DOLOR 2007;22:96-101

Diagnosis and treatment of cancer related pain

O.A. de León-Casasola

LECTURE OBJECTIVES

- Review the fundamental steps for evaluating cancer pain in patients.
- Discuss the available therapies for managing cancer pain.
- Develop a plan for evaluating and treating cancer pain patients.

Advances in cancer treatment have improved survival among cancer patients, prioritizing the need for effective pain control for improving quality of life. Patients with advanced or terminal cancer are more likely than those in the early stages to have pain as their chief complaint. The incidence of pain varies depending upon the type of neoplasm, stage and extent of spread. Although various investigators have tried to define the prevalence of pain in cancer patients, the lack of objective diagnostic tests for pain has led to figures ranging from 20-50% of all patients in early stages to 55-95% in the latter stages of diagnosis[1]. Thus, pain is a common symptom in cancer patients. Next to incurability, it is the most feared complication of contracting the disease. With the current therapeutic modalities available to the clinician about 90-95% of cancer pain can be controlled[2]. However, studies by Cleeland CS using Eastern Cooperative Oncology Group physicians show that the majority of cancer pain is under treated by these specialists, especially women, minorities, and the elderly[3]. The American Cancer Society Advisory Group on Cancer Pain Relief found three major barriers to effective cancer pain control - physician barriers, patient barriers and regulatory barriers. Inadequate assessment of pain by physicians and nurses was demonstrated by Grossman to be one of the most important causes of treatment failure[4]. Widespread misconceptions and knowledge deficits have also been shown to cause this poor assessment of pain by health care providers. Guidelines for the treatment of cancer pain have been developed by the World Health Organization, the American Society of Anesthesia, and the Agency for Health Care Policy and Research in an attempt to rectify these issues[5,6].

ASSESSMENT OF CANCER PAIN

Assessment of cancer pain begins with a thorough understanding of the complex nature of pain. The International Association for the Study of Pain in 1979 defined pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage". This definition stresses the importance of the emotional and suffering aspects of pain. In studies by Bond MR, cancer patients were noted to have increased levels of hypochondriases and neuroticism[7,8]. Bond was able to show restoration to a normal personality with the relief of pain. It has been noted that uncontrolled pain is a major factor in suicidal deaths of patients with cancer[9,10].

Woodforde JM and Fielding JR found that patients who were emotionally disturbed did not respond as well to therapy and died sooner then their counterparts who weren't in pain and emotionally stable[11]. Moreover,

Department of Anesthesiology
University at Buffalo, School of Medicine
Buffalo. New York

Dirección para correspondencia:
Óscar A. De León-Casasola
Department of Anesthesiology
University at Buffalo, School of Medicine
Buffalo. New York
E-mail: Oscar-deleon@roswellpark.org

Wells DG showed that patients with depressive symptoms or a depressive disorder are more likely to be disabled and more likely to have pain[12]. These studies show that the relief of pain goes beyond reducing the nociceptive component of pain it also has bearing on patient outcome. All too often, psychological variables are proposed to explain continued pain or lack of response to therapy, when medical factors have not been adequately addressed.

TYPES OF CANCER

Cancer pain can be somatic, visceral, or neuropathic. Somatic pain is associated with tissue damage, and results from the activation of nociceptors in either peripheral or deep tissues. The C and A δ fibers transmit the pain sensation from the periphery to various parts of the midbrain and neocortex. The quality of this pain is described as a well localized, aching, or gnawing pain. Bone pain and postsurgical pain are common causes of this condition.

