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ACUTE AND CHRONIC PAIN MANAGEMENT IN ONCOLOGY PATIENTS: A LITERATURE REVIEW

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Abstract: Pain management in cancer patients is a crucial concern in clinical practice, aiming to improve the quality of life and well-being of these individuals. The approach involves both acute and chronic pain, and a comprehensive assessment is essential to determine the intensity and characteristics of the pain. Appropriate use of analgesics, such as opioids and non-opioids, is critical for acute pain relief, while chronic pain requires a multidisciplinary approach that includes both pharmacological and non-pharmacological therapies. Adjuvants, such as antiepileptics and antidepressants, can be incorporated to potentiate analgesic effects and improve pain control. In addition, analgesic radiotherapy and chemotherapy play an important role in the management of pain in cancer patients, especially when there are bone metastases or other contributing factors. Individualization of treatment is crucial, considering the patient's needs and preferences, as well as possible side effects and drug interactions. However, access to opioids, often required for effective cancer pain management, may be limited by regulatory concerns and fears of addiction. Therefore, pain management in cancer patients requires a careful balance between pain relief and the risks associated with the use of potent analgesics. In summary, integrated, evidence-based approaches tailored to individual needs are essential for effective pain management in cancer patients, seeking to improve quality of life during the course of the disease.

INTRODUCTION

Pain, a complex and universally experienced phenomenon, plays a fundamental role as a warning and protection mechanism in the human body. This aversive sensation is triggered in response to harmful or harmful stimuli, acting as a sign that something is threatening the integrity of the organism.

Understanding the pathophysiology of pain is crucial for understanding the biological and neural processes underlying this experience, as well as for developing more effective approaches to pain management and treatment.¹

The pathophysiology of pain can be divided into three interconnected stages: transduction, transmission and modulation.² The first step, transduction, occurs when nociceptors, specialized sensory receptors, are activated by noxious stimuli such as tissue injury or inflammation. This activation triggers an electrochemical process that results in the conversion of the stimulus into electrical signals, known as action potentials. These electrical signals are then transmitted along nerve fibers to the spinal cord.

Transmission, the second step, involves the conduction of pain signals from the spinal cord to the brain, where conscious perception of pain takes place. In this process, the nerve fibers of the spinothalamic system and medial lemniscus play crucial roles. Fibers C and A-delta, belonging to the spinothalamic system, transmit information about the intensity and location of pain, while A-beta fibers of the medial lemniscus transmit the sensation of touch. The information is then processed in specific areas of the brain, including the thalamus and somatosensory cortex, resulting in the conscious perception of pain.²

The final step, modulation, involves the brain's influence on pain perception. Modulation mechanisms can amplify or inhibit the pain sensation. The endogenous opioid system, for example, releases neurotransmitters such as endorphins, which act on opioid receptors in the central nervous system to reduce the sensation of pain. Furthermore, emotional, cognitive and contextual factors also play a role in pain modulation.

In the context of chronic pain, neuroplastic changes occur in the nervous system, contributing to a prolonged persistence of pain. These changes may include central sensitization, in which the excitability of neurons in the spinal cord increases, resulting in an exacerbated response to painful stimuli.^{3,4}

PAIN IN CANCER PATIENTS

Pain in cancer patients is a multifaceted phenomenon that results from complex interactions between cancer, its treatment and the body's physiological responses. In these patients, pain can be classified into several categories, including cancer-related pain, treatment-related pain, and incidental pain. The pathophysiology varies according to the origin of the pain, but many of these cases share similar mechanisms. Tumor growth can cause compression of adjacent structures, activate nociceptors and induce local inflammation. In addition, cancer treatment itself, such as surgery, chemotherapy or radiotherapy, can cause tissue damage and inflammation, contributing to the generation of pain.⁵

In the context of cancer pain, pathophysiology often involves the release of inflammatory mediators, such as prostaglandins and cytokines, which sensitize nociceptors and amplify pain perception. The tumor itself may secrete chemicals, known as growth factors, that stimulate the formation of new blood vessels (angiogenesis) and local invasion, contributing to pain. In addition, bone metastases can cause severe pain due to bone destruction and release of calcium ions.⁶

