



CANCER PAIN AND THERAPY

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SUMMARY – Cancer pain is not a homogenous and clearly understood pathological process. The best treatment is a combination of drug and non-drug measures. Pain is divided into visceral, bone or neuropathic pain and has characteristics of continuous or intermittent pain. Cancer bone pain therapy remains centered on strong opioid, radiotherapy and bisphosphonates. Invasive procedures are aimed to improve neurological function, ambulation and pain relief. Solid tumors often demand surgery. Treatment of acute postoperative pain is crucial for the prevention of chronic pain. Chemotherapy and radiation sometimes also cause pain. The management of cancer pain has improved because of rapid diagnosis and treatment, understanding of analgesics and the cooperation of patients and their family. The presence of special pain centers in hospitals also raise standard of cancer pain management. Drug therapy with non-opioid, opioid and adjuvant drugs is the base of such management. The side effects must be monitored and timely treated. Methods of regional nerve blockade in pain control are numerous. Placement of epidural, intrathecal and subcutaneous catheters, conductive nerve blocks with continuous delivery of mixed local anesthetics are very successful for selected patients. Conventional physical therapy involving lymphatic drainage is useful. Acupuncture, psychotherapy and similar methods are also applicable.

Key words: *cancer pain, opioids, non-opioids, adjuvant drugs, regional nerve block, integrative medicine*

Introduction

Not everyone with cancer has cancer pain. Cancer pain takes many forms. It can be constant, intermittent, mild, moderate or severe and dull, sharp or burning. The form of pain depends on a number of factors, including the type of cancer, how advanced it is, localization and pain tolerance. Every patient has different pain sensitivity and we must apply individual pain treatment. With more than 2.7 million new cases in Europe, cancer is a leading cause of death worldwide

accounting for nearly 10 million deaths in 2020. Cancer survival around the world generally improves but there is a lot of difference between countries. Croatia is unfortunately at the bottom of European countries for the majority of types of cancer. The most important future job will be to improve preventive campaigns, treat cancer patient as soon as possible after diagnosis, improve, and apply all complementary forms of treatment like pain control, nutrition, physical therapy etc.

Cancer pain

Pain is the commonest presenting feature that leads to a diagnosis of cancer and remains the most feared symptom by patients throughout the course of the disease. Beuken-van Everdingen showed that pain prevalence rises with disease progression and affect

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approximately 64% of patients with advanced cancer. Approximately 45% of all patients with advanced cancer experience pain of moderate to severe intensity¹. Greco *et al* estimated that approximately 32% of patients were not receiving analgesia proportionate to their pain severity². Although patients understandably express that they want to be pain free, in general, they do not actually expect their pain to go completely³. Bender *et al* identified that patients are keen to understand the cause of their cancer pain, what to expect, options for pain control and how to cope with cancer pain including talking with others and finding help⁴. The key priorities in pain management strategies for patients with advanced cancer should be to help them achieve a balance between pain and adverse effects of analgesia to optimize physical function and support for self-management.

Cancer pain does not represent a homogenous and clearly understood pathological process. There is a large range of different cancer types requiring individual assessment and treatments. In addition, not every pain in cancer patients is caused by active tumor. Around two-thirds to three-quarters of pains are related to tumor, and around 10-20% are related to cancer treatments (particularly chemotherapy end surgery) with around 10% related to comorbid pain⁵. A mechanism-based discussion of pain therapies is confined to pathophysiological processes occurring at a molecular or cellular level and the consequent biological targets for treatment. Physiological mechanisms in cancer pain are broadly described as nociceptive, inflammatory or neuropathic. The principal approach to cancer-pain management has been based on the World Health Organization's (WHO) method for cancer pain relief. The foundation of this approach is the concept of matching the strength of analgesia to severity of pain, ranging from basic analgesics to strong opioids. Other approaches include adjuvant analgesia, corticosteroids, radiotherapy and interventional procedures. This approach can result in satisfactory pain control for around 73% of patients with cancer pain, leaving at least a quarter of patients with inadequate control⁶. Strong opioids are generally effective with approximately 75% of patients achieving satisfactory pain control after first or second line opioid treatment, with no significant differences in efficacy between morphine, oxycodone, fentanyl and buprenorphine. This results in approximately a 3-point mean reduction on a 0 to 10 pain rating scale. Unfortunately, data supporting the use of adjuvant analgesia in tumor-related cancer pain are weak, particularly for

