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Treatment options are expanding to improve the management of pain that can accompany metastatic bone disease.

The Management of Pain in Metastatic Bone Disease

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Background: Metastatic bone disease is a common cause of pain in cancer patients. A multidisciplinary approach to treatment is often necessary because simplified analgesic regimens may fail in the face of complex pain generators, especially those involved in the genesis of neuropathic pain. From the origins of formalized guidelines by the World Health Organization (WHO) to recent developments in implantable therapies, great strides have been made to meet the needs of these patients.

Methods: The authors review the existing literature on the pathophysiology and treatment options for pain generated by metastatic bone disease and summarize classic and new approaches.

Results: Relatively recent animal models of malignant bone disease have allowed a better understanding of the intimate mechanisms involved in the genesis of pain, resulting in a mechanistic approach to its treatment. Analgesic strategies can be developed with specific targets in mind to complement the classic, opioid-centered WHO analgesic ladder obtaining improved outcomes and quality of life. Unfortunately, high-quality evidence is difficult to produce in pain medicine, and these concepts are evolving slowly.

Conclusions: Treatment options are expanding for the challenging clinical problem of painful metastatic bone disease. Efforts are concentrated on developing alternative nonopioid approaches that appear to increase the success rate and improve patients' quality of life.

Introduction

Metastatic bone disease is among the most common causes of cancer pain.^{1,2} However, a significant number of these lesions cause no pain or the incidence of pain is unrelated to the size of the tumor.³ The causes leading to the development of pain within a bone tumor have been difficult to investigate, mainly because for many

years, a suitable animal model of cancer pain did not exist. Injection of mouse osteolytic sarcoma cells into the intramedullary space of the mouse femur was the first model created in 1999.⁴ This and newer models have provided advanced insight into the intimate mechanisms of cancer pain.

Primary peripheral nociceptor afferents express a wide variety of receptors that detect noxious stimuli. This is in contrast to most other sensory modalities for which peripheral terminals typically respond to one type of stimulus. The vanilloid receptor-1 (VR1) detects heat, protons (acidity), and lipid metabolites; mechanically gated ion channels respond to mechanical stimuli; purinergic receptors react to adenosine trisphosphate (ATP) and adenosine diphosphate (ADP); and a growing number of other receptors respond to molecules of the "inflammatory soup" such as cytokines, histamine, serotonin, nerve growth factors, prostaglandins, and endothelins.⁵

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Sustained stimulation of these nerve fibers produces plastic changes that contribute to lowering the threshold level of activation. This process is known as peripheral sensitization, the underlying cause of the clinical phenomena of hyperalgesia (mild noxious stimulus is perceived as highly painful) and allodynia (stimulus that would normally be perceived as non-noxious is perceived as noxious), which are hallmarks of neuropathic pain (Fig 1).

Tumors are composed of many types of cells other than malignant ones, including inflammatory mediating immune cells such as macrophages and lymphocytes, and every drug generated to antagonize the products of inflammation, whether recently developed or relied on over the years, has a place in the treatment of pain generated at these sites. Tumors are also acidic, particularly osteoclast-activated osteolytic tumors.⁶ Bisphosphonates induce osteoclast apoptosis and are now used as agents for management of painful bone metastases, as discussed below. Tumor growth activates mechanically sensitive ion channels by distension of nerve fibers, frequently entrapping them and possibly causing aberrant regeneration, a common pathway to neuropathic

transformation, which is another process susceptible to modulation by an increasing number of drugs.

Another phenomenon observed in the cancer pain animal models is the extensive neurochemical reorganization in the spinal cord segments that receive input from primary afferent neurons. These innervate the tumor-bearing bone, demonstrating further means of amplification and perpetuation of the perception of pain or “central sensitization,”⁷ an event also susceptible to neuromodulating drugs.

With expanded understanding of the neurophysiology and related pharmacology of cancer bone pain, we can continue refining the clinical approach to alleviate pain and suffering in these patients, which is the original and possibly most important duty of the medical profession.

Pain Assessment

The presence of bone metastasis can be determined by recording an accurate history, performing a detailed physical examination, and ordering the appropriate imaging studies.

A pain history should include a description of the pain, its onset, radiation, triggering and relieving fac-

