Cancer Pain

Vandana Sharma | Oscar de Leon-Casasola

BACKGROUND

Cancer pain is a result of cancer growth in human tissues or the pain produced by any of the therapies implemented to treat it. Ideal management starts with a thorough assessment via the history and physical examination, as well as the judicious use of diagnostic testing in an attempt to define the pathophysiologic components involved in the expression of pain to implement optimal analgesic therapy. Adequate pain control can be achieved in the great majority of patients with the implementation of aggressive pharmacologic treatment consisting of the use of opioids and adjuvants. With the implementation of these strategies, 90% to 95% of patients may achieve adequate pain control. Consequently, 5% to 10% of patients will need some form of invasive therapy. Thus, when following specific guidelines, the great majority of patients with cancer-related pain may expect adequate pain control in the 21st century. Control of pain and related symptoms is a cornerstone of cancer treatment in that it promotes an enhanced quality of life, improved functioning, better compliance, and a means for patients to focus on matters that give meaning to life. In addition to their salutary effects on quality of life, mounting evidence suggests that good pain control influences survival.

EPIDEMIOLOGY

Approximately 6.35 million new cases of cancer are diagnosed annually worldwide, half of which originate in developing nations and 1.04 million occur in the United States alone. Mortality is high; one in five deaths in the United States is a result of cancer, which means about 1400 cancer-related deaths per day. The morbidity is equally concerning inasmuch as up to 50% of patients undergoing active treatment and in up to 25% of patients undergoing active treatment and in up to 25% of patients undergoing active treatment and in up to 90% of patients with advanced cancer. According to several studies, including a survey of oncologists in the Eastern Cooperative Oncology Group (ECOG) and a survey of 1103 consecutive admissions to a U.S tertiary care cancer hospital, 73% of patients in active treatment admitted to having pain, with 38% reporting severe pain. Despite the availability of simple, cost-effective treatments, inadequately controlled pain remains a significant problem. This is important because of the negative influence of pain on patients’ performance status.

Performance status, as measured by the ECOG and Karnofsky scales (Table 23.1), is a global rating of patients’ overall functional status. When performance status is low, as is often the case when pain is severe, patients may find it difficult to tolerate the chemotherapy recommended; indeed, they may not be considered candidates for chemotherapy. Further benefits of good pain management often include improvement in nutrition, rest, and mood, all of which contribute to quality of life and have the potential to influence the outcome of antineoplastic therapy.

ASSESSMENT OF PAIN INTENSITY

Questionnaires have been used to aid in standardizing patients’ assessment. Ideally, this assessment is completed by patients before their evaluation. The Wisconsin Brief Pain Inventory (BPI) and the Memorial Pain Assessment Card are becoming increasingly well accepted. The characteristics of the different assessment tools are noted in the following outline:

1. Wisconsin BPI:
   a. It is a fifteen-minute questionnaire that can be self-administered.
   b. It includes several questions about the characteristics of the pain, including its origin and the effects of previous treatments.
   c. It incorporates two valuable features of the McGill Pain Questionnaire, a graphic representation of the location of the pain and groups of qualitative descriptors. Severity of pain is assessed by a series of visual analog scale (VAS) scores that quantify pain at its best, worst, and on average. The perceived level of interference with normal function is quantified with a VAS also.
   d. Preliminary evidence suggests that the BPI is cross-culturally applicable and is useful, particularly when patients are not fit to complete a more thorough or comprehensive questionnaire.

23
### Table 23.1 Methods of Assessing Performance Status

<table>
<thead>
<tr>
<th>ECOG Scale*</th>
<th>Karnofsky Scale†</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>1</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
<td>60</td>
</tr>
<tr>
<td>5</td>
<td>50</td>
</tr>
<tr>
<td>6</td>
<td>40</td>
</tr>
<tr>
<td>7</td>
<td>30</td>
</tr>
<tr>
<td>8</td>
<td>20</td>
</tr>
<tr>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>10</td>
<td>0</td>
</tr>
</tbody>
</table>


2. **Memorial Pain Assessment Card:**
   a. It is a simple, efficient, and valid instrument that provides rapid clinical evaluation of the major aspects of pain experienced by cancer patients.23
   b. It is easy to understand and use and can be completed by experienced patients in 20 seconds.
   c. It consists of a two-sided, 8.5- × 11-inch card that is folded so that four separate measures are created.
   d. It features scales intended for measurement of pain intensity, pain relief, and mood and a set of descriptive adjectives.

3. **Edmonton staging system:**
   a. It is performed by health care providers.
   b. It was developed to predict the likelihood of achieving effective relief of pain in cancer patients.24,25
   c. The system’s originators provided validation that treatment outcome can be accurately predicted according to five clinical features (neuropathic pain, movement-related pain, recent history of tolerance to opioids, psychological distress, and a history of alcoholism or drug abuse).
   d. Staging requires only 5 to 10 minutes and no special skills are needed to complete it.
   e. Its value lies in prospective identification of potentially problematic patients, thereby further legitimizing clinical research on control of symptoms by introducing better standardization and improving our ability to critically assess the results of various therapeutic interventions in large population of patients.

4. **Pediatric cancer pain assessment:** This includes Beyer’s The Oucher, Eland’s color scale–body outline, Hester’s poker chip tool, McGrath’s faces scale, and others.26-29

5. **Numerical rating scale (NRS) or VAS:**
   a. Pain is often assessed on an 11-point NRS from 0 (no pain) to 10 (worst pain imaginable).
   b. The VAS is a 10-cm line without markings from no pain to worst pain; patients mark their pain score and a measurement in centimeters defines their level of pain.

