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REVIEW

Clinical Management of Pain in Advanced Lung Cancer

Claribel P.L. Simmons[1], Nicholas MacLeod[1] and Barry J.A. Laird[1,2]

[1]Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh, UK. EH4 2XR. [2]European Palliative Care Research Centre (PRC), NTNU, Trondheim, Norway. Corresponding author email: barry.laird@ed.ac.uk

Abstract: Lung cancer is the most common cancer in the world and pain is its most common symptom. Pain can be brought about by several different causes including local effects of the tumor, regional or distant spread of the tumor, or from anti-cancer treatment. Patients with lung cancer experience more symptom distress than patients with other types of cancer. Symptoms such as pain may be associated with worsening of other symptoms and may affect quality of life. Pain management adheres to the principles set out by the World Health Organization's analgesic ladder along with adjuvant analgesics. As pain can be caused by multiple factors, its treatment requires pharmacological and non-pharmacological measures from a multidisciplinary team linked in with specialist palliative pain management. This review article examines pain management in lung cancer.

Keywords: analgesia, lung cancer, pain management

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Introduction

Lung cancer is the most common cancer in the world with 1.61 million new cases diagnosed every year.[1] Pain is the most common symptom in cancer patients in general as it also is for lung cancer specifically.[2] The majority of patients with lung cancer have an advanced stage of the disease at clinical presentation. Symptoms may result from local effects of tumor, from regional or distant spread, or from distant effects not related to metastases (paraneoplastic syndromes).

Patients with lung cancer experience more symptom distress than patients with other types of cancers.[3] Symptoms such as pain may be associated with worsening of other symptoms including depression and fatigue,[4] and may affect quality of life.[5] It has been demonstrated that early palliative care intervention, including good symptom management, improves quality of life and may increase survival.[6] Pain resulting from lung cancer can be classified by two methods: either by the type of pain or according to the origin of the pain. The location or origin of the pain may determine the type of pain experienced. Pain can also be affected by the histological type and biological behavior of the lung cancer present.[7] Pain in patients with lung cancer can be differentiated according to its origin, namely intra-thoracic or extra-thoracic, the latter of which may be the consequence of cancer complications.

Pain

Definition

Pain is defined as an 'unpleasant sensory or emotional experience associated with actual or potential tissue damage, or described in terms of such damage.'[8] It impacts greatly upon physical and psychosocial functioning. Pain is often multi-factorial in origin; therefore it follows that its management needs to be multi-disciplinary in order to address each aspect of pain.

Incidence

Cancer pain can be characterized by two syndromes, namely acute pain and chronic pain syndromes. The acute cancer pain syndrome is usually due to a definable acute injury or illness.[9] This could be secondary to cancer disease events such as hemorrhage into a tumor, bone pain secondary to a pathological fracture, visceral pain from acute intestinal obstruction or perforation of a viscous. Acute cancer pain has a definite onset and its duration is limited and predictable. It is associated with clinical signs of sympathetic over activity such as tachycardia, hypertension, sweating, pupillary dilatation and pallor.

Chronic cancer pain can result from the same causes as acute pain but is differentiated by its longevity. In the UK, this is termed background pain and is defined as 'constant or continuous pain of long duration'.[10] Background pain refers to pain persisting for more than 12 hours per day. It often has a gradual or ill-defined onset with the potential to progress in severity. It is estimated that approximately 75% of cancer patients live with chronic pain, this pain is secondary to nociceptive or neuropathic syndromes which represent direct effects of the cancer.[11] Chronic pain must be approached differently with the dual aim of relieving the pain as well as preventing further recurrences of pain.

Many patients develop flares of pain, despite reporting acceptable analgesia for the majority of the day. The term given to this type of pain is breakthrough cancer pain (BTCP). Breakthrough pain has been defined as a 'transitory exacerbation of pain in patients receiving chronic opioid therapy with acceptable analgesia.'[12] Patients may be severely limited by breakthrough pain, which impacts greatly upon patients' quality of life and causes psychological burden.[13,14] Breakthrough cancer pain can either have rapid or gradual onset and can vary in duration from a few minutes to a few hours. BTCP may be spontaneous in onset with no known precipitant, or may be incident in nature with an identifiable precipitant, such as movement, or other triggers specific to the patient.[15] The transitory nature of this pain poses challenges for management. Analgesia for breakthrough cancer pain therefore is required to mimic the profile of these episodes with rapid onset and short duration.

Pathophysiology

Cancer cells and the subsequent effects of tissue damage cause the production of noxious substances which stimulate the peripheral nerve endings of the C and A-delta primary afferent fibers. Stimulation of these fibers results in the lowering of activation thresholds, the recruitment of quiescent nociceptors, and the activation of NMDA-receptor-channel complex leading to dorsal horn sensitization. This process results in

pain generation and maintenance. The changes in the dorsal horn therefore need to be targeted to relieve pain and prevent pain recurrence.[16]

Physiological pain is termed nociceptive pain. This is due to stimulation of the sensory nociceptors, located in tissues, when damaged. Somatic pain, from the skin and superficial structures, is usually well localized and can be described as aching, sharp, throbbing or pressure-like. Visceral pain, from deep structures, is less well localized. It often presents as referred pain and may be described as a deep, aching pain.[16]