antiepileptic and antidepressant drugs. This is contrary to good evidence of effectiveness in no cancer patients^{7,8}. Cancer-related pain is divided by anatomical origin into visceral, bone or neuropathic pain and has characteristics of continuous (background) or intermittent (episodic) pain.

Vardeh *et al.* have recently proposed a concept for pain assessment for all etiologies which forms a hierarchy comprising pain state (e.g. inflammatory or neuropathic) pain mechanism (e.g. peripheral or central sensitization), and, finally, molecular targets (e.g. nerve growth factor or N-methyl-D-aspartate receptors)⁹. However, basic science research in cancer pain has demonstrated a complex and incompletely understood picture. Bones metastases are the most common cause of cancer pain. It can happen when cancer starts in or spreads. This type of pain is a unique mixture of inflammatory and neuropathic mechanisms with a large number of potential molecular targets. Treatments developed against these molecular targets include denosumab, which interferes with the receptor activator of nuclear factor kappa-b ligand, and tanezumab, which inhibits nerve growth factor^{10,11}. In routine clinical practice, effective cancer bone pain therapy remains centered on strong opioids, radiotherapy and bisphosphonates. Interventional procedures may have a role for selected patients. Recording a pain assessment and ensuring that health care professionals use this within the consultation with patient can result in a significant decrease in usual pain. Pain assessment data need to be integrated into pain management decision.

Useful techniques for pain relief

Pain from the cancer can be caused by tumor pressing on nerves, bones or organs. When a tumor spreads to the spine, it can press on the nerves of the spinal cord. The first symptom of spinal cord compression is usually back or neck pain and sometimes it is severe. Numbness or weakness may also happen in an arm or leg. Coughing, sneezing or other movements often make the pain worse. Spinal cord compression must be treated right away to keep one from losing control of one's bladder or bowel or being paralyzed. Treatment for spinal cord compression involves radiotherapy, steroids, sometimes surgery. External radiation may be used to treat the weakened bone. Sometimes a radioactive medicine is given to strengthen a bone. Bisphosphonates are drugs that can also help make weakened bones stronger and

help keep the bones from breaking. Invasive procedures are aimed at maintaining or improving a neurological function and ambulation, spinal stability, durable tumor control, and pain relief. Percutaneous vertebroplasty (PVP) is the treatment of multiple vertebral metastases and has a good analgesic effect. PVP not only improves the quality of life of patients significantly, but also prevents further vertebral collapse and the invasiveness of intraspinal tumors, avoiding the nerve dysfunction caused by spinal cord compression. Surgery for spinal metastases consists of simple decompressive laminectomy. You may still need pain medicines, but sometimes these treatments themselves, can greatly reduce your pain. Lumbar epidural steroid injections under fluoroscopic guidance are used very commonly for the treatment of low back and lower extremity radicular pain. These procedures have been shown to be effective for pain relief in the short term and are relatively safe^{12,13}.

Bone pain can also happen as a side effect of medicines known as growth factor drugs or colony-stimulating factors. These drugs may be given to help prevent white blood cell counts from dropping after treatment. They help body to produce more white blood cells, which are made in the bone marrow. Because the bone marrow activity is higher bone, pain can occur.

