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APPROACH TO THE MANAGEMENT OF PAIN IN A PATIENT WITH CANCER IN THE COMMUNITY HOSPITAL

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ABSTRACT

Pain is a common symptom in patients with cancer. Up to two-thirds of patients with cancer experience pain that requires a strong opioid for pain relief. Cancer pain management can be challenging as the pain experience differs among patients. A patient's response to opioids and other analgesia depends on several factors such as the character and cause of pain, and the pharmacodynamics and pharmacokinetics of the drug. Optimising pain control is important, as pain can impact negatively on many aspects of a patient's life such as mood, sleep, social interactions, cognition, and physical function, resulting in physical, emotional, and existential suffering. We will use the following case study to illustrate the process of pain assessment and the importance of understanding the aetiology of the pain in a patient with cancer. We will also discuss the pharmacological and non-pharmacological management of cancer pain.

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CASE REPORT

Mr X is a 72-year-old man, who was diagnosed with stage 4 metastatic urothelial cancer. It was histologically proven on a trans-urethral biopsy of the bladder tumour, after he presented with gross haematuria in October 2018. He underwent palliative chemotherapy and radiotherapy over a period of about two years. Unfortunately, he had disease progression with new metastases to his lungs, pelvic bones, and right gluteus medius muscle. In view of disease progression despite treatment, he was recommended for best supportive care (BSC). Since then, he had been on follow-up with his oncologist and the home hospice care team. In addition, he was on monthly subcutaneous (SC) Denosumab 120 mg. The prognosis given to him by his oncologist was estimated to be about three to four months.

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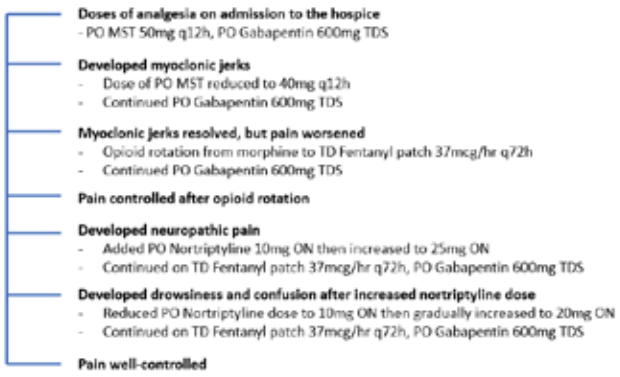
Six months after stopping anti-neoplastic treatment, Mr X was admitted to the acute hospital for fever and worsening lower back and right buttock pain. After extensive investigations, his fever was attributed to malignant fever and there was no localising source of infection. His pain in the lower back and right buttock was nociceptive in nature with a component of incident pain, secondary to metastases to the pelvic bones and muscles. His analgesia doses were adjusted, and his pain was then well-controlled with regular oral (PO) Morphine sulphate tablets (MST) 50 mg every 12-hourly (q12h) and PO Gabapentin 600 mg three times per day (TDS) prior to his transfer to the inpatient hospice (within the community hospital).

Whilst in the inpatient hospice, Mr X was observed to have myoclonic jerks of both his upper limbs. There were no other signs of opioid toxicity such as respiratory depression and pin-point pupils. After ruling out other possible causes of myoclonus, it was concluded that Mr X's myoclonus resulted from the side-effect of morphine. His dose of morphine was thus reduced and his myoclonic jerks resolved. However, the reduction in morphine dose resulted in the worsening of his pain. A decision was made to opioid-rotate morphine to transdermal (TD) Fentanyl patch 37 mcg/hr every 72 hours (q72h). Pain control was again achieved after opioid rotation, and there was no recurrence of the myoclonic jerks.

Mr X subsequently developed neuropathic pain over bilateral lower limbs, worse on the right, likely secondary to nerve compression from pelvic bone and new spinal metastases. He described the pain as a "shield or band" over his lower limbs, with episodes of sharp and pulling pain extending down his limbs. He was distressed by the pain and intermittent, sudden jerking movements of bilateral lower limbs, which led to poor sleep. He was started on PO Nortriptyline 10 mg every night (ON) and this was increased to 25 mg ON after a week. Unfortunately, Mr X could not tolerate the increased dose and became increasingly drowsy and confused. The dose of Nortriptyline was hence reduced and then slowly titrated up to a dose of 20 mg ON (refer to **Figure 1**).