Evaluation of pain should be integrated with a detailed oncologic, medical, and psychosocial assessment. The initial evaluation should include an evaluation of the patient’s feelings and attitudes about the pain and disease, family concerns, and the patient’s premorbid psychological history. A comprehensive but objective approach to assessment instills confidence in patients and family that will be valuable throughout treatment. A comprehensive evaluation of patients with cancer pain includes the following:

- The *reason for the visit* is determined to ensure appropriate triage (e.g., patients with severe pain because of bowel obstruction may need to be sent to the emergency center for urgent treatment).
- An *oncologic history* is obtained to gain knowledge of the context of the pain problem and includes diagnosis and stage of the disease; a history of therapies implemented, including a list of the chemotherapeutic agents used, types of surgery, site of radiotherapy, and outcome (including side effects); and the patient’s understanding of the disease process and prognosis.
- The *pain history* should include any premorbid chronic pain and, for each new pain site, its onset and evolution, site and radiation areas, pattern (constant, intermittent, or unpredictable), intensity (best, worst, average, current)
on VAS scales, quality, exacerbating and relieving factors, interference of the pain with usual activities, neurologic and motor abnormalities (including bowel and bladder continence), vasomotor changes, and current and past analgesics (use, efficacy, side effects). Previous analgesic use, efficacy, and side effects should be cataloged. Prior treatments of pain should be noted (radiotherapy, nerve blocks, physiotherapy, etc.).

- The medical record and radiologic studies should be reviewed. Many of the treatments of cancer may cause pain themselves (chemotherapy- and radiotherapy-induced neuropathy or postoperative pain syndromes such as post-thoracotomy and post-mastectomy pain syndrome), and many specific cancers may cause well-established pain patterns as a result of known probable sites of metastasis, including (1) metastasis of breast cancer to long bones, the spine, chest wall, brachial plexus, and spinal cord; (2) metastasis of colon cancer to the pelvis, hips, lumbar plexus, sacral plexus, and spinal cord; and (3) metastasis of prostate cancer to long bones, the pelvis, hips, lung, and spinal cord.

- The psychosocial history should include marital and residential status, employment history and status, educational background, functional status, activities of daily living, recreational activities, support systems, health and capabilities of the spouse or significant other, and past history of (or current) drug or alcohol abuse.

- The medical history (independent of the oncologic history) should include coexisting systemic disease, exercise intolerance, allergies to medications, medications in use, previous illness and surgery, and a thorough review of systems, including the following:
  - General (anorexia, weight loss, cachexia, fatigue, weakness, insomnia)
  - Neurologic (sedation, confusion, hallucination, headache, motor weakness, altered sensation, incontinence)
  - Respiratory (dyspnea, cough, pneumonia)
  - Gastrointestinal (dysphagia, nausea, vomiting, dehydration, constipation, diarrhea)
  - Psychological (irritability, anxiety, depression, dementia)
  - Genitourinary (urgency, hesitancy, hematuria)

- The physical examination must be thorough, although at times it is appropriate to perform a focused examination of particular problems. In patients with spinal pain and known or suspected metastatic disease, a complete neurologic examination is mandatory.

- A care team meeting should be arranged if applicable.

- The need for further studies should be determined.

- Formulate a clinical impression (diagnosis). Multiple diagnoses usually apply, and it is optimal to use the most specific known diagnosis, such as somatic pain from a vertebral metastasis, severe pain in a patient with metastatic non-small cell carcinoma of the lung, and neuopathic pain from a paravertebral mass invading the nerve root as it exits the vertebral foramen. Nausea and vomiting with severe weight loss and fatigue, as well as constipation, should be identified.

- Formulate recommendations (plan) and alternatives for each problem. For instance, with respect to the examples just presented in formulating a clinical impression, one could perform magnetic resonance imaging (MRI) of the spine, add a controlled-release opioid administered daily and transmucosal fentanyl citrate for breakthrough pain, implement therapy with a combination of a tricyclic antidepressant and an anticonvulsant with instructions on titration, prescribe an antiemetic before meals and as needed for nausea, prescribe a bowel stimulant and bulk-forming compound twice daily for constipation, and evaluate in 2 weeks to determine the need for a short course of steroid therapy.

- Call an oncologist or the primary care provider, or both, if applicable. Have a discussion with the referring physician, primary care provider, and/or oncologist to establish short- and long-term plans.

- Conduct an exit interview.
  
  - Explain the probable cause of the symptoms in terms that the patient can understand.
  - Discuss the prognosis for relief of symptoms, management options, and specific recommendations. In addition to writing prescriptions, oral and written instructions must be provided. Educational material regarding medications, pain management strategies, or procedures should also be provided. Potential side effects and their management should be discussed.
  - Arrange for follow-up with clinic contact information.
  - Dictate a summary of the evaluation to the referring and consulting physicians.

### CLASSIFICATION OF CANCER PAIN

#### TIME RELATED

#### ACUTE PAIN

Acute pain is frequently associated with sympathetic hyperactivity and heightened distress. It is often temporally associated with the onset or recrudescence of primary or metastatic disease, and its presence should motivate the clinician to aggressively seek its cause and adjust the pharmacologic therapeutic scheme.

#### SUBACUTE PAIN

Some patients experience subacute pain for 4 to 6 weeks after a major surgical procedure. This type of pain is largely undertreated and deserves special attention because it may affect the patient’s ability to perform activities of daily living after discharge from the hospital.

#### CHRONIC PAIN

Treatment of pain of a chronic nature mandates a combination of palliation, adjustment, and acceptance. With time, biologic and behavioral adjustment to the symptoms occurs, and hopefully the associated symptoms will be blunted. Chronic pain with superimposed episodes of acute pain (breakthrough pain) is probably the most common pattern observed in patients with ongoing cancer pain.

#### INTENSITY

Consistent use of measurements of pain intensity aids in monitoring a patient’s progress and may serve as a basis for interpatient comparisons. High pain scores may alert the clinician to the need for more aggressive treatment or hospitalization (or both) for rapid control of symptoms via...
intravenous patient-controlled analgesia (IV PCA) or for antineuropathic medications with a rapid titration protocol.

**PATHOPHYSIOLOGY**

A mechanistic approach is useful when formulating the initial treatment plan, as suggested in the example above.