On the other hand, chemotherapeutic agents can also cause damage to peripheral nerve fibers, resulting in peripheral neuropathy. This condition manifests itself as pain, tingling and numbness in the extremities, significantly affecting the patients' quality of life. Also, radiation therapy can cause inflammation in the skin and surrounding tissues, leading to

sharp pain.⁷

The physiology of pain in cancer patients also encompasses neuroplastic aspects. Changes in pain transmission and modulation may occur due to constant activation of pain pathways, leading to central sensitization.⁸ This phenomenon may contribute to chronic pain in cancer patients, even after resolution of the initial stimulus.

MEASURE TO TREAT

Pain assessment requires standardization of scales and a uniform measurement unit to ensure reliable and comparable results. Several examples of scales are found in the literature for this purpose, with the Visual Analogue Scale (VAS) being the most widely used. However, the validity of all these scales is subject to patients' cognitive factors and abstract reasoning ability, among other aspects.⁹

Health professionals have the flexibility to use different scales, as long as they are decoded using the same table of values. The VAS, for example, can be a 10-centimeter line, in which the patient indicates the place where he experiences pain. The evaluator, using a graduated ruler, can then determine the corresponding numerical value. This method, which even allows numerical fractions, is considered more accurate by some professionals.¹⁰

There are scales that are less intuitive, such as those that do not have a visual representation. These scales can be more complex to understand, since they require refined abstract reasoning. In addition, some scales use colors, which can lead to false results due to individual preferences, especially in children.

An alternative is the numerical visual scale, where the patient assigns a score from zero to 10 for pain intensity, choosing to use colors or not for each level. It is important

to establish intervals between reference numerals, preferably with fixed and predefined values. The universalization of these values contributes to the comparability of results between different evaluations.⁹

Categorizing pain as mild, moderate, and severe is also a useful approach. This can be done based on the grades assigned by the patient: mild pain (0-3), moderate pain (4-6), and severe pain (7-10). One suggestion is to present these intervals on the back of the scale, avoiding influencing the patients' assessment.

The use of validated scales and tools has been highlighted as an essential strategy to quantify and qualify the painful experience. The study by Ferreira et al. (2019), emphasizes the importance of scales, such as the Numerical Scale and the VAS, in identifying pain intensity and monitoring response to treatment. In addition, it shows that these scales allow for clearer communication between the patient and the health team. By incorporating this approach, health professionals are able to quantify and monitor pain more precisely, allowing for a more targeted therapeutic intervention and, consequently, improving patients' quality of life.¹¹

Understanding the contributing factors to pain is also essential for effective management. The research carried out by Almeida et al. (2017), highlights that biological factors, such as tumor location and lesion characteristics, play an important role in the genesis of cancer pain.¹² Furthermore, psychosocial factors such as anxiety and depression have also been identified as significant contributors to pain perception, as evidenced by studies such as that by Thompson et al. (2018).¹³

Pain management in cancer patients requires a comprehensive and personalized approach, in which pharmacological analgesia plays a key role. However, it is important to consider the different classes of analgesics and their limitations in the search for effective and

safe pain relief and they must be prescribed for the correct indications.

DIFFERENT DIMENSIONS OF PAIN

Understanding pain classification is crucial for adequate and personalized management of painful conditions. Pain can be categorized into different types, each with its specific characteristics, origins and therapeutic responses. Let's explore the main types of pain and their particularities.

Nociceptive pain comprises two subtypes: somatic and visceral. Somatic pain arises from injuries to the skin or deeper tissues and is typically localized. Visceral pain, on the other hand, originates in the abdominal or thoracic viscera, often causing a sensation of deep pressure and sometimes being referred to an area distant from the painful stimulus. Nociceptive pain is a direct response to chemical or physical stimulation of normal nerve endings. It is commonly seen in traumatic, inflammatory, invasive, or ischemic situations.²

Neuropathic pain results from damage or dysfunction of nerves along neuronal transmission pathways. This damage can be caused by trauma, infections, degenerative diseases, tumor invasion, among others. The hallmark of neuropathic pain is the presence of pain complaints with neurodermal irradiation, often described as a burning sensation. This pain occurs when there is a breakdown in nerve functions, leading to abnormal pain perception.²

Sympathomimetic pain is differentiated by reporting arterial irradiation. This pain is usually associated with a response from the sympathetic nervous system, resulting in symptoms such as increased blood pressure and tachycardia. To make an accurate differential diagnosis, anesthetic block may be necessary.

