SYMPOSIUM ARTICLE
UDC: 616-006:615-085:616.8-009.7:616-008.6

Cancer pain syndromes and pharmacotherapy of cancer pain

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KEY WORDS: *Neoplasms; Pain; Drug Therapy; Analgesics*

Cancer-related pain afflicts some 9 million people worldwide annually. Pain is usually a direct result of tumor in 75%-80% of patients; it is caused by anticancer treatments in 15%-19% of patients and is unrelated to cancer and its treatments in 3%-5%. This coincidental pain is related to debility, decubitus (nociceptive) and post-herpetic neuralgia (neuropathic-peripheral and central). Pain is also caused by diagnostic procedure used in cancer treatment. Numerous distinct cancer pain syndromes have been recognized and described (1-3).

SYNDROMES RELATED TO DIRECT TUMOR INVOLVEMENT

The best characterized pain syndromes related directly to the neoplasm are those due to involvement of bony and neural structures.

Pain caused by bone metastases

Bone metastases are the most frequent cause of cancer-related pain present in 30% to 70% of all cancer patients and more frequently secondary to multiple myeloma and cancers of the prostate, breast, lung, kidney, and thyroid. Pain is usually constant, localized to the area of metastasis; it may be greatest at night and aggravated by movement and weight bearing. Pain is described as dull and aching, and there may be referred pain, muscle spasm, or paroxysms of stabbing pain, particularly when bony lesions are accompanied by nerve compression. Pain can suddenly become more intense in the event of a pathological fracture. Metastatic bone disease is a frequent cause of morbidity in advanced cancer patients with a subsequent high incidence of skeletal complications (fractures, spinal cord compression, hypercalcemia) and severe pain. Incidental pain or movement-related pain is present in almost 20% of patients with episodes of breakthrough pain. Bone metastases may be considered a cause of incidental pain with the need of rescue doses of analgesics in patients already successfully treated for pain at rest by means of opioids regularly administered. Bisphosphonates represent a new class of drugs with inhibitory activity on bone resorption and on inflammatory processes. From the analysis of the published studies it appears that bisphosphonates and, in particular, intravenous disodium pamidronate, and partially clodronate, are not only able to reduce the onset of skeletal complications but they also have an analgesic effect and the possibility of improving the mobility, above all in patients with osteolytic metastases due to breast cancer and multiple myeloma (4). zoledronic acid 4 mg in 100 mL of fluids every 28 days intravenously is indicated in patients with prostate cancer and bone metastases (5).

The vertebrae are the most common sites of bone metastases. Pain due to vertebral metastases with or without epidural spinal cord compression is exacerbated by lying and relieved by sitting; the opposite is true for herniated disc pain or facet joint disease. The main complications of vertebral metastases are vertebral collapse, radiculopathy, and epidural spinal cord compression.

Epidural metastasis is a threatening complication of bone metastasis to the vertebral spine. In most cases the tumor enters the epidural space from the adjacent vertebral metastases or there is an invasion through the intervertebral foramina by the tumors in the thorax or the retroperitoneal sites. Epidural metastasis is a medical emergency because a delay in the diagnosis and treatment of this condition produces permanent neurological damage (6).

The pain referred by the patient is at the spinal level with a radicular distribution when the nerve roots are involved and this is one of the first signs of the disease that may precede neurological damage by a few weeks. More than 70% of patients with spinal cord compression have lytic or blastic lesions in the region of pain, radiological evaluation should be completed with MRI or myelograms to study the epidural space before neurological deficits develop. The treatment consists of using corticosteroids and analgesics in association to radiation therapy and surgery.

Pain caused by neural invasion

Pain coming from neural invasion is found in 20% to 40% of patients (1-3). Invasion or compression of somatic nerves by tumor provokes burning, dysesthesic pain, often with an intermittent lancinating component. Muscle weakness and atrophy may be present if the affected structure is a mixed or motor nerve. Tumoral infiltration of peripheral nerve, plexus and root produce well-defined pain syndromes. Pain due to peripheral nerve involvement most commonly occurs as a consequence of a paravertebral, retroperitoneal or chest wall/rib lesion.

A paravertebral mass may damage one or more spinal nerves and provoke radicular pain along the distal course of the nerve. Back pain may also be due to a paravertebral lesion and must be distinguished from that due to invasion of the vertebral body or of the spinal canal.

Lesions occurring at cervical, brachial and lumbosacral plexuses causes pain that is difficult to control in cancer patients. Pain is due to tumoral infiltration of these structures or compression by fibrosis after radiotheraphy to adjacent structures; in the latter the pain is less intense. Pain can precede neurological signs also in plexopathies.

Pain caused by infiltration of viscera and vessels

Infiltration of viscera causes poorly localized deep-seated aching pain, often accompanied by referred pain. Involvement of the tissue capsule produces more severe sharp pain, which is well localized and associated with local tenderness. Infiltration of hollow viscera will cause colic and pain which is poorly localized and often associated with referred pain.