_Somatic pain_ is described as a constant, well-localized pain often characterized as aching, throbbing, sharp, or gnawing. It tends to be responsive to opioids and nonsteroidal anti-inflammatory drugs (NSAIDs—cyclooxygenase-2 inhibitors) and amenable to relief by interruption of proximal pathways via neural blockade when indicated.

_Visceral pain_ originates from injury to organs. This pain is transmitted by fibers that travel along the sympathetic nervous system. Visceral pain is characterized as vague in distribution and quality and is often described as a deep, dull, aching, dragging, squeezing, or pressure-like sensation. When acute, it may be paroxysmal and colicky and can be associated with nausea, vomiting, diaphoresis, and alterations in blood pressure and heart rate. Mechanisms of visceral pain include abnormal distention or contraction of smooth muscle walls (hollow viscera), ischemia of visceral muscle, serosal or mucosal irritation by algesic substances and other chemical stimuli, distention and traction or torsion on mesenteric or renal nerves. Chemotherapeutic agents associated with peripheral nerve structures such as post-thoracotomy, post-mastectomy, post–tumor resection, and postsurgical pain syndromes include abnormal distention or contraction of smooth muscle walls (hollow viscera), rapid capsular stretch (solid viscera), ischemia of visceral muscle, serosal or mucosal irritation by algesic substances and other chemical stimuli, distention and traction or torsion on mesenteric attachments and the vasculature, and necrosis.

_Visceral involvement_ often produces referred pain (e.g., shoulder pain of hepatic origin).

_Neuropathic pain_ is defined as pain caused by injury or irritation to some element or elements of the nervous system. Examples of neuropathic pain syndromes include tumor growth around nerve structures; postsurgical pain syndromes such as post-thoracotomy, post-mastectomy, post–tumor resection, and postsurgical pain; or pain induced by chemotherapeutic agents affecting peripheral nerve structures. Chemotherapeutic agents associated with this problem include vinca alkaloids (vincristine, vinblastine), cisplatin, paclitaxel (Taxol), docetaxel (Taxotere), vinorelbine (Navelbine), and bortezomib (Velcade). Neuropathic pain is often resistant to standard analgesic therapies and frequently requires an approach using combinations of opioids, tricyclic antidepressants, anticonvulsants, oral or topical local anesthetics, corticosteroids, N-methyl-D-aspartate (NMDA) blockers, and others.

**TEMPORAL ASPECTS OF PAIN**

**CONSTANT PAIN**

Such pain is most amenable to drug therapy administered around the clock, contingent on time rather than symptoms. It is best managed by long-acting analgesics or, in selected cases, infusion of analgesics.

**BREAKTHROUGH PAIN AND INCIDENT PAIN**

Breakthrough pain that is related to a specific activity, such as eating, defecation, socializing, or walking, is referred to as incident pain. Incident pain is best managed by supplementing the preventive around-the-clock regimen with analgesics that have a rapid onset of action and a short duration. Once a pattern of incident pain is established, escape or rescue doses of analgesics can be administered in anticipation of the pain-provoking activity. Breakthrough pain that occurs consistently before the next scheduled dose of around-the-clock opioids is called end-of-dose failure (plasma concentrations fall below minimum effective analgesic concentrations) and is ideally managed by reducing the intervals between doses. In contrast, increasing the doses of long-acting opioids under these circumstances may increase the incidence of side effects. Under a strict definition, breakthrough pain is pain that may occur at any time during the day; it increases to a high intensity very rapidly and has duration of 30 to 45 minutes. Consequently, it is important to recognize the differences among these three types of breakthrough pain to implement adequate therapy.

**INTERMITTENT PAIN**

This type of pain is very unpredictable and can best be managed by the administration of potent analgesics with a rapid onset and short duration as needed.

**SPECIFIC CANCER PAIN SYNDROMES**

**METASTASES**

Bone tumor infiltration or bone metastasis is cited as the most common cause of cancer pain and is most often seen with stage IV carcinoma of the prostate, breast, thyroid, lung, or kidney. The pain is usually constant, dull, achy or gnawing, and often intense with movement or weight bearing. Approximately 25% of patients with bone metastases experience pain. Pressure and chemical irritation of nerve endings in the periosteum may cause pain. As pressure increases, the cytokines prostaglandin E2 (PGE2) and other cytokines are elaborated by osseous metastases. These cytokines are thought to contribute to pain by sensitization of peripheral nociceptors. NSAIDs and steroids are postulated to reduce pain from bony metastases by inhibition of the cyclooxygenase pathway of arachidonic acid breakdown, thus decreasing the formation of PGE2. As deposits enlarge, stretching of the periosteum, pathologic fractures, and perineural invasion contribute to the pain, and requirements for analgesics increase. Palliative radiation therapy is used successfully to relieve pain emanating from bony metastases. However, pain relief may not be seen in 100% of cases. Thus, other forms of therapy may need to be implemented.

Vertebral body metastases are associated with carcinoma of the lung, breast, and prostate. Localized paraspinal, radicular, or referred pain within the dermatomal distribution of the affected nerve structure is usually the first sign of metastasis to the spine. It is often manifested as severe local, dull, steady, aching pain and is frequently exacerbated by movement and weight bearing. On physical evaluation, local
midline tenderness may be present, as well as corresponding neurologic changes associated with either nerve compression or epidural–spinal cord compression. Invasion of the second cervical vertebra may result in pain referred to the occiput, and C7-T1 invasion may produce interscapular pain.41

BASE OF SKULL METASTASIS
Metastasis to the base of the skull is usually accompanied by headache and a spectrum of neurologic findings, especially when the cranial nerves are involved. Symptomatic metastasis to the skull is usually, but not always, a late finding.32 Plain radiography, scintigraphy, and computed tomography (CT) are helpful for the diagnosis of bony disease, whereas MRI and lumbar puncture are useful in evaluating soft tissues and detecting leptomeningeal disease, respectively.43

Musculoskeletal pain in the form of myofascial pain is frequently seen in cancer patients.44 Patients with bone metastases and those with post–radical neck dissection syndrome are frequently affected by this condition. Stress, anxiety, muscle overuse to compensate for the lack of bone support, or the absence of other muscles resected during cancer surgery may play an important role in the development of this condition. Thus, treatment should be multidisciplinary and include pharmacologic therapy, trigger point injections, and physical rehabilitation with the use of orthotic devices as needed.

