Challenges, opportunities and the role of palliative medicine in cancer

In a recent seminar hosted in Sydney, Professor Ahmedzai from the UK discussed the paradigm shift from treating patients dying of cancer to people living with their disease. This summary of that presentation has been produced to enable those who could not attend to benefit from the valuable learning opportunities provided at the presentation. These included: i) the changing landscape of cancer as a chronic disease for many patients, and the implications for palliative care delivery; ii) insights into the mechanisms of pain at all stages of the disease, including treatment-induced pain and focusing on practical approaches to tailoring care, including patient selection, initiation of targeted therapies and multimodal analgesia; iii) the role of opioids and considerations for special patient populations, including a practical approach to patient assessment, titration, rotation and screening of hepatic impairment; and iv) challenges and opportunities for the future positioning of palliative medicine in relation to oncology and interventional pain medicine.

Changing landscape of oncology and role of supportive and palliative care

In the 1970s and early 1980s, cancer management was a relatively straightforward process consisting of diagnosis, cure in rare possible cases and palliation. Contemporary management is much more comprehensive and includes multiple disciplines, covering prevention, early and accurate (molecular) diagnosis, cure if possible, prolonging life, palliation, rehabilitation and end-of-life care.

The Multinational Association for Supportive Care in Cancer defines ‘supportive care’ in cancer (all stages) as the ‘prevention and management of adverse effects of cancer and its treatment; this includes physical and psychosocial symptoms and side effects across the entire continuum of the cancer experience, including the enhancement of rehabilitation and survivorship’. Professor Ahmedzai described the model of supportive care for the Adult Cancer Survivorship programme he helped develop in Sheffield. The model takes into account the disease along with the patient and their family in directing therapy (Figure 1), and involves supporting a patient with cancer and their family throughout the entire duration of care, including coping with the disease and its treatment, outcomes, survivorship and end-of-life care. Oncologists also benefit from the programme, allowing them to deliver the best, state-of-the-art treatment. Supportive care is dependent on the patient’s needs, not just disease stage, and requires a large multidisciplinary team that can operate in a virtual environment.

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Figure 1. Sheffield model of supportive care for patients with cancer (Adapted from Ahmedzai & Walsh. Semin Oncol 2000;27:1–6)

Abbreviations used in this review:
- CNS = central nervous system
- NGF = nerve growth factor
- PR = prolonged release
- QOL = quality of life
- CPD/CME = continuing professional development/continuing medical education
- NCRI = National Cancer Research Institute
- EORTC = European Organization for Research and Treatment of Cancer
- QLQ = quality of life

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Professor Ahmedzai studied medicine at the Universities of St Andrews and Manchester. He obtained his clinical training in oncology and respiratory medicine in Glasgow, and in 1985 he became Medical Director of the Leicestershire Hospice, where he established the first UK palliative care research programme. From 1994–2015, he was Professor of Palliative Medicine at the University of Sheffield, where he combined an academic career while heading one of the UK’s busiest hospital palliative care teams. He is now NIHR National Specialty Lead for cancer research, with the remit for supportive care and community-based studies. He also chairs the NCRI Supportive and Palliative Care clinical studies group.

He led the Adult Cancer Survivorship programme in Sheffield and has pioneered consumer involvement in cancer research. Sam led the EORTC Quality of Life Group, which produced the EORTC QLO-C30, the world’s leading tool for measuring QOL in cancer. He advises NICE on development of guidelines for end-of-life care and technology appraisals. He initiated the Association for Palliative Medicine’s Science Committee and is editor-in-chief of Current Opinion in Supportive and Palliative Care and of the Oxford University textbook series on Supportive Care.
Cancer pain

Cancer treatments are improving and patients are living longer, as evidenced by declining mortality rates despite increasing incidence rates. However, the treatments needed to achieve this improved survivorship have led to more adverse effects. An important adverse effect is pain, which arises from various causes (initial symptoms, procedures/surgeries, treatments, metastatic disease and end of life); data from a systematic review have indicated that 35% of patients with cancer experience pain early in their disease (mostly from surgery), 59% experience pain during the course of their treatment, and 64% with advanced disease experience end-of-life pain. While there were insufficient data for analysing pain among cancer survivors in this systematic review, there are data reporting pain rates of 36% at 5 years after thoracotomy for lung cancer and 47% at 2 years after mastectomy for breast cancer. Furthermore, neuropathic pain has been reported for half of patients with multiple myeloma 2 years into remission, some of which is due to their treatment.

