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EVOLUȚIA DURERII ONCOLOGICE GREU TRATABILE SUB TRATAMENT INDIVIDUALIZAT: FACTORI PREDICTIVI

PREDICTIVE FACTORS FOR THE EVOLUTION OF DIFFICULT-TO-TREAT CANCER PAIN UNDER INDIVIDUALIZED TREATMENT

REZUMAT

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Totodată, vă invităm să luați parte la ședința publică de susținere a tezei de doctorat.

Vă mulțumim.

1. INTRODUCTION

Insufficiently controlled oncologic pain remains a persistent concern despite the presence of both national and international treatment guidelines. Despite the use of potent opioids, a significant proportion of patients continue to experience severe pain (Zoëga et al., 2013). Furthermore, inadequate pain control affects over a third of individuals experiencing oncologic pain (Greco et al., 2014).

A holistic approach to pain is one of the premises of palliative care, aiming to control the symptoms of oncologic patients and improve their quality of life. This methodology investigates the pain of oncologic patients, extending beyond the mere physical aspect to encompass the psycho-emotional, social, and spiritual dimensions. Unfortunately, the psycho-emotional distress experienced by oncologic patients is frequently underdiagnosed and undertreated, hindering the therapeutic success. Screening for psycho-emotional suffering followed by its treatment plays a pivotal role in augmenting the management of oncologic pain and subsequently elevating the quality of life for these patients.

The theoretical part has been structured into 8 chapters.

Chapter 1 outlines the rationale behind the choice to study difficult-to-treat pain in oncology patients, the relationship between pain and psycho-emotional distress, as well as the impact of pain on the quality of life in oncology patients.

Chapter 2 defines pain, describes the epidemiology, etiology, and pathophysiology of pain, and classifies pain based on its mechanisms. Additionally, this chapter describes the holistic approach to oncologic patients with pain.

Chapter 3 discusses the factors involved in the occurrence of difficult-to-treat pain and how they influence pain and treatment in oncologic patients.

Chapter 4 provides a synthesis of information concerning the presence of psycho-emotional distress in oncologic patients, including its prevalence, mechanisms of occurrence, assessment, the link between physical symptoms and psycho-emotional suffering in oncologic patients, and its impact on pain.

Chapter 5 presents relevant information drawn from specialized literature concerning the connection between pain and depression, specifically, it delves into the shared neural circuits existing between these clinical entities, playing a pivotal role in their pathogenesis.

Chapter 6 synthesizes literature-derived information on the administration of analgesic medication in oncologic patients with pain, including principles of analgesic administration, the stepwise approach to analgesia, defining pain control, barriers to achieving it, and a comprehensive overview of opioid medication.

Chapter 7 describes the rationale for using adjuvant medication in the management of oncologic pain, the types of adjuvant medications used in oncologic patients. It outlines the spectrum of adjuvant medications employed in oncology patient care, aligning recommendations with established guidelines, and consolidates empirical evidence from clinical studies.

Chapter 8 presents arguments regarding the relationship between oncologic pain and the quality of life in oncologic patients and describes how the assessment of quality of life is carried out in oncologic patients.

The special part has been structured into 8 chapters that describe the conduct of a comprehensive study designed to explore the constituents of intractable pain among oncology patients necessitating palliative care. It seeks to identify factors enabling the tailoring of personalized treatments for this kind of patients.

This study is the first study conducted in Romania that evaluates the complexity and multidimensionality of oncologic pain, the presence of intractable pain factors, and the influence of pain and intractable pain factors on the quality of life in advanced cancer patients with palliative care needs. It intervenes by providing individualized treatment that takes into account pain intensity, the pathophysiological type of pain, and the presence of intractable pain factors, including psycho-emotional suffering.

2. CANCER PAIN

Definition

According to the International Association for the Study of Pain (IASP), pain is defined as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage" (Raja et al., 2020). The involvement of the individual's psycho-emotional aspect in pain, alongside the physical aspect, highlights the impact of pain on the entire person.

The concept of "total pain " was introduced by Dame Cicely Saunders in the 1960s, signifying the experience of pain by an individual through its physical, psycho-emotional, spiritual, and cultural dimensions. Physical pain often coexists with psychological pain, which manifests through emotional suffering, including depression, anxiety, uncertainty, and hopelessness. Depression stands out as the most prevalent form of psychological pain associated with physical pain, worsening the quality of life and complicating pain management (Kwon et al., 2013; Laird et al., 2009; Syrjala et al., 2014).

Cognitive-behavioral responses to pain are components associated with physical pain that are identified within the holistic approach to pain. Consequently, patients may exhibit cognitive denial of pain due to cultural or spiritual beliefs or fear of recognizing the presence of a progressive disease as a failure (Schwabish, 2011).

The social response of individual to oncologic pain is characterized by social isolation, withdrawal from various interpersonal activities, burdening of family members, and the inability to afford the necessary analgesics for pain control (Carlson et al., 2013).

Spirituality and religion can influence how patients perceive and manage pain, the extent of this influence varying according to the patients' religion affiliation or individual beliefs (Brant, 2017).

The cultural environment of individuals influences their perception of pain, their ability to cope with pain, and the conceptual meaning attributed to it (Brant, 2017). For instance, there is a tendency for Asian patients to normalize pain, while Western patients actively seek health status triggered by pain (Kwok & Bhuvanakrishna, 2014).

The holistic approach to oncologic pain involves identifying the psychological, behavioral, and social suffering associated with pain, aiming to employ psychosocial and cognitive-behavioral interventions within pain management (Brant, 2017).

Epidemiology

Pain commonly arises at the moment of cancer diagnosis, throughout the progression of the disease, and during oncologic treatment (Mihailescu et al., 2021). The prevalence of oncologic pain varies based on the stage of the disease. The majority of pain occurs in the advanced and terminal stages of oncologic disease, affecting more than two-thirds of patients. Additionally, the intensity of pain is influenced by the disease stage, with patients in advanced or terminal stages experiencing more severe pain compared to active oncology patients (van Den Beuken-van Everdingen et al., 2016; van den Beuken-van Everdingen et al., 2007). A recent meta-analysis identified the global prevalence of moderate to severe oncologic pain as 30.6% (Snijders et al., 2023).

Etiology and Pathophysiology

Oncologic pain is caused by the presence of primary or secondary tumors, as well as by multimodal treatment. Primary or secondary tumors can cause pain through bone, visceral, or nervous invasion, while the treatment performed causes pain through nerve damage or nociceptive effects caused by chemotherapy, radiotherapy or surgery (Bennett et al., 2012; Grond et al., 1996).

Properly identifying the cause of the pain aids in establishing a comprehensive diagnosis, which in turn determines optimal pain management (Bennett et al., 2019).

Classification of Pain – Types

The pathophysiological types of pain are nociceptive and neuropathic. The concomitant presence of neuropathic and nociceptive pain defines mixed pain. Understanding the pathophysiological type of oncologic pain guides the clinician in the therapeutic approach to pain (Fink & Gallagher, 2019). Nociceptive pain arises from the stimulation of peripheral nociceptors (somatic, visceral). Oncologic somatic pain is due to tissue infiltration by the primary/secondary tumor or tissue damage from oncologic therapeutic interventions (Leppert et al., 2016). Oncologic visceral pain is caused by the presence of primary or secondary tumors in the viscera, resulting in compression, distension, inflammation, and ischemia (Bennett et al., 2019).

Neuropathic pain occurs due to damage to peripheral and central pathways. In oncologic patients, the presence of neuropathic pain is a result of nerve damage from the primary/secondary tumor, oncologic treatments, or comorbidities (Jakubów et al., 2020).

Pain Assessment

The assessment of oncologic pain includes information about location, onset, temporal intensity patterns, underlying pathophysiological mechanisms, etiology, and the impact of pain on the individual. This examination forms the basis for establishing a comprehensive diagnostic framework upon which an effective treatment plan is developed. Central to this process is the appraisal of pain intensity, pivotal for the initiation of pain management strategies and continual monitoring of their efficacy (Kim & Jung, 2020).

The assessment of pain is an iterative process, conducted dynamically at scheduled intervals by a multidisciplinary team of medical professionals (Minello et al., 2019). This dynamic evaluation encompasses not only an ongoing assessment of the underlying continuous pain but also periodic pain exacerbations, evaluating the effectiveness of analgesic treatments, and identifying potential drug interactions that might influence the pain management approach (Leppert et al., 2016).

