Advances in Cancer Pain

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Advances in cancer pain research and management are an example of the advances that have occurred within the field of neuro-oncology, the medical discipline that includes the diagnosis and treatment of primary central nervous system neoplasms, metastatic and nonmetastatic neurological complications of cancer originating outside the nervous system, and pain associated with cancer. Progress in the diagnosis and treatment of cancer, coupled with advances in our understanding of the anatomy, physiology, pharmacology, and psychology of pain perception, has led to improved care of the patient with pain of malignant origin. Currently, specialized methods of cancer diagnosis and treatment provide the most direct approach to treating cancer pain by treating the cause of the pain. Yet, before the introduction of successful antitumor therapy, when treatment of the cause of the pain has failed or when injury to bone, soft tissue, or nerve has occurred as a result of therapy, appropriate pain management is essential.

Numerous studies support the observation that patients with cancer pain are best treated with a multidisciplinary approach using the expertise of a wide range of health care professionals. The goal of such pain therapy for patients receiving active treatment is to provide them with sufficient relief to tolerate the diagnostic and therapeutic approaches that are needed to treat their cancer. For patients with advanced disease, pain control should be sufficient to allow them to function at a level they choose and to die relatively free of pain. The management of the symptom pain should be only one component of a broad palliative care approach for patients with cancer. Control of other symptoms, treatment of psychological distress, and attention to the religious, spiritual, and existential dimensions of the patient’s illness experience should be concurrently addressed to maintain the patient’s quality of life throughout the cancer illness from diagnosis to death.

ADVANCES IN CANCER PAIN: BASIC RESEARCH

Extensive information about ascending and descending central nervous system pathways that process and modulate nociceptive information has helped to frame a scientific rationale for the use of new and improved methods of cancer pain treatment. A brief review of the basic research advances in the neuroanatomy, physiology, and pharmacology of pain provides a background for discussing the advances in clinical pain management. Detailed information now supports the theory that activation of peripheral receptors in both superficial and deep structures as well as viscera by mechanical and chemical stimuli excites afferent discharges. Nonnociceptive messages are transmitted through rapidly conducting Aβ fibers, and nociceptive information is signaled through slowly conducting Aδ- and C-fiber afferents. The receptor endings of Aβ fibers most often respond to one sensory stimulus, whereas most C-fiber receptors are multimodal and respond to multiple high-threshold stimuli. These primary sensory afferents have their cell bodies in the dorsal root ganglion, and their axons enter the spinal cord via the dorsal root. The synaptic connections of these primary afferents with the corresponding second-order nociceptive neurons in the spinal dorsal horn are the initial site of processing for sensory information, and act as a relay in transmitting noxious signals to the central nervous system. They ascend or descend from 1 or 2 segments in the dacro-lateral fasciculus and synapse in specific

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lamina in the dorsal horn: lamina I and lamina II. Evidence suggests that myelinated nociceptors project to laminae I and V, unmyelinated nociceptors to lamina II and possibly lamina I, and nonnociceptive myelinated afferents only to deep laminae.

The dorsal horn is a critical site for modulating sensory input, and recent studies have elaborated the molecular biology and pharmacology of pain modulation at this site. Sensory transmission is mediated through neuropeptides, substance P, calcitonin gene–related peptide, and the excitatory amino acids (EAAs), both glutamate and aspartate. Excitatory synaptic transmission from the primary afferent is modulated by the N-methyl-D-aspartate (NMDA) receptor as well as non-NMDA receptors. After EAA-NMDA receptor interaction, intracellular calcium influx and mobilization of intracellular calcium lead to subsequent changes in second-messenger systems. Protein kinase C modulates these activities. One second messenger system that is activated after EAA-NMDA receptor interaction is the generation of nitric oxide via the enzyme nitric oxide synthase. There is also an increase in transcription of immediate early gene c-fos, which may regulate the subsequent expression of endogenous opioid genes, preproenkephalin and preprodynorphin. The receptor activation of NMDA initiates and maintains central sensitization and the component known as windup. These phenomena are manifestations of persistent signaling from primary sensory afferents. Central sensitization is thought to be the major mechanism underlying neuropathic pain, and accounts for the hyperpathia and enlarged cutaneous receptor fields that occur after nerve injury.2

At the level of the second-order neurons in the dorsal horn, sensory processing occurs through interactions among neurochemical transmitters released by primary afferents including γ-aminobutyric acid, glycine, adenosine, bombesin, cholecystokinin, dynorphin, enkephalin, neuropeptide Y, neurotensin, substance P, somatostatin, and vasoactive intestinal polypeptide. Several ascending pathways arise from these second-order neurons and decussate in the central gray of the spinal cord to become the neospinothalamic and paleospinothalamic tracts. These tracts project to discrete regions of the thalamus and cortex. The neospinothalamic pathway subserves pain intensity and localization, whereas the phylogenetically older paleospinothalamic pathway subserves the arousal and emotional component of pain.