Neuropathic pain is caused by peripheral or central nervous system injury. It is often described as burning, shooting and may be associated with altered sensation. Neuropathic pain is associated with a loss of opioid receptors in sensory afferents and an increased release of glutamate (a neuro-excitatory amino-acid) in the dorsal horn. Activation of glial cells, neuroma formation, increase in sodium channels, and calcium channel activation results in sensitization of the dorsal horn and higher centers. This resultant hyper excitability causes spontaneous pain, hyperalgesia, and allodynia in areas adjacent to the nerve damage. An injured sensory nerve may produce absent or abnormal sensation. These changes thus lead to a variable response to opioids.[2,17]

Causes of pain in advanced lung cancer

The three main causes of pain in patients with advanced lung cancer are skeletal metastatic disease (34%), pancoast tumor (31%) and chest wall disease (21%).[18]

In order to manage pain in lung cancer patients it is essential to understand and use general principles of pain management. The analgesic options include opioids which may be combined with adjuvant analgesics for optimal palliation of pain. Pain refractory to general management may require specialist skills and techniques.

Principles of Pain Management

The World Health Organization's (WHO) Analgesic Ladder for Cancer Pain Relief provides a stepwise approach to managing pain in patients with cancer.[19] The WHO analgesic ladder is simple to follow and applicable to all pain, regardless of its etiology. Step 1 advises the use of paracetamol or a non-steroidal anti-inflammatory drug. If pain is not satisfactorily controlled, it is appropriate to move to Step 2 Analgesia which includes the use of weak opioids, usually codeine. In practice, patients with severe pain usually need Step 3 Analgesia, the use of strong opioids. Morphine is the usual first-line Step 3 opioid however there are many alternatives to morphine now.[20] At any step, in the analgesic ladder adjuvant analgesics can be used.

There have been concerns about the life shortening effects of opioids when considering administration of these drugs for symptom alleviation at end of life. One study has shown that there was no significant survival difference between those patients who were taking opioids and those who were not.[21] It also showed that patients with lung metastases required lower doses of opioids, compared to patients with spinal metastases. Increased age was also associated with decreasing opioid doses.

Commonly used analgesics and doses are given in Table 1.

Opioids

Morphine is the usual first line strong opioid employed to manage cancer pain. Morphine's effects are mediated by specific opioid receptors both within the central nervous system and peripherally. Morphine's main peripheral action is on smooth muscle. However, in the presence of inflammation, the normally silent peripheral receptors become activated.[22] Morphine is mostly metabolized in the liver via glucoronidation yielding the metabolites morphine-6-glucuronide (M6G) and morphine-3-glucuronide (M3G). M6G has a greater analgesic potency than morphine itself while M3G is a non-analgesic. Both glucuronides accumulate if renal failure occurs, resulting in prolonged duration of action and greatly increased risk of severe side effects, namely neurotoxicity and respiratory depression.

Opioids can be administered orally, intravenously, subcutaneously, sublingually, intrathecally, and topically depending on its indication and available routes for administration. It has immediate release and sustained release preparations for ease of use. Both immediate and sustained release preparations have equivalent analgesic effects.[23,24] When opioids are prescribed, a laxative should be prescribed concurrently to alleviate the onset of opioid induced constipation (OIC).

The main route of administration of morphine is orally. Ideally two types of formulation are required: normal release (for dose titration initially

Table 1. Common analgesics for pain in patients with lung cancer.

Analgesic	Name	Typical starting dose (oral)	Maximum dosage
Acetaminophen	Paracetamol	1 g qds	4 g daily
Non-steroidal anti-inflammatory	Ibuprofen	400 mg tds	2.4 g daily
Weak opioid	Codeine phosphate	30 mg–60 mg qds	240 mg daily
Strong opioid (Dose requirements should be individually titrated according to pain, analgesic response to pain and side effects)	Morphine	10 mg every 4–6 hours for opioid naïve patients	
	Oxycodone	5 mg every 4–6 hours	
	Hydromorphone	1.3 mg every 4–6 hours (immediate release hydromorphone capsules are only available in strengths of 1.3 mg and 2.6 mg)	(Modified release hydromorphone capsules are only available in strengths of 2 mg, 4 mg, 8 mg, 16 mg and 24 mg)
Tricyclic antidepressants	Amitriptyline	10 mg nocte	75 mg (neuropathic pain)
	Nortriptyline	10 mg nocte	75 mg (neuropathic pain)
	Imipramine	10 mg daily	75 mg (neuropathic pain)
	Clomipramine	10 mg daily	75 mg (neuropathic pain)
Serotonin and noradrenaline reuptake inhibitor	Duloxetine	60 mg od	120 mg
Selective serotonin reuptake inhibitors	Citalopram	20 mg	60 mg
Alpha—2—adrenergic agonists	Clonidine	50 mcg bd	150 mcg
Anticonvulsants	Gabapentin	300 mg gradually titrated upwards, given in divided doses, usually tds	3.6 g
	Pregabalin	75 mg bd	300 mg
	Carbamazepine	100 mg od	1.6 g
	Clonazepam	500 mcg nocte	4–8 mg
NMDA receptor antagonists	Ketamine	10 mg qds	400 mg
Corticosteroid	Dexamethasone	4–8 mg od	Varies according to indication

Abbreviations: od, once daily; bd, twice daily; tds, three times daily; qds, four times daily; nocte, night-time.

and breakthrough analgesia) and modified release (for maintenance therapy).[20] The starting dose will be determined by previous analgesic treatment.

Morphine, like other strong opioids is titrated until the desired analgesic benefit is achieved.

