

Advances in the therapy of cancer pain: from novel experimental models to evidence-based treatments

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ABSTRACT

Cancer related pain may be due to the malignant disease itself, or subsequent to treatments, such as surgery, chemotherapy or radiation therapy. The pathophysiology of pain due to cancer may be complex and include a variety of nociceptive, inflammatory, and neuropathic mechanisms. Despite modern advances in pharmacotherapy, cancer pain remains overall under-treated in a world-wide scale, and a main reason is lack of understanding of its pertinent pathophysiology and basic pharmacology.

Recently, pertinent animal models have facilitated understanding of the pathobiology and have advanced the pharmacology of cancer pain, with significant translational applicability to clinical practice. Furthermore, quantitative and qualitative systematic reviews, integrating the best available evidence, indicate the validity of treatments that fit into an expanded view of the WHO-analgesic ladder. Appropriate current treatments include a valid therapeutic role of non-opioid and opioid analgesics, adjuvants -such as gabapentin, biphosphonates, palliative radiation therapy and radiopharmaceutical compounds, and interventional pain therapy (including neuraxial drug infusion and vertebroplasty for spine metastases) in selected patients.

Overall, experimental animal models simulating cancer pain have been useful in providing pertinent information on the pathophysiology of cancer pain, and provide a testing ground for established and novel therapies, which are validated by clinical evidence. This is clinically significant, considering the epidemiological dimensions and the problematic nature of cancer pain.

Key words: cancer, pain intractable, palliative care, neoplasm metastasis, analgesics non-narcotic, analgesics opioid.

The epidemiology of cancer pain today

Despite several recent advances in the management of pain and palliative care, intractable pain from cancer remains a significant epidemiological, clinical and social/financial burden in the world today. Judging from the data reported by the World Health Organization (WHO) (World Health Organization

(WHO) Cancer Control Programme. Available online at <<http://www.who.int./cancer>>), on a world-wide scale more than 11 million people are diagnosed with cancer every year. So, it is estimated that there will be 16 million new cases of cancer every year by 2020. Cancer-related morbidity is 7 million deaths per year (1), but, as a result of advances in cancer therapy most cancer patients survive longer now. Nevertheless, prolonged survival is associated with a parallel increased prevalence of pain, one of the main manifestations of cancer and its con-

sequences. In a category of patients, also, cancer disease may have been successfully cured, but the chronic pain disease may still persist.

Even in countries with advanced health care systems, the current prevalence of persisting pain in cancer patients remains overall high (52%) (2). The prevalence of pain in patients with advanced disease, such as in patients with metastases to the bones, has been even higher, reaching 61%. Cancer pain is particularly troublesome regarding its intensity and impact on quality of life in the presence of metas-

tases to the bones, emergence of frequent episodes of breakthrough pain, and abnormal cutaneous sensitivity, including allodynia and hyperalgesia. Paradoxically, even patients who were receiving therapy with opioids (42%) reported persisting pain, which was actually of higher intensity than the pain in those who were not on opioids. These patients, despite being on opioids, suffered also from more frequent breakthrough pain, and demonstrated higher impairment of daily activities and quality of life. Finally, a significant percentage (30%) of patients suffering from severe pain were not receiving opioids or any analgesics at all.

In a more wide scale, it has been estimated that the mean prevalence of cancer pain ranges between 20 and 100% in the general adult population, with higher values amongst those suffering from advanced cancer (3). In certain countries treatment of cancer pain is even more inadequate, and this has been attributed to under-utilization or not proper use of analgesic treatments by physicians which constitutes a problem of an even greater magnitude (4-7). Certain subgroups of cancer patients seem to suffer more than others from pain. Meuser et al have confirmed that the prevalence and intensity of cancer-related pain is much higher amongst those patients with metastatic disease or advanced stages of cancer. The prevalence of pain amongst those with advanced, metastatic cancer reaches 95%, and its intensity ranges between 7-8 in a VRS 1-10 scale, also despite the fact that 92% of these patients receive opioids and 42% adjuvant analgesics. These findings have been attributed to inappropriate doses prescribed, or administration from inappropriate routes, apparently due to insufficient education of physicians and other health care professionals, or even due to fear of undesirable side effects (8, 9). Overall, lack or failure of treatment to control cancer pain has been attributed mainly to lack of appropriate knowledge or ineffective individual assessment for pertinent symptoms, resulting in under-utilization or improper use of analgesic

resources. Lack of understanding of the specific pathophysiology of pain induced by cancer, and particularly by metastatic cancer to the bones, is a major obstacle. Most current treatments have been established as a result of accumulating clinical experience or as a consequence of clinical studies only.

Nevertheless, pertinent animal models recently have significantly contributed to relevant knowledge, the translation of which to clinical practice, may improve cancer pain treatment by guiding appropriate, effective therapies.

The pathophysiology of cancer pain

The causative etiology of cancer is usually complex and multi-factorial. The disease of cancer itself may cause pain as a result of direct tumor expansion, progressing to invasion and damage to nearby tissues, and /or as a result of nerve infiltration causing neuropathic pain, or due to paraneoplastic syndromes. However, all of the treatment modalities used to treat cancer have the capacity to cause pain, too. This is the case with chemotherapy, radiation therapy and surgical procedures. Specifically, chemotherapeutic agents, such as platinum compounds (cisplatin, oxaliplatin or carboplatin) may produce pure painful sensory neuropathies, while others such as vincristine, or suramin may induce mixed sensorimotor neuropathies, with or without autonomic involvement (10). The same is the case with paclitaxel or docetaxel, promoters of the polymerization of tubulin that leads to mitotic cell arrest, which are deleterious to neurons and glia, and result in cumulative, predominantly sensory, painful peripheral neuropathy (11). The overall incidence of neuropathic pain after chemotherapy is high (30-70%) (12). Radiation therapy may also induce injury, leading to microvascular insufficiency and fibrotic changes affecting the nerves and perineural tissues (13), with clinical painful manifestations ranging between 25 and 47% (14). Finally, surgery for diagnostic or therapeutic purposes, may lead to chronic pain as

well, with incidence reaching high rates (60-90%) in some cases, such as after surgery for breast cancer (15-18). Post-mastectomy pain syndrome may be particularly troublesome and adversely impair the quality of life of female breast cancer survivors. It is also likely that certain individuals with cancer suffer from multiple painful syndromes, of varying etiology and underlying mechanisms. Other conditions, separate from cancer, may also produce pain in cancer patients, such coexisting painful conditions, infections (herpes zoster), etc. Nevertheless, pain in patients with cancer most commonly occurs from pressure, infiltration or tumor invasion into structures with high sensitivity sensitive to noxious stimulation, such as bones, nerves, viscera, pleura, blood vessels and other soft tissues. Pain from metastatic tumors damaging bones, pain from nerve compression from tumor growth, from involvement of pleural membranes, distention of capsular organs, and other mechanisms is very common. In terms of specific pathophysiology, the cancer pain may be mechanistically classified as "nociceptive" or "neuropathic". Nociceptive pain originates as a result of tissue damage or inflammation of somatic or visceral tissues, wherein mechanical, chemical or thermal noxious stimuli activate peripheral nociceptive nerve terminals. These nerve endings transduce noxious stimulation into electrical and synaptic signaling, that subsequently conveys nociceptive signals to the dorsal horns of the spinal cord. In neuropathic pain, nerve injury or various alterations originating from the disease or attempts to treat it therapeutically, result in increased excitability at the sites of the injury and the peripheral sensory neuronal somata in the dorsal root ganglia (DRG). Subsequent aberrant electrical signaling ends up in enhanced synaptic transmission and activation of postsynaptic neurons in the spinal cord. Other mechanisms may participate in the pathogenesis of pain in the latter case, such as enhanced neuronal cell death, activation of sympathetic mechanisms, or dynamic reorganization

of the synaptic network at the dorsal horns (19, 20).