When visceral structures are stretched, compressed, invaded, or distended, visceral nociceptors are activated. Since C-mediated pain fibers enter on both sides of the spinal cord through autonomic ganglia, a poorly localized, noxious pain is reported. Patients often describe the pain as deep, squeezing, crampy, and colicky in nature. Referred (viscerosomatic) pain, such as shoulder complaints when the diaphragm is invaded with liver tumor, and nausea and vomiting are associated conditions. Pancreatic and colon carcinomas may produce this condition. Direct injury to neural tissue from tumor infiltration or erosion or from cancer therapies can result in a noxious, intractable condition known as neuropathic pain. Associated sensory, motor, and autonomic deficits can accompany the symptoms of burning, squeezing, and paroxysmal, sharp pain. Examples of this pain include brachial and lumbar plexopathies, and peripheral neuropathies like postthoracotomy pain syndrome. There is a high incidence of patient suffering associated with neuropathic pain largely because it is often difficult to adequately treat these conditions.

CLINICAL ASSESSMENT

Treatment failure can be directly attributed to an inadequate assessment of the patient with cancer pain. Initial treatment should be based on pain etiology and type of pain. A detailed analysis of the pain condition in each patient should form the basis of rational therapy[13].

Prior to beginning treatment, the clinician should perform a detailed history and physical examination. The first step in the assessment of patients with cancer pain is a thorough history and physical exam. Based on the findings of this examination diagnostic studies should be ordered, a preliminary diagnosis, treatment goals and a treatment plan are then established. Following the initial evaluation, on subsequent visits, the patient's status should be reassessed as tumor growth is a dynamic and evolving process.

HISTORY AND PHYSICAL EXAMINATION

In order to determine what further testing a patient may require the site, character and duration of the patient's pain should be elicited. Although review of the past medical history and what, if any, therapeutic measures have been previously tried to relieve the pain, may provide valuable information when developing a treatment plan. Most patients with cancer pain have numerous other symptoms. They often suffer from insomnia, depression, fatigue, anxiety, anger, anorexia, and also the side effects of therapeutic interventions such as nausea and vomiting, dysphoria, headache, pruritus, constipation, and lightheadedness. It is essential to take into account all of these symptoms when developing a therapeutic plan since these symptoms impact on the quality of life, and most are amenable to therapy. Physical examination should include a complete neurological examination. Neurologic deficits from direct tumor invasion or compression are common and are frequently painful. The examination should also be directed towards determining if any therapeutic blocks will benefit the patient.

PAIN INTENSITY

One of the most difficult aspects of pain control is the accurate assessment of pain intensity. Although difficult to gauge, it is important because it provides a basis for developing a treatment plan and evaluating the effectiveness of therapeutic interventions. Also, if a patient's pain level increases during treatment it may indicate disease progression which needs to be diagnosed in consideration of further anti-tumor therapy. The best methods available to us are the

VAPS and the McGill Pain Questionnaire. Fishman B, et. al. (1987) reported that the Memorial Pain Assessment Card (MPAC) was easy to use and could distinguish pain intensity from both pain relief and global suffering[14].

DIAGNOSTIC TESTING

The patient's prior test results should be reviewed, especially procedures like CT scans, MRI, bone scans, scopings and staging procedures, in order to assess the location and extent of the tumor. Additional testing may be necessary depending on the findings of the history, physical examination, and previous tests. The most commonly ordered tests were plain radiographs, computerized tomography (CT) of the body, myelography and magnetic resonance imaging (MRI) or CT of the head. It must be appreciated that diagnostic testing may at times be painful, e.g. lumbar puncture, electromyography, and endoscopic studies. These tests should only be ordered if the results will alter therapy. Positioning and transport of patients in pain is poorly tolerated, and attempts should be made to minimize any incidental pain by premedicating patients in advance of moving them.

TREATMENT PLAN

Following a thorough review of the patient's clinical records, history, physical examination, and diagnostic tests, a preliminary treatment plan should be established. When developing a treatment plan, the ultimate goal of the therapy must be considered. Treatment plans often vary depending upon patients' prognoses, extent of disease, physical condition and age. In patients undergoing active cancer therapy, immediate relief of pain is the most important aspect of the plan. Functional status and quality of life issues are also critically important to assess. Pain relief sufficient enough to allow the patient to tolerate diagnostic and therapeutic interventions should also be provided. Patients with terminal disease should have the treatment plan formulated upon the wishes of the patient and his family. Ensuring that the patient is comfortable is an important aspect of the management of these patients. Provision of supportive care, including nursing and psychological services should be made available to the patient and his (her) family as part of a comprehensive treatment plan. The involvement of hospice in the patient's care should also be considered.

