Interventional Therapies for Cancer Pain Management: Important Adjuvants to Systemic Analgesics

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Abstract
Optimized use of systemic analgesics fails to adequately control pain in some patients with cancer. Commonly used analgesics, including opioids, nonopioids (acetaminophen and non-steroidal anti-inflammatory drugs), and adjuvant analgesics (anticonvulsants and antidepressants), have limited analgesic efficacy, and their use is often associated with adverse effects. Without adequate pain control, patients with cancer not only experience the anguish of poorly controlled pain but also have greatly diminished quality of life and may even have reduced life expectancy. Interventional pain therapies are a diverse set of procedural techniques for controlling pain that may be useful when systemic analgesics fail to provide adequate control of cancer pain or when the adverse effects of systemic analgesics cannot be managed reasonably. Commonly used interventional therapies for cancer pain include neurolytic neural blockade, spinal administration of analgesics, and vertebroplasty. Compared with systemic analgesics, which generally have broad indications for control of pain, individual interventional therapies generally have specific, narrow indications. When appropriately selected and implemented, interventional pain therapies are important components of broad, multimodal cancer pain management that significantly increases the proportion of patients able to experience adequate pain control. (UNCCN 2007;5:851–858)

Inadequately controlled pain produces immense physical and psychological suffering, including decreased functional status, diminished appetite, insomnia, depression, anxiety, and loss of control or hope. Without adequate pain control, those with cancer not only experience the anguish of poorly controlled pain but also have greatly diminished quality of life and may even have reduced life expectancy. Moreover, in the past 2 decades, as the mortality rates from certain malignancies have declined, the population of cancer survivors facing the hardship of chronic pain has increased. Cancer patients who have poorly controlled pain during the acute disease phase are at increased risk for developing chronic pain. Fortunately, multiple modalities exist to manage cancer pain, including direct antineoplastic therapies, systemic analgesics, interventional pain procedures, and cognitive behavioral therapies. In most cases, the management of cancer pain begins with readily available analgesics, as outlined by the World Health Organization’s analgesic ladder (see steps 1–3 in Table 1). Although systemic analgesics are effective in most cancer patients, up to 21% of patients continue to have inadequately controlled pain despite undergoing optimized treatment with systemic analgesics. When systemic analgesics are inadequate or when the risk/benefit ratio is favorable, various interventional procedures, including peripheral nerve blocks, spinal analgesics, and vertebroplasty, may play an important role in cancer pain management (see step 4 in Table 1).

In certain circumstances, including vertebroplasty for compression fracture or celiac plexus block for pancreatic cancer, intervention should not be delayed for extensive trials of conservative therapy. Unnecessarily delaying interventional techniques may result in difficultly accomplishing specific interventions when advanced care is necessary but the patient’s performance status has declined.

Key Words
Cancer pain, pain management, chronic pain, palliative care

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Localized cancer pain may be controlled by systemic including neurolytic injections, vertebroplasty, and spinal analgesics (with continuation of systemic analgesics when needed). Adjuvant drugs, including antidepressants, corticosteroids, or anticonvulsants, are recommended for each step of the ladder, when needed.

*Earlier use advocated when risk/benefit ratio is favorable.

When considering the use of interventional pain therapies for cancer pain, an accurate clinical and radiologic assessment of the specific pain in question is essential to guide technique selection and implementation. Localized cancer pain may be controlled by destroying peripheral nerves or plexuses using chemical or thermal modalities; however, diffuse, generalized cancer pain is unlikely to be controlled with selective peripheral neurolysis. Spinal analgesics, especially when based on epidural or subarachnoid administration of combination analgesics involving opioid, local anesthetic, or clonidine, are an especially potent tool for managing appropriate cancer-related pain. Vertebraloplasty plays a unique role in managing pain from pathologic vertebreal compression fractures caused by osteoporosis, metastasis, or myeloma. Because many interventional therapies have a specific anatomic site of action, whereas patients with metastatic cancer may have multiple anatomic sites of pain, interventional pain procedures may not eliminate all pain but are best used as a component of multimodal management of cancer pain.