Patients can self-assess their pain through questions, the Numeric Rating Scale (NRS), the Visual Analog Scale (VAS), and scales in specific questionnaires (Caraceni et al., 2002). Given the multidimensionality of pain, patient self-assessment of pain should include information about physical pain (Bennett et al., 2019), its impact on mental health (Zigmond & Snalth, 1983), and quality of life (Brooks, 1996). Patient self-assessment of pain intensity is the fundamental support for initiating symptomatic treatment and evaluating treatment effectiveness (Kim & Jung, 2020).

3. FACTORS INVOLVED IN DIFFICULT-TO-TREAT PAIN

The presence of difficult-to-treat pain factors represented by neuropathic pain, incident pain, psycho-emotional suffering, confusion, and substance dependence (Bruera et al., 1989), makes the therapeutic approach to cancer pain challenging due to inadequate pain control.

Oncologic Neuropathic Pain

The diagnosis of neuropathic pain is established by correlating data from the medical history, clinical examination, and paraclinical tests (Finnerup et al., 2016). Patients with oncologic disease and neuropathic pain report higher pain intensities, and the impact of the symptom on their quality of life and daily activities is significantly greater compared to patients without neuropathic pain (Oh et al., 2017). Opioid monotherapy is often ineffective, and patients with oncologic neuropathic pain require the addition of adjuvant analgesics (Oldenmenger et al, 2009).

Incident Pain

Incident pain is the onset of pain secondary to a trigger. Frequently, incident pain is bone pain induced by movement due to the presence of a primary or secondary bone tumor or oropharyngeal pain induced by swallowing in patients experiencing cancer-related mucositis (Davies et al., 2013; Mercadante, 2019).

Treating these patients is challenging, as incident pain is a marker of intractable pain due to the increased need for opioids and the increased risk of side effects associated with them (Fainsinger et al., 2009; Mercadante, 2019).

Cognitive Function Impairment

Cognitive impairment due to dementia and other age-related cognitive pose challenges in addressing pain among geriatric oncology patients due to their reduced ability to articulate and assess pain (Brant, 2018). The presence of delirium in hospitalized oncologic patients is associated with higher levels of pain compared to oncologic patients without delirium (De La Cruz et al., 2017).

Substance Dependence

Smoking status is associated with higher levels of oncologic pain compared to non-smokers (Logan et al., 2010).

Identifying alcoholism has been described as a poor prognostic factor for the control of oncologic pain (Parsons et al., 2008). There is no screening for identifying alcoholism, although it is stipulated as a factor predisposing to poor control of oncologic pain (Mihailescu et al., 2021).

Current tobacco use and a history of smoking in patients with advanced cancer are associated with elevated levels of pain, leading to increased opioid consumption and even their misuse (Mercadante et al., 2017).

4. PSYCHO-EMOTIONAL SUFFERING IN CANCER PATIENTS

Due to the increased survival rates among oncology patients resulting from the emergence of new therapeutic modalities, an increase in emotional distress has been observed in this population (Mitchell et al., 2011; Santre et al., 2014).

Prevalence of Psycho-Emotional Suffering in Cancer Patients

Psycho-emotional suffering affects approximately 30% of palliative care patients with cancer (Lloyd-Williams et al., 2009; Lo et al., 2010). The occurrence of depression in oncology patients varies based on the disease stage, reaching up to 28% in those requiring palliative care. Owing to under-recognition by both patients and medical personnel, depression remains frequently undetected in clinical practice (Sanjida et al., 2016).

Mechanisms of Psycho-Emotional Suffering in Cancer Patients

Depression and anxiety in cancer patients most commonly occur as a result of the patient's psychological reactions to the diagnosis, treatment, recurrence, prognosis, and the end of life (Hoffman et al., 2009).

The diagnosis of a life-threatening illness and the initiation of treatment represent significant events in the lives of patients, triggering defense mechanisms manifested through depressive symptoms (Vehling et al., 2011).

Assessment of Psycho-Emotional Suffering in Cancer Patients

Routine identification of anxiety and depression in cancer patients is recommended (Riba et al., 2019). The use of standardized scales for assessing psycho-emotional distress ensures a consistent evaluation of the included symptoms, providing coherence in the dynamic assessment and between evaluators. These tools can be used in diagnosing anxiety or depression in combination with clinical interviews (Li et al., 2011).

5. COMMON NEURAL CIRCUITS OF PAIN AND DEPRESSION

The pathogenesis of pain and depression involves modifications in several neurotransmitters/ neuromodulators (Mihailescu-Marin et al., 2020) and neurotrophins (Lorena et al., 2012), alterations in cortical regions (Sheng et al., 2017) responsible for their synthesis, and an aberrant immune response (Euteneuer et al., 2011; Poleshuck et al., 2013; Uher & Bob, 2013). Understanding these molecular mechanisms underlying the pathophysiology of pain and depression has practical implications in developing new therapeutic strategies targeting these frequently co-occurring entities.

Modifications of Neurotransmitters/Neuromodulators

Decreased availability of serotonin (5-HT) and norepinephrine (NE) in certain cortical regions and alterations in serotoninergic and adrenergic pathways are common mechanisms in both pain and depression (Mihailescu-Marin et al., 2020).

Dysfunction of the dopaminergic system and alterations in the activity of D2 dopaminergic neurons are evident in both clinical conditions (Glantz et al., 2010; Sagheddu et al., 2015). Chronic pain is associated with changes in dopamine activity in the limbic system (Martikainen et al., 2015).

The cannabinoid system plays a role in the development of chronic pain and depression by involving its components in neurotransmission processes, neuroendocrine processes, and inflammatory processes found in both clinical conditions (Huang et al., 2016).

Substance P is a neurotransmitter that modulates the activity of 5-HT and NE in the central nervous system through the Neurokinin 1 receptor and interneurons (Herpfer & Lieb, 2005).

Glutamate and its receptors are involved in the development of chronic pain and depression (Sheng et al., 2017). At the spinal level, the exacerbation of excitatory system activity associated with decreased inhibitory activity leads to central hyperalgesia and the progression of pathological pain (Nozaki et al., 2011).

Modifications of Neurotrophins

Brain-derived neurotrophic factor (BDNF) is involved in the transmission pathway of neuropathic pain, acting as a bridge between microglia and neurons (Coull et al., 2005). In depressive patients, reduced BDNF activity has been identified in areas involved in depression (Jiang et al., 2017).

Structural Alterations in Cortical Regions

The involvement of the prefrontal cortex in the onset of pain and depression is supported by neuroplasticity changes implicated in the development of both conditions (Sheng et al., 2017).

In chronic pain, neuroplastic changes have been identified in the hippocampus, including a decrease or loss of its volume (Fasick et al., 2015). In depressive patients, structural alterations have been identified, including reduced volume in the prefrontal cortex and hippocampus, which are correlated with the severity of depression, as well as a reduction in prefrontal cortex synapses in post-mortem studies (Chan et al., 2016; Kang et al., 2012).

Involvement of the Immune Response

The role of the immune system in the pathogenesis of chronic pain and depression is supported by the presence of high levels of proinflammatory cytokines in patients with these conditions (Fasick et al., 2015).

The involvement of TNFα in chronic pain and depression is supported by functional changes in the hippocampus in response to the inhibition of NE release by TNFα (Reynolds et al., 2004).

6. ANALGESIC MEDICATION IN PAIN MANAGEMENT

The primary objectives of pain treatment in oncology patients are to achieve adequate analgesia, maintain optimal daily functioning, minimize side effects, and avoid inappropriate drug consumption (NCCN, 2018).

Principles of Analgesic Administration

The treatment of chronic oncologic pain is administered regularly to maintain a constant plasma level of the medication, which provides optimal pain control while avoiding concentration peaks that can lead to side effects. In addition to regular medication, as-needed medication is used to address episodic pain. Oral administration of analgesics is preferred due to its good tolerance and ease of use by patients and their families (Ripamonti et al., 2011). Patient and family education is important for achieving proper pain management that addresses both pain control and side effects (NCCN, 2018). The dose of the analgesic, the type of analgesic, and the route of administration are individualized based on the patient's needs (Ripamonti et al., 2011).

