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Recent advantages in cancer pain management

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Abstract

Pain is the most feared symptom associated with cancer and the most prominent symptom reported in cancer patients. Pain management has been extremely difficult to achieve, despite the availability of a number of pharmacological and nonpharmacological approaches, including the use of analgesics, biological therapy, targeted cancer therapies and tumour shrinking paradigms such as chemotherapy and radiation. The correct use of the analgesic ladder advised by World Health Organisation (WHO) can lead to adequate long- term pain control in most patients with advanced cancer disease.

Opioids are the primary and most effective treatment for cancer-induced pain remaining the cornerstone of pharmagological treatment. Adequate analgesic treatment is not only intended to reduce pain, above all it is aimed to increase the quality of life for cancer patients.

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INTRODUCTION

World Health Organisation (WHO) in year 2008. reported that the patients at the time of cancer diagnosis suffered moderate to severe pain in 30–40% off patients, while 60–100% off patients with advanced disease suffered severe pain.

Pain in patients with cancer can be caused by the cancer itself, associated with tumor compression, caused by chemotherapy or radiation and by surgical treatment. Pain caused by cancer is mostly nociceptive pain and can occur as somatic or visceral. Neuropathic pain is a result of tumour infiltration or compression of nerves (eg. muscle spasms, lymphedema, constipation, bed sores). Pain caused by chemotherapy is a result of development of polyneuropathy. Post radiation damaging leads to radiation plexopathy (brachial, lumbar) and radiation myelopathy. Neuropathy as a result of surgical treatment occurs predominantly after particular surgical procedures and the most common is postthoracotomy pain, postmastektomy pain, pain after radical neck dissection or post amputation pain *(1, 2, 3)*.

Patients with malignant diseases represent a very specific group of patients due to increase in pain in these patients is often associated with the progression of disease and stress.

Furthermore, cancer pain causes variety of symptoms known as »cytokine-induced sickness behaviour«. This condition includes pain, sleep disturbance, cognitive impairment leading to depression, lethargy, anorexia, chronic fatigue. It is believed that the trigger for the development of behavioural problems is primarily due to continous release of proinflammatory cytokines such as IL-1, IL-6, and TNF-alpha *(4)*.

Since the cancer pain is associated with a variety of other sings and symptoms strongly influencing the everyday living, the efficient treatment of cancer pain is crucial for quality of life.

A basic recommendation

A basic recommendation for the treatment of cancer pain has been proposed in 1986. by WHO and it consists of the three step analgesic ladder *(5)*. First step include the treatment of mild pain and the application of nonopioids drug (paracetamol, NSAIDs, COX-2 inhibitors, metamizole) is recommended. Second step implies the treatment of moderate pain by weak opioids (Zaldiar, tramadole, codeine). Third step recommends strong opioids (morphine, fentanyl, methadone, oxycodone) for the treatment of severe pain (Figure 1.).

Since the implementation of this scale in clinical practice for cancer pain relief has shown to bee too slow and insufficient, last few years it has been modified. Cancer pain is usually very intensive, and recently it has been proposed that the initial application of the strong opioids should be recommended instead of gradual augmentation from nonopioid drugs and weak opioids. This type of pain management is called analgesic lift.

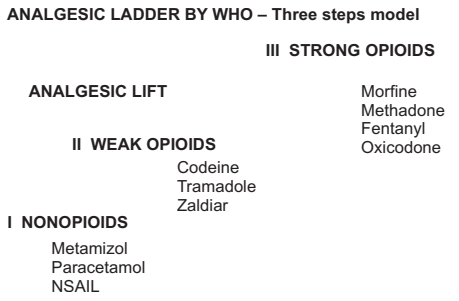

Figure 1.

Selection of analgesic for cancer pain relief depends on pain intensity, pain duration, ethiology of pain, degree of patients sensitivity to pain, tolerability of analgesics, previous use of analgesics, and the possibilities of getting used to. To achieve adequate pain relief by suppressing different pain pathways usually is recommended the use off two or more analgesics which have a synergistic effect in order to minimize adverse effects compared with the use of high doses of just one drug. The dose and effect of analgesics is individual. Recent research on human models indicate that the analgesic response is written in the individual genetic map explaining the fact that the analgesic dose insufficient for one patient in another patient can cause symptoms of over dosage *(2, 6)*.

Opioid analgetics

Delay prescription of opioid analgetics for cancer patients is very common due to fear off their effect to cause the addiction (physical and psychological), development of tolerance, multiple side effects and most of all because there is lack of knowledge including medical stuff.

Central effects of opioids

Central effects of opioids include analgesia, sedation, euphoria or dysphoria, respiratory depression, antitusic effect, emetic effect, miosis and development of tolerance.

Peripheral effects of opioids

Peripheral effects of opioids include slowing gastric emptying (pyloric constriction), slowing gut motility and increased intestinal muscle tone, contraction of the sphincter of the gall bladder, and increased muscle tone of the bladder, decrease in vascular tone and release of histamine *(7, 8)*.

Side effects of opioids

Common side effects of opioids are constipation, sedation, nausea and vomiting, delirium, myoclonus, pruritus and respiratory depression *(9)*.

