receptor, respectively) and the later discovered Nocicpetin/OrphaninFQ opioid peptide (NOP) receptor [89]. These receptors are G-protein coupled receptors and upon activation initiate an intracellular cascade resulting in 1) the inhibition of adenylate cyclase (responsible for cAMP production), 2) opening of inwardly rectifying K^+ channels and

3) closing of voltage-gated Ca^{2+} channels [89]. Caution must be exercised with weak opioids as the rate of metabolism by Cytochrome P450 enzymes defines analgesic efficacy and side effects. In addition, codeine seemed effective for only 1 month until strong opioids were necessary for adequate analgesia [90, 91]. A randomized RCT trial showed significant impairment of cancer pain by low-dose morphine compared with weak opioids, with similar tolerability and an earlier effect, suggesting low-dose morphine can be used [90, 92]. This forwards the therapy option towards Step 3 and to date, the first choice to treat moderate to severe pain with strong opioids remains morphine [90, 93]. MOP receptor drugs have shown superior analgesic efficacy and have been used for centuries as they seem to be the most potent analgesics [94]. Available options for administration are oral and transdermal, showing similar efficacy, and advocated is the use of epidural or intrathecal pumps if relief is inadequate [90]. Concerning side effects of MOP receptor drugs are addiction and dependency. The opioid crisis is prove and accounted for 33.000 deaths per year in the US by opioid misuse [94–96]. In addition, cancer survivors showed higher opioid prescription compared to controls [97]. The total estimated economic burden due to opioid addiction, dependency, abuse and overdose is $78.5 billion, from which $28.9 billion is due to increased health care and abuse treatment [98]. Furthermore, analgesic efficacy of MOP receptor compounds is affected by long term opioid treatment as tolerance develops over time [99, 100]. This is inevitable in cancer patients since high doses are required for pain management [101]. The mechanism that contributes pre-synaptically to tolerance remains to be elucidated but TRPV1 receptor upregulation in spinal cord and dorsal root ganglions has been shown to accompany tolerance [99, 100].

Challenging is to find analgesics with a similar potency and efficacy compared to MOP receptors, without dependency and addiction. Targeting the DOP and KOP receptor showed efficacious pain relief with a lower abuse potential, making them promising targets for treating pain [102]. Specifically for CIBP, both DOP and KOP receptor agonists showed pain attenuation in animal models of CIBP [103, 104]. It has been shown that a selective KOP receptor agonist blocked pain without altering bone loss, tumor size or cancer cell proliferation [105]. Additionally, a DOP receptor agonist showed equal analgesic efficacy and 4.5-fold potency compared to morphine in a mouse CIBP model [106]. Despite potential analgesic efficacy, MOP receptor agonists remain the clinical mainstay [107, 108]. Interest in the NOP receptor increased after the discovery of similar, yet distinct features compared to the classical opioids [109]. The effects of classical opioids are immediately blocked by naloxone and independently of administration location, they attenuate pain. The analgesic NOP receptor effect remains after naloxone and interestingly, spinal or peripheral activation exerts anti-nociceptive effects, while supra-spinally it acts pro-nociceptive [85, 109]. Following these discoveries, the NOP receptor showed anti-rewarding and anti-abuse effects in rodents [85, 110–113]. Furthermore, NOP receptor expressing Chinese Hamster Ovary cells showed rapid internalization after activation and a quick recycle process to reactivate receptors occurred at the membrane, potentially reducing the development of tolerance. However, compensatory mechanisms that remain to be elucidated may be overlooked [114]. The NOP receptor has been specifically used to target CIBP and both the endogenous ligand Nociceptin and a synthetic selective NOP receptor agonist (Ro65–6570) showed significant analgesia [85]. Furthermore, NOP receptor activation downregulates IL-6 production [115] and is suggested to inhibit T cell proliferation [116]. Altogether, the anti-rewarding and anti-abuse effects, cytokine production involvement and selective attenuation of CIBP, makes the NOP receptor an interesting target.

