Review

Recent Trends in Cancer Pain Management

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The number of cancer patients in the world is increasing. According to WHO estimates, globally 10 million new cancer cases are diagnosed each year. It is estimated that by the year 2020, there will be 20 million new cancer cases. Even though high incidence of cancer is reported from developed countries, developing countries bear half of the global cancer burden. The majority of the world's cancer patients present with advanced disease and for such patients the only realistic treatment option is pain management and palliative care. Some cancer patients need pain relief at all stages of their disease; pain occurs in one third of patients receiving anticancer treatment. For these, pain relief and anticancer treatment should go hand in hand. Thirty three percent of patients receiving active treatment for metastatic disease have significant cancer related pain, and these percentage increase to 60-90% in those with advanced disease. Unfortunately, 25% of cancer patients die without adequate pain relief in spite of appropriate tools for adequate pain control being available.[1]

The prospect of suffering from unrelieved pain is one of the most feared aspects of a cancer diagnosis for most patients and their families.[2] Optimal management parallels that of cancer treatment and involves careful assessment, individualization of therapy, close follow-ups, and a proactive approach. Adequate control of pain can be achieved in the vast majority of patients with the rigorous and aggressive application of measures that are ultimately quite straightforward.

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CAUSES OF CANCER PAIN:

Pain associated with cancer may be a result of tumour pressure in 75-80% of patients or anticancer treatment in 15-19% patients or it may be unrelated to cancer and treatment (3-5%).[3]

Pain in cancer can be grouped into four causal categories:

- Cancer itself, e.g. soft tissue, visceral, bone, neuropathic, metastatic
- Treatment related, e.g. chemotherapy – related mucositis, postoperative syndromes, radiation induced
- Debility, e.g. constipation, muscle spasm / tension
- Concurrent disorder, e.g.spondylosis, osteo-arthritis.

Pain management: Several practice guidelines exist for the treatment of cancer pain.[4, 5] All cancer pain guidelines acknowledge that analgesic therapy is the cornerstone of pain management. The goal of such therapy is to achieve optimal pain relief with minimum or tolerable side effects within an acceptable time frame.

Despite published guidelines for pain management[6], many cancer patients experience

considerable pain and approximately half of them receive inadequate analgesia.[7] In the Eastern Co-operative Oncology Group (ECOG) study close to two-thirds of the physicians reported their own reluctance to prescribe opioids and 30% of the physicians said that they would wait until the patient has 6 months or less to live before they would start maximal analgesia.[8]

Most frequent causes of under treatment of cancer related pain are 1) discrepancy between patient and physician in judging the severity of the patient's pain 2) reluctance to prescribe opioid analgesics for fear of developing addiction, tolerance and side-effects 3) the fact that pain management is not a primary concern in health care system 4) high cost of analgesic medication which are nonrefundable and not easily available 5) analgesic treatment often considered only for advanced or terminal cancer patients.

PHARMACOLOGICAL MANAGEMENT:

The World Health Organization (WHO) has described a 3-step analgesic ladder as a framework for pain management.[4] This ladder has been shown to provide adequate analgesia to 90% of cancer patients and more than 75% of the terminally ill cancer patients.[9] It involves a step approach based on the severity of pain. If the pain is mild (pain score 1-4), one may begin with prescribing step 1 analgesics, such as NSAIDs (nonsteroidal antiinflammatory drugs). If pain persists or worsens (mild to moderate pain, pain score 5-6), step 2 analgesics such as weak opioids are indicated. If still pain is uncontrolled (moderate to severe pain, pain score 7-10), strong opioids such as morphine, hydromorphone, fentanyl should be started. At each step, an adjuvant drug or modality such as radiation therapy, chemotherapy or some surgical intervention may be considered in some selected patients.

It has been suggested that a fourth "interventional" step be added to 3 step analgesic ladder because although most cancer pain can be effectively treated with opioids alone or in combination with nonopioids and adjuvant drugs, not all pain is alleviated by this approach.[9] This fourth step includes use of nerve blocks, spinal (epidural and subarachnoid) administration of local anaesthetics, opioids, α 2 agonists, spinal cord stimulation, and surgical interventions, vertebroplasty, radiofrequency ablation as dictated by patient condition.

