

Management of chronic malignant pain – an updated review

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ABSTRACT

Cancer Pain is a multi-dimensional pain experience which involves diverse neurophysiological changes and is associated with significant cognitive, emotional and sociocultural problems. Globally, the incidence is very high and usually it is undertreated. Lack of knowledge about managing malignant pain is an important cause of undertreatment. All types of pain are possible with malignancies. Assessment of pain characteristics is vital for proper management. The WHO step ladder pattern is the cornerstone of management. There are different pharmacological and non-pharmacological methods. Morphine is the choice opioid being administered by various routes. All drugs should be used as round the clock regimen. Opioid switch is opted to tackle tolerance. Nerve blockade especially with alcohol are still being used. Newer treatment modalities like implantable intrathecal pumps, dorsal column stimulation are in the pipeline for future. A passionate counselling may frequently release knotted conundrum of difficult analgesic strategies.

Keywords:

Chronic, cancer, pain, analgesia step

INTRODUCTION

Pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.¹ Cancer Pain (CP) is a multidimensional pain experience which involves diverse neurophysiological changes and is characterized by significant cognitive, emotional and sociocultural responses.² In India the estimated number of people living with malignancy is around 2.5 million with an every year addition of 7 lakh new cases. It is often presumed that malignancy is terminal and they do not need pain care. But the truth is otherwise. Moderate to severe pain is experienced by 40 to 50% of cancer patients: very severe pain experienced by 25 to 30% of cancer patients: 80% of terminal stage cancer patients experience moderate to severe pain. Nearly one out of two patients with cancer pain is undertreated.³ It is difficult to calculate life expectancy in cancer patients as there are numerous factors which influence active life in

malignant patients but with pain. As new modes of treatment increase survival rates, cancer patients will live longer with pain from the disease and its treatment. Hence it is mandatory to address the issue of analgesia in malignant patients.

WHY SHOULD MALIGNANT PATIENTS GET PAIN?

Cancer pain can be due to pain caused by the cancer itself, pain related to treatment (chemo or radiotherapy) other incidental pain, including osteoarthritis, degenerative disc disease, and diabetic neuropathy.¹⁻³ Mostly (70% approximately) cancer pain is due to tumour involvement of the soft tissue, viscera, nerves, or bone and or due to secondary structural changes in the body (e.g., muscle spasm). Up to 25% of cancer pain may be due to treatment, including chemotherapy, radiotherapy, immunotherapy, and/or surgery.⁴ Such pain is usually increased with associated psychological and spiritual distress.

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WHAT TYPE OF PAIN?

The simple classification of pain are (1) **Nociceptive** : somatic, visceral (a tumour invading the skin, muscles metastases to bone or an organ) (2) **Non nociceptive** : peripheral, central, psychogenic.⁵

Post-amputation limb pain, post-thoracotomy pain, post-mastectomy pain, brachial plexopathy and celiac infiltration are some of the etiological factors for neuropathic pain. Treatment, both chemo and radiotherapy can cause neuropathic pain which can be increased by psychological factors. It is clear from this classification that all types of pain are possible in malignancies.

In terms of time profile all the three types of pain, acute, subacute and chronic are possible but the last one is more niggling and frequently neglected. The uncontrolled pain can have physical, emotional and social impacts. Recently, cancer pain as a distinct entity is understood as a result of processes that involve cross-talk between neoplastic cells, host's immune and peripheral and central nervous systems.² Cancer-induced bone pain (CIBP), is understood complex pain state with nociceptive and neuropathic characteristics. The reason may be a stimulation of nerve tissues or creation of acidic environment.

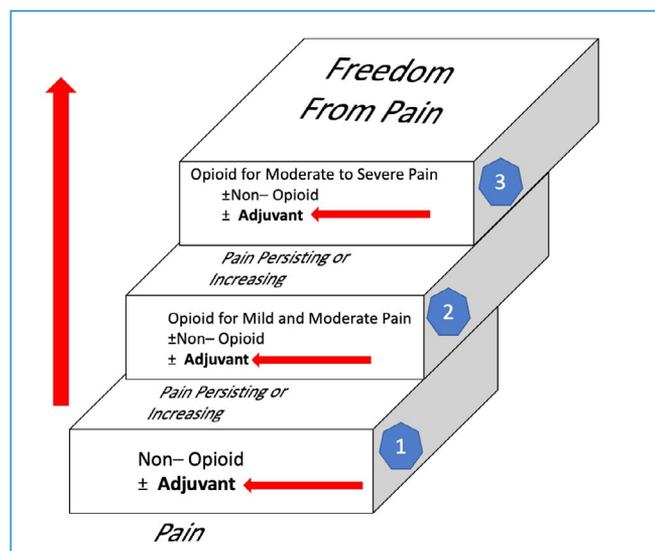
ASSESSMENT

There is no approach to management without a systematic assessment. The evaluation should include onset, type, site, absence/presence of radiating pain, duration, intensity, relief episodes, temporal patterns of the pain, number of breakthrough pains, a possible pathophysiology, rest and/or moving pain and the presence of any trigger factors. Assessment of functional status, social and psychological issues, drug history with side effect profile and coincident diseases like diabetes which may have other pain profiles needs to be done. Sleep patterns and assessment of caregivers need a mention. Every time, it needs a reassessment after an intervention.⁶ This assessment as part of the care assumes importance in that we should understand that nerve blocks for pain of psychological origin may not be very fruitful.

