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Review

Principles and Management of Cancer Pain

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Abstract

Palliative care has a critical importance in oncologic treatment and cancer pain treatment is an important part of the palliative care treatment program including physical, psychological, social and spiritual components. Most of the patients with cancer experience pain in any stage of their disease therefore pain treatment is a necessity in these patients. On the other hand, studies have shown that there is an insufficient pain treatment in cancer patients due to problems related with physicians or the patients. For this purpose, the principles and management of cancer pain heavily in the light of the current literature was aimed to be evaluated.

Keywords: Cancer, pain, treatment (Minimum is 5, add 2 or more).

INTRODUCTION

According to the World Health Organization (WHO), "Palliative care is a way of dealing that improves the life quality of the patients and their families facing the problems associated with life-threatening illness, through the prevention and alleviation of suffering, the early identification of problems, the best assessment, treatment of pain and the other problems such as; physical, psychosocial and spiritual" (Sepúlveda et al., 2002; Farbicka and Nowicki, 2013).

The number of people needing palliative care is increasing due to the aging population, increasing prevalance of cancer and the overall morbidity and mortality resulting from cancer. Therefore, providing good quality of life in accordance with the standards of the WHO becomes more and more important (Farbicka and Nowicki, 2013).

Definition and prevelance of cancer pain

The International Association for the Study of Pain (IASP) defines pain as; an unpleasant sensorial and emotional experience accompanying with potential or existing tissue damage or described by such damage (Swarm et al, 2014).

It is a fact that cancer pain is a constant reminder for progressive and incurable nature of disease therefore it can be psychologically devastating (All and Huycke, 1999). Moderate and severe pain problems have been reported in 25-35% of cancer patients who are continuing treatment and in 75-90% of advanced-stage cancer patients (Paice and Ferrell, 2011; Sabistan et al., 2012). Severe pain problem which cause functional dysfunction has been reported in more than %36 of cancer patients who has metastatic disease (Cleeland et al., 1994). In a study about the use of painkillers in the palliative treatment of patients with lung cancer, 92% of patients have described pain; 52% of these patients attributed pain to their disease and 38% of the patients stated that their pain is associated with cancer treatment (Simone et al., 2012). In the same study it has been reported that 33% of the patients do not use painkillers becuse of the fear of addiction and the lack of financial resources although they have pain (Simone et al., 2012). Also in this study it has been shown that, analgesic usage is higher in the group receiving chemotherapy and

radiotherapy than the group undergoing surgery (Simone et al., 2012).

Futoshi et al. evaluated 113 lung cancer patients who have admitted to the emergency service between the years of 2010 and 2011. 143 visits were recorded and %49 of these visits were found to be related with cancer-related issues (Kotajima et al., 2014). Respiratory symptoms (34.3%), pain (24.3%) and gastrointestinal (12.9%) events were the most common cancer-related issues recorded (Kotajima et al., 2014). In the same study, they also observed that emergency department visits, admissions, ambulance use and hospital mortalities have increased with the progression of the cancer stage (Kotajima et al., 2014).

Barriers for adequate pain treatment

Pain treatment even with high doses of narcotics does not change the survival of cancer patients who are in the end of life (Azoulay et al., 2011) but influences the continuity to treatment, recovery or peaceful death of the patients (Farbicka and Nowicki, 2013).

Although current treatment modalities provide adequate pain control in 80% of cancer patients it has been reported that pain is not cured properly in these patients (Perron and Schonwetter, 2001). Of course there are impediments of insufficient pain control due to patients such as; adverse effects of drugs, cost of treatment, fear of addiction (Simone et al., 2012) and the treatment will not work anymore. Also approximately 50% of the cancer patients do not speak about their pain so they are at risk of inadequate pain assessment (Wilkie and Keefe, 1991). There are also impediments of insufficient pain control due to physicians such as; rarely using standardized pain assessment tools in clinical practice (Dalton et al., 1996) and underestimating the severity of patients' pain (Anderson et al., 2004), insufficient analgesic treatment (Ward et al., 2008), spending less time with patients who have unresolved pain (Harris et al.,1985), interrupting the patients or suddenly changing the subject while they are talking about their pain (Berry et al., 2003).