SYNDROMES RELATED TO TREATMENT

Postsurgical pain syndromes

They are characterized by either persistent pain after surgical procedure or recurrent pain after the initial surgical pain has been resolved. The clinical characteristics relate to the location and extent of nerve injury. Painful neuropathy may occur after any surgical procedure but most frequently follows thoracotomy, mastectomy, neck dissection, and nephrectomy. Pain develops several months postoperatively and is a continuous dull ache with intermittent lancinating pain or a continuous burning dysesthesia with hyperesthesia. Similarly, patients undergoing amputation can develop a constant aching or burning pain in the stump or in the phantom limb.

Postradiotherapy pain syndromes

Radiation fibrosis involving either the brachial or lumbosacral plexus causes painful neuropathy, starting a few months up to many years after treatment. Radiotherapy also produces painful mucositis and painful myelopathy, which usually arises after six months and may occur if the spinal cord has been radiated by a higher dose than spinal cord tolerance.

Post chemotherapy pain syndromes

Vinca alkaloids, cisplatin, procarbazine, and taxol produce dose-related peripheral neuropathies, usually manifested as dysesthesia in the feet and later in the hands. Vincristine neuropathy may also give rise to cranial neuralgia, including jaw claudication. Chemotherapy causes painful mucositis and phlebitis; tissue necrosis may occur if there is extravasation of drugs into the tissues. Painful myalgia and arthralgia occur with the abrupt withdrawal of corticosteroids.

ANALGESIC DRUGS

In 1986, the World Health Organization (WHO) proposed a strategy for cancer pain treatment based on a sequential three-step analgesic ladder.

A number of clinical studies have confirmed the analgesic effectiveness of this approach, whatever the social cultural environment. Despite these published guidelines, many cancer patients experience considerable pain, and approximately half of them do not receive adequate analgesia. An effective pain-relieving therapy must: (1) prevent the onset of pain: for this purpose drugs have to be administered "by the clock", taking into account the half-life, bioavailability and duration of action of the different drugs; (2) be simple to administer, thus easy to manage for the patient himself and his family, especially when the patient is cared for at home. The oral route appears to be the most suitable to meet this requirement, and, if it is well tolerated, must be considered as the preferential route of administration; (3) be individualized: the dosage, the type and the route of drugs used must be administered according to each patient's needs. Individualized pain management should take into account the stage of disease, concurrent medical conditions, characteristics of pain, and psychological and cultural status of the patient. Aspirin, paracetamol and the nonsteroidal anti-inflammatory drugs (NSAIDs) given as single analgesic treatment are recommended as the sole treatment of mild pain or combined with opioids for moderate to sever pain. NSAIDs are commonly defined as "peripheral" analgesics, although there is increasing evidence that they have a central or nor exclusively prostaglandin-mediated action. Toxicity resulting from the use of the NSAIDs remains the most significant factor limiting their role in cancer pain management (7).

According to the WHO, opioid analgesics are the mainstay of therapy for cancer-related pain and the WHO expert committee introduced morphine as a major pain-relieving drug and has strongly asserted the necessity of making it available all over the world.

Since 1977, oral morphine has been used by hospices and palliative care units as the drug of choice for the management of chronic cancer pain of a moderate to severe intensity because it provides effective pain relief, is widely tolerated, simple to administer, and comparatively cheap. Important studies investigated the clinical pharmacology and pharmacokinetics of oral morphine. Ideally, two types of formulation are required: immediate release (for dose titration) and sustained-release (for maintenance treatment). Every 12-hour administration of sustained-release oral morphine and every 4-hour administration of immediate-release oral morphine provide similar analgesic efficacy and side effect profiles in the treatment of chronic pain. The guidelines of the Expert working Group of the European Association for Palliative Care regarding the correct administration of morphine via various routes were published recently (8,9).

Oral methadone is considered to be a useful alternative to oral morphine in treating moderate to severe cancer pain. Methadone is a synthetic opioid analgesic displaying agonistic activity. Methadone is characterized by a large inter-individual variation in pharmacokinetics and by a rapid and extensive distribution phases (half-life of 2-3 hours) followed by a slow elimination phase (beta half-life of 15 to 60 hours) that may cause accumulation problems if doses are too large or the dosing intervals are too short over a long period of time. This is the main reason why attention is required when using this drug in treating chronic cancer pain. Methadone presents the potential to control pain that does not respond to morphine or other opioids because methadone shows incomplete cross-tolerance with other mu-opioid receptor agonist analgesics, moreover there is the possibility of using it instead of other opioids when accumulation of active metabolite is the cause of side effects such as myoclonus, sedation, confusion, nausea and vomiting. Methadone is a more potent opioid than believed. The dose ratio between methadone and the other strong opioids varies significantly (from 1:4 until 12-14:1) according to the type and doses of opioids previously administered. For this reason, caution is recommended when switching from any opioid to methadone, especially in patients who are tolerant to high doses of opioid (8,10).

Hydromorphone is another strong opioid used in clinical practice. It is an analogue of morphine with similar pharmacokinetic and pharmacodynamic properties. By mouth and by injection, hydromorphone is about 5 times more potent than morphine. Oral administration hydromorphone reaches its peak effect slightly more rapidly than morphine, and also has a shorter duration of action. It may be necessary to administer hydromorphone at 2- to 3-hour intervals. Hydromorphone is an effective alternative to morphine in patients who seem to be developing morphine unresponsiveness or morphine intolerance and it is particularly useful for subcutaneous infusion. It seems to cause less pruritus than morphine. The drug is expensive and is not available in many countries.

