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FULL PAPER

The effectiveness of opioid treatment in patients with chronic cancer pain experiencing breakthrough cancer pain (BTcP): Biomarker evaluation in the tetrahydrobiopterin pathway

Ardhian Wardana*|Christrijogo Sumartono Waloejo|Herdiani Sulistyo Putri|Wiwiek Indriyani Maskoep

Department of Anesthesiology and Reanimation, Faculty of Medicine, Airlangga University – Dr. Soetomo General Academic Hospital, Surabaya, Indonesia

***Corresponding Author:**
Ardhian Wardana
Email: ardhian.wardana@gmail.com
Tel.: +62 81330240220

Chronic pain is a serious issue among cancer patients, with nearly half of all cancer patients experiencing it. Approximately 5-20% of these patients report suffering from severe pain that impacts their quality of life, and unresolved chronic pain may even affect the survival of cancer patients. Breakthrough cancer pains (BTcP) are a major concern for many people around 60% of cancer patients who experience pain. Despite efforts to improve pain management, many countries still report errors in assessing and treating this type of pain. Opinions about prescribing opioids for cancer pain have changed over time. Tetrahydrobiopterin (BH4) regulation may play a part in cancer pain mechanisms. A brief summary of the effectiveness of opioid treatment is provided in this study in chronic cancer pain patients who experience BTcP, assessed by biomarkers in BH4 pathway.

KEYWORDS

Chronic cancer pain; opioid; breakthrough cancer pain; BTcP; tetrahydrobiopterin; BH4.

Introduction

The number of cancer patients is increasing as the population ages. Pain is a common manifestation in patients diagnosed with cancer, and its prevalence increases during and after cancer therapy [1]. Recent advances in oncology, including the latest pain management guidelines, drug development, and new treatment strategies, may reduce the frequency and severity of pain. Mental health problems often accompany chronic pain and can greatly reduce quality of life, such as fatigue and depression, and reduced function. Some evidence suggests that untreated chronic pain may affect survival in cancer patients [2]. *Breakthrough cancer pain* (BTcP) is highly prevalentt in all types and stages of cancer, and it is associated with a significant physical, psychological, and economic burden. Many countries still struggle with poor identification and treatment of cancer pain, despite efforts to improve its adequate management [3].

Breakthrough cancer pain (BTcP) needs to be evaluated systematically and appropriately

managed in all cancer patients with pain. The high-grade breakthrough cancer pain (BTcP) phenotype is described as a sudden increase in pain severity, unpredictability of pain, rapid onset of symptoms, and negative impact on activities of daily living and quality of sleep. High-grade BTcP demands intensive pain reassessment, regular therapy adjustments, and meticulous patient monitoring [4].

In most patients, cancer pain (Table 1) worsens with the course of their disease. Although cancer pain is most common in patients with metastatic disease, the onset and severity of pain depends on the type of cancer and treatment. Despite advances in the development of techniques for the diagnosis and treatment of most oncological conditions, there has been little progress in the management of cancer pain. Currently, there is no standardized way to assess cancer pain. Therefore, further research should be aimed at developing multifactorial and patient-centred techniques that allow for an individualised approach to management [5].

Prevalence of Chronic Pain, Cancer Pain, And Breakthrough Pain In Cancer Patients

Recent systematic reviews of the literature on the prevalence and severity of pain in cancer patients show that both the prevalence and severity of pain have decreased over the past decade. The data collected on the prevalence of pain revealed an overall prevalence of 44.5%. The group with the lowest prevalence of pain was the curative treatment group (35.8%). Despite the decrease, a systematic review showed that the prevalence of pain is still high, especially in patients with metastatic and terminal cancer (54.6%) [2].

Chronic pain is a common occurrence in cancer patients, with around 50% experiencing it. Of these patients, 5-20% report severe pain that significantly impacts their quality of life. BTcP is a prevalent condition that affects approximately 60% of cancer patients who experience pain. Despite advancements in pain assessment, patient education, and treatment options, cancer pain remains inadequately controlled in about one-third of patients, particularly the elderly. The frequency of moderate to severe pain is 38.0%, ranging from 31% after curative treatment to 45% in late stages cancer. However, the management of high intensity pain is often poor, even in people with palliative care at the end of life [3].