Analgesia steps

The choice of analgesic treatment is based on the severity of pain. The intensity of pain dictates the step-wise approach to analgesic therapy. The World Health Organization (WHO) classifies pain relief medication into three analgesia steps:

- Step I - non-opioids used for mild pain,
- Step II - weak opioids used for moderate pain,
- Step III - strong opioids administered for severe pain.

Step I and III drugs can be combined (WHO, 1990). Each tier of analgesic therapy can be complemented with adjuvant medications when necessary (NCCN, 2018).

Pain Control

Understanding the pathophysiological mechanisms of pain, along with a comprehensive assessment of oncologic pain, is essential for effective treatment (Leppert et al., 2016). Different pathophysiological pain types exhibit varied treatment responses and pain control. Patients with neuropathic pain often exhibit a challenge in responding to analgesic treatment (Hershman et al., 2014), resulting in weaker pain control compared to those with nociceptive oncologic pain (Rayment et al., 2013).

Barriers in Pain Control

Multiple barriers hinder the adequate treatment of oncologic pain, affecting both healthcare professionals and patients. Among professionals, a lack of medical knowledge concerning the assessment and treatment of oncologic pain, combined with apprehensions about side effects, tolerance, and dependence, poses a significant obstacle (Kwon, 2014). Patients' misunderstandings about analgesic use, including the belief that pain is uncontrollable, are substantial obstacles to effective pain management. Additionally, inadequate doctor-patient communication is recognized as a significant barrier to pain control (Jacobsen et al., 2009). Education directed at both healthcare professionals and patients is pivotal in overcoming these barriers (Marie et al., 2013).

Opioid Medication

The therapeutic pathway typically initiates with the utilization of mild opioids for managing oncologic pain prior to advancing to stronger options. Strong opioids are notably the preferred medications for addressing moderate to severe pain in individuals with progressive oncological conditions (Brozović et al., 2022). Morphine, in particular, is commonly suggested as the primary oral opioid for alleviating pain in those with advanced or progressive cancer (NICE, 2012).

7. ADJUVANT MEDICATION IN PAIN MANAGEMENT

Adjuvant medication is combined with opioid medication to improve analgesia. The choice of the type of adjuvant used in oncologic pain depends on the type of pain, associated symptoms (such as anxiety, depression), and the patient's comorbidities (Jakubów et al., 2020, Mosoiu et al., 2013).

Adjuvant analgesic medication encompasses different classes of drugs that can be prescribed either as monotherapy or in combination with an opioid. Anticonvulsants and antidepressants are usually used for pure neuropathic pain or mixed oncologic pain, but recently, they have also been used for bone pain caused by metastases (van den Beuken-van Everdingen et al., 2017).

The classes of adjuvant analgesics that can be used in oncologic pain include anticonvulsants, tricyclic antidepressants (TCA), selective serotonin and norepinephrine reuptake inhibitors (SNRI), N-methyl-D-aspartate receptor antagonists, topical agents, and others (cannabinoids, clonidine, corticosteroids) (Lefebvre et al., 2021).

Antidepressants

International guidelines recommend the use of tricyclic antidepressants (TCA) and serotonin and norepinephrine reuptake inhibitors (SNRI) as first-line treatment for neuropathic pain. While most studies demonstrate superior efficacy of TCAs over SNRIs, SNRIs are more frequently used in practice due to their superior safety profile (Cruccu & Truini, 2017).

The National Comprehensive Cancer Network (NCCN) recommends venlafaxine and duloxetine as the drugs of choice for oncologic neuropathic pain (NCCN, 2018).

Mirtazapine is a tetracyclic antidepressant that, due to its pharmacological profile, can be used to treat various symptoms commonly experienced by cancer patients. While randomized clinical studies regarding mirtazapine's efficacy in cancer-related neuropathic pain are lacking, its influence on sleep and depression can improve quality of life and alleviate pain (Economos et al., 2020).

Anticonvulsants

Anticonvulsants, such as gabapentin and pregabalin, can be useful for patients with oncologic neuropathic pain. They can also help reduce opioid doses and minimize their side effects. Doses can be increased by 50-100% every 3 days. In the elderly and patients with renal insufficiency, a slower titration is recommended to reduce the risk of drowsiness (Howard & Brant, 2019; NCCN, 2019).

Benzodiazepines

Benzodiazepines, through their action on GABA receptors, have therapeutic effects on chronic, neuropathic, and inflammatory pain (Sheng et al., 2017). Due to the fact that anxiety is experienced as a painful component in anxious and agitated patients, and patients with chronic pain frequently experience anxiety, benzodiazepines have been used as adjuvants in analgesia when opioid monotherapy has not controlled pain (Triozzi et al., 1988).

Guidelines

Depending on the components involved in cancer-related pain, WHO guidelines recommend using adjuvant analgesics in addition to opioids for neuropathic/mixed pain and using adjuvants as monotherapy for pure neuropathic pain (Jongen et al., 2013).

National Clinical Palliative Care Protocols recommend combining psychotropics (antidepressants and anticonvulsants) with analgesic medication (opioid and non-opioid) for patients with oncologic neuropathic pain. Recommended antidepressants are TCA, duloxetine, venlafaxine, and mirtazapine. Recommended anticonvulsants are gabapentin and pregabalin (Mosoiu et al., 2013).

There is no consensus regarding the use of psychotropics as monotherapy versus their combination with opioids as first-line treatment for oncologic neuropathic pain. The European Society for Medical Oncology recommends associating psychotropics with opioid medication for insufficiently controlled neuropathic pain. Some international societies (Canadian Pain Society, European Federation of Neurological Societies) recommend using specific psychotropics (pregabalin and duloxetine) as first-line therapy for neuropathic pain (Cruccu & Truini, 2017).

Data from clinical studies

Clinical data on the effectiveness of adjuvant medications in managing oncological pain remains conflicting due to the heterogeneity and poor quality of studies conducted among oncological patients.

A meta-analysis conducted in 2021, which assessed the effectiveness of adding gabapentin to opioid medication in patients with inadequately controlled opioid or adjuvant medication for oncologic neuropathic pain, showed a significant improvement in pain by adding gabapentin to opioid medication (Bao et al., 2021).

A systematic review conducted in 2015 showed a significant reduction in neuropathic pain in oncology patients by adding anticonvulsants or antidepressants to opioid medication compared to opioid monotherapy (Guan et al., 2016).

On the other hand, another systematic review published in 2018 showed no statistically significant differences between the group that combined gabapentinoids with opioid medication and the group treated with opioids (Kane et al., 2018).

Although there is no strong evidence regarding the use of antidepressants and anticonvulsants in oncology patients with neuropathic pain due to small studies with a low number of patients, these drugs are widely accepted in monotherapy or in combination with other analgesics in the management of neuropathic pain in these patients (Medioni et al., 2019).

8. PAIN AND QUALITY OF LIFE IN CANCER PATIENTS

Enhancing the quality of life constitutes a fundamental objective within the realm of palliative care. This aspect is a pivotal indicator of symptom alleviation, serving as an assessment parameter for appropriately managing patients experiencing oncological pain (Liang et al., 2015).

Relationship Between Pain and Quality of Life in Cancer Patients

Pain and quality of life are linked through common characteristics (Yildirim et al., 2005), and pain control is a determining factor in health-related quality of life (HRQoL) (Mystakidou et al., 2004; Yildirim et al., 2005).

Several factors have an impact on the quality of life in individuals undergoing oncologic pain, including pain intensity, clinical status, and disease stage. Patients enduring severe pain tend to exhibit a notably lower quality of life compared to those experiencing moderate or mild pain. In terms of clinical condition, Deng et al. noted that patients with a prognosis of less than 2 weeks displayed higher pain levels and experienced more pronounced impairment in their quality of life relative to those with a prognosis of over 2 weeks (Deng et al., 2012).

Quality of Life Assessment in Cancer Patients

Measuring the quality of life provides valuable information that can determine treatment adjustments, the selection of specific medications, and the prevention of medication side effects (Kolator et al., 2018).

The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) stands as the most extensively employed tool for assessing the quality of life among individuals with oncological conditions (Garratt et al., 2002). The application of this instrument in clinical practice significantly contributes to enhancing doctor-patient communication and HRQoL (Velikova et al., 2004).

SPECIAL PART – PERSONAL RESEARCH

1. INTRODUCTION

Despite the presence of established national and international protocols governing the management of pain in oncology patients, the therapeutic strategy for individuals grappling with oncologic pain continues to pose a formidable challenge for healthcare providers.