LEPTOMENINGEAL METASTASIS, MENINGEAL CARCINOMATOSIS
These conditions are frequently seen with primary malignancies of the breast and lung and with lymphoma and leukemia; it is secondary to diffuse infiltration of the meninges. About 40% of patients have headache or back pain, presumably caused by traction on the pain-sensitive meninges or traction on cranial or spinal nerves or secondary to raised intracranial pressure.33,45 Headache is the most common initial complaint; it is characteristically unremitting and may be associated with nausea, vomiting, nuchal rigidity, and changes in mental status.36 Neurologic abnormalities may include seizures, cranial nerve deficits, papilledema, hemiparesis, ataxia, and cauda equina syndrome. The diagnosis may be suggested by the T2 phase of MRI, and it is usually confirmed via lumbar puncture and cerebrospinal fluid (CSF) analysis, which typically shows elevated protein and decreased glucose, as well as malignant cells.47 The natural history of patients with leptomeningeal metastasis is a gradual decline and death over a period of 4 to 6 weeks, although survival is often extended to 6 months or more when radiation therapy or intrathecal chemotherapy (or both) is instituted.48 Steroids may be useful in the management of headache, as well as the neuropathic pain associated with spinal cord and nerve involvement.

SPINAL CORD COMPRESSION AND PLEXOPATHIES
Spinal cord compression is usually heralded by pain in the presence of neurologic changes. An urgent radiologic workup is mandatory in patients with neurologic deficits, particularly motor weakness, bandlike encircling pain, or incontinence. Prompt treatment in the form of radiotherapy or spinal stabilization and high-dose IV steroids may limit the neurologic morbidity.49 Plexopathies are the result of tumor growth around nerve plexuses in the upper or lower extremity. Cervical plexopathy is most commonly due to local invasion by head and neck cancer. Symptoms include aching preauricular, postauricular, or neck pain. Brachial plexopathy is most commonly caused by upper lobe lung cancer (Pancoast syndrome or superior sulcus syndrome), breast cancer, or lymphoma. Pain is an early symptom that usually precedes the neurologic findings by up to 9 months.50,51 The lower cord of the plexus (C8-T1) is affected most frequently, and pain is usually diffuse and aching and radiates down the arm, often to the elbow and medial (ulnar) aspect of the hand.52,53 When the upper part of the trunk is involved (C5-6), pain is generally found in the shoulder girdle and upper portion of the arm and radiates to the thumb and index finger. Horner’s syndrome, dysesthesias, progressive atrophy, and neurologic impairment (weakness and numbness) may occur. Brachial plexus invasion may be associated with contiguous spread to the epidural space.49,54-56 Lumbosacral plexopathy may be due to local soft tissue invasion or compression from tumors of the rectum, cervix, or breast, sarcoma, and lymphoma; pain is usually the initial symptom in 70% of such patients.57 The pain is usually described as aching or pressure-like and only rarely is dysesthetic.57 Depending on the level involved, pain is referred to the low back region, abdomen, buttock, or lower extremity.57,58 This medical problem must be differentiated from spinal cord invasion or cauda equina syndrome, for which urgent diagnosis and treatment are mandatory. Clinical experience shows that brachial plexopathies respond better to medical therapy with opioids, tricyclic antidepressants, and anticonvulsants, whereas lumbosacral plexopathies may require early intervention with intrathecal opioid, bupivacaine, and clonidine therapy.

PAIN ASSOCIATED WITH CANCER TREATMENT
Oral mucositis typically occurs within 1 to 2 weeks of the initiation of chemotherapy. This condition is most common with the use of methotrexate, doxorubicin, daunorubicin, bleomycin, etoposide, 5-fluorouracil, and dacarbazine.59 Mucositis is often most severe when chemotherapy is combined with radiation treatments involving the head and neck region. Treatment may require hospitalization for IV PCA opioid therapy. Ambulatory care may necessitate transdermal opioids, local anesthetics, or doxepin swishes.

Painful polyneuropathy occurs most commonly with vincristine (motor and sensory involvement), vinblastine, paclitaxel, docetaxel, a platinum derivative (predominantly sensory involvement), vinorelbine, and bortezomib.60 Symptoms commonly include burning dysesthetic pain in the hands and feet. The majority of these patients will respond to medical therapy with opioids, tricyclic antidepressants, and anticonvulsants. However, the small number of patients who do not achieve adequate pain control with this strategy will usually show a significant response to the use of spinal cord stimulation.

Postsurgical chronic pain syndromes are most common after mastectomy, thoracotomy, radical neck dissection, nephrectomy, and amputation.61 The clinical characteristics generally include aching, shooting, or tingling pain in the distribution of peripheral nerves (e.g., intercostobrachial, intercostals, cervical plexus), with or without skin hypersensitivity. One study suggested that the incidence of
post-mastectomy pain was higher after conservative surgery than after modified radical mastectomy (33% vs. 17%). In this same study, 25% of patients experienced postoperative phantom breast pain. The exact incidence of postsurgical pain syndromes is unclear but appears to be in the 25% to 50% range by some estimates. Medical therapy with opioids, tricyclic antidepressants, and anticonvulsants is successful in the great majority of patients. Those who fail pharmacologic therapy will benefit from intrathecal therapy (post-thoracotomy, post-mastectomy syndromes), spinal cord stimulation (post-thoracotomy, post-mastectomy syndromes), or even peripheral subcutaneous nerve stimulation (post-radical neck dissection, post-thoracotomy syndromes).

Headache is present in 60% of patients with a primary or metastatic brain tumor, half of whom classify it as their primary complaint. It is typically steady, deep, dull, and aching with moderate intensity and is rarely rhythmic or throbbing. It is usually intermittent and may be worse in the morning and with coughing or straining. Symptoms often improve with radiation therapy, NSAIDs, or corticosteroids.