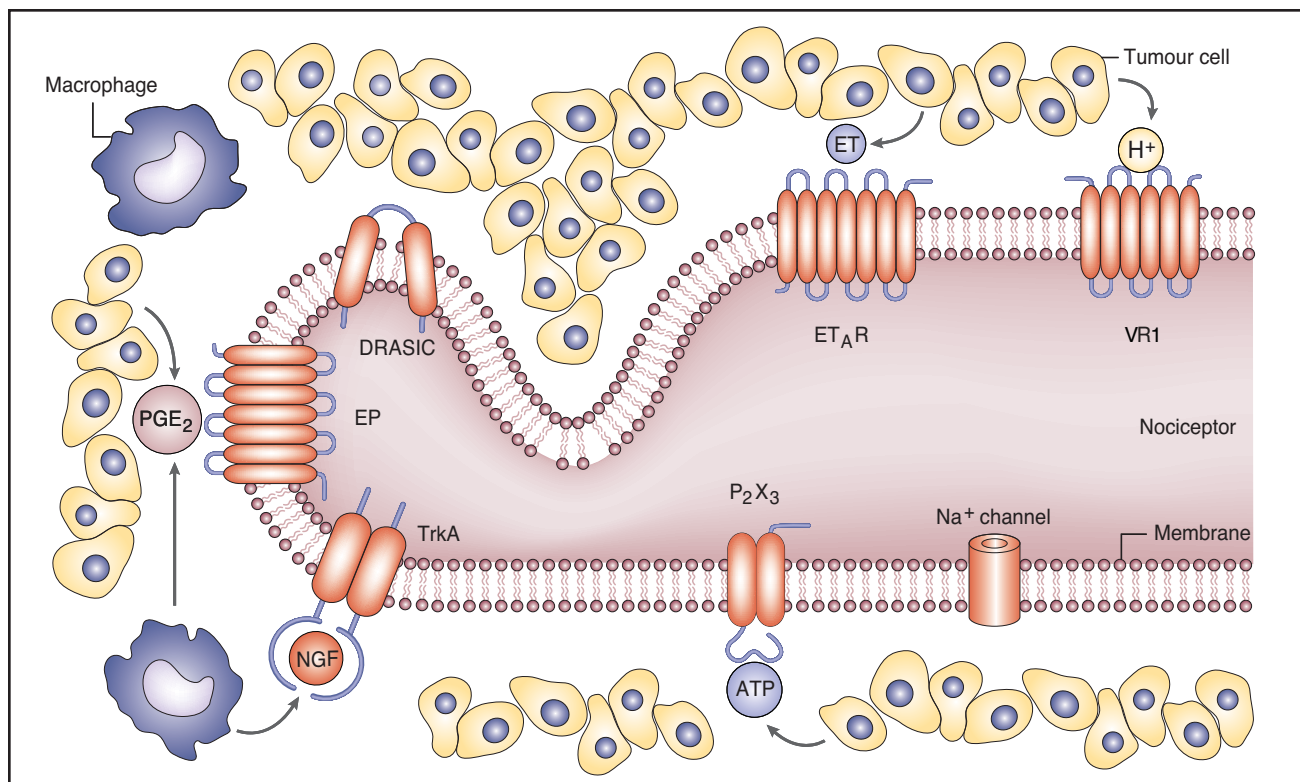


Fig 1. — Detection by sensory neurons of noxious stimuli produced by tumors. Nociceptors (pink) use several different types of receptor to detect and transmit signals about noxious stimuli that are produced by cancer cells (yellow) or other aspects of the tumor microenvironment. The vanilloid receptor-1 (VR1) detects extracellular protons (H^+) that are produced by cancer cells, whereas endothelin-A receptors ($ET_A R$) detect endothelins (ET) that are released by cancer cells. The dorsal-root acid-sensing ion channel (DRASIC) detects mechanical stimuli as tumor growth mechanically distends sensory fibers. Other receptors that are expressed by sensory neurons include prostaglandin receptors (EP), which detect prostaglandin E_2 (PGE_2) that is produced by cancer and inflammatory cells (macrophages). Nerve growth factor (NGF) released by macrophages binds to the tyrosine kinase receptor TrkA, whereas extracellular ATP binds to the purinergic P_2X_3 receptor. Activation of these receptors increases the excitability of the nociceptor, inducing the phosphorylation of the 1.8 and/or 1.9 sodium channels (Na^+ channel) and decreasing the threshold required for nociceptor excitation. From Mantyh PW, Clohisy DR, Koltzenburg M, et al. Molecular mechanisms of cancer pain. *Nat Rev Cancer*. 2002; 2(3):201-209. Reprinted by permission from Macmillan Publishers Ltd.

tors, as well as the patient's own report of pain intensity, which should be nonjudgmentally assessed by the clinician. Several tools are available to describe pain intensity: the Numerical Rating Scale, which is the most commonly used, the Visual Analog Scale, the Iowa Pain Thermometer Scale, and the Faces Pain Scale.

Several factors can prompt the clinician in the appropriate direction: (1) Metastatic bone pain has a gradual onset, becoming progressively more severe, and it is usually localized and often felt at night and/or on weight bearing. (2) The vast majority of bone metastases originate from cancers of the breast, lung, prostate, thyroid, and kidney. (3) The most common sites of spread in the skeleton include the spine, pelvis, ribs, skull, upper arm, and leg long bones. (4) Even though multilevel involvement occurs in about 80% of metastases to the vertebral bodies, they tend to be more frequently encountered in the thoracic region of the spine, followed by the lumbosacral and cervical regions. (5) Pain located in the occipital or nuchal region radiating to the posterior skull and exacerbated by neck flexion could be related to atlas (C1) bone destruction. (6) Pain referred to the interscapular region could be related to C7-T1 syndrome from tumor invasion of these vertebrae. (7) Pain in the iliac crest or sacroiliac joint could originate at T12 or L1 level, whereas pain in the buttock or posterior thigh that increases when lying down and relieved when standing could be a referred pain from sacral segments. (8) Pain with a rapid crescendo and radiating in a band-like fashion around the chest or abdomen could indicate an epidural compression that represents an oncologic/neurologic emergency. Spinal cord compression is usually accompanied by sensory loss, abnormal reflexes, weakness, and autonomic dysfunction. (9) Pain in the groin or knee could originate in the hip.

The character of the pain in bone metastasis can be somatic (musculoskeletal), neuropathic (with protopathic and/or epicritic features, caused by nerve irritation or damage by the invading tumor) or mixed, which appears to be more common.

Magnetic resonance imaging (MRI) is the most accurate imaging modality in detecting very early skeletal metastases. Computed tomography (CT) scanning can be used for patients who cannot tolerate an MRI or who are not candidates for MRI (such as those having metal implants or using a spinal cord stimulator). Radionuclide bone scan is useful to identify the extent of bone lesions throughout the body.

Nonpharmacologic Management

Cutaneous Stimulation

Cutaneous stimulation includes the application of superficial heat (thermotherapy) and cold (cryotherapy). Thermotherapy employs local hot packs, hot water bottles, electric heating pads, and immersion in warm water, whereas cryotherapy utilizes ice packs, towels

soaked in ice water, or commercially prepared chemical gel packs. These forms of cutaneous stimulation should not be applied over tissues that have been exposed to and damaged by radiation therapy. Modalities to deliver deep heat, such as short-wave diathermy, microwave diathermy, and ultrasound, should be used with caution in patients with active cancer disease, and they should never be applied directly over a cancer site.⁸

Transcutaneous Electrical Nerve Stimulation

Transcutaneous electrical stimulation (TENS) is a method of applying low-voltage electrical stimulation to large, myelinated fibers. The TENS unit may provide pain relief by keeping the pain gate closed. According to the gate-control theory proposed by Melzack and Wall in 1962 (*Brain*. 1962;331-356), stimulation of the large myelinated nerve fibers inhibits the transmission of the pain stimuli via unmyelinated C fibers and small myelinated delta fibers. TENS might also ameliorate pain by causing the release of beta endorphins and Met-enkephalins (endorphins involved in pain transmission).

