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Bone Pain and Muscle Weakness in Cancer Patients

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Abstract

Purpose of review—In this article we will discuss the current understanding of bone pain and muscle weakness in cancer patients. We will describe the underlying physiology and mechanisms of cancer-induced bone pain (CIBP) and cancier-induced muscle wasting (CIMW), as well as current methods of diagnosis and treatment. We will discuss future therapies and research directions to help patients with these problems.

Recent Findings—There are several pharmacologic therapies that are currenly in pre-clinical and clinical testing that appear to be promising adjuncts to current CIBP and CIMW therapies. Such therapies include resiniferitoxin, which is a targeted inhibitor of nociptive nerve fibers, and selective androgen receptor modulators, which show promise in increasing lean mass.

Summary—CIBP and CIMW are a significant causes of morbidity in affected patients. Current management is mostly palliative; however, targeted therapies are poised to revolutionize how these problems are treated.

Keywords

Cancer-induced bone pain; muscle weakness; bone metastesis; cachexia

INTRODUCTION

With the rising incidence of cancer worldwide and advances in treatment, there has been an increase in the number of patients living with debilitating complications of chronic cancer. The most common cause of cancer-induced pain arises from bone metastases.[1] Of advanced cancer suffers, 60–84% are estimated to experience varying degrees of bone pain.[2] Cancer-induced bone pain (CIBP) involves both neuropathic and inflammatory pain pathways, associated with tumor, stroma, and adjacent tissues, including peripheral and central nerves.[1]

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Compliance with Ethical Guidelines

Conflict of Interest

Leonidas Koniaris, Daniel Milgrom, Neha Lad, and Teresa Zimmers declare no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

The establishment of animal models have helped to elucidate the relationship between tumor, pain and neuronal interactions.[3] This in turn has helped in our understanding of this disease process and is helping to develop new targetted therapies to treat CIBP. Evaluation of patients with CIBP requires a comprehensive assessment of their current health status including the development of a trusting relationship, obtaining a thorough history of the pain, understanding the doses and durations of pain medications used to date, evaluation of psychological status, performing a thorough physical exam including neurologic exam, and reviewing diagnostic studies and laboratory findings. The ultimate goal is to develop an individualized treatment plan to obtain an acceptable quality of life.[2]

1.0 BONE PAIN IN CANCER

Myeloid leukemia, prostate, lung, and breast cancers are the malignancies most commonly associated with bone metastases. Although methods such as magnetic resonance imaging (MRI), computed tomography (CT) scan and 18-fluorodeoxyglucose positron emission tomography (FDG-PET/CT) may provide early diagnosis of bone metastases, the current treatment options remain mostly palliative and thus are generally reserved for patients once they become symptomatic. The importance of addressing symptoms must not be understated, as pain will drastically decrease quality of life (QoL), and furthermore, there is mounting evidence that survival for cancer patients is linked to symptom control.[4].

1.1 CLINICAL PRESENTATION AND ASSESSMENT OF CIBP

CIBP is one of the leading causes of significant morbidity in cancer patients. Early diagnosis and therapy are important to improve QoL. CIBP may present with symptoms that range from dull, vague, persistent pain to intermittent, sharp, severe pain and is generally exacerbated by physical activity. A careful history is required in making the diagnosis, whereas physical examination aided by various diagnostic modalities helps in confirmation of the pain’s etiology. CIBP usually presents gradually and is progressive. It is usually related to weight bearing or movement, and develops into shooting neuropathic pain and pathologic fractures. Commonly involved sites are vertebrae, pelvis, femur, ribs and skull.[2] Patients also describe bouts of severe, intermittent pain despite analgesic intervention, called breakthrough pain, which is a sign of inadequate pain management.[5]

1.2 DIAGNOSTIC APPROACH TO BONE METASTASES

Biochemical findings, like elevated serum calcium, decreased renal function, increased urine calcium and urine hydroxyproline (an indirect measure of increased bone turn over), serum alkaline phosphatase level, and decreased osteocalcin (especially in multiple myeloma) aid in the diagnosis of bone involvement in cancer patients. Also, electrocardiography may demonstrate a shortened QT interval secondary to hypercalcemia. Diagnostic imaging with plain films (x-ray), bone scintigraphy (BS), MRI, CT scan and FDG-PET/CT are commonly used techniques. The diagnostic strategy is greatly influenced by pathology, available imaging modalities, and location of skeletal metastasis. A recent study from Denmark compared the diagnostic accuracy of the above modalities and with pathologic reports of bone biopsies. The sensitivity of MRI and FDG-PET/CT was better than CT, whereas CT

had higher specificity than FDG-PET/CT. For osteolytic and mixed lesions MRI and FDG-PET/CT were more sensitive as compared to CT and vice versa for osteosclerotic lesions. For spinal lesions, MRI had the highest sensitivity (92%) and specificity (80%); whereas for non-spinal lesions, FDG-PET/CT had the highest sensitivity (97%) and specificity (69%), but was not significantly different from MRI or CT. X-ray and BS were found to be inferior in diagnostic accuracy when compared to the other modalities.[6] In the case of an equivocal bone lesion in patients with hepatocellular carcinoma, single-photon emission computed tomography (SPECT) combined with spiral CT is found to be more accurate.[7]. 18F-NaF/FDG-PET/CT was found to be superior to whole body MRI and BS for evaluation skeletal disease in breast and prostate cancer, since it detects extra-skeletal disease which can significantly alter disease management.[8, 9].