MANAGEMENT

In the decades before the development of the guidelines, most patients with cancer were dying with uncontrolled pain, but the Brompton cocktail (a mixture of alcohol with cocaine) was a popular

Figure 1: WHO step ladder management of cancer pain



remedy.⁷ Then in the 1980s, World Health Organisation (WHO) has given a standard step ladder pattern (Figure 1) of pain care.⁸ It addresses the social and basic living of the person rather than a big scientific message. Still there are barriers of therapy which can be detailed below. There are numerous modifications like inclusion of nerve blocks, acupuncture, massages, counselling etc. to the original step ladder treatment.

POSSIBLE BARRIERS OF PAIN MANAGEMENT⁹

- lack of knowledge among health professionals regarding cancer pain assessment and management
- fear of the adverse effects of opioids
- misconceptions about analgesic use
- concerns about pain communication

Although pain research has developed many analgesic drugs, opioids still remain the mainstay of the management of cancer pain .

MILD PAIN (WHO Analgesic Ladder Step 1)

It will have visual analogue score (VAS) less than 3 out of 10. The treatment will be Step 1 of WHO ladder pain management. Non-opioids, such as paracetamol and NSAIDs with adjuvants are ideal for the first step. Paracetamol dosage can go up to 1 gm 8 hourly while NSAIDs like piroxicam can be used. This regimen is definitely useful for short term use. All drugs should be used as round the clock regimen and assessment followed by treatment of breakthrough pain is the cornerstone of management.¹⁰ Breakthrough pain (BTP) defined as 'a transitory flare of pain that occurs on a background of relatively well controlled baseline pain'. Typical

BTP episodes are of moderate to severe intensity, rapid onset (minutes) and usually short in duration (approximately 30 min).¹¹ Side effects of NSAIDs like gastritis, bleeding and renal problems need to be frequently monitored. Combining two NSAIDs does not improve analgesia and increases toxicity. NSAIDs and paracetamol combination are having conflicting results. COX-2 selective inhibitors may increase the risk of thrombotic cardiovascular adverse reactions and do not offer protection from renal failure. Antidepressants, antipsychotics, anticonvulsants, corticosteroids, anxiolytics, psychostimulants, bisphosphonates and lidocaine patch are some of the adjuvants.¹²

ADJUVANTS

Regarding the adjuvants, anticonvulsants like **gabapentin** up to 300 mg tid even though a sedative at this dose, is very effective in neuropathic pain. **Amitriptyline** is effective with an advantage of anti NMDA action. **Steroids** may be beneficial in the management of cancer as they are anti-inflammatory, antiemetic, stimulate appetite, elevate mood, and reduction of peripheral edema especially cerebral edema. Intravenous **lidocaine** is effective for a variety of painful neuropathic conditions. **δ-9-tetrahydrocannabinol** has been demonstrated to have analgesic effects and reduce chemotherapy induced nausea and vomiting. **Bisphosphonates**, such as pamidronate and clodronate, are highly effective for some cases of bone pain secondary to metastatic cancer.¹³ **Flupirtine** a newer drug even though less efficacious, is an NMDA antagonist and if given in doses of 100 mg tds can be a very useful adjuvant.¹⁴ The effect of **melatonin** as an antinociceptive seems to be accomplished by the action on the MT2 receptor and has been shown in animal models of pain perception, including neuropathic and inflammatory pain.

MODERATE PAIN (WHO Analgesic Ladder Step 2)

Moderate cancer pain having VAS between 3-6/10 is treated following step 2 of WHO ladder pain management guide. It is treated with a combination of acetaminophen, aspirin or NSAID plus a weak immediate release opioid such as codeine, dihydrocodeine, tramadol or propoxyphene. Tramadol 1.5 mg/kg every six hours oral is a reasonable supplement. Codeine was also found equianalgesic with tramadol. To administer weak opioids such as codeine, tramadol and dihydrocodeine in combination with nonopioid analgesics is the current recommendation. **Tapentadol** is a newer oral opioid with effective use

as a mild opioid for decreasing malignant pain.¹⁵ As an alternative to weak opioids, low doses of strong opioids in combination with nonopioid analgesics are considered by a few. **Consider adjuvants in every step!**

MODERATE TO SEVERE PAIN (WHO Analgesic Ladder Step 3)

