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Updates in Cancer Pain Management

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Abstract

***Background:** Pain is a common symptom in cancer patients and it is the most disturbing complications affecting the quality of life markedly. The incidence of pain depends on the type and stage of the cancer. There are many barriers that prevent treatment of cancer pain as fear of addiction, side effects and fear of distracting physicians from treating the cancer. The objective of this review is to illustrate different types, effects and various tools of the cancer pain control as well as a how to choose the ideal technique suitable for your pain.*

***Conclusion:** Cancer pain is multifactorial with complicated Pathophysiology, but early diagnosis, careful history and good assessment lead to ideal selection of treatment plane either medications or interventions according to WHO step ladder. interventional therapies for cancer pain include; cordotomy, myelotomy, sympathectomy, peripheral neurectomy, dorsal rhizotomy and ganglionectomy, dorsal root entry zone lesioning, and others. And, early interventional is favorable due to many reasons; avoiding central pain, general condition of patients is still good and cancer itself not metastatic everywhere.*

Keywords: Cancer pain- WHO step ladder- Postoperative pain- VAS scale- Opioids

Introduction

Many cancer patients suffer from intractable pain, with an increasing incidence as the disease progresses [1]. An elevated percentage of patients experience significant pain in the terminal stages, so pain is a common symptom in cancer patients and is the most disturbing complications. [2-4] Thus, quality of life is markedly affected causing:

Physical: Decreased functional capability, nausea, poor appetite, and poor sleep.

Psychological: Increased anxiety, fear, depression, difficulty in concentraton.

Social: Diminished social relationships, sexual function, and increased caregiver burden.

Spiritual: Increased suffering, altered meaning, and reevaluation of religious beliefs.

The incidence of pain in patients with cancer depends on the type and stage of the disease; [5]

- 30-45% of cancer patients have pain increases to75%by advancing cancer.
- 40-50% of patients describe pain as moderate to severe.
- 25-30% describe as very severe or excoriating.
- Pain is due to cancer itself in 70% of patients.
- Pain related to cancer treatmentis25%.
- The remainder 5% is unrelated to cancer.

Most Common Types of Cancer Pain: [6]

Bone Metastases

- Multiple, found in vertebrae; pelvis; proximal long bones and skull and described as dull and aching and exacerbated with movement.

Epidural Metastases and Spinal Cord Compression

- A new or worsened localized back pain with radicular pain if nerve roots are involved.

Blexopathies

- Cervical; brachial and lumbo-sacral plexuses are infilterated by tumour or damaged by radiation or surgery and pain described by both local and radiating components.

Peripheral Neuropathies

- Peripheral nerves can be damaged by: tumour-fibrosis- surgery- chemotherapy-viral infection and pain is described as dysethetic and burning in character.

Abdominal (Visceral) Pain

- Pain is constant or colicky, difficult for patient to localize, worse after eating, associated with nausea and referred widely to distant cutaneous sites.

Mucositis

- Mostly due to inflammation of epithelium and pain of GIT from mouth to anus, caused by chemotherapy and/or radiation and often intense and interferes with oral intake. [7]

Pathophysiology of Cancer Pain

Nociceptive Pain

Caused by stimulation of an intact; normally functioning nervous system.

Somatic

Affecting highly innervated superficial areas, with precise localization of pain as skin, muscles, tendons and bones.

Visceral

Diffusely innervated organs (liver, kidney, spleen,…) with poor localization of pain.

Neuropatheic Pain

The Pain is tingling, burning, electrical-like or shooting with area of sensory loss, may be intermittent or constant. It is a result of the tumor causing direct pressure on nerves or neural invasion by growth of the cancer; it also may be because of therapy. -Neuropathic pain may persist despite absence of persistent injury. [8.9]

Barriers that Prevent Ideal Treatment of Cancer Pain

Patient Related Barriers

Patients fear of psychological addiction or physical dependence, the incidence of addiction in cancer patients is less than 1%. Physical dependence refers to the pharmacologic property of opioid that causes withdrawal, or abstinence syndrome and occurs when the drugs are abruptly discontinued. This syndrome can be avoided by a tapering schedule slowly over a period of time. [10]

Concerns about adverse effects of medications, fear of distracting physicians from treating the cancer. [11]

Physician Related Barriers

The most significant barriers are poor education and assessment of pain treating doctors. Clearly, more education is needed to assist both patients and physicians in the management of cancer pain. [12]

The World Health Organization (WHO) has stated that "nothing would have a greater impact on improving cancer pain treatment than implementing existing knowledge". [13]

Assessments of Cancer Pain must Include

1- A detailed history, including an assessment of the pain Intensity, Character, Onset, Course, Duration, Location, Radiation, Timing, Associated symptoms, What makes pain better or worse, How does this pain affect your daily living (sleep, work activity, and mood), What does the pain mean to you and previous treatments. [14]

2- Physical examination and the neurological examination.