Oxycodone

Oxycodone hydrochloride is a semi-synthetic congener of morphine. It may be useful in patients with renal failure due to the lack of detectable clinically relevant active metabolites. The equi-analgesic dose of oral oxycodone is between half and two-thirds that of oral morphine.[25]

Hydromorphone

Hydromorphone is a semi-synthetic opioid agonist with a rapid onset and shorter duration of action than morphine. It is a potent mu-selective agonist similar to morphine and between 5 and 10 times as potent.[20] There are no major differences between hydromorphone and morphine concerning efficacy and adverse effects when comparing equivalent dosages.[26]

Methadone

Methadone is a synthetic opioid with mixed properties. It is a mu opioid receptor agonist, possibly a delta opioid receptor agonist, an NMDA-receptor channel blocker, and a presynaptic blocker of serotonin re-uptake. It has no known active metabolites, low tolerance development, and long duration of analgesia.[27] Its half-life is long and unpredictable and therefore should be prescribed under specialist advice.

Fentanyl

Fentanyl is a pure mu agonist. It is generally not administered orally due to it undergoing extensive first-pass metabolism. Preparations which are absorbed through the oral or nasal mucosa are,

however, available. It is lipophilic which facilitates absorption through the skin. Trans-dermal administration is useful for patients with stable pain and stable opioid requirements. Fentanyl lacks active metabolites and is useful in patients with renal failure.

Opioids for breakthrough cancer pain

In BTCP which is gradual onset (approximately 30 minutes) and lasts longer than one hour, standard immediate release opioid preparations (eg, oral morphine) are sufficient. In BTCP which is rapid onset (5–10 minutes) and short duration (less than 60 minutes), fentanyl is a good choice of opioid. A number of preparations exist which are either absorbed through the nasal or oral mucosa. Due to it being lipophilic, it is rapidly absorbed through the oral or nasal mucosa enabling it to have a quick onset of action. Fentanyl preparations specifically developed for BTCP exist in several preparations including a lozenge, a soluble film, a buccal tablet, and a nasal spray. There is a lack of evidence comparing fentanyl products for BTCP and there is no consensus on the correct dose when prescribing rapid acting opioids for BTCP.[28] Each fentanyl product should be titrated to the most effective dose that provides adequate analgesia with minimal side effects.

Opioid induced constipation

One of the most commonly encountered side effects from opioids is OIC. A meta-analysis of 11 placebo-controlled randomized studies in non-malignant pain showed that OIC affects an average of 41% patients taking an oral opioid for up to eight weeks.[29] The cause of OIC is multifactorial. Opioids interfere with normal gastrointestinal motility by delaying transit, stimulating non-propulsive motility, segmentation and tone, and stimulation of sphincters such as the pylorus and ileocaecal sphincter through their effect on enteric neurons. Opioids also stimulate the absorption of fluids, mainly by delayed transit and by stimulating mucosal sensory receptors that activate a reflex arc that facilitates further fluid absorption.[30–32]

Some opioids are less constipating than others. Tapentadol hydrochloride is a μ-opioid agonist that also inhibits norepinephrine reuptake.[33] It has been shown to have a more favorable gastrointestinal side effect profile than the classic μ-opioid receptor agonist oxycodone.[34] Fentanyl is also less constipating than equi-analgesic doses of morphine. Transdermal fentanyl was associated with a significantly lower use of laxatives compared to oral morphine in one study.[35] Another study comparing transdermal fentanyl with sustained release oral morphine demonstrated a patient preference for transdermal fentanyl. The reasons given by the patients included better analgesia, less constipation, and an enhanced quality of life with transdermal fentanyl.[36]

Most patients taking an opioid require a laxative to counteract the OIC. These include osmotic and stimulant laxatives. An adjunct to existing laxative therapy for patients with OIC receiving palliative care is methylnaltrexone. Methylnaltrexone is a quaternary ammonium derivative of naltrexone, an opioid antagonist similar to naloxone, but it is less lipid soluble, so less likely to cross the blood-brain barrier. Methylnaltrexone blocks acute morphine-induced delay in orocecal transit time without affecting analgesia or causing central opioid withdrawal symptoms.[37] It is administered as a subcutaneous injection and contraindicated in cases of known or suspected gastrointestinal obstruction.

Naloxone itself has a low systemic bioavailability. The oral fixed-ratio combination of oxycodone prolonged-release and naloxone prolonged-release has been shown to be superior to oxycodone prolonged-release alone, offering effective analgesia while significantly improving OIC. One study demonstrated a significant improvement in Bowel Function Index scores with the oral fixed-ratio combination of oxycodone prolonged-release and naloxone-prolonged release, without compromising the analgesic efficacy of the oxycodone component.[38]

Opioid toxicity

There is no "top dose" of morphine or other strong opioids; however the dose limits may be hit by opioid related side-effects. When patients start to demonstrate symptoms of opioid related toxicity (vivid dreams, nightmares, pseudohallucinations (shadows at the periphery of the field of vision), hallucinations, somnolence, cognitive impairment etc.) then they have reached the limits of tolerance to an individual opioid. In such situations, if analgesia has been achieved, the dose of strong opioid can be reduced. If analgesia has not been achieved, then often patients are switched from one opioid to another. The rationale for this practice is that different opioids work

on different subsets of opioid receptors or there may be a genetic predisposition to different opioids. In such cases, following an opioid switch, analgesia may be achieved at a lower equi-analgesic level or side-effects of the new opioid may be better tolerated.[39]

Adjuvant analgesics

Adjuvant analgesics are drugs whose primary purpose is not analgesia, but have analgesic benefits. In practical terms, the majority of common adjuvant analgesics are used for pain management. Adjuvant analgesics are often first line therapy for certain types of pain. Antidepressant analgesics are most commonly prescribed for neuropathic pain.[40] The majority of the evidence for their use is based on patients with chronic pain. They are thought to enhance availability of monoamines at synapses within neural pathways that are part of the descending pain modulating system. The most important modes of action include inhibition of norepinephrine reuptake, and serotonergic and dopaminergic effects. Early use of antidepressants as adjuvant analgesics is also justified when pain is accompanied by depression.