Descending pathways, the most important of which originate from the periaqueductal gray nuclei of the midbrain, synapse in the raphae magnus nucleus of the midbrain. From this nucleus, a medial pathway, the dorsal longitudinal fasciculus, projects to the dorsal horn to modulate pain transmission. This pathway represents an important descending inhibitory pathway. A more laterally placed descending pathway from the locus ceruleus to the dorsal horn also plays a role in pain modulation at the spinal cord level.

Opiate receptors, stereospecific binding sites on the end of free nerve endings that bind exogenous opioids, are localized in the ascending and descending pain pathways. These receptors mediate the multiple pharmacological effects of the opioid analgesics. Subpopulations of opioid receptors including high- and low-affinity μ receptors and γ, κ, and δ receptors are localized to specific areas of the brain, spinal cord, and peripheral nervous system. More recently, several opioid receptor subtypes have been cloned, and quantitative changes in the messenger RNA for these receptors have been determined in experimental models. The cloning of these subtypes of receptors that mediate different pharmacological effects and are then located in specific cerebral, spinal, and peripheral sites offers the possibility of developing new analgesics targeted for specific receptors. For example, μ receptors modulate predominantly supraspinal analgesia, whereas δ and κ receptors are important in modulating analgesia at the spinal cord level. The periaqueductal gray region in the midbrain and the dorsal horn in the spinal cord are rich in these receptors and are the supraspinal and spinal sites that mediate opioid analgesia. The use of brainstem and spinal cord stimulation and the administration of opioid analgesics directly into the cerebrospinal fluid, bathing the selective opioid sites in patients with cancer who are in pain, are procedures based on this knowledge. Pain transmission at the spinal cord level can be inhibited by the direct application of morphine onto the spinal cord, and these studies have led to the use of spinal opioid analgesia in clinical pain states.

There is now increasing information about the molecular basis of opioid tolerance development. A variety of NMDA receptor antagonists have now been demonstrated to both attenuate and reverse experimental opioid analgesic tolerance. Therefore, the confluence of NMDA receptors in pain transmission and in the development of tolerance has provided new insights into the role of opioid receptors in analgesia.

These advances in our understanding of pain modulatory systems and their neuroanatomical and neuropharmacological correlates have had a major impact on the treatment of patients with cancer pain. A better understanding of the molecular biology of both nociceptive and neuropathic pain is facilitating the wide application of a variety of agents, both opioid and nonopioid, to treat cancer pain.

ADVANCES IN CLINICAL CANCER PAIN: CLINICAL MANAGEMENT

Increased attention for the need to develop a public health program to provide cancer pain management has created the impetus to define the epidemiology and ethnography of cancer pain. These studies demonstrate that one third of the adult patients with cancer who are in active therapy and two thirds of the patients with advanced disease have significant pain.1 The prevalence of pain increases with disease progression, and the intensity, type, and location of the pain vary according to the primary tumor site, extent of disease, and treatments used. Multiple causes and sites of pain are common, with up to 81% of patients reporting 2 or more distinct complaints and 34% reporting 3 types of pain. In the landmark study of 1308 oncology patients followed up by the Eastern Cooperative Oncology Group, 56% of patients reported moderate to severe pain 50% of the time.4 Multiple reviews have demonstrated that pain associated with direct tumor involvement is the most common cause of cancer pain, occurring in upwards of 83% of patients on inpatient pain services and up to 65% of pa-
Patients seen in outpatient pain clinics. Bone pain is the most common type, with tumor infiltration of nerve and hollow viscus as the second and third most common pain locations. Pain is the most frequent symptom in patients with neurological complications of cancer. Pain associated with cancer therapy occurs in upwards of 15% to 25% of patients who undergo surgery, radiation therapy, or chemotherapy. Three percent to 10% of patients have pain caused by noncancer-related problems. In children with cancer, pain is commonly associated with procedures and is reported to occur in up to 60% of children who receive active therapy. Detailed reviews have defined the common neurological and nonneurological pain syndromes in patients with cancer and have outlined specific evidence-based algorithms for their evaluation and treatment.

Concurrent with increased knowledge of the common pain syndromes have been advances in the development of analgesic assays to measure acute, chronic, and experimental pain in patients with cancer. Validated analgesic assay methods using sophisticated measurement instruments, new study designs, and innovative statistical analyses have facilitated acute and chronic pain studies.