CANCER PAIN

In 1986, the World Health Organization (WHO) developed a three-step guideline, called the WHO analgesic ladder, to improve the management of increasing levels of cancer pain[5]. NSAID therapy is recommended by the WHO for use at all three steps on the analgesic leader, either alone or in combination with an opiate or adjuvant analgesic (other drugs which enhance analgesic effects).

INFLAMMATION AND CANCER PAIN

Cancer pain is often triggered by the release of inflammatory cytokines from active tumors[15,16]. NSAIDs produce analgesia in part by inhibiting the release of these inflammatory mediators, thus reducing nociceptive transmission. The most common cause of cancer pain is tumor infiltration of bone. Bone metastases occur as a consequence of breast cancer, prostate cancer, lung cancer, or multiple myeloma. One likely mechanism of pain secondary to bone metastasis is the secretion of PGs by carcinomas. For this reason, NSAIDs should be included in any regimen to control pain associated with bone metastasis.

REGIONAL BLOCKS[17]

Regional blocks with neurolytic agents have been most helpful in treating well-localized somatic or visceral pain. Commonly used neurolytic substances are 3-12% phenol and 25-100% alcohol. Therapeutic diagnostic blocks with local anesthetics are considered essential by many to evaluate the effect and the impact of the resulting motor deficit. Neurolytic substances are thought to act by causing Wallerian degeneration of the nerve fiber by means of protein denaturation and destruction of the myelin sheath.

STELLATE GANGLION BLOCK

Stellate ganglion is responsible for sympathetic nerve conduction to the ipsilateral upper extremity and

head. Neurolytic block of this structure is indicated in severe arm pain from brachial plexopathies, postherpetic neuralgias and complex regional pain syndromes (CRPS) type I or II. Because of the potential complications such as intravascular injection of the vertebral artery, phrenic and superior laryngeal nerve block and intrathecal injection, many clinicians are reluctant to perform neurolytic stellate ganglion nerve block. Moreover, the risk of Horner syndrome after neurolysis is ever present.

CELIAC PLEXUS BLOCK

A block of this plexus affects visceral pain in the midabdomen, and has been widely accepted for the treatment of pancreatic cancer pain. The incidence of pain relief has been reported to be more than 84%, although occasionally repeat blocks are required. However, recent studies have suggested that this block is not effective in the face of metastatic disease[18]. Complications include hypotension, intrathecal, epidural, or intravascular injection of the aorta or vena cava, puncture of the surrounding organs, mainly kidney, intestine or lung. Anterior spinal artery syndrome is a known complication of this block.

SUPERIOR HYPOGASTRIC PLEXUS BLOCK

The hypogastric plexus controls sympathetic activity to the pelvis and lower extremities. Since visceral fibers carrying nociceptive impulses from the pelvis travel with these sympathetic fibers, cancer pain syndromes that may be amenable to pain relief with a hypogastric nerve block include cervical, proximal vaginal, uterine, ovarian, testicular, prostatic, and rectal cancers.

Potential complications include intravascular injection and hematoma formation secondary to the proximity of the iliac vessels to the needle paths, intramuscular injection with consequent paraspinal muscle spasms, and less frequent renal or ureteral puncture. Although complete pain relief following this block is achieved in about 67% of the time, the block often increases comfort of most patients and minimizes need for opioids with their attendant side effects. Just as with the celiac plexus block, it is not effective when there is disease extension beyond the viscera of the pelvis.