Prolonged, intense nociception originating from tissue damage (such as after bone destruction from metastases) or inflammation (such as from mechanical or chemical activation of nociceptors by tumor), may produce sensitization at peripheral (and subsequently at central) afferent sensory pathways, enhancing their responsiveness to incoming stimuli. A variety of transmitters are known to mediate the development of sensitization or excitation of peripheral sensory neurons. These transmitters include protons and potassium ions, adenosine triphosphate (ATP), bradykinin, serotonin, prostaglandins, and leukotrienes. Elevated afferent traffic of nociceptive signaling from peripheral tissues, or aberrant ongoing firing of injured peripheral sensory neurons results in enhanced synaptic transmission (via increased release of excitatory aminoacids -such as glutamate, and neurokinins -such as substance P), leading to enhanced post-synaptic responses at dorsal horn neurons. Thus the latter also get sensitized to incoming stimuli. Central sensitization may even result in spontaneous firing of postsynaptic neurons at the dorsal horns, even in the absence of incoming stimuli from the periphery. The activation of the NMDA receptor, with aberrant calcium influx and up-regulation of complex intracellular signaling cascades, leading to altered gene expression and altered post-translational modification, is pivotal in the mediation of central sensitization. Central sensitization results in manifestations, such secondary hyperalgesia in tissues beyond the area of the injury, allodynia, and enhanced, persistent pain states. Painful nerve injury (like after invasion of neural plexuses by tumor, or after injury by surgery, chemotherapy or radiation therapy) in particular, is exceptionally capable of inducing sensitization at peripheral and central nerve pathways. Peripheral and central neurons respond with spontaneous, ectopic firing, and the resultant signaling results in aberrant plasticity involving the central nervous system, possibly at all levels. Subsequent clinical manifestations include

unpleasant pain sensations (burning and shooting or lancinating pain) allodynia and hyperalgesia, combined with sensory changes, including dysesthesia or loss of normal sensation in painful areas.

The mouse bone cancer pain model

Pain from cancer metastasizing to the bones is manifested as dull and achy in quality, initially episodic and of moderate intensity, but progressively getting more frequent and more intense. Bone cancer pain eventually becomes constant, severe, and particularly disabling. Bone cancer pain usually has a constant, ongoing component, which may be interrupted by episodes of breakthrough pain, which may not, or may be related to certain activities, such as turning in bed, sitting, standing, or walking.

Metastases to the bones are a very common cause of pain amongst cancer patients. The majority of cancer patients with metastases to the bones will experience severe pain. In addition to pain, disability, lack of independence and limited mobility may be equally debilitating problems in these patients, and significantly impair their quality of life. Collapse from tumors metastasizing to the vertebrae of the spine may also produce significant neurological compromise, even paraplegia and/or bowel and bladder incontinence, by compression to the spinal cord and/or the spinal nerve roots.

Metastases to the bones occur whenever tumor cells, transferred usually via the blood flow, attach to bone marrow and matrix, wherein reside and uncontrollably proliferate. This aberrant cellular growth results in stimulation of osteoclasts, producing osteolytic damage to the bone, and osteoblasts, producing new bone formation. These opposing processes occur in varying combinations, depending on the type of the tumor, but, overall by altering the normal bone remodeling, they result in damage of varying degree. This is clinically manifested with pathological fractures, pain, neurological impairment, and hypercalcemia.

Treatment is mainly based on analgesic medications, such as opioids and NSAID medications administered alone or in combinations, but effective pain control may be limited by the development of side effects in high doses. Other treatment options may be helpful, such as radiation therapy or interventional techniques, but even these are not without significant drawbacks. One of the main reasons for lack of specific, efficacious treatments is the lack of clear understanding of the basic pathophysiology involved in the genesis of pain from metastases to the bones, and its relevant pharmacology.

Animal models of pain have so far facilitated understanding of mechanisms of several types of pain, such as neuropathic (21, 22) or acute post-operative pain (23). Several of these animal models have been shown to be highly predictive of the pathobiology and pharmacology pertinent to human pain states (24).

Until recently no specific animal model existed with regard to simulating the basic pathogenetic mechanisms of cancer pain. The latter remained essentially unknown, and reflected to treatments that were mainly empirically driven rather than based on understanding of the mechanisms and pertinent pharmacology. Most therapies were guided by available clinical observations and studies. Available information from pertinent experimental studies was minimal. Regarding pathophysiology and mechanisms of pain produced by cancer, a known fact was that there is minimal direct innervation of tumors (25), while tumor cells may produce sensitization and/or direct excitation of primary afferent neurons by release of pro-nociceptive mediators, such as prostaglandins, cytokines and various growth factors (26-28).

In an attempt to understand the pathophysiology of cancer pain in a manner that would produce new pertinent knowledge leading to novel therapies for pain, Schwei and Mantyh developed a pertinent mouse model of bone cancer pain, in order to elucidate specific mechanisms that produce pain after

metastases to the bones (29). This has been proven to be a very successful animal model and reliably simulates several features of the cancer-induced bone pain in humans (30). In this model, osteolytic sarcoma cells are injected directly into the intramedullary (bone marrow) space of the femoral bone, and retained within this space by an amalgam plug in the site of the injection, which is sealing the needle hole. Thus, the tumor cells are contained and start proliferating within the intramedullary space, developing changes that characterize a metastatic bone lesion. As the experimental metastatic tumor grows within the femoral bone, subsequent to the bone destruction and stimulation of nociceptive pathways, the following manifestations develop that can be measured or objectively documented as specific and objective end-points:

1. Radiographic findings indicative of bone destruction. In parallel to tumor growth there is radiographic evidence of progressive loss of mineralized bone. This bone destruction increases as the time goes by from the time of the injection. Approximately one week after the sarcoma cell injection there is histological evidence of bone destruction, which becomes radiologically evident by 10 days to two weeks. Usually by the third week post-injection there is complete demineralization and extensive damage of the underlying bone, with pathological fractures frequently evident (31). At about the same time (2-3 weeks) tumor cells break through the bone expanding into the nearby soft tissues, producing a swelling of the extremity size.

2. Quantifiable tumor growth. Transfection of the tumor cells with a fluorescent marker allows observation and quantification of the tumor growth and migration within the bone. It has been thus shown that usually within one week labeled tumor cells are localized nearby the injection site, while after approximately two weeks they have proliferated and occupied the entire intramedullary space within the femoral bone. Later on, these tumor cells break through the bone into the limb soft tissues (2-3

weeks after cell inoculation), producing a macroscopic increase of the limb size from the fourth week (32). Radiologic, histopathologic and macroscopic expansion of the tumor correlates well with behavioral manifestations of pain.