Causes and types of cancer pain

Cancer pain may arise from different etiologies and these can be mainly divided into three groups: 1) Causes directly related to the tumor (%60-80): Bone and soft tissue infiltration, compression of the nerve or blood and lymphatic vessels, lymphedema, tumour necrosis, brain edema. 2) Causes depending on the treatment of cancer (%20-30): Diagnostic procedures, surgery, radiotherapy, chemotherapy. 3) Other mechanisms that are not related with cancer and cancer treatment (%10-15): Head-ache, diabetic neuropathy, myofascial origins of pain, osteoarthritis, postherpetic neuralgia**,** decubitus ulcer, thrombophlebitis.

Pathophysiologically there are three types of pain, which are categorized as somatic, visceral and neuropathic. Somatic pain in cancer patients is generally due to soft tissue inflammation or to metastatic bone disease (Chang, 1999). This type of pain is described as sharp and pity in nature and is usually well localized so that the patient can often point directly to the site of the metastatic lesion.

Visceral pain arises from direct stimulation of afferent nerves due to tumor infiltration of the soft tissue or viscera (Dahl, 1996). Stretching, distension or ischemia of the viscera, radiation or chemotherapy may also cause visceral pain. This pain tends to be poorly localized and can be deep, aching, or colicky (Perron and Schonwetter, 2001).

Neuropathic pain is due to neuronal injury either by the effects of treatment or by tumor invasion. This kind of pain is constant and described as flammable, tingling, burning, prickle or electrical in nature (Perron and Schonwetter, 2001). Neuropathic pain may have a corresponding neurological deficit (Perron and Schonwetter, 2001).

Treatment options based on the type of the pain

Visceral pain is generally opioid responsive and opioids are the cornerstones of the therapy (Perron and Schonwetter, 2001).

For somatic pain non-steroidal anti-inflammatory drugs (NSAIDs) are the mainstay of the treatment (Perron and Schonwetter, 2001). There is no certain evidence showing that one non-steroidal anti-inflammatory drug is more effective than the other (McNicol et al., 2005). Therefore, the treatment should begin with lower cost drugs. If a NSAID is not effective in alleviating the symtpoms, transition to another NSAID can be considered. If there is no significant relief with NSAIDs, corticosteroids (CCS) can be started. If significant improvement has not been observed despite the use of NSAID and/or CCS in patients with bone metastasis, the patients should be referred to a radiation oncologist for further evaluation (Perron and Schonwetter, 2001).

Neuropathic pain may not be responsive to NSAIDs or opioids. For this reason a stepwise approach consisting of adjuvant analgesics such as; tricyclic antidepressants, anticonvulsants followed by corticosteroids and local anesthetics is recommended in the treatment of neuropathic pain (Perron and Schonwetter, 2001). First of all nerve damage with compression should be excluded. If nerve damage is suspected, CCS can be administered as initial therapy. In patients with neuropathic pain but nerve compression is not suspected, tricyclic anti-depressants and anticonvulsants can be used initially (Perron and Schonwetter, 2001).

Principles of cancer pain treatment

The principles of the cancer pain treatment consists of; general principles, assessment, treatment and re-assessment stages (Swarm et al, 2014). The goal of the comprehensive pain assessment is to find the cause of the pain and indentify optimal therapies (Swarm et al, 2014). Individualized pain treatment should be based on the type and cause of pain, performance status of the patient and patient-centered goals of care (Swarm et al, 2014).

General principles

Pain treatment is an important part of the oncologic treatment. Multidisciplinary team may be required. Psychosocial support both emotional and informational should be available. Spesific educational material should be provided to patients and families (Swarm et al, 2014).

Assessment

Patients should be assessed for pain at every meeting. Pain severity should be graded by the patients and nature of pain should be characterized. If there is a new pain, comprehensive pain assessment should be done and should be carried-out regularly on clinical follow-up (Swarm et al, 2014).

The first step in the effective treatment of cancer pain is measurement and graduation of the pain intensity. Pain sensation is entirely subjective. Thus pain severity can only be assessed by the patient himself. For this purpose, the most frequently used standardized scales are; Visual Analogue Scale (VAS), Numerical Rating Scale, Verbal Rating Scale (Ripamonti et al., 2012). According to VAS;

0 point refers to 'no pain', 1-3 point refers to 'mild pain', 4-6 point refers to 'moderate pain', 7-10 point refers to 'severe pain'.