Why pain is common and important in cancer

As people are living longer, cancer and its associated pain are becoming more common. All pain associated with cancer has a negative impact on recovery. Our increased understanding of cancer has been accompanied by an increased understanding of its associated pain, and both are complex. Furthermore, pain due to new toxicities associated with the ever-increasing options for cancer treatment can be difficult to manage. Comorbidities can also be an important source of pain, especially in older patients.

Chronic pain associated with cancer is mediated by immune/inflammatory mechanisms (Figure 2). Damage to the tissues initiates a sequence of events, including local inflammation and spinal neurotransmission, culminating in CNS sensitisation. In response to signals received by the brain from damaged tissue via ascending neurological pathways, the brain sends pain inhibitory signals back to the tissue via descending neurological pathways. A wide range of receptors in nerve membranes can be activated by tissue damage to cause inflammation and neuronal damage. The pain signals they generate (action potentials) are maintained via ion channels. In response to this, there is upregulation of receptor and ion channel gene expression, resulting in more receptors and ion channels in the nerve, including abnormal Na+ channels that cause unpleasant, spontaneous pain.

Targeting pain

Traditional targets of cancer pain include prostaglandins, which are inhibited by NSAIDs and cyclo-oxygenase-2 inhibitors. New targets include TRPV1, for which an antagonist is described mechanisms by which pain signals are inhibited in presynaptic neurons (e.g. Na+ and Ca2+ channel blockers). He also described mechanisms by which pain signals can be prevented from occurring, including increasing K+ influx into the neuron. Opioids increase K+ influx, and also inhibit Ca2+ channels. However, some signals are still able to be propagated across the synapse to activate the postsynaptic channels NMDA, NK1 and GABA. Of these, activation of NMDA and NK1 receptors opens Ca2+ and Na+ ion channels, respectively, thereby increasing pain. Antagonists are available for NMDA receptors, but not NK1. Activation of GABA receptors inhibits pain, and this can be enhanced by benzodiazepines and barbiturates. Noradrenaline (norepinephrine) mediates descending inhibitory pain pathways. Noradrenaline is broken down quickly in the neurons, so noradrenaline reuptake inhibitors are useful.

Multimodal analgesia

The recommended treatments described in Australian guidelines for cancer pain constitute multimodal analgesia. Multimodal analgesia takes advantage of the various mechanisms involved in pain by combining analgesics and antihyperalgesic drugs that have different neuronal targets with interventional pain medicine (e.g. local anaesthetic injections) and validated nonpharmacological interventions (e.g. hypnosis, acupuncture). The effects of the different modalities can be synergistic or additive. Because much lower drug doses can be used in multimodal analgesia, it is often well tolerated with fewer adverse effects. For example, there are several targeted ways of treating pain associated with bone cancer at any stage, including the use of anticancer therapies (radiotherapy, chemotherapy, hormone therapy, biologic agents), bisphosphonates, nerve blocks/spinal anaesthetics, vertebroplasty/kyphoplasty, analgesic drugs and physical therapy/exercise.

Opioids: adverse effects and management

The principles of opioid therapy for cancer pain were discussed. Opioids are the medication of choice for severe cancer pain, but excessive use can cause not only adverse effects, but also opioid-induced hyperalgesia. Ideally they should be used in combination with nonopioid pharmacological agents and nonpharmacological therapies, and they should only be prescribed in conjunction with comprehensive patient assessments, documented treatment plans and outcomes, and with cautious titration. Responses to opioid therapy, including analgesia efficacy, adverse effects and the development of aberrant behaviours, must be proactively monitored.

Choice of opioids

Opioids available for cancer pain today range in potency, although there is no real pharmacological basis for categorising them as weak or strong. Morphine has often been considered to be the gold standard. Professor Ahmedzai discussed what he believes are the criteria for a drug to be considered the gold standard. These include reliable efficacy, minimal side effects, safe metabolism and elimination and multiple routes of administration and formulations, all of which morphine fails to meet.

Science of opioid receptors

Opioid receptors are present throughout the body. They are 7-transmembrane G-protein coupled receptors, of which there are three main types for endogenous opioids (µ [≥2 subtypes] and κ [≥2 subtypes] and δ [many subtypes]). There is also an ‘opioid-receptor like’ receptor (ORL1) for nociception which, unlike with other endogenous opioids, increases pain when activated.