However, the use of TENS to alleviate cancer pain is controversial, and further research is needed to help guide clinical practice. Two Cochrane reviews showed that there is insufficient evidence to determine the effectiveness of TENS in treating cancer-related pain⁹ and that large randomized controlled multicenter trials of TENS in chronic pain are needed.¹⁰

Massage Therapy

Massage therapy can help ease general aches and pains, especially in patients who are bed-bound or who have limited mobility. A recent pilot study that included 30 Taiwanese cancer patients with bone metastases assessed the effects of massage therapy on pain, anxiety, and physiologic relaxation over a 16- to 18-hour period.¹¹ Massage therapy had a positive impact on pain and anxiety, providing an effective immediate benefit [$t(29) = 16.5$, $P = .000$; $t(29) = 8.9$, $P = .000$], short-term benefit, in 20 to 30 minutes [$t(29) = 9.3$, $P = .000$; $t(29) = 10.1$, $P = .000$], intermediate benefit, in 1 to 2.5 hours [$t(29) = 7.9$, $P = .000$; $t(29) = 8.9$, $P = .000$], and long-term benefit, in 16 to 18 hours [$t(29) = 4.0$, $P = .000$; $t(29) = 5.7$, $P = .000$]. The most significant effect occurred 15 minutes after the intervention [$F = 11.5$ (1, 29), $P < .002$] or 20 minutes after the intervention [$F = 20.4$ (1, 29), $P < .000$], and no patients have reported any adverse effects as a result of massage therapy.

Exercise

As a general rule, patients should be encouraged to remain active; prolonged immobilization could lead to decreased musculoskeletal endurance and psychosocial regress. For these patients, hydrotherapy can provide a reduced-gravity environment and thus decrease pain experienced with movement, facilitate muscle relaxation,

and improve overall emotional state. If immobilization is required to prevent or stabilize fractures, exercise should be limited to a self-administered range of motion. In addition, clinicians need to educate families and caregivers on the proper application of orthotic devices as well as assistance with exercises that would not significantly increase pain.

Chiropractic or Osteopathic Manipulative Techniques

Due to the potential for harm in patients with metastatic cancer of the bone, the use of chiropractic or osteopathic manipulative techniques is not recommended.

Psychotherapeutic Management Relaxation Techniques

Relaxation techniques include simple focused-breathing exercises, progressive muscle relaxation, pleasant imagery, meditation, and music/art-assisted relaxation. These techniques are easy to learn and do not require special training. They could reduce symptoms such as fatigue and nausea/vomiting and could improve mood, sleep, and quality of life in cancer patients.

Mindfulness-Based Stress Reduction

Mindfulness-based stress reduction has been shown to improve not only chronic pain, including cancer pain and low back pain, but also a patient's mood and level of stress.

Hypnosis

Hypnosis can be used in palliative cancer care mainly to control nausea, particularly anticipatory nausea related to chemotherapy. It can also be used to increase the pain threshold, by decreasing either the annoying sensation or the attention given to the pain, and to improve both overall and mental well-being. Only a few small randomized controlled trials have been conducted to explore the effects of hypnosis on the pain associated with cancer.¹¹⁻¹⁴

Psychotherapy

Psychotherapy should be offered to patients who have a history of psychiatric illness or who develop clinical signs of depression. Psychotherapy can also be used as an adjuvant to medical treatment for patients with a history of addiction; this condition makes pain management in these patients a challenging task.

Medical Management Calcitonin

Calcitonin acts by inhibiting sodium and calcium resorption by the renal tubule and by reducing osteoclastic bone resorption. However, the role of calcitonin appears to be limited by its short duration of action and rapid development of tachyphylaxis.

Two double-blind clinical trials of patients with metastatic bone pain treated with calcitonin were conducted to study pain relief as the major outcome measure, assessed at 4 weeks or longer.¹⁵ Both studies, which included 90 participants in total, showed no evidence that calcitonin was effective in controlling complications due to bone metastases, improving quality of life, or prolonging patient survival. Calcitonin did provide some relief of neuropathic pain, although its mechanism of action is uncertain, possibly via the serotonergic system in the hypothalamus and limbic system.

Bisphosphonates

Bisphosphonates bind to the surface of the bone, have a direct apoptotic effect on osteoclasts, impair osteoclast-mediated bone resorption, and reduce the tumor-associated osteolysis that is initiated by the development of skeletal metastases. However, their role in pain relief for bone metastases remains uncertain even though they are part of standard therapy for hypercalcemia of malignancy.

There are two classes of bisphosphonates: (1) non-nitrogen containing, such as etidronate, clodronate and tiludronate, and (2) nitrogen containing, such as pamidronate, alendronate, ibandronate, risedronate, and zoledronic acid, which are more potent osteoclast inhibitors.

A Cochrane review of 30 randomized controlled studies (21 blinded, 4 open, and 5 active control) including 3,682 subjects showed that the results did not provide sufficient evidence to recommend bisphosphonates for an immediate effect as first-line therapy for painful bone metastases.¹⁶ Moreover, a retrospective Turkish study on 372 patients that compared different radiotherapy protocols (30 Gy in 10 fractions, 20 Gy in 5 fractions, and 8 Gy in a single fraction) with or without bisphosphonates showed that when combined with palliative radiotherapy, bisphosphonates did not have any additive effects on pain palliation in the management of painful bone metastases. Results from another study that included 372 cancer patients showed that, when combined with palliative radiotherapy, bisphosphonates did not have any additive effects on pain palliation in the management of painful bone metastases.¹⁷ In addition, a single radiotherapy fraction provided equal pain palliation as multiple fractions.²⁷

Conversely, a study conducted in Greece¹⁸ and another in Canada¹⁹ showed that zoledronic acid is the only bisphosphonate that has demonstrated statistically significant, long-term clinical benefits through the prevention and delay of skeletal-related events (SREs) in patients with metastatic lung cancer and prostate/renal cancer, respectively. Also, these studies suggested that the longer a patient receives zoledronic acid, the better its effect on survival and time to progression.

Denosumab

Denosumab is a monoclonal antibody with affinity for receptor activator of nuclear factor κ B ligand (RANKL),

which is secreted by osteoblasts. By binding to RANKL, denosumab prevents osteoclast formation, leading to decreased bone resorption and increased bone mass and thus preventing SREs.