In elderly patients, the presence of limited communicative skills or cognitive impairment make self-reporting of pain more difficult. When cognitive deficits are severe, observation of pain-related behaviors and discomfort (i.e. facial expression, body movements, verbalization or vocalizations, changes in interpersonal interactions, changes in routine activity) is recommended for assessing the presence of pain but not the pain intensity (Ripamonti et al., 2012; Kaasalainen, 2007; Gordon et al. 2005; Van Herk et al., 2007; American Geriatrics Society, 2002).

Treatment

The goals of the pain treatment are increased comfort, function and safety (Swarm et al, 2014). Physicians have to accept that cancer pain treatment is necessary and the treatment should start as early as possible to provide the biggest benefit.

The aim of analgesic therapy in cancer patients is to optimize the analgesia with minimal side effects. Analgesics for chronic pain should be prescribed on a regular basis and not on an 'as required' schedule (Ripamonti et al., 2012). Expected side effects of analgesic therapy should be avoided and education of the patient and family or the caregiver should be optimized. Also hospitalization should be considered in acute pain crisis (Swarm et al, 2014).

Re-assessment

In order to be sure that the selected analgesic treatment has the maximum effect and the side effects are as small as possible, pain intensity should be reassessed at regular intervals (Sepúlveda et al., 2002).

'By The Ladder' Method

World Health Organisation (WHO-1986) suggests 'by the ladder' method in the pharmacological treatment of pain. It is considered that tolerance development is slowing down by the use of this method and also when used correctly it allows pain control in 75% or more of patients with cancer pain (McCaffery, 1992).

In this approach, Non-opioid ± Adjuvant therapy is recommended for mild pain (VAS 1-3), Weak opioid ± Non-opioid ± Adjuvant therapy is recommended for moderate pain (VAS 4-6), Strong opioid ± Non-opioid ± Adjuvant therapy combination is recommended for the treatment of severe pain (VAS 7-10) (WHO Expert Committee, 1990).

The appropriate use of analgesics according to WHO guidelines provide adequate pain control in 75% or more of patients with cancer pain (McCaffery, 1992). If the pain severity increases during pharmacologic therapy, invasive techniques can be used (Ventafridda et al., 1987).

Adjuvant analgesics

Adjuvant analgesics are not analgesics pharmaceutically but they can increase the effects of analgesics or can show analgesic effect alone in some pain syndromes.Thus, they can be called as secondary or co-analgesics. These agents include; antidepressants **(**Amitriptyline, Nortryptilin, Imipramine), anticonvulsants **(**Phenytoin, Carbamazepine, Valproic acid, Gabapentin, Pregabalin), corticosteroids **(**Dexamethasone, Predni-sone), benzodiazepines and neuroleptics (Lee et al., 2014). Also bisphosphonates and calcitonin can reduce

the pain in bone metastasis (Lee et al., 2014).

Non-Opioids

Non-opioids consists of paracetamol, acetylsalicylic acid and NSAIDs. Acetylsalicylic acid is not used in cancer treatment because of its side effects in chronic use. Non-opioids are useful alone in mild pain but their combinations with opioids provide additive analgesia in moderate to severe pain. Combination of two non-opioids does not increase the analgesic effect but increases the frequency of adverse effects. There is a ceiling effect for analgesia in non-opioid group but there is no potential for tolerance or physical dependence (Swarm et al., 2014). There are adverse effects due to NSAIDs. Major adverse effects of NSAIDs include renal toxicity, gastrointestinal bleeding, cardiac toxicity, hepatic dysfunction, trombocytopenia, coagulopathy. Minor side effects are nausea, vomiting, dyspepsia, heartburn, bloating and constipation (Swarm et al., 2014).

Opioids

Opioids are the most potent analgesic agents indicated in moderate to severe pain. They form analgesia by binding specific opioid receptors in the brain and spinal cord. Prototype of the opioids is morphine. It is known as the 'gold standart' in palliative care because it is effective, inexpensive and easy to titrate. Also it can be administered using many routes such as oral, subcutaneous, parenteral, rectal and spinal (Perron and Schonwetter, 2001). Weak opioids are codeine, dihydrocodeine and tramadol. Morphine, fentanyl, oxycodone and hydromorphone are the strong opioids (British Pain Society, 2010).