3.4 Primary vs. secondary tumor treatment

Differences should be kept in mind when treating tumors, nevertheless, anti-NGF antibody therapy has been observed to relief early and late stage CIBP in a primary bone tumor model and a metastatic-like prostate bone cancer model [37]. In addition, zoledronate has been shown effective in reducing the risk of skeletal related events in multiple myeloma, prostate and breast cancer bone metastasis [117]. Denosumab indicated superiority to zoledronate in preventing skeletal related events in bone metastasis compared to solid tumors, suggesting a treatment option for bone metastasis [118]. Primary bone tumors are characterized by high complexity and heterogeneity in genomic alterations and are therefore challenging for developing targeted therapeutic strategies [41] which also may not satisfactorily address their metastatic counterparts [119].

3.5 Non-pharmacological interventional treatment

The WHO analgesic ladder has proven to be very helpful, nevertheless, an estimated 12% of patients remains inadequately treated for CIBP [120]. Therefore, a fourth step has been proposed that includes interventional approaches to provide a minimal acceptable quality of life [120–122]. As such, percutaneous neurolysis is performed using chemical agents or thermal energy upon celiac plexus, splanchnic nerve, superior hypogastric plexus, brachial plexus and epidural and intrathecal [120, 122]. Commonly used neurolytic agents are absolute alcohol (diluted to 50% alcohol), 6% aqueous phenol and 6% phenol in glycerine [120].

Finally, PET/CT allows the distinction between osteolytic and osteoblastic lesions and thereby detect more subtle responses to treatment regimens [123]. Using CT in the surgical planning could shift the priority of debulking dense bone to surgical reconstruction when bone metastasis is more osteolytic instead of osteoblastic [39].

4. Bone cancer pain: research techniques

The current treatments are often targeted against pain as a symptom and therapy options specifically for CIBP are rare. To elucidate the complex mechanism of action of CIBP and develop novel analgesics, further research is warranted. As such, *in vitro* techniques are an option, however, these capture a minor aspect of the complexity and as long as no technique exists that simulates this, *in vivo* research is inevitable. Nevertheless, it should be conducted highly ethically and additional regulations were established in 2009 to maintain the animals' welfare by following 3R's (Reduction, Refinement and Replacement) [124]. Furthermore, to test a nociceptive phenotype in a comfortable manner, more focus is towards animals' ethological and evolutionary preserved behavior. Finally, the *in vivo* model that is used should represent the disease and clinical symptoms as close as possible. Three criteria are important in the validation of animal models [125], 1) Face validity: the biology and symptoms as seen in humans are similar in the animal model, 2) Predictive validity: if the clinical intervention has an equal response in the animal model and 3) Construct validity: the target one is investigating exerts the same biological processes in both organisms, e.g. opioid receptors are responsible for pain relief.

4.1 *In Vivo* models for bone cancer pain

At start, to reflect metastases as closely as possible, cancer cells were injected either intravenously or intra-cardially. Face validity is achieved but uncontrolled