Oxycodone is a synthetic opioid derived from thebaine and structurally similar to codeine, however it is nearly 10 times as potent as codeine. Oxycodone hydrochloride has good oral bioavailability and its analgesic effect lasts from 3 to 5 hours. Patients who change from oral oxycodone to morphine are pain-free when relative milligram potency ratios of 1:1 to oral morphine and 3:1 to intravenous morphine are used. When given parenterally, oxy-

codone and morphine are almost equipotent. There is some evidence that oxycodone produce less hallucinations in respect to morphine. Sustained-release oxycodone has demonstrated K-agonist activity which produces markedly more sedation than mu-agonists. Such formulation is the most expensive among strong opioids.

Fentanyl citrate has a very high potency (about 75 times more than morphine), and is skin compatible having a low molecular weight with good solubility and thus suitable for transdermal administration. Transdermal fentanyl offers the advantage of providing continuous administration of a potent opioid, avoiding the use of syringes and expensive drug-infusion pumps for the treatment of cancer pain. However, the use of transdermal fentanyl is not indicated in opioid naive patients, during the opioid titration phase and to control breakthrough pain. When switching from one opioid to transdermal fentanyl, the patient has to continue taking 50% of previous opioid dose during the first 24 hours. There is some clinical and preclinical evidence showing that transdermal fentanyl produce less constipation in respect to morphine and other strong opioids (8).

While a large number of adjuvant drugs have been suggested to have analgesic effects, unfortunately the evidence is largely anecdotal and few controlled trials of these drugs have been conducted.

Tricyclic antidepressants (amitriptyline, imipramine, desipramine): have been found to be useful in a variety of neuropathic pain syndromes, especially when pain has prominent dysesthetic or burning character. The evidence for their role in malignant neuropathic pain is less clear. In one placebo-controlled study of terminal patients, the administration of imipramine was accompanied by decreased requirements for morphine. A trial of tricyclic antidepressants may be useful in any patient whose pain has responded inadequately to standard pharmacological management with opioids. The toxic effects of these drugs are mainly autonomic (dry mouth, postural hypotension) and centrally mediated (somnolence, confusion).

Anticonvulsants (carbamazepine, phenytoin, valproic acid, clonazepam, gabapentin): these drugs have been proposed mostly for the management of the lancinating neuropathic pain similar to pain associated with trigeminal neuralgia. Considerable anecdotal experience has accumulated for the use of these agents for neuropathic cancer pain syndromes, including neural invasion by tumor, radiation fibrosis or surgical scarring, herpes zoster, and deafferentation. Side effects of therapy are potentially serious, particularly in patients with advanced cancer, and can include bone marrow depression, hepatic dysfunction, ataxia, and diplopia. Periodic monitoring of complete blood count and liver function tests are recommended.

Gabapentin analgesic effects have been recently demonstrated in experimental studies and in preliminary clinical trials. It has been studied in cancer pain as an adjuvant to opioid analgesia. The potential role of gabapentin is to improve analgesia without worsening opioid side effects (11,12). Gabapentin is not metabolized by the liver microsomal system and does not interact with the metabolism of many other drugs. This characteristic is particularly attractive in the advanced cancer population. It could also interfere with the mechanisms of opioid tolerance.

Corticosteroids: dexamethasone has been found to be effective in spinal cord compression and in treating headache due to endocranic hypertension. Uncontrolled studies suggest that the administration of corticosteroids to selected patients with advanced cancer results in decreased pain and improved appetite and activity. Although corticosteroid administration is very frequent in advanced cancer patients, their beneficial effects have been reported in a few controlled studies.

Local anesthetics: the efficacy of intravenous administration of local anesthetics to control non-malignant neuropathic pain has been evaluated in different studies. Most protocols use a brief infusion of lidocaine that, when effective, produces short-lived analgesia typically lasting a few hours. The efficacy of intravenous and subcutaneous administration of lidocaine in patients with cancer neuropathic pain has shown contradictory results (11).

Bisphosphonates represent a further valid therapy to add to an already consolidated list of therapies such as radio, chemo, endocrine; radioisotopes; analgesic drugs, orthopedic and physiatric in the pain management of patients with bone metastases.

CONCLUSION

Successful pain management requires treatment of what Cecily Saunders described as the patient's TOTAL PAIN: physical, psychologic, social, spiritual and cultural. Physical pain is only one potential cause of suffering; thus, successful pain control requires attention to some or all of the other aspects of care and suffering and this, requires a multidisciplinary approach to treatment; failure to do this frequently results in unrelieved pain.

Each patient has his/her own threshold of pain. Adequate sleep, elevation of mood, diversion, empathy, and understanding all can raise an individual's pain threshold. Alternatively, fatigue, anxiety, fear, anger, sadness, depression, and isolation can lower the pain threshold.

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