Agents targeting opioid receptors

Therapeutic opioids are not all the same. The original endogenous opioid to be used by humans, morphine, has been the basis for the development of many other synthetic opioids. However, buprenorphine was derived from thebaine (also found in opium poppies). Drugs that target the µ receptor only (e.g. morphine, fentanyl) tend to be associated with opioid-induced hyperalgesia. Oxycodone targets the µ and κ opioid receptors, resulting in reduced sedative, hallucinatory and pruritic effects. In addition to targeting µ and κ opioid receptors, buprenorphine is the only available opioid that targets ORL1 receptors, endowing it with special...
properties, including a ceiling for respiratory depression and it is antihyperalgesic. It also provides 60-fold greater analgesia potency than morphine, with no evidence of a ceiling analgesic effect within its accepted dose range, and it can be combined with other opioids.

In 2012, the EAPC (European Association for Palliative Care) guidelines stated for the first time that there were no important differences between morphine and oxycodone when given orally, with a weak recommendation for use of either as a first choice step III opioid for moderate-to-severe cancer pain. Professor Ahmedzai also noted that no randomised study has shown morphine to be superior to any other modern synthetic opioid.

### Opioid (adverse) effects

As there are opioid receptors throughout the body, there is great potential for a wide range of opioid effects. Common opioid effects include constipation, dry mouth, drowsiness, nausea/vomiting, cognitive impairment/hallucinations, itching, urinary retention and respiratory depression. Less recognised effects include endocrine suppression and immunosuppression. An assessment of side effects associated with analgesic medications among patients with multiple myeloma found that those who experienced analgesic-associated side effects had significantly worse health-related QOL scores than those who did not. In addition, it is important to be vigilant for tolerance and hyperalgesia, variable immunomodulation and testosterone suppression in patients receiving long-term opioids.

Factors that need to be weighed when considering opioid therapy for a patient include: i) the stage and likely prognosis of their disease; ii) the severity and likely prognosis of their pain; iii) the possibility of oncological or interventional reduction in pain; iv) their age and general condition/frailty; v) comorbid conditions, particularly organ failure; vi) propensity and tolerance of opioid effects; and vii) concomitant medications (particularly those with sedative properties). A paper from Melbourne (in patients with cirrhosis) provides very good information regarding clinical considerations for use of opioids. In particular, the importance of appropriate evaluation in a given specific environment is covered, as are evaluations of the patients’ overall burden and their treatment status and strategy. It also includes a very useful table summarising the metabolism and pharmacokinetics of various analgesic drugs.

### Constipation

Constipation has been described as one of the commonest and most troublesome opioid effects. It already affects many patients with advanced cancer, and those receiving opioids have a 5-fold greater incidence. Over half of patients receiving long-term opioids require ≥2 types of medications to manage constipation.

Opioids induce constipation via activation of μ receptors, which are present on myenteric and submucosal neurons throughout the entire gastrointestinal tract. They suppress forward peristalsis, increase sphincter tone, increase fluid absorption and reduce intestinal secretions. A systematic review found a lack of high-grade randomised trial evidence for the use of laxatives and rectal treatments for opioid-induced constipation, and all they offer is palliation.

### Novel targeted treatment

A novel targeted approach is to use peripheral gastrointestinal opioid receptor antagonists, while allowing opioids to penetrate the CNS to exert their analgesic effects. One way of achieving this is by combining oxycodone (opioid agonist) with naloxone (opioid antagonist) in a 2:1 ratio in a slow-release preparation. Slow release of naloxone in the gut blocks the opioid effect of oxycodone that causes constipation, and almost all the naloxone that is absorbed is extensively metabolised in the liver with bioavailability of <3%. Meanwhile, oxycodone is absorbed and is around 80% bioavailable.

To investigate this opioid agonist/antagonist combination, a study randomised patients with constipation while receiving opioids for cancer pain to receive daily oxycodone 120mg alone or combined with naloxone 60mg (TARGIN® tablets) for 4 weeks. The results showed a significant improvement in constipation within 1 week, with a 20% reduction in laxative use and no between-group difference for reduction in pain, QOL or adverse events (Figure 3). There was also no evidence of opioid withdrawal due to naloxone during the 4-week randomised phase or in a 6-month extension phase in which all participants received the combination and which showed preserved bowel function and stable pain control. Similar results were seen in another study using higher daily doses of 180mg for oxycodone and 90mg for naloxone in a 24-week extension phase.