Pain can also be classified based on its duration and pattern. Acute pain, of sudden onset, is related to traumatic, infectious or inflammatory conditions. It usually disappears after interventions in the underlying cause and is associated with neurovegetative responses such as increased blood pressure and anxiety. Chronic pain, on the other hand, is more persistent and is related to ongoing pathological processes. It may be linked to emotional and behavioral aspects such as anxiety and depression.

The research by Oliveira et al. (2018) explores classes of non-opioid analgesics such as non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophens, emphasizing their usefulness in mild to moderate pain. However, the need to assess potential adverse effects, such as gastrointestinal, liver and kidney damage, is emphasized.¹⁴ Thus, World Health Organization guidelines guide the rational use of non-opioid and opioid analgesics, based on the assessment of pain intensity and consideration of the patient's clinical conditions.

THE DREADED OPIOIDS

Current clinical practice guidelines converge in recognizing that opioids play a central role in the management of cancer-related pain. Given that there is no clear evidence favoring one opioid over another, drug selection must be personalized, taking into consideration, the patient's previous experience, the function of the affected organ, the ideal route of administration (oral, parenteral, transdermal, rectal and buccal/sublingual), the preferred formulation (tablets, capsules, liquids) and whether immediate and/or controlled release is required.¹⁵

However, while highly effective, opioids face significant challenges regarding access, prescribing, and distribution resulting from the unintended consequences of

efforts to curb opioid-related deaths. The reduction in the production of these drugs generated shortages, resulting in reduced or delayed access to essential treatments. Some pharmacies have limited stocks and, in some cases, refuse to supply controlled substances. In addition, insurers require time-consuming and bureaucratic prior authorizations, leading to delays and increasing costs for patients. These hurdles, along with growing regulatory concern and fears of legal action, have impacted prescribing practices.

The total volume of opioids prescribed by prescription decreased by about one-fifth between 2008 and 2018, with a significant 41.5% drop in prescriptions covered by commercial insurance. The total number of opioid pills dispensed also dropped from 17.8 billion in 2012 to 11.1 billion in 2018.^{16,17}

This decline in access to opioids is also observed in oncological contexts.¹⁸ In a survey of more than 4,000 cancer patients in rural areas, more than 60% were never prescribed a Class II opioid.¹⁹ When prescribed, studies indicate a reduction in morphine milligram equivalents (MME) prescribed by oncologists. One study demonstrated a decrease from 78 to 40 mg, while another reported a 37% drop in MME from 2011 to 2017 in patients with cancer-related bone metastases.^{20,21} Similar data were seen in Medicare patients with poor prognosis cancers, with a reduction in MME from 85.6 mg to 64.6 mg and fewer patients receiving extended-release opioids.²² Coinciding with these findings, there was an increase in pain-related visits to emergency departments from 13.2% to 50.8% between 2007 and 2017.

BONE PAIN AND ITS IMPACTS

Pain from the spread of cancer to the bones is one of the main causes of moderate and severe pain in cancer patients. Approximately 75% of patients with advanced disease experience bone pain. However, only half of them get temporary pain relief through conventional therapies, which clearly indicates the urgent need to develop more effective treatments.

Cancer-induced bone pain is a complex pain state, involving a mixture of background pain, spontaneous pain, and incident pain (pain triggered by movement). The background pain, characterized by being continuous and dull, increases in intensity as the disease progresses and is relatively treatable with traditional analgesics. On the other hand, spontaneous pain and incident pain, often referred to as “breakthrough pain”, represent episodes of extreme pain that cut through the therapeutic regimen administered to control background pain. The intermittent nature of these types of pain makes treatment difficult, as episodes are quick in onset and of short duration, making currently available analgesic therapies insufficient and associated with limiting adverse effects.