The literature extensively underscores numerous risk factors associated with hard-to-manage pain as addressed in the introductory section, encompassing neuropathic pain, incident pain, psycho-emotional distress, and the usage of alcohol and tobacco. These factors markedly contribute to the intricacies involved in the comprehensive management of oncologic pain.

A reciprocal correlation is noted between the manifestation of pain and the onset of depression among individuals dealing with oncologic conditions. Patients with inadequately managed pain display a heightened susceptibility to developing depression in contrast to those not experiencing depression. Moreover, patients with concurrent depression and pain tend to report more intense pain experiences (Fitzgerald et al., 2015; Syrjala et al., 2014).

The assessment of the non-physical aspects of oncologic pain and its management through both non-pharmacological and pharmacological interventions is designed to enhance the control of oncologic pain and, consequently, elevate the overall quality of life for patients.

2. AIM AND OBJECTIVES OF THE RESEARCH

The aim of this study is to explore the elements that make oncologic pain difficult to treat and to identify factors that allow individualization of treatment in cancer patients with palliative care needs.

The study's objectives are as follows:

1. To identify the presence of the four factors of difficult-to-treat pain, as defined by Bruera (incident pain, neuropathic pain, psycho-emotional suffering, chronic substance consumption) within the cohort of cancer patients necessitating palliative care.
2. To identify predictive factors and predictive models for difficult-to-treat pain and their influence on patients' quality of life.
3. To discern the response to individualized treatment based on the pathophysiological nature of pain, measured by a targeted 2-unit reduction on the Numeric Rating Scale (NRS) pain intensity scale.
4. To monitor the progression of the psycho-emotional dimension of difficult-to-treat cancer pain among patients requiring specialized palliative care.
5. To follow up the use of individualized treatment, including psychotropic medications, in patients experiencing difficult-to-treat cancer pain and requiring specialized palliative care needs.
6. To evaluate the quality of life in patients with difficult-to-treat cancer pain and necessitating specialized palliative care within the framework of individualized treatment.

3. RESEARCH HYPOTHESES

Following the objectives of the study several working hypotheses were formulated and tested during the clinical trial:

1. The presence of any difficult-to-treat pain factor (psycho-emotional suffering, incident pain, neuropathic/mixed pain, pre-existing substance abuse) is correlated with higher pain intensities in cancer patients requiring palliative care compared to those without these factors.
2. Individualized treatment in patients with difficult-to-treat cancer pain and psycho-emotional suffering that includes the use of psychotropic medications leads to a reduction in the intensity of cancer-related pain.
3. Individualized analgesic treatment decreases the intensity of difficult-to-treat cancer pain regardless of its pathophysiological type in cancer patients with palliative care needs.
4. Within the spectrum of difficult-to-treat pain factors, neuropathic/mixed pain is linked to a heightened necessity for the incorporation of psychotropic medications within individualized analgesic treatment for palliative care oncology patients.
5. The implementation of individualized analgesic treatment in palliative care oncology patients is associated with an improvement in the quality of life.

4. GENERAL METHODOLOGY

Study Description

The present study is prospective, longitudinal, quasi-experimental, conducted with oncology patients requiring palliative care and suffering from difficult-to-treat oncologic pain. The study was conducted from January 1, 2019, to October 1, 2020, at the adult inpatient unit of the Hospice Casa Speranței Foundation in Brașov, and patients were followed up to 28 days from their inclusion in the study.

Patients were evaluated over a 28-day period starting from their admission to the Hospice Casa Speranței Foundation's inpatient unit and signing the informed consent. Patients were admitted within the first 14 days and then monitored on an outpatient basis on days 21 and 28 of the study.

Patients who did not complete the study included cases that could no longer be followed, patients who withdrew from the study, patients whose health deteriorated, preventing the provision of information, or patients who passed away during the study. Study participants were informed by the investigator about the purpose, duration, and requirements of the study and signed the informed consent. The research received approval from the Ethics Committee of Transilvania University in Brașov and the Ethics Committee of the Hospice Casa Speranței Foundation in Brașov.

The study protocol adhered to the National Clinical Protocols for Palliative Care in Romania (Moșoiu et al., 2013), which specify the use of analgesic treatment based on the severity of pain and recommend the association of adjuvant medication (psychotropics, corticosteroids) based on the patient's comorbidities and the pathophysiological mechanism of pain.

Population

The study population consisted of individuals with oncologic disease requiring palliative care, admitted to the adult inpatient unit of the Hospice Casa Speranței Foundation.

Inclusion criteria for the study were as follows:

- Age >18 years;
- Present consciousness level;
- Oncologic disease confirmed by histopathological examination;
- Eastern Cooperative Oncology Group (ECOG) performance status < 4;
- Uncontrolled pain;
- Presence of one or more risk factors for difficult-to-treat pain (neuropathic or mixed pain, anxiety or depression, chronic alcohol or tobacco use, incident pain);
- Absence of cognitive disorders (dementia, delirium).

Exclusion criteria for the study included:

- Unconfirmed oncologic disease;
- Primary psychiatric disorders (schizophrenia, bipolar disorder, major depressive disorder, anxiety disorder, cognitive disorder) that were present before and concomitant with the oncologic disease, except for depression or anxiety reactive to the disease or oncologic treatment;

- Performance status (ECOG) of 4;
- Short life expectancy (days or weeks);
- Non-oncologic pain;
- Primary or secondary brain tumor patients.

Data Management

The diagnosis of oncologic pain was established by correlating clinical data with paraclinical investigations at elucidating the underlying pain mechanism.

The diagnosis of incident pain was established through a comprehensive clinical assessment aligning with the definition of "a transient exacerbation related to a predictable or unpredictable triggering factor despite the presence of relatively stable and adequately controlled background pain" (Davies et al., 2009).

Considering that pain and psycho-emotional suffering are frequently encountered together in oncology patients, the study quantified psycho-emotional suffering at the time of enrollment. Patients were evaluated based on clinical data and by completing the Hamilton Depression and Anxiety Rating Scales on days 1, 7, 14, 21, and 28 by the physician.

To highlight the impact of oncologic pain, quality of life was assessed by patients completing the EORTC QLQ-C30 scale at the time of study inclusion, as well as on days 14 and 28 of the study.

Collection of demographic and clinical data, encompassing medical history details such as the primary cancer site, presence of metastases, ongoing disease treatment, pain onset and location, alcohol and tobacco consumption, and prior medication administered before study inclusion, were systematically compiled and recorded.

Research Instruments

The evaluation of patients with difficult-to-treat oncologic pain was carried out using the following scales: Modified Brief Pain Inventory (Mosoiu et al., 2013), Hamilton Anxiety Rating Scale (Hamilton, 1959), 17-item version of the Hamilton Depression Rating Scale (Vrasti, 2019), and the EORTC QLQ-C30 scale (Fayers et al., 2001), applied at regular intervals throughout the study.

Pharmacological Interventions

The study protocol strictly followed the guidelines outlined in the National Clinical Protocols for Palliative Care in Romania (Moșoiu et al., 2013). These protocols detailed the hierarchy of analgesic treatment based on pain severity and recommended the incorporation of adjuvant medications, such as psychotropic drugs and corticosteroids, contingent upon the patient's comorbidities and the specific pathophysiological basis of the pain.

Individualized treatment plans involved the utilization of non-opioids, minor opioids, and major opioids, selected in accordance with the WHO pain scale to address pain intensity. These were complemented by psychotropic medications specifically chosen based on the pathophysiological type of pain and the concurrent psycho-emotional suffering, particularly the levels of anxiety or depression upon admission.

Patients with oncologic pain and scores ≥ 14 on the Hamilton Depression Scale received analgesic treatment, which was combined with antidepressants such as venlafaxine, doxepin, or mirtazapine on day 1 of the study, as follows:

1. Patients with neuropathic/mixed pain received doxepin at a dose of 25 mg/day, with the possibility of weekly increments of 25 mg, depending on pain control and tolerability;
2. Patients with nociceptive pain received venlafaxine at a dose of 37.5 mg/day, with the possibility of weekly increments of 37.5 mg;
3. For patients with contraindications to doxepin or venlafaxine or patients with adverse reactions to their administration, mirtazapine was used as a reserve medication due to its beneficial effects on other symptoms present in oncology patients (appetite improvement, anxiolytic effect) at a dose of 15 mg/day, with the possibility of weekly increments of 15 mg/day.