3- Psychosocial assessment emphasizes the effect of pain on patients and their families and friends.

4- Appropriate diagnostic and investigative workup to find out the cause of the pain as laboratory study, ultrasound, CT and MRI.

5- Different Pain measurement scales used in cancer patients:

Intensity can be assessed using a variety of tools including the Visual Analog Scale (VAS), numerical or verbal rating scale, brief pain inventory (BPI) or multidimensional questionnaires, they allow frequent reassessment of pain. [15]

6- Subsequent assessments should evaluate the effectiveness of the therapeutic plan and, if pain is unrelieved, determine whether the cause is related to the progression of disease, a new cause of pain, or the cancer treatment. [16]

Discussion

Management of Cancer Pain include the following Steps

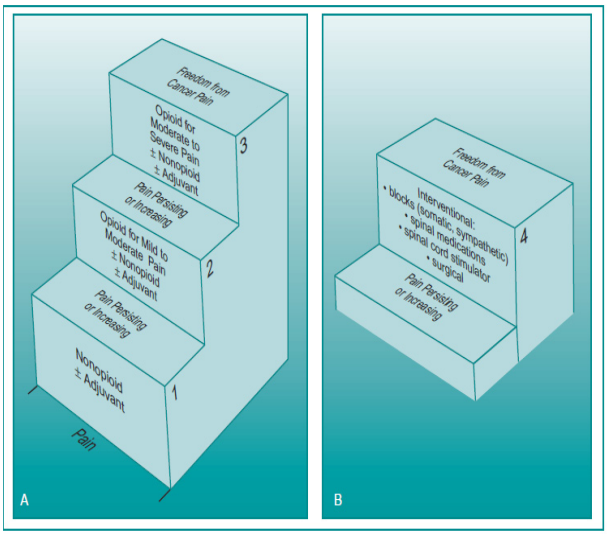
Identifying and Treating the Pathology

Oncologic pain is multifactorial and most of physicians' specialties must be involved in management as multidisciplinary approach which also important to consider and establish a risk: benefit ratio for each analgesic technique and provide a comparison to other available options to ensure a good quality of life for the patient. [17]

Management of Pain itself

A simple, well-validated, and effective method for assuring the rational titration of therapy for cancer pain has been devised by World Health Organization (WHO) in 1986. It has been shown to be effective in relieving pain for approximately 90% of patients with cancer and over 75% of cancer patients who are terminally ill (Fig1).

The WHO ladder serves as cornerstone of treatment; this multidimensional ladder offers greatest potential for maximizing analgesia, minimizing adverse effects and beginner practitioners could easily follow. [18]



The five essential concepts in the WHO approach to drug therapy of cancer pain are:

i) By the mouth.

ii) By the clock.

iii) By the ladder.

iv) Individualization.

v) With attention to detail. [19]

The first step in this ladder is the use of acetaminophen, or NSAIDs for mild to moderate pain. Adjuvant drugs to enhance analgesic efficacy, or to treat concurrent symptoms that exacerbate pain may be used at any step. [20]

The 2nd step is done when pain persists or increases, a weak opioid such as tramadol, codeine or hydrocodone should be added (not substituted) to the NSAID, this combination provides additive analgesia. [21]

Pain that is persistent, or become moderate to severe, should be treated by adding stronger opioid or using higher dosages as shown in the **third step**. Opioids like morphine, hydromorphone, oxycodeine, methadone or fentanyl are used. [22]

The "4th Step" Interventional Procedure: Some have added a fourth step in the WHO analgesic ladder to consider procedural interventions. [23]

Pharmacotherapy

It plays a vital role in the management of cancer pain, as almost 80 - 90% of the pain can be reasonably controlled using different analgesics along with the adjuvant.