Several studies have shown promising results when comparing denosumab to zoledronic acid. A recently published study enrolled patients with castration-resistant prostate cancer from 342 centers in 39 countries. A total of 950 men were randomly assigned to receive 120 mg subcutaneous denosumab plus intravenous placebo, and 951 men received 4 mg intravenous zoledronic acid plus subcutaneous placebo, every 4 weeks until the primary analysis cutoff date. The median time to the first on-study SRE was 20.7 months (95% confidence interval [CI], 18.8–24.9) with denosumab compared with 17.1 months (95% CI, 15.0–19.4) with zoledronic acid (hazard ratio = 0.82; 95% CI, 0.71–0.95; $P = .0002$ for non-inferiority; $P = .008$ for superiority). denosumab was superior to zoledronic acid in preventing SREs.²⁰

A similar study that included patients with advanced breast cancer showed that denosumab was superior to zoledronic acid in delaying time to first on-study SRE (hazard ratio = 0.82; 95% CI, 0.71–0.95; $P = .01$ for superiority) and time to first and subsequent (multiple) on-study SREs (rate ratio = 0.77; 95% CI, 0.66–0.89; $P = .001$). Overall survival, disease progression, and rates of adverse events and serious adverse events were similar between the two groups.²¹

Finally, a study comparing denosumab with zoledronic acid in the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) showed that denosumab was non-inferior (trending to superiority) to zoledronic acid in preventing or delaying first on-study SRE.²²

Corticosteroids

The mechanism of action of corticosteroids is blocking the synthesis of cytokines that contribute to both nociception and inflammation. The role of corticosteroids in treating spinal cord compression is well known. When spinal cord compression is suspected, patients should be treated with corticosteroids and evaluated with whole-spine MRI or myelography within 24 hours. Providers should initiate definitive treatment (radiotherapy or surgical decompression) within 24 hours of diagnosing cord compression.

A Canadian study involving 41 patients indicated that 8 mg dexamethasone given just before palliative radiotherapy can significantly decrease the incidence of pain flare during the first 2 days immediately after radiotherapy.²³

Analgesics

The World Health Organization (WHO) analgesic ladder is the most widely used guideline for the medical treatment of cancer pain. Many studies have contributed to

its validation.^{24,25} It advocates 3 basic steps according to the severity of symptoms (Fig2A).

Step 1 consists of nonopioid analgesics when pain is mild. Nonsteroidal anti-inflammatory drugs (NSAIDs) and COX-2 inhibitors, acetaminophen, adjuvants, and topical analgesic compounds comprise this group. Much controversy has revolved around the safety of NSAIDs; currently, their use is advised with caution, particularly in the elderly.²⁶ Adjuvants typically refer to drugs that, although are not analgesics per se, can be used for this indication in special circumstances. Several antiepileptics and antidepressants are first-line therapies in the management of neuropathic pain. The most commonly used agents include gabapentin, pregabalin, and tricyclic antidepressants (eg, amitriptyline, nortriptyline).

Step 2 introduces weak opioids such as hydrocodone, codeine, and low-dose oxycodone for pain that is mild to moderate. Other μ receptor agonists with dual mechanisms of action include tramadol and, most recently, tapentadol. These drugs reduce much of the side effects profile of pure opioids and have added effects on neuropathic pain. Propoxyphene (Darvocet, Darvon) has been taken off the market due to concerns of cardiac arrhythmias.

Step 3 consists of stronger opioids such as morphine, hydromorphone, fentanyl, high-dose oxycodone, meperidine, and methadone.

For patients with chronic cancer pain, a combination of long- and short-acting opioids is recommended. The long-acting opioids, whether they are pharmacologically long-acting (such as methadone or levorphanol) or pharmaceutically long-acting (a slow-release delivery system such as extended-release morphine, oxycodone, oxymorphone or hydromorphone), are used for the chronic baseline cancer pain. The short-acting opioids that require repetitive dosing are used for the acute pain.

Regarding breakthrough pain, which is defined as an abrupt, short-lived, and intense flare of pain in the setting of chronic stable pain managed with opioids,²⁷ there is an increasing trend to the use of transmucosal lipophilic drugs (eg, oral transmucosal fentanyl citrate, fentanyl buccal tablets, sublingual fentanyl, intranasal fentanyl spray, fentanyl pectin nasal spray, fentanyl buccal soluble film) due to the rapid effect of these drugs, which is clinically observable 10 to 15 minutes after administration.^{28,29} Breakthrough pain has been reported to occur in 50% to 70% of cancer patients.³⁰ Patients with pain located in the spine, back, and pelvis may be at risk for resistant breakthrough pain.³¹ Breakthrough pain can be categorized as somatic, visceral, or mixed, and also as idiopathic (spontaneous), incidental, and end-of-dose failure (when the pharmacokinetics of the analgesic do not match the patient's dosing schedule).³²

Ketamine, an *N*-methyl D-aspartate (NMDA) receptor antagonist, is a less commonly known analgesic. It

is effective in treating intractable severe pain caused by metastasis, trauma, chronic ischemia, or central neuropathic pain. Ketamine is effective even when megadoses of intravenous, epidural, or oral opioids prove ineffective or when opioid tolerance has developed.

A recent Italian study³³ investigated the use of ketamine 100 mg daily for 2 consecutive days along with methadone in patients with increased incidental pain and adverse effects from opioids. The results were encouraging, but further research is needed. Another study from Israel examined the benefits of using ketamine in patients with severe bone pain in whom high intravenous doses of morphine, meperidine, or fentanyl and patient-controlled intravenous and epidural analgesia were insufficient.³⁴ Within 5 to 10 days of ketamine and opioid protocols, pain was controlled and after an additional 5 to 7 days, ketamine could be discontinued and pain was controlled on oral regimens compatible with outpatient care.

Hormonal Therapy

Hormonal-dependent tumors metastatic to the bone are generally associated with slower disease progression and longer survival. Tumors in which hormonal

therapy is of proven benefit include breast, prostate, and endometrial cancers.³⁵⁻³⁷

Interventional Management

The WHO analgesic ladder was developed in 1982 as a global public health program to address the problem of untreated cancer pain, particularly at the end-of-life stage.³⁸ Prior to the release of these guidelines in 1986, numerous barriers that prevented the effective treatment of cancer pain existed, and descriptions of dying patients in pain were depicted as “a cruel and callous disgrace.”³⁹ With advances in the understanding of opioid analgesics and the newly created specialty of palliative medicine, the WHO analgesic ladder had a major impact on the management of patients who suffered mild to severe cancer-related pain. At the core of its creation, one of the central premises was its simplicity — simple enough to be adopted even by underprivileged societies.