Breakthrough cancer pain (BTcP) has been observed in both oncological and non-oncological patients, including those without background pain. Epidemiological data suggest a high prevalence of BTcP in populations suffering from severe background pain, and it has been correlated with several comorbid factors. The prevalence of BTcP ranges from 40% to 80% in oncological patients and is over 55% in non-oncological patients [6]. It is associated with more advanced disease, but there is wide disparity between sites and patient subgroups. During end-of-life (EOL), BTcP becomes a more troublesome problem, affecting almost all cancer patients daily with high intensity. A study of the cyclic pattern of BTcP episodes in end-stage cancer patients found that patients experienced an average of 7.2 episodes over a 7-day period. The study also found that around 80% of these episodes were experienced between 8.00 a.m. and noon [4].

Regarding cancer type, pain is highly prevalent in pancreatic cancer, head and neck cancer, lung cancer, breast cancer, and non-Hodgkin's lymphoma. In addition, a substantial percentage of cancer patients, estimated to be between 33 and 95% in different reports, experience BTcP levels two to three times a day. The incidence of BTcP differs by stage of the tumor, with over 70% of cases occurring in advanced stages. In addition, the prevalence varies by tumour type, with the highest rates found in patients with pancreatic cancer (71%) and colorectal cancer (62%), and the lowest rates Prevalence also varies by tumor type, with the greatest incidences reported in patients diagnosed

with pancreatic cancer (71%) and colorectal cancer (62%), and the lowest in patients diagnosed with multiple myeloma (32%) and lymphoma (22%). Seventy-five-point five percent of patients described a high intensity of BTcP. Tormenting events, whether anticipated or not, can aggravate crises and cause significant physical, psychological and economic distress. The most common consequences include anxiety, depression, and sleep disturbances. The inevitability of subsequent events instils fear in many affected populations, resulting in reduced daily activities, mobility, and strained family and social relationships [3].

Definition of Breakthrough Cancer Pain

Breakthrough cancer pain (BTcP) is described as a sudden and transient worsening of pain in patients with chronic pain that has characteristic listed shown in table 2 and is otherwise well-controlled. Originally, BTcP was described as an unpredictable exacerbation of pain in cancer patients with chronic pain treated therapeutically with opioid medications. Over time, this definition has been extended to include exacerbations of pain that can occur spontaneously or in association with specific triggers. However, this term has not gained universal acceptance in the healthcare community because the main characteristics of this type of pain are very different from those of exacerbation pain [5]. The term '*breakthrough*' was initially vague due to linguistic reasons, a lack of clear concordance in some languages, and the need to define whether an exacerbation of pain implied the presence of underlying pain [6].

Characteristics of breakthrough pain

Breakthrough cancer pain (BTcP) can generally be classified into two subtypes. Spontaneous BTcP occurs without a specific trigger and is unpredictable. This subtype of BTcP typically has a longer onset and duration. Incident-type pain, on the other hand, is triggered by known factors. In such cases, management has to be based on a balancing of activity and background analgesia. Incident-type Breakthrough cancer pain (BTcP) has a more rapid time to peak intensity and a lesser duration. These relapses may resolve spontaneously with rest, even though the pain may remain for an unpredictable length of time after stopping activity. Therefore, patients may experience interference in their daily lives, as they may avoid triggering BTcP, limit their activities, or seek individualized strategies to prevent BTcPs from occurring [7].

Over 80% of BTcP patients reported a major adverse effect on their daily life. The average number of attacks per day was 2.4, with an average intensity of 7.4 on a scale of 0-10. The average episode of uncontrolled breakthrough cancer pain (BTcP) lasts between 30 and 40 minutes. It can be clearly distinguished from background pain, which is classed as well-tolerated on a clinical basis and does not require adjustment of the dosage of opioid therapy. BTcP significantly impacts the patient's quality of life [8].

To diagnose breakthrough cancer pain (BTcP), patients must be on a stable and effective analgesic regimen that provides well-controlled background pain, shown in Figures 1 and 2. The maximum intensity of BTcP should be moderate to severe and clearly differentiate from the background pain severity. It has been documented that a 3-point discrepancy on a numerical pain scale is a reliable indicator of treatment demand. This subgroup of patients was less likely to be prescribed BTcP drugs, possibly due to the prolonged time to significant pain relief and lower satisfaction with BTcP treatment, which was mostly oral morphine [9,10].

In approximately two-thirds of cases, the beginning of BTcP is relatively short, peaking within 10 minutes. The offset time is variable, with an average of 45 minutes and a range of minutes to 1-2 hours. However, if pain

persists after 1-2 hours without treatment, it suggests that the background pain is poorly controlled and requires an adjustment in opioid dose. Based on these considerations, Breakthrough cancer pain (BTcP) should be considered a severe episode of pain with a rapid onset and resolution [9,10].