Surgical pain is often part of the treatment for cancers that grow as solid tumors. Depending on the kind of surgery, some amount of pain is usually expected and can last a few days to weeks. Treatment of acute postoperative pain is of crucial importance for the prevention of chronic pain. Algometry can be used in preoperative stage to estimate the intensity and strength of postoperative pain and to adjust the analgesia protocol. Pressure algometer is an instrument for measuring sensitivity to pressure or to pain and it attempts to objectify sensitivity to pain of a particular patient. The wound catheter placement at the end of the operation and administration of local anesthetics completes the multimodal intravenous analgesia¹⁴.

Phantom pain is a longer-lasting effect of surgery. If you had an arm, leg or even a breast removed, you may still feel pain or another unusual or unpleasant feelings that seem to be coming from the absent body part. Many methods have been used to treat this type of pain, including pain medicine, physical therapy, antidepressant medicines and TENS.

Chemotherapy and radiation treatments sometimes also cause pain. Peripheral neuropathy manifest

itself as pain, burning, tingling, numbness, weakness, clumsiness, trouble walking or unusual sensations in the hand, arms, legs and/or feet. It is due to nerve damage caused by certain types of chemotherapy, vitamin deficiencies, a tumor pressing on a nerve or other problems such as diabetes and infection. Chemotherapy can cause mouth sores (stomatitis or mucositis) and pain in the mouth and throat, which cause problems with eating, drinking and even talking. Radiation mucositis and other radiation injuries cause pain depending on the part of the body that is treated and cause skin burns, and scarring. Glutamine is a major dietary amino acid that is both a fuel and nitrogen donor for healing tissues damaged by chemotherapy and radiation. Evidence supports the benefit of oral glutamine to reduce symptoms and improve quality of life of cancer patients. Benefits include not only better nutrition, but also decreased mucosal damage (mucositis, stomatitis, pharyngitis, esophagitis, and enteritis)¹⁵. Intestine and bladder are also prone to radiation injury and patients may have pain in these areas if these areas are treated.

Control of cancer pain

The management of cancer pain has improved over the last 20 years. The reason is better cancer diagnosis and treatment, a greater understanding of analgesic drug therapy, insistence of patients and their families that pain be better controlled, and a consensus that adequate symptom control and a good quality of life are particularly important in patients with advanced disease. The presence of a special center also serves to raise the standard of cancer pain management in hospitals. Drug therapy with non-opioid, opioid, and adjuvant drugs is the base of such management. As a first step, we must take a detailed history of the complaint of pain and perform a careful physical examination. Investigations should be reserved for cases where there is doubt about the cause of pain, or where a decision about further anticancer treatment depends upon the precise localization of the disease. Assessment is a vital preliminary step toward the satisfactory control of cancer pain. It includes understanding not only the physical but also the psychological, spiritual, interpersonal, social, and financial components that make up the patient's "total pain". Characterization of the patient's pain as mild, moderate, or severe provides a basis for appropriate drug therapy. Information about past illnesses, current level of anxiety and depression, suicidal thoughts, and the degree of functional inca-

capacity help to detect patients who may require more specific psychological support. Depression may occur in as many as 25% of cancer patients. The therapeutic strategy varies from country to country and from patient to patient. The integration of the method into a more comprehensive program of care for cancer patients is recommended¹⁶. While complete relief of pain is not always possible, the method can be used to help all patients considerably. The Croatian Pain Society currently promotes a multidisciplinary pain management program as the standard of care for patients with chronic pain. This Society issued guidelines for therapy of cancer pain aimed at equalizing pain therapy of patients in different hospitals.

