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Case Report Open Access

Holistic Approach to Complex Cancer Pain

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Abstract

Cancer pain is a major cause of disability and suffering at the end of life. Cancer pain affects a significant number of patients at the end of life. This case report seeks to highlight some of the complexities associated with managing cancer pain in terminally ill patients.

Keywords: Cancer pain; Palliative care; Opioid rotation; Methadone

Introduction

Nearly 74% of patients with advanced/metastatic cancer will suffer from pain at the end of life. Alarmingly up to 42-51% of these patients will endure suboptimal control of this symptom [1]. It is imperative that patients with difficult pain syndrome are recognised early. This case report spotlights attempts to effectively address complex cancer pain.

Background

Mr S is a 52 year-old gentleman who had enjoyed his independence and mobility despite a long history of hypertension, dyslipidaemia, and ischaemic heart disease. He is a divorcee and stays with his sister. His siblings described him as a cheerful and optimistic person. He enjoyed spending time with his family and cooking for them especially during festive seasons.

Oncological history

Mr S was diagnosed with supraglottic laryngeal squamous cell carcinoma in October 2013. The disease was stage 4A at diagnosis, with involvement of the tongue base and superior portions of the lateral pharyngeal constrictors, as well as bilateral cervical lymph nodes. He had a total laryngectomy, left thyroidectomy, total glossectomy and bilateral modified radical neck dissection with free flap reconstruction in December 2013. This is followed by adjuvant chemo radiotherapy. He also had a long-term tracheostomy and percutaneous endoscopic gastrostomy for feeding post-operatively. Histology of the excised tumour showed moderately differentiated squamous cell carcinoma.

Follow-up CT neck and thorax done in November 2015 showed recurrence disease with metastasis to bilateral pleural bases as well as right upper lobe, which was then confirmed histologically. The right pleural base mass measured about 4.2 × 1.5 cm and there was erosion of the mass to the adjacent right first rib causing pain over right chest. He was started on fentanyl patch 6 mcg/hour and referred to home hospice care service.

Mr S was admitted early January 2016 for worsening right chest pain. He described it as a background of constant stabbing pain at the right chest, with episodes of exacerbation characterised by sudden pulling pain that radiated to his right axilla, clavicle, arm and upper back around the scapular region. His baseline pain score was 5/10 and at times of exacerbation, the score increased to 7-8/10.

They are sometimes triggered by movement of right upper limbs, however, it may also be spontaneous especially in the night time. He also experience allodynia along his right neck, clavicle and arm. Mr S has learnt to live with minimal movement of his right upper limb because of the incident pain. The home hospice team escalated his fentanyl patch to 18 mcg/hr and added on gabapentin 300 mg bd but his symptom persisted, requiring up to 10 breakthrough doses of mist morphine per day.

Psychosocial history

Mr S had lost contact with his ex-wife and his 17 years-old son for many years. He has 5 siblings; 2 sisters and 3 brothers. He is the fourth child amongst his siblings. He lives with his eldest sister and her family in an apartment. He is a Christian and used to work as a car mechanic until his diagnosis of cancer in 2013.

He is fully aware of his medical condition and is willing to try any treatment option that his medical oncologist could offer. His family members are also very supportive. He shared with that his biggest regret in life is to indulge in gambling at younger age which led to his divorce. It upsets him very much whenever he thinks of the past.

Issues and progress in ward

The impression made was mixed right chest nociceptive and neuropathic pain secondary to right pleural metastasis that has eroded into the 1st rib. Mr S was started on fentanyl infusion 40 mcg/hr upon admission to ward.

Gabapentin dosage was also increased from 300 mg bd to 300 mg/300 mg/600 mg at 8 am/2 pm/10 pm respectively. Despite the increment of medications, the pain was still not optimally controlled with baseline pain score of around 4/10. He was still having distressing exacerbations of pain especially at night between 10 pm till 7 am, requiring up to 4 breakthrough doses of fentanyl every night.

Thus fentanyl infusion was titrated up to 70 mcg/hr and nortriptyline 10 mg per day was added. In addition, he was also started

on lignocaine 5% patch applied over right infraclavicular, arm and scapular region, from 10 pm till 10 am daily. At the same time, pain team consultation was made for intercostal nerve block.