Patients with scores < 14 on the Hamilton Depression Scale received analgesic treatment with or without an anticonvulsant (gabapentin) based on the type of pain and the mechanism of action of the analgesic medication administered before their enrollment in the study. The scores were interpreted as predominantly reactive psycho-emotional distress to uncontrolled symptoms. Accordingly, patients with neuropathic/mixed pain received analgesic treatment combined with gabapentin, starting at 300 mg/day on day 1 of the study, with the possibility of weekly increments of 300 mg, depending on pain control and tolerability, while patients with nociceptive pain received non-opioid or opioid treatment based on pain intensity.

Patients with oncologic pain and scores ≥18 on the Hamilton Anxiety Scale received analgesic treatment combined with an anxiolytic such as lorazepam, alprazolam, or diazepam, depending on the treatment administered before their enrollment in the study.

Patients with scores < 18 on the Hamilton Anxiety Scale received analgesic treatment, either combined with or without an anticonvulsant, based on the type of pain. The scores were interpreted as predominantly reactive psycho-emotional suffering to uncontrolled symptoms.

Treatment response was defined as a decrease of 2 points in the maximum pain score within 24 hours. Patients received analgesics as needed for breakthrough pain associated with regular medication. If patients requested more than 2 as-needed doses per 24 hours, the regular analgesic dose was adjusted by increasing the dose per 24 hours, or the patient was escalated to a higher level of analgesia if pain intensity increased or the maximum dose of a step II or III analgesic was reached. The use of other medications, including those for managing other symptoms that may be present in oncology patients requiring palliative care, was allowed.

Statistical Analysis

Based on the information collected from the patient's medical history, physical examination, and the completion of scales, a database was generated and used for statistical analysis. Current data were collected using Microsoft Excel 2020 software and interpreted using IBM SPSS version 26.0 and MedCalc version 20.305 software. Various statistical tests were used for data interpretation, with a significance level set at $p<0.05$.

5. RESEARCH RESULTS

Between January 1, 2019, and October 1, 2020, 81 patients were enrolled in the study, of which 72 patients completed the study, 4 patients passed away, and 5 patients changed their place of residence. The mean age of the study patients was 66.24 years. The majority of patients with difficult-to-treat pain in the study group (73.62%) were patients over the age of 60. The gender ratio was approximately 1.2:1, with slightly more females than males. The majority of patients (75%) came from urban areas.

Regarding the primary site of malignant tumors, the top three locations were digestive cancer, present in a quarter of the included patients, followed by urogenital cancer in 20.83% of patients, and breast cancer in 18.06% of patients in the study group. The most frequent primary site of cancer in women was breast cancer (18.06%), while in men, digestive cancer was predominant (15.28%).

Neuropathic/mixed pain was identified in 68.05% of patients, while nociceptive pain was present in 31.95% of patients in the study group. Nociceptive pain was significantly more common in patients with digestive cancers ($p = 0.01$, chi-square test).

The majority of patients (70%) presented with metastatic disease. Among these, 62% had multiple metastases, with the most common location being in the bones.

The difficult-to-treat pain factors analyzed in this study included incident pain, neuropathic/mixed pain, chronic alcohol consumption, chronic tobacco use, and psycho-emotional suffering (anxiety and depression).

Incident pain was the most prevalent difficult-to-treat pain factor, present in 70.83% of the patients.

In patients with incident pain, the average maximum pain intensity was higher than in patients without incident pain throughout the study, based on evaluations conducted on days 1, 14, and 28.

On day 1 of the study, there was a statistically significant difference between the average maximum pain intensity reported by patients with incident pain and the average maximum pain intensity in patients without incident pain ($p = 0.01$, Mann-Whitney test), a difference that persisted throughout the study but was no longer statistically significant on day 28 ($p = 0.27$, Mann-Whitney test).

Throughout the study, the mean values of the maximum pain intensity reported by patients with incident pain and those without incident pain showed a decreasing trend, with statistically significant differences between evaluations on days 1, 14, and 28 ($p = 0.001$, Kruskal-Wallis test).

Neuropathic/mixed pain ranked third in the frequency among difficultpain factors, occurring in 68.05% patients (n=49) of the study group.

The maximum pain intensity in patients with neuropathic/mixed pain on day 1 of the study (mean = 7.06, SD = 1.65) was higher than in patients with nociceptive pain (mean = 5.83, SD = 1.72) with a statistically significant difference ($p = 0.001$, T-test). A similar pattern was observed on day 28, with a statistically significant difference in maximum pain intensity between patients with neuropathic/mixed pain and those with nociceptive pain ($p = 0.02$, T-test). Analyzing the dynamics (from day 1 to day 28) of the maximum pain intensity in the two groups of patients, a statistically significant decrease in maximum pain intensity was observed in both categories ($p = 0.0001$, Welch test).

Chronic alcohol consumption was acknowledged in 51.39% of patients. Both the maximum and mean pain intensity decreased significantly between assessments on day 1 and day 28 ($p = 0.001$, t-test) for patients

with and without chronic alcohol consumption. Comparing the mean pain scores on day 1 and day 28 between patients with and without chronic alcohol consumption did not reveal statistically significant differences.

Chronic tobacco use was identified in 63.89% of patients. There were no statistically significant differences regarding the mean values of maximum and mean pain intensity in patients with chronic tobacco use versus those without chronic tobacco use on both day 1 and day 28. Comparing the mean values of maximum and mean pain intensity on day 1 versus day 28 in patients with chronic alcohol consumption and those without chronic alcohol consumption led to statistically significant differences ($p = 0.001$, T-test).

The assessment of psycho-emotional suffering on day 1 of the study using the Hamilton Anxiety Scale and the Hamilton Depression Scale revealed the presence of clinically significant anxiety and depression in over 50% of the patients. Patients with clinically significant anxiety were defined as patients with scores on the Hamilton Anxiety Scale >=14, and clinically significant depression was defined as the presence of scores on the Hamilton Depression Scale >=8.

Throughout the study (comparing day 1 to day 28), a statistically significant decrease in the maximum and mean pain intensity reported by patients with identified anxiety using the Hamilton Anxiety Scale ($p = 0.001$, T-test) and those without anxiety ($p = 0.01$, T-test) was observed. Comparing the mean pain scores on day 1 and day 28 for patients with anxiety versus patients without anxiety did not show statistically significant differences.

In patients identified with depression using the Hamilton Depression Scale, higher pain intensity values were observed, both on day 1 and day 28, compared to patients without depression, but without statistically significant differences.

The initial assessment on day 1 of the study revealed that a substantial majority of patients (approximately 91%) reported moderate to severe pain intensities. However, by the conclusion of the study, there was a notable transition, with 87.5% of patients reporting a downshift in their pain intensity to mild levels.

Analyzing the pain intensity reported by patients using the numeric scale, a decrease in all pain scores evaluated by the study patients is observed (maximum score - the highest pain rating, minimum - the lowest rating, average score - the mean value reported by them, and current score - the rating assigned to pain at the time of assessment), with statistically significant differences between assessments on days 1, 14, and 28 ($p=0.0001$, T-test). The most significant decrease in scores was observed on day 14 when patients were still under continuous supervision.

Patients identified with psychosocial distress, including clinically significant anxiety (N=39) or clinically significant depression (N=49), displayed a decrease in the mean values of the total scores of the Hamilton Anxiety and Depression Scales, with statistically significant differences ($p=0.001$, 2x2 ANOVA).

Changes in the items of the Hamilton Depression and Anxiety Scales were also evaluated. Specifically, the assessment of depressive mood in the Hamilton Depression Scale revealed a statistically significant average decrease of 1 point when comparing day 1 with day 28 ($p=0.0001$, T-test). Consequently, by day 28, patients no longer reported alterations related to mood, such as feelings of sadness, helplessness, or lack of hope, which they spontaneously indicated on day 1 of the study.

Anxiety assessed by the Hamilton Anxiety Scale improved on day 28 compared to day 1, with an average score decrease of 1.41, which was statistically significant ($p=0.01$, T-test). Thus, the symptom intensity decreased from moderate to mild.