Figure 1. Sequence of events and medication changes in the hospice



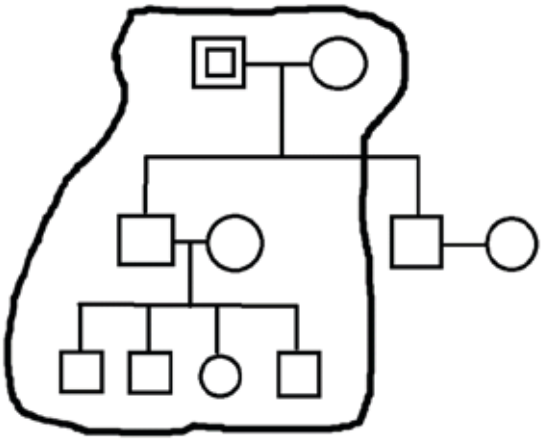
During the initial weeks of Mr X's stay in the inpatient hospice, he cried frequently and complained of severe pain at night, and requested for breakthrough doses of opioids. When the team explored with Mr X the reasons for the increased breakthrough doses, he shared that he was worried about not having anyone to attend to him when he needed assistance at night or when he was alone. Thus, he used pain as a reason to call for the nurses frequently in order to ensure that they would respond to his calls for assistance. The team reassured Mr X, and the nurses checked on Mr X more frequently at night. This resulted in a reduction in the frequency of nurses being called and opioid requirements.

Mr X's pain has been better controlled since his admission. Even though his function has deteriorated and requires moderate assistance after becoming chairbound, his mood and sleep have improved.

Social History

Mr X is married with two children (refer to **Figure 2**). He and his wife reside with their eldest son and his family in a condominium unit. Mr X used to work as a carpenter and has been retired since his cancer diagnosis. He was independent in his basic activities of daily living (bADLs) till two weeks prior to his hospital admission. Mr X and his family are aware of Mr X's diagnosis and prognosis, and their main concern is achieving optimum symptom control. In view of his increased care needs and goals of care, Mr X was transferred to an inpatient hospice.

Figure 2. Genogram of Mr X and his family



DISCUSSION AND FOCUSED LITERATURE REVIEW

Pain is defined as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage" by the International Association for the Study of Pain (IASP).[1] In patients with cancer, pain was prevalent in 39.3 percent after curative treatment, 55.0 percent during anticancer treatment, and 66.4 percent in advanced, metastatic, or terminal disease.[2]

Chronic pain can be broadly classified into[3]:

1. Nociceptive pain, which is pain due to tissue disease or damage
2. Neuropathic pain, which is pain due to somatosensory system disease or damage
3. Mixed pain, which consists of both nociceptive and neuropathic pain

Nociceptive pain can be somatic or visceral in origin. Somatic pain, which involves pain arising from the skin, muscle, and bone, may be described as being aching, throbbing, or pressing in nature. Visceral pain, which arises from organs or viscera, may be described as being aching, cramping or gnawing in nature.[4]

The Edmonton Classification System of Cancer Pain (ECS-CP) is a tool for cancer pain classification and prognostication of the complexity of pain management. It comprises five features[5]:

1. Mechanism of pain (presence of neuropathic pain)
2. Incident pain
3. Psychological distress
4. Addictive behaviour
5. Cognitive function

These factors predict increased complexity of pain management as measured by the outcomes of longer duration to achieve stable pain control, more adjuvant treatments, and higher opioid doses. Other factors that were associated with more days to achieve stable pain control include younger age and initial higher pain intensity.[6]

In Mr X's situation, he had mixed nociceptive and neuropathic pain, with predominantly neuropathic pain features. According to the ECS-CP, the features that contributed to his complex pain included the presence of neuropathic pain, incident pain, and psychological distress. Management of his pain was challenging, requiring judicious opioid dose titration and rotation, multiple adjuvants for pain control, and a prolonged period of more than one week to achieve adequate pain control.

