HHS Public Access

Author manuscript

Curr Opin Support Palliat Care. Author manuscript; available in PMC 2021 June 01.

Published in final edited form as:

Curr Opin Support Palliat Care. 2020 June ; 14(2): 107–111. doi:10.1097/SPC.0000000000000496.

Potential Therapeutic Treatments of Cancer Induced Bone Pain

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Abstract

Purpose of Review: The treatment of cancer-induced bone pain (CIBP) has been proven ineffective and relies heavily on opioids, the subject of highly visible criticism for their negative side effects. Alternative therapeutic agents are needed and the last few years have brought promising results, detailed in this review.

Recent findings: Cysteine/glutamate antiporter system, x_c^-, cannabinoids, kappa opioids, and a ceramide axis have all been shown to have potential as novel therapeutic targets without the negative effects of opioids.

Summary: Review of the most recent and promising studies involving CIBP, specifically within murine models. Cancer pain has been reported by 30-50% of all cancer patients and even more in late stages, however the standard of care is not effective to treat CIBP. The complicated and chronic nature of this type of pain response renders over the counter analgesics and opioids largely ineffective as well as difficult to use due to unwanted side effects. Pre-clinical studies have been standardized and replicated while novel treatments have been explored utilizing various alternative receptor pathways: cysteine/glutamate antiporter system, x_c^-, cannabinoid type 1 receptor (CB1R), kappa opioids, and a ceramide axis (S1P/S1PR1).

Keywords

cancer-induced bone pain; antiporter system x_c^-; CB2; kappa opioid; S1P/S1PR1

Introduction

The prevalence of cancer, with almost 40% of Americans receiving a diagnosis at some point in their lifetime, has brought enough attention to research that treatments and care have been studied and improved, subsequently increasing life expectancy [1]. Increased lifespan in patients can result in more complicated, harder to treat pain, and decreased quality of life. When cancer metastasizes to bone, causing cancer-induced bone pain (CIBP), it presents a unique issue to the condition with many treatment challenges, including complex pain management.

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Conflicts of interest

The authors have no conflicts of interest to report.

Unlike other types of cancer pain, CIBP has elements of acute, inflammatory and neuropathic pain, as well as characteristics unique to the condition, discussed in great detail in a review by Falk and Dickenson of the University of Copenhagen [2]. Acute pain consists of afferent fiber activation through extreme temperature, mechanical or chemical injury to surrounding tissue, i.e. fracture of a diseased bone. Inflammatory pain occurs through mediator cells released by damaged tissue and creates changes in the central nervous system, a symptom of the acidic tumor environment within the bone [2]. Neuropathic pain is caused by damage to sensory nerve fibers and the subsequent changes in ion channels, caused by tumor burden to nerves or chemotherapy. In addition, CIBP manifests through different experiences of pain: chronic, breakthrough, and incident (movement-induced) [3]. Breakthrough pain, intense but brief, can often cause difficulty with movements and interrupts general life, while chronic pain is often dull and lasting, that can be quite intense and debilitating. The unpredictable nature of breakthrough pain and the longevity of chronic pain create a challenge in treating pain. The standard of care, currently consisting of over the counter analgesics and a range of opioids, cannot treat this unique combination of pain effectively [4].

Specifically, opioid-based pain management for CIBP is ineffective because of its dose-limiting effects and negative impacts on bone remodeling [5]. Opioids have been proven to be highly addictive with the potential of a fatal overdose, making them dangerous for treating both very intense and long-lasting pain. Furthermore, patients taking opioids for chronic pain quickly develop analgesic tolerance and are often unable to achieve the same pain relief over time [6]. Opioids add an additional burden on those being treated for CIBP because they can slow or stop bone remodeling and even increase bone brittleness, greatly impeding the treatment of bone cancer [7]. These shortcomings, combined with a handful of other painful and inconvenient side effects, such as constipation and sedation, demonstrate the need for novel treatments for CIBP. Fortunately, over the last 18 months, substantial progress has been made in understanding CIBP, with studies published on many potential therapeutic targets such as cysteine/glutamate antiporter system x_c^-, cannabinoids, kappa opioids, and sphingosine-1-phosphates, all of which will be described in this review.