Cervicofacial pain syndromes are most common in patients with head and neck cancer. The head and neck are richly innervated by contributions from cranial nerves V, VII, IX, and X and the upper cervical nerves, so the pain varies in character. When cranial nerves are involved, the symptoms represent those of trigeminal, glossopharyngeal, or intermittent neuralgia, with sudden, severe lancinating pain radiating to the face, throat, or ear, respectively. The pain may be accompanied by dyesthesias, trigger points, and impaired swallowing, breathing, and phonation. Pharmacologic therapy with opioids, tricyclic antidepressants, and anticonvulsants is useful in the great majority of these patients. In those whom pharmacologic therapy fails, radiofrequency lesioning of the sphenopalatine or gasserian ganglion may be useful.

Radiation therapy may be associated with both acute and chronic pain syndromes. Acutely, mucositis and cutaneous burns may be seen. Chronically, postradiation syndromes include osteoradionecrosis, myelopathy, plexopathy, soft tissue fibrosis, and the emergence of new secondary neurogenic tumors.
The noninvasive route should be maintained as long as possible for reasons that include simplicity, maintenance of independence and mobility, convenience, and cost. Treatment should be directed toward relief of pain and suffering, which includes consideration of all aspects of function (e.g., disturbances in sleep, appetite, mood, activity, posture, and sexuality), and attention should be paid not only to the physical but also to the emotional, psychological, and spiritual aspects of suffering.

For a specific description of the different agents that may be used for pharmacologic noninvasive therapy, please refer to Chapters 36 to 42.

INTERVENTIONAL PAIN MANAGEMENT

When a comprehensive trial of pharmacologic therapy fails to provide adequate analgesia or leads to unacceptable side effects, consideration should be given to alternative treatments.

CONTINUOUS SUBCUTANEOUS INFUSION OF OPIOIDS

This modality was frequently used in the past and proved to be effective. However, the advent of IV PCA therapy and long-term IV lines such as peripherally inserted indwelling central catheter (PIC) lines have made it somehow obsolete in this population of patients.

INTRAVENOUS INFUSION OF OPIOIDS WITH PATIENT-CONTROLLED ANALGESIA DEVICES

The most frequent indication for this form of therapy is severe pain and the need to rapidly titrate opioids in the hospital setting to achieve adequate pain control. Moreover, in the ambulatory setting, this modality is indicated for patients in whom the oral route is not available because of gastrointestinal obstruction, malabsorption, uncontrolled nausea and vomiting, or dysphagia or when the requirement for opioids is large because of tolerance. Some modifications in the implementation of this therapy have been used once the patient is no longer able to control the device. Thus, nurse- or family-controlled analgesia is an acceptable alternative in these circumstances. Consequently, patients will need to be treated in a controlled environment such as hospice or at home with the help and monitoring of family members. In such circumstances visiting nursing services will be required.

INTRASPINAL ANALGESIA

Neuraxial analgesia is achieved by the epidural or intrathecal administration of an opioid alone (very rarely) or in combination with other agents such as bupivacaine, clonidine, or ziconotide. With the use of neuraxial analgesia, pain relief is obtained in a highly selective fashion without motor, sensory, and sympathetic effects, thus making these modalities highly adaptable to the home care environment. At its inception, the principle of neuraxial opioid therapy was that introducing minute quantities of opioids in close proximity to their receptors (substantia gelatinosa of the spinal cord) achieves high local concentrations. Thus, neuraxial analgesia was potentially superior to that achieved when opioids were administered by other routes, and since the total amount of drug administered is reduced, side effects were minimized. Currently, the biggest advantage is the ability to use multiple agents to target neuropathic, somatic, and visceral components.

In general, patients with a survival expectancy of longer than 3 months will be candidates for intrathecal therapy with a permanent intraspinal catheter and an implanted subcutaneous pump. Conversely, patients with a survival expectancy of less than 3 months will require epidural therapy with an implanted system (the Du Pen epidural catheter or the Sims epidural Port-a-Cath) connected to an external pump with PCA capabilities. Either way, patients will need a trial with an epidural catheter placed at the site where nociception is being processed in the spinal cord. At Roswell Park Cancer Institute, we conduct this trial on an outpatient basis, and if successful, we proceed to implant the permanent device. For this purpose, we suggest the following protocol:

**Epidural Trial**

- **Catheter position:** dermatomal specific under fluoroscopic guidance
  1. Opioids:
     - Morphine: 0.1 (60 mg) to 0.2 (120 mg) mg/mL
     - Hydromorphone: 0.03 (20 mg) to 0.12 (80 mg) mg/mL
  2. Bupivacaine: 1 to 2 mg/mL
  3. Clonidine: 3 to 5 µg/mL
  4. Total volume: 600 mL
- **Determining epidural opioid doses:**
  1. If the patient is receiving more than 300 µg/hr of fentanyl, 1200 mg/day of morphine sulfate (MS), 600 mg/day of oxycodone, or 160 mg/day of methadone:
     - Hydromorphone: 0.12 mg/mL
  2. If the patient is receiving between 100 and 300 µg/hr of fentanyl or equivalent dose:
     - Hydromorphone: 0.06 mg/mL
  3. If the patient is receiving less than 100 µg/hr of fentanyl or equivalent dose:
     - Hydromorphone: 0.03 mg/mL
- **Basal infusion:** 2 mL/hr
- **No bolus during the first 72 hours, then 2 mL every 10 minutes**
- **The goal is to determine patient requirements**
- **Trial for 7 days as an outpatient**

If the patient had a successful trial, defined as a reduction in pain of greater than 80%, we proceed to implant an intrathecal system if indicated by the survival expectancy. We suggest the following protocol to achieve a success rate higher than 80%:

- **Conditions for success:**
  1. Place the tip of the intrathecal catheter in the dermatome corresponding to the area of nociception
  2. For severe somatic pain, combinations of local anesthetics and an opioid will be needed
  3. For neuropathic pain:
     - Place the tip of the catheter below L3-4: initial therapy with an opioid and clonidine
     - Place the tip of the catheter above L1-2: initial therapy with an opioid and bupivacaine
The doses and drugs that we use in our practice are as follows:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Range of Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>1.0-20 mg/day</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>0.5-25 mg/day</td>
</tr>
<tr>
<td>Sufentanil</td>
<td>10-100 µg/day</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>6-20 mg/day</td>
</tr>
<tr>
<td>Clonidine</td>
<td>250-2000 µg/day</td>
</tr>
</tbody>
</table>

Thus, compounding by a trained pharmacist will be needed. The goal is to concentrate these drugs to twice the daily dose so that the pumps may be programmed to deliver 0.5 mL/hr. In this way, patients will need pump refills monthly, and it will not be a burden on their quality of life by having to come frequently to the pain specialist’s office. The steps that we use to implement the therapy are as follows:

- **Step 1:**
  1. Opioid plus bupivacaine:
     - MS, 3 to 25 mg/day, or hydromorphone, 0.5 to 15 mg/day (25 mg of MS per day = 4 mg of hydromorphone per day)
     - Bupivacaine: 6 to 20 mg/day
  2. Opioid plus clonidine:
     - Clonidine: 250 to 2000 µg/day

- **Step 2:** Opioid plus bupivacaine plus clonidine

- **Step 3:** At this point, ziconotide
- If the patient’s insurance does not pay for hydromorphone, bupivacaine, or clonidine, the use of morphine plus ziconotide may be an alternative. However, limitations include the following:
  1. Trials are unpredictable because ziconotide may not be administered in the epidural space. Consequently, the patient will need to undergo a trial once the implanted system is in place
  2. Patients may not allow you to carry out a titration protocol over a 4- to 6-week period:
     - The starting dose is 2.4 µg/day with weekly increases of no more than 2.4 µg/day
     - Therapeutic effects are not usually seen until a dose of 10 µg/day is reached

- **Other issues to consider when initiating ziconotide include the following:**
  3. Rinse the pump with 2 mL of the 25-µg/mL solution three times
  4. Start low and go slow:
     - Slower titration is tolerated better
     - Initiate therapy at a dose of 2.4 µg/day (0.1 µg/hr) and titrate to patient response
     - Titration increments should not be more than 2.4 µg/day and ideally should be implemented every week
     - Maximum recommended dose: 19.2 µg/day (0.8 µg/hr)

If triple therapy with an opioid, bupivacaine, and clonidine at optimal doses is not working, troubleshooting the system is a must. In doing so, consider the following:

- **Pump:** The computer program analysis for volume and volume present within the pump need to be within 10% of each other; otherwise, pump or system failure (e.g., obstruction) should be suspected.

- **Catheter:** A myelogram will be needed to determine whether obstruction is present and the position of the tip of the catheter. When performing a myelogram through the diagnostic port of the pump, remember that this port accommodates only a 25-gauge Huber needle. Moreover, consider the following:
  1. The dead space of the catheter when injecting contrast medium
  2. The need for a bolus dose after the study is completed

In a recently published multicenter prospective randomized clinical trial by Staats and coauthors in which intrathecal therapy was compared with continued medical management, a slight trend toward better analgesia was noted in the intrathecal group (not statistically significant), but an improved side effect profile and increased survival were seen in the intrathecal group. There is also a report from the MD Anderson group in abstract form in which significant improvement in pain scores (NRS score of 7.6 to 4.8) and oral intake (morphine equivalent drug dose [MEDD] of 300 vs. 80) was documented following intrathecal opioid pump implantation.

The cost of implementing intrathecal therapy is initially high because of equipment acquisition cost. In contrast, the cost of implementing long-term epidural therapy is low. Two studies evaluated the cost of implementing therapy with these two modalities. These analyses show a “break-even” point at approximately 3 months. Thus, epidural therapy becomes very expensive after 3 months, which is one of the reasons to limit its use in patients with survival expectations of less than 3 months.

A consensus panel published current practice data on intrathecal medication management. A survey of 413 physicians managing 13,342 patients showed a variety of medications being used in the intrathecal pump, including morphine (48%); morphine and bupivacaine (12%); hydromorphone (8%); morphine and clonidine (8%); hydromorphone and clonidine (8%); morphine, clonidine, and bupivacaine (5%); morphine and bupivacaine (3%); and others (<3%). Other drugs mentioned included fentanyl, sufentanil, ziconotide, meperidine, methadone, ropivacaine, tetracaine, ketamine, midazolam, neostigmine, droperidol, and naloxone.

**NERVE BLOCKS**

**LOCAL ANESTHETIC NERVE BLOCKS**

Local anesthetic injections can be implemented for diagnostic or therapeutic purposes, or for both.

**Diagnostic blocks** help characterize the underlying mechanism of pain (nociceptive, neuropathic, sympathetically mediated) and discern the anatomic pathways involved in pain transmission. Their main indication is as a preliminary intervention conducted before a therapeutic nerve block or other definitive therapy. This helps the clinician determine the potential for subsequent neurolysis if indicated. Although the results often have good predictive value, they are not entirely reliable.

**Therapeutic injections of local anesthetics,** with or without a corticosteroid, into trigger points may provide lasting relief of myofascial pain.

**Epidural steroid—local anesthetic injections** are unlikely to provide long-lasting relief for neuropathic pain of neoplastic origin. However, they will produce significant analgesia in
patients who may not tolerate rapid titration of antineuro-
pathic medications.

Local anesthetic injections administered into sympathetic
ganglia may contribute to lasting pain relief in patients with
complex regional pain syndrome (CRPS) type 2, a condi-
tion frequently seen in cancer patients. This syndrome
may arise as a result of tumor invading into nervous system
structures (e.g., brachial or lumbosacral plexopathy), post-
surgical pain syndromes, or chemotherapy-induced periph-
eral neuropathy. Local anesthetic blockade of the stellate
ganglion or lumbar sympathetic chain has been used with
some success to temporarily relieve pain in these patients.