In the context of interventional cancer pain management, neuroablative techniques are performed before chemical neurolysis for both diagnostic and prognostic purposes. Neurolytic blockade has a narrow risk/benefit ratio and the potential to cause significant untoward effects; therefore, neural destruction is generally considered when conservative modalities are exhausted. Neurolytic blockade of somatic nerves may be complicated by postneurolysis neuritic pain or the development of deafferentation pain, which may typically develop several weeks to months after neurolysis. Concern for neuritic and deafferentation pain generally restricts use of neurolytic blockade of somatic nerves to patients with advanced malignancies or those with short life expectancy.

Interventional pain procedures should be performed by clinicians with the skill, training, and expertise to safely perform these procedures and manage potential complications. This is especially important in cancer pain management because unique challenges are present when these interventions are performed in the setting of malignancy. Extensive surgery, radiation therapy, or tumor mass may alter anatomy, necessitating technique modification. Special attention to technique is required because this population may have increased risk for infection because of immunosuppression from chemotherapy, steroids, or general debilitation. Furthermore, cancer patients are often opioid-tolerant and therefore, if procedural sedation is required, significantly greater doses may be required.

The goals of interventional pain therapies include 1) reduced pain intensity, 2) decreased requirement of systemic analgesics to allow reduction in analgesics associated adverse effects, and 3) improved quality of life and functional status. Some studies suggest that, through improving patients' dietary intake and general function, interventional pain procedures may increase the survival of patients with cancer pain. However, other trials do not support this finding. Although an association between pain control and survival is a possibility that needs further evaluation, the urgent need of cancer patients with inadequate pain control from systemic analgesics should lead to more consistent and timely use of interventional pain therapies. Furthermore, opioid-induced hyperalgesia may be seen in cancer patients, especially during rapid dose escalation. In extreme cases, a paradoxical increase in pain may occur in response to increasing doses of opioid. With opioid-induced hyperalgesia, increased sensitivity to pain stimuli and pain that becomes more diffuse seem to occur, extending beyond the distribution of pre-existing pain. Interventional therapies may
be especially indicated in management of cancer pain when opioid-induced hyperalgesia is present.

**Sympathetic Blocks for Visceral Cancer Pain**

Cancer patients often experience visceral pain arising from the deep organs of the thorax, abdomen, and pelvis. Visceral pain tends to be vague and poorly localized compared with somatic pain. Afferent visceral pain nerve fibers pass through the paravertebral sympathetic ganglia, and therefore blockade of visceral sympathetic innervation can be an effective tool in controlling visceral cancer pain.

**Celiac Plexus and Splanchnic Nerve Block**

Pancreatic cancer and other upper abdominal malignancies are frequently associated with severe pain and nausea. Opioid analgesics provide good pain control for most patients in these settings, but may provide inadequate relief to others. Opioids further impede gastrointestinal motility and thereby contribute to nausea or constipation. Afferent pain fibers from upper abdominal viscera (including the stomach, liver, gall bladder, pancreas, spleen, kidneys, adrenals, omentum, mesentery, small bowel, and proximal colon through the splenic flexure) pass through the celiac plexus along the anterolateral surface of the aorta at the T12–L1 vertebral level. The visceral pain fibers then pass through the splanchnic nerves to reach the spinal cord in the mid-to-lower thoracic levels. Neural transmission of upper abdominal visceral pain can be blocked at either the level of the celiac plexus or splanchnic nerves. Local anesthetic celiac plexus or splanchnic block may provide temporary pain relief and can be used to clarify the extent to which a given patient’s pain may respond to neurolytic blockade. For long-term pain relief, neurolytic celiac plexus block (NCPB) or neurolytic splanchnic block (NSB) is performed with alcohol or phenol. Both blocks are performed under radiologic guidance using either fluoroscopy or computed tomography (CT). Typically, NCPB or NSB provides pain relief for several weeks to a few months. These injections can be repeated if pain returns but, because of the short life expectancy of persons with advanced upper abdominal malignancy, repeat injection is rarely needed.