By 1996, however, critical reviews were highlighting drawbacks of the WHO ladder (Fig 2A), mostly the fact that it consistently failed to provide sufficient relief in 10% to 20% of patients.^{40,41} In many instances, the ladder was described as an oversimplification of a complex problem. It was for these cases that interventional tech-

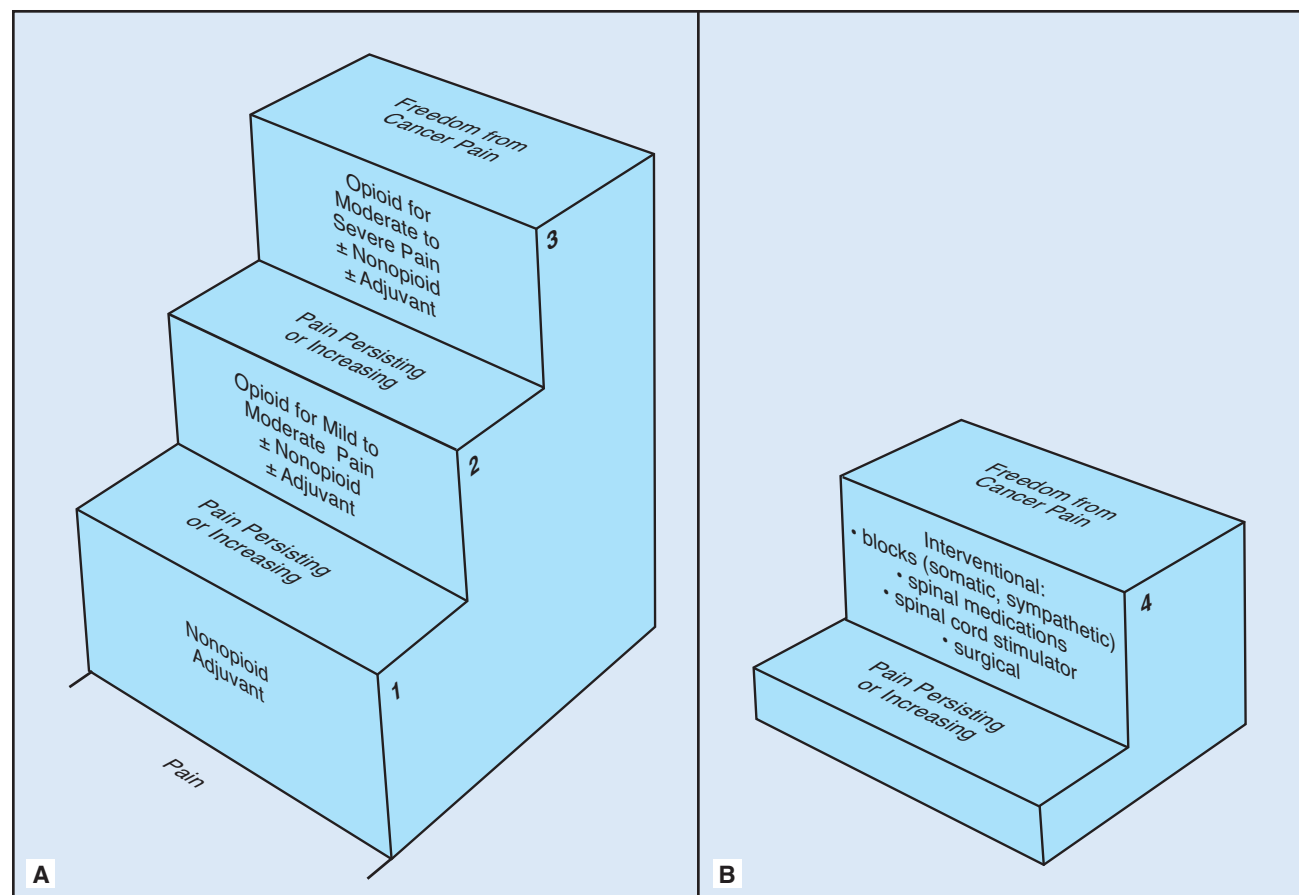


Fig 2A-B. — (A) The 3-step analgesic ladder developed by the World Health Organization. Reproduced by permission of WHO. Cancer Pain Relief. Geneva: WHO; 1986. <http://www.who.int/cancer/palliative/painladder/en/>. (B) The proposed fourth step. From Miguel R. Interventional treatment of cancer pain: the fourth step in the World Health Organization analgesic ladder? *Cancer Control*. 2000;7(2):149-156. Reproduced by permission of *Cancer Control: Journal of the Moffitt Cancer Center*.

niques were considered. The use of the interventional approach when systemic analgesia was unsuccessful, due to either uncontrolled pain and/or unacceptable side effects, was termed “the fourth step of the ladder” (Fig 2B).⁴² Failure of systemic analgesia can be closely related to specific pain generators and amount of malignant disease burden. Pain of neuropathic origin, for example, is known to be a poor respondent to opiates and conventional adjuvant therapies.^{43,44}

Furthermore, there is growing evidence of the pervasive effects caused by the chronic use of opiates. These include a complex process of progressive central sensitization known as opioid-induced hyperalgesia that may actually lead to increased perception of the experience of pain and a reduced ability to cope,⁴⁵ cognitive dysfunction, hypogonadism, intractable constipation and/or nausea, psychosocial implications such as addiction, pseudo-addiction, diversion, and abuse of controlled substances, all of which can lead to destructive behaviors and disrupt the patient’s social and family support system.⁴⁶ The prevalence of substance abuse problems in the cancer patient, although lower than the general population, remains a cause for concern.⁴⁷ With the increasing number of cancer survivors and thus a heightened prevalence of chronic pain in these patients,⁴⁸ some have proposed that the long-practiced paradigm of the WHO ladder, which may limit the ability of cancer survivors to return to normal life and activities, be turned “upside down,” with earlier utilization to the interventional and adjuvant therapies.⁴⁹

Metastatic disease to the bone illustrates the concerns stated above. The nervous system is closely related to the bony structures that surround it. The management of malignant disease in the vicinity often focuses on preventing invasion of the adjacent nervous structures and treating the ominous symptoms of pain and/or neurologic deficits. The appearance of secondary malignant disease in the bone signals progression to systemic disease, and local control and palliation become priorities. In these instances, when issues regarding pain control are common, implementing the “fourth step” of the ladder should be considered. Moreover, given the predictable course of many of these lesions, a multidisciplinary approach must be undertaken early on.