Cancer Pain Management

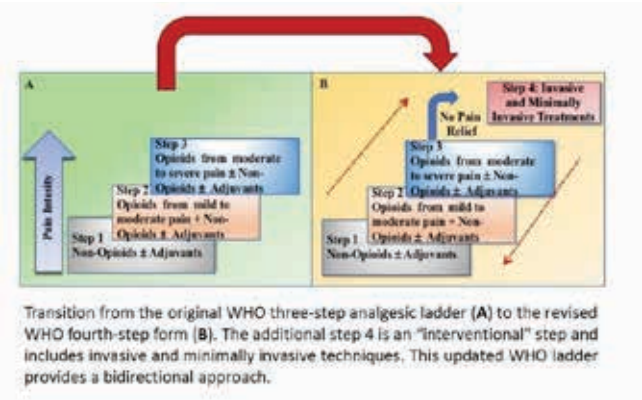
The WHO analgesic ladder was first developed in 1986 to manage cancer pain. The choice of analgesia depends on the severity of pain. It consisted of three steps[7]:

1. Step 1 (mild pain): non-opioid analgesics such as non-steroidal anti-inflammatory drugs (NSAIDs) or acetaminophen with or without adjuvants
2. Step 2 (moderate pain): weak opioids with or without non-opioid analgesics, and with or without adjuvants

3. Step 3 (severe and persistent pain): potent opioids with or without non-opioid analgesics, and with or without adjuvants

Given limitations of the original analgesic ladder, such as its unidirectionality, views that weak opioids contribute very little towards pain control, and lack of integration of non-pharmacological treatments into the therapy path, a fourth step was added to the ladder (refer to **Figure 3**).[7] This fourth step includes the use of invasive and minimally invasive treatments, including epidural analgesia, ablative procedures, and nerve blocks among many others.

Figure 3. WHO analgesic ladder[7]



Transition from the original WHO three-step analgesic ladder (**A**) to the revised WHO fourth-step form (**B**). The additional step 4 is an "interventional" step and includes invasive and minimally invasive techniques. This updated WHO ladder provides a bidirectional approach.

Strong opioids are the mainstay of analgesic therapy in managing moderate to severe cancer-related pain, and the opioid of choice is oral morphine.[4]

Opioid Rotation

Opioid rotation describes the process of changing one opioid to another due to intolerable adverse effects with adequate analgesia or increasing side effects of the opioid when its dose is increased because of inadequate pain relief.[8] Opioid rotation aims to improve or eliminate opioid toxicity, while achieving adequate pain control. This is possible due to incomplete cross-tolerance of opioids to the different opioid receptor subtypes, resulting in differences in analgesic effects and adverse reactions by different opioids.[9,10]

A study that was done to evaluate the prevalence of side effects of morphine in cancer patients who were taking the drug for pain management showed 77 percent had dry mouth, 43 percent had myoclonus, 23 percent had urinary hesitancy and constipation, 13 percent had sedation, and 10 percent had nausea.[11] Other side effects include respiratory depression and cognitive impairment, including hallucinations, nightmares, and agitation.[12] Prolonged morphine use, renal failure, and dehydration can also increase morphine metabolites, increasing the risk of opioid toxicity.[13]

Medications may be given to help relieve the side effects such as constipation or nausea from opioids, but when patients have persistent intolerable side effects despite the medications, opioid rotation may be considered.

Other indications for opioid rotation include tolerance to a given opioid drug, a change in patient's clinical state such as renal or liver failure, or in terminally ill patients where oral administration of medications may no longer be feasible and will require other routes of administration of opioids.[12]

In Mr X's case, he developed myoclonus likely secondary to morphine, despite his stable renal and hepatic functions. The myoclonus was distressing for him as it affected his ability to use his phone or hold things well. The evidence is limited to case reports in terms of pharmacological treatment for opioid-induced myoclonus.[14] The dose of morphine was reduced in an attempt to control Mr X's myoclonus, but it resulted in the worsening of his pain. The decision was then made to opioid-rotate in view of intolerable side effects of myoclonus and poorly controlled pain. With the opioid rotation from morphine to fentanyl, Mr X's myoclonus resolved and his pain was also better controlled.