The appropriate opioid dose is the dose that relieves patient's pain throughout the dosing interval without causing unmanageable adverse effects (Swarm et al., 2014). The rapidity of dose escalation should be related to the severity of the symptoms. Calculate dosage increase based upon total opioid dose taken in the previous 24 hours. If the patient's comfort is provided in the given dosing regimen, long-acting medication should be started. Also it should be noted that there is not a ceiling effect for opioids (Swarm et al., 2014; Perron and Schonwetter, 2001).

Opioids should be titrated with caution in patients with decreased renal or hepatic function, chronic lung disease, sleep apnea, poor performance status and elderly (Swarm et al., 2014; Perron and Schonwetter, 2001). In a study by Vigano et al., it has been reported that elderly patients are much more affected from acute and chronic toxicities of opioids therefore opioids should be started at lower doses and titrated carefully (Vigano et al., 1998).

Oral route is the most preferred route in chronic opioid therapy because it is the least invasive, easy and safe way to provide adequate analgesia. Intravenous or subcutaneous routes can be used in patients who can not swallow or absorb opioids enterally, rapid onset of analgesia is required and side effects are occured due to oral intake. Rectal, transdermal, transmucosal routes can be considered in order to increase the patient comfort (Swarm et al., 2014). It has been shown that pain control is provided in 75-85% of patients with the use of oral, rectal and transdermal opioids (Jacox et al., 1994[a]).

Opioid therapy should not be stopped abruptly in patients using chronic opioid because discontinuation of the opioids may lead to acute withdrawal reactions (Perron and Schonwetter, 2001). Although constipation and sedation are the most common side effects of opioids, there are also potential side effects such as nausea and vomiting, pruritus, delirium, confusion, respiratory depression, motor and cognitive impairment, urinary retention and sleep disturbances (Swarm et al., 2014; Jacox et al., 1994[b]).

Also it should be stated that the use of placebo in the treatment of cancer pain is unethical (Swarm et al., 2014) because several studies have reported that non-opioids and opioids are superior to placebo in controlling cancer pain (Ripamonti et al., 2012).

Invasive interventions

Whenever complex pain management methods exceeds the capabilities of the primary physician or oncologist, consultation with an expert who is specialized in Pain Medicine becomes necessary. Because if pain cannot be controlled with medication, interventional treatments may be beneficial.

More invasive techniques include spinal opioid application (epidural, intrathecal), neurolytic blocks, neurosurgical procedures like neurostimulation and neuroablation methods, or implantation of drug delivery systems (Ventafridda et al., 1987). These methods can reduce or eliminate systemic opioid requirement in suitable patients. Also appropriate patient selection and trained staff is very important during invasive procedures because they can lead to serious complications.

Non-pharmacological approaches

Nonpharmacologic techniques are shown to be effective in relieving cancer pain and some of the cancer centers suggest these modalities (Foley, 1985). These interventions can not replace the other pain treatment methods but some of them can reduce the need for pain management.

Nonpharmacologic interventions consist of physical and psychosocial components. Physical approaches

include massage, acupuncture, exercise, heat therapy, transcutaneous electrical nerve stimulation and immobilization. Psychosocial approaches include relaxation techniques, hypnosis, supportive groups, patient training, family counseling, and psychotherapy (Perron and Schonwetter, 2001). Such methods are usually offered by hospice organizations or palliative care teams and they can be applied if requested by the patient and family or if recommended by the clinician (Perron and Schonwetter, 2001).

CONCLUSIONS

Pharmacological approaches are the mainstay in the treatment of cancer pain and opioids are the basis of analgesic therapy. A comprehensive pain assessment should be performed and the analgesics should be administered on an individual basis according to type and severity of the pain using 'WHO-analgesic ladder method'. Non-pharmacological approaches and invasive techniques could be considered in appropriate patients.

Adequate pain control has critical importance to improve the quality of life in cancer patients and the treatment should start as early as possible to provide biggest benefit for patients. It is believe that effective application of known methods instead of new medical drugs and techniques is enough to provide an effective treatment of cancer pain.

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