Tricyclic antidepressants

Tricyclic antidepressants alone or in combination with other adjuvant analgesics, have been shown to be effective in treating neuropathic pain.[41] Tricyclic antidepressants include tertiary amines (amitriptyline) and secondary amines (nortriptyline and desipramine). Subtypes of tricyclic antidepressants inhibiting both serotonin and noradrenaline reuptake (amitriptyline, imipramine, clomipramine) have a slightly greater analgesic effect compared to the more selective inhibitors for noradrenaline reuptake (desipramine, nortriptyline, maprotiline). However, the newer secondary amines have fewer side effects. Care must be taken when prescribing tricyclic antidepressants which are contraindicated in patients with ischaemic heart disease and glaucoma. Caution must be exercised when prescribing them to patients at risk of orthostasis such as patients with autonomic neuropathy or elderly patients. Non tricyclic antidepressant drugs are generally better tolerated and safer to use.

Selective norepinephrine reuptake inhibitors

Serotonin norepinephrine reuptake inhibitors (SNRIs) have been proven to have analgesic efficacy. Mainly non-cancer populations of patients with diabetic neuropathy have been examined to ascertain the analgesic effects of antidepressants. This is the case for SNRIs including duloxetine.[42] There have been no comparative trials within the SNRI class and there are no clinical trials in patients with cancer pain.

Serotonin selective reuptake inhibitors

Serotonin selective reuptake inhibitors have a favorable side effect profile however there is minimal evidence of analgesic efficacy. Studies have suggested benefits for paroxetine and citalopram.[43,44] Studies have shown analgesic benefit from venlafaxine, in particular for painful polyneuropathy.[45]

Alpha—2 adrenergic agonists

Clonidine has been studied in non-malignant neuropathic pain, however its side effects are poorly tolerated in elderly patients.[46] Spinally administered Clonidine has analgesic properties in patients with cancer pain and is more efficacious for neuropathic than nociceptive pain.[47] There is less evidence for tizanidine which has been approved as an anti-spasticity agent. It has been shown to have analgesic efficacy in myofascial pain syndrome,[46] and the prophylaxis of chronic daily headache.[48]

Anticonvulsants

Anticonvulsants have been extensively studied in the management of neuropathic pain.[49] Both gabapentin and pregabalin have been shown to be effective in neuropathic pain management. They are excreted by the kidneys and rarely have drug-drug interactions. Both are chemical analogues of GABA but do not act as a GABA-receptor agonist, acting instead at the alpha-2-delta voltage gated subunit of the calcium channel in the dorsal horn. Gabapentin is used for central and peripheral neuropathic pain.[50] Pregabalin is also licensed for peripheral and central neuropathic pain and has been studied in diabetic neuropathy, post herpetic neuralgia, and central pain due to spinal cord injury.[51–53]

Other anticonvulsants used for analgesia include carbamazepine, sodium valproate, and phenytoin. These drugs have increased side effect profiles which must be kept in mind when prescribing for patients with cancer. Clonazepam is often used for patients with neuropathic pain however there is a paucity of

evidence to support its analgesic efficacy.[54] There is also limited evidence of analgesic benefits from benzodiazepines; however, in clinical practice their use is justified by the coexistence of anxiety with pain.

Other analgesics

NMDA receptor antagonists

The N-methyl-D-aspartate (NMDA) receptor is involved in CNS changes that underlie chronic pain and modulate opioid mechanisms, specifically tolerance.[55] Ketamine acts as an NMDA antagonist and may be useful in some pain types, such as neuropathic pain.[56] Ketamine is a parenteral general anesthetic that can be used in sub-anesthetic doses to relieve pain, particularly in opioid-tolerant patients.[57] This should only be administered under specialist advice. The evidence for other NMDA receptor antagonists such as amantadine, in cancer pain, is limited.

Corticosteroids

Corticosteroids may be a useful adjunct in cancer pain syndromes. These include neuropathic pain, bone pain, headache secondary to raised intracranial pressure, pain secondary to organ capsule distension, pain due to obstruction of a hollow viscus, and pain secondary to lymphedema. Dexamethasone is commonly used due to having less mineralocorticoid effects and its long half-life. Other glucocorticoids such as prednisolone and methylprednisolone may be used. The side effects of steroids must be carefully considered when prescribing for patients with cancer and the lowest dose providing symptomatic relief should be sought.