There are inherent biologic and physical factors limiting the effectiveness of imaging technologies. Specificity is diminished by an inability to distinguish between metastatic tumor burden versus joint degeneration. Flare from increased radiotracer uptake in previously diagnosed, new, or undetected lesions after initiating therapy may also make image interpretation difficult. Scans are used to assess disease progression and response to therapy. However, by monitoring bone activity, a pleotropic drug which affects bone remodeling rather than cancer cells may lead to misinterpretation of results.[10] Scan duration, resolution and artifactual uptake are challenges which can be overcome by more disease-specific targeted imaging techniques.[10]

1.3 PATHOPHYSIOLOGY

Understanding the molecular aspects of the pathogenesis of bone metastases and subsequent complications associated with their development underlies the basis of developing targeted therapies. The development of tumor metastases involves sequential steps, including progressive tumor growth, vascularization, invasion, detachment, embolization, survival in circulation, arrest at site of metastasis, extravasation, evasion of host defense, and progressive growth.[11] There is disruption of the fundamental balance between osteoclasts, osteoblasts, and signaling pathways involved in controlling bone density. Osteoclasts and precursor osteoclasts express receptor activator of nuclear factor kappa β (RANK), ligand of RANK (RANKL) - the key stimulator of bone resorption, and cytokine osteoprotegerin (OPG), which inhibits bone resorption.[12, 13]

a. Osteolytic Metastases

Osteolytic metastases are more common than osteoblastic metasteses and are seen with breast and lung tumors and multiple myeloma. Metastatic cells produce many factors, such as parathyroid hormone related peptide (PTHrP), TGF-β, interleukins (ILs)- IL-1, IL-6, colony stimulating factor-1 (CSF-1), insulin-like growth factor-1 (IGF-1), prostaglandins, CXCR4, which interact with osteoblasts to modulate the RANK-RANKL pathway to stimulate osteoclast precursors and alter the microenvironment, starting the vicious cycle of osteolysis.[14]

PTHrP is known to be one of the most critical mediators of osteoclastic activation. It works by binding PTH-receptor 1 (PTH-R1), inducing RANKL expression and OPG

downregulation in osteoblasts.[12, 14–18] Deleted in Liver Cancer 1 (DLC1), a metastasis suppressor gene, acts through its RhoGTPase activating protein (RhoGAP) activity, which inhibits RhoA, RhoB, RhoC and cell division cycle 42 (cdc42) via hydrolysis of GTPase bound GTP.[19] DLC1-Rho signaling regulates osteoclastogenesis by blocking TGF-β-induced PTHrP secretion, and thus regulates metastatic colonization of circulating breast cancer cells. Experiments in mice have demonstrated enhanced bone metastasis in breast cancer cells lacking DLC1.[20] Data suggest that chemokine receptor CXCR4/CXCR7 and its ligand CXCL12/stromal derived factor-1α(SDF-1α) are highly expressed in skeletal metastases, especially in breast cancer cells.[15, 16, 21] Hypoxic microenvironments in bone (pO2 1–7%) stimulate hypoxia-inducible factor-1α(HIF-1α). HIF-1α stimulates hypoxia response elements (HRE) and multiple factors, such as vascular endothelial growth factor (VEGF)[22], IGF-2, and CXCR4, have been implicated in metastatic bone colonization.[15] Hypoxia and constitutively active HIF-1α in MDA-MB-231 human breast cancer cells was found to be associated with increased osteoclast formation and decreased osteoblast differentiation, thereby promoting progression of bone metastasis. [23] Tumor hypoxia enhanced expression of connective tissue growth factor (CTGF) and IL-11, which initiate invasive angiogenesis and expression of hypoxia-associated genes, have been shown to contribute to the development of bone metastasis in hepatocellular carcinoma.[24]

b. Osteoblastic Metastases

Endothelin-1 (ET-1) growth factor induces osteoblastic proliferation via the ET-1A receptor (ETAR), as well as enhances expression of bone specific proteins osteocalcin, osteonectin, and alkaline phosphatase. Osteoblastic metastases from prostate and breast carcinoma are found to high levels of ET-1 and ETAR. The ETAR antagonist ABT-627 (Atrasentan) has been shown to block development of macroscopically evident osteoblastic metastasis.[15, 25, 26]