Standards for Evaluation

In order to investigate alternative CIBP treatments, it’s important to have a consistent and reproducible model, which for CIBP has been done using an animal model. Thompson, et al. 2019 [8] published a thorough review of the procedures and methods of murine bone-derived pain models, including CIBP and the adjacent bone pain models, including fracture and osteoarthritis, that are often comorbid with CIBP.

Capitalizing on a review article by Slosky et al. 2015 [4] that delves into the history of many of the methods, Thompson has created a simple, straightforward collection of methods essential for studying CIBP. Until 1999, an intracardiac model introduced cancer cells into the left ventricle of rodents, allowing the cancer cells to spread indiscriminately around the body. While the cancer cells often metastasized to bone, creating a model similar to natural progression of bone cancer, the global tumor burden was nonspecific, uneven, and unreproducible, making the model impossible to replicate and the animals too unhealthy for

accurate behavioral evaluation [9]. While this method could have accounted for the natural process of metastasis, the nonspecificity and low survival rates of the animals have led to a different procedure that is the current standard for CIBP studies: direct, intramedullary injection of the cancer cells, contained by a bone sealant. Additionally, CIBP studies often use syngenic models, or cancer cells from the same species that are then inoculated with them to allow for study of immune system interaction, as nonsyngenic models require immunocompromised animals to be successful. In addition to the detailed description of the surgical procedure for the intramedullary murine CIBP models, Thompson describes the flinching, guarding and other behavioral tests that are necessary for evaluating pain response. A study by Sliepen et al. 2019 [10] adds an additional behavioral test for CIBP: measurement of the condition's inhibition of burrowing as a more complex behavior affected by the condition.

Cysteine/Glutamate Antiporter System x_c^-

While CIBP can be severe and acute, tumor masses often do not develop direct innervation until the late stages of the disease after bone degradation. Instead, the acidic and enzymatic tumor environment provokes the nociceptors within the highly innervated surrounding bone tissue, leading to chronic inflammatory pain response. Slosky et al. 2016 [11] published a study extensively investigating one of the mechanisms of this extracellular component of CIBP and how to effectively treat it.

The study references preliminary data from Singh [12] [13], citing evidence that glutamate, an excitatory neurotransmitter, is released from the cysteine/glutamate antiporter system, x_c^- *in vitro* murine breast cancer cells. The x_c^- system is responsible for maintaining intracellular and extracellular oxidant levels by exchanging extracellular cysteine for intracellular glutamate, which activates N-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4 isoxazolepropionic acid (AMPA), and metabotropic-type glutamate receptors in the surrounding bone tissue, creating a potential target for CIBP treatment.

Slosky advanced the *in vitro* studies by Singh to *in vivo* murine models, administering the direct x_c^- inhibitor, sulfasalazine (SSZ), to test subjects, providing evidence confirming that tumor-cell release of glutamate through antiporter system x_c^- is a key component of CIBP. Additionally, SSZ is already an FDA-approved drug and since it was shown to attenuate known CIBP behaviors of flinching and guarding, it will likely be fast-tracked into adjunct therapies for human patients.

In terms of mechanisms, the study examines the role of antiporter system x_c^- in mobilizing cells' antioxidant defenses, confirming an upregulated expression in times of oxidative stress from bone cancer environments. They demonstrated that downregulating peroxynitrite expression subsequently downregulated the antiporter system x_c^- decreased CIBP response, providing yet another potential therapeutic target. Slosky et al. 2016 provides key understanding of the role the cysteine/glutamate antiporter system x_c^- plays in CIBP through both SSZ and peroxynitrite, and provides evidence of the key role glutamate expression plays in the bone cancer tumor environment *in vivo*.

Two studies by Fazzari et al. [14] [15], are in association with the Singh lab referenced by Slosky, and leverage antiporter system x_c^-. The 2017 study investigates the efficacy of another direct x_c^- inhibitor, capsazepine (CPZ) on glutamate release, concluding that CPZ also reduced CIBP response using similar mechanisms to those identified by Slosky. The 2019 study, however, Fazzari et al. focuses on another aspect of the system, glutamate precursors glutamine and glutaminase (GLS), which are heavily metabolized by tumor cells and the reaction-causing enzyme, respectively. The altered metabolism and rapid proliferation of cancer cells creates a reliance on glutamine as a source of nitrogen and for the production of many other amino acids, making it a promising target for antiporter system regulation [16].