NCPB is most commonly used in pancreatic cancer, where its use has been extensively studied. Good to excellent pain control is achieved in 70% to 90% of patients undergoing NCPB for pancreatic cancer pain, with similar results for other upper abdominal malignancies. After NCPB, patients often experience a significant improvement in appetite. One study found that patients undergoing NCPB experienced not only improved pain control but also improved mood and longer survival compared with those undergoing saline (placebo) celiac block. However, a subsequent study failed to confirm improvement other than pain relief. Although effect on survival remains a topic for further investigation, NCPB is effective for pain management in upper abdominal malignancy. However, successful NCPB is less likely in patients with extensive disease involving somatic and neural structures. Furthermore, in patients with extensive retroperitoneal disease encompassing the celiac plexus, spread of injectate may be poor, which may limit the effectiveness of the block.

Adverse effects of NCPB or NSB include temporary orthostatic hypotension (caused by decreased sympathetic vascular tone) and diarrhea (from opposed parasympathetic innervation to the alimentary tract). These symptoms generally resolve spontaneously within 1 to 2 days. Other potential complications include hematoma, infection, local anesthetic toxicity, pneumothorax, hematuria, and injury to spinal nerve roots. Paraplegia is a devastating but rare complication after NCPB, with an estimated occurrence of 1 in 700. The theoretical mechanism of paralysis is injury to, or vasospasm of, the artery of Adamkiewicz, the major segmental artery that supplies the anterior two thirds of the distal spinal cord. NCPB remains a useful tool for palliation of abdominal pain in advanced malignancy; it potentially provides 70% to 90% of patients with good to excellent pain relief, with risk for serious adverse effects comparable to that of other palliative therapies (chemotherapy, radiation therapy, or surgical intervention) often offered to patients with advanced malignancy for symptom control.

**Superior Hypogastric Nerve Block**

Superior hypogastric nerve block interrupts pain innervation of pelvic organs. Neurolytic superior hypogastric plexus block (NSHB) may provide analgesia for malignancies involving the cervix, uterus, ovaries, proximal vagina, testes, prostate, bladder, descending colon, and rectum. However, successful NSHB may not be possible in patients with extensive retroperitoneal disease encompassing the plexus, because it may prevent appropriate spread of neurolytic solution.
Furthermore, NSHB is not likely to provide good pain control if the tumor invades somatic or neural structures. These blocks are performed with radiographic imaging to guide needle placement. Although NSHB is generally well tolerated, potential complications include hematoma formation, inadvertent injection into the iliac vessels, ureteral puncture, lumbar or sacral nerve root injury, perforation of an intervertebral disc, sexual dysfunction, and changes in bowel or bladder function. Case reports suggest that NSHB is an effective tool in managing pelvic visceral cancer pain, but no controlled clinical trials have been published.

**Impar Ganglion Block**

Neurolysis of the impar ganglion has been reported to alleviate cancer pain originating from perineal viscera. The impar ganglion, a solitary structure that marks the termination of the paravertebral sympathetic chain, is located anterior to the sacrococcygeal junction. Local tumor invasion, especially from rectal cancer, may decrease the efficacy of the block by preventing spread of the neurolytic solution. Complications include perforation of the rectum and periosteal injection. No controlled studies are available to determine the efficacy of this injection.

**Nerve Blocks for Head and Neck Cancer Pain**

Head and neck cancer pain is often challenging to manage because of the erosive nature of the malignancy, dense sensory innervation of the region, and regional anatomic changes from surgical or radiation therapy. Although most head and neck cancer pain is controlled with systemic analgesics, neural blockade may be indicated for refractory pain. Carefully assessing the location and nature of the pain is important to applying the most appropriate nerve block (Table 2). Neural destructive lesions in the head and neck must be managed carefully to avoid increasing patient morbidity through excessive or unintended sensory or motor deficits. A trial of local anesthetic block is often used to help determine the extent of sensory or motor deficit expected from neurolysis. Neurolytic blockade of the gasserian (trigeminal) ganglion has been largely replaced by radiofrequency lesioning techniques that provide better control of lesion distribution and greater analgesic efficacy. Peripheral neurolysis in the head and neck may be associated with delayed development of neuritis or deafferentation pain, and therefore should only be used in patients with intractable pain and short life expectancy.

