Review Article

Cancer pain management-current status

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Abstract

Cancer pain is still one of the most feared entities in cancer and about 75% of these patients require treatment with opioids for severe pain. The cancer pain relief is difficult to manage in patients with episodic or incidental pain, neuropathic pain, substance abuse and with impaired cognitive or communication skills. This non-systematic review article aims to discuss reasons for under treatment, tools of pain assessment, cancer pain and anxiety and possibly carve new approaches for cancer pain management in future. The current status of World Health Organization analgesic ladder has also been reviewed. A thorough literature search was carried out from 1998 to 2010 for current status in cancer pain management in MEDLINE, WHO guidelines and published literature and relevant articles have been included.

Key words: Cancer pain, neuro-ablative procedures, opioids

Introduction

Pain management in cancer patients is a challenging and continuous task. Proper use of therapeutic approaches should result in excellent pain control in nearly 95% of patients with cancer pain but unfortunately, cancer pain, still remains grossly undertreated throughout the world. In this review we aim to discuss some recent and relevant issues in this area and any significant research in pain management that could be accommodated in future for cancer pain management. A thorough literature search was carried out from 1998 to 2010 for current status in cancer pain management in MEDLINE, World Health Organization (WHO) guidelines and published literature and relevant articles have been included.

Epidemiological Analysis

Cancer pain is still one of the most feared entities in cancer and about 75% of cancer patients with pain require treatment with opioids for severe pain.[1] Current data from WHO and hospice care centers suggests that oral morphine alone can take care of 85% of patients with cancer pain while others suggest that cancer pain management may require alteration in the route of opioid administration, addition of co-analgesics, anti-neoplastic therapies and neurosurgical modalities. Proper use of these therapeutic approaches should result in excellent pain control in nearly 95% of patients with cancer pain but unfortunately, cancer pain, still remains grossly undertreated throughout the world.[2]

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Reasons for Under Treatment

Poor resources in developing countries

Eighty five percent of world population live in developing countries and account for 20% of global gross national product. Out of nine million case of new cancer patient in the world, 50% are in developing countries. The income is low in developing countries and the cancer load high and thus the resources for cancer pain alleviation are grossly inadequate.[3]

Unavailability of morphine

WHO reports that 80% of cancer patients have no access to opiates. It is an ironical that while we have access to the moon, cancer patients do not have access to morphine. WHO has come forward and interacted with governments to balance controlled drugs policies and update existing cancer pain treatment guidelines. Most cancer patients need palliative care and pain control. WHO strongly advocates pain relief for moderate and severe cancer pain. In low socioeconomic countries, capabilities of the system, to provide such care are

either absent or too restrictive. WHO is a developing and promoting palliative care and pain relief protocol for national health systems and strongly advocates morphine use with palliative care settings.[4]

Unconquered barriers

The barriers for cancer pain relief as described in a review in 1999[5] still exist today. These barriers are misconception about cancer pain drugs e.g. addiction, lack of communication amongst healthcare providers and patients, acceptance of inevitability of chronic pain, poor or absent assessment procedures, lack of formal training in pain management and regulatory. The situation in developed nations is no better. A recent study in Australian caregivers highlighted barriers to pain management as addiction, fear of disease progression, side effects and tolerance in decreasing order of concern.[6]

Physicians opiophobia

Despite significant advances in pain management a significant number of physicians still have opiophobia and a lack of knowledge about chronic pain. Thus, educational strategies to overcome these barriers assume importance.[7]

Problems with communication

The problems with communication occur in patients who fail to get pain relief with usual medications and their daily activities get affected. They seek alternative therapies for pain control but hesitate to discuss their pain and are highly concerned about analgesic drug side effects. Those seeking alternative therapies suffer the risk of poorly controlled pain. Screening of patients for pain is therefore vital if new developments in cancer pain management are to be utilized effectively.[8]

Taming the unruly: A multifaceted dynamic target

The character of cancer pain is not fixed, it is recurring and often with complex multiple etiologies. The tumor or its evaluation contributes for up to 90% of pain while rest is attributed to other non related pain generators. Out of this 90%, 70% is due to tumor invasion or compressing soft tissue, bone, or neural structures while 20% of pain is due to procedures related to evaluation or therapeutics.[9]

Surgery is a frequent cause of pain in patients with cancer and can consist of biopsy, removal, or debulking of a tumor or management of a complication of the tumor. These procedures are often associated with injury to local nerves and postoperative pain, which can later lead to neuromas and chronic pain syndromes. Surgically induced nerve injuries are most commonly seen after breast cancer surgery, thoracotomy, radical neck dissection, and limb amputation.[10] These neuromas and chronic pain syndromes are severe and difficult to manage.