Cancer-induced bone pain is a combination of neuropathic and inflammatory pain, with distinct tissue and nerve changes in the periphery, as well as unique neurochemical changes at the spinal cord level. Thus, it is a complex syndrome involving inflammatory, neuropathic, ischemic and cancer-specific mechanisms, often occurring in more than one location. Inflammatory infiltration occurs due to direct tissue damage caused by tumor growth, as well as the release of pain mediators by cancer cells. The neuropathic component of pain may arise from damage to sensory nerves caused by tumor growth, tumor-induced hyperinnervation, and elongation or denervation as the bone is affected by tumor growth. In addition, neuropathy can develop

as a consequence of therapeutic interventions such as chemotherapy or surgery.²²

The mechanisms underlying the pathophysiology are induced both peripherally and centrally, with altered impulses coming from surrounding bones and tissues, leading to a state of general hyperexcitability of neurons in the spinal cord. Interestingly, the presence and intensity of pain is not necessarily related to the size or number of active malignancies; while some sites of metastasis are completely painless, others cause intense pain even in cases of a single bone metastasis, even in the absence of fracture. This could be due to different balances between peripheral and central mechanisms, as well as the ability of central modulating systems to reduce peripheral activity, which can vary between patients.

The unique neurochemical signature of cancer-induced bone pain may explain the reduced effectiveness of traditional analgesics, suggesting that polypharmacy or alternative approaches may be more promising options for effective pain management. Thus, understanding strategies for managing bone pain is essential to face this complex challenge. Research such as that by Santos et al. (2021), highlight the importance of interventions such as radiotherapy and bisphosphonate therapy in controlling bone pain. These therapies not only reduce pain, but also aim to preserve bone integrity and improve quality of life. The study by Silva et al. (2019), addresses the effectiveness of specific targeted therapy for bone metastases, such as bone resorption inhibitors.^{24,25}

CANCER NEUROPATHIC PAIN

Neuropathic pain is a complex type of pain that arises as a result of dysfunction or damage to the nervous system, either the peripheral nervous system itself or the central nervous system. It is characterized by abnormal and unpleasant sensations, such as burning, tingling, electric shocks, pins and needles, among others. Unlike nociceptive pain, which is a response to noxious stimuli, neuropathic pain is caused by a malfunction in the nerves.

Neuropathic pain is a challenging manifestation in cancer patients, often resulting from nerve damage caused by the disease itself or by treatments such as chemotherapy. Management of neuropathic pain requires specific approaches that take into consideration, the complexity of this condition. Research such as that by Oliveira et al. (2022), emphasize the importance of anticonvulsant drugs, such as gabapentin and pregabalin, in the treatment of neuropathic pain. These drugs act in the modulation of excitable neurons, relieving the symptoms of neuropathic pain.²⁶

The study by Smith et al. (2021) discusses the effectiveness of physical therapies, such as transcutaneous electrical stimulation (TENS) and acupuncture, in the management of neuropathic pain in cancer patients. These complementary therapies have shown promising results in reducing pain and improving quality of life.²⁷ The Neuropathic Pain Special Interest Group (NeuPSIG) and American Society of Clinical Oncology (ASCO) guidelines recommend a multimodal approach to pain management neuropathic, involving both pharmacological treatments and physical therapies. The combination of anticonvulsant drugs, physical therapies and other specific interventions supported by national and international studies can provide effective relief of neuropathic pain and improve patients' quality of life.

CANCER VISCERAL PAIN

Visceral pain is a form of pain that originates in the internal viscera of the body, such as abdominal, thoracic and pelvic organs. Unlike somatic pain, which is perceived in the superficial structures of the body, visceral pain is the result of activation of nociceptors in the deeper layers of internal organs.