### Table 2: Head and Neck Nerve Blocks

<table>
<thead>
<tr>
<th>Nerve Block</th>
<th>Indication</th>
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<tbody>
<tr>
<td>Trigeminal (gasserian) ganglion</td>
<td>Facial cancer pain in the distribution of the V2 and V3 divisions of the trigeminal nerve</td>
</tr>
<tr>
<td>Mandibular nerve</td>
<td>Painful malignancy involving the jaw and anterior two thirds of tongue</td>
</tr>
<tr>
<td>Maxillary nerve</td>
<td>Painful tumors of the middle third of the face (maxilla, cheek, nasal cavity, hard palate)</td>
</tr>
<tr>
<td>Glossopharyngeal nerve</td>
<td>Localized pain arising from the base of tongue, soft palate, or nasopharynx</td>
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**Nerve Blocks for Thoracic Chest Wall Pain**

Chemical neurolysis of intercostal nerves may be used for pain originating from the thoracic wall, including metastatic lesions involving the ribs. One case series describes 46 cancer patients whose pain was successfully managed with serial phenol intercostal nerve blocks, but little additional literature documents the efficacy of this technique. Pneumothorax is an frequent complication when the correct technique is used. Other potential complications include vascular uptake of the injected solution and a single report of paraplegia. Neurolytic thoracic paravertebral block can be used for pain involving a small number of thoracic segments. The procedure involves injection of solution in the space immediately lateral to the vertebral body to target the somatic spinal nerves as they emerge from the intervertebral foramina. Because of the complex anatomy of the thoracic region, experts recommend that the technique be performed with radiologic imaging. Complications include pneumothorax and inadvertent spread of solution into the epidural or spinal space. Because of the potential for significant untoward events, neurolytic intercostal and thoracic paravertebral blocks are limited to intractable pain in cancer patients with poor prognosis.

Neurolytic blockade of the chest wall is less commonly used now than in the past because of the availability of spinal analgesic techniques (see next page), which offer greater efficacy and lower risk for adverse effects. Spinal analgesic therapies have the added burden (and cost) of an implanted pump/reservoir.
and spinal catheter, in addition to the ongoing need for refill and maintenance of the spinal drug administration system. Furthermore, an emerging therapy for palliating chronic chest wall pain is pulsed radiofrequency of the dorsal root ganglion or intercostal nerves.\textsuperscript{21}

**Neuroaxial Neurolysis**

Spinal neurolytic blocks are used less frequently now than in prior decades, likely reflecting a more sophisticated use of systemic and other spinal analgesic therapies and increased awareness of potential complications of neurolytic techniques. Although no prospective studies have been reported of spinal neurolytic techniques in the management of cancer pain, case series indicate a potential role for these procedures when other analgesic measures have failed. The subarachnoid injection of a neurolytic agent is a technique that aims to produce a chemical posterior rhizotomy, thereby interrupting transmission of pain signals from a painful area.\textsuperscript{22} Subarachnoid neurolytic blocks are best used for unilateral nerve injury in terminally ill patients with preexisting colostomy and permanent bladder catheter (because of risk for postneurolysis incontinence) or in those with well-localized, unilateral pain of the chest wall. Published data suggest that subarachnoid neurolysis may provide good results in as many as 60\% of patients, with relief lasting for up to 12 months.\textsuperscript{21} With appropriate patient selection and meticulous technique, complication rates range from 1\% to 14\%, which may be acceptable for certain patients. For example, if a bladder catheter is already used, bladder incontinence may not be an issue; however, ambulatory, continent patients will almost never accept the possibility of incontinence even if pain relief through alternative methods is inferior.