NEUROLYTIC BLOCKS

Neurolytic blocks have played an important role in the man-
agement of intractable cancer pain. This modality should
be offered when pain persists despite the implementation
of aggressive comprehensive medical management or when
drug therapy produces unwanted and uncontrollable side
effects. Patient selection is essential, and some of the impor-
tant variables to consider include (1) the severity of the
pain, (2) pain that is expected to persist despite chemother-
apy or radiotherapy, (3) pain that cannot be modified by less
invasive or risky means, (4) a clinical picture that the pain
is somatic or visceral in origin, and (5) a short life expectancy.

Alcohol and phenol are the two agents commonly used
to produce chemical neurolysis. Ethyl alcohol is a pungent,
colorless solution that readily can be injected through
small-bore needles and is hypobaric with respect to CSF. For
peripheral and subarachnoid blocks, alcohol is generally
used undiluted (referred to as 100% alcohol, dehydrated
alcohol, or absolute alcohol), whereas a 50% solution
is used for celiac plexus blocks. The alcohol should not be
exposed to ambient room temperature for a long period
because absorbed moisture dilutes it. Alcohol injection is
typically followed by intense burning pain and occasionally
erythema along the targeted nerve distribution.

Phenol is fairly unstable at room temperature. Its shelf
half-life is about 1 year when refrigerated and kept away
from light. Phenol can be used in 3% to 15% concentra-
tions and with saline, water, and glycerol or radiologic con-
trast agents. It is relatively insoluble in water, and as a result,
concentrations in excess of 6.7% will result in a suspension
at room temperature without adding glycerin to increase its
solubility in water. Phenol with glycerin is hyperbaric in
CSF but is so dense that even when warmed, it is difficult to
inject through needles smaller than 20 gauge. Phenol has a
biphasic action: its initial local anesthetic action produces
subjective warmth and numbness, which usually gives way
to chronic denervation over a day’s time. The hypoalgesia
after phenol is not as dense as after alcohol, and the qual-
ity and extent of analgesia may fade slightly within the first
24 hours of administration, particularly when used for
epidural neurolysis.

The use of subarachnoid (intrathecal) injections of alco-
hol or phenol for the management of intractable cancer pain
has significantly decreased in the United States since poly-
pharmacy intrathecal analgesia was implemented. Because
alcohol and phenol destroy nervous tissue indiscriminately,
careful attention to selection of the injection site, volume
and concentration of injectate, and selection and position-
ing of the patient are essential to avoid neurologic compi-
lications, a risk that is responsible for the decrease
in its use. Most authorities agree that neither alcohol nor
phenol offers a clear advantage except to the extent that
variations in baric properties may facilitate positioning of
the patient. With the exception of perineal pain treat-
ment, alcohol is usually preferred for intrathecal neurolysis
since most patients are unable to lie on their painful side, as
required for intrathecal phenol neurolysis. In an analysis
of 13 published series documenting treatment with intrathe-
ical rhizolysis in more than 2500 patients, Swerdlow reported
that 58% of the patients obtained “good” relief, “fair” relief
was observed in an additional 21%, and in 20% of patients
“little or no relief” was noted. The average duration of
relief is estimated to be 3 to 6 months, with a wide range of
distribution. Reports of analgesia persisting 1 to 2 years are
fairly common. In representative series using alcohol (n
= 252) and phenol (n = 151), a total of 407 and 313 blocks
were performed, respectively. In these two series, neither
motor weakness nor fecal incontinence occurred, and
of eight patients with transient urinary dysfunction, inconti-
ence persisted in just one.

Subarachnoid neurolysis can be performed at any level
up to the midcervical region, above which the risk for
spread of drug to the medullary centers and the potential
for cardiorespiratory collapse increase. A hyperbaric
phenol saddle block is relatively simple to perform and is
particularly suitable for many patients with a colostomy and
urinary diversion.

Until recently, epidural neurolysis was performed infre-
quently. The results were inferior to those obtained with
subarachnoid blockade, presumably because the dura acts
as a barrier to diffusion, thereby resulting in limited contact
between the drug and targeted nerves.

PERIPHERAL AND CRANIAL NERVE BLOCKS

Peripheral nerve blockade has a limited role in the manage-
ment of cancer pain. Blockade of the ganglion of Gasser,
within the foramen ovale at the base of skull or its branches,
may be beneficial for facial pain. However, the indica-
tions in patients with tumor-related pain are truly minimal
because a neuropathic pain component is usually pres-
ent. Thus, the risk for deafferentation pain is significantly
increased with chemical neurolysis. Again, the use of intra-
spinal therapy by means of an implanted cervical epidural
catheter or intraventricular opioid therapy has become a
better option for these patients.

VERTEBROPLASTY

Many cancer patients with metastatic vertebral compression
fractures (VCFs) or osteoporotic VCFs have movement-
related back pain. Percutaneous vertebroplasty (PV) is a
minimally invasive procedure that involves injection of bone
cement (usually polymethylmethacrylate [PMMA]) into the
fractured vertebral body to alleviate the pain and hopefully
enhance structural stability. This procedure is performed
by placing needles under biplanar fluoroscopic guidance
via a unipedicular or bipedicular approach. PMMA mixed
with sterile barium is injected in a careful, controlled man-
ner to avoid unintended spread of cement into the spinal
canal or into veins within the affected vertebra. Injection is
stopped as soon as cement starts approaching the posterior
third of the vertebral body. Four studies evaluated the effi-
cacy of PV in patients with vertebral fractures. Two of them
found no differences between the treatment and placebo
groups. The third study reported better pain relief on the first postoperative day, but no difference from placebo thereafter, and the fourth study reported significant pain control at 1 week and 1 month, but not at 3, 6, and 12 months. It therefore appears that PV is a questionable alternative for patients with vertebral fractures.