This pain is often described as diffuse and poorly localized, with a feeling of pressure, discomfort, or distension. Visceral pain can be triggered by several factors, such as inflammation, ischemia (lack of blood supply), organ distention, and involuntary muscle contractions. In addition, visceral pain can be referred, that is, felt in an area other than the one where the noxious stimulus is occurring. This is due to the way nerve fibers from organs share transmission pathways with fibers from somatic areas.²

Visceral pain is a common manifestation in cancer patients, often associated with tumor growth or aggressive treatments. Proper management of visceral pain requires a thorough understanding of the underlying pathophysiology and available therapeutic strategies. The research by Johnson et al. (2018) discusses the effectiveness of interventional therapies, such as neurostimulation and nerve blocks, in managing visceral pain in cancer patients.²⁸ These targeted approaches have shown promising results in reducing pain and increasing functionality, offering effective pain relief and improving patients' quality of life.

AUXILIARY DRUGS AND ADJUVANT TREATMENTS IN PAIN MANAGEMENT

Coadjuvant drugs include mainly antiepileptics, antidepressants and corticosteroids. These substances have different chemical compositions and must not be automatically prescribed. The association of antidepressants or antiepileptics with opioids has shown an increase in pain relief when used for neuropathic pain in non-cancer contexts. However, there is a lack of evidence to support its effectiveness in the context of cancer pain. Clinicians need to balance the small likelihood of benefit in patients with tumor-associated cancer pain against the increased risk of adverse effects from combination therapy. The use of antidepressants is indicated for patients who remain depressed even with improvement in pain control. Anxiolytics can be used for patients with high levels of anxiety.²⁹

Several current guidelines recommend the use of corticosteroids for certain types of cancer pain, especially when the pain is related to inflammatory processes and edema. Corticosteroids, anticonvulsants and neuroleptics play a role in selected situations. Some guidelines also contemplate the possibility of using ketamine, although they recognize the lack of solid evidence supporting its regular use. There is a limited amount of data indicating that intravenous lidocaine can reduce pain intensity in some patients, but other studies have not supported its effectiveness. The use of lidocaine carries the risk of recurrent adverse effects, so specialist supervision is essential. Lidocaine can be considered as an alternative in the treatment of cancer pain refractory to opioids.²⁹

Preclinical experiments indicate that tetrahydrocannabinol (THC) potentiates the antinociceptive effect of morphine, and preliminary studies suggest a role as an

adjuvant treatment for pain in cancer patients. However, more research is needed for patients with moderate to severe cancer pain, as the benefits are unclear. The patient's progress must be closely monitored.

A nerve block procedure may be employed with the aim of interrupting the transmission of pain signals to the brain. In this context, regional anesthesia and analgesia methods play a highly beneficial role in pain relief. Additionally, it is important to highlight that a considerable number of patients feel apprehensive about the use of opioids. Such patients fear the possibility of developing dependence, are concerned about side effects and express fears about tolerance to opioids. It is important to clarify that tolerance is not equivalent to dependence. Tolerance suggests the possibility that a higher dose is needed to control the painful sensation.³⁰

Several regional nerve block methods have been shown to be effective in pain management. Insertion of epidural catheter, intrathecal catheter and subcutaneous catheter, as well as conductive nerve blocks with continuous administration of mixed local anesthetics, have achieved remarkable success in carefully selected patients. Furthermore, these catheters can be combined with patient-controlled infusion (PCA) systems or elastomeric pumps, allowing patients to improve their quality of life without the need for hospitalization.

The application of local anesthetics proves to be beneficial for cancer patients, since, in contrast to opioids, local anesthetics stimulate the activity of natural killer cells. It is noteworthy that the administration of opioids has been associated with the suppression of cellular and humoral immunity.