Pain Assessment

Intensity of pain can be assessed by self-reporting by the patient but could be better assessed with visual analogue scales (VAS), numerical rated scales (NRS) and verbal rated scales (VRS).[11] A good assessment of cancer pain is required for better results of treatment. *Initial Screening* - if pain is present, it should be quantified and characterized. Emergent pain situations should be identified. *Comprehensive assessment* - should be used for identifying etiology, patho-physiology and specific pain syndromes.

Ongoing comprehensive assessment — should identify pain related to oncologic emergencies, bone fracture, epidural metastasis and pain not related to oncologic emergencies.[12] The situation is grim in developing countries, as patients report very late in advanced stage of cancer, with severe pain which at times is the presenting symptom. Even those reporting earlier may not be diagnosed early or may not be able to afford therapy.[3]

Non communicating patient

Patients with cognitive disorders, unconsciousness or with intubation may not be able to self report their pain. Unable to express or articulate, their pain related behavior can be observed and assessed. The American Society for Pain Management Nursing has come forward for helping such patients by developing some pain assessment tools which can be valuable for both the clinician and the cancer pain patient.[12] The following tools are in the developmental stage:

- The Assessment of Discomfort in Dementia Protocol (ADD)
- Checklist of Nonverbal Pain Indicators (CNPI)
- The Pain Assessment in Advanced Dementia Scale (PAINAD)
- Behavioral Pain Scale (BPS) tested in adults and intensive care
- Critical-Care Pain Observation Tool (CPOT) tested in adults and intensive care

Cancer pain and anxiety

Anxiety and pain can be understood with a multidimensional framework that accounts for somatic, emotional, cognitive, and behavioral aspects of these conditions. Patients who have cancer or treatment-related pain are more likely to be anxious than cancer patients without pain. Patients with cancer pain and anxiety may cause difficult diagnostic dilemmas because some degree of anxiety is a normal response to having a severe medical illness. Furthermore, the somatic symptoms of anxiety often overlap with symptoms related to underlying disease processes or treatment effects. The degree of disruption in

a patient's life often is the critical factor in distinguishing normal from maladaptive anxiety. Making an accurate diagnosis will help guide anxiety treatment and screening instruments can facilitate the recognition of those patients in need of further assessment. The relationship between pain and anxiety is complex and bidirectional, with interactions occurring on physiologic and psychological levels. There are a variety of psychopharmacologic, psychotherapeutic, and complementary/alternative treatments available. A comprehensive approach to care includes these approaches in an individualized way. Terminal sedation is examined as a compassionate option for relieving intractable distress at the end of life.[13]

Hair analysis for compliance assessment

An objective measure of patient compliance to opioids in cancer pain management has been described by measuring opioid concentration pattern in patient's hair since self reporting of pain is largely under reported. Its main attraction is its non invasiveness without giving pain to patient and the stability of the drugs in hair matrix.[14] Further research is necessary as there are limitations like individual hair growth difference and less clear dose-concentration relationship. At present it could be valuable for measuring patient's compliance of all or none type.

Management of Cancer Pain

The advancement in cancer pain management has been attributed to:

i. Better understanding of etio-pathogenesis of cancer pain and various pain syndromes
ii. Use of newer diagnostic modalities Computed Tomography (CT), Magnetic Resonance Imaging (MRI), Isotope Bone Scanning.
iii. Use of newer drugs (Hydromorphone, Oxycodone, Methadone) and newer routes of administration e.g. nebulized or inhaled Fentanyl
iv. Improvement in adjuncts to neuro-ablative techniques (Image Intensifier, CT, MRI, Ultrasound Guided endoscopic procedures) and vertebroplasty.

