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Pain management in lung cancer

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Abstract

Lung cancer is the leading cause of cancer-related mortality worldwide. Not only burdened by the limited overall survival, lung cancer patient also suffer from various symptoms, such as pain, that implicated in the quality of life. Cancer pain is a complicated and transiently dynamic symptom that results from multiple mechanisms. This review will describe the pathophysiology of cancer pain and general approach in managing a patient with lung cancer pain. The use of opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), and adjuvant analgesia, as part of the pharmacology therapy along with interventional strategy, will also be discussed.

Key word: pain, lung cancer, therapeutic strategy

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Introduction

Pain influenced the total quality of life significantly; unfortunately, pain is under-assessed and undertreated globally. Chronic pain is one of the main problems in cancer survivor population and prevalence varies between 16% and 50% [1]. In meta-analysis report, prevalence of pain was > 50% among six type of cancers; head and neck cancer 70%, gynecological cancer 60%, gastrointestinal cancer 59%, lung cancer 55%, breast cancer 54%, and urogenital cancer 52% [2]. Among patient with advanced metastatic stage including lung cancer, the prevalence even reached about 75–90% [3]. Pain is also among the common symptoms that could bring lung cancer patient to search for medical care [4]. The severity of chronic cancer-related pain is associated with shorter survival in advanced non-small cell lung cancer (NSCLC), independently of known prognostic factors [5].

Definitions

Pain is an unpleasant sensory and emotional experience that is associated with actual or po-

tential tissue damage or described in such terms [6]. There are three main types of pain: somatic (nociceptive) pain, visceral pain, and neuropathic pain. Somatic pain is the most common type of pain in patients with cancer, and is characterized as well localized, intermittent, or constant and described as aching, gnawing, throbbing, or cramping [7]. Visceral pain usually occurs when lung cancer metastases to the intra-abdominal organ [8]. Neuropathic pain is pain that arises as a direct consequence of a lesion or diseases affecting the somatosensory system [9]. Neuropathic pain can affect up to 40% in patients with cancer, which could be related to the tumor, treatment or comorbid diseases [10]. Breakthrough pain (BTP), is defined as transitory, severe flares of pain that occur in opioid-treated patients with chronic background pain [11, 12]. Pain associated with lung cancer is characterized by multiple expressions, due to either the progression of the disease and/or induced by oncological treatment [13]. Refractory pain, or intractable pain, is defined as not responding to standard treatments [14]. Post-thoracotomy pain syndrome (PTPS) is defined as pain that recurs or persists along a thoraco-

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tomy incision at least two months following the surgical procedure [15, 16]. The most frequently used standardized scales to assess pain are visual analog scales (VAS), a verbal rating scale (VRS) and a numerical rating scale (NRS) [17].

Risk factors

Sociodemographic status, health status, and depression were associated with severity of pain in lung cancer [18]. Moreover, younger age, lower perceived health status and higher levels of other cancer symptoms (fatigue, shortness of breath and difficulty eating) were also significantly associated with a higher likelihood of reporting moderate to severe lung cancer pain [19]. Among lung cancer patients, current smokers reported pain and receiving pain treatment more often than former smokers [20]. The coping style has also been reported to affect pain. In one report, the repressive group showed statistically significant lower mean scores for pain quality and pain catastrophizing compared to the low-anxious group, high-anxious group and defensive high-anxious [21]. Genetic variations study revealed that interleukin (IL)-8-T251A were the most relevant genetic factor for lung cancer pain [22, 23].

Pathophysiology

The neurophysiology of cancer pain involves inflammatory, neuropathic, ischemic and compression mechanisms at multiple sites, and knowledge of these mechanisms and the ability to decide whether a pain is nociceptive, neuropathic, and visceral or a combination of all three will lead to best practice in pain management [24]. Many of the same inflammatory factors that promote tumor growth, such as $TNF\alpha$ and NF- κ B, are also function as pain modulators [25]. These putative mediators subsequently sensitize and activate primary afferent nociceptors in the cancer microenvironment [26]. Nociceptive pain was the major pathophysiological subtype in lung cancer pain, but neuropathic pain accounted for 30% (range 25–32%) of cases [27]. Cytokines associated with inflammation or tissue damage due to tumor growth and spreads have been thought to contribute to pain hypersensitivity by modifying the activity of nociceptors [28]. Furthermore, tumors growing in the vicinity of peripheral nerves can compromise the integrity of the nerve, inducing a neuropathic condition accompanied by persistent pain, hyperalgesia, or allodynia [29]. Other mediators that have been studied to be

