

# INTEGRIRANI PRSTUP I SUVREMENE STRATEGIJE LIJEČENJA KARCINOMSKE BOLI



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Prema Međunarodnom udruženju za proučavanje boli (IASP), kronična karcinomska bol karakterizirana je trajnom neugodom koja je uzrokovana primarnim tumorom, metastazama, ili je uzrokovana terapijskim intervencijama. Bol je čest simptom u onkoloških pacijenata, javlja se u više od 44% slučajeva, a u uznapredovalim stadijima bolesti prevalencija je viša od 70%. Iako bol nije izravno ugrožavajući čimbenik, jedan je od najčešćih i najvećih uzroka onesposobljenosti te značajno narušava kvalitetu pacijentova života. Uzrokuje poremećaj sna, smanjenje apetita, društvenu izolaciju te ograničava svakodnevne aktivnosti pacijenta. Nekontrolirana bol dovodi do anksioznosti, depresije, sklonosti suicidu, te strah od boli postaje veći od straha od same smrti. Usprkos napretku dijagnostike i liječenja tumora posljednjih godina, loše kontrolirana bol još je uvijek značajan problem. Važno je pacijenta upoznati s mogućom pojavom boli u bilo kojem stadiju bolesti te za vrijeme ili nakon dijagnostičkih i terapijskih postupaka. Napredak u liječenju onkoloških bolesnika omogućio je dulje preživljenje, pa i izlječenje pojedinih bolesnika. Posljedično tome, sve je veća skupina pacijenata koji su preživjeli onkološku bolest, tzv. „cancer survivors“. Gotovo 47% pacijenata ove skupine ima kroničnu bol koja je povezana s ranijim kirurškim zahvatima, kemoterapijom, radioterapijom ili pate od kronične boli koja nije povezana s onkološkom bolešću. Bol je u onkoloških bolesnika najčešće mješovitog tipa te obuhvaća nociceptivnu i neuropatsku komponentu. Ključ postizanja adekvatne analgezije krije se u pravilnome prepoznavanju uzroka i karaktera boli. Prilikom stvaranja programa liječenja važno je educirati pacijenta o pravilnome uzimanju lijekova, uključiti ga u proces liječenja, a navedenim postizemo bolju procjenu i suradljivost u liječenju. Postupak liječenja i propisivanja terapije najčešće je vođen trostupanjskom ljestvicom boli prema Svjetskoj zdravstvenoj organizaciji (SZO). Sve češće se govori o modificiranoj četverostupanjskoj ljestvici, kojoj se pridružuju i minimalno invazivne odnosno intervencijske tehnike u liječenju boli. Izbor vrste i doze analgetika ovisi o intenzitetu boli te je potrebno postići adekvatan omjer između optimalne analgezije s najmanje nuspojava. Analgetici su dio integriranog pristupa liječenja onkoloških pacijenata, a on obuhvaća primarno onkološko liječenje, intervencijske terapijske mogućnosti te neinvazivne tehnike poput rehabilitacijskih i psiholoških intervencija. Prilikom izbora načina primjene lijeka preferira se oralni put primjene osim kada to nije moguće radi povraćanja, crijevne opstrukcije, disfagije, teške konfuzije, nuspojava opijata te u slučajevima kada izraziti intenzitet boli zahtijeva brzu eskalaciju doze. Transdermalna primjena lijeka trebala bi biti rezervirana za pacijente sa stabilnom