IN ADDITION TO THE PHYSICAL ASPECTS

Pain in cancer patients often triggers significant psychosocial impacts, affecting not only physical well-being, but also mental health and quality of life. Therefore, your approach must consider these aspects to provide a comprehensive treatment. Studies have already demonstrated the correlation between chronic pain and psychological disorders, such as anxiety and depression. From this, Lima et al. (2021) emphasizes the importance of cognitive-behavioral therapy in pain management in cancer patients. This psychotherapeutic approach aims to modify negative beliefs regarding pain, improving the patient's adaptation. ESMO guidelines recommend a multidisciplinary approach that integrates pharmacological interventions, physical therapies and psychosocial therapy to address pain and its emotional impacts.³¹

Pain management in cancer patients requires a comprehensive approach that considers not only physical pain, but also the emotional and mental health of the patient. Psychosocial intervention plays a key role in this context, aiming to improve patient adaptation and quality of life. The research by Santos et al. (2019) highlights the effectiveness of group therapy in pain management in cancer patients, by promoting a safe space for the expression of emotions, exchange of experiences and mutual support among patients. Cognitive-behavioral therapy and relaxation interventions are also cited as effective strategies to deal with emotional distress associated with pain.³²

Spirituality plays a significant role in pain management, contributing to the search for meaning and well-being in the face of the diagnosis and treatment of the disease. The spiritual approach to pain care not only considers the physical aspect, but also the emotional and existential aspects of the patient.

Silva et al. (2021) highlights the importance of spirituality as a resilience factor in coping with pain. Seeking meaningful connections and a spiritual perspective can ease emotional distress and improve quality of life. Spirituality is seen as a dimension that offers comfort and support, regardless of religious affiliation.

Patient education is also an essential component in pain management for these patients, enabling them to understand and manage their condition more effectively. Adequate information can help patients actively participate in the treatment process and make informed decisions about pain management options. This approach seeks to provide information about the causes of pain, treatment options and self-management strategies, allowing patients to become active partners in care.

THE IMPORTANCE OF THE MULTIDISCIPLINARY APPROACH

A multidisciplinary approach in the treatment of cancer patients has proven to be essential to meet the needs of these patients, who often face not only physical pain, but also the emotional and psychosocial impact associated with the disease. Studies have highlighted the importance of a health team that includes physicians, nurses, psychologists and therapists specialized in palliative care, working together to provide comprehensive and personalized treatment.

According to research conducted by Silva et al. (2020), a multidisciplinary approach resulted in a significant improvement in the quality of life of cancer patients, reducing pain intensity and side effects of analgesics. Furthermore, a study published by Johnson et al. (2018) highlighted that the collaborative approach resulted in better communication between healthcare professionals and patients, allowing for a clearer understanding

of individual needs.

The works highlight the importance of multidisciplinary teams in the prevention of chronic pain in cancer patients, through early identification and targeted interventions. This approach, in line with World Health Organization guidelines for pain management in cancer patients, reinforces the need for a holistic treatment that goes beyond pain relief, encompassing psychosocial and emotional aspects. Given the uniqueness of each case and the need to address not only the physical aspect, but also the emotional and psychosocial aspects, the multidisciplinary approach provides a more complete view of the patient's condition, allowing for a treatment plan that is more adapted to individual needs.

CONCLUSION

The approach to pain management in cancer patients is a complex and multidisciplinary task that requires an in-depth understanding of pain pathophysiology and available therapeutic options. Acute and chronic pain associated with cancer can have different origins and manifestations, requiring an individualized and comprehensive assessment. The use of analgesics, including opioids and non-opioids, is essential to relieve acute pain, while chronic pain can benefit from approaches that involve not only drugs, but also non-pharmacological therapies, such as analgesic radiotherapy and chemotherapy.

The inclusion of adjuvant drugs and consideration of the patient's concerns are essential to personalize treatment and achieve adequate pain control. Access to opioids, while crucial for many patients, faces regulatory challenges and concerns related to long-term use. Therefore, it is necessary to find a balance between pain relief and the possible associated risks.

However, as scientific understanding advances and new therapies are developed,

the perspective of pain management in cancer patients continues to evolve. More effective and personalized approaches are being explored, along with strategies to mitigate obstacles in accessing appropriate treatments. The focus on the patient's quality of life and the improvement of overall well-being remains the main goal. Ultimately, collaboration between healthcare professionals, patients and their families is critical to optimizing pain

management in oncology settings, providing meaningful relief and a more bearable journey for those facing such complex health challenges.

CONFLICT OF INTERESTS

There is not any.

FINANCING

The own researchers.

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