Epidural injection on neurolytic solution is generally considered for intractable pain only when other interventions, such as spinal analgesics, subarachnoid neurolysis, or sympathetic neurolytic blockade, are judged inappropriate. Epidural neurolysis is typically accomplished with daily injections of small volumes of neurolytic solution administered through a temporary percutaneous catheter over a few days, so that the extent of neurolysis is titrated to the degree required.\textsuperscript{21} Although they improve the accuracy of neurolysis, repeated epidural neurolytic injections over several days may be unacceptable because of the resultant delay for pain relief or the burden of undergoing repeated procedures.

**Spinal Administration of Analgesics**

The potential usefulness of spinal analgesics, including epidural and subarachnoid (intrathecal) administration, has greatly expanded in recent years. Spinal analgesic therapies for cancer pain are not limited to opioid alone but often involve custom compounded solutions, which may include opioid, local anesthetic, clonidine, or ziconotide.\textsuperscript{23} Simple, percutaneous epidural, or subarachnoid (intrathecal) catheters are still used to provide pain relief to patients with advanced disease and very short life expectancy (days to weeks), but for long-term use (several weeks to years), subarachnoid catheters with implanted infusion pumps are used most often. Examples of settings in which patients may benefit from spinal analgesics include brachial plexopathy from axillary recurrence of breast cancer or Pancoast tumor, lumbar or sacral metastases with radicular pain, or intractable pain from intra-abdominal malignancies.\textsuperscript{23}

The improved analgesic efficacy of spinal opioid administration compared with systemic administration is caused by regional delivery of opioid close to spinal sites of action, with reduction in adverse effects (especially sedation) through reduced delivery of opioid to the brain. Sedation and other opioid-related adverse effects may be further reduced with spinal administration of nonopioid analgesics. If the catheter tip is close to the spinal dermatomal level of pain, moderate doses of spinal local anesthetic may produce marked analgesia without significant muscle weakness. Clonidine has significant analgesic effect when administered spinally, especially when used for neuropathic pain. Ziconotide, a synthetic analogue of a peptide toxin found in venomous marine cone snails, is a potent spinal analgesic but clinical use has been limited by significant adverse effects. With the availability of revised dosing guidelines shown to minimize adverse effects,\textsuperscript{25} ziconotide will likely be used increasingly for resistant cancer pain. Although a potent tool for pain control, combinations of spinal analgesics must be used cautiously. It is well recognized that the efficacy of spinal opioid may be limited by sedation, but nonopioid spinal analgesics also have dose-limiting adverse effects: local anesthetic may cause numbness, weakness, and hypotension, and clonidine may cause sedation, hypotension, and bradycardia.
With careful selection and dose titration, combinations of spinal analgesics may be used effectively, and often with tolerable adverse effects, for palliation of otherwise intractable cancer pain.

Percutaneous epidural catheters are commonly used for epidural analgesia for acute pain (postoperative, traumatic, obstetrical) but also can be used in cancer pain management when pain relief is needed for short periods (e.g., pathologic fracture pending surgical fixation, severe pain limiting positioning for diagnostic imaging or radiation therapy, severe pain at the very end of life). Percutaneous subarachnoid catheters have been used in cancer pain management, but special attention to sterile technique is needed to minimize the incidence of bacterial meningitis. Simple percutaneous spinal catheters are inexpensive and require little or no specialized equipment for placement in most patients, allowing their use even in terminal cancer patients who may be unable to be transferred to a hospital or procedure center for more invasive therapies. Over several weeks to months, risks for infection or catheter displacement increase significantly with percutaneous spinal catheters. For longer-term use, subarachnoid catheters are tunneled to implanted infusion pumps. Implanted pumps are refilled every 1 to 2 months using a needle placed percutaneously through an injection port into the pump reservoir. If the efficacy of spinal analgesia is uncertain in a specific clinical setting, a temporary trial of spinal analgesics (through a percutaneous catheter) is typically undertaken before proceeding with spinal pump implantation. Guidelines directing the use of spinal analgesics and techniques are available, but the clinical use of spinal analgesics therapies remains largely empiric. Prospective clinical trials are needed to further clarify the role of spinal analgesic therapies in managing various cancer pain syndromes.