INTRASPINAL THERAPIES

When the pain cannot be controlled with oral medications, or side effects limit the titration process, the intraspinal route is considered. When opioids alone are used, profound analgesia is achieved at a much lower dose, without the motor, sensory, or sympathetic block associated with intraspinal local anesthetic administration. However, in cancer patients, the presence of neuropathic pain is the most frequent reason to use an intraspinal technique, and the addition of a local anesthetic, clonidine, or both is necessary to achieve adequate pain control. Combinations of opioids with local anesthetic and/or clonidine act synergistically to produce effective analgesia while decreasing the side effects of compounds. Very infrequently, patients will not achieve adequate pain control with triple drug intrathecal therapy. In the future the use of adenosine, aspirin, and ziconotide may become a viable alternative for patients with complex pain problems. There are several systems available for the delivery of drugs intraspinally:

- Percutaneous catheters are used for conventional perioperative epidural anesthesia and analgesia, although, they may be used for both short-term epidural and intrathecal analgesic therapy. They are made of polyamide, nylon, or polyurethane, and because they can produce skin irritation at the site of insertion, they are not suitable for long-term therapy. It appears that the longer the catheter stays in place, the greater is the risk of infection. To decrease the risk of infection at the site of entry, catheters are typically tunneled through the subcutaneous tissue to exit 8-10 cm away from the point of insertion.
- Surgically implanted catheter with subcutaneous port site for injection (Port-a-cath system) requires surgical insertion of the injection port in the subcutaneous tissue and anchoring to the muscle fascia to avoid migration and inversion. The advantages of this system over a percutaneous epidural approach include a lower incidence of skin and subcutaneous tissue infection and decreased incidence of catheter dislodgment and kinking.
- Surgically implanted catheter for drug administration via an external PCA pump (Dupen's permanent epidural catheter) allows patients to receive continuous epidural administration of medications administered via an external PCA pump. These catheters are usually used successfully for up to 12 months, at which time epidural fibrosis starts