OPIOIDS

Opioids, the major class of analgesic used in management of moderate to severe pain, are effective, easily titrated and have a favourable benefit to risk ratio. Most patients with cancer pain require fixed dosing to manage the constant pain and prevent the pain from worsening if needed rescue dose should be combined with regular fixed –schedule opioid to control the episodic exacerbation of pain, often referred to as 'break through' pain.

A series of case report have demonstrated the clinical problems of inadequate pain control with escalating opioids doses in the presence of dose limiting toxic effects including hallucination, confusion, hyperalgesia, myoclonus, sedation and nausea.[10] These problems can be managed by switching to an alternative opioid with result being improved pain management and decreased toxic effects.[11] Switching from one opioid to another requires familiarity with a wide range of opioids and the use of opioids dose conversion tables. When using these ratios it must be understood that guidelines should be reviewed and patient should be monitored more closely during the switching phase.

Transdermal fentanyl patches currently available are formulated to provide analgesia lasting upto 72 hours. This preparation is not suitable for rapid dose titration and should be used for relatively stable analgesic requirements when rapid increase or decreases

in dosages are not likely to needed. Oral transmucosal fentanyl is used for the relief of breakthrough pain. In a large open label multicenter study, 92% of patients received relief from breakthrough pain. Side effects were consistent with other opioid therapies, including sedation, constipation and nausea.[12]

OPIOIDS ADDICTION

The treatment of cancer pain leads to addiction in less than 1% of patients who have no history of drug addiction.[13] Addiction is a psychological and behavioral syndrome characterized by loss of control over drug use and compulsive, continuous use despite harmful side effects. Persons addicted to opioids crave the psychic effects of these drugs. In a large prospective study, only 4 cases of iatrogenic addiction could be identified among 11882 patients with no history of addiction who had received opioids in the hospital setting.[14] Physical dependence is not the same as psychological addiction. Physical dependence refers to pharmacological property of opioids that causes withdrawl syndromes to occur when the drugs are abruptly discontinued. This syndrome can be avoided by a tapering schedule.

ADJUVANT DRUGS

Adjuvant drugs are valuable during all phases of pain management to enhance analgesic efficacy, treat concurrent symptoms and provide independent analgesia for specific types of pain. Commonly used adjuvant drugs are antidepressant, corticosteroid, and local anaesthetic. Other agents used for specific conditions e.g. bisphosphonates for bone metastasis, baclofen for spastic pain, clonidine, gabapentine, ketamine for neuropathic pain. Gabapentine is increasingly reported as useful for the management of neuropathic cancer pain.[15] Bisphosphonates most frequently used are clodronate, palmidronate and zoledronic acid. These are recommended for bone pain and for prevention of skeletal complication in patients with metastatic bone pain. Palmidronate has been recommended in the dose range of 60-90 mg intravenously over 2 hrs every 3-4 weeks. However, pooled results from 2 multicenters double –blind, randomized, placebo –controlled trials using palmidronate 90 mg every 3 weeks failed to demonstrate a benefit for bone pain.[16] Zoledronic acid is a potent bisphosphonate that can be given in the dose of 4-8 mg every 3-4 weeks.[17, 18]

Corticosteroids can be helpful in patients with pain due to acute nerve compression, visceral distension, increased intracranial pressure and soft tissue infiltration. Dosage recommendations vary from a trial of low –dose therapy, such as dexamethasone 1-2 mg or prednisone 5-10mg twice daily with subsequent tapering to the minimal effective dose.

NEUROLYTIC NEURAL BLOCKADE:

Neurolytic blocks are used to interrupt the pain pathways. These are useful in the control of intractable visceral cancer pain. Neurolysis is typically achieved chemically using injection of alcohol (50-100%) or phenol (7-12%). Two neurolytic blocks commonly used to provide analgesia and add in pain management are the coeliac plexus block and superior hypogastric plexus block. Although these interventions may provide complete analgesia in some cases, they are typically used as adjuncts to opioid therapy to optimize treatment of cancer pain. When used with opioids, neurolytic blocks allow opioid doses to be reduced, resulting in fewer side effects associated with opioids.