The Wnt family are cysteine-rich glycoproteins that mediate bone emybronic bone development and promote adult bone formation. They have autocrine and paracrine effects, enhancing proliferation and induction of osteoblastic activity in prostate cancer bone metastasis. Metastatic prostate cancer cells express the Wnt inhibitor dickkopf-1 (DKK-1) early in the development of skeletal metastasis. As disease progresses, DKK-1 expression decreases and unmasks Wnt osteoblastic activity, leading to osteosclerosis at metastatic sites. The initial osteolytic phase, mediated by DKK-1, RANKL, and PTHrP, causes an altered tumor environment. This leads to hypoxia and production of HIF-1α, VEGF and ET-1, thereby promoting osteoblastic activity.[27] A recent study showed significant inhibition of ERα signaling in prostate cancer cells *in vivo* leading to inhibition of osteoblastic lesions and formation of lung metastases.[28]

c. Hypercalcemia

Hypercalcemia is commonly seen in advanced stages of cancer.[29] PTHrP, which is secreted by various cells, mediates nearly 80% of malignancy-related hypercalcemia.[30] PTHrP acts on the same receptors as PTH in the bone, kidneys and intestine, increases bone resorption via RANKL, and increases calcium absorption in the intestine and reabsorption in the kidneys, leading to hypercalcemia.[31] Excessive calcium release from bone coupled

with abnormal retention of calcium in circulation and osteolytic metastases accounts for approximately 20% of malignancy-related hypercalcemia.[29, 30] Studies also demonstrate that in lymphomas and some other ovarian germ cell tumors, increased activity of 1α-hydroxylase and formation of 1,25-dihydroxycholecalciferol contributes to hypercalcemia.[29, 30]

d. Mechanism of Pain

While a multitude of factors contribute to pain caused by bone metastases, the exact mechanisms still remain unclear. The mechanisms hypothesized to cause bone pain are: a. stimulation of endosteal nerve endings resulting in destruction of bone tissue and release of chemical agents such as prostaglandins, bradykinin, substance P, and histamine; b. increasing stretch of the periosteum by enlarging tumors; c. fractures; and d. growth of tumor into surrounding tissues, especially nerves.[32]

Cancer cells promote proliferation and activity of bone-destroying osteoclasts via activation of the RANKL/RANK pathway. Osteoclast-mediated resorption of bone occurs through formation highly acidic resorption ‘pits’ between the osteoclasts and bone, stimulating the TRPV1 and ASIC3 channels expressed by a significant population of nerve fibers that drive bone cancer pain.[33–35] Mineralized bone undergoes loss of mechanical strength and stability due to the action of osteolytic and osteoblastic tumors. Extensive remodeling due to these effects can result in distortion from what would otherwise be an innocuous mechanical stress, activating the mechanosensitive nerve fibers of the bone.[33]

Cancer cells and surrounding stromal cells secrete a variety of factors (for example: bradykinin, endothelins, IL-6, nerve growth factor (NGF), and proteases), which sensitize or directly excite primary afferent neurons.[33] Studies have shown NGF to activate Trk-A-expressing sensory neurons directly, sensitizing TRPV1. The retrograde transport of NGF/TrkA complexes into nociceptor neurons induces and increases synthesis of the neurotransmitters substance P and calcitonin gene-related peptide, transcription factors (ATF3), and sodium channels, thus modulating supporting cells in dorsal root ganglia (DRG) and peripheral nerves.[33, 36–38]

Murine models of sarcoma, breast, and prostate derived bone cancer have shown active and pathological sprouting and neuroma formation by sensory and sympathetic nerve fibers that innervate the skeleton.[33] This sprouting requires NGF and sustained administration of anti-NGF or Pan Trk (Trk A, Trk B, Trk C). Inhibition of pathological sprouting and neuroma-like structure formation in sensory nerve fibers significantly inhibits pain generation.[33, 39–42] Several animal studies have shown sensitization of the spinal cord innervating the tumor bearing tissues by modification in levels of dynorphin, ATF3, astrocytes, microglia, c-Fos expression and substance P internalization.[33, 43]

1.4 THERAPEUTIC MANAGEMENT OF CIBP

The approach towards management of CIBP involves gradual escalation from conservative to interventional techniques based on response and severity of symptoms.