Several instruments, including the Brief Pain Inventory, the Memorial Pain Assessment Card, the Memorial Symptom Assessment Scale, and the Edmonton Symptom Assessment Scale, have facilitated repeated measurements over time that allow a correlation of pain intensity with functional activity and quality of life. These validated methods have provided the tools to study pain interventions and outcomes of therapy not only of analgesic agents but also of chemotherapeutic and radiation therapy protocols’ impact on pain.

The unique development of new paradigms of human experimental pain using intradermal capsaicin and specific noxious stimuli, coupled with neurophysiological and psychophysical methods, has allowed the testing of potentially new agents that have an impact both on the development of windup and on central sensitization, the important neurophysiological components of nerve injury. The availability of these new human experimental neuropathic pain paradigms provides the opportunity for the rapid assessment of new agents. By combining these analgesic assay methods with functional magnetic resonance imaging and positron emission tomography, further insights into the central mechanisms of pain modulation and the distinctions between the components of perception and affective responses have been identified. In short, the expanding analgesic assay methods have created new opportunities to better understand the central and peripheral mechanisms of pain in patients with cancer.

At the same time, advances in clinical pharmacology characterized by the availability of specific and sensitive methods to analyze opioids and peptides in plasma and cerebrospinal fluid and to correlate these drug levels to pharmacodynamic effects have led to the development of pharmacokinetic-pharmacodynamic models. Such models are particularly useful in achieving a better understanding of drug distribution and elimination and have been specifically used to design appropriate drug-dosing regimens for patients with cancer. These studies have served as the underpinnings for the use of patient-controlled analgesic pumps; they have also helped to better define the role of opioids’ active metabolites. For example, studies of morphine and its active metabolite morphine-6-glucuronide have been performed using these techniques. Because of the results of these studies, morphine-6-glucuronide is recognized as a potent analgesic with a much longer half-life (12-14 hours) than morphine (3-4 hours). Morphine-6-glucuronide is cleared by the kidney and accumulates in patients with compromised renal function. Using both pharmacokinetic and pharmacodynamic data, the pharmacokinetics of cerebrospinal fluid distribution of opioid drugs has facilitated the development of dosing algorithms for both epidural and intrathecal opioid administration.

In short, these advances in the clinical pharmacological aspects of opioids have facilitated a better understanding of and scientific guidelines for the use of opioid analgesics by novel routes of drug administration, including transmucosal, transdermal, epidural, intrathecal, and intraventricular routes. Such pharmacokinetic-pharmacodynamic models have again helped to develop and provide clinically relevant scientifically based guidelines for the use of slow-release preparations, which are commonly used for pain management in patients with cancer and are currently available for morphine, hydromorphone, and oxycodone and for fentanyl by the transdermal route.

Increased attention has been focused on the need to maximize analgesia and to minimize adverse effects, and there have been advances in our understanding of the role of various adjuvant analgesics in cancer pain management. These advances have led to a better understanding of (1) the role of the tricyclic antidepressants and selective serotonin reuptake inhibitors in neuropathic pain; (2) the role of methylphenidate in treating the sedative effects of opioids; (3) the safety and efficacy of haloperidol to manage opioid- and steroid-induced delirium; (4) the efficacy of corticosteroids in treating headache in patients with brain metastases, back pain in patients with epidural cord compression, and bone pain in patients with metastatic prostate cancer; (5) the use of topical local anesthetics (eg, Emla cream) to reduce pain after venous or arterial catheterization, lumbar puncture, and bone marrow aspiration; (6) the use of bisphosphonates in reducing bone pain in patients with multiple myeloma and breast cancer; and (7) the role of gabapentin in peripheral neuropathy and postherpetic neuralgia.

Notwithstanding these advances, cancer pain is difficult to manage and neuropathic pain remains a major challenge. Numerous pilot studies and case reports have been published recently that suggest the potential role of a wide variety of adjuvant analgesics in managing neuropathic pain. These analgesics include anticonvulsants (eg, carbamazepine, baclofen, and valproic acid), oral local anesthetics (eg, methylenedihydrochloride), neuroleptics (eg, pimozide), and peptides (eg, calcitonin). To date, the lack of well-controlled trials limits the development of evidence-based guidelines. Empirical use of these drugs in sequential drug trials is suggested to manage intractable pain in patients with cancer.
As previously mentioned, recent attention has focused on NMDA receptors and their role in neuropathic pain. Both ketamine and dextromethorphan have been shown to provide pain relief in patients with cancer. Studies of dextromethorphan in combination with morphine have shown increased analgesic effects as compared with morphine alone. Ketamine, commonly used as an anesthetic, has been shown to produce analgesia in subanesthetic doses. Animal studies of ketamine and dextromethorphan have demonstrated the ability of these drugs both to prevent the development of neuropathic pain and to limit the development of tolerance. Increased attention is now focusing on the clinical aspects of these drugs and their role in managing neuropathic pain in patients with cancer.