NSAIDs, COX-2 Inhibitors, ASA, and Acetaminophen

NSAIDs and acetylsalicylic acids prevent formation of prostanoids from arachidonic acid. That is controlled by two separate cyclooxygenase enzymes (COX-1 and COX-2) this results in not only an anti-inflammatory response but also leading to the gastric ulceration and bleeding, interstitial nephritis with renal impairment, and thrombocytopenia with bleeding tendency. [24]

Newer selective COX-2 inhibitors are maintaining an anti-inflammatory response with low risk of side effects that occur with non selective inhibitors of COX enzymes. Recently, however, COX-2 inhibitors have received attention because of an increased incidence of stroke and myocardial infarction when used in high doses. NSAIDs also have a ceiling analgesic effect. [25]

Acetaminophen is analgesic and antipyretic but not anti-inflammatory. Health care providers must be mindful of the risk of acetaminophen hepatotoxicity

and cholestatic jaundice at sustained doses of 4 grams per day in adults. [26]

Opioids

In treating patients with moderate to severe cancer pain, opioids (in particular morphine) are the main stay and gold standard with which other treatment modalities are compared. [27]

It was believed that endogenous substances present in the body which when released are bound to the opioid receptor and provide analgesia. This receptor binding can be reversed by naloxone. These endogenous substances were later identified as enkephalins, ß-endorphins, and dynorphin. [28]

Three separate opioid receptors were identified as: mu (m), kappa (K), and delta (d). The major receptor associated with analgesia is mu, opioid act at the central as well as spinal cord level. Classification schemes include whether the opioid is a full agonist (morphine, oxycodone), partial agonist (buprenorphine), or mixed agonist-antagoinst (nalbuphine, pentazocine). [29]

- **Morphine**

This is the most popular and extensively used opioid. It is available as oral tablets (immediate and sustained release tablets), syrup as well as injectable forms for intramuscular, subcutaneous, intravenous, intrathecal and epidural route. It does not have ceiling effects, so they can be escalated to a very high dose levels titrated according to pain relief and side effects. Morphine can be started at 30 mg twice daily doses and if needed, canbe escalated to even 200-800 mg daily on a divided dose. [30]

- **Oxycodone**

It is a pure opioid agonist with an activity profile similar to that of morphine but with better oral bioavailability and effective role in neuropathic pain. It is given in the doses of 20 mg orally either twice or thrice daily. [31]

- **Hydromorphone**

It is a semisynthetic derivative of morphine that is about 7 times more potent. It is available in oral (immediate-release and controlled release) begin in dose of 6mg once, parenteral, and intra spinal preparations. It is a safer drug for those patients with renal failure who are undergoing dialysis. [32]

- **Methadone**

Which is an N-methyl-D-aspartate (NMDA) receptor antagonist, also blocks the reuptake of serotonin and norepinephrine (Bulka, 2002). This unique feature makes methadone a particularly useful choice for the treatment of neuropathic pain. It has prolonged analgesic half-life of methadone (Davis, 2001) so it displays complex and erratic pharmacokinetics requiring extreme vigilance in initiation and dose titration. [33]

- **Tramadol**

It is a centrally acting analgesic. Technically, it is a synthetic weak oral opioid that binds to the mu opioid receptor and blocks reuptake of serotonin and norepinephrine, and promotes neuronal serotonin release so it considered for neuropathic pain. Tramadol is thought to be approximately one-tenth as potent as morphine in cancer patients therefore, the ceiling dose is generally considered to be 400mg/day. [34]

- **Fentanyl**

Which is now, widely used as transdermal or transmucosal delivery systems. It is available as 25, 50, 75 and 100 mcg transdermal patches. Action usually starts within a couple of hours and reaches peak levels within 18 – 24 hours, while effect lasts for almost 72 hours. It is associated with reduced gastrointestinal toxicity, constipation, nausea and better patient's tolerance. However, the cost of it may be a significant factor. [35]

Side effects of opioids include sedation, nausea, vomiting, itching, constipation, myoclonus, and respiratory depression. Long-term use of opioids is associated with physical dependence, tolerance (which is reduced by rotating opioids), and addiction (that is rarely seen in patients with cancer pain when use is appropriate; however, patients with a history of previous addiction may be at increased risk). [36]

Adjuvants

Adjuvant analgesics are defined as drugs with a primary indication other than pain that have analgesic properties in some painful conditions.

Anti-spasmodics: as the visceral pain may be associated with excessive spasm of the smooth muscle and colicky pain. [37]

Tricyclic antidepressants (TCAs): have efficacy in treatment of associated depression and disturbed sleeping pattern and also in the management of associated neuropathic pain (as the pathophysiology of visceral pain shares many features with neuropathic pain, including contributions from peripheral and central sensitization, altered descending inhibition and similar molecular targets). Doses effective for neuropathic pain are usually lower than those effective for depression. [38]

The major mechanism of the analgesic effect of TCA was related to inhibition of norepinephrine or serotonin reuptake or of both. Common side effects include sedation, confusion, orthostatic hypotension; weight gain, tacky- arrhythmias, anticholinergic effects, and the starting dose isusually 10 mg every night, and then gradually titrated. [39]