potrebom za opioidnim analgeticima. Transdermalna primjena lijeka kontraindicirana je u titracijskoj fazi liječenja, u opioidno naivnih pacijenata te u liječenju probijajuće boli. U svim stadijima liječenja boli, neopioidni analgetici poput paracetamola i nesteroidnih antireumatika (NSAR) mogu biti dio multimodalne strategije liječenja. Opioidni analgetici najčešći su izbor u analgetskoj terapiji, a dijelimo ih prema mogućnosti da kontroliraju slabu do umjerenu te umjerenu do jaku bol. Druga stepenica liječenja prema SZO-u ima nekoliko kontroverzi, a odnose se na upitnu učinkovitost slabih opioida u liječenju. Dosadašnje studije nisu pokazale značajnu razliku u učinkovitosti lijekova prve i druge stepenice liječenja, a u tijeku su studije koje ispituju ulogu druge stepenice liječenja. Uslijed nedostatka dokaza o učinkovitosti tramadola, dihidrokodeina i kodeina u liječenju karcinomske boli, brojni autori predlažu napuštanje druge stepenice ljestvice SZO-a s preporukom administracije niže doze jačih opioida s ciljem postizanja većeg analgetskog učinka. Navedeno za sada nije u smjernicama liječenja SZO-a, a razina dokaza jest II, C. Jaki opioidi glavna su linija analgetske terapije u liječenju umjerene i jake boli. Iako postoje brojni opioidni analgetici, jedan nije superioran drugome. Morfin je najrasprostranjeniji i najpropisivaniji analgetik. Pacijentima s oštećenom funkcijom jetre ili bubrega potrebno je prilagoditi vrstu i dozu analgetika zbog toga što nakupljanje toksičnih metabolita može dovesti do životno ugrožavajućih simptoma poput konfuzije, halucinacije te poremećaja stanja svijesti. Nakon uvođenja opioidnog analgetika s vremenom može doći do smanjenja analgetskog učinka uslijed razvoja tolerancije. Povećanjem doze analgetski učinak može izostati, a mogu se pojaviti i nuspojave odnosno komplikacije u vidu opioidne hiperalgezije (OIH) ili opioidima inducirane konstipacije (OIC). U slučaju da se neželjeni učinci ne mogu kontrolirati, potrebno je lijek zamijeniti drugim opioidom, a navedeno se naziva opioidna rotacija. Cilj opioidne rotacije je postići bolji analgetski učinak ili smanjiti intenzitet nuspojava. Rotacija analgetika nije tek zamjena jednoga lijeka za drugi, već je potrebno poznavati ekvivalentske doze različitih opioida. Izbor lijeka potrebno je prilagoditi kliničkoj slici, komorbiditetima te drugim lijekovima i koanalgeticima koje pacijent uzima. Dodatna karakteristika karcinomske boli jest probijajuća bol s različitom prevalencijom ovisno o studijama, a prosječno javlja se u 59% bolesnika. Probijajuća bol definira se kao epizoda jake boli koja se javlja u pacijenata s pozadinskom boli koja je kontrolirana stabilnom dozom opioida. Probijajuća bol liječi se lijekovima koji se uzimaju u slučaju potrebe odnosno napada probijajuće boli. Budući da napad probijajuće boli nastupa relativno brzo, učinak lijeka treba biti brz. Razvijene su formulacije lijekova čiji nastup djelovanja nastupa brzo, za 10-15 minuta. Primjenjuju se oralnim putem, u obliku bukalnih ili sublingvalnih tableta te intranazalnog spreja. Navedeni oblici lijekova primjenjuju se kod pacijenata koji već primaju opioidne analgetike te u onih čija je dnevna doza ekvivalentnog morfina barem 60 mg. Karcinomska bol nerijetko ima i neuropatski karakter, javlja se u oko 40% slučajeva. Često je neprepoznata i time neadekvatno liječena. Neuropatska karcinomska bol često je uzrokovana oštećenjem somatosenzornog sustava uslijed kirurškog liječenja, radioterapije ili kemoterapije. Adjuvantne analgetike poput antidepressiva (amitriptilin, duloksetin) ili antiepileptika (pregabalina,

gabapentin) koristimo u liječenju neuropatske komponente boli. Navedeni lijekovi najčešće se koriste u kombinaciji s opioidnim analgeticima. Od prilike 10% pacijenata trpi bolove koje je teško kontrolirati oralnom ili parenteralnom primjenom lijekova te je potrebno posegnuti za invazivnim mogućnostima liječenja. One obuhvaćaju blokade ili neolizaciju živaca, intratekalanu primjenu lijeka te stimulaciju kralježnične moždine. Nefarmakološke metode liječenja nadopuna su farmakološkima, a ovisno o stadiju i tipu maligne bolesti razlikuju se indikacije, mogućnosti te njihova učinkovitost. One uključuju akupunkturu, meditaciju, jogu, Tai Chi, Qi Gong, terapiju glazbom te art terapiju. Cilj ovih metoda je umanjiti bol, umor, tegobe anksioznosti i depresije, ali i potencijalno umanjiti potrebu za uzimanjem lijekova. Zaključak: Bol je čest i kompleksan klinički problem u onkoloških pacijenata, a nerijetko je loše kontrolirana. Liječenju boli treba pristupiti individualno prema multimodalnom i interdisciplinarnom principu. Cilj liječenja treba biti poboljšanje i unaprjeđenje kvalitete života pacijenata.

### **Ključne riječi**

karcinomska bol, liječenje boli, rehabilitacija

## **INTEGRATED APPROACH AND MODERN STRATEGIES FOR CANCER PAIN MANAGEMENT**

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According to the International Association for the Study of Pain (IASP), chronic cancer pain is characterized by persistent discomfort caused by the primary tumor, metastases or as a consequence of therapeutic interventions. Pain is a common symptom in patients with cancer, occurring in more than 44% of cases, while in advanced stages of the disease its prevalence exceeds 70%. Although pain is not directly life-threatening, it is one of the most common and significant causes of disability and substantially impairs a patient's quality of life. It leads to sleep disturbances, reduced appetite, social isolation and limitations in daily activities. Uncontrolled pain results in anxiety, depression, suicidal ideation, and fear of pain may become greater than the fear of death itself. Despite advances in cancer diagnostics and treatment in recent years, poorly controlled pain remains a significant problem. It is essential to inform patients about the possible occurrence of pain at any stage of the disease, as well as during or after diagnostic and therapeutic procedures. Advances in oncology have enabled longer survival and some patients are free of disease completely. Consequently, there is a growing population of cancer survivors. Nearly 47% of patients in this group experience chronic pain related to previous surgical procedures, chemotherapy, radiotherapy, or suffer from chronic pain unrelated to cancer. Cancer pain is most often of a mixed type, encompassing both nociceptive and neuropathic components. The key to achieving adequate analgesia lies in proper identification of the cause and nature of the pain. Pain management and prescribing practices are most commonly guided by the three-step analgesic ladder of the World Health Organization (WHO). A modified four-step ladder is discussed, incorporating interventional pain