Metastatic bone disease can be focal, multifocal, or generalized, and so will the procedural approach. The first two can be discussed together.

The solitary or oligofocal vertebral lesion presents with pain as the most common and earliest symptom, typically nocturnal.^{50,51} At initial stages, the pain is thought to be somatic due to invasion of the receptor-rich periosteum from the receptor-poor marrow. Neuropathic pain may follow when epidural extension, compression fracture, or spinal cord compression occurs. The average time frame from initial pain presentation to complications is 7 months.⁵² Ominous signs include

rapid progression of back pain in a crescendo pattern, radicular pain exacerbated by recumbency or strain, and neurologic deficits such as weakness, sensory loss, autonomic and sphincter dysfunction, and osteotendinous reflex abnormalities.⁵³ The initial clinical suspicion is often confirmed by imaging studies such as MRI, CT, or bone scan. An accurate pathological diagnosis is paramount for prognosis and patient survival regardless of treatments offered, especially when there is no prior history of cancer.⁵⁴ Therefore, a bone biopsy is frequently considered at different stages, depending on the presentation.

Conventional external-beam radiotherapy (EBRT) is the mainstay treatment of painful vertebral lesions, without mechanical instability, that do not involve the nervous system.⁵⁵ EBRT may provide profound pain relief, prevent pathological fractures, and delay neurologic dysfunction. In addition, newer radiation techniques, collectively known as stereotactic radiosurgery, may offer several advantages such as increased radiation dose to the target area with reduced incidence of radiation toxicity. It may also offer the ability to treat patients in 1 or 2 days rather than the several days needed for conventional radiation; these newer techniques may also be more efficacious for radioresistant tumors such as renal cell carcinomas and sarcomas. The conventional wisdom regarding EBRT and solitary bone lesions, although anchored on evidence that functional outcomes are comparable to surgery, has often been challenged in the literature.⁵⁴

For patients who present with painful pathological vertebral compression fractures (VCRs) but no neurologic compromise, newer percutaneous vertebral augmentation procedures (most notably vertebroplasty and kyphoplasty) offer a novel option. These minimally invasive procedures consist of an injection of bone cement (polymethylmethacrylate) in a fractured or disrupted vertebral body via a percutaneous cannula placed in the vertebral body using a uni- or bi-pedicular approach. This provides structural support and minimizes mechanical pain. In addition, the cement may have intrinsic analgesic and antitumor properties. Kyphoplasty differs from vertebroplasty in that the injection of the bone cement occurs after creation of a cavity in the vertebral body by inflation of a balloon. This will allow a low-pressure injection, thus minimizing complications from extravasation.⁵⁶ The first vertebroplasty report, which came from France in 1987, was used for the treatment of aggressive vertebral hemangiomas.⁵⁷ With experience, two other indications were found: osteoporotic vertebral VCFs and spinal tumors. The safety and efficacy of these procedures have been acclaimed in some large, multicenter, randomized controlled trials such as the FREE study⁵⁸ and challenged in others.⁵⁹ The Cancer Patient Fracture Evaluation (CAFE) trial was a randomized controlled trial at 22 sites in Europe, the

United States, Canada, and Australia. In this trial, 134 cancer patients with 1 to 3 VCFs were randomized to receive kyphoplasty vs nonsurgical management. The primary endpoint was functional status as measured by the Roland-Morris disability questionnaire (<http://www.rmdq.org/>). At 1 month, a statistically significant difference was seen in favor of those who received kyphoplasty, and no complications were reported with this approach.⁶⁰ Experience with the use of vertebral augmentation procedures has allowed the expansion of their reach from the classic uncomplicated VCF to special situations such as prophylaxis against imminent fracture,⁶¹ treatment when there is epidural involvement, and combined techniques with EBRT and radiofrequency ablation (RFA).

Whether displaying neurologic symptoms or not, vertebral lesions with epidural extension, also described as breach of the posterior cortex, have been primarily surgically managed. However, many patients with these lesions are poor surgical candidates or have a limited life expectancy. Vertebral augmentation again has a role along with XRT and RFA. Those who are no longer candidates for radiation therapy seem to receive the most benefit from RFA,⁶² but vertebroplasty, in the face of epidural extension with VCFs, has been used alone^{63,64} and in combination with RFA.^{65,66} Combination radiosurgery and kyphoplasty has also been used, with fiducial markers for radiation placed during the kyphoplasty an average of 12 days prior.⁶⁷ Many of these patients had received XRT in the past. Intraoperative radiotherapy during kyphoplasty (kypho-IORT) is a novel approach used to deliver a single dose of 10 Gy to the spinal lesion during a kyphoplasty procedure.^{68,69}

Residual pain after successful vertebral augmentation procedures is estimated to average 23%. Although there is no literature as to what are the likely pain generators, degenerative changes in the adjacent structures such as facets and discs are the logical causes, leading to persistent axial back pain and radiculopathy. Interventional procedures such as epidural corticosteroid injections, facet joint injections, trigger point injections, intercostal nerve blocks, and sacroiliac joint injections have been successfully employed for further relief of painful symptoms.^{70,71,72}

Localized metastatic disease in other bones can also be painful, particularly when the original somatic pain becomes neuropathic due to invasion of adjacent neural structures. When these lesions respond poorly to XRT alone or in combination with reconstructive surgery, injection of bone cement has been evaluated with excellent results. In acetabular lesions compromising ambulation, Maccauro et al⁷³ presented a retrospective study of 25 patients undergoing cement acetabuloplasty when surgical reconstruction was not an option. All patients obtained marked clinical and functional improvement initially, with a mean duration of pain relief

of 7.3 months. No major complications were observed. Many other sites are amenable to this technique when conventional treatments fail. In a prospective report of 50 patients, Anselmetti et al⁷⁴ successfully applied this technique to the femoral shaft, pelvis, ribs, knee, tibia, humerus, and sacrum. Seven of the 50 patients underwent RFA in the same session. No complications were reported, but at 1 month, 2 of 15 patients treated at the femoral diaphysis suffered pathological fractures. Combination cementoplasty and RFA has also been described with good results.⁷⁵

When a neuropathic component is present, the resulting pain can be more difficult to treat and frequently fails systemic analgesia. An evaluation for XRT or surgery, while always worth exploring, often leads to the need for alternative palliative approaches. Interventional pain techniques can be beneficial in this situation.