Cannabinoids

Cannabinoids have potential therapeutic value as analgesics,[58] and there are several clinical trials in progress looking at the use of sublingual cannabinoids in patients with cancer pain. The oro-mucosal spray Sativex is currently unlicensed in the UK for cancer pain however it is approved in some other countries for the treatment for neuropathic pain due to multiple sclerosis and as an adjunctive analgesic in patients with advanced cancer.[59]

Topical analgesics

Topical preparations of analgesics are useful in pain which is localized to a defined area of skin. Topical preparations have minimal systemic side effects and are well tolerated. Topical lidocaine plasters containing 5% lidocaine are currently licensed for the relief of post-herpetic neuralgia, but have been used in patients with cancer.[40] Lidocaine can also be prepared as a topical cream for application under an occlusive dressing.[60] Topical capsaicin cream is also used for neuropathic pain.[61] Capsaicin affects the synthesis, storage, transport and release of substance P in nociceptive fibers. It comes in varying strengths, the stronger of which are licensed for intermittent application.

The high potency 8% capsaicin topical patch is licensed for treating patients with post herpetic neuralgia. It is licensed in Europe for the treatment of peripheral neuropathic pain in non-diabetic adults. In controlled trials it has demonstrated pain relief for up to 3 months with a single 30 minute or 60 minute application.[62]

Interventional Procedures

Prior to embarking on interventional procedures, the likely benefits and potential risks need to be considered and compared with those of continuing with pharmacological management. Typically interventional management of cancer pain does not substitute for other modalities but can improve pain control and allow for a reduction in systemic medications and their side effects. Where there are unacceptable side effects from oral or parenteral opioids, then invasive methods may be preferred.

Most interventional procedures involve interruption to or modification of nerve conduction with the aim of diminishing pain from a target area. The procedures may be considered to be non-destructive or destructive. In non-destructive procedures, nerve blockade or modulation is achieved by the deposition of reversible pharmacological agents. These may be given by bolus injection. Alternatively catheter placement allows for the continuous delivery of pharmacological agents. Placement can be adjacent to peripheral or autonomic nerves or placement may be in the spinal canal with the aim of modulating neuronal activity of the spinal cord.

Peripheral nerve blocks have a limited role in cancer pain management. There is no controlled trial evidence but case studies describe pain relief for short periods with the local anesthetic blockade of the regional nerve supply to a target area. Nerve blocks

may be useful for acute cancer pain such as intercostal nerve blockade for a pathological rib fracture. In order to prolong the analgesic effect, an infusion of local anesthetic adjacent to a neural plexus (eg, brachial plexus) or other nerves may be used.[63,64]

Neurolytic blockade of peripheral nerves (eg, intercostal neurolysis) produces short term relief of pain and has a median duration of 3 weeks.[65] Other studies have reported an incidence of neuritis with neurolytic blockade and advise that neurolytic agents be limited to those with a short life expectancy.[66]

Neuroaxial blocks may be epidural or intrathecal. An epidural neuroaxial block of local anesthetic and steroid can provide temporary pain relief where a vertebral metastasis is associated with nerve compression. A neuroaxial saddle block can be used for perineal pain of somatic origin (more common in advanced pelvic cancer) especially where bladder and bowel function are already compromised. For patients who require prolonged analgesia, a neuroaxial infusion may be administered. These are considered for patients with advanced cancer whose pain cannot be controlled with systemic medication, or the use of systemic medication is limited by unacceptable side effects at doses below those required to give adequate pain relief. A neuroaxial infusion, either epidurally or intrathecally, gives good control in the majority of cases.[67] The most effective drugs to infuse neuroaxially are opioids. Patients who are unresponsive to large doses of systemic opioids are unlikely to respond to spinal opioids. Other drugs that appear to be effective spinally include local anesthetics (Bupivacaine), alpha-2 agonists (Clonidine), and ziconotide. The procedure for inserting a neuroaxial infusion is undertaken in centers experienced in these specialized techniques and their aftercare. There are different neuroaxial systems ranging from percutaneous lines to fully implanted programmable pumps. The fully implanted systems carry less risk of infection and have lower maintenance requirements but the operation is more prolonged.[68] Costing of neuroaxial infusions currently suggests that implanted systems are more cost effective than the percutaneous system after 3 months.[69] There is evidence from randomized controlled trials of improved pain relief and less drug related side effects compared with medical therapy for fully implanted systems.[70] A percutaneous catheter, injection portal, or fully implanted system can be inserted; however the device is selected according to individual patient factors including their prognosis.

The common causes of intrathoracic pain in malignancy are non-small-cell lung cancer and mesothelioma. This pain is often poorly localized in respect to the primary tumor site and in mesothelioma pain resulting from local infiltration of the intercostal nerves may become a prominent feature. Intercostal nerve blocks can be very effective in certain patients. More aggressive anesthetic interventions such as intraspinal analgesia or cordotomy may be required especially in mesothelioma.