INTRASPINAL ANALGESICS:

Although a relatively recent development, spinal opioid administration has an established role in management of severe cancer pain. In 1979 for the first time spinal opioids were used[7], since then spinal route for opioids administration has been used to achieve effective reversible spinal analgesia with increasing popularity. Opioids and other analgesic agents can be introduced directly into the central nervous system by infusion into

either the subarachnoid or epidural space. It produces effective analgesia with doses lower than dose used in oral or parenteral administration. As is the case with oral dosing of opioids, intraspinal dosing is individualized. The appropriate dose is based on patient's age and pain syndrome, as well as the systemic doses of the opioid that produces analgesia. In general, the dose of morphine used for epidural or intrathecal administration is one tenth and one hundredth, respectively, that of an intravenous dose.

Morphine is the only opioid approved by US Food and Drug Administration (FDA) for the treatment of cancer pain via intraspinal administration; however, other opioids are commonly used including hydromorphone, fentanyl, and sufentanil. Currently, the nonopioid agents that are most commonly used in the management of cancer pain are clonidine and bupivacaine. Clinical experience has shown that with careful patient selection and dose adjustment, adverse effects from spinal opioids generally can be anticipated and managed. Ziconotide, a calcium channel blocker, is currently being evaluated in clinical trials for the treatment of severe chronic pain in patients who either cannot achieve adequately controlled pain with systemic opioids or who are intolerant to systemic opioids.[19] In the future spinal opioids and novel nonopioid drugs will likely play an important role in pain management as a mainstay of diverse analgesic therapies; combination spinal analgesia is the subject of a current systematic review.[4]

Various technical considerations are important to the successful application of long-term spinal analgesic therapy. Long-term spinal analgesia requires catheter access to the subarachnoid or epidural space; the catheter may be simple, percutaneous catheter for intermittent injection or part of a totally implanted computer controlled infusion pump system.[7] No single system is appropriate for all clinical settings, any spinal system may be associated with complications such as infection, catheter dislodgement or other technical failure, which must be properly assessed and managed. A percutaneous epidural catheter is widely available, inexpensive and may be used for days to weeks, however even with careful technique; there is a risk for epidural infection and abscess. The routine use of bacterial filters (0.2 micron) may help decrease the risk of infection but epidural abscess remains a concern. The long-term efficacy of epidural analgesia may be limited by epidural fibrosis.

Percutaneous subarachnoid catheters have been used in palliative care of terminally ill persons with increasing frequency in recent use. The concern of infection and meningitis appears to be reasonably managed by use of bacterial filters and a sterile technique that strictly minimizes the changing of external infusion pump reservoirs and tubings. For long-term use, implanted infusion pumps for subarachnoid administration of analgesics have the lowest risk of infection and a low rate of technical complications. Implanted pumps have the highest initial cost among all spinal administration systems, but appear to be cost effective in the long run (several months to years) due to low drug and maintenance cost.[20,21]

SPINAL CORD STIMULATION:

Spinal Cord Stimulation is a means where by the pain is blocked from effectively reaching the brain by interference with the spinal transmission of certain pain signals. Spinal Cord Stimulation (SCS) does not block all signals, and thus, leave the ability to feel certain pain signals that are protective. The mechanism of analgesia produced by SCS is still unclear. Some hypothesis involve antidromic activation of central inhibitory mechanisms, increase in substance –P release, and actual block of transmission of electrochemical information anywhere in the dorsal spinothalamic tract.

The use of electro stimulation in patients with cancer pain is limited, but neuropathic states are amenable to therapy, and a reduction of supplemental opioids is commonly seen depending on the amount of neuropathic contribution to overall pain. Postthoracotomy pain and radicular lower extremity pain after radical pelvic tumor resection are possible candidates for SCS therapy.

The main drawbacks to SCS include high cost and difficulty in predicting which patients will gain lasting benefits. Implantation of permanent SCS is preceded by a temporary trial of SCS, which adds to the cost, but helps to determine its potential benefit. Even after a successful trial, only 20-80% of patients experience long term analgesia from SCS.[4] Analgesic failure may be due to technical difficulties, placebo response during initial trial, and development of tolerance to SCS or progression of underlying pathology

The controversies and uncertainties of its use not withstanding, SCS is an analgesic therapy that is successfully utilized in a number of settings, generally after inadequate response to systemic analgesics. SCS is minimally invasive but expensive anaesthetic technique worthy of consideration when the palliation of appropriate symptoms has been resistant to other measure.