3. Manifestations of spontaneous and evoked pain. Radiographic findings of bone destruction, as well as tumor growth, are paralleled by reproducible and measurable behavioral manifestations of pain. These are proportional to the extent of the tumor growth and bone damage, and include flinching and guarding of the paw, that can be spontaneous, or evoked by palpation. Thus these manifestations simulate the mechanically induced episodes of breakthrough pain in humans. All these behavioral manifestations of pain develop in parallel and correlate well with the progression of bone damage and the expansion of tumor into the soft tissues (33). There is also initially decreased responsiveness to thermal stimuli (thermal hypoalgesia). With the expansion of the tumor, however, thermal hypoalgesia is replaced by thermal hyperalgesia (increased responsiveness to noxious heat) after the fourth week, while initial manifestations of spontaneous pain and mechanical hyperalgesia intensify reaching a peak 3 weeks post-injection. The initial paradoxical thermal hypoalgesia has been attributed to activation of endogenous opioid mechanisms (32). These mediate descending analgesic systems or inhibitory circuits in the dorsal horns. Activated endogenous opioid mechanisms may explain the fact that some patients may remain free of any painful manifestations of metastatic bone cancer until the later stages of the disease. The subsequent development of thermal hyperalgesia may be secondary to release of pro-nociceptive substances by the tumor cells, such as endothelin-1, a mediator able to induce thermal hyperalgesia (34). Furthermore tumor development has been shown to induce development of spontaneous electrical activity and sensitization of C-fibers which provide innervation in and around the affected bone (35). The role of endogenous opioid-ergic

analgesia systems has been also demonstrated by Mantyh's group, in another animal cancer pain model, wherein genetically modified transgenic mice under control of a promoter, spontaneously develop pancreatic cancer. Only mice with advanced pancreatic cancer, but not those in early stages, display spontaneous, morphine-reversible visceral pain behaviors. However, rats with early stage cancer exhibit significant pain behaviors too, after administration of opioid receptor antagonists (naloxone or naltrexone). These findings indicate that endogenous CNS opioid-dependent mechanisms tonically modulate pancreatic cancer pain at early and late stages, and may mask cancer pain in early stages (36). It is likely that in several types of cancer, the slow and gradual development of tumor growth provides a persistent, ongoing low-grade nociceptive input to the CNS that induces the activation of endogenous modulatory circuits. These suppress initial pain, but are overridden at later, more advanced stages of cancer, leading to the eventual perception of cancer pain.

The specificity of this experimental model of metastatic bone cancer pain, induced by cancer tumors metastasizing to the bones, as well as its capacity to simulate the underlying pathophysiological mechanisms, is indicated by the following observations:

1. Structural and functional reorganization of the dorsal horns of the spinal cord as a result of incoming pain signaling is a well-known manifestation of chronic pain states. However, the reorganization pattern observed in the mouse model of metastatic bone pain is specific, and distinctly different than the patterns observed after chronic inflammatory or neuropathic pain. In addition, these alterations correlate well with the extent of bone destruction as a result of the tumor growth. Specifically, in this model, afferent traffic of signals of pain induce a significant, distinct pattern of neuroplasticity with reorganization of the spinal cord segments that receive these signals. Ipsilateral to the affected bone in the spinal cord, a mas-

sive astrocyte hypertrophy develops, as evident by a profound increase in glial fibrillary acidic protein (GFAP) staining, without neuronal loss. There is also an ipsilateral up-regulation in the expression of the pro-hyperalgesic peptide dynorphin and c-fos protein in neurons in the deep laminae of the dorsal horn. Additionally, normally innocuous palpation of the limb with cancer induces the internalization of the substance P receptor, and c-fos expression in lamina I neurons, as well as behaviors indicative of pain (allodynia).

2. This model is representative of the basic mechanisms involved in the mediation of bone cancer pain. This was shown by selectively blocking the aberrant osteoclastic activity, that accompanies cancer growth in the bone, by osteoprotegerin (OPG). Osteoprotegerin is a decoy receptor that inhibits osteoclasts by binding a specific ligand (OPGL) that activates them. Osteoprotegerin inhibits bone destruction by osteolysis, the neurochemical reorganization of the spinal cord, as well as the behavioral manifestations of pain.

The correlation between anatomical progression and behavioral manifestations of pain, as well as similarities in the relative potency of treatments needed to suppress pain, indicate also the fact that this model simulates reliably several features of the clinical disease in humans. With regards to the latter, it has been shown that both the pain behavior induced in the mouse model of bone cancer pain, as well as the clinical pain in humans with bone metastases, are equally poorly responsive to opioids, compared to inflammatory pain (37). These observations validated the mouse metastatic bone pain model as adequate to elucidate mechanisms responsible for bone cancer pain, as well as the pertinent pharmacology, which may guide the development of new drugs to fight this type of pain (38).

Other cancer pain models

Variations of the cancer bone pain model developed by Mantyh's group,

are the models of tumor-induced bone destruction and hyperalgesia, produced by implantation of sarcoma cells into the mouse humerus or calcaneus bones. In these latter models, osteolysis begins six days after inoculation and also correlates well with the development of hyperalgesic behavioral responses (34, 39).

Information derived from the mouse bone cancer pain model

Utilizing the mouse metastatic bone pain model, the following information has been derived:

The role of osteoclasts.

Osteoclasts play a key role in the pathogenesis of pain. Osteoclasts are highly differentiated multinucleated cells, derived from monocyte lines, that play a role in normal bone remodeling by bone resorption. In metastases to bones, what primarily mediates bone destruction and pain is aberrant activation of osteoclasts.

In the bone cancer pain model, within a few days after tumor injection, a marked increase in the number of osteoclasts occurs, associated also with signs of maturation (such as presence of multiple nuclei) (40). Proliferation and hypertrophy of osteoclasts develops in both osteolytic and osteoblastic types of metastatic cancer disease. Active osteoclasts in contact with mineralized bone are continually internalizing products of mineralization, thus destroying the bone, and leading to pain via several specific mechanisms:

1. **Altered bone remodeling and mechanical instability.** As a result of the activity of the osteoclasts leading to osteolysis, normal bone architecture and structural integrity is disrupted, leading to mechanical instability of the bone. Certain parts of the bone, such as the periosteum and bone marrow, contain a rich innervation by peripheral sensory neurons. The disruption of mechanical stability of the bone may produce mechanical deformation of the periosteum, which results in pain by stimulation of mechanoreceptors present on the sensory neurons that

densely innervate it, as well as the bone. Deformation of the periosteum may thus generate intense, sharp pain from stimulation of these mechanoreceptors (41).

2. **Local extracellular acidosis.** Osteoclastic activity leads to release of protons (H^+) and the development of an acidic extracellular micro-environment (pH 4.0-5.0) in the vicinity of osteolysis. This is essential for the osteoclast-mediated bone resorption, but also stimulates pH-sensitive nociceptors, which extensively innervate the bones, thus producing pain. Additionally, protons may be released directly by the tumor cells, as well. Low extracellular pH is a characteristic feature of tumors, and especially those with necrosis. On the other hand, sensory neurons mediating pain express a variety of channels that can open as a response to sensing protons. These include the transient receptor potential vanilloid 1 (TRPV1) and the acid sensing ion channel 3 (ASIC 3) channels, which are sensitized and activated as a result of pH drop after accumulation of protons. Thus noxious stimulation by acidosis may initiate pain signaling mediating cancer pain (30, 42-44).

3. **Release of pro-algesic factors.** Osteolysis produced by activated osteoclasts, results in release of growth factors, such as tumor growth factor β (TGF- β), which are normally contained in the bone (45, 46). These growth factors can directly activate nociceptors and produce pain (47). Other pro-hyperalgesic peptides, such as dynorphin, associated with chronic pain states induced by peripheral nerve injury (48, 49) are also up-regulated by bone cancer pain.

4. **Nerve injury.** Excessive activity of the osteoclasts may also result in direct injury of peripheral sensory fibers, thus leading to neuropathic pain. This has been shown by Sevcik et al who documented a significant up-regulation of activating transcription factor 3 (ATF-3), a marker of nerve fiber injury, by metastatic bone cancer pain (40).