Anterolateral cordotomy can be undertaken as a percutaneous or open procedure, involving intervention on the side of the spinal cord opposite to that of the pain to ablate the spinothalamic tract fibers. Consequently it reduces the sensation of touch and temperature in addition to pain. While percutaneous cordotomy can only be performed in the cervical area, the spinothalamic fibers can be divided by open operation in the thoracic cord. This avoids any risk to respiration and to the upper limbs when the pain is below the waist. Patients with severe unilateral pain arising in the thorax or lower extremities are most likely to benefit from cordotomy.[71] Impressive results have been observed in patients with chest wall pain.[72] The percutaneous technique is generally preferred; open cordotomy is usually reserved for patients who are unable to lie in the supine position or are not able to undergo a percutaneous procedure.[73]

Chest wall pain due to tumor invasion or somatic and neural structures can also be treated with rhizotomy, the segmental or multi-segmental destruction of the dorsal sensory roots. Rhizotomy is achieved by surgical section, chemical neurolysis, or radiofrequency ablation and can be an effective method of pain control with refractory localized pain syndromes. Chemical rhizotomy produced by the instillation of a neurolytic solution (eg, phenol) into either the epidural or intrathecal space can be performed at any level up to the mid-cervical regions, above which the spread of neurolytic agent to the medullary centre carries an unacceptable risk of cardio respiratory collapse.[74]

Interpleural analgesia has also been used to rapidly reduce acute exacerbations of cancer pain via bolus injection or continuous infusion. It may be tried when traditional neural blockade techniques fail either

due to inability to deliver sufficient drug volume due to tumor spread or altered anatomy. It has also been used to treat post thoracotomy pain. It should be noted however that currently epidural analgesia has emerged as the analgesic technique of choice for thoracotomy pain. Interpleural analgesia can be used as a valuable diagnostic tool for predicting the efficacy of permanent neurolytic block. Interpleural analgesia involves the administration of local anesthetic agents through a catheter positioned inside the pleural cavity to anaesthetize intercostal nerves. The mechanism of action appears to be diffusion across the parietal pleura. The catheter lies between the parietal and visceral pleura. Complications include pneumothorax and local anesthetic toxicity.[75,76] Several studies, however, have shown limited or no improvement in analgesia with interpleural analgesia.[77–79] Paravertebral blocks can be used for chest wall pain. They are typically used to relieve acute chest wall pain from rib fractures and to manage acute and chronic post thoracotomy pain.

Painful pathological fractures of vertebra that do not respond to the conservative treatment of medication or steroid epidurals can be considered for cemented vertebroplasty. Open studies in myeloma and metastatic cancers report pain relief is often complete in around 80% of patients.[80] Percutaneous cementoplasty involves the injection of acrylic bone cement into malignant bone cavities to relieve pain and stabilize the bone. This is useful when treating bone pain from pelvic bone metastases which are not responding to pharmacological management.[81]

Challenges in Pain Management in Lung Cancer

Understanding and practicing the general principles of pain management is paramount to managing pain in patients with advanced lung cancer. However there are disease complications specific to patients with lung cancer which cause severe pain and necessitate the use of specialist therapies or techniques to palliate symptoms including pain—Table 2.

Bone metastases

Approximately 20% of patients with non-small cell lung cancer (NSCLC) have bone metastases at presentation of the disease.[82] In small cell lung cancer (SCLC) bone metastases are present in up to 40% of patients.[82] Pain caused by bone metastases has multiple causes. Periosteal inflammation and elevation is the most common mechanism of pain from bone metastases. Lung cancer metastases to bone are predominately lytic. Cancer induced bone pain has been shown to have unique characteristics and is a complex pain state. Sensory and sympathetic neurons are present within the bone marrow, mineralized bone and periosteum and all these compartments are affected by tumor cells. Cancer induced bone pain is thought to arise via the activation and ultimately destruction of the primary afferents within bones. Metastatic bone pain is therefore complex to manage due to nociceptive, neuropathic and visceral stimulation overlapping.[83,84]

Table 2. Common causes of pain in patients with lung cancer.

Intra-thoracic causes of pain	Extra-thoracic causes of pain
• Chest pain ○ Pleural invasion ○ Chest wall invasion ○ Obstructive pneumonitis ○ Pulmonary embolus ○ Tumor invasion ○ Costopleural syndrome	• Metastasis ○ Bone ○ Liver ○ Brain • Hypertrophic osteo-arthropathy

The gold standard treatment for pain due to bone metastases is radiotherapy.[85] Evidence suggests that single fraction treatment is as effective as fractionated therapy.[86–88]

If a metastasis occurs in a weight bearing bone, prophylactic surgical stabilization should be considered before a pathological fracture occurs.[89] Post-operative radiotherapy is recommended regardless of the type of surgical procedure chosen for bony metastases.[90]

Bisphosphonates have assumed an important role in the treatment of patients with bone metastasis. They prevent bone resorption at sites of bone remodeling. Zoledronic acid has been shown to be effective treatment for bone metastasis in patients with lung cancer.[91] It has also been shown to prevent skeletal related events such as pathological fractures, spinal cord compression, hypercalcaemia or pain requiring surgery.[92] In a study of NSCLC, patients treated with zoledronic acid had a significantly reduced incidence of skeletal related events.[93] Intravenous radioisotope infusion can also be used to manage pain from bony metastases and is

especially useful in patients with widespread bony metastases.[94]

Chest pain

Chest pain is a frequent and disabling symptom, worsening with disease progression and is present in approximately 20% of patients presenting with lung cancer.[95] Pain is frequently on the ipsilateral chest as the tumor site. It should be treated using the principles described above, however often requires radiotherapy to palliate pain due to destruction of bone or surrounding tissue.