management techniques. The choice of analgesic type and dose depends on pain intensity, and an optimal balance between effective analgesia and minimal side effects should be achieved. Analgesics represent only one component of an integrated approach to cancer care, which also includes primary oncological treatment, interventional therapies, and non-invasive methods such as rehabilitation and psychological interventions. When selecting the route of drug administration, the oral route is preferred unless contraindicated due to vomiting, intestinal obstruction, dysphagia, severe confusion, opioid-related side effects, or when severe pain intensity requires rapid dose escalation. Transdermal drug delivery should be reserved for patients with stable opioid requirements. It is contraindicated during dose titration, in opioid-naïve patients and in the treatment of breakthrough pain. At all stages of pain management, non-opioid analgesics such as paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs) may be included as part of a multimodal treatment strategy. Opioid analgesics are the most commonly used agents in analgesic therapy. The second step of the WHO ladder remains controversial due to questionable efficacy of weak opioids. Existing studies have not demonstrated a significant difference in effectiveness between first- and second-step medications, and ongoing research continues to evaluate the role of the second step. Due to insufficient evidence supporting the effectiveness of tramadol, dihydrocodeine and codeine in cancer pain management, many authors propose skipping the second step of the WHO ladder in favor of administering lower doses of strong opioid to achieve superior analgesic effects. This approach is not yet included in WHO guidelines, and the current level of evidence is II, C. Strong opioids are the mainstay of analgesic therapy for moderate to severe pain. Although numerous opioid analgesics are available, none has proven superior to others. Morphine remains the most widely used and prescribed analgesic. In patients with impaired liver or renal function, both the type and dose of analgesics must be adjusted, as accumulation of toxic metabolites may result in life-threatening symptoms such as confusion, hallucinations, and altered consciousness. Over time opioid therapy may lead to reduced analgesic efficacy due to tolerance development. Increasing the dose may fail to improve analgesia and may instead result in adverse effects or complications, such as opioid-induced hyperalgesia (OIH) or opioid-induced constipation (OIC). If adverse effects cannot be adequately controlled, switching to another opioid, known as opioid rotation may be indicated. The goal of opioid rotation is to achieve improved analgesia or reduce side effects. This process requires knowledge of equianalgesic dosing and careful consideration of the patient's clinical condition, comorbidities and concomitant medications, including co-analgesics. An additional characteristic of cancer pain is breakthrough pain, with reported prevalence varying across studies and averaging approximately 59%. Breakthrough pain is defined as an episode of severe pain occurring in patients with otherwise controlled baseline pain managed with stable opioid doses. It is treated with rescue medications administered as needed during pain episodes. Since breakthrough pain develops rapidly, rapid acting analgesics are necessary. Formulations with an onset of action within 10–15 minutes have

been developed and are administered orally in the form of buccal or sublingual tablets or as nasal sprays. These formulations are indicated for patients already receiving opioid therapy and whose daily morphine-equivalent dose is at least 60 mg. Cancer pain frequently has a neuropathic component, occurring in approximately 40% of cases. It is often underrecognized and consequently inadequately treated. Neuropathic cancer pain commonly results from damage to the somatosensory system due to surgery, radiotherapy or chemotherapy. Adjuvant analgesics such as antidepressants (amitriptyline, duloxetine) and antiepileptics (pregabalin, gabapentin) are used in treatment of neuropathic pain, most often in combination with opioid analgesics. Approximately 10% of patients experience pain that is difficult to control with oral or parenteral pharmacotherapy, necessitating invasive treatment options. These include nerve blocks or neurolysis, intrathecal drug administration and spinal cord stimulation. Non-pharmacological treatment methods complement pharmacological therapy. These methods include acupuncture, meditation, yoga, Tai Chi, Qi Gong, music therapy, and art therapy. Their aim is to reduce pain, fatigue, anxiety and depressive symptoms, as well as potentially decrease the need for analgesic medications. Conclusion: Pain is a common and complex clinical problem in cancer patients and is frequently inadequately controlled. Pain management should be individualized and based on a multimodal and interdisciplinary approach. The primary goal of treatment is to improve and enhance the patient's quality of life.

### Keywords

cancer pain, pain management, rehabilitation

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