The results of recent studies of methadone, a commonly used second-line opioid analgesic to manage cancer pain, suggest that methadone may provide analgesia through both an opioid and a nonopioid mechanism. Animal studies indicate that methadone may be different from other µ opioids, such as morphine, hydromorphone, and oxycodone, because the d- and the l-isomers of methadone's racemic mixture bind to the NMDA receptor. Animal studies show that d-methadone is weak or inactive as an opioid but is antinociceptive in a neuropathic pain model as an antagonist at the NMDA receptor. These studies suggest that methadone analgesia may result in part from the d-isomer potentiating the opioid antinociceptive effect of l-methadone. The NMDA receptor antagonists attenuate the development of morphine; therefore, d-methadone may also act to attenuate the tolerance to the opioid components of racemic methadone.

These advances in the basic and clinical aspects of analgesic drug therapy have led to a reconsideration of the understanding of the concepts of opioid responsiveness, tolerance, and psychological dependence. These new insights have facilitated a broader use of opioids in both cancer and non-cancer–related pain syndromes.

**Opioid Responsiveness**

It is now well recognized that opioids provide analgesia over a continuum and that neuropathic pain is less responsive to opioid drug therapy. This conceptual framework has important clinical implications, as it is the basis for the major pharmacological principle of “dosing to effect.” Each patient should be given a trial of an opioid titrated to limiting adverse effects to determine the opioid’s efficacy in treating a particular type of cancer pain. Such an approach has demonstrated that somatic, visceral, and neuropathic pain responds in a variable manner to opioids and that sequential clinical trials are the only approach to determine opioid dose and efficacy for an individual patient.

**Tolerance**

Tolerance is the term that is used to describe a reduced effect of a drug as a consequence of its prior administration. The chronic use of opioids in the patient with cancer pain has provided a natural experiment to show that tolerance is not a limiting factor to the long-term use of opioids. Studies of the long-term use of opioids in patients with cancer pain over the last 25 years have demonstrated that tolerance develops at different rates to each of the opioid’s effects. Tolerance development to the respiratory depressant effects of opioids has provided protection to patients with cancer as they escalate their doses to obtain improved analgesia. These studies in patients with pain demonstrate that changes in the pain stimulus, ie, progression of tumor in patients with cancer pain, are the most common cause for dose escalation. With chronic pain, stable doses of opioids can provide continuous pain relief for long periods of time without dose escalation. Cross-tolerance is not complete among the opioids used in clinical practice, and analgesia can be obtained by switching to an alternative opioid. Opioid rotation provides the opportunity to maximize analgesia and to minimize adverse effects. It is particularly interesting to note that there appears to be no limit to tolerance and that large doses can be used to provide analgesia with minimal adverse effects. Physician concern that the development of analgesic tolerance limits the chronic use of opioids has not been validated in clinical studies in patients with cancer pain. A better understanding of the role of NMDA antagonists in preventing the development of tolerance offers the opportunity to enhance analgesia and to maintain stable doses over long periods.

**Psychological Dependence**

Fears of addiction continue to be a barrier to the widespread use of opioids for cancer pain management. Experience with large numbers of patients treated for cancer pain with opioids has demonstrated that there is a negligible risk of psychological dependence. Increased opioid availability is not associated with increased illegal drug trafficking or recreational use. Patients with cancer who take opioids chronically will develop physical dependence, which can be precipitated by abrupt drug withdrawal. With effective pain management, patients commonly reduce their opioid doses, and their drug use should be slowly tapered to prevent the appearance of a withdrawal state.

Despite these important advances in our knowledge about cancer pain, large numbers of patients remain inadequately treated according to recently published surveys of patients with cancer who have serious life-threatening illness, patients in nursing homes, and patients with cancer in outpatient oncology clinics. The elderly, minorities, and women are most affected by this undertreatment of pain. The lack of integration of this extensive database to manage cancer pain into undergraduate and graduate medical education is a major “systems” barrier to effective treatment of cancer patients with pain. There is an urgent need to institute into practice what we know now, as it can provide pain relief to large numbers of patients with cancer. Widespread attention to this need has led to the development of state-based cancer pain initiatives created as grass roots organizations to advocate for patients’ rights for adequate treatment of their pain symptoms. Professional organizations need to mandate education in cancer pain management to bring these important advances to the patients who need them.