The anticonvulsant drugs: mechanism of the analgesic activity of them is blocking sodium channels, GABA receptor agonist and increased membrane stability to control neuropathic element with visceral pain. Gabapentin starts with 100 to 300 mg/day, pregabalin is given commonly nowadays in the doses of 75-150 mg twice daily due to better linear pharmacokinetics and oral bioavailability. The most common adverse effects are somnolence, dizziness, and unsteadiness. [40]

NMDA receptor blockers: The NMDA receptors are activated as a result of barrage of pain signals from the periphery that activates glia cells and release pro-inflammatory cytokines which in turn increases the neuronal excitability and result in central sensitization and 'wind up phenomena. [41]

Ketamine, is administered by intravenous infusion or orally, and reducing opioid requirements. It has been shown to attenuate and reverse morphine tolerance by inhibition of NMDA receptors also can reduce central component of visceral pain but its use is associated with significant side effects such as nausea, vomiting, vivid dreams, hallucinations and headache. [42]

Alfa 1-Adrenergic blocker: to control sympathetically mediated pain (SMP) by phentolamine infusions. Variation in response may be attributed to inadequate dosing in some patients Common complications of phentolamine infusion included hypotension and tachycardia. [43]

Corticosteroids: possess analgesic properties in cancer pain due to obstruction of a hollow viscous (bowel or ureter) or to organ capsule distention, their analgesic effects by (1) inhibiting prostaglandin production and reducing inflammation (2) decreasing capillary permeability and reducing peri-tumor edema; and (3) directly affecting membrane stabilization,which decreases neuronal excitability. [44]

A high-dose can be used in acute episode of severe pain, and low-dose for patients with advanced cancer who continue to have pain despite optimal dosing of opioids. Corticosteroids have several indications; they can improve appetite, nausea, malaise, and quality of life. Adverse effects are hypertension, hyperglycemia, immuno-suppression, gastrointestinal ulceration, and psychiatric disorders. [45]

Alfa 2-Adrenergic agonists and local Anesthetics: Intraspinal clonidine and local anesthetic have been shown to reduce pain (especially neuropathic pain) in patients with severe intractable cancer pain partly responding to opioids. [46]

Antipsychotics, benzodiazepines, laxatives, antihistamines, anticholinergics, somatostatin analogue (octreotide) and psychostimulants: may have analgesic effects in cancer patients and are also used to treat cancer related symptoms or complications of cancer treatment such as: dizziness, vertigo, nausea, vomiting, diarrhea, constipation, confusion, delirium, also can reduce opioid-induced somnolence, improve cognition, treat depression, and alleviate fatigue. [47.48]

Radiation, Chemotherapy and Palliative Surgery: Which is used primarily to treat cancer, can also be helpful in alleviating cancer pain in some circumstances. It can be used to reduce the size of some tumors which, takes pressure off organs and nerves and relieve pain. [49]

Invasive interventions

It is indicated in those patients who have not responded to conventional pharmacological therapies, those who have undesirable side effects, those who are non compliant with their medications, or to help for physical rehabilitation. [50]

All invasive modalities have an associated risk: benefit ratio. For this reason, it is essential that physicians seek specialized training and have in-depth understanding of both anatomy and the imaging techniques available, which will not only improve efficacy but decrease untoward side effects. [51]

Factors to consider before any interventions are:

1) Nature and severity of symptoms that interfere with the patient's activities and activities of daily life,

2) Response to previous treatment,

3) Disease status,

4) Physical and psychological status of the patient,

6) General conditions that surround patients like home support, and

7) General assessments that must be done before any interventional technique include:-[52]

- Obesity, smoking, diabetes and hypertension which are unfavorable.
- Patient medication specially anticoagulants and antiplatelets
- Laboratory to eliminate exclusion criteria which are:-
- Severe anemia if HB < 7 gm/dl, platelet< 50.000 and WBCs >11.000.
- Serum albumin < 3 gm/dl (exclude all cases of implant as wound gapping may occur).
- Coagulation profile: PT > 16 sec, PC < 60 % and INR > 1.5.