5. **Inflammation.** Within a tumor mass, in addition to malignant cells, several

other cell types may be contained, such as inflammatory cells. Tumor-associated macrophages have been estimated to comprise a considerable portion (2–60%) of the total tumor mass (50, 51). This is also the case in the mouse bone cancer pain model, wherein 5–10% of the mass have been macrophages (52). Inflammatory cells and malignant cells secrete a variety of substances that sensitize or excite primary afferent nociceptors. These mediators include but are not limited to prostaglandins, cytokines, and various growth factors such as epidermal growth factor, nerve growth factor, transforming growth factor and platelet-derived growth factor. These mediators have the capacity to sensitize and/or excite primary afferent nociceptors, thus contributing to clinical pain and hyperalgesia (26–28, 53). Prostaglandins, highly involved in nociceptive processes and mediation of pain, have been shown to be released at high levels by tumors and tumor-associated macrophages, that express high levels of cyclo-oxygenase (42). Thus, NSAIDs may have a significant therapeutic role in the management of cancer pain.

6. The role of nerve growth factor (NGF) and endothelin. Specific attention and attempts aiming at pharmacological suppression have focused on NGF and endothelin-1. The potentiating role of NGF in mediating inflammatory and neuropathic pain states has been well recognized (54–57), as well as the antihyperalgesic effect of NGF sequestration (55). Secretion of NGF by tumor cells has been also implicated in the pathophysiology of cancer pain (58). The results of a study, wherein anti-NGF therapy produced significant analgesia, as well as reversed indices of peripheral and central sensitization in the mouse bone cancer pain model, indicate the potential role of NGF as a mediator of neural sensitization and mediator of pain (59). Cancer tumors express high levels of a family of vasoactive peptides, called endothelins. Plasma levels of endothelins have been associated with pain severity in cancer patients (60). Release

of endothelin-1 from tumor cells (34) has been implicated in the induction of thermal hyperalgesia. Furthermore, in the same model of bone cancer pain in mice, tumor growth has been reported to induce development of spontaneous electrical activity and sensitization of C-fibers, which provide innervation in and around the affected bone (35). It has been shown that some small unmyelinated primary afferent fibers express endothelin receptors, the activation of which may result in sensitization or excitation (61).

7. Glial activation resulting from the bone cancer pain. The role of activation of glial cells, such as astrocytes, has gained recently significant recognition as contributing to the pathogenesis of chronic pain (62, 63). Painful osteolytic destruction of the femoral bone as a result of experimental tumor growth results in ipsilateral hypertrophy of astrocytes in the spinal cord, as measured using the glial fibrillary acidic protein (GFAP) marker (29, 64, 65).

Data guiding treatments for bone cancer pain: translational implications.

Opioids.

There is no doubt that pain from metastases of tumors to the bones responds to opioids. In sarcoma-injected mice, El Mouedden and Meert demonstrated that acute treatment with fentanyl, sufentanil, and morphine, were effective in reducing bone cancer pain-related behaviors in a dose-dependent manner (33). Nevertheless, this analgesic response is rather poor compared to the responses in other types of pain (32). Morphine analgesia, also, does not affect limb use during forced ambulation, which is decreased (as expected) in the bone cancer pain model (66). Only very high doses (40 mg/kg) produced some slight amelioration, consistent with other observations, as well (37). This may help explain the fact that pain with activity or movement in humans, suffering from metastatic bone disease, may often be resistant to analgesic therapy with opioids or require high doses for suppression.

Compared to inflammatory pain behavior of the same intensity, mice need 10 times more morphine for effective suppression of pain behavior induced by the bone cancer model (37). This is consistent with observations in humans suffering from metastases to the bones, requiring much higher doses of opioids for pain control, compared to other types of pain. This very low potency of morphine to improve performance at forced ambulation (rotarod) may imply that the bone cancer pain model leads to some kind of ambulatory breakthrough pain during forced ambulation. Thus, it reproduces the observation that breakthrough pain episodes respond poorly to morphine in humans with advanced cancer, wherein the incidence and severity of these episodes (especially during weight bearing or ambulation) increases with the magnitude of osteolytic damage (67).

Clinically, opioids effectively relieve cancer pain, although high doses have to be administered at times, especially to suppress incident “breakthrough” pain, or pain from nerve involvement. The direct effect of these commonly used drugs on tumor growth has been also investigated in vitro and in vivo. In vitro morphine has an inhibitory effect on growth of several human cancer lines, by suppression of tumor promoters, such as tumor necrosis factor α (TNF- α) (68). On the other hand, morphine may enhance tumor growth in animals inoculated with tumor cells (apparently via an immunosuppressant effect) (69), and reduce survival of rats with tumors (70). Clinically, ongoing, under-treated pain from cancer in humans may reduce survival by inducing a stress response with subsequent suppression of the immune system, a notion supported by experimental evidence in animals. Rats with painful stress from tumors exhibit reduced survival (71), while stress facilitates carcinogenesis in rats, in a fashion inhibited by opioid antagonists (72). Thus, whether opioids reduce or promote cancer growth is a matter of controversy.

In this context, the question whether opioids aggravate or inhibit cancer

growth was investigated by Sasamura et al, who inoculated melanoma cells into the hind paw of mice. Animals developed hyperalgesic responses, of moderate intensity initially (between days 7-10 post injection) and subsequently of severe intensity (after two weeks post-injection), in parallel with swelling of the injected paw volume. Metastases to the lungs were evident after post-inoculation day 12. Compared to control animals, mice treated with repeated subcutaneous morphine injections in doses that completely inhibited hyperalgesia, or sciatic neurectomy (thus interrupting nociceptive traffic from the site of tumor growth), exhibited marked inhibition of tumor growth and lung metastases. These findings indicate that effective relief from cancer pain inhibits tumor and the progression of metastatic disease (73). In the same study, diclofenac also inhibited the hyperalgesia at the early phases (during the first three weeks post-inoculation) indicating the relevant contribution of inflammatory mechanisms in the mediation of tumor-induced hyperalgesic responses.

Considering the additional experimental evidence that different types of stress may suppress immunity and enhance cancer growth and metastatic spread (74-78), as well as additional evidence indicating that morphine analgesia attenuates surgery-induced enhancement of metastatic colonization in rats (79), it is arguable that effective relief from pain by medication or neural blockade in cancer patients in addition to improving comfort and quality of life, does have the capacity to inhibit tumor expansion and metastatic spread as well.

Biphosphonates

Biphosphonates relieve pain from metastases to bones. Biphosphonate compounds are drugs with high affinity to calcium ions that are contained in the hydroxy-apatite crystals of the bones, something that results in a significant distribution and binding of these drugs into the mineralized bone tissue (more than 50% even after a single dose) (80). At these sites, they have the capacity

to suppress the activity of the osteoclasts, and consequently to inhibit bone resorption and lysis (81). Thus, they are helpful in the management of osteoporosis, as well as in the treatment of tumor-induced osteolysis and bone cancer pain.

This was also shown experimentally in the mouse bone cancer pain model, wherein alendronate, a biphosphonate compound, decreases pain, as well as destruction of bone and sensory nerve fibers, produced by the uncontrollable activation of the osteoclasts. Sevcik et al injected osteolytic sarcoma cells, stably transfected with green fluorescent protein (GFP), into the intramedullary space of the mouse femur. Mice were in parallel treated with alendronate (chronically, from the time of the injection until bone cancer pain became severe), or vehicle (40). Sarcoma-injected animals developed a significant spontaneous and evoked pain behavior, which was significantly attenuated by alendronate. Alendronate also facilitated limb use, ambulation, and tolerance of palpation or pressure. Improvement in behavioral parameters, paralleled the attenuation of markers indicative of peripheral or central sensitization, induced by the tumor. Specifically, alendronate reduced the levels of ATF-3, a marker of neuronal injury. It also attenuated the expression of galanin, which was significantly increased in vehicle-treated, sarcoma-injected rats. Galanin levels increase in peripheral sensory neurons in several chronic pain models (82). GFAP labeling in the spinal cord, indicative of glial activation by astrocyte hypertrophy by bone cancer pain in sarcoma-injected animals, was significantly attenuated by alendronate, compared to vehicle-treated mice. Finally, treatment of sarcoma-injected mice with alendronate significantly decreased galanin (which is involved in the maintenance of chronic pain, and was upregulated in the sarcoma-injected, vehicle-treated mice). Finally, it was shown that alendronate reduces tumor-induced bone destruction, via decreasing the number of activated osteoclasts without affecting their total

number. Alendronate treatment did not change viable tumor load (defined as the percent of the intramedullary space occupied by viable, non-necrotic tumor tissue), although both tumor growth and tumor necrosis increased.