Current Status of WHO Three Step Analgesic Ladder

Introduced in 1986, the WHO three step analgesic ladder for cancer pain control has been praised for its simplicity and clarity but also been criticized for its efficacy, omissions and for issues like inclusion of weak opioids and intervention therapies in step 2 and 4 respectively.[15] The lack of superiority of weaker opioids over the full doses of non-steroidal anti-inflammatory drugs (NSAIDS) in step 2 had been highlighted by Francis *et al.* in a systemic review in 2007[16] and has questioned the justification for a need of overstaying in step-2 for a patient with severe pain and feared inadequate pain relief. Such patients may directly require step 3 management thus bypassing step 2. Fear amongst caregivers to prescribe morphine is another reason for overstaying of patients in Step 2.

Step up, step down

This version of the analgesic ladder can be used in a bidirectional fashion: The slower upward pathway for chronic pain and cancer pain, and the faster downward direction for intense acute pain, uncontrolled chronic pain, and breakthrough pain.[17] The advantage of this proposal is that one can ascend slowly one step at a time in the case of chronic pain and, if necessary, increase the rate of climb according to the intensity of the pain. However, one can start directly at the fourth step, in extreme cases, to control pain of high intensity, using patient-controlled analgesia pumps for continuous intravenous, epidural, or subdural administration. When the pain is controlled, one can "step down" to medications from step 3.[17] Though morphine is still considered the gold standard in step 3, oxycodone, hydromorphone, fentanyl and methadone have become the drugs of choice in some countries.

Scheduling and titration

As soon as the pain is assessed minimum opioid dose that provides effective pain relief with minimum side effects is titrated. The breakthrough pain dose is also decided, which is approximately ten percent of the total daily dose. Requirement of more than four breakthrough doses per day necessitates the introduction of slow release formulation.[11]

The analgesic ladder requires use of right drug in right doses, at right intervals, by the mouth, by the clock, by the ladder, and for the individual. Though a dose range of five to 1000 mg morphine could be used (due to its lack of ceiling effect) doses higher than 200 mg should prompt physicians to reconsider the diagnosis in favor of a neuropathic or morphine resistant pain and should invite alternative supportive measures like neuro-ablation and opioid rotation for better pain control and lesser toxicity. The use of adjuvant like anti-emetics, anti-diarrheal, anti-depressants, anti-psychotics, anticonvulsants, corticosteroids, psycho-stimulants are available in each step. Since this 3 step ladder arrangement provides pain relief to 77-100 percent of patients, the need for inclusion of interventional modalities as a fourth step in the ladder could not generate clear consensus.

Carving Newer Approaches

Mechanistic based approach

Apart from the traditional WHO ladder, new ways have been suggested like a 'mechanistic based approach' with a patho-physiological foundation for cancer pain management. Scientifically this assumes logic since the patient gets treated specifically only for the component of pain that is involved e.g., visceral, somatic, neuropathic etc. Visceral pain results from stretching, compression, infiltration of viscera and is quite common in cancer patients. Somatic pain results from bony metastasis or surgery and is aching and more localized. Neuropathic pain is due to infiltration or compression by tumor and is burning or electric shock like in character. Each component is required to be assessed separately and managed.[18] Good history, physical examination and special tests are required to arrive at specific component of pain involvement. The management of pain thus is better, quicker and with lesser side effects.

Opioid rotation

Patients who do not respond to a particular opioid may respond to another opioid as there are variants of mu opiate receptors and patients vary greatly in their response to different opioids. This sequential opioid trial is called opioid rotation which aims to find out the best opioid with least side effects. Studies in this area revealed 15 splice variants of morphine opiate receptor-1(MOR-1) in mice which defer in response to morphine, fentanyl, methadone and morphine-6-glucuronide. Humans have 11 of such variants.[19]

Topical opioids

The evidential presence of peripheral opioid receptors conceptualized the scientific foundation for topical application of opioids in some oral ulcerative cancer and non cancer pain. A systemic review on use of topical opioids was inconclusive due to heterogeneity of available data regarding its efficacy, onset and duration of analgesia.[20]