Selective diagnostic nerve blocks that offer short-term relief are used as conduits leading to ablative procedures such as RFA, cryoablation, and phenol and alcohol neurolysis, seeking long-term analgesia. The central premise of these neuroablative procedures is their ability to achieve selective C and A δ fiber (pain fibers) neurolysis in a given nerve, preserving to a higher or lesser degree the anatomical integrity of the peri-, epi-, and endoneurium (which will allow future reinnervation), as well as sensory and motor fiber function. This is possible by taking advantage of the smaller diameter and relative lack of myelin of the pain fibers. Autonomic fibers usually cannot be spared since they are small and unmyelinated.

While almost any nerve may be subject to this approach, those controlling the motor function of the extremities are treated with more caution due to the potential for loss of limb function. Consequently, these techniques have been most commonly described for axial pain such as intercostal nerve-mediated pain from rib metastases or postthoracotomy pain and postamputation pain. Particular attention has been given to pulsed radiofrequency of the dorsal root ganglion and nerve roots. RFA has been the preferred neurolytic technique, given its ability to control the size of the lesion by tissue temperature feedback control.⁷⁶⁻⁸⁰

In other cases, the risk of loss of limb function, shortened life expectancy, or a possible endpoint to the source of the pain by active oncologic treatment may warrant a different approach. The placement of a temporary catheter for the continuous infusion of local anesthetic (regional analgesia) is a reliable, safe, and feasible option, particularly in end-of-life care. Infusions of local anesthetics are the most common. Volume and concentration dictate the depth of the nerve blockade — specifically, the development of anesthesia and motor block vs analgesia. This allows a titration range that can accommodate the changing needs of each patient. By tunneling these catheters under the skin, infection risk

is acceptable so they can be left in place for extended periods of time. This also leads to more stability of the catheter, thus reducing the risk of migration.⁸¹⁻⁸³

Femoral/sciatic nerve and brachial plexus as well as epidural catheters have been used successfully.⁸⁴⁻⁸⁸ The drawback associated with these catheters is the need for constant care. The infusate solution requires frequent refills, the mobility of these patients is restricted to some degree in every case, and complications of obstruction and catheter migration are common. Infections are rare, but the bacterial colonization rate is significant in these catheters, even after short-term (48-hour) infusions.⁸⁹

Epidural catheters deserve special attention. With the discovery of spinal opioid receptors in the 1970s,⁹⁰ the field of neuraxial analgesia found an alternative to local anesthetic administration that could minimize the side effects of motor blockade and autonomic dysfunction. Epidural opioids, more specifically hydrophilic opioids such as morphine and hydromorphone, can provide segmental analgesia when placed close to the spinal level corresponding dermatomes. Their use in the hospice setting has been well documented,⁹¹ and despite advances in other forms of neuraxial analgesia such as intrathecal (IT) infusions that require less labor-intensive follow-up, they continue to have a place in the care of intractable pain in cancer patients at the end of life. The lack of randomized controlled trials for these techniques can be explained by several factors: only a small percentage of cancer patients require their use, randomization can be difficult to implement due to concerns of informed consent and ethics, primary endpoints are difficult to define in these patients, and study participant cohorts would be highly heterogeneous.

Additional interventional alternatives are available to manage localized bone cancer pain, such as neurostimulation and spinal cord stimulation.

Neurostimulation is a field of neuromodulation with the potential to offer high levels of analgesia to patients with neuropathic pain in whom the steps of the WHO analgesic ladder have been insufficient. Dorsal column stimulation was originally described in a case report in 1967,⁹² and it was based on the “gate control theory” proposed 2 years earlier.⁹³ The basic concept of spinal cord stimulation is centered on the early findings that, in spinal transmission, when an increased input of a sensory modality is applied, it can “close the gate” to other modalities, effectively modulating the conveyance of these signals to higher centers in the central nervous system. More specifically, electrical stimulation of the dorsal column has a neuromodulatory effect on the activity of the ascending pain pathways.

Spinal cord stimulation and, more recently, peripheral nerve stimulation have unique mechanisms of action in the treatment of neuropathic pain and may be the only alternative available when all other therapeutic

interventions have failed. Implementation of this therapy requires an initial placement of percutaneous leads with electrical contacts at the target neural structure (typically the dorsal column) for a trial. The position of these contacts is somatotopic and requires the patient to be awake to offer feedback on where the stimulation is felt. The patient then uses an external pulse electrical generator at home for an average of 5 days. If there is more than 50% pain relief, along with some objective measures such as a decrease in opioid consumption and improvement in activities of daily living, a permanent implant can be scheduled. This entails creating a subcutaneous pocket to place a pulse generator unit similar to a pacemaker and anchoring the new leads to prevent them from moving, since precise position is critical for continued benefit (Fig 3).

Successful use of neurostimulation in cancer patients has been documented in the literature.⁹⁴⁻⁹⁶ Proceeding with this option remains an individualized decision, particularly in the setting of a critical or often terminal illness. A good patient-physician relationship as well as the assistance of other supportive services can help in making the transition to neurostimulation.