Biphosphonates may exert analgesic effects via other mechanisms as well, not related to the inhibitory effects on osteoclasts. These drugs have been shown to relieve pain in peripheral neuropathic pain syndromes, of non-malignant etiology, such as complex regional pain syndromes (83, 84). Kawabata et al reported that etidronate and alendronate suppress adjuvant-induced mechanical allodynia in rats, which might be clinically relevant. Anti-allodynic effect of biphosphonates was reversible by glibenclamide in a fashion suggesting involvement of adenosine triphosphate-sensitive potassium (K_{ATP}) channels (85). These channels are present on peripheral sensory neurons and are involved in the pathophysiology of nociception and neuropathic pain (86), so that their activation by biphosphonates may induce a peripheral analgesic effect, as well.

Osteoprotegerin

Osteoprotegerin (OPG), a molecule that belongs to the soluble tumor necrosis factor (TNF) receptor superfamily (87-89) seems to be a very promising candidate as a potential therapeutic agent in the management of bone cancer pain. Osteoprotegerin acts as a secreted decoy receptor that binds to, and thus sequesters a cognate ligand, the OPG ligand (OPGL). The bound, sequestered ligand is thus prevented from activating its cellular target, which is the receptor activator of nuclear factor- κ (RANK receptor), a specific receptor expressed on mature osteoclasts. The RANK receptor is essential for the function of osteoclasts, because it mediates their activation and bone resorption.

The OPG ligand in the adult is derived mainly from the osteoblasts, as well as from activated T cells. Osteoblasts are cells essential in the bone remodeling, by directly producing new bone formation, as well as by secreting the OPG

ligand which subsequently regulates the bone resorption by stimulating by the osteoclasts (90). Thus osteoclastic activity is coupled to osteoblastic activity, resulting in a balanced bone remodeling process. This normal process of remodeling is however disrupted in bone cancer resulting in aberrant and out of proportion bone destruction and pain. Immune T cells may be also activated by cytokines and growth factors released by tumor cells, and also be a source of OPG ligand release. Considering the capacity of OPG ligand to stimulate osteoclasts, it is an important mediator of bone cancer pain, wherein bone damage and hyperalgesia are mediated by increased activity of the osteoclasts.

Honore et al, employing the mouse bone cancer pain model, reported that treatment with OPG completely abolishes cancer-induced bone destruction, reduces the number of osteoclasts at sites of tumor, substantially suppresses spontaneous and evoked pain-related behaviors, and finally prevents the neurochemical reorganization of the spinal cord seen in mice with bone cancer pain (38, 91). The latter action of osteoprotegerin includes attenuation of dynorphin immunoreactivity in laminae III-IV neurons, reduced c-fos immunoreactivity in neurons in laminae V-VI, as well as reduced GFAP in laminae I-X, (indicative of blocked astrocyte hypertrophy in the spinal cord by OPG). Palpation induced substance P release, substance P receptor internalization, and palpation-induced c-fos expression seen in the spinal cords of sarcoma-injected mice were also blocked by osteoprotegerin. The action of OPG was rapid. Within 2 days after a single injection there was a substantial inhibition of bone absorption, but in this study it was administered as daily subcutaneous injections (91).

The mechanism of action of OPG, on blocking cancer-induced bone destruction and pain via inhibition of the actions of OPG ligand on osteoclasts, is supported by the observation that OPG eliminates activated osteoclasts at the site of the tumor growth, as well as

tumor induced osteolysis, but has no substantial effect on the tumor growth itself. Nevertheless, in the mice treated with OPG, pain was reduced in parallel with the reduction of bone damage.

The potential of OPG as a very promising therapeutic agent against cancer pain remains to be investigated in human patients. OPG so far seems to be free of any side effects, and has actually been successfully administered in postmenopausal women for the management of osteoporosis (92).

Non-steroidal anti-inflammatory drugs and acetaminophen

NSAID are frequently used as analgesics in cancer patients. Saito et al employing the mouse bone cancer pain model investigated the pharmacological efficacy of selective COX-1 or COX-2 inhibitors, non-selective COX inhibitors, acetaminophen and morphine on bone cancer pain. Analgesia was assessed after drugs were administered 2 weeks post-injection of sarcoma cells into mouse femur (a time point at which radiographic examination demonstrated severe destruction of the injected femur, associated with significant pain-related behaviors). Oral administration of acetaminophen, indomethacin, and morphine, but not of SC560 (a COX-1 selective inhibitor) or celecoxib, produced an analgesic effect, while co-administration of subanalgesic doses of morphine with acetaminophen enhanced the analgesic effect of the latter (93). Thus, experimental evidence was provided supporting the efficacy of the classical (but not selective COX inhibitors) against bone cancer pain.

Diet

Alternative therapies, some of them based on diet alterations, are recently emerging as part of cancer pain management on a more frequently basis. Zhao et al investigated the effect of the type of diet on three experimental models of bone cancer pain by inoculation of sarcoma cells into the intramedullary space of the mouse humerus, femur or calcaneus. Diets based on casein or soy proteins had no impact on parameters reflecting cancer growth, nor did

affect the antihyperalgesic pharmacological effect of morphine. However, mice subjected to the femur bone cancer pain model exhibited significantly less mechanical hyperalgesia. So it is likely that soy diet may be beneficial in bone cancer pain (39).

Anti-NGF therapy

Because NGF release by tumor cells has been implicated as a possible mediator of cancer pain, Sevcik et al investigated the therapeutic potential of anti-NGF therapy employing the mouse model of bone cancer pain (59). Both spontaneous and movement-induced pain behaviors were attenuated by a novel antibody that sequesters NGF (anti-NGF, mAb 911, Rinat Neuroscience Corp., Palo Alto, CA, USA), in a magnitude greater than that of high dose morphine. Several neurochemical changes indicative of peripheral and central sensitization were also reduced by this therapy: The expression of ATF-3, a marker of nerve injury, is attenuated, activated macrophage infiltration is limited, while at the spinal cord dynorphin expression and immediate early gene activation (upregulated in sarcoma injected mice) is reduced, too. The results of this study indicate that anti-NGF therapy is particularly effective in blocking bone cancer pain, but efficacy in humans remains to be determined clinically.

Endothelin receptor antagonists

Because endothelins, acting on specific receptors present on the membrane of a subpopulation of small unmyelinated primary afferents, sensitize these nociceptors thus mediating cancer pain, their antagonism may have a role in cancer pain management. In the mouse bone cancer pain model, an endothelin A receptor selective antagonist produced significant alleviation of spontaneous and evoked pain behaviors after acute or chronic administration. The latter also resulted in attenuation of peripheral and central sensitization (94). This provides a target for therapeutic interventions, considering the role of endothelins in clinical pain as well (34).

Bradykinin antagonists

In the mouse bone cancer pain model,

Sevcik et al showed that spontaneous and movement evoked pain behaviors may be significantly attenuated by blockade of the bradykinin B1 receptor, even in advanced bone cancer (95). Peripheral sensory neurons normally express both B2 (at high levels) and B1 receptors (at low levels), but the latter get up-regulated following peripheral inflammation or injury, such as tumor-induced (42). In these cases, also, bradykinin released by tumor cells may be associated with increased receptor activation, resulting in pain.