This study targets GLS through potent allosteric inhibitor, CB-839, increasing the reactive oxygen species (ROS) to activate x_c^- without the cancer cells having access to intracellular glutamate. In theory, this would cause the tumor burden to favor the antioxidative properties of x_c^- without having the glutamate resources for growth [17]. However, Fazzari et al. did not see any attenuation of pain behaviors in the CIBP model or consistent tumor growth control. The deeper understanding of how the balance of glutamate and cysteine factors into CIBP response will provide clarity in future treatment studies.

Miladinovic et al. 2019 [18], also in association with Singh, examines the role of antiporter system x_c^- activation in spinal microglia, a central component of neuroinflammation and chronic pain. The results of a mouse model indicate that tumor-produced glutamate upregulates x_c^- expression and activation in microglia, which increases CIBP response, providing evidence of yet another potential therapeutic target within the antiporter system.

Chronic Inflammatory Pain: Cannabinoid and Kappa Opioid Receptors

Zhang et al. 2018 published a study of the peripherally-restricted cannabinoid 1 receptor (CB1R) agonist 4-{2-[-(1E)-1[(4-propylhaphthalen-1-yl)methylidene]-1H-inden-3-yl] -ethyl} morpholine (PrNMI) effectively attenuating CIBP in mice [19]. Cannabinoid receptor agonists have produced promising results in chronic pain studies and have been shown to improve bone integrity through balancing osteoclast and osteoblast populations, making them ideal candidates for a potential novel treatment for CIBP. The use of these agonists was originally limited by the undesirable psychotropic effects in the central nervous system, but by targeting only the peripheral CB1Rs, the antiallodynic effects are allowed without the unwanted side effects [20]. This study also investigated cannabinoid side effects still present in the periphery, such as decreased body temperature, catalepsy, and decreased movement, noting that while mild sedation was observed, there were no signs of anxiety or decreased limb movement. Zhang's study confirms both the activation of CB1R receptors and the peripheral selectivity using a pretreatment of CB1R antagonist, SR141716, peripherally and centrally, respectively.

This study is one of the first of its kind to examine CB1Rs in CIBP models, but builds from a study by Lozano-Ondoua et al. 2013 [21], which investigated cannabinoid 2 receptor (CB2R) agonists in the same condition. While the analgesic and antiallodynic properties of CB1Rs are not fully understood, it is hypothesized that these receptors are upregulated on

the peripheral terminals of primary afferents of tissues under pathological conditions, such as CIBP. Additionally, CB1Rs are primarily present on the nerve fibers innervating the bone, with some low levels in osteoclasts and osteoblasts, while CB2Rs are more present in osteoclasts, osteoblasts, and osteocytes, indicated by Lozano-Ondoua et al. to inhibit osteoclast activity and subsequently prevent cancer-induced bone loss [22]. The trajectory of cannabinoid-type receptor studies is detailed at length in the discussion section of Zhang et al., but it's clear that these studies show potential for advancing the understanding of CIBP mechanisms and producing novel treatments for clinical use.

In addition to cannabinoid type-receptors, a study by Edwards et al. 2018 [23] has indicated the therapeutic potential of targeting kappa opioid receptors (KOR) to relieve inflammatory pain in CIBP models. Common, clinically prescribed opioids such as morphine and benzodiazepine (that have failed to provide adequate management of CIBP) act on the mu opioid receptor (MOR), separate from the KORs targeted in this paper. In fact, KOR agonists have been shown to produce antinociception and attenuate morphine-induced dependence without as many dangerous side-effects [24]. This study leverages peripheral administration of KOR agonist, U50,488 and notes that clinically viable KOR agonists will likely be peripherally restricted like those in the CB1 studies, or functionally selective in order to reduce dysphoric effects [25].