These patients will be having VAS more than 6/10. Strong opioids are the mainstay of analgesic therapy in treating moderate to severe CP.¹⁶ In a few countries, pain relief is hampered by unavailability of, or a difficult access to opioid analgesics. Morphine, methadone, oxycodone, hydromorphone, fentanyl, alfentanil, buprenorphine, heroin, levorphanol, oxymorphone are the most used strong opioids in Europe. The opioid of first choice for moderate to severe cancer pain is oral morphine. Intravenous morphine is one third of the oral dose. Transdermal fentanyl and buprenorphine are easy alternatives to patients with gastro-intestinal problems and also in patients with hemodialysis. Opioid switching is a practice used to improve pain relief and/or drug tolerability.¹⁷ The most frequent switch is from morphine, oxycodone, hydromorphone, fentanyl to oral methadone. Individual titration of dosages by means of normal release morphine administered every 4 h plus rescue doses (up to hourly) for BTP (break through pain) are recommended in clinical practice. Laxatives must be routinely prescribed for both the prophylaxis and the management of opioid-induced constipation. Metoclopramide and antidopaminergic drugs are recommended for treatment of opioid-related nausea/vomiting. Intravenous opioids; buccal, sublingual and intranasal fentanyl drug delivery systems have a shorter onset of analgesia in treating BTP episodes as replacement to oral morphine. Radiotherapy (RT), radioisotopes and targeted therapy given in association with analgesics have an important role in the management of bone pain. Quetiapine, an antipsychotic medication has been tried in CIBP (bone pain).¹⁸

The relative potency and intrinsic activity is tabled below.¹⁹

Pentazocine, nalbuphine, and nalorphine are ideal examples of mixed agonists/antagonists. Because of their antagonistic activity these *mixed agonists/antagonists*.²⁰ *should not be administered to patients who are receiving opioid agonists as this may precipitate withdrawal syndrome and reverse pain relief.* Methadone has a long duration of action as it is

Table 1: Relative drug profile of individual narcotics

Drug	Relative potency	Intrinsic activity	Half life (hrs)
Propoxyphene	0.5	Very low	6
Codeine	0.1	Very low	3
Buprenorphine	25	low	5
Pethidine	0.1	low	3
Morphine	1	moderate	2
Methadone	1	moderate	30
Fentanyl	100	high	3
Sufentanil	500	Very high	2

extensively bound to proteins and dissociates slowly, therefore producing less withdrawal symptoms.

Other modes: Radiotherapy has specific and critical efficacy in providing pain relief caused by bone metastases, present in about 75% of patients with cancer-related disease, and metastatic spinal cord compression (MSCC). RT, surgery and dexamethasone are the possible treatment options for MSCC.²¹

We need not stick on to the ladder every time. Go up or go down any time if the patient needs.

Start an opioid, increase dose till either the effect comes or the side effect comes!

Change opioid which has better intrinsic activity. Change route if first pass metabolism is a hindrance.

Nerve blocks: Regional nerve blocks at brachial plexus, lumbar plexus and epidural infusions of local anesthetics have been the main stay of interventional management in malignant pain.²² In a few instances, it should be remembered that a non-neurolytic block may give a permanent relief. Epidural steroid injection may be useful for the control of lumbar radiculopathy associated with epidural metastases. Local anesthetic blocks may be useful in predicting the efficacy of neuroablative procedures, such as gasserian ganglion ablation, surgical rhizotomy, and celiac plexus neurolysis. However, it is important to remember that pain may recur due to possible increased synaptic activity, development of aberrant connections from neuronal sprouts and sensitization to neurotransmitters.²³ Cancer patients often develop myofascial pain, which is secondary to bony, neural, or visceral pain. Myofascial pain is characterized by tender spontaneously painful foci in muscles, known

as trigger points.²⁴ Injections of these trigger points with local anesthetic can bring about effective relief of pain. Regarding neurolytic blocks, visceral blocks like celiac, hypogastric and ganglion impar blocks are better as such a residual paralysis may happen in other somatic blocks.²⁵ Pain may recur after three months of the time of intervention.²⁶ Untreated substance abuse in patients with malignant pain complicates management and limits clinician's ability to adequately control pain and other associated symptoms. This factor should be considered when encountering difficulty of achieving analgesia.²⁷

NEWER NON PHARMACOLOGICAL METHODS

Dorsal Column Stimulation (DCS), is a minimally invasive, outpatient technique that involves placement of electrodes in the dorsal epidural space. Implantable intrathecal pumps are effective but the technical knowhow to use it must be familiarised among all pain physicians.²⁸ Scrambler therapy, transcranial current stimulation are the other options.²⁹

CONCLUSION

To conclude, a proper assessment of the patient with type and intensity, the need of a method of analgesia, following the ladder pain path and if needed, step up or down is the prime step. Remember the use of adjuvants in each step. Oral morphine is used widely. Neurolytic blocks especially visceral may be effective but definitely with enough concerns on permanent palsies. Also give an eye on psychosocial aspects. It's essential to use a technique the patients need and not the technique we know!

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