Gabapentin

Gabapentin, a novel anticonvulsant with antihyperalgesic effects, acting as an inhibitor of voltage-gated calcium channels (96) that control neurotransmitter release on peripheral sensory neurons (97), is used widely in the management of pain originating from peripheral nerve injury (98, 99).

Sensory fibers innervating the affected femur have been shown to become sensitized and injured, following inoculation of sarcoma cells in the mouse bone cancer pain model. The tumor-induced sensory nerve injury is characterized by upregulated expression of activating ATF3 in the nuclei of injured neurons (a specific marker of nerve injury), increased expression of galanin on sensory neurons, as well as signs of glial activation and hypertrophy of satellite cells and macrophage infiltration within the ipsilateral dorsal root ganglia. These changes are accompanied by behavior manifestations of spontaneous and movement-induced pain. Chronic treatment with gabapentin, without affecting bone destruction or tumor growth, attenuated both spontaneous and movement-evoked bone cancer pain behaviors, thus justifying its use as a potential adjuvant in bone cancer pain (100). Similar results have been shown also by Donovan-Rodriguez et al in another study employing a metastatic bone cancer pain model (101). In this study cancer induced bone pain was established in rats after inoculating cancer cells into the tibia, resulting in neuronal hyper-excitability at the superficial dorsal horns of the

spinal cord, accompanied by behavioral manifestations of pain. Gabapentin administered acutely and chronically normalized the hyperexcitable superficial dorsal horn neuronal response, significantly reducing electrical-evoked and mechanical-evoked (but not thermal-evoked) responses. Chronic administration of gabapentin also significantly attenuated pain behavior in injected rats, restoring responses to preoperative baseline degrees.

Results demonstrating an analgesic effect of gabapentin against cancer-induced pain have been shown by Kuraishi et al, in another cancer pain model, after orthotopic inoculation of melanocytes into the plantar region of mouse hind paw. This produced marked tactile allodynia and mechanical hyperalgesia, which were inhibited by oral gabapentin without effects on gross behaviors. Diclofenac, mexiletine, clonidine and suramin were without effects on allodynia and hyperalgesia. Subcutaneous injections of and NG-nitro-L-arginine methyl ester were also without effects. Repeated administration of gabapentin (150 mg/kg, p.o.) produced constant inhibitions, suggesting no analgesic tolerance (102). These studies indicate the potential of gabapentin as a useful adjuvant drug in the management of cancer pain.

Clinical management of cancer pain. What is the evidence?

Pain secondary to cancer is complex and its treatment should be individualized in order to achieve optimum effect. Successful management depends upon understanding of all factors possibly involved in mediating and sustaining pain in a particular individual, as well as upon familiarity with all established and novel therapeutic approaches. Systemic pharmacologic management aiming at reducing nociceptive input, modulating transmission of pain to the central nervous system, or altering central perception of pain remains as the mainstay of the treatment. The classical algorithm based on the analgesic ladder

introduced by the WHO (103) provides a general frame of action, so that no cancer patient should live or die with unrelieved pain (104) (105).

The three-step analgesic ladder includes the regular administration of non-opioid analgesics for mild pain (step 1), weak opioids for mild to moderate pain (step 2), and long-acting strong opioids (round the clock) with immediate-acting opioids (as needed for breakthrough pain) for moderate to severe pain (step 3). The ladder also mandates the use of non-opioid analgesics (NSAIDs), adjuvant drugs (such as anticonvulsants, antidepressants or corticosteroids) and additional measures for pain relief, when appropriate (106). These non-opioid analgesics and adjuvants need to be included at each step of the WHO ladder, if pain cannot be treated adequately by the standard analgesics alone (107). Proper use of the WHO three step analgesic ladder provides effective relief in the majority of cancer patients with pain (106).

The appropriate selection of adjuvants (such as anticonvulsants, like gabapentin, to control neuropathic manifestations, and/or tricyclic antidepressants, which provide additional analgesic efficacy against certain types of pain or other symptoms like insomnia or depression) should be guided by proper identification of the exact nature of pain, and an attempt to establish a diagnosis as precise as possible with regard to exact nature of the painful syndrome. Sometimes, failure to achieve therapeutic efficacy may be secondary to pharmacokinetic reasons, such as inadequate route of administration. The latter may be corrected by choosing more suitable routes, such as transdermal and transmucosal fentanyl in patients with poor absorption of oral opioids from the gastrointestinal tract. Furthermore, when advancing into higher steps of the analgesic ladder a reassessment is necessary whether adjuvant and non-opioid analgesics are necessary. Not infrequently, discontinuation of these drugs may result in worsening of pain, because certain types of pain may be particularly responsive to these drugs.

Most neuropathic pain syndromes are resistant to opioids (108) but may respond adequately to gabapentin (98, 99) or antidepressants (109-111). Furthermore, combinations of analgesics, such as gabapentin with opioids, result in synergistic effects which potentiate the analgesic benefit of each component (112). Finally, any therapeutic plan should also include the use of physical therapy, psychotherapeutic, spiritual or religious, as well as anesthetic interventional (113-116) and neurosurgical approaches, whenever necessary. The new models of cancer pain have recently facilitated a mechanism-based understanding of the factors that generate and maintain cancer pain as well as pertinent pharmacology. Findings from these studies have the potential to provide new mechanism-based therapies that may improve the quality of life and survival of cancer patients, but eventually therapies need to be endorsed by accumulating evidence, such as that provided by converging lines of research. Systematic reviews of the best available evidence on cancer pain management is a valuable source of information guiding the implementation of novel therapies or the continuing application of existing ones (117). The availability of such reviews on pain management and palliative care is increasing through the efforts of groups such as the Cochrane Collaboration. The dissemination of pertinent evidence to health professionals dealing with cancer patients with pain has the potential of improving the quality of patient care.

Preventative treatments

Pain related to cancer and its treatments may be prevented by suitable preventative strategies. Studies by Fassoulaki et al. have demonstrated that suitable perioperative analgesic regimens, mainly based on multimodal analgesic techniques, can significantly reduce the incidence and severity of chronic post-mastectomy pain in women after breast surgery for cancer (15-18). These regimens are based on the concomitant perioperative use of gabapentin, sodium channel blockers

(administered topically or systemically) and local anesthetics administered topically or in nerve infiltrations.

Opioid analgesia for cancer pain

Wiffen et al conducted a systematic review in order to assess the efficacy of oral morphine in relieving cancer pain, as well the incidence and severity of side effects (118). Forty five published randomized controlled studies (on 3061 subjects) were included in the meta-analysis, in which morphine was shown to be an effective analgesic for cancer pain. Pain relief did not differ between sustained-release and immediate-release morphine formulations. Sustained release morphine doses were effective for 12 or 24 hour dosing, depending on the formulation. Adverse effects were not uncommon but only 4% of patients discontinued treatment because of intolerable adverse effects. Methadone, a synthetic opioid, seems to offer certain pharmacokinetic and pharmacodynamic advantages over morphine in the context of cancer pain management (119), including longer half life, as well as a weak inhibitory effect on the N-methyl-D-aspartate (NMDA) receptor (120). The implications of the latter action may be a lower propensity to induce tolerance or opioid-induced hyperalgesia, and some suppression of signaling mechanisms leading to central sensitization. Nevertheless, the pharmacokinetic behavior of this drug is characterized by unpredictability and significant inter-individual variability, indicating extreme caution in its dosage titration. With regards to cancer pain management, Nicholson conducted a relevant systematic review on eight randomized controlled trials of methadone against active or placebo comparator in patients with cancer pain (five double blinded, two crossover with 356 recruits and 326 completing patients) (121). Methadone's analgesic efficacy was shown to be similar to that of morphine while adverse events were also similar in incidence and severity to those experienced with morphine. Nevertheless, the majority of studies involved single

dose comparisons or short-term use, something that may overlook the potential of methadone accumulation leading to delayed onset of adverse effects with chronic administration. Fixed interval dosing schedules conducted over several days are associated with a high risk of serious morbidity and mortality. The complex and highly individual pharmacokinetics of methadone require that experienced clinicians take responsibility for initiating, titrating and monitoring this drug.