involved in the cancer-related pain are nerve growth hormone [30, 31], bradykinin [32–34], endothelin-1 [35, 36], proteases-activated receptor 2 (PAR2) [37, 38], proton and acid-sensing receptor [39, 40]. Carriers of the specific IL-6 (i.e. IL-6-174C/C) genotypes required 4.7 times higher dose of opioids for pain relief compared with other genotypes [41]. Persistent idiopathic facial pain associated with mediastinal involvement in non-small cell lung cancer (NSCLC) may occur at presentation or at relapse [42]. Lung cancers rarely metastasize to the spleen, however if it is the case, the patient could suffer abdominal pain [43, 44]. Patients who undergo thoracotomy for lung cancer also have been reported to experience ipsilateral shoulder pain [45].

General approach in cancer pain management

Medical professionals' practices and knowledge regarding cancer pain management have been said as inadequate, especially due to differences between physicians and nurses in knowledge and practices for cancer pain management [46]. Effective communication is needed for optimal cancer pain management [47]. Open communication and disclosure also played important roles in the appraisal of pain symptoms [48]. Lung cancer patient who continues to smoke should be motivated intensively to quite in order to reduce the level of pain [19]. In general, the following aspect should be taken into consideration: (1) the medication regimen should be kept as simple as possible to avoid further side effect and cost burden; (2) the oral route of administration is preferred, and if is not possible, rectal or transdermal delivery is often feasible; and (3) for parenterally administered medication, the intravenous or subcutaneous routes should be used because intramuscular administration has the disadvantages of increased pain with administration and unpredictable absorption [49].

The mainstay of cancer pain management is systemic pharmacotherapy [50]. The World Health Organization (WHO) has developed a 3-step pain ladder to help the health care professional effectively manage pain, classifying pain intensity according to severity and recommending analgesic agents based on their strength [51]. In step 1, pain can be managed with nonsteroidal anti-inflammatory drugs (NSAIDs) and other non-opioid analgesics [52]. If pain persists or increases, step 2 requires opioids for mild to moderate pain along with NSAIDs and non-opioid analgesics [53]. Step 3 of the ladder is applicable to many can-

cer pain syndromes and includes opioids for moderate to severe pain in conjunction with NSAIDs and non-opioids [54]. Appropriate pain treatments in cancer include opiates, adjuvant medications, nerve blocks, and nondrug interventions [55].

Lung cancer pain management

Opioids

The second step of the WHO analgesic ladder comprises opioid analgesics such as tramadol, codeine, dihydrocodeine, and dextropropoxyphene [56]. Morphine activates the μ -opioid receptors, resulting in not only analgesia and sedation, but also euphoria, respiratory depression, constipation, and pruritus [57]. An opioid receptor is significantly implicated in anti-nociceptive processes and is found to be represented in the regions involved in nociception and pain [58]. All opioids are effective in controlling cancer pain and there is no proof that one opioid is better than another one [59]. However in poorly responsive patients, it is possible to do rotation from one drug to another [60]. Opioid rotation is a therapeutic maneuver aiming in improving analgesic response and/or reducing adverse effects, including a change to different medication using the same administration route, maintaining the current medication but altering administration route, or both [61]. Opioids could be administered through oral, transdermal, intravenous, subcutaneous, rectal, or intraspinal [62]. Opioids are normally administered at relatively low dose initially, and the dose is increased only if the pain is unchanged or increased during next pain level assessment [63]. In acute exacerbation of pain (i.e. BTP), fentanyl buccal tablet (FBT) provides a rapid onset of analgesia (10–15 minutes) by enhancing fentanyl absorption across the buccal mucosa [64]. For continuous chronic pain, opioids should be administered around-the-clock and several long-acting formulations are available that require administration only once or twice daily [65]. For example, transdermal fentanyl, common controlled-release transdermal formulations, combines a strong opioid with a 72-hour release profile and the benefits of a parenteral route, avoiding the first-pass metabolism [66].

Cancer patients received a significantly higher cumulative opioid dose compared with dementia and chronic obstructive pulmonary disease patients [67]. Various clinical studies demonstrated tramadol analgesia and acceptable toxicity in patients with cancer pain [68]. Lung cancer patients enrolled in the European Pharmacogenetic Opioid Study (EPOS) received opioids

varied from 10 to 5072 mg (mean 414, median 175) however only minority of patients achieved complete pain relief [69].