Choice of Technique

The life expectancy of the cancer patient is an important consideration for selection of an appropriate interventional technique. Some techniques may provide analgesia for several days to a few weeks. Others, such as neurolytic blocks, may provide analgesia for a few months while some, like the implantable drug delivery devices, may provide good pain relief for several years. Implantable devices are therefore more appropriate in patients with a life expectancy of at least 1 to 2 years. The benefits together with the immediate and long-term risks of any planned procedure must be thoroughly explained to the patient. [53.54]

The procedure most likely to be effective should be selected. If there is more than one choice, select the one with the fewest and least serious adverse effects but, at the same time, bears an acceptable probability of achieving the desired pain control. [55]

The Common Interventions for Cancer Pain Include

- **Sympathetic Nervous System Block**

There are several sites for sympathetic blockade that can be employed to treat cancer pain arising from the visceral organs. The sympathetic chain at the appropriate level can also be targeted and blocked for specific pain complaints. Neurolysis is performed in almost all of the sympathetic blocks as catheter placement is difficult and can be impractical. [56]

Coeliac plexus, splanchnic, lumbar, hypogastric and Ganglion Impar block (diagnostic by local anesthetics or destructive by neurolytics). [57]

The coeliac plexus can be targeted for pain arising from upper abdominal cancers. The superior hypogastric plexus can be blocked for cancer pain from pelvic organs such as ovaries, bladder and prostate. The ganglion impar block is effective for anal or vaginal cancer pain. [58]

- **Continuous Epidural or Intrathecal Infusion Drugs**

Regional analgesic techniques, such as neuraxial opioid and local anaesthetic administration, are usually considered first because they do not compromise neurological integrity. Ablative or neurodestructive procedures, which have a narrow risk-benefit ratio, should be deferred as long as pain relief can be achieved with non-ablative modalities. The administration of local anesthetics, opioids, corticosteroids, baclofen or alfa 2 agonist. [59.60]

Numerous adverse effects of intrathecal morphine have been reported with fatigue, lethargy and sweating being most common and persistent. Others include pruritus, nausea, vomiting, urinary retention, constipation, oedema, weight gain, loss of appetite, dry mouth, myoclonic jerks/ spasms, headaches, sleep disturbances (e.g. insomnia) and sexual disturbances (e.g. loss of libido). [61]

- **Selective Lesioning of Visceral Pain Pathways**

DREZ, dorsal or saddle rhizotomy, percutaneous cordotomy in refractory unilateral cancer pain. [62]

- **Neuromodulation**

Continuous neuraxial drug delivery can be achieved using implantation of spinal cord stimulation (SCS) suppresses pain by the role of dorsal column pathways in maintaining visceral pain. [62]

The drug can be delivered using an external syringe pump or a totally implanted intrathecal drug delivery (ITDD) system. The European Association of Palliative Care recommends the principal indication for ITDD in cancer patients is the failure of conventional analgesics to achieve satisfactory analgesia despite escalating doses of strong opioids, and/or patients experiencing severe dose limiting side effects.22A Cochrane systematic review supports the use of intrathecal opioid therapy for pain that has not been adequately controlled by systemic treatment. [63]

- **Spine Interventions**

As Epidural steroid inection, selective nerve root neuro-modulation by Radiofrequency and vertebroplasty. These are effectively applied to improve metastatic bone pain. [64]

Complementary Medicine

Transcutaneous electrical stimulation (TENS), delivers mild electrical stimulation to painful regions, application of heat or cold or a combination of both is also used. [65]

Acupuncture by applying Pressure on certain meridian points can be exerted by insertion of small-gauge needles (acupuncture) or a combination of needles and low frequency electric current (electro-acupuncture). Their effects are due to release of multiple endogenous analgesic substances (e.g., serotonins and endorphins) and also to effect ascending inhibitory gate theory through GABA receptors. [66]

Physiotherapy

It is provided within a cognitive behavioral therapy (CBT) framework, exercise and massage that are important as they optimizing range of motion, strength, and neuromuscular control can reduce instability and pain associated with disuse. [67]

Psychotherapy

By cognitive behavioral therapy (CBT) which is aimed to reverse the impact of pain, but the pain itself also usually improves. It should be provided by the multi-disciplinary team including a psychologist. [68]

Behavioral therapy

By combination strategies include meditation, hypnosis, music therapy, systematic desensitization, biofeedback, yoga and relaxation. Hypnosis is used also to relieve nausea and vomiting associated with chemotherapy. [69]

Conclusion

Cancer pain is multifactorial with complicated Pathophysiology, but early diagnosis, careful history and good assessment lead to ideal selection of treatment plane either medications or interventions according to WHO step ladder. interventional therapies for cancer pain include; cordotomy, myelotomy, sympathectomy, peripheral neurectomy, dorsal rhizotomy and ganglionectomy, dorsal root entry zone lesioning, and others. And, early interventional is favorable due to many reasons; avoiding central pain, general condition of patients is still good and cancer itself not metastatic everywhere.

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