In view of the distribution of the pain, MRI thoracic spine/right hemi-thorax/right brachial plexus was carried out to assess the extent of disease at the area of interest, which showed:

1. Significant interval enlargement of the known pleural based soft tissue mass at the right upper lobe, causes erosion of the right 1st to 4th ribs. It also abuts the right pectoralis muscle.
2. The mass involves the right brachial plexus in the costo-clavicular space.

Traditional interventions such as an intercostal nerve block were not offered given multiple ribs and wide area of involvement and Mr S was not keen on intrathecal analgesia.

Despite a good response to escalating doses of fentanyl initially Mr S's pain evolved and was no longer responding to breakthrough doses of fentanyl.

With his sleep disturbed by the pain and Mr S increasingly distressed by the apparent failure of the team to control the pain the decision to rotate to methadone 10 mg/day, commence dexamethasone and 10 fractions radiotherapy to the right pleural mass was made.

Pain control was eventually achieved using the following treatment/measures:

1. Increased dose of methadone to 12.5 mg/day.
2. Gabapentin 300 mg/300 mg/600 mg.
3. Dexamethasone 8 mg om, tailing dose by the time of hospital discharge.
4. Lignocaine 5% patch (3 patches per day).
5. Radiotherapy.

Discussion and Focused Literature Review

Points of discussion

1. Complex cancer pain.
2. Adjuvant therapy for neuropathic pain.
3. Opioid rotation.
4. Use of methadone and the equianalgesic dose conversion.

Complex cancer pain

Bruera et al. [2] offered an assessment process for the staging of cancer pain. The staging system included the assessment of the following:

Pain mechanism (A1 visceral pain, A2 bone or soft tissue, A3 neuropathic pain, A4 mixed, A5 unknown).

1. Pain characteristic (B1 non incidental pain, B2 incidental pain).
2. Previous opioid dose (C1 <60 mg morphine/day, C2 60-300 mg/day, C3>300 mg/day).
3. Cognitive function (D1 intact, D2 cognitive failure).
4. Psychological distress (E1 absent, E2 present).
5. Tolerance (F1 none, F2 tolerance present).
6. Past history of alcohol or drugs (G1 none, G2 present)

The cancer pain was divided into Stage I-III as below in Table 1.

Stage I: Good prognosis	A1: visceral C1: <60 mg morphine/day B1: nonincidental D1: normal cognition E1: no somatization F1: no tolerance G1: no alcohol or drugs A2: bone or soft tissue C2: 60-300 mg morphine/day
Stage II: Intermediate prognosis (any patient who is not stage I or III)	A4: (mixed, if not stage III) C3: >300 mg morphine/day, if not stage III D2: cognitive failure, if not stage III A5: unknown
Stage III: Poor prognosis	A3: neuropathic, any B,C,D,E,F,G B2: incidental, any A,C,D,E,F,G E2: somatization, any A,B,C,D,F,G F2: tolerance, any A,B,C,D,E,F G2: alcohol or drugs, any A,B,C,D,E,F
Adapted from Bruera et al. [2]	

Table 1: Clinical Staging System

In keeping with Bruera et al., pain classification, Mr S was deemed to have Stage III (poor prognosis) cancer pain as a result of his right pleural metastasis with 1st to 4th ribs erosion and right brachial plexus involvement. In keeping with Fainsinger et al. [3] data patients with neuropathic pain and incident pain required higher mean morphine equivalent daily dose (MEDD) and more adjuvant treatment to achieve stable pain control. Younger age (<60 years) patients, neuropathic pain, incident pain, psychological distress, and addiction were also associated with longer time to achieve stable pain control [3,4].

Adjuvant therapy for neuropathic pain

Gabapentin is a 3-alkylated analogue of gamma amino butyric acid, which modulates calcium-channel subunits, a mechanism thought to be important in neuropathic pain. Gilron et al. [5] conducted a randomized, double-blinded, four-period crossover trial on 57 patients to compare the efficacy of a combination of gabapentin and morphine with that of each as a single agent in patients with neuropathic pain. It was shown that gabapentin and morphine combined achieved better analgesia at lower doses of each drug than either as a single agent.

Gilron et al also conducted another double-blind, crossover trial that shows that combined gabapentin and nortriptyline is more efficacious than either drug given alone for neuropathic pain. He recommended the use of this combination in patients who show a partial or suboptimal response to either drug given alone [6].