Breakthrough pain is a common and distinct component of cancer pain with a negative impact on quality of life. Breakthrough pain is a transient increase in the pain intensity over the background pain: usually breakthrough pain is of rapid onset, severe in intensity, and generally self-limiting with an average duration of 30 minutes. At present the current approach to managing breakthrough pain is using supplemental analgesia (also known as "rescue" analgesia), employing immediate-release medication at a dose proportional to the total around-the-clock opioid dose. The problem is that not infrequently immediate-release opioids, such as immediate-release morphine, may fail to produce prompt analgesia. Inability to swallow or poor absorption from the gastrointestinal tract have been implicated, thus indicating the need for alternative (preferably non-invasive) routes of administration.

Zeppetella and Ribeiro assessed the evidence for the use of opioids in the management of breakthrough pain in cancer patients, by looking at four studies (393 participants) investigating with the use of oral trans-mucosal fentanyl in the management of breakthrough pain (122). Oral trans-mucosal fentanyl was shown to be an effective analgesic for breakthrough pain, superior to placebo and morphine. Pain intensity scores were lower and pain relief scores were higher for patients receiving oral trans-mucosal fentanyl at all times, as well as global assessment indices (122).

Development of unwanted phenomena associated with the chronic use of opioids, such as side effects associated

with high doses, tolerance, and hyperalgesia, may provide a hindrance to their continuing use on certain patients. In these cases, ketamine, an anesthetic and analgesic agent with a partial antagonist effect on the NMDA receptor, may be helpful as an adjuvant to opioids, but its use may be limited by psychomimetic effects. Bell et al determined the effectiveness and adverse effects of ketamine as an adjuvant to opioids in the treatment of cancer pain, by looking at four randomized controlled trials and 32 case studies/case series reports, comparing ketamine to placebo or active control (123). Two eligible trials concluded that ketamine improves the efficacy of morphine in the treatment of cancer pain, at the expense of hallucinations in some patients. Hallucinations may also occur in morphine alone. However, considering the small number of patients and the significant heterogeneity in these studies, it is not possible to conclude with certainty about the benefits and harms of ketamine as an adjuvant to opioids for the relief of cancer pain.

Non-steroidal anti-inflammatory drugs (NSAIDs) and/or acetaminophen for cancer pain

Non-steroidal anti-inflammatory agents are widely used to treat cancer pain, alone—in the initial WHO analgesic ladder step—, or in combination with opioids—in the subsequent steps. In order to assess which agent is most clinically efficacious for relieving cancer-related pain, or even what may be the additional benefit of combining an NSAID with an opioid in this setting, McNicol et al looked at 42 pertinent trials involving 3084 patients, in a qualitative systematic review (124). They concluded the following:

1. NSAIDs appear to be more effective than placebo for cancer pain;
2. There is no clear evidence to support superior safety or efficacy of one NSAID over another;
3. Trials of combinations of an NSAID with an opioid have shown either no difference (4 out of 14 papers), a statis-

tically insignificant trend towards superiority (1 out of 14 papers), or at most a slight but statistically significant advantage (9 out of 14 papers), compared with either single entity.

4. No generalizations can be made regarding efficacy and safety of NSAIDs for cancer pain.

It seems likely that particular subpopulations of patients suffering from cancer pain may particularly benefit from inclusion of NSAIDs in their analgesic regimen. These may be patients with painful metastatic disease affecting the bones or patients with significant pain, mediated by predominant inflammatory mechanisms. However, this needs to be confirmed by additional evidence.

Biphosphonates

Certain malignancies (such as breast cancer, kidney cancer, thyroid cancer, multiple myeloma) are very frequently complicated by metastatic disease or lytic lesions affecting the bones. Bony metastatic disease, in particular, affects more than half of women with breast cancer during the course of their disease, and management of pain arising from this condition may be challenging. Tumors that compromise bone or nervous structures due to the bone destruction process may be very painful. As mentioned above, pain occurs as a result of bone destruction and, as more destruction ensues, more pain can be experienced. Functional limitation and neurological impairment may be additional problems. Relief of pain from bone metastases is based on treating the cancer itself, radiotherapy, conventional analgesics (opioids and/or NSAIDs) and specific drugs such as biphosphonates, calcitonin or radioactive agents.

In the mouse bone cancer pain model it has been clearly demonstrated that biphosphonate compounds inhibit osteoclast-mediated bone resorption, and suppress associated pain behaviors (40). Therapeutically they have a role in treating painful metastatic disease involving bones, as well as tumor related hypercalcemia. Pavlakis et al reviewed the clinical efficacy of biphos-

phonates in treating bone pain, quality of life and survival in 2189 women with early and advanced breast cancer by looking at 21 randomized studies (125). In women with advanced breast cancer and clinically evident bone metastases, the use of bisphosphonates (oral or intravenous) reduces the risk of developing an adverse skeletal event such as pathological fracture, as well as delays the time to skeletal event. The bisphosphonate most effective in reducing the risk of developing a skeletal event by 41% was intravenous zoledronate (4 mg). Bisphosphonates may also significantly reduce bone pain in women with advanced breast cancer and clinically evident bone metastases, thus improving global quality of life. Nevertheless, treatment with bisphosphonates does not appear to affect survival in women with advanced breast cancer. Toxicity associated with bisphosphonates is generally mild and infrequent.

Yuen et al reviewed the efficacy of bisphosphonates in relieving pain in patients with bone metastases from prostate cancer, in 10 randomized controlled studies that involved 1955 patients (126). Response rates to treatment were higher for the treatment group, showing a trend of improved pain relief in the bisphosphonate group, while the rates for skeletal events, such as pathological fractures, were lower for the treatment group, as well. A significant increase in nausea was observed in patients who received bisphosphonates compared to placebo, but no increase in other adverse events was observed. There was no statistically significant difference between the bisphosphonate group and the control group in terms of prostate cancer death, disease progression, radiological response and prostate specific antigen (PSA) levels. Regarding the choice of bisphosphonates or the dose and the route of administration, there are insufficient data so far. Therefore, bisphosphonates should be considered for patients with metastatic prostate cancer for the treatment of refractory bone pain and prevention of skeletal events, but more research is needed to guide the choice

of bisphosphonates, optimal treatment schedule as well as cost-benefit comparisons.

Djullbegovic et al, in addition, reviewed whether adding bisphosphonates to standard therapy in multiple myeloma decreases skeletal-related morbidity (pathological fractures), skeletal-related mortality, as well as overall mortality (127). They also determined the effects of bisphosphonates on pain, quality of life and incidence of hypercalcemia. They looked at 11 randomized trials, investigating the use of bisphosphonates in myeloma (1113 patients) compared with placebo or no treatment as a control group (1070 patients). Analysis demonstrated that bisphosphonates are beneficial in preventing pathological vertebral fractures and in providing relief from pain. The benefit was most apparent with clodronate and pamidronate. However, there was no significant effect of bisphosphonates on mortality, on the reduction of non-vertebral fractures, or on the incidence of hypercalcemia. There were also no significant adverse effects associated with the administration of bisphosphonates.