**SPINAL CORD STIMULATION**

This technique has been used successfully for refractory neuropathic chronic pain states in patients with chronic nononcologic pain. There is a lack of studies evaluating its use for cancer pain states. However, at Roswell Park Cancer Institute we have used it successfully in patients with CRPS type 2, such as those with postsurgical pain syndromes, chemotherapy-induced peripheral neuropathy, and postradiation nerve injury. Patient selection is very important in the cancer population because MRI at this point is contraindicated after this device is placed and medical oncologists rely on this study to monitor the progress of disease in these patients.

**NEUROSURGICAL PALLIATIVE TECHNIQUES**

Neurosurgical palliative techniques have fallen into less favor as more medications and reversible, titratable, lower-risk techniques have largely replaced these procedures. Pituitary ablation entails destruction of the gland by injecting a small quantity of alcohol through a needle positioned transnasally under local general anesthesia. This technique is effective in relieving pain originating from disseminated bony metastases, particularly those secondary to hormone-dependent tumors (breast and prostate). Commissural myelotomy has been reported to be efficacious in relieving cancer pain refractory to more conservative therapy. Percutaneous cordotomy produces a thermal lesion within the substance of the spinal cord and reliably relieves unilateral, but not bilateral, upper limb pain. As with pituitary ablation, a high degree of skill and expertise is necessary, but the pain relief is often profound and the rigors of a major neurosurgical procedure are avoided.

**BEHAVIORAL INTERVENTIONS**

Several behavioral pain management techniques have been used in patients with cancer, including hypnosis, relaxation, biofeedback, sensory alteration, guided imagery, and cognitive strategies. Relaxation and imagery training significantly reduce VAS scores in patients in whom mucositis develops after bone marrow transplantation. This training is probably most effective for patients who have no significant psychological or psychiatric problems and for insightful psychology-minded patients.

**HOME-BASED AND HOSPICE CARE**

For years, hospice has been regarded as a place where people go to die, but in its purest form, it is a philosophy of care that is “a blend of clinical pharmacology and applied compassionate psychologic care.” In the United States, hospice care has been developed primarily as a home-based service, with a minority of institutions offering short inpatient stays to stabilize refractory symptoms and provide respite for overwhelmed families.

The principles of home-based pain management are in most respects similar to those that apply to ambulatory and inpatient pain management. Differences generally relate to the recognition that further curative therapy is futile rather than that care is being provided at home. No compromise in quality of care based on where it is delivered is justified. Hospice care is comfort oriented and focuses specifically on alleviating symptoms rather than necessarily treating their underlying cause. Factors that influence the selection of home treatment are advanced incurable disease, realization and acceptance of the appropriateness of palliative care (care directed at preserving comfort and quality of life rather than curing the tumor and extending life), and a desire to die in familiar surroundings. Many difficulties associated with providing intensive palliative care at home can be reconciled by education and orientation of the family, and such care can be performed in coordination with health care institutions, home care nursing, and laboratory and pharmacy services.

**SUMMARY**

Acute and chronic pain is highly prevalent in cancer patients. Inadequate assessment and treatment of pain and other distressing symptoms may interfere with antitumor therapy and markedly detract from quality of life. Even though a strong focus on control of pain is important independent of disease stage, it is a special priority in patients with advanced disease who are no longer candidates for potentially curative therapy. Though rarely eliminated, pain can be controlled in the vast majority of patients with the implementation of an aggressive comprehensive medical management strategy. In the small but significant proportion of patients whose pain is not readily controlled with noninvasive analgesics, a variety of alternative invasive and noninvasive measures, when selected carefully, are also associated with a high degree of success. To this end, it is very reassuring to conclude that at this point we have the appropriate tools to adequately treat cancer-related pain in close to 100% of patients.

**KEY POINTS**

- Uncontrolled acute or chronic pain still affects 40% to 45% of patients afflicted with cancer. Despite the availability of a multitude of simple cost-effective pain treatments, inadequately controlled pain remains a significant problem in cancer patients.
- Cancer-related pain is mostly due to invasion of organic structures by the tumor (directly or by metastasis), is related to cancer treatment (surgery, chemotherapy, radiation therapy), or in a small minority, is due to chronic pain syndromes.
- Various standardized questionnaires can be used in pain clinics to assess pain intensity. Furthermore, a comprehensive patient assessment can be done by performing a thorough history and complete physical examination, along with subsequent analysis of diagnostic studies, which will lead to an appropriate diagnosis in virtually all patients.
**KEY POINTS—cont’d**

- Cancer pain can be classified on the basis of various pain parameters, such as time, intensity, pathophysiology of the pain, and temporal aspect of the pain or by the evolution of various cancer pain syndromes.
- Cancer pain can be adequately controlled in the majority of patients (≈95%) with aggressive pharmacologic treatment, with only a minority requiring invasive therapy. Treatment of cancer pain should be directed toward relief of pain and suffering and improvement in function and the psychological aspects of cancer diagnosis and pain.
- Oral and transdermal opioid analgesics are the mainstay of therapy for pain in cancer patients. Other adjuvant analgesics can be added to oral opioids for adequate control of pain if neuropathic pain is present. When oral pharmacotherapy fails, alternative modalities can be considered, including subcutaneous opioid infusion, intravenous patient-controlled analgesia with opioids, neuraxial opioids, and invasive procedures such as intrathecal pump implantation, peripheral nerve radiofrequency lesions, and neurolytic procedures.
- Patients with a survival expectancy of longer than 3 months are generally considered candidates for intrathecal therapy with a permanent intraspinal catheter and an implanted subcutaneous pump. Patients with a survival expectancy of less than 3 months will require epidural therapy with an implanted system. Before either neuraxial procedure, an epidural catheter trial is conducted to assess the need for implantation of the permanent device.
- Behavioral therapy has an important role in the treatment of pain. In patients with advanced or incurable disease, palliative therapy for control of pain and preservation of quality of life with home-based and hospice care can be undertaken.
- Overall, with judicious use of the various modalities available, including noninvasive oral and intravenous pharmacologic therapy combined with invasive therapy when needed, control of cancer pain is possible in the vast majority of patients.

**SUGGESTED READINGS**


REFERENCES


REFERENCES