Lignocaine patch 5% is effective based on 5 class I or II RCTs in post-herpetic neuralgia with brush-induced allodynia, but the therapeutic gain is modest against placebo, and the level of evidence is lower than for systemic agents [7]. However this transdermal form has good safety profile due to its low systemic absorption and is well tolerated with only minimal local adverse effects such as mild skin reactions.

As pain control was still poor despite escalating dose of gabapentin, Nortriptyline was added for its synergistic effect. Unfortunately, Mr S didn't have any significant improvement in pain with this combination. Instead he developed side effects such as dry mouth and urinary retention from the tricyclic anti-depressant when the dose was increased to 25 mg ON. Nortriptyline was subsequently stopped. Mr S also received oral dexamethasone for its anti-inflammatory properties.

Given the concerns about side effects a transdermal Lignocaine patch 5% was employed. This reduced the sensation of allodynia.

Opioid rotation

As overall pain remained poorly controlled, opioid rotation was proposed to improve pain relief and reduce adverse effects. Such opioid rotations occur in 21-44% of patients with cancer pain receiving opioids and satisfactory pain control and a reduction in adverse effects has been reported in 50-90% of patients. For Mr S, escalating dose of fentanyl failed to provide adequate analgesia. He was still having severe pain with frequent exacerbations which affects his daily activities and mood. It was felt that further increase in dose for the same opioid would not result in optimal pain control.

The choice of the opioid depends on the indication of opioid switch, intended route of administration, severity of pain, evaluation of patients' compliance, concomitant symptomatology, possibility of drug-drug or drug-disease interactions as well as the availability and costs.

Use of Methadone and the Equianalgesic Dose Conversion

Equianalgesia refers to the ratio of the doses of two opioids, required to produce the same analgesic effect. According to Athina et al. [1], equianalgesic doses should be used only as an initial estimate due to the following reasons:

Ratios are primarily derived from studies not originally designed to evaluate equianalgesic dosing.

Most have wide confidence intervals and large standard deviations (SDs).

Large inter-patient variability.

Incomplete cross tolerance among opioids. Patients who have been on chronic, high-dose opioid therapy may be particularly sensitive to a new opioid.

In most cases, calculated dose equivalent of a new opioid must be reduced by 25-50% due to inter-patient variability and incomplete cross tolerance [1,8]. Other factors to be taken into consideration during dose conversion include intensity of pain and adverse effects, comorbidity, concomitant drugs, and possible pharmacokinetic factor that limits the effectiveness of a certain drug.

Methadone is an effective opioid analgesia for difficult pain syndromes. Besides its activity at the opioid receptors, namely μ and delta opioid agonist, methadone is also an inhibitor of serotonin and noradrenaline reuptake in the central nervous system and a moderate antagonist at the N-methyl-D-aspartate (NMDA) receptor. These properties make methadone a powerful analgesic for neuropathic pain. Methadone is also attractive because of its lack of neuro-active metabolites, clearance independent of renal function, good oral bioavailability of approximately 80%, low cost, and long half-life thus fewer doses needed per day [9,10]. However, there is wide inter-individual variation in the metabolism of methadone due to genetic polymorphisms in the enzymes responsible for metabolism of methadone, namely the CYP450 3A4, CYP450 2D6 and CYP450 2B6 [11]. This results in variable plasma half-life of methadone, ranging from 13 to 58 hours, causing unpredictable accumulation of methadone in the initial days of treatment.

Methadone was chosen for Mr S in view of its activity at the opioid and NMDA receptors. Methadone was also felt to best address Mr S's mixed nociceptive and neuropathic pain which describes the pain that Mr S had. Its low cost is also an attractive reason as Mr S faced financial difficulties paying for his treatment. The oral route of administration of methadone also makes it a convenient drug for Mr S is as he has been very competent in feeding through his PEG. Moreover, he is not at risk of developing intestinal obstruction.

Due to methadone's complex pharmacokinetic/pharmacodynamics profile, opioid rotation from other opioids to methadone can be challenging. Weschules, et al. conducted a systemic review to analyse the evidence comprising methadone conversion methods and its associated dosing ratios. There was wide variation in the dose ratios employed, but the most frequently used ratios were 4:1, 5:1, and 10:1. In general, 4:1 ratio was used for converting patients from <90 mg MEDD, 5:1 for <400 mg MEDD and 10:1 for >400 mg MEDD [10]. Further study also found the morphine/methadone dose ratio is influenced by reasons for opioid rotation and previous opioid dose [12].