Neuropathic Pain and Management

Neuropathic pain, as defined by the IASP, is "pain caused by a lesion or disease of the somatosensory nervous system". It is present in about 39 percent of patients with cancer pain, either neuropathic pain alone or mixed pain.[15] It is characterised by altered sensation in terms of positive (hypersensitivity) and negative (hyposensitivity) signs and symptoms.[16]

The Leeds assessment of neuropathic symptoms and signs (LANSS) pain scale is a screening tool for neuropathic pain. It comprises of a questionnaire of five questions about the pain symptoms and two components on sensory testing. It evaluates the presence of the following symptoms and signs (refer to **Table 1**) and are scored on a maximum of 24 points.[17] A LANSS pain scale score of 12 or more suggests that a neuropathic component is likely contributing to the patient's pain.

Table 1. LANSS pain scale[17]

Questions on symptoms	Points if present
Unpleasant sensation in the skin	5
Colour of skin is affected by the pain	5
Abnormally sensitive skin in the area of pain	3
Pain that comes on suddenly and in bursts for no apparent reason	2
Skin temperature in the painful area has changed abnormally (feels hot and burning sensation)	1
Sensory testing	
Allodynia	5
Altered pinprick threshold	3

Other screening tools for neuropathic pain that are available include PainDetect, ID-Pain, and Douleur neuropathique (DN4).

Mr X scored 18 on the LANSS pain scale (unpleasant sensation in the skin, abnormally sensitive skin in the area of pain, pain that comes on suddenly and in bursts for no apparent reason, allodynia, altered pinprick threshold), which supported the diagnosis of neuropathic component of pain.

Adjuvant analgesics are commonly used in the pharmacological treatment for neuropathic pain. These medications are administered along with opioid medications to optimise pain relief and possibly reduce adverse effects of opioids by allowing the use of a lower dose of opioids.[18] Recommended first-line medications include tricyclic antidepressants (TCAs), serotonin-noradrenaline reuptake inhibitors (SNRIs), pregabalin, and gabapentin. Weaker recommendations for treatment use include second-line medications of lidocaine patches, capsaicin high-concentration patches, tramadol, and third-line medications of strong opioids and botulinum toxin A. The number needed to treat (NNT) and number needed to harm (NNH) for the first-line medications are listed below (refer to **Table 2**).[19]

Table 2. NNT and NNH for adjuvant analgesics[19]

Drugs	NNT	NNH
TCAs	3.6	13.4
SNRIs	6.4	11.8
Pregabalin	7.7	13.9
Gabapentin	7.2	25.6

Studies have shown greater pain relief in combination therapies of gabapentin and TCAs or opioids compared with a single drug alone. However, many of these studies were done in non-cancer patients with neuropathic pain.[20,21]

Mr X was initially titrated on gabapentin to manage his neuropathic pain. Unfortunately, as he developed worsening neuropathic pain despite the high dose of gabapentin, the decision was made to add on a TCA (nortriptyline). The combination therapy of an opioid with gabapentin and nortriptyline improved his pain.

Bone Pain and Management

Bone is the third most common site of metastasis in patients with cancer, after the lungs and liver. The common primary cancers with associated bone metastasis are multiple myeloma, breast, prostate, lung, thyroid, kidneys, and ovaries.[22] The sites most frequently affected by bone metastasis are the spine, pelvis, ribs, and proximal limb girdles.[23] Bone metastases may lead to complications known as skeletal-related events (SREs), which include pathological fractures, pain or impending fractures requiring surgery or radiation to the bone, and malignant spinal cord compression.[18,24] In the management of pain from bone metastases, we should also consider prevention of SREs and progression of pain. A multidisciplinary approach should be adopted in the management of bone pain, including pharmacological, non-pharmacological, and other interventions.