I. NON-PHARMACOLOGICAL APPROACH

The International Association for the Study of Pain defines pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or descrbied in terms of such damage.” As such, cancer patients’pain is highly influenced by various psychological and social factors. Interventions such as meditation, relaxation techniques, guided imagery, hypnosis, cognitive behavioral coping skills, therapist contact[44] form an essential part of a conjoint palliative approach.[45]

II. PHARMACOTHERAPY

Most physicians treat CIBP according to the World Health Organization’s three-step ladder for cancer pain relief. This entails treating pain initially with a non-opiod medications, then escalating to opiods of increasing strength, and adding adjuvant therapies as needed as the patient’s pain increases.[45]

a. Nonsteroidal Anti-inflammatory Drugs (NSAIDs)—NSAID mechanism of action is via the inhibition of the cyclooxygenase [COX (COX1 & COX2)] enzymes, which catalyze formation of prostaglandins from arachidonic acid as a critical step in the inflammatory response.[3] COX-2 is highly expressed in tumor cells and peripheral macrophages around tumor cells, where it is involved in tumor cell invasion, migration and metastasis. COX-2 has been shown to reduce tumor burden in sarcoma-bearing bones in addition to reducing pain and bone destruction in an *in vivo* murine model.[46] However, various phase II and III trials found increased cardiovascular events from COX-2 inhibition, thereby tempering the enthusiasm for use of COX-2 inhibitors in cancer patients.[47, 48]

b. Opioids—Opioids are one of the most frequently used analgesics for CIBP. They act on opioid G-protein coupled receptors (μ, κ, and δ), inhibiting substance P release in the dorsal horn.[47] Opiods are used by nearly 80% of cancer patients for pain control. Sustained and on-demand formulations are used in conjuction to provide pain suppression and breakthrough pain relief respectively. Opiods have limiting side effects of nausea, itching constipation, tolerance, development of addiction, and respiratory depression.[3, 45] Furthermore, a study in a murine model demonstrated prolonged exposure to opiods might worsen CIBP, accelerate bone loss, and increase incidence of spontaneous fractures.[49] Opioids synergize with NSAIDs, benzodiazapines, and anti-depressant therapies, which may improve pain control and limit the need for opioids. The concomitant use with benzodiazepines risks exacerbating some of the deleterious side effects of opioids, particularly respiratory depression. Increasingly, combination of low dose pregabalin-antidepressants with opioids has been found to be effective in the management of neuropathic CIBP.[50]

c. Bisphosphonates—Older generation bisphosphonates (i.e. clodronate and etidronate) were metabolized by osteoclasts into cytotoxic ATP analogs, interfering with mitochondrial membrane, potentially leading to osteoclast apoptosis. Newer generation nitrogen-containeing intravenous bisphosphonates (i.e. pamidronate, ibandronate and zoledronate) are internalized by osteoclasts and inhibit the farnesyl pyrophosphate (FPP) synthase enzyme, active in prenylation of several GTPases involved in bone resorption. This causes

accumulation of isopentyl pyrophosphate and adenosine monophosphate, which conjugate to form an endogenous ATP analogue that inhibits mitochondrial adenine nucleotide translocase (ANT) and leads to osteoclast apoptosis.[51] Multiple studies have demonstrated efficacy of bisphosphonates in reducing skeletal complications and CIBP.[52] Zoledronate, in addition to reducing skeletal morbidity, has been reported to have direct antitumor properties: induction of tumor cell apoptosis, inhibition of cancer cell invasion[53], limiting metastatic outgrowth in visceral tissues[51, 54], and causing decrease in VEGF levels, thereby potentially slowing bone disease.[55, 56] While bisphosphonates are useful adjuvants in the treatment of CIBP, they do not themselves block pain, and must be used in conjuction with other therapies.[57] Intravenous bisphosphante therapy requires dental evaluation and follow-up to monitor for osteonecrosis of the jaw as well as renal monitoring and caution for patients with kidney disease or who are taking other nephrotoxic agents.[51]

d. Novel Targeted Therapies

Denosumab: Denosumab is a monoclonal antibody against RANKL. It is a potent inhibitor of osteoclast-mediated bone resorption. Multiple phase III trials have shown an increase in bone mineral density, a decreased risk of fractures, and a delay in skeletal-related events (SRE) with use of denosumab [15]; however, data regarding overall survival remains controversial.[58] Denosumab was superior to zolendronate in preventing SRE in patients with advanced disease regardless of performance status and disease extent.[59]

Atrasentan: ET-1 receptor sensitization and/or activation has been associated with hyperalgesia of CIBP. The ET1A receptor antagonist atrasentan is under phase II trials for bone metastates in renal carcinoma patients.[60] However, a meta-analysis of its use in prostate cancer showed a significant decrease in CIBP and SRE with a delayed rise in PSA and bone alkaline phosphatase.[61]

Osteoprotegerin: OPG combines with RANKLto inhibit activation of RANK on osteoclasts, thereby preventing bone destruction induced by tumor cells.[3, 62] OPG has been shown to have inhibitory potential in breast cancer-induced bone destruction.[63]

Dasatinib: Src is a prototypic member of a nonreceptor tyrosine kinase family that is involved in various critical cellular functions, including cell morphology, cell growth, proliferation, differentiation, adhesion, migration and survival.[15] Dasatinib, a Src inhibitor, has been show to reduce metastatic potential and induce apoptosis in preclinical studies of pancreas, head and neck, and lung cancers.[15] Also, *in vivo* and *in vitro* studies show suppression of Src causes inhibition of breast cancer cells and reduced incidence of metastasis.[64]