The results of the study found a long-lasting antinociceptive effect of U50,488, (confirmed by KOR antagonist, *nor*-binaltorphimine) without seeing any negative effects on tumor proliferation or bone degradation. Their twice-a-day, week long study showed pre-U50,480 injection baselines to be improved in comparison to vehicle on the last day, suggesting repeated administration to be beneficial to chronic pain treatment without creating tolerance. This paper paves the way for future studies of KOR agonists in CIBP and provides promising evidence in support of clinical treatments targeting the aspect of inflammatory pain.

Neuropathic Pain: S1P/S1PR1

With much of the most recent work revolving around acute and inflammatory pain directly involved with the tumor or tumor microenvironment, Grenald et al. 2017 [26] published a promising study focusing on the neuropathic-type pain associated with CIBP. Neuropathic pain occurs when there is an injury directly to the sensory nerves, which alters the ion channels that produce action potentials and distinct pathology into the dorsal horn of the spinal cord and spinal glia [2]. This can happen after chemotherapy or surgical treatments damages nerves, or if the tumor burden pinches or grows through nerves in the bone. Although no treatment exists to target it, neuropathic pain is present in about a quarter of bone cancer patients and hypothesized to be the source of continued pain in recovering patients [27].

The ceramide, sphingosine-1-phosphate (S1P), and S1P receptor subtype 1 (S1PR1) axis has been identified as a crucial part of neuropathic pain response by Janes et al. 2014 [28], and Grenald et al. examined its role in neuropathic pain response seen in CIBP, becoming one of the first studies to focus on this aspect of pain response in CIBP. The notable findings

include the sphingolipid metabolism (production of S1P) is upregulated in the tumor environment, likely sensitizing local afferents and contributing to spinal S1P production and neuropathic pain. This study also leveraged known S1PR1 antagonist, Fingolimod (FTY720) to create irreversible downregulation of S1P production and neuropathic pain response. The efficacy of FTY720 through regulating interleukin 10 (IL-10) production by astrocytes provides novel insight into the neuropathic mechanisms of CIBP and identifies the S1P/S1PR1 axis as a therapeutic target for clinically treating this aspect of pain. Additionally, FTY720 is an FDA-approved drug currently used to treat multiple sclerosis patients, making this study even more notable for its' fast-track clinical viability.

Conclusion

The multifaceted pain response that defines CIBP makes treatment a complicated endeavor, but recent studies have had significant breakthroughs. The 2019 review from Thompson et al. created a tangible standard for animal bone pain models, Slosky et al., Fazzari et al., and Miladinovic et al. examined different aspects of the antiporter system x_c^-, further clarifying its role in CIBP and tumor growth. Edwards et al. and Zhang et al. examined kappa opioid and cannabinoid receptors, respectively, to create promising evidence for clinical treatments of CIBP. Grenald et al. addressed the neuropathic pain associated with CIBP and laid a solid foundation for future studies and clinical uses. These advancements indicate future improvements for the currently ineffective treatment for CIBP.

Acknowledgements

We would like to thank the Vanderah and Largent-Milnes labs at the University of Arizona.

Financial support and sponsorship

This work was supported by the National Institutes of Health National Institute on Drug Abuse [R01CA14215] and by the Comprehensive Pain and Addiction Center (CPAC), University of Arizona Health Sciences.

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15**. Fazzari J, & Singh G (2019). Effect of glutaminase inhibition on cancer-induced bone pain. Breast Cancer: Targets and Therapy, *Volume* 11, 273–282. doi: 10.2147/bctt.s215655This study leverages the findings of the previous studies on antiporter system x_c^-, but targets glutamate precursors. While this did not prove to be an effective treatment for CIBP, it elucidates the mechanisms of the glutamate transport system within CIBP environments and includes a detailed discussion with promising leads for future studies.

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Key Points

- Cancer-induced bone pain (CIBP) is a complicated pain response that is not effectively treated by the current standard of care.
- Syngenic intramedullary injections are the standard for CIBP models.
- Inhibition of tumor-released glutamate through the cysteine/glutamate antiporter system, x_c^- has shown promising results to treat CIBP.
- Peripherally restricted cannabinoid 2 (CB2) and kappa opioid receptor agonists have been shown to reduce CIBP.
- Neuropathic pain elements of CIBP have been shown to be reduced by sphingosine-1-phosphate receptor 1 (S1PR1) antagonists.