Among the factors contributing to difficult-to-treat pain, the predictive factors for higher pain intensity on day 1 of the study were incident pain, neuropathic/mixed pain, and clinically significant anxiety. The presence of incident pain was directly proportional and statistically significant correlated with the maximum pain intensity on day 1 of the study (r=0.29, p=0.01). Likewise, the presence of neuropathic/mixed pain was directly proportional and statistically significant correlated with the maximum pain intensity on day 1 of the study (r=0.32, p=0.005). The predictive model for maximum pain intensity on day 1 of the study, including the presence of neuropathic/mixed pain, incident pain, and clinically significant anxiety, was statistically significant.

On day 28, neuropathic/mixed pain, the presence of depression, and clinically significant anxiety were predictors for maximum pain intensity, with a positive correlation. Of these, the most significant predictor was neuropathic/mixed pain. The predictive model for maximum pain intensity on day 28 included the presence of neuropathic/mixed pain and the total score of the Hamilton Depression Scale on day 28.

Based on pain intensity, 47.22% of patients received major opioids, 48.61% received minor opioids, and only 4.17% of patients received non-opioid treatment. Major opioids were used more frequently in patients with neuropathic/mixed pain (55.10%) compared to patients with nociceptive pain (30.44%), with a statistically significant difference of p = 0.04 (T-test). The majority of patients (93.05%) received psychotropic treatment in addition to analgesic treatment. The most commonly associated class of psychotropics was the class of antidepressants (61.11%). The use of antidepressants and anxiolytics was more frequent in patients with neuropathic/mixed pain.

The treatment response for patients in the study, defined as a minimum 2-point decrease in the maximum pain score, was 88.90%. Regarding therapeutic response based on pathophysiological type, patients with nociceptive pain were more responsive to treatment (91.30%) compared to those with neuropathic/mixed pain (87.80%), without statistically significant differences (p = 0.65, chi-square test).

Analyzing the evolution of the maximum pain intensity and the mean value of the total scores on the Hamilton Depression Scale, (day 1 - day 28), for the 44 patients with scores >=14 on the Hamilton Depression Scale who received analgesic treatment associated with an antidepressant, a parallel decrease in pain intensity and Hamilton Depression Scale scores was observed, with statistically significant differences between the initial assessment (day 1) and the final assessment (day 28) (p = 0.001, T-test).

The correlation between the quality of life parameters in patients with difficult-to-treat pain and pain intensity throughout the study was evaluated. On day 1, role functioning (r=-0.436, p=0.0001), physical functioning (r=-0.032, p=0.006), and social functioning (r=-0.24, p=0.04) were inversely correlated and statistically significantly associated with maximum pain intensity. Symptoms directly and significantly correlated with maximum pain intensity on day 1 included insomnia (p=0.392, p=0.0007) and fatigue (r=0.238, p=0.04).

On day 14 of the study, maximum pain intensity was inversely correlated and statistically significantly associated with cognitive functioning (r=-0.25, p=0.02) and social functioning (r=-0.22, p=0.05). Among the symptoms included in the EORTC QLQ-C30 scale, fatigue was directly correlated and statistically significantly associated with maximum pain intensity (r=-0.38, p=0.0009).

On day 28, maximum pain intensity was inversely correlated and statistically significantly associated with emotional functioning (r=-0.25, p=0.03) and social functioning (r=-0.28, p=0.01). Insomnia was directly correlated and statistically significantly associated with maximum pain intensity (r=0.26, p=0.02).

Comparing quality of life parameters evaluated using the QLQ C-30 scale throughout the study, an improvement in the global health status was observed (day 1 - mean=39.58, CI=35.48 - 43.68, day 14 -

mean=63.42, CI=59.71 - 67.13, and day 28 - mean=60.64, CI=56.78 - 64.51). The most pronounced change occurred on day 14, corresponding to the end of the hospitalization period, and on day 28, a minor decrease compared to day 14 was observed.

In patients with cancer-related pain and clinically significant anxiety, quality of life domains affected by the presence of psycho-emotional suffering associated with pain were emotional functioning, which was statistically significantly lower in patients with anxiety throughout the study (p=0.001), and digestive disturbances such as nausea and vomiting, which were more frequently reported by patients with anxiety throughout the study (p=0.01). Fatigue in patients with associated anxiety was more pronounced on the day of enrollment in the study (p=0.01).

In patients with cancer-related pain and clinically significant depression, quality of life was evaluated. On the day of enrollment, the global health status and social functioning were significantly lower in patients with associated depression (p=0.01 for both items). Physical, emotional, and cognitive functioning remained at lower levels throughout the study in patients with associated depression ($p<0.05$). Fatigue, as well as nausea and vomiting, were symptoms with significantly higher scores in patients with associated depression throughout the study (p=0.05 for fatigue and p=0.04 for nausea and vomiting).

Quality of life evaluation in patients with difficult-to-treat pain based on the pathophysiological type of pain did not reveal statistically significant differences in global health status throughout the study between patients with neuropathic/mixed pain and those with nociceptive pain. Regarding physical functioning and role functioning, statistically significant lower values were observed on day 1 of the study (p=0.002 and p=0.01, respectively), but these differences were not maintained throughout the study.

Comparing emotional functioning between patients with neuropathic/mixed pain and those with nociceptive pain, statistically significant lower values were observed in patients with neuropathic pain throughout the study (p=0.05). Additionally, statistically significant greater financial difficulties were noted throughout the study in patients with neuropathic/mixed pain compared to patients with nociceptive pain (p=0.001).

6. DISCUSSIONS

The mean age of the patients in the study group was 66.24 years, which is consistent with the average age of cancer patients reported in the literature, approximately 66 years (NCI, 2021). The majority of patients with difficult-to-treat pain in the study group (73.62%) were over the age of 60.

The distribution by gender among the study group showed a 1.2:1 ratio in favor of females. European statistics indicate variations in gender ratios in cancer based on the type of cancer (Dyba et al., 2021).

In the study group, most patients (75%) came from urban areas, possibly due to greater accessibility to inpatient care for patients residing in urban environments.

The most common oncological disease sites identified in the study were: digestive system, representing 25% of the total patients, followed by urogenital site present in 20.83% of patients, and breast localization encountered in 18.06% of patients. The distribution of cancer sites by gender in the study group corresponds to the frequency of cancer in the general population, with breast cancer frequently encountered in females and digestive cancer in males. Similarly, according to epidemiological estimates in Europe, the frequency distribution of cancer types in females is as follows: breast cancer ranks first, followed by colorectal, lung, and uterine body cancer, while in males, the top three sites are prostate, lung, and colorectal cancer (Dyba et al., 2021).

All 72 patients included in the study had advanced oncological disease in the metastatic or advanced locoregional stage.

The analysis of patients in the study regarding the stage of oncological disease showed a predominant number of patients in the metastatic stage, accounting for approximately 70% of the study population, compared to patients in the advanced locoregional stage, which represented 30%. The predominance of patients with metastatic disease can be explained by the late request for palliative care services by oncological patients due to various attitudes and beliefs of healthcare professionals and patients regarding palliative care.

Bone metastases were the most frequently identified secondary determinations in the study patients. Similar data regarding the primary location of metastases in oncological patients are reported in the specialty literature (Zajączkowska et al., 2019).

In the present study, abdominal-pelvic pain was significantly more common in patients with nociceptive pain, while spinal pain was significantly more common in patients with neuropathic/mixed pain. Similar results were identified in a study by Bechakra and colleagues, in which nociceptive pain was more frequently identified in patients with gastrointestinal cancer (Bechakra et al., 2018).

Factors contributing to difficult-to-treat pain included incident pain, neuropathic/mixed pain, chronic substance use, and psycho-emotional suffering (anxiety and depression). These factors are associated with a negative prognosis for achieving adequate control of oncological pain. They are represented by a younger age, a neuropathic component of pain, incident pain associated with bone metastases, emotional distress, and high pain levels at the initiation of treatment (Mercadante, 2019). Alcohol or tobacco consumption status is associated with the exacerbation of symptoms in advanced cancer patients and increased opioid use, considered risk factors for difficult-to-treat pain (Dev et al., 2019; Mercadante, 2019).

Incident pain was present in 70.83% of patients. The increased prevalence of incident pain in the study patients is due, on the one hand, to the screening performed to identify it, and on the other hand, to the advanced stage of oncological disease in which patients admitted to a palliative care unit were found.

Incident pain is intermittent pain caused by specific activities, frequently encountered in patients with bone metastases, limiting their activity and affecting their quality of life (Mercadante et al., 2018). Incident pain caused by the presence of bone metastases was identified in approximately 40% of patients with episodic pain (Mercadante et al., 2018).