Calcitonin

The hormone calcitonin, by limiting osteoclastic activity, has the potential to relieve pain in non-malignant chronic pain conditions (such as complex regional pain syndromes, Paget's disease and osteoporosis) (128-130), in cancer patients (131), and also to retain bone density, thus reducing the risk of fractures. Martinez et al assessed the effectiveness of calcitonin in controlling metastatic bone pain and reducing bone complications (hypercalcemia, pathological fractures and nerve compression) in patients with bone metastases (132). Of the two small studies included in the review, one study showed a non-significant effect of calcitonin in the number of patients with total pain reduction, while the second study provided no evidence that calcitonin reduced analgesia consumption in patients with painful bone metastases. Overall, there was no evidence that calcitonin was effective in controlling

complications due to bone metastases, improving quality of life, or patients' survival. Furthermore, although not statistically significant, a greater number of adverse effects were observed in those who received calcitonin. So, the limited evidence currently available does not support the use of calcitonin to control pain from bone metastases. Nevertheless, some selected patients might benefit if other treatment options have failed.

Gabapentin

Basic studies, employing animal cancer pain models, indicate an analgesic effect of gabapentin against cancer pain, as well. It is likely that the drug possesses a generic analgesic and antihyperalgesic effect by modifying channels involved in nociception (86, 96) and neurotransmitter release (133). Confirmation from clinical studies, have shown that gabapentin is effective against pain in cancer patients, as well (134-149).

Gabapentin can be particularly helpful in patients with neuropathic pain (burning pain, shooting pain, allodynia) due to cancer, particularly when pain does not respond to opioids (137, 142, 147, 148, 150). Both pain and dysesthetic symptoms respond well to this drug, which also has an opioid sparing effect as well (142). Effective doses range between approximately 100 and 3000 mg daily (144). Gabapentin has been also helpful in relieving abdominal pain from upper abdominal malignancies, such as pancreatic cancer infiltrating the celiac plexus, thus sparing the need for blockade of the latter structure (145). It is helpful in reducing pain associated with painful procedures in cancer patients (140), as well as in reducing myoclonic movements associated with the use of high doses of opioids in cancer pain (143). Side effects include mainly somnolence, drowsiness and headache (136, 142, 144).

Non-pharmacological management

In addition to appropriate pharmacotherapy, relief of pain from bone metas-

tases can be achieved by treating the tumor using administration of radioactive agents or radiation therapy. Thus, in order to determine the efficacy of radioisotopes to control pain in patients with bone metastases, complications due to bone metastases (hypercalcemia, pathological bone fracture and spinal cord or nerve compression), as well as its efficacy in terms of patient survival and adverse effects, Roque et al looked at randomized controlled trials that compared radioisotopes with placebo, and where the major outcome was either pain or complications of bone metastases assessed at least four weeks after treatment (151). Radioisotopes did actually have a small effect on pain with no difference in analgesic use. Leukocytopenia and thrombocytopenia were the main secondary effects associated with the administration of radioisotopes.

Radiation therapy is another therapeutic modality frequently used for palliation against painful metastatic disease. Sze et al reviewed randomized studies comparing single fraction radiotherapy with multifraction radiotherapy on metastatic bone pain relief and prevention of bone complications (152). Eleven trials that involved 3435 patients were identified. The overall pain response rates for single fraction radiotherapy and multifraction radiotherapy were 60% and 59% respectively, indicating no difference between the two radiotherapy schedules. There was also no difference in complete pain response rates for single fraction radiotherapy and multifraction radiotherapy. However, patients treated by single fraction radiotherapy had a higher re-treatment rate (with 21.5% requiring re-treatment) compared to 7.4% of patients who received multifraction radiotherapy. The pathological fracture rate was also higher in single fraction radiotherapy patients. Three percent of patients treated by single fraction radiotherapy developed pathological fracture compared to 1.6% for those treated by multifraction radiotherapy. The spinal cord compression rates were similar for both treatments.

Interventional treatments for pain control in cancer

The discovery of endogenous opioids and opioid receptors in the central nervous system (CNS) (153-155), and novel techniques of delivery, have allowed the optimization of opioid therapy by delivering the medication centrally (or neuraxially) rather than systemically in patients refractory to systemic treatments. These patients may obtain relief from neuraxial opioid therapy, by epidural, subarachnoid or intra-cerebroventricular infusion. Ballantyne et al have compared intra-cerebroventricular therapy with other neuraxial treatments and attempted to determine whether the former has any benefits over epidural or subarachnoid administration, in terms of efficacy, adverse effects, and complications. Their search did not retrieve any controlled trials, so data from uncontrolled studies were used to compare incidences of analgesic efficacy, adverse effects, and complications. These reported excellent pain relief among 73% patients who received intra-cerebroventricular infusion, compared with 72% of patients with epidural, and 62% subarachnoid administration. Unsatisfactory pain relief was low in all treatment groups. Persistent nausea, persistent and transient urinary retention, transient pruritus, and constipation occurred more frequently with epidural and subarachnoid infusions, while respiratory depression, sedation and confusion were most common with intra-cerebroventricular technique. The incidence of pump infection for epidural and subarachnoid administration was zero. Thus, neuraxial opioid therapy can be effective for managing pain not adequately controlled by systemic treatment in cancer patients.

Various neurolytic procedures may be efficacious for pain control in cancer patients, if pharmacological management fails, or is limited by uncontrollable side effects, or for pain limited in certain anatomical areas, such as the upper abdomen. In the latter case, five randomized controlled trials support the efficacy of celiac plexus blocks for upper abdominal pain secondary to pancreatic or other cancer (117).

Vertebroplasty is a novel procedure by which malignant lesions producing painful pathological fractures of the vertebral bodies can be treated. This procedure consists of fluoroscopically guided percutaneous injection of methyl methacrylate cement (or similar biomaterial) into the collapsed vertebral body. Vertebroplasty thus results in bone strengthening, structural restoration and marked or complete pain relief in most cases (156-158). It also prevents the vertebra from further collapse causing spinal cord compression (159, 160). The pain relief and vertebral consolidation have been attributed to the internal "casting" of the trabecular microfractures by the methyl methacrylate injection (161). The main indications for vertebroplasty are osteolytic metastases and myeloma, painful hemangioma, and osteoporotic vertebral fractures with intractable pain despite optimal medical treatment (156, 157, 162). This procedure does have a role in the management of pain in patients suffering from metastases to the spine, something supported by a large number of studies (156, 158, 160, 162-170). Success rates, with regard to pain relief and functional improvement, are approximately 90%, for up to one year follow up (165-168, 170). Compli-

cations are extremely rare (165, 171), but because of the potential of methyl methacrylate leakage causing intravascular embolic phenomena or compression on the spinal cord or nerve roots, the technique requires expertise and performance in a multidisciplinary environment wherein neurosurgical support is available.

Uncontrolled case series may also highlight a potential for neurosurgical modalities such as cordotomy or rhizotomy for cancer pain relief, when other options have failed (172). Other approaches, such as hypnosis or cognitive-behavioral therapy may be helpful in appropriate patients (117), but definite evidence from adequate studies is still missing (173).

In conclusion, management of pain due to cancer has a potential for improvement, and pertinent animal pain models over the last years have significantly advanced our current knowledge on the pathophysiological mechanisms and pharmacology of cancer pain, especially pain from metastatic disease to the bones. These models are useful tools that guide current therapies and provide a testing ground for mechanism-based novel therapeutic approaches. Several very promising treatments, currently under consideration for clinical use, have originated from these animal models. On the other hand techniques and approaches, such as those based on systematic and qualitative reviews of the literature, confirm efficacious treatments at the clinical levels. Thus, advancement of knowledge amongst researchers and clinicians may result in improvement in the quality of pain control and quality of life of cancer patients.

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