Gene therapy in cancer pain

Efforts are on rise for inclusion of genetically engineered viruses, expressing specific neurotrophins, responsible for controlling neuropathic pain in rat models. Similarly, genes, encoding endogenous opioids can be transferred to dorsal root ganglion (DRG) after inoculation in the related dermatome thus ensuring continuous release of inhibitory neurotransmitters. Proenkephalin coded genetically modified herpes simplex viruses have been used in rodent models for metastatic bone cancer pain, inflammatory and neuropathic pain. For cancer pain, vector mediated enkephalin expression is shown to be additive to morphine.[21]

TENS therapy for bony metastasis

A recent Cochrane review of transcutaneous electrical nerve stimulation (TENS) therapy in cancer pain could not find sufficient evidence to justify the role of this modality in cancer pain.[22]

Antidepressants

The use of antidepressants in cancer pain is on rise. They are particularly indicated for managing anxiety and depression, hot flushes and neuropathic pain as adjuvant in cancer pain. Cost, side effects, drug interactions are the limitations in their use and thus warrant the necessity of techniques to identify proper patient for antidepressants and to monitor toxicities.[23]

Radiotherapy

Pain due to local invasion or compression by tumor mass preferably require localized treatment like radiotherapy if possible. Local neural compression, radicular pain and cerebral metastasis are particularly suitable clinical situations for this mode of therapy.

Recent Arrivals

Drugs

The most recent arrivals in opioids with Food and Drug Administration (FDA) approval are extended release oxymorphone for acute and persistent pain and ultrafast acting fentanyl effervescent buccal tablets, for breakthrough pain.[17] Hydromorphone and oxycodone are similar in availability efficacy and tolerability. Both are available as normal release and modified release formulations. Oxycodone is an effective alternative to morphine with similar side effect profile and analgesic efficacy. Oxycodone is an opioid analgesic with high oral bioavailability in humans (60%) compared with morphine.[24] Oxycodone is increasingly used worldwide to treat acute and chronic pain. Oxycodone in higher doses for terminal cancer pain is efficiently safe without any relation to shorter survival times.[25]

Breakthrough pain

One of the newer additions in cancer pain management is the concept of breakthrough pain (BTP) which is a transient escalation of pain superadded to a controlled base line pain and occurs in 40-80% of cancer patients. It has a high intensity, starting spontaneously without patient's activity and rapidly reaches a crescendo. The duration of the pain is short and typically lasts for 30 to 45 minutes.[19] Its presence signifies severe pain, stress, functional inability and poor quality of life. Although BTP is recognized as an important and often problematic aspect of cancer pain, but has no pain assessment tool.[26] The preferred treatment for BTP would be rapidly acting pure strong mu agonist like fentanyl however, oral transmucosal fentanyl, intravenous morphine or

sub cutaneous morphine could be helpful in relieving BTP. Patient's age, gender and the pain duration have no association with BTP but are significantly associated with neoplasm, metastasis, non-opioid and adjuvant treatment, neuropathic and somatic pain.[20]

Recent developments in buccal transmucosal administration of lipophilic (e.g. fentanyl) or unionized drugs for direct absorption into systemic circulation have revealed that these drugs can have transcellular movement. Oral mucosa has large surface area with consistent blood supply and uniform temperature. This favors rapid absorption of lipophilic agents. Hydrophilic agents like morphine follow paracellular route to find their way to systemic circulation.[19]

Current Status of Neuro-Ablative Procedures

Use of neuroablative procedures in cancer pain relief had improve quality of life in patients when compared to oral analgesics.[27,28] These neuro-ablative procedures provide better pain relief when used in early stages of cancer. Neuro-ablation is the physical interruption of pain pathways either surgically, chemically or thermally. Neuromodulation is the dynamic and functional inhibition of pain pathways either by administration of opioids and other drugs intraspinally or intraventricularly or by stimulation.[29] The revolutionary success of neuroablative procedures in controlling cancer pain has largely been attributed to improvement in procedural techniques as well as simultaneous use of imaging techniques like fluoroscopy, CT, MRI or Ultrasound guided endoscopic procedures. Some of the commonly performed neuro-ablative procedures are:

Celiac plexus block

Neurolytic celiac plexus block (NCPB) is an established, well-developed and most widely applied pain block in optimizing palliative care for cancer of the upper abdominal viscera. With a half life exceeding four weeks, the block enables patients be weaned from opioids or at least allow dose reduction. Unfortunately the probability of freedom from pain diminishes with increased survival time. The selection of techniques should match the existing facility and the extent of malignancy as the analgesic results are independent of the technique chosen. A successful pain relief occurs in 85% and 73% of pancreatic and other abdominal malignancies respectively.[30] Block failure have been attributed to tumor invading beyond the territory of celiac plexus and its component nerves. Concomitant somatic characterization of pain (e.g. peritoneal involvement) requires other therapeutic measures. Commonly encountered adverse effects are transient local pain, diarrhea and hypotension while more serious neurological and non-neurological adverse effects are seen only in 1% of patients.[31] Although NCPB improve pain relief in patients with unresectable pancreatic cancer but has not shown to improve quality of life (QOL) and survival when compared to systemic analgesics.[32]

Endoscopic ultrasound guided celiac plexus neurolysis

The suboptimal pain relief with narcotics in pancreatic cancer pain management and serious consequences with NCPB has increased the use of endoscopic ultrasonography (EUS) guided celiac plexus neurolysis block. EUS guided direct celiac ganglion neurolysis provided pain relief in 94% patients with moderate to severe pain of unresectable pancreatic carcinoma.[33] Hence EUS aids have been suggested as part of a multidisciplinary pain management team.

Superior hypogastric plexus block

The effectiveness of superior hypogastric plexus neurolysis in relieving pain has been observed in 69% of the patients but additional neurolytic blocks, using higher volumes of the neurolytic agent may be needed in patients with extensive retroperitoneal disease, as this group gets moderate to poor pain relief with conventional dose.[19] This block provided both effective pain relief and a significant reduction in opioid usage up to 43% in 72% of the patients.[34]

A diagnostic block without using any neurolytic agent performed on a patient with chronic non malignant penile pain after transurethral resection had effective pain relief for more than six months.[35] The usefulness of this block in chronic benign pain conditions has not been adequately documented.

Ganglion impar block

Ganglion impar is a retroperitoneal solitary unpaired ganglion of two sympathetic chains in body join at sacro-coccygeal junction and is associated with visceral pain of perineal malignancies.[36] Patients complain of a vague and poorly localized pain leading to sensations of burning and urgency may be benefitting from this block but lacks sufficient data to ascertain its clinical usefulness.

Percutaneous vertebroplasty

Percutaneous vertebroplasty alleviates persistant crippling pain and prevents problems of reduced mobility particularly in older patients.[37] The procedure involves percutaneous injection of radiopaque polymethylmethacrylate (PMMA) cement with image guidance into a painful compressed vertebra to stabilize compression fractures of metastatic solid malignancy. This is an effective palliative procedure and can be combined with other treatment modalities like radiotherapy and chemotherapy. The procedure requires fluoroscopy or CT guidance in sedated patients lying prone or in the lateral decubitus position for injecting acrylic bone cement which

strengthens the vertebra and prevents further compression and hence stabilization. *Kyphoplasty* is a different version of vertebroplasty in which a balloon or "tamp" is inflated inside a collapsed vertebral body before PMMA injection. Creation of a space inside vertebra before cement injection minimizes extravasation and embolisation of the cement and helps in restoration of vertebral height and kyphotic defect correction but requires general anaesthesia.[38]

Pre-sacral neurolytic block for pain relief from pelvic cancer

This block is performed with a lateral CT guided approach for the treatment of unrelieved pelvic and perineal pain in advanced cancer.[39]

Percutaneous cordotomy

A recent review of terminally ill patients treated with percutaneous cervical cordotomy (PCC) has highlighted the procedure as being efficacious in 43 patients. This option thus is still open in those cancer pain patients where every modality has been tried.[40]

Legal Issues

The most important message that physicians must communicate to any person with chronic pain is that, currently, no medication exists that will take away more than 30% of the pain they experience. Chronic pain is a chronic disease and, like diabetes or hypertension, requires chronic concessions and lifestyle modifications.[41]

In conclusion, cancer pain is manageable yet poorly managed. Proper assessment, availability of oral morphine, co-analgesics and use of advanced technology are the main pillars of cancer pain management. Development of firm attitudes by physicians to confront and control cancer pain along with creation of awareness amongst caregivers and patients is required.

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