There have been several clinical styles of rotating other opioids to methadone that are considered efficacious and acceptable:

1. Three-day switch/Edmonton method (3DS)
2. Rapid conversion/stop-and-go method (RC)
3. Ad libitum/Morley-Makin method (AL)

The 3DS method suggests the administration of a morphine equivalent dose that is reduced by 1/3 per day. In tandem with this process 1/3 of the calculated methadone dose over a three day period. The RC method means stopping the fentanyl and providing the new opioid at a fixed ratio, with frequent assessment and dose titration subsequently. For AL method, 1/10 of equivalent daily morphine dose of methadone is given as needed every 3 hours. When daily requirements of methadone were stable, the doses were divided into 12-hourly dose. Studies have been done to compare the effectiveness and safety of these different methods. The RC method is found to be associated with more adverse effects than AL or 3DS method. However, advocates of RC method argued that RC gives a faster onset of analgesic effect. It is found that time to achieve dose stabilisation with RC is shorter (around 3 days) compared to AL (3-6 days) and 3DS method (3-11 days) [9,11].

In Mr S's case, the RC method was employed to rotate his fentanyl to methadone with the intention of achieving a faster analgesia as he was very distressed by the severe pain. Although this method has been found to cause more adverse effects or toxicity, this risk was attenuated by the fact that he received close monitoring at inpatient palliative care unit. Moreover, a lower conversion ratio of 10:1 was used for Mr S.

His opioid dosage prior to methadone rotation was:

Subcutaneous fentanyl 70 mcg/hr = Total oral morphine equivalent daily dose (MEDD) of 168 mg.

Total oral methadone requirement =168 ÷ 10 × 0.7(30% dose reduction for cross-tolerance)

≈ 10 mg/day =2.5 mg/6 h

The dose of methadone was increased to 12.5 mg/day subsequently. Optimal pain control was eventually achieved and Mr S was discharged home with home hospice service. A medical oncology outpatient review was also scheduled for discussion about palliative chemotherapy.

Holistic Review

There was also his mood to be considered. Aware of his progressive disease Mr S's mood became very low and felt helpless especially when he realised that his wish of re-uniting with his ex-wife and son may not be fulfilled. This needed to be addressed amongst his physical pain as psychological distress known to be prognostic factor for difficult pain syndrome [2,3].

Knowing that Mr S has a strong faith in his religion, his sister made arrangement for his church members and the pastor to visit him in the ward. They shared with him their testimonials about overcoming obstacles in life and prayed with him. His close friends also came by to give him further spirituality support.

The multidisciplinary approach was employed. The art therapist engaged him with drawing sessions and the physiotherapist brought him for walks and accompanied him to watch his favourite cooking programme. He was also reviewed by medical social worker who provided good psychosocial support.

With the active involvement of the teams, there was marked improvement in his mood. However, Mr S was still upset and teary whenever he thought of his ex-wife and son. While the social worker was trying all means to trace the contact details of his ex-wife, a psychologist review was also made to provide him counselling. Much to Mr S's surprise, the social worker managed to contact his ex-wife and successfully arranged a meeting for them in the ward. His family also took the opportunity to take a photograph of the three of them, which Mr S happily displayed at his bedside.

Reflection

Complex cancer pain is uncommon but we do encounter such cases in palliative care practice. It often brings much distress to patients and their loved ones. Although its management can be very challenging, complex pain can be controlled given more time, avoiding the ideas of euthanasia. The severity of pain often requires aggressive albeit proportional management.

This case gives an example of the management of complex cancer pain. It reemphasizes the importance of holistic patient assessment and care involving multidisciplinary team. It is equally important to practice evidence-based medicine particularly in managing complex cases. Often a second opinion or team based reasoning is involved for better accountability and transparency. Mr S's experiences also highlight some of the reasons for the lack of consistency in the manner that patients with complex pain are treated and how effective their care is provided.

Holistic care replete with psychological, existential and social awareness must complement clinical skills if unnecessary suffering is to be curtailed and the tenets of Palliative Medicine are to be met.

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