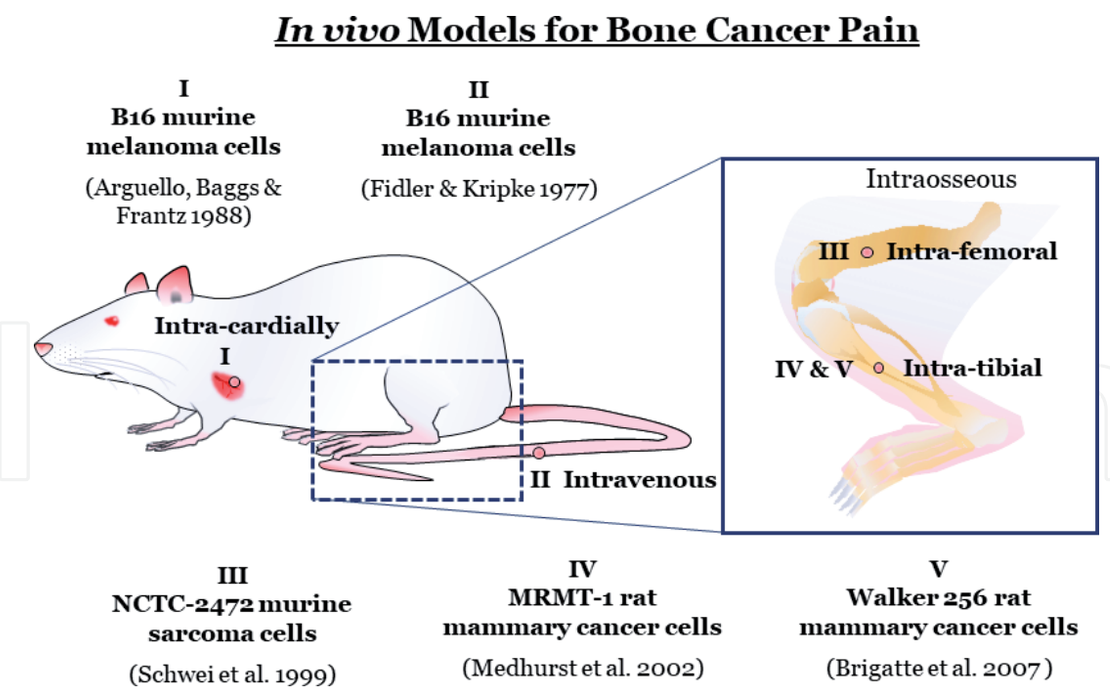


Figure 2.
A representation of the different in vivo models to study cancer induced bone pain.

growth of tumors occurs [32, 126, 127]. Next came the technique of injecting osteosarcoma-derived mesenchymal cells (NCTC-2472) directly into the long bones of mice [128]. This technique indicates good face and predictive validity, resulting in a controlled late-phase CIBP model, reflecting the clinical course with a comparable responsiveness to systemic opioid treatment [32, 128]. Finally, construct validity had been optimized using syngeneic cell lines (originating from the same species). The first example was rat mammary gland carcinoma cells (MRMT-1 cell line) inoculation into the tibia of rats [129]. The main characteristics after inoculation of cancer cells are: development of allodynia and hyperalgesia, progressive tumor growth, profound destruction and rebuilding of bone and no external tumor growth into other organs. In addition, upregulation of TNF-α, Interferon- γ (IFN-γ), IL-1β, IL-4, IL-10 and IL-6 occurs in tumor-bearing animals [49, 130]. Fine-tuning occurred with another rat breast cancer cell line (Walker 256 cells) inoculated into the tibia [131]. This model has been reviewed extensively and develops spontaneous pain, hyperalgesia, allodynia as well as ambulatory pain, indicates progressive tumor growth with osteolysis and no external growth, including upregulation of IL-1β, NGF, PGE_2, IL-6 and TNFα [132]. This model has been subjected to a detailed pharmacological profiling using standard analgesic drugs for CIBP in a clinical setting and is suggested to be one of the most suitable preclinical models for novel compound identification and assessment [132, 133]. No study has been conducted comparing the Walker 256 model with the MRMT-1 model (**Figure 2**).

5. Conclusion

Cancer-induced bone pain (CIBP) causes life-altering pain in 75 to 90% of the advanced stage cancer patients. The movement-induced incident and breakthrough events cause a severe impairment of the quality of life of patients and explain the difficulty to treat this unique type of pain. There remains a high unmet medical need for CIBP treatment since around one-third of the advanced cancer patients

is still undertreated [90]. Apparent from the mechanism of actions is that CIBP concerns distinct processes and could be treated by pharmacological and non-pharmacological options. Strategies are to combine therapies, such as co-administration of zoledronate via a new innovative nano-agent with cisplatin and alendronate for breast cancer metastases and bone resorption, showing remarkable inhibition of tumor cell proliferation, osteoclast activation and bone pain relief [134]. Mixed ligands are another strategy, such as Cebranopadol, a mixed NOP/Opioid receptor ligand, indicating antinociceptive and antihypersensitive effects in a rat model of CIBP [135]. A meta-analysis comparing the efficacy of NSAID, opioids and monoclonal NGF antibodies indicate the latter provide superior pain relief, noteworthy is that this was in osteoarthritis [136]. As new strategies are arising, bisphosphonates and denosumab are the first-line therapies for bone metastases [38] and continuing research is warranted to elucidate the CIBP mechanism for identifying novel analgesic compounds.

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