**Figure 3.** Effect of oxycodone alone versus in combination with naloxone on bowel function (a) and pain scores (b) in patients with constipation while receiving opioids for cancer pain (Adapted from Ahmedzai SH et al. Palliat Med 2012;26:50–60).

Patients with impaired hepatic function may have higher naloxone concentrations in their systemic circulation due to reduced hepatic metabolism, which theoretically could antagonise the analgesic effects of the oxycodone (or other opioid) and induce withdrawal symptoms. Therefore patients receiving TARGIN should be regularly monitored for deteriorating hepatic function, and if they begin to experience moderate-to-severe hepatic impairment (TARGIN is contraindicated in patients with moderate or severe hepatic impairment), a plan to switch them off TARGIN should be implemented, with a conservative approach recommended for switching to a single opioid formulation.

### Opioid switching

Opioid switching should be considered for:

- patients whose pain is controlled but have intolerable adverse effects
- patients whose pain is not adequately controlled and dose increase is not possible due to the risk of adverse effects
- patients whose pain is not adequately controlled by rapid opioid dose increase, even if adverse effects do not emerge.

For patients who require opioid switching, the equi-analgesic dose for the new agent needs to be calculated, and then reduced by 25–50% to allow for interindividual variability of response and also the phenomenon of incomplete cross-tolerance. These guidelines should also be followed when switching from TARGIN (oxycodone/naloxone) to oxycodone alone, with extra caution exercised when switching patients with any degree of hepatic impairment. Immediate-release opioids may be offered for breakthrough pain over the first 2–3 days until the appropriate dose of the new prolonged-release opioid has been reached.
Professor Ahmedzai talked about anecdotal cases associated with switching from TARGIN to other opioids or vice versa where patients have experienced acute opioid toxicity or withdrawal, suggesting that the dose conversions did not allow for incomplete cross-tolerance. There are also risks associated with switching if current hepatic and renal function has not been evaluated. It is therefore important to always refer to the manufacturer’s prescribing recommendations.

**Important considerations for switching**

- Titratin of TARGIN according to a patient’s pain level with no response should raise the suspicion of underlying hepatic impairment
- Increased pain may not always indicate disease progression
- Check liver function tests if there is suspicion of hepatic impairment
- Do NOT switch to PR oxycodone in a 1:1 equi-analgesic ratio if moderate or severe liver dysfunction is detected
  - Ideally, PR oxycodone should be avoided in advanced liver disease
  - If PR oxycodone must be used, consider a starting dose of <50%, dependent on severity of liver disease
- Switch should reflect current recommended approach according to the Therapeutic Guidelines for Palliative Care

**TARGIN in hepatic impairment**

TARGIN is contraindicated in patients with moderate-to-severe hepatic dysfunction, and should be used with caution in patients with mild hepatic impairment or renal impairment. For naloxone, there is little or no discernible difference in systemic naloxone concentrations between patients with healthy livers and those with mild hepatic impairment, but a large difference between those with mild impairment and those with moderate or severe impairment. In terms of plasma concentrations, a 10mg oral dose of naloxone in patients with moderate-to-severe hepatic failure is equivalent to giving them an intravenous bolus of 0.4mg, which is what is usually used clinically to reverse an opioid overdose. Renal impairment has no discernible effect on naloxone concentrations.

The function and capability of the liver for substance metabolism is increasingly impaired by malignancy progression, due to reductions in general hepatic blood flow, decreases in hepatocyte number or function and/or port-systemic shunting. Other factors that can impair hepatic function to be considered include oxygen-sensitive CYP450 system, reduced protein production (e.g. albumin, which affects drug binding) and a range of other clinical symptoms (e.g. oedema, ascites, hepatic encephalopathy and hepatorenal syndrome). Professor Ahmedzai described two hypothetical cases to illustrate the importance of assessing hepatic impairment when treating patients with TARGIN.