Anti-NGF: New potential therapies in clinical phases of development target molecules like NGF, a molecule which is integrally involved in the upregulation, sensitization and disinhibition of neurotransmitters in the primary afferent nerves. Anti-NGF therapy could be effective in blocking CIBP due to NGF.[51]

Resiniferatoxin (RTX): RTX is an ultrapotent agonist of the transient receptor potential vanilloid 1 (TRPV1) receptor. RTX acts on TRPV1 to allow for prolonged calcium influx, inducing cytotoxicity and death selectively in nociceptive fibres expressing TRPV1. Treatment with RTX has been shown to significantly improveme pain control in dogs with CIBP compared to standard of care analgesic therapy.[65]

Other therapies: Preclinical studies show TRPV1 and cannabinoid 2 receptor agonists could be used as adjuncts to ameliorate opioid side effects.[51] CXCL12/CXCR4 is found to play a central role in cancer cell proliferation, invasion and dissemination in various malignancies and is a potential drug-target in cancer management.[66]

III. RADIATION THERAPY (RT)

a. External Beam Radiation Therapy (EBRT)—EBRT is the most common form of RT used for palliation of CIBP. EBRT is produced in a linear accelerator which projects electrons onto a tungsten target, producing megavoltage photons directed towards bone lesions. The treatment usually takes 10–15 minutes per dose and relief can be acheived in 50–80% patients. The acute side effects of radiation therapy are generally self-limiting and consist mainly of fatigue. Late side-effects in this patient group are relatively uncommon given the short life expectancy.[67] A systematic review of 24 randomized control trials (RCT) showed that single fraction administration of 8 Gy was statistically superior in pain response with minimal iatrogenic toxicity.[68] Evaluation of QoL following RT for patients with CIBP found improvement in symptoms and function using the Brief Pain Inventory score in all 17 studies included in the analysis.[69] Post-operative RT after surgical stabilization of metastatic bone disease has been found to be effective in local disease control. Along with bisphosphonates it might have the additional effect of delaying local progression.[70] Dexamethasone has been shown to reduce radiation-induced pain flare in the treatment of painful bone metastases in a double-blind randomized control trial.[71]

b. Stereotactic Body Radiation Therapy (SBRT)—SBRT uses image-guidance technology to deliver single or multiple fractions of high dose RT and can deliver nearly 2 to 7-times the standard palliative dose.[72] A systematic review showed SBRT provided excellent local control with lower toxicity in patients with metastatic renal cell carcinoma.[73] Although pain relief is higher in in SBRT, cost effectiveness of SBRT in comparison with EBRT in patients with a shorter expected survival (<11 months) remains contested.[74]

c. Role of Re-irradiation—Re-irradiation is effective and comparable to initial RT and should be recommended to patients suffering from ongoing CIBP irrespective of initial response to RT.[75]

d. Radioisotopes—*Strontium-89 (S^{89})* is a beta-emitting radioisotope with a half-life of 50.5 days. Osteoblastic bone metastases have higher uptake than surrounding bone. Therefore S^{89} is used for the treatment of metastatic prostate or breast cancer with significant pain relief in 60–92%.[76]

Samarium-153 (Sm^{153}) is a beta-emitter with a half-life of 1.9 days. It is chelated to ethylene diamine tetramethylene phosphate (EDTMP) which targets bone matrix as

pyrophosphate. It is used in various primary tumors and confers a superior survival in breast cancer patients at a higher dose.[76]

Other isotopes like Tin-117m (Sn^{117m}), Radium-223 (Ra^{223}), and Rhenium-186(Re^{186}) are being tested in various clinical trials for CIBP in prostate and breast cancer. All of these therapies have distinct advantages over EBRT, which requires large areas of RT and is limited by toxicity.

e. MRI-guided Focused Ultrasound Ablation—Ultrasound ablation is a promising alternative therapy that was first tested in uterine fibroids. It uses non-invasive, non-ionizing ultrasound for pain palliation and tumor control. The interaction between the ultrasound beam and tissues results in a rise in cell temperature, leading to coagulative necrosis at a thermal range of 65–85 degrees C, which is limited to focal tissue volumes of 0.2–5mm^3 and has negligible effect on surrounding tissue. The major advantages of this technology are the ability to be performed in an outpatient setting with three-dimensional MRI visualization for precise planning, continuous temperature mapping with MR thermometry, and immediate post-treatment assessment.[77, 78]