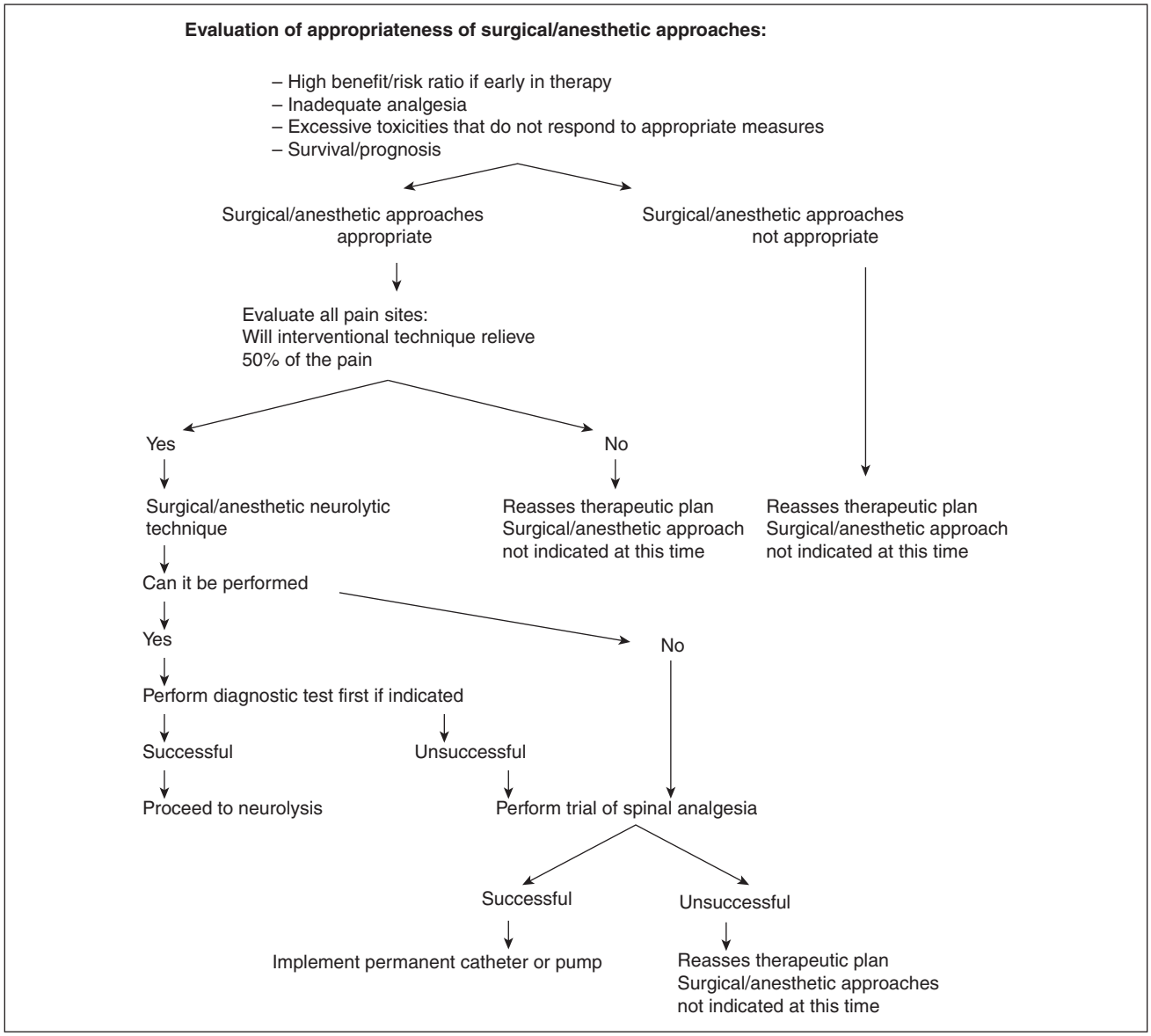

Figure 1. Surgical/anesthetic strategies *(adapted from NCCN Practice Guidelines in Oncology 2001;1).*

to develop. If this problem occurs, it is advisable to switch to intrathecal therapy since the epidural space is no longer functional conduit for drug administration.

– Surgically implanted catheter with implanted infusion pump at a fixed rate (Arrow) or IsoMed constant flow pumps (Medtronic) are made of titanium and silicone rubber and are available in different reservoir sizes. Changes in dosing are accomplished by modifying the concentration of the drugs placed in the pump.

– Surgically implanted catheter with implanted programmable infusion pump (Synchromed) has the advantage over the continuous flow implantable pumps in that four modes of drug administration may be programmed: continuous, complex continuous, single bolus and continuous with periodic bolus.

Key issues to guarantee a successful therapy include the positioning of the tip of the catheter at the corresponding site of nociception in the spinal cord, and the use of combinations of opioids and adjuvants.

NEUROSURGICAL PROCEDURES

Neurosurgical techniques directed towards specific peripheral or central nervous system structures can benefit a highly selected group with refractory cancer related pain. They can be divided into two categories: reconstructive and ablative. For patients with pain from spinal metastatic disease, the newer surgical methods of anterior decompression and stabilization provide reliable pain control while preventing serious neurologic progression. Minimally invasive techniques for vertebral stabilization, such as vertebroplasty, may also effectively relieve pain from spinal metastases associated with low morbidity. Traditionally, stereotactic and functional neurosurgical techniques have been used to produce selective lesions in neuroanatomic pathways that mediate pain. Cordotomy is still the most often performed surgical procedure. It targets the spinothalamic tract, and it can be done by using either a percutaneous or open surgical approach.

The following decision algorithm is adapted from the National Comprehensive Cancer Network's guidelines for cancer pain treatment. It helps the clinician decide when and what invasive therapies should be used (Fig. 1).

CONCLUSION

Palliative care clinicians and oncologists are increasingly using coxibs to manage cancer pain, due to their opioid-sparing effect and their lack of the adverse effects typically associated with NSAID or opiate therapy. More widespread use of coxibs will greatly reduce the needless pain and suffering that cancer patients unnecessarily experience because of outdated clinical perceptions.

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