The most common and simplest method of administration of analgesics for the treatment of malignant pain is an **oral route**. Analgesics must be taken »on hour«, »on demand« is allowed only for breakthrough pain. Breakthrough pain has been defined as a transitory increase in pain intensity over a baseline pain intensity in patient receiving in time administered analgesic treatment. The use of a short half-life opioid, such as immediate-release morphine is suggested for breakthrough pain.

Only if the oral route is absolutely impossible, other alternative routes are recommended.

Intravenous route is indicated in patients with advanced tumours of the oesophagus, neck, gut obstruction, etc., which leads to an inability to swallow or with recurrent nausea and vomiting which prevents the absorption of drugs. Intravenous use of opioids can be achieved by rapid titration, but patients must be continuously monitored and it usually requires hospitalization. Intravenous analgesia can be used in household conditions, as continuous infusion controlled by the patient (**Patient Controlled Analgesia PCA)**.

Subcutaneous administration of opioids could be recommended when the oral application can not be applied. When subcutaneous infusion is applied, the location of drug application should be changed frequently.

Intramuscular injections are not recommended, because they are painful, the absorption of analgesics is unpredictable especially in dehydrated and hypotensive patients.

Rectal administration of opioids is an alternative route when the patient can not take medicine orally because of nausea and vomiting or intestinal obstruction. Most of analgesics intended for oral use can be applied rectal (e.g. morphine tablets) *(10)*.

Epidural application of analgesics is intended primarily for postoperative analgesia because it provides analgesia at the origin of painful stimuli, which enables rapid patient mobilization, reduces stress response, encourage faster gut motility and reduces the intensity and

frequency of side effects. Epidural analgesia is achieved primarily by opioid analgesics which are commonly combined with local anaesthetics that have proinflamatory effect. There are a number of other medications that can be applied as additives such as clonidine, ketamine, epinephrine, neostigmine, naloxon, to extend and improve epidural analgesia and diminish side effects *(11, 12)*.

Transdermal drug administration has brought a revolution in the treatment of chronic pain because drug release rate is controlled and constant plasma concentration of the drug is maintained over a long period. When the anagestic is applied transdermally the patients are not constantly focused on their pain and its treatment. Transdermal preparations contributed significantly to the quality of treatment of cancer pain particularly in patients who have difficulty swallowing.

The most recent application of analgesics for cancer pain are: oral tranmucosal route, sublingual route, intranasal and inhalation route *(10)*.

Adjuvant drugs

Adjuvant drugs cure side effects of analgesics (eg. antiemetic and laxatives), enhance pain relief usually caused by nerve compression (eg. corticosteroids), cure comparative psychological disorders such as insomnia, anxiety and depression (sedative, anxiolytics and antidepressants) *(14)*.

Biological therapy

Biological therapy is a type of treatment that works to enhance immune system to fight against cancer cells or to control side effects of other cancer treatments like chemotherapy. Biological therapy keeps cancer from spreading to other parts of patients body, stop or slow the growth of cancer cells and make it easier for immune system to destroy, or get rid of cancer cells *(15)*.

Cancer vaccines

Cancer vaccines are a form of biological therapy. While other vaccines are given before the disease occurs, cancer vaccines are given after the cancer appears. Cancer vaccines may help the body to fight against the cancer and can be effective to prevent cancer reoccurrence *(16)*.

Targeted cancer therapies

Targeted cancer therapies are drugs or other substances that block the growth and spread of cancer by interfering with specific molecules involved in tumor growth and progression. These substances are usually called »molecular targets«, »molecularly targeted drugs«, »molecularly targeted therapies«, or other similar names. By focusing on molecular and cellular changes that are specific to each cancer, targeted cancer therapies may be more effective than other types of treatment, including and , and less harmful to normal cells *(17)*. Targeted cancer therapies interfere with cancer cell division (proliferation) and spread in different ways. Many of these therapies focus on that are involved in cell signaling pathways, which form a complex communication system that governs basic cellular functions and activities, such as cell division, cell movement, how a cell responds to specific external stimuli, and even cell death. By blocking signals that tell cancer cells to grow and divide uncontrollably, targeted cancer therapies can help stop cancer progression and may induce cancer cell death through a process known as . Other targeted therapies can cause cancer cell death directly, by specifically inducing apoptosis, or indirectly, by stimulating the immune system to recognize and destroy cancer cells and/or by delivering toxic substances to them *(17)*.

No pharmacological interventions

No pharmacological interventions used in cancer pain management are: neuromodulation techniques (TENS, SCS, DBS, acupuncture), therapeutic nerve blocks, physical and occupational therapy, psychological and behavioural techniques and neurodestructive techniques *(18)*.

CONCLUSION

Cancer pain is chronic pain that is the result of a complex pathophysiological events between the three major systems: nervous, endocrine and immune system. Understanding the network of complex interactions between the nervous, immune and endocrine system will contribute to the targeted treatment of patients with cancer pain. Additionally, patients with cancer have reduced immune system due to numerous factors, particularly the pain. Immunosuppression contributes to increased tendency of developing infections and promoting tumour growth.

Treatment of cancer pain is multimodal. Although opioid pharmacotherapy can be considered the cornerstone in the treatment of malignant pain, other pharmacological and non-pharmacological methods should be considered as very important part of pain treatment. Additionally, psychological support to the patients and their family should be mandatory.

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