The intensity of pain in patients with incident pain was identified as higher throughout the study (day 1, 14, and 28) compared to the intensity in patients without incident pain, a fact explained by pain episodes triggered by factors related to the presence of metastases, in especially of bone metastases, which resulted in higher pain scores being reported by patients who had associated incident pain.

In the conducted study, a statistically significant reduction in the mean and maximum pain intensity was observed across the study's duration for patients both with and without incident pain. This decrease was attributed to the implementation of individualized treatment strategies following comprehensive patient evaluations.

Neuropathic/mixed pain was identified in 68.06% of the study group. The increased prevalence of neuropathic/mixed pain in the study group can be explained by conducting the study in an inpatient palliative care unit for patients with advanced-stage cancer who are admitted for symptom control. Existing literature indicates a higher incidence of neuropathic pain among patients receiving inpatient palliative care services when compared to those accessing outpatient care. Additionally, the greater prevalence of neuropathic pain in individuals with advanced-stage diseases has been linked to increased tumor mass and the presence of metastases (Roberto et al., 2016). The holistic approach adopted toward patients in the palliative care unit is postulated to have contributed to the identification of these higher prevalence rates by illuminating the underlying mechanisms of oncological pain and systematically diagnosing pain in the study's subjects.

Regarding the pain intensity based on the pathophysiological type of pain, patients with neuropathic/mixed pain had higher pain intensity levels compared to nociceptive pain throughout the study, with statistically significant differences between the maximum and mean pain scores on days 1 and 28 for the two patient groups. Similar results in the literature have shown higher pain intensity in patients with a neuropathic component compared to those without (Kerba et al., 2010; Yanaizumi et al., 2021).

Chronic alcohol consumption and tobacco use prior to study inclusion were identified in over 50% of the study patients. The average values of both maximum and mean pain intensity, in patients with and without chronic alcohol consumption, decreased over the course of the study.

The study data did not show significant differences in the maximum and mean pain intensity between smokers and non-smokers when evaluating on days 1 and 28. However, the literature suggests that smokers express higher pain intensity and have a higher need for opioids compared to non-smokers, presenting an increased risk of maladaptation to stressful situations (Dev et al., 2019; Dev & Haider, 2020).

Current academic research focusing on psycho-emotional distress among oncology patients remains limited, with the majority of studies concentrating on the physical suffering stemming from the disease and its therapeutic interventions (Ferrari et al., 2019).

In the present study, varying degrees of anxiety assessed using the Hamilton Anxiety Scale were present in 54.17% of patients. The increased prevalence of anxiety in the study patients is due, on one hand, to the holistic approach used for the study patients, which included the identification of psycho-emotional

distress associated with oncological pain, and on the other hand, to the advanced stage of the disease in the included patients. Higher prevalence of anxiety is known to occur in patients with advanced cancer compared to those with localized disease (Salvo et al., 2012; Zweers et al., 2018). The average maximum pain intensity on day 1 was approximately 10% higher in patients with varying degrees of anxiety compared to those without anxiety. However, the reduction in pain intensity on day 28 was relatively similar for both patient groups. This shows that it was not the anxiolytic therapy that facilitated the reduction in pain but the individualized pain management, which led to a decrease in anxiety along with a decrease in pain intensity.

Depression in varying degrees, identified using the Hamilton Depression Scale, was present in 69.44% of patients. The presence of depression had a slight influence on the average pain intensity on day 1 (patients with varying degrees of depression had pain intensity 5% higher than patients without depression). However, differentiated treatment for patients did not influence the degree of pain improvement on day 28, as patients received targeted treatment based on the type of pain and the psycho-emotional suffering associated with it.

In this study, the reduction in pain intensity showed similar patterns in patients with varying degrees of depression and those without depression. This suggests that pain intensity is influenced by individual factors that contribute to different pain expressions regardless of the treatment administered.

In patients with Hamilton Depression Scale scores of >=14, the addition of antidepressants at the beginning of the study significantly reduced the maximum pain score and, simultaneously, significantly reduced the Hamilton Depression scores. This is due to the co-analgesic effect of the antidepressant used for pain relief and its influence on reducing pain and psycho-emotional distress. Similar results were identified when treating depression concurrently with pain management, contributing to pain relief (Lee et al., 2015). Although causality between depression and pain relief is challenging to establish, the results of this study suggest that depression is an important psychological factor that can hinder effective pain management in the absence of intervention on the non-physical component of pain.

Most patients in the study presented with moderate/severe pain during the initial evaluation. This outcome aligns with published literature reporting the highest pain severity in patients with advanced oncological disease (Stage IV, terminal cancer) (Wyatt et al., 2013).

Pain intensity in the study patients showed statistically significant regression throughout the study (day 1-14-28) under individualized treatment instituted after a comprehensive assessment. The intensity of pain scores (maximum, minimum, mean, and those at the time of evaluation) was minimal on day 14 (the time when patients were still under continuous medical supervision), with a slight increase on day 28 of the study.

The treatment response in the study group of patients was 89.90%. This result is similar to the data found in the literature, where the percentage of patients achieving adequate control of oncological pain using the WHO analgesic ladder is around 90% (Schug et al., 1990; Zech et al., 1995). Patients with nociceptive pain were more responsive to treatment (91.30%) compared to patients with neuropathic/mixed pain (87.80%). The study results confirm the literature's data, which suggests that the neuropathic mechanism of pain is one of the reasons why pain in oncological patients is inadequately controlled (Bennett et al., 2012; Jongen et al., 2013; Oldenmenger et al., 2009). The pathophysiological mechanism underlying oncological pain is often mixed, which may explain the resistance to treatment.

Despite using individualized treatment, neuropathic/mixed pain remained more intense throughout the study, indicating its persistently challenging nature compared to nociceptive pain. Other contributing factors likely play a role in maintaining its severity.

Patients with neuropathic/mixed pain in the study required more opioids to reduce pain intensity to a level comparable to that in patients with oncological nociceptive pain.

Regarding the consumption of antidepressants and anxiolytics in patients with neuropathic/mixed pain versus patients with nociceptive pain, no statistically significant differences were identified between the two groups of patients.

Analyzing potential predictive factors for maximum pain intensity on day 1, a positive correlation was found for incident pain, neuropathic/mixed pain, and clinically significant anxiety. The most significant predictive factor for maximum pain intensity on day 1 was neuropathic/mixed pain, with its presence associated with higher pain intensities. On day 28, neuropathic/mixed pain, the presence of depression, and clinically significant anxiety were predictive factors for maximum pain intensity, with a positive correlation. Among these, neuropathic/mixed pain was the most important predictive factor.

One of the objectives of this study is to evaluate the quality of life in patients with advanced cancer and difficult-to-treat pain, with this study being the first to assess changes in self-reported quality of life by patients with advanced cancer receiving palliative care.

Analyzing the results obtained using the EORTC QLQ-C30 scale, it can be stated that the 14 days of hospitalization brought benefits in global health status, physical functioning, role functioning, emotional functioning, social functioning, and symptom improvement, especially fatigue, dyspnea, loss of appetite, and constipation. Close monitoring of patients throughout the 14 days of the study, with the regular assessment of symptom presence to alleviate suffering, led to symptom relief and improved health status. Pain and fatigue were identified as the most severe symptoms evaluated in the three time periods using the EORTC QLQ-C30 scale in the study group.

In patients with difficult-to-treat pain associated with psycho-emotional suffering, quality of life was also affected.

Functioning (physical, emotional, and cognitive) was lower on day 1 of the study and remained at lower levels in patients with clinically significant depression compared to patients without depression. This is due to the influence of mood on daily activities, cognitive abilities, and social interactions. Similarly, emotional functioning was statistically significantly lower in patients with clinically significant depression in all moments of evaluation.

In patients with clinically significant anxiety, emotional functioning was reduced during the study, on days 1, 14, and 28, when evaluating quality of life. Among the symptoms, fatigue showed higher levels in patients with clinically significant anxiety only on day 1 of the study; the presence of nausea and vomiting was more frequent in patients with clinically significant anxiety on the enrollment day and throughout the study.

Numerous studies conducted in different countries have highlighted the negative impact of pain on the physical, psychological, social aspects, as well as functionality and financial status of oncological patients (Ovayolu et al., 2013; Potter & Higginson, 2004; Yun et al., 2003).