**Percutaneous Vertebroplasty and Kyphoplasty for Painful Compression Fractures**

Percutaneous vertebroplasty (PV) and kyphoplasty (PK) are related procedures for managing painful vertebral compression fractures caused by osteoporosis, primary neoplasm (e.g., multiple myeloma), or metastatic tumor. These image-guided minimally invasive procedures stabilize a compressed vertebra by introducing polymethylmethacrylate bone cement into the compressed vertebral body through large-bore needles. PV and PK provide good to excellent pain relief in 80% to 90% of persons with painful compression fractures caused by osteoporosis and 50% to 85% of those with painful compression fractures of neoplastic origin. Neither PV nor PK need delay treatment of spinal metastases with radiation therapy, but instead may provide rapid onset of pain relief, which may facilitate the use of appropriate antitumor therapies.

In PV, the bone cement is injected through the needles into the interstices of the vertebral body marrow space. PK is similar to PV, with the addition of steps to include temporary placement of a high-pressure balloon into the vertebral body. Inflating the PK balloon develops a cavity within the vertebral body that is subsequently filled with bone cement. PK balloon expansion may partially restore vertebral height, but lack of consensus exists regarding the selection of PV versus PK for managing painful vertebral compression fractures. Comparative studies between PV and PK are currently unavailable. Serious complications related to PV or PK are rare but can be devastating. The bone cement can extrude outside the vertebral body into the spinal canal, causing neural compromise. Furthermore, venous embolism of cement may occur, producing symptomatic pulmonary embolism or even cardiovascular collapse. Because the risk for serious adverse effects is low and the likelihood of providing good to excellent pain relief is reasonably high, PV and PK are good options for managing pain caused by vertebral compression fractures.

When considering PV or PK, radiologic examination of the spine is necessary to evaluate the location and number of involved vertebrae. Neuraxial imaging (magnetic resonance imaging [MRI] or CT scan) is used to evaluate possible extension of bone fragments or tumor into the spinal canal. PV and PK are most likely to result in pain improvement when used to treat recent compression fractures, although pain relief can be obtained from fractures older than 1 year. MRI is the most useful imaging modality for detecting acute vertebral fractures, because vertebral marrow edema (indicative of an acute compression fracture) is readily identified. Bone scan is less useful because it will identify increased activity in compressed vertebrae for up to 2 years after onset of the fracture, long after the fracture may have spontaneously stabilized. PV of PK can be performed at more then one vertebral level if multiple compression fractures are...
Interventional Therapies for Cancer Pain Management

Emerging Areas of Research

Pulsed radiofrequency (PRF) is an emerging intervention that uses brief bursts of radiofrequency energy to nondestructively alter central and peripheral components of the nociceptive pathways. PRF is a potential substitute for neurodestructive techniques such as chemical neurolysis or radiofrequency thermal ablation. PRF is appealing because it does not produce deafferentation pain or neuritis. PRF is performed by percutaneously inserting electrodes in proximity to target neural structures, including dorsal root ganglion or peripheral nerves. The electrical field produced by PRF has been shown in vitro to alter synaptic transmission and produce neurobiologic effects. The clinical literature supporting the efficacy of PRF is growing, and recently a randomized double-blind trial supported the efficacy of PRF for palliation of chronic pain. In the future, PRF could have significant usefulness in treating cancer pain. Much attention has been focused recently on pharmacogenetics: the genetic-mediated, interindividual differences in drug response. This individual variability may also extend to interventional therapies. Perhaps in the future experts will consider genetic profiling to guide interventional pain treatment planning.

Conclusions

Although most cancer pain is controlled with oral analgesic therapy, interventional pain therapies play a valuable role in the multimodal management of cancer pain. Oncologists and palliative care specialists must understand the precise indications and appropriate timing of pain procedures so that the interventions can be successfully implemented. As further advances are made in interventional therapies, their effectiveness will likely improve and their indications may expand. Because clinical use of interventional pain therapies is currently largely empiric, an important goal is to improve the quality and volume of clinical research to formulate evidence-based practice paradigms for interventional pain therapies. Fortunately for persons with inadequately controlled cancer pain, interventional therapies are available that may significantly enhance pain relief.

References