IV. INVASIVE PROCEDURES

a. Surgical Management—There is a significant palliative role for surgery in patients with CIBP in conjunction with other modalities. Surgical intervention is usually indicated for impending pathologic fractures, spine instability that threatens spinal cord function, or the development of nerve deficits. Based on pathology and patient prognosis, interventions may range from conservative measures to fracture stabilization with internal fixation or arthroplasty.[79] A systematic review assessed pain and functional outcomes following surgical management of metastases to the humerus, femur and pelvis and found pain relief in 93, 91, and 93% of subjects respectively and improved function in 94, 89 and 94% of subjects respectively. In this study, there was a also substantial risk of perioperative complications (17%) and mortality (4%).[80]

Vertebroplasty is a technique involving fluoroscopic, percutaneous injection of polymethylmethacrylate and bone cement into the vertebral body for stabilization and pain relief in patients with compression fractures. *Kyphoplasty* involves placement of an inflatable balloon into the vertebral body with subsequent injection of bone cement. Both procedures can be performed under local or general anesthesia and are shown to provide effective and safe reduction in pain and improvement in mobility.[81] For palliative treatment of spinal metastases, the increasing use of minimally invasive techniques of tumor resection and decompression of neurologic elements have resulted in improved recovery with minimal morbidity and mortality.[82]

b. Intra-thecal analgesia—For patients requiring higher doses of opioids with unacceptable systemic side-effects, intra-thecal therapy may be a good alternative. Various intra-thecal analgesics including morphine sulphate, hydromorphone, and bupivacaine have proven efficacity.[83]

c. Laser-induced thermotherapy—The use of Nd:YAG laser has been reported in a small case series as a treatment of treat spinal metastasis under CT—guidance. A total of 1400–2600J energy delivered over 60–90 minutes has yielded 30–45% reductions in CIBP without complications.[84]

2.0 MUSCLE WEAKNESS IN CANCER

Cancer cachexia is a complex metabolic condition characterized by skeletal muscle wasting (with or without fat loss), anemia, reduced caloric intake, and altered immune function, which contributes to increased disability, fatigue, diminished QoL, and reduced survival.[85, 86] Skeletal muscle wasting and resultant functional impairment significantly affect QoL. Cancer-related muscle loss is multifactorial, resulting in asthenia and functional impairment similar to that seen in patients with age-related sarcopenia as well that manifested by active muscle break-down.[87, 88] The common metabolic abnormalities to cancer cachexia and sarcopenia include altered hormone levels, elevated cytokines, increased insulin resistance, increased muscle proteolysis, elevated acute phase proteins, and altered nutrient utilization.[87] Many experts believe, however, that muscle loss in cancer is a more active process, mediated by a number of pro-inflammatory cytokines, as well as members of the TGFβ-superfamily including activins[89] and myostatin.[90, 91]

2.1 CLINICAL PRESENTATION AND ASSESSMENT OF CANCER INDUCED MUSCLE WEAKNESS (CIMW)

CIMW is one of the major symptoms of cancer cachexia. CT and DXA imagine can be used to quantify sarcopenia which correlates with clinical asthenia, fatigue, reduced tolerance to treatments, impaired QoL and reduced survival.[88]

2.2 PATHOPHYSIOLOGY OF CIMW

The skeletal muscle loss due to cachexia results from decreased protein anabolism, increased proteolysis, or a combination of both. The four major proteolytic pathways in skeletal muscle are:

1. The lysosomal system, which includes the cysteine proteases and cathepsins B, H, and, L, as well as aspartate protease cathepsin D, mainly degrades extracellular proteins and cell receptors.
2. The calcium-activated calpains I and II, which mainly cause tissue injury, necrosis and autolysis.
3. The ATP-dependent ubiquitin proteasome proteolytic pathway, which works with the calpain system to degrade myofilaments. This pathway plays a predominant role in degradation of myofibrillar proteins particularly in patients with a weight loss of >10%.[92]
4. The STAT3 pathway, which directly induces myocyte atrophy.[93, 94]. It induces muscle-specific E3 ubiquitin ligases [e.g. muscle atrophy F box (encoded by

MAFbx/atrogin-1) and muscle RING finger 1 (MuRF1)], which cause polyubiquitation of proteins targeted for degradation.[95]

Cachexia is known to feature tumor-induced activation of the host immune system and elevated proinflammatory cytokines IL-1β, IL-6, interferon(IFN-γ), TNF- α, and proteolysis inducing factor (PIF), all of which may primarily stimulate a catabolic state in skeletal muscle.[85, 96, 97] On a subcellular level, skeletal muscle weakness in cancer is due to a decrease in the number of strongly bound cross-bridges and a reduction in myosin-actin cross-bridge kinetics characterized by an increased myosin attachment time.[98] Chemotherapeutic agents like doxorubicin cause increased oxidative stress via formation of reactive oxygen species and activate caspases leading to loss of muscle mass and atrophy via the E3 ubiquitin-ligase proteasome pathway.[99] The mechanism of muscle wasting involves multiple host and tumor factors, decreased levels of testosterone and IGF-1, and decreased food intake contributing to both antianabolic and procatabolic processes.[85]