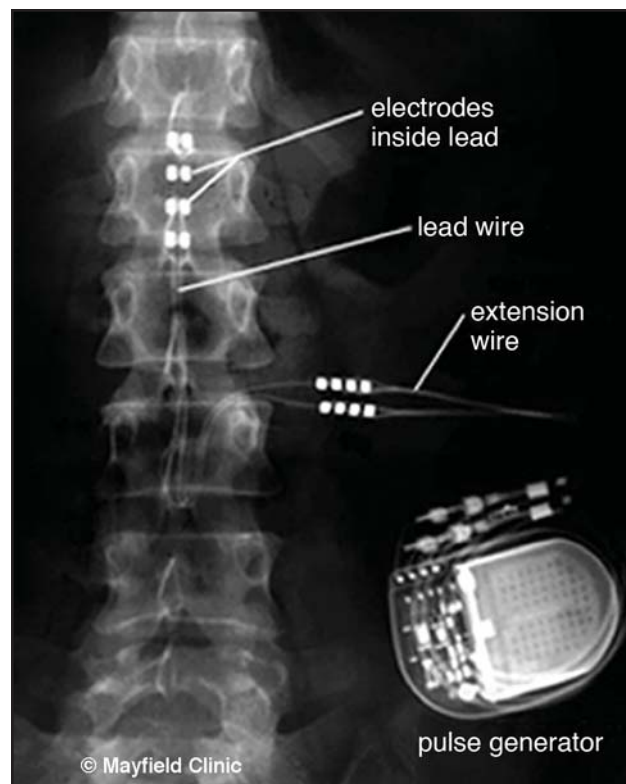


Fig 3. — Implementation of spinal cord stimulation, which requires placement of percutaneous leads with electrical contacts at the target neural structure. The position of these contacts requires the patient to be awake to offer feedback on where stimulation is felt. The patient then uses an external pulse electrical generator for an average of 5 days. If there is more than 50% pain relief, along with objective measures such as a decrease in opioid consumption and improvement in activities of daily living, a permanent implant can be scheduled. This entails creating a subcutaneous pocket to place a pulse generator unit and anchoring the new leads to prevent movement. Reprinted with permission.

Metastatic bone disease can be widespread and may call for more than localized, targeted approaches when interventions for pain are needed. When optimized systemic analgesia fails, intrathecal infusions might be considered.

The first use of opioids infused in the cerebrospinal fluid (CSF) for cancer patients was reported in 1979 by Wang et al.⁹⁷ Since then, numerous advances have been made in the indications for implantable infusion pumps, drugs used, and patient selection. There are several advantages with this therapy. The potency of intrathecal opioids is multiplied by a factor of 1:300 compared to oral administration.⁹⁸ Additional benefits are minimized side effects and the ability to use combination infusates with drugs that are approved only for IT administration (ziconotide) or that are more effective through this route (eg, local anesthetics, clonidine). Because the CSF courses throughout the entire central nervous system, IT therapy is not segmental in principle and may provide analgesia virtually anywhere in the body.



Fig 4. — Example of intrathecal (IT) infusion. These can be administered through tunneled percutaneous catheters or implantable drug delivery systems that are now available with computerized programmable features, including patient-controlled dosing. Reprinted with permission.

Although the use of implanted IT therapy in chronic nonmalignant pain remains controversial, its use in cancer is rarely argued. In a multicenter randomized trial comparing analgesia delivered via an intraspinal implantable drug delivery system to comprehensive medical management in 201 patients with refractory cancer pain, IT therapy was significantly superior in clinical effectiveness (defined as at least 20% pain level rating decrease).⁹⁹ Side effects were similar; however, decreased rates of depression and mental status changes were reported, as well as improved survival (53.9% alive at 6 months in the IT therapy group compared with 37.2% in the medical management group).

IT infusions can be administered through tunneled percutaneous catheters or implantable drug delivery systems (IDDSs) that now come with computerized programmable features, including patient-controlled dosing (Fig 4). IDDS insertion is recommended when the patient's life expectancy is longer than 3 months.¹⁰⁰

The list of drugs that can be used in the IT space, whether on- or off-label, continues to expand (Table) and reflects the ongoing efforts to combine different mechanisms of action that may act synergistically against neuropathic pain.

Ziconotide is one of a small number of drugs that are approved by the US Food and Drug Administration for use in IT therapy. Ziconotide, a synthetic peptide derived from the sea snail *Conus magus*, selectively blocks N-type voltage calcium channels at presynaptic terminals of the dorsal horn and is used for IT administration only. Validated for cancer pain by Staats et al,¹⁰¹ ziconotide is an effective drug for neuropathic pain but is associated with many possible side effects.

Table. — Drugs Commonly Used Intrathecally for Pain Relief

Opioids	Morphine Hydromorphone Fentanyl Meperidine Methadone
α2-Adrenoceptor Agonists	Clonidine Tizanidine Dexmedetomidine
Local Anesthetics	Bupivacaine Ropivacaine Tetracaine
Muscle Relaxants	Baclofen
NMDA-Receptor Antagonists	Ketamine
Others	Ziconotide Gabapentin Midazolam

The excellent analgesic properties of intrathecal ketamine has also been demonstrated in cancer patients, although evidence of neurotoxicity has limited its clinical application. However, in terminal cancer patients with a short life expectancy, it is a valid alternative.¹⁰²

A combination of several interventional therapies may be needed for each individual. For example, a patient may have widespread malignant disease to the spine that is initially well controlled with systemic analgesia. The patient may then develop a pathological VCF that benefits from vertebral augmentation and epidural corticosteroid injection if radicular symptoms are present. This patient is also likely to progress to opioid tolerance and ultimate failure of systemic analgesics, thus requiring IT therapy to improve quality of life.

Radiotherapy and Radionuclides

Radiotherapy and radionuclides are successfully used to treat pain symptoms related to metastatic bone disease and are discussed in a separate article in this issue (Yu H-HM, Tsai Y-Y, Hoffer SE; pp 84-91).

Conclusions

The overriding goal in treating cancer pain is to maintain our patients' quality of life throughout all stages of their disease. While advances have been made in our understanding of the mechanisms of cancer pain, as well as how and when we treat metastatic pain, alleviating the pain of bone disease continues to present demanding clinical challenges. Several options are available to effectively control pain resulting from focal, multifocal, or generalized metastatic bone cancer. These options include nonpharmacologic, psychotherapeutic, and interventional management approaches. Overall, treatment is best approached in a multidisciplinary setting that allows patients to not only benefit from pain relief but also maintain their quality of life.

With expanded knowledge of the neurophysiology and related pharmacology of cancer bone pain, we can continue refining the clinical approach to alleviate pain and suffering in these patients.

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