**Case 1: TARGIN used in progressive hepatic failure**

The first case described was a 67-year-old man with stage 4 bowel cancer who was experiencing pain due to vertebral metastases, which had been well controlled with oxycodone/naloxone 20mg/10mg. When the effectiveness of analgesia decreased after 8 weeks, the dose was doubled, resulting in partial benefit, but further loss of analgesia was reported 2 weeks later. He was admitted after referral to a palliative care specialist, and was switched to an equivalent dose of PR oxycodone. Within 24 hours, narcosis had occurred, and he required several doses of intravenous naloxone. Professor Ahmedzai went on to explain this sequence of events was the result of the development of subclinical hepatic impairment due to silent hepatic metastases. At the time of admission, his liver enzyme levels had become elevated, although his bilirubin level remained normal and no ascites or encephalopathy was present. His exposure to the increased systemic naloxone penetration during the prior 2 weeks had led to gradual reversal of analgesia, and the equi-analgesic switch to oxycodone resulted in acute opioid toxicity.

**Case 2: Starting TARGIN in patient with hepatic impairment**

Case 2 was a 42-year-old female immunotherapy trial participant with metastatic (bone, lung and liver) melanoma who had been receiving PR morphine plus laxatives. After developing increasing pain and fatigue, she withdrew from the trial and was referred to palliative care. She was started on oxycodone/naloxone 20mg/10mg, and the following day she experienced a major pain crisis requiring hospital admission. Professor Ahmedzai commented that while it could be reasonable to switch her from morphine to TARGIN due to intolerable constipation, the equi-analgesic conversions had failed to take her significant hepatic impairment into account, and the oxycodone was effectively reversed by the high level of naloxone penetration into the CNS.

**Measuring hepatic function**

In terms of drug elimination capacity, no adequate well-established marker for hepatic function currently exists. The Child-Pugh score is the most widely used means of evaluating hepatic function, but it was not developed to predict drug elimination capacity, so it can only provide general guidance for dosage adjustments. In the efficacy trials for TARGIN, simple exclusion criteria relevant to liver function were used as an alternative to the Child-Pugh score. Participants with an AST, ALT, ALP or GGT level ≥3 times the upper limit of normal or a total bilirubin level ≥1.5 times the upper limit of normal were excluded from the trial to ensure that their pain control was not compromised.

The manufacturer of TARGIN tablets is aware of the risks in patients with hepatic impairment and is actively monitoring the situation. A search of its international drug safety database for reports describing hepatic impairment found that <1% were due to overdose and only 0.7% were associated with drug withdrawal syndrome.

**Lessons from anecdotal cases of adverse events reported during TARGIN use**

- Follow manufacturer’s recommendations
- Regularly monitor hepatic and renal function
- Exercise caution in patients with mild hepatic function
- Do not use in patients with moderate or severe hepatic impairment
  - Plan to switch to buprenorphine or fentanyl
- Do not use with methadone
  - Interferes with naloxone metabolism
- Be vigilant for opioid-induced hyperalgesia

**Pyramid model for multimodal management of cancer pain**

The importance of multimodal analgesia for the spectrum of patients who experience or have experienced cancer is increasing with the wide range of currently available pharmacological agents and emerging drugs in the pipeline, as well as the various interventional and non-pharmacological approaches. Professor Ahmedzai presented a modern multimodal approach for managing pain in patients with cancer, based on a pyramid (Figure 4). In this model, oncologists look after the cancer treatment, supportive care is provided by the appropriate specialists in pain management, psychology, rehabilitation and nursing care, and palliative care is provided in advanced disease and at end of life. He also posed the challenge whether the role of palliative care can be extended into supportive care and also to cancer survivors, who are attempting to return to a normal daily life, and have similar pain management requirements to other cancer patients.

**Figure 4.** 21st century pyramid model for a multimodal approach for pain in patients with cancer (Adapted from Ahmedzai SH. Lancet 2001;357:1304–5)
Take-home messages
- Supportive care makes excellent cancer care possible
- Pay attention to cancer-related pain at all stages
  - Postsurgery, during chemotherapy, survival, end of life
- Both supportive and palliative care have potentially major roles in survivors as well as end-of-life patients
- Adopt a holistic approach
  - Consider patient’s age, family situation, comorbidities, organ function, polypharmacy
- Employs multimodal analgesia for smart, targeted pain management
  - Maximum efficacy, minimum adverse effects
- Follow manufacturer’s recommendations

References
19. TARGIT Drug Safety Database, Mundipharma Ltd. [Full text]