The use of opioid in lung cancer pain is not without problems. Preclinical studies have demonstrated that opioid receptor agonists increase the rate of non-small cell lung cancer (NSCLC) growth and metastasis [70]. Opioid receptor expression was increased significantly in cancer samples from patients with lung cancer compared with adjacent control tissue [71]. From *in vitro* study, opioid receptor regulates growth factor receptor signaling and epithelial-mesenchymal transition (EMT) in human NSCLC cells that is required for cells proliferation and migration [72]. Intraoperative opioid use is associated with decreased overall survival (OS) in stage I but not stage II-III NSCLC patients [73]. There has been an association between increased doses of opioids during the initial 96 hours postoperative period with a higher recurrence rate of NSCLC within 5 years which could be related to suppression of natural killer cells by opioid analgesics [74]. However, a study from single institution recently revealed that opioids were found to have no negative influence on survival time [75]. Moreover, morphine showed a beneficial effect on dyspnea in terminally ill lung cancer patients [76].

Non-opioid drugs

Anti-inflammatory drugs such as acetaminophen/paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs) could be used for mild cancer pain, and although adding a NSAID to an opioid for stronger cancer pain is efficacious, but the risk of long-term adverse effects has not been quantified [77]. One finding showed there is insufficient data to support the addition of NSAIDs to WHO Step III opioids to improve analgesia or to reduce opioid dose requirement [53].

Adjuvant analgesics

Adjuvant analgesics are defined as drugs with a primary indication other than pain that have analgesic properties in some painful conditions [78]. These type of drug were classified as: (a) multipurpose adjuvant analgesics such as antidepressants, corticosteroids, α 2-adrenergic agonists, neuroleptics, (b) neuropathic pain such as anticonvulsants, local anesthetics, N-methyl-D-aspartate receptor antagonists, (c) bone pain (calcitonin, bisphosphonates, radiopharmaceuticals), (d) musculoskeletal pain (muscle relaxants), or pain from bowel obstruction (octreotide, anticholinergics) [78]. For the first line of neuropathic

pain, the National Institute for Health and Care Excellence (NICE) recommends amitriptyline, duloxetine, gabapentin or pregabalin as initial treatment for neuropathic pain [79].

Interventional options

Although the use of oral analgesics for the control of cancer pain has been demonstrated to be successful in most patients, some patients will fail to respond to pharmacological therapy or will suffer unacceptable adverse effects [80]. Several intervention strategies have been studied with various efficacies, such as neuraxial infusion, paravertebral blocks, and cordotomy [81]. Indications for neuraxial infusion include pain refractory to systemic opioids after trials of dose escalation and/or opioid rotation and the occurrence of unacceptable side effects [82]. Paravertebral blocks usually performed for post-thoracic surgery analgesia [83]. For lung cancer located in the apex, known as the Pancoast tumor, it can cause pain due to compression of the brachial plexus. The addition of paravertebral cervical nerve block could relieve the lung cancer (Pancoast tumor) patient from pain [84]. The target of computed tomography (CT)-guided percutaneous cordotomy is the lateral spinothalamic tract located in the anterolateral region of the spinal cord at the C1-C2 level [85, 86]. CT-guided percutaneous cordotomy has been shown to provide sufficient pain relieve among lung cancer patient, including Pancoast tumor, and mesothelioma [87–90]. Lastly, there are insufficient data to say whether acupuncture is effective in treating cancer pain in adults [91].

Role of radiotherapy in reducing pain in lung cancer

Radiation was indicated in the palliation of hemoptysis, chest pain, dysphagia, and dyspnea in a patient with lung cancer [92]. A randomized trial showed palliative radiotherapy of 17 Gy mid-point dose in two fractions 1 week apart does relieve chest pain in lung cancer pain [93]. Generally, a significant number of patients achieved complete resolution of symptoms and palliation of chest pain with the fractionated regimen of radiotherapy [94]. However, radiotherapy was found to be ineffective for reducing morphine dose in patients with bone metastasis from lung cancer [95].

Conclusion

Pain affects the majority of lung cancer patient and, if it's left under-treated, it will implicate

in the significant reduction of quality of life. Lung cancer pain could be a nociceptive pain, visceral pain, or neuropathic pain. General approach in managing lung cancer pain follows the WHO pain ladder strategy. Despite its disadvantage in the increased incidence of recurrence, opioid remain the mainstay of lung cancer treatment. Interventional options serves as the alternative strategy if the optimal dose of opioid failed to relieve the patient from pain.

Conflict of interest

The authors declare no conflict of interest.

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