RADIOFREQUENCY ABLATION

Radiofrequency ablation (RFA) is the destruction of neural tissue with heat generated within tissues by a high –frequency electrical current. As RFA is more predictable than chemical lesions, RFA is now used for a variety of pain conditions e.g. painful bony metastasis, dorsal root ganglion ablation, cervical thoracic and lumbar facet enervation and lesioning of the sympathetic chain at different levels. There are few prospective studies on the use of RFA for back pain with encouraging results.[22] However, as with other neuroablative techniques, pain relief is often accompanied by numbness, and there is a risk of dysaesthesia and motor weakness.

VERTEBROPLASTY

Vertebroplasty is relatively new minimally invasive techniques used to treat painful vertebral compression fractures, in which an acrylic polymer cement (methylmethacrylate) is injected into a collapsed vertebral body under guidance of fluoroscopy and / or computed tomography. A French group first reported percutaneous vertebroplasty in 1987 for the treatment of painful hemangiomas.[23] Afterwards it has been advocated in variety of lesions eg. Painful vertebral metastasis, osteoporotic compression fractures and traumatic compression fractures.[24]

SURGICAL ANALGESIC TECHNIQUES

Neurosurgical techniques for the pain management of cancer pain can be resective, reconstructive or ablative. Improvements in pharmacotherapy, including the availability of intraspinal delivery of opioids, have reduced the use of ablative neurosurgical techniques, such as cordotomy, rhizotomy and thalamotomy. Nevertheless there still remains role for these procedures in the management of cancer pain.

NEUROSTIMULATORY PROCEDURES

Transcutaneous nerve stimulation and acupuncture are neurostimulatory procedures. These are acted as a powerful catalyst in the study of the neurophysiology and neuro-pharmacology of pain. Exact mechanism is unclear, the success in using a non drug treatment with minimal side effects is surely appealing for symptom management in palliative care.

ANTINEOPLASTIC INTERVENTIONS

Radiotherapy, surgical procedures and chemotherapy may also play in management of cancer associated pain for some malignancies.

RADIOTHERAPY:

Approximately 40% of patients referred for radiation treatment have advanced cancer that doesn't response to curative treatment and is accompanied by pain.

Radiotherapy is effective for many symptoms where their basis is local tumour interference with normal tissue structures through pressure or infiltration e.g. metastatic bone pain, spinal cord and cauda equina compression, brain metastasis, mediastinal compression and superior vena cava obstruction.

Local, half body or whole body radiation enhances the effectiveness of analgesic drug and other noninvasive therapy by affecting the cause of pain. Single or multifraction regimens of external beam radiation therapy are equally effective when radiation is administered for pain relief. A single intravenous injection of beta particle –emitting agents as iodine^{131} phosphorus^{32} and strontium as well as investigational new drugs rhenium^{186} and samarium^{153} can relieve pain of wide spread bony metastasis.

SURGERY:

Curative excision or palliative debulking of a tumour has potential to reduce pain directly, relieve symptoms of obstruction or compression and improve prognosis, even increasing long term survival.

CHEMOTHERAPY AND BIOTHERAPY:

Pain relief often occurs after chemotherapy for responsive tumours such as lymphoma, small cell lung cancer, germ cell tumours and possibly breast cancer. Biological response modifiers now play an established role in the treatment of certain cancer e.g. interleukin -2 in renal carcinoma, interferon as adjunctive therapy in melanoma. Other modifiers include granulocyte –macrophage stimulating factor

COGNITIVE –BEHAVIORAL INTERVENTIONS

These interventions give the patient a sense of control and to develop coping skills to deal with disease and its symptoms. Interventions introduced early in the course of illness are more likely to succeed because they can be practiced by patients while they have sufficient strength and energy.

CONCLUSION:

Most patients with cancer pain can achieve adequate analgesia with conventional oral pharmacological therapy, and opioid and nonopioid analgesic therapy remains the cornerstone of cancer pain management. Nevertheless, chronic cancer pain can be psychologically devastating because it is a constant reminder of the incurable and progressive nature of the disease; therefore, all available measures appropriate to the patient should be explored.

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