2.3 CURRENT THERAPEUTIC APPROACH TO CIMW

Unlike starvation, cancer cachexia does not respond to nutritional supplementation. Although caloric replacement up to 1.5mg/kg has shown some benefit in stabilizing weight, [100] benefits of nutritional supplementation may be limited.[85] Essential amino acid (EAA) supplements, including ~2.5g of leucine, HMB supplements and vitamin D may improve muscle mass and function parameters.[101] Exercise therapy can help maintain or slow the loss of physical function.[101]

2.4 CURRENT AND POTENTIAL PHARMACOLOGIC THERAPIES FOR CIMW

5-HT3 antagonists

Mirtazapine and olanzapine provide 24-hour nausea control and increased appetite in cancer patients. They have the added benefit of controlling anxiety and aiding with better sleep.[96]

Megesterol acetate

This progetagen, combined with *thalidomide,* an anti-TNFα agent, has shown to significantly increase appetite with consequent improvement in body weight and QoL due to anti-inflammatory properties.[102] Megesterol carries an increased risk of thromboembolism, while thalidomide is known to cause birth defects in pregnant patients.

Enobosam

This nonsteroidal, selective androgen receptor modulators (SARMs), is in a phase III trial. Treatment with this medication has demonstrated increased lean body mass and is promising as an agent for the prevention and treatment of skeletal muscle wasting.[103] This medication prevents the need for non-selective systemic steroids, which carry significant side effects.

Ghrelin analogues

Anamorelin, is an oral ghrelin-receptor agonist with appetite-enhancing and anabolic effects, which has shown promising results in phase III trials.[104]

Myostatin antagonists

Using a soluble receptor antagonist of myostatin (sActRIIB) in cachectic tumor-bearing animals has shown improvement in muscle weight and force through myostatin blockade.[105]

β2 adrenoreceptor-selective agonist

Formoterol, promotes muscle growth and skeletal muscle hypertrophy in animal models. Espindolol, a nonspecific β1 and β2 adrenoreceptor antagonist with intrinsic sympathomimetic activity at the β2 adrenoreceptor has a novel anabolic-catabolic transforming property. These are prospective new drugs particularly beneficial for patients suffering from cancer cachexia with declined cardiac function.[106] Combination of sActRIIB with formoterol appears to be very promising in animal studies.[107]

3.0 ALTERATION OF BONE AND MUSCLE PHYSIOLOGY IN CANCER

CIMW is a major clinical problem in advanced stage cancer, and is usually associated with bone pain, fractures, hypercalcemia and nerve compression.[87] Bone and muscle function are interdependent physiologically. However, in cancer patients, accelerated bone resorption due to metastases increases “osteokines,” which significantly alter muscle function. Similarly, factors released from muscle can further exacerbate bone’s role in muscle dysfunction.[87] Normal excitation-contraction (E-C) coupling in skeletal muscle involves release of sequestered calcium from the sarcoplasmic reticulum into the cytoplasm via the activated ryanodine receptor/calcium release channel (RyR1), leading to calcium-dependent actin-myosin cross-bridging and muscle contraction.[108] Modifications to RyR1 from chronic oxidative stress causes disruption of RyR1 and its stabilizing subunit calstabim1, resulting in leaky calcium channels. In addition, TGFβ, a critical bone remodeling factor can mediate oxidative stress, and thereby further contribute to muscle dysfunction.[87]

3.1 Muscle Dysfunction Associated with Bone Metastasis in Cancer

Muscle secretes many factors, collectively called “myokines,” which affect other tissues. They include bone active molecules like IGF-1 and FGF-2, myostatin (also called growth differentiation factor 8 [GDF8])[109], and IL-6.[110–113] IGF-1 and FGF-2 stimulate bone formation,[114, 115] and myostatin deficiency increases bone density.[116, 117] Conversely, Indian hedgehog (Ihh) promotes myoblast survival and myogenesis in mouse and chick embryos.[87, 118] Preclinical mice model data show that predominantly osteolytic MDA-MB-231 breast cancer, A549 lung cancer, PC3 prostate cancer and JJN3 multiple myeloma or mixed osteolytic/osteoblastic bone metastases result in lower muscle specific force, lower muscle strength, and RyR1 modifications consistent with leaky calcium channels regardless of weight loss or lower muscle mass as compared to non-tumor bearubg mice.[119] This suggets that there is a relationship between tumor-induced osteolysis-linked alterations in the bone microenvironment and skeletal muscle dysfunction. The RyR1 calcium release channel stabilizer Rycal (S107) improves the function of the leaky RyR1 channels by inhibiting oxidation-induced depletion of channel stabilizing subunit catstabin1 from the RyR1 complex, thereby stabilizing the closed state of the channels and preventing aberrant

calcium leakage. Experiments of S107 function have shown improved forelimb grip strength in mice with breast cancer bone metastases. However, S107 does not affect development or progression of bone metastasis, tumor burden, body weight, muscle mass, or distribution of fat and lean mass compared to vehicle treated mice.[119] Thus, S107 treatment suggests that there is no direct correlation between bone destruction and reduced muscle function. Further studies are needed to assess the potential role of S107 in clinical practice to improve CIMW.