Patients with chest wall pain due to tumor invasion or neurolysis of intercostal nerves, chemical rhizotomy (injection of small volumes of a neurolytic agent into the epidural or intrathecal space) may provide significant relief for a period of time. It is exceedingly rare for someone to need this and one survey reported only 16 out of 1205 patients required intra-spinal therapy to control pain.[96] (See section on interventional procedures)

Costopleural syndrome

Mesothelioma is typically present with chest pain which may be pleuritic, lateralized, dull or diffuse. It typically progresses relentlessly during the course of mesothelioma and is often difficult to control. In mesothelioma this syndrome is referred to as a 'costopleural syndrome'. The pain frequently has neuropathic components due to entrapment of intercostal thoracic, autonomic or brachial plexus nerves.[97]

Percutaneous cervical cordotomy has been proven to provide relief of pain in patients with costopleural syndrome.[97] This procedure interrupts the spinothalamic tract at C1/2 causing a contralateral loss of pain perception below the level of the lesion.[98] Complications of cordotomy include thermo-anesthesia, troublesome dysesthesia and persisting motor weakness. One study reported a reduction in pain in 83% of patients following this procedure and 38% were able to stop opiate completely[99] (See section on interventional procedures).

Liver metastases

Metastases to liver frequently cause right upper quadrant abdominal pain. This pain is secondary to stretching of the liver capsule either due to liver enlargement which may be secondary to metastatic lesions or hemorrhage into the liver from a metastatic deposit resulting in pain. Diaphragmatic irritation may result in referred pain to the ipsilateral shoulder. Analgesic options for this include corticosteroids to reduce edema, swelling and inflammation.

Brain metastases

Brain metastases from NSCLC occurs in approximately 33% of patients,[100] whilst 10% of patients with SCLC present with brain metastases at the time of diagnosis. It is reported that 50% of patients with SCLC have brain metastases at 2 years.[101] Treatment of pain involves reducing cerebral edema if present, with a corticosteroid (Dexamethasone). Alternatively headaches can be managed with radiotherapy. Other options for treating brain metastases include surgical resection, stereotactic radiosurgery, or chemotherapy.

Malignant pleural effusions

A malignant pleural effusion can also be a source of pain, in addition to causing symptoms of dyspnoea and cough. Thoracocentesis is recommended for symptom relief and pleurodesis should be performed should the pleural effusion recur after thoracocentesis. There are several pleurodesis agents including talc, tetracycline and bleomycin.[102] Drainage of a symptomatic pleural effusion may not always relieve pain especially if there is parenchymal or pleural disease present. Therefore a thorough pain assessment is required after thoracocentesis.

Hypertrophic pulmonary osteo-arthropathy

Hypertrophic pulmonary osteo-arthropathy is defined by the presence of clubbing and periosteal proliferation of the tubular bones associated with lung cancer or other lung disease. It typically causes a symmetrical painful arthropathy affecting the ankles, knees, wrists and elbows. It will improve if the tumor is resected however in advanced lung cancer nonsteroidal anti-inflammatory drugs (NSAIDs) or bisphosphonates are mainstay of treatment.[103]

Spinal cord stimulation

Spinal cord stimulation (SCS) has been used for treatment of intractable cancer pain. It has been estimated that up to 40% of chronic cancer pain has a

neuropathic component, a type of pain that responds favorably to spinal cord stimulation.[104] Spinal cord stimulation is based on the principle enunciated in the 'gate-control theory' of pain proposed by Melzacke and Wall in 1965 which postulated that the spinal cord stimulation analgesia stimulates large diameter afferent fibres.[105] This stimulation in effect 'closes the gate' to pain transmission. It is thought that spinal cord stimulation blocks the pain by stimulating the dorsal columns which may inhibit transmission through the pain conducting spinothalamic tract as well as increase activity in descending anti-nociceptive pathways.[106,107] One study has found spinal cord stimulation to provide an effective alternative treatment option for select patients suffering from cancer related chest wall pain who have failed conservative treatment.[108]

Radiotherapy

Radiotherapy (RT) is well established in the palliative treatment of lung cancer. Indeed, 40%–50% of lung cancer patients receive radiotherapy, and, in 90% of these patients, the intent is palliative.[109,110] The main indications for RT are cough, haemoptysis, pain, dyspnoea and airway obstruction.[111–113] As with any treatment, it is vital that the treating radiation oncologist weighs up the pros and cons of treatment and discusses these with the patient so that the patient can come to an informed decision regarding their treatment.

Several studies have compared various dose and fractionation schedules in NSCLC. However, despite this, there is no real consensus on the optimal regime. This is due to the fact that reliable cancer therapies (RCTs) that have looked at this have reported contradictory results.[113–125]

A Cochrane review in 2006 looked at palliative radiotherapy regimes for NSCLC.[126] Fourteen randomized controlled trials were identified. All 13 studies that investigated symptoms reported that major thoracic symptoms improved following RT. While there was no strong evidence to suggest that a higher dose was associated with better or longer lasting palliation, there did appear to be a modest survival advantage to higher doses of radiation in those patients who were performance status 0 or 1. However, higher doses of radiation were noted to be associated with more acute side effects, particularly radiation esophagitis and this should always be considered when prescribing a higher dose such as 36 Gray in 12 fractions.

From the larger studies that have investigated the response rate to pain from thoracic RT, this seems to be in the region of 50%–80%.[127] Although endobronchial brachytherapy has been used to palliate symptoms such as cough, haemoptysis and dyspnoea, it has not been looked at in terms of pain palliation and so has not been covered in this review.[128,129] There is little data on the effectiveness and safety of re-irradiation for locally recurrent NSCLC. However, review article by Jemeric et al concluded that, in selected patients, chest re-irradiation appears to be feasible, safe and effective at relieving symptoms associated with recurrence.[130]

One study discussed the pros and cons of 39 Gy in 13 fractions with 17 Gy in 2 fractions with patients who met the eligibility criteria for the Medical Research Council (MRC) study which compared these two regimes.[131] Of the 92 patients enrolled, 55% chose the longer schedule due to longer survival and better control rate. The shorter regime was chosen due to shorter treatment time, cost and better symptom control. All patients were satisfied with being involved in the decision-making process. Surprisingly, 56% of those choosing the shorter regime had their treatment altered by their treating oncologist whereas only 4% who chose the longer regime had their treatment altered by their oncologist. This reflects the biases of the treating oncologists.