For the pharmacological management of pain from bone metastasis, apart from treating the underlying cancer and use of analgesia (e.g., opioids, NSAIDs), bone-modifying agents such as bisphosphonates and denosumab can be used.[25] These agents are used in patients with bone metastases to prevent SREs and delay the onset or recurrence of pain.[4] Denosumab was found to be more effective in delaying the time to the first SRE and reducing the risk of first and subsequent SRE compared to zoledronic acid, pamidronate, and placebo.[26]

Non-pharmacological management can be prescribed concurrently with other therapies. This involves a review by the rehabilitation physicians and the allied health team, including the physiotherapists and occupational therapists. Prescription of orthosis and splints can be considered. In addition, techniques on how to change the positions of patients or the use of equipment aids can help manage symptoms and improve function and mobility.

Patients whose bone pain is not controlled by pharmacological treatment should be considered for other interventions such as radiotherapy, radioisotope (e.g., radium-223), or bone augmentation (e.g., vertebroplasty, cryoablation, nerve blocks).[22,23]

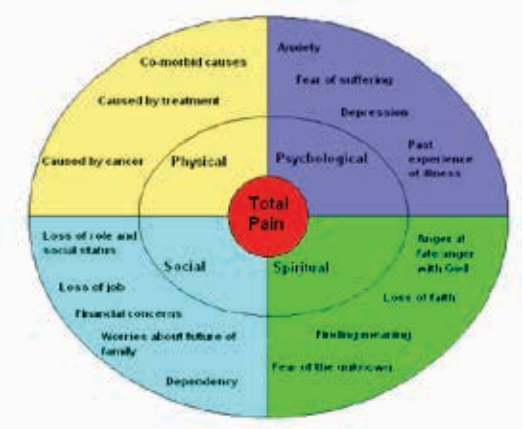
Mr X underwent radiotherapy for his bone metastasis while also receiving SC Denosumab during his course of disease. Subsequently, his pain from the extensive bone metastases was controlled adequately with pharmacological treatment.

Total Pain

Dame Cicely Saunders, the founder of the first modern hospice, introduced the idea of "total pain", which includes physical, psychological, social, and spiritual distress (refer to **Figure 4**).[27] This is especially important in managing a patient with cancer, whose pain is often complex and chronic, with multiple co-existing causes for his or her pain.[28]

Figure 4. The experience of "total pain"

Adapted from IASP 2009 Information Sheet on Total Cancer Pain



Hence, in the assessment of pain, we must consider patients' past experiences, their cancer journeys, and psychological well-being, in addition to their physical symptoms. This requires a multidisciplinary approach comprising of efforts from the doctors, nurses, social workers, and other allied health members such as the physiotherapists, occupational therapists, dieticians, and speech therapists.

In Mr X's case, he had underlying psychological distress of insecurity and anticipatory anxiety from pain, which manifested and was interpreted as physical pain. This resulted in the unnecessary increase in opioid breakthrough doses given. With the involvement of a multidisciplinary team in the care of Mr X, we eventually managed to achieve good pain control for Mr X.

It is crucial to identify and address these aspects of total pain to optimise pain control, as poorly controlled pain can result in negative mood such as depression and anxiety, insomnia, and cognitive and functional decline, as well as existential fear in patients.[29]

CONCLUSION

Pain is a common symptom in cancer patients and its management can be challenging due to multiple factors. In the case of Mr X, the challenges we faced included the side effects from opioids as well as adjuvants, and his underlying anxiety and fear, which resulted in some time taken before adequate and satisfactory pain control was achieved.

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LEARNING POINTS

The main learning points from Mr X's case were:

- **Management of pain in patients with cancer requires a multimodal approach. Consider the addition of adjuvants and interventions early, especially in patients with complex cancer pain, to achieve optimal pain control faster and reduce opioid requirements.**
- **When adding on a new medication or adjusting existing analgesia, it is important to monitor patients regularly for side effects. Making the changes one at a time will allow us to identify the offending drug if the patient develops side effects. It is also advisable to start new medications at low doses and titrate up the dose gradually.**
- **The concept of total pain is important when approaching any patient with advanced illness. The fact that underlying psychological, social, or spiritual distress may also be manifested or reported as physical pain by the patient reminds family physicians to explore these aspects of patients when assessing pain. This reduces the risk of unnecessarily high doses of pharmacological treatment that may cause undesirable side effects on patients.**