The use of analgesic drugs is the mainstay of cancer pain management. When used correctly, analgesics are effective in a high percentage of patients. A three-step "analgesic ladder" is suggested. In patients with mild pain, non-opioid drugs such as aspirin, paracetamol, or any of the non-steroidal anti-inflammatory drugs will be adequate. In patients with moderately severe pain, if non-opioids do not provide adequate relief when given on a regular basis, codeine or an alternative weak opioid should be prescribed. Non-opioid drugs, specifically the nonsteroidal anti-inflammatory drugs, appear to act peripherally by inhibiting prostaglandin systems, whereas the opioids act centrally by binding to specific opioid receptors. Because of this difference, combinations of these two types of drug produce additive analgesic effects. In patients with severe pain, morphine, as a strong opioid, is the drug of choice. Paracetamol is currently recommended for mild-to-moderate pain. However, patients with moderate-to-severe cancer pain that is already being treated with a strong opioid are unlikely to gain any additional benefit. Morphine has a relatively short half-life, its pharmacokinetics is linear, and it is relatively easy to titrate the dose against the pain. Corticosteroids are commonly used in patients with cancer both as chemotherapeutic agents and as analgesics. Several studies have reported relief of pain by corticosteroids in patients with epidural spinal cord compression or infiltration of a nerve by the tumor, and in metastatic bone disease. The effective analgesic dose varies considerably from patient to patient. The right dose of an analgesic is that which gives adequate relief for a reasonable period of time, preferably four hours or more. Unlike the doses of non-opioids, weak opioids, and mixed opioid agonist-antagonists, the doses of morphine and other strong opioids can be increased indefinitely. Published data indicate that it is rare for a patient to need more than 200 mg of

morphine by mouth every four hours. The patient taking medication orally is not restricted in activity by the route of administration but the parenteral administration of a drug restricts the patient to either hospital or home and requires additional people to perform it.

Chronic pain and breakthrough cancer pain have a high prevalence in all cancer types and stages. First, we must prescribe the lowest initial dose of immediate release opioids; oxycodone or hydromorphone. The combination of oxycodone/naloxone could reduce opioid-induced constipation^{17,18}. Transdermal administration of fentanyl or buprenorphine is indicated for the treatment of severe chronic pain that requires continuous administration of long-term opioid. The most often used tablets for the breakthrough cancer pain is morphine sulphate, which can be combined with paracetamol or nonsteroidal analgesics. Pain is often worse at night and disables patient's sleep. The use of a larger dose of morphine at bedtime, compared with the daytime, results in more prolonged relief of pain and better sleep. Morphine can be combined with pregabalin or tramadol for better pain relief. The common side effects of the strong opioid are constipation, nausea and vomiting and must be monitored and treated with antiemetics and laxatives. Clinically important respiratory depression is rare. An initial treatment review is sometimes necessary within hours, normally within one or two days, and always after the first week. Pain monitoring could be performed by visiting clinicians or by phone call. Additionally, a nurse calls patients and checks symptoms and possible side effects.

The adjuvant drugs

The adjuvant drugs mainly include antiepileptic, antidepressants and corticosteroids. These drugs have different chemical structure and should not be prescribed routinely. Combining antidepressant or antiepileptic drugs with opioids has resulted in increased pain relief when used for neuropathic pain in non-cancer conditions. However, evidence to support their effectiveness in cancer pain is lacking. Clinicians should balance the small likelihood of benefit in patients with tumor-related cancer pain against the increased risk of adverse effects of combination therapy¹⁹. An antidepressant is indicated for patients who remain depressed despite improved pain control. Anxiolytics may be used for very anxious patients. Multiple current guidelines recommend corticosteroids for some types of cancer pain, particularly where pain is relat-

ed to inflammation and oedema²⁰. Corticosteroids, anticonvulsants, and neuroleptic drugs have a role to play only in selected cases. Some guidelines include the option to use ketamine but acknowledge the lack of evidence to support its routine use. There is limited data that intravenous lidocaine may reduce pain intensity in some patients but a lack of efficacy has been seen in other trials. Use of lidocaine comes with a risk of frequent adverse effects and therefore specialist supervision is needed. Lidocaine could therefore be considered as an option for the treatment of opioid-refractory cancer pain. Pre-clinical experiments show that tetrahydrocannabinol (THC) enhances the anti-nociceptive effect of morphine, and preliminary studies indicated a role as an adjuvant treatment for pain in cancer patients²¹. Further research is needed in patients with moderate and severe cancer pain because it is not clear if there is benefit. The patient's progress should be monitored carefully.