3.2 Bone Derived Factor(s) causing Muscle Dysfunction

Bone matrix stores many growth factors known to affect muscle, such as Activin A, TGFβ, IGF-1, and bone morphogenic protein 2 (BMP-2).[111] The high affinity Activin type 2 receptor, ActRIIB, mediates signaling of a small group of TGFβ family members (Activin A, myostatin, GDF-11) and plays major role in regulating muscle mass.[113, 120, 121] In a murine model of cachexia, ActRIIB blockade prevents muscle wasting, induces muscle satellite cell mobilization and differentiation, and significantly prolongs survival.[122] However, it remains unclear from these studies if the effect is due to blockade of Activin A, myostatin or GDF-11 signaling due to receptor overlap.[111, 123]

During osteoclastic resorption, TGFβ is released from mineralized bone. In MDA-MB-231 mice with bone metastases, TGFβ was shown to induce more SMAD3 phosphorylation in skeletal muscle compared to mice without metastases.[119, 124] TGFβ-1 receptor kinase inhibitor (SD-208), bisphosphonates (e.g. zoledronate - which inhibit osteoclastic resorption thereby lowering the release of TGFβ), and a pan-TGFβ neutralizing antibody (clone 1D11), have all shown a decrease in TGFβ in various experimental models, either in combination or alone. This in turn lowered skeletal muscle SMAD3 phosphorylation and preserved calstabin 1 binding to RyR1 complex, resulting in improved muscle function. Combination therapy showed additional benefit by lowering tumor burden and number of osteoclasts. TGFβ inhibition improves muscle function, and bone-derived TGFβ contributes to CIMW, at least in part by inducing oxidation of RyR1.[119] TGFβ released from the bone matrix due to increased catabolism upregulates membrane protein Nox4 in the sarcoplasmic reticulum. Nox4 oxidizes the RyR1 channel and causes a calcium leak, lowering tetanic calcium, impairing muscle force production and contributing to muscle weakness in cancer with bone metastases. GKT137831m, a Nox1/Nox4 inhibitor, prevents skeletal muscle oxidation and nitrosylation of RyR1, restores calstabin binding, and improves extensor digitorum longus force in mice with MDA-MB-231 bone metastases as compared to vehicle treated mice; however, it did not block upstream TGFβ signaling and SMAD3 phosphorylation. In addition, it has no effect on osteolytic lesion size, muscle mass, body weight, or grip strength. Thus, targeting skeletal muscle weakness caused by the TGFβ-Nox4-RyR1 axis represents a novel therapeutic approach for patients.[125]

IGF-1 stimulates myogenic cell proliferation and differentiation[126, 127], while BMP-2 signaling leads to muscle hypertrophy and thereby regulates muscle mass.[111] These are potential targets for restoring muscle mass. Additionally, vitamin D repletion may help functional status, as vitamin D deficiency studied in rodent models using vitamin D receptor knock-out (VDRKO) mice resulted in an increase in sinking episodes in a forced swim test.[111, 128]

MicroRNAs (miRNA) *in vivo* inhibit osteoclast activity and reduce osteolytic bone metastasis. Serum levels of soluble intracellular adhesion molecule (sICAM1) correlate with bone metastasis burden. These levels are affected by activation of NFκB signaling by bone metastatic cancer cells[129], and two osteoclast mRNAs, miR-16 and miR-378[130], which are elevated in osteoclast differentiation,. Hence, miRNAs could be potential therapeutic targets and clinical biomarkers of bone metastases.[130, 131]

CONCLUSION

The closely interrelated bone and muscle physiology is altered in cancer patients. The myokines secreted by skeletal muscle cells significantly impact the surrounding bone. Likewise, bone releases multiple growth factors during physiologic remodeling and affects muscle function. The metastasis of tumor cells to bone causes disruption between osteoclasts and osteoblasts along with various signaling pathways. The alteration of the microenvironment due to increased proinflammatory cytokines released from osteolytic bone resorption accelerates myofibrillar degradation and apoptosis. Clinically this manifests as a spectrum ranging from muscle weakness and fatigue to cachexia in skeletal muscle accompanied by bone pain, fractures, and neuropathy. Diagnosis is mainly clinical, while imaging and biochemical studies may aid in cases of challenging cases. Although the primary approach remains conservative, various therapeutic interventions have been formulated based on factors involving the metabolism of bone and skeletal muscle. Novel therapeutic agents targeting the molecular mechanism appear to be promising. Further studies are needed identify the exact mechanisms of the different cancers that metastasize to bone and interplay between bone and muscle to help develop effective targeted therapies.

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