Most data looking at pain palliation in lung tumors has focused on NSCLC rather than SCLC. This is because SCLC is typically a central disease that causes dyspnoea, pneumonia due to obstruction, and superior vena cava obstruction (SVCO) more commonly than pain. In addition, SCLC is a chemosensitive disease and so, in the palliative setting, RT is more commonly reserved for patients who have either had a poor response to chemotherapy or are too frail to be considered for systemic therapy. In these patients, given the very poor survival rate, short fractionation schedules are recommended.

The Royal College of Radiologists recommend either a single 10 Gy fraction of RT or 17 Gy in two fractions for patients with moderate to poor performance status.[132] These recommendations are based on the three Medical Research Council studies that were performed in the 1980's and early 1990's.[117,118,120] If 17 Gy in two fractions is favored, consideration must be given to spinal cord shielding

as radiation myelopathy was suspected in one patient in MRC 1991 and confirmed in one patient in MRC 1992, both of whom received 17 Gy in two fractions. In view of the third MRC trial, those patients with good PS (0–1) should be considered for a higher fractionated dose such as 36 Gy in 12 fractions.

Radiotherapy has an important role to play in the palliation of pain in advanced lung cancer. Although there is not widespread agreement on the dose and fractionation schedules that should be used, there is general agreement that short fractionations should be considered for all patients with poor performance status. For those patients with advanced lung cancer and good performance status, consideration should be given to higher doses of fractionated radiotherapy given the possible survival advantage. However, this must be weighed against the increased toxicity of such regimens, in particular radiation esophagitis. Oncologists should be aware of their own personal biases when discussing different RT regimes with their patients.

Intractable pain

In the event that pain cannot be controlled, particularly if dose escalation of opioids is limited by systemic side effects, epidural or intra-thecal analgesia may be considered (see section on interventional procedures). Spinal opioids can be used in combination with local anesthetic or Clonidine in patients who have intolerable adverse effects with systemically administered opioids.[133] This route of opioid administration is only performed by specialists who are skilled in the procedure and its monitoring. It is most useful in intractable pain occurring to the lower part of the body and involves the placement of a delivery system consisting of a catheter and a port or a pump that can be internalized for prolonged use.

Intra-ventricular opioids are useful for recalcitrant pain due to tumors affecting the brachial plexus. It requires the placement of a ventricular catheter connected to a subcutaneous reservoir that can be accessed.[134]

Neural blockade (see section on interventional procedures) can sometimes control intractable pain when all other therapies fail. Temporary block with a local anesthetic is initially applied prior to a planned neurolytic block to assess side effects as well as to predict the likely outcome.[134]

Additional Approaches

Patients with lung cancer experience multiple symptoms both from complications of the cancer itself in addition to cancer related treatments. Dyspnoea is a commonly reported symptom in lung cancer and it has been noted that the incidence of dyspnoea is higher when pain and anxiety are high.[135,136] It is therefore necessary to treat dyspnoea in an holistic manner addressing pain control in addition to ensuring adequate pharmacological treatment with inhaled bronchodilators, corticosteroids, anxiolytics, oxygen therapy, and opioids. Emphasis must be placed on the benefit of non-pharmacological therapies for dyspnoea which include breathing exercises, relaxation techniques and psychological support. A similar approach must be taken with all symptoms in patients with lung cancer, which may be directly related to the cancer or due to other co-morbidities.

Psychological distress is also related to the symptoms of patients with cancer and consequently psychological support and care must be integral to the patient's treatment.[4] Untreated psychological distress may exacerbate pain or other symptoms. It is therefore important to ensure that patients have access to a counseling and spiritual support. Psychological therapies are all primarily aimed at promoting relaxation, controlling stress and anxiety and improved coping mechanisms and adjustment.[137]

Complementary therapies are used as adjuncts to current evidence based management. They are supportive measures that assist in symptom control, enhance well-being, and contribute to overall patient care.[138] Complementary therapy has been integrated into the management of patients with cancer and it has been noted that the uptake of complementary and alternative medicine increases with advancing disease, unmet patient needs, and helplessness.[139] There is a minimal evidence supporting the use of complementary and alternative therapies.[140] It is important to evaluate herbal and other dietary products for side effects and potential interactions with chemotherapy and other medication.

Acupuncture has been shown to be of benefit to patients with lung cancer and can be used concurrently for neuropathic pain, nausea and vomiting, smoking cessation and for pain.[141]

Non-pharmacological methods to manage pain include cutaneous stimulation techniques (heat and

cold applications) acupuncture, psychosocial methods of care, holistic management and pastoral care.

Conclusion

In conclusion, an active multidisciplinary approach is required to manage pain in patients with advanced lung cancer. Pain can be multifactorial in this patient population and therefore may require several different analgesics along with specialist palliative general and pain management. As lung cancer continues to be both prevalent and carry a high symptom burden, the importance of optimum pain management increases.

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