Regional analgesia

A nerve block procedure can be used to stop pain signals from being sent to the brain. In this context the methods of regional anesthesia and analgesia is very useful for pain relief. Furthermore, a large number of patients are afraid of taking opioids. They have a fear of addicting to opioids, fear of side effects and developing tolerance to it. Tolerance is not addiction. Tolerance means that you might need a higher dose to control your pain. Methods of regional nerve blockade in pain control are numerous. Placement of epidural catheter, intrathecal catheter, subcutaneous catheter, conductive nerve blocks with continuous delivery of mixed local anesthetics are very successful for selected patients. Listed catheters may be combined with PCA pumps or elastomeric pumps, which enable a patient a better life quality without being admitted. Application of local anesthetic is useful in cancer patients because local anesthetics, contrary to opioids stimulate the activity of natural killer cells. Opioids administration has been shown to suppress cell-mediated and humoral immunity²².

Additional useful procedures

Specifically designed nutrition education is very useful for the management of chronic pain and it contribute to decrease in cancer pain. The main benefits are improved meal consumption pattern along with reduced consumption of food with pro-inflammatory effect²³. Physical therapy has important role for pain

control in cancer patients. Physical therapists design personalized exercise and treatment programs to help cancer survivors increase their physical activity. Physical activity has been shown to reduce or prevent many cancer-related problems. It is not limited only to exercise but includes magnetotherapy, TENS, ultrasound electrotherapy and lymphatic drainage. Some people find some pain relief through acupuncture, infiltration trigger points, massage, psychotherapy, relaxation exercises, music-based interventions, meditation and hypnosis²⁴. In some cases, it may be legal to use medical marijuana for cancer pain²⁵.

Conclusion:

Adequate pain assessment and management are critical to improve the quality of life and health outcomes in this population. A strong opioid remains the drug of choice for treating moderate or severe pain in patients with advanced cancer. Future research should focus on defining the efficacy of NSAIDs, anti-depressants, anticonvulsants, corticosteroids and the likely role for non-pharmacological approaches in management of pain in patients with advanced cancer.

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Sažetak

KARCINOMSKA BOL I TERAPIJA

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Karcinomska bol nije homogen i potpuno razjašnjen patološki proces. Najbolja terapija je kombinacija medikamentozne terapije i nemedikamentoznih postupaka. Možemo je podijeliti na visceralnu, koštanu i neuropatsku bol i ima karakteristike kontinuirane ili povremene boli. Terapija koštane boli fokusirana je na jake opioide, radioterapiju i bifosfonate. Cilj invazivnih metoda liječenja boli je poboljšati neurološku funkciju, pokretljivost i olakšanje boli. Solidni tumori često zahtijevaju operaciju. Liječenje akutne poslijeoperacijske boli je od iznimne važnosti u prevenciji nastanka kronične boli. Kemoterapija i radioterapija ponekad također uzrokuju bol. Liječenje karcinomske boli je poboljšano bržom dijagnostikom i terapijom, boljim poznavanjem analgetika i suradnjom s pacijentom i njegovom obitelji. Postojanje specijaliziranih centara za bol u bolnicama također je podiglo standard u liječenju boli. Liječenje boli medikamentozno neopioidima, opioidima i drugim pomoćnim lijekovima je osnova liječenja boli. Nuspojave lijekova moraju se neprestano pratiti i na vrijeme liječiti. Metode regionalne nervne blokade u liječenju boli su brojne. Plasiranje epiduralnih, intratekalnih i supkutanih katetera s kontinuiranom isporukom mješavine lokalnih anestetika veoma su uspješne kod određenih bolesnika. Fizikalna terapija s limfnom drenažom je korisna. Akupunktura, psihoterapija i slične metode su također primjenjive.

Ključne riječi: *Karcinomska bol, opioidi, non-opioidi, adjuvantni lijekovi, regionalni živčani blok, integrativna medicina*