Regarding the pathophysiological type of pain, patients with neuropathic/mixed pain statistically showed lower physical functioning, emotional functioning, and role functioning on the day of study enrollment, and this difference did not persist throughout the study. The higher financial difficulties in patients with neuropathic/mixed pain may be due to the more complex medication regimens, which incur additional costs. Additionally, physical functioning and role functioning are lower in these patients, resulting in lower financial income. Financial difficulties have proven to be a significant predictor of the quality of life in oncological patients (Cramarossa, 2013). Furthermore, the impact of pain on the quality of life was

significant in patients with neuropathic/mixed pain. The administration of opioid treatment is effective in managing dyspnea. This could explain the lower scores on the EORTC QLQ-C30 item regarding dyspnea in patients with nociceptive pain, which is more responsive to opioid treatment.

Patients with neuropathic/mixed pain reported more intense pain on the pain scale within the EORTC QLQ-C30 compared to patients with nociceptive pain. The greater pain reported by patients with neuropathic pain aligns with the results obtained through pain intensity measurement using the NRS. However, the specialized literature presents varied outcomes regarding functionality: patients experiencing neuropathic pain exhibited lower levels of physical, social, and cognitive functionality in contrast to those with nociceptive pain, with no observed distinction in terms of general health status and emotional functionality between the two patient groups. In a similar study, pain, as gauged by the pain scale in the EORTC QLQ-C30 questionnaire, was notably higher among patients with neuropathic pain (Rayment et al., 2013).

One notable limitation of this study is the absence of a control arm. Given that the intervention consisted of implementing individualized treatments according to the specific pain mechanisms and the presence of factors related to difficult-to-treat pain, the observed pain alleviation cannot be specifically attributed to a particular class of medications.

Another limitation of the study is the inclusion of patients with multiple types of pain who received different treatments. Therefore, it is not possible to determine which type of pain responds better to a specific treatment.

Owing to the lack of homogeneity in this study, encompassing patients with psycho-emotional distress resulting associated with oncologic pain, it remains unclear whether the administered antidepressant acted as a co-analgesic by increasing the pain threshold and/or as an antidepressant by mitigating perception of pain.

Although the number of patients included in the study is in line with data from the literature, which states that <5% of oncological patients are enrolled in clinical trials (Unger et al., 2016), the sample size did not allow for the division of the cohort into subgroups and the performance of more complex statistical analyses.

Future research should aim to determine whether the combination of psychotropic drugs yields superior efficacy compared to opioid monotherapy in managing hard-to-treat pain.

7. CONCLUSIONS

1. This study aimed to explore the individualized approach to patients with difficult-to-treat oncological pain by integrating psychotropic medication into the treatment regimen after a prior holistic assessment.
2. The holistic approach to oncological pain included identifying psycho-emotional suffering and other factors contributing to difficult-to-treat pain with the goal of pain control and improved patient quality of life.
3. The study sought to explore the factors influencing the intensity of pain and the quality of life in oncological patients with palliative care needs.
4. Incident pain was the most frequently encountered difficult-to-treat pain factor in the study cohort. This was explained by the advanced stage of the patients' disease, which often included bone metastasis as the most common form of dissemination.
5. Incident pain, neuropathic/mixed pain, and psycho-emotional suffering are predictive factors for pain severity.
6. Neuropathic/mixed pain was identified as the single most significant predictive factor in the prediction model for maximum oncological pain intensity.
7. Patients with incident pain experienced more intense pain compared to those without incident pain. This phenomenon is explained by the exacerbation of pain due to the presence of a triggering factor that cannot be altered, impacting the patient in terms of physical suffering and functional status.
8. Pain intensity in patients with neuropathic and mixed pain was statistically significantly higher throughout the study compared to the pain intensity in patients with nociceptive pain. The neuropathic component of pain represents a risk factor for difficult-to-treat pain.
9. This study demonstrated that using a holistic evaluation approach that integrates pain as a complex, multidimensional phenomenon, followed by individualized treatment, results in pain improvement regardless of the pathophysiological type, even though neuropathic pain intensity remained higher throughout the study.
10. Combining psychotropic medication with analgesic medication significantly reduced pain intensity in patients with neuropathic pain, considered difficult to treat.
11. The association of psycho-emotional suffering with oncological pain is frequently encountered, with a known negative mutual influence between the two clinical conditions.
12. Quality of life in oncological patients with palliative care needs showed improvement throughout the study under individualized treatment, both in terms of functionality and symptom management.
13. General health status, cognitive functionality, physical functionality, and emotional functionality improved significantly during the study, with the most significant positive effect on day 14. Symptom improvement, primarily related to fatigue, dyspnea, loss of appetite, and constipation, was also observed.

14. Among oncological patients experiencing psycho-emotional suffering, emotional functionality assessed within the quality of life assessment scale was lower compared to patients without psycho-emotional suffering.

8. CONTRIBUTIONS OF THE WORK AND POSSIBILITIES FOR FURTHER UTILIZATION OF THE RESULTS

This study represents a pioneering investigation in Romania, delving into the intricate realm of oncologic pain by concurrently analyzing both physical and non-physical pain dimensions, examining the complexities associated with hard-to-treat pain factors, forecasting the challenges in achieving optimal control over oncologic pain, and evaluating how pain, coupled with hard-to-treat factors, impacts the overall quality of life in oncologic patients necessitating palliative care.

The identification of the pathophysiological mechanism of pain and the presence of psycho-emotional suffering aimed at individualizing the choice of co-analgesic treatment to improve treatment response and, consequently, the patient's quality of life.

The findings of this study have unveiled a dynamic interplay between oncologic pain and psycho-emotional distress, necessitating the need to discern and address associated psycho-emotional suffering that may exacerbate pain and complicate treatment endeavors.

The results strongly advocate for the creation of comprehensive guidelines for the assessment and treatment of pain in oncologic patients. These guidelines should incorporate feasible tools for screening psycho-emotional, social, and spiritual distress, designed to adapt to patients' individual conditions and treatment strategies in accordance with their unique requirements.

It is imperative to equip healthcare professionals with comprehensive training to accurately identify and address oncologic pain within national healthcare strategies. Moreover, identifying methods to enhance various aspects of quality of life, such as functionality in both physical and non-physical domains and symptom management for oncological patients.

The interdisciplinary approach to patients suffering from pain offers the advantage of alleviating pain not only through analgesic treatments but also by identifying all facets that contribute to the holistic pain experience.

Constant improvement of intervention strategies for oncological pain patients is essential, given the complexity of diagnosis and treatment. A prospective study on oncological patients with neuropathic pain to identify whether combining psychotropics with analgesics is superior to opioid monotherapy could encourage professionals to use co-analgesics for patients with a neuropathic pain component.

This research significantly contributes to the evaluation of the quality of life in oncologic patients requiring palliative care and experiencing difficult-to-treat pain. It stands as the inaugural study in Romania exploring the impact of difficult-to-treat pain factors on pain intensity and quality of life.

Identifying methods to enhance various aspects of quality of life, such as functionality in both physical and non-physical domains and symptom management, represents future research directions.

9. DISSEMINATION OF RESULTS

The dissemination and utilization of results have been achieved through:

1. Publication of three articles in national and international journals.

   Articles published in ISI-rated journals (Impact Factor 3.098):

   - Mihailescu-Marin, M. M., Mosoiu, D. V., Burtea, V., Sechel, G., Rogozea, L. M., & Ciurescu, D. (2020). Common Pathways for Pain and Depression-Implications for Practice. American Journal of Therapeutics, 27(5), e468–e476. https://doi.org/10.1097/MJT.0000000000001235
   - Mihailescu-Marin, M. M., Mosoiu, D. V., & Dima, L. (2022). Comprehensive Targeted Treatment for Neuropathic and Nociceptive Pain in Palliative Care Patients. American Journal of Therapeutics, 29(5), e512–e519. https://doi.org/10.1097/MJT.0000000000001536

   Article published in a BDI-rated journal:

   - Mihailescu-Marin, M. M., Mosoiu, D. V., Mosoiu, C., & Dima, L. (2021). Prevalența durerii greu tratabile în îngrijirea paliativă. Jurnalul Medical Brașovean, nr 2, 2021. https://webbut.unitbv.ro/index.php/jmb/issue/view/current

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