Breakthrough cancer pain (BTcP) may occur spontaneously or incidentally due to a triggering event. In incident-type BTcP, pain is provoked by an observable trigger, which may or may not be predictable. This type of BTcP tends to have a rapid onset and short duration. The two most frequent types of breakthrough cancer pain (BTcP) are movement-related bone pain, often caused by bone disease, and swallow-related pain, caused by oral mucositis [9,10].

In general, experiencing 3-4 episodes of BTcP per day is considered acceptable if the pain can be managed effectively throughout the day. The decision to use BTcP medications should not be based on pain attacks, but rather on individual patient needs. Some patients prefer to limit their activities to prevent BTcP episodes, while others are willing to tolerate a large number of BTcP episodes every day. This is particularly true for bedridden patients with low activity levels, such as those with fractures. Therefore, patient preferences should be considered when making treatment decisions. From a therapeutic perspective, the aim is to optimize background analgesia through tailored opioid use, assisted by the application of adjuvant analgesics to find the best balance of background analgesia and intended activity [10].

Certain tumors may show unique characteristics. Patients diagnosed with head and neck cancer experience more episodes of breakthrough cancer pain (BTcP), which can be predicted mainly through food consumption. This may be due to the prevalence of severe mucositis, causing pain when swallowing. In a similar way, patients with pancreatic pain report experiencing pain after meals [10].

Breakthrough cancer pain (BTcP) is an indication of poorly controlled pain due to the failure of existing analgesic therapy. This means that BTcP is associated with inadequate opioid therapy. Furthermore, it is important to note that the properties of BTcP can change during the progression of the underlying disease. Several reports have shown that patients with advanced cancer who have lower Karnofsky scores, who are being cared for by a palliative care team and who may be in the terminal phase of their disease, experience fewer breakthrough cancer pain (BTcP) episodes per day, which are later in onset and less predictable than patients assessed in a pain clinic or oncology ward who may be in the early stages of their disease. Understanding the various types of BTcP allows for better individualized treatment planning and improved outcomes. Treatment for BTcP should be based on pain characteristics, optimization of pain background, disease status, and patient preferences, which are likely to change over time [10].

TABLE 1 Proposed classification of cancer-related pain according to ICD-11 [11]

Level 1	Level 2	Level 3	Level 4
Cancer-related pain	Cancer pain	Visceral cancer pain	
		Bone cancer pain	
		Neuropathic cancer pain	
	Post-cancer treatment pain	Post-cancer medicine pain	Painful chemotherapy-induced polyneuropathy
		Post-radiotherapy pain	Painful radiation-induced neuropathy
		Post cancer surgery pain	

TABLE 2 Structured pain assessment [11]

History	Pain location, onset, duration, severity, and quality, as well as alleviating and aggravating factors. Special emphasis on episode pain
	Impact on mood, usual activities, function, and quality of life and sleep
	Previous pain and treatment history
	On-going response to treatment and adverse effects
	Comorbidities impacting pain (e.g., chronic disease, surgery, trauma, mood, cognitions, substance use disorder, and medications)
	Personal characteristics (e.g., age, sex, race, religion, culture, and language)
	Expectations of pain management and current understanding of the condition, including what significance the patient attaches to the pain
Physical examination (focused according to the presenting condition)	Relevant, physical, neurological and musculoskeletal assessment
Review if clinical records	Comorbid diseases, previous chronic pain history, and age-related frailty
Investigations	Laboratory tests Imaging studies Neurophysiological evaluations

Treatment of chronic cancer pain

The treatment of cancer pain should be characterized as integrative pain care. Integrative care is defined as the combination of two or more healthcare strategies in a collaborative, consultative, and coordinated multidisciplinary context. It may incorporate management approaches from different areas of complementary and alternative medicine, conventional medicine, or both. For the treatment of chronic pain, a variety of pharmacological and non-pharmacological therapies is the most appropriate choice, although drug-based therapies can be detrimental due to their possible adverse effects, such as causing various drug addictions. Nevertheless, there is a wide range of non-pharmacological interventions that we can classify as peripheral interventions, cognitive-behavioral interventions and other interventions (acupuncture, placebo, surgical treatment, and nerve blocks) [11].

The use of analgesic drugs as enclosed in Table 3, is the mainstay of cancer pain management. For patients experiencing moderate pain, non-opioid medicines such as aspirin, paracetamol or other non-steroidal anti-inflammatory drugs are sufficient. In patients with moderate pain, if non-opioid drugs do not provide adequate pain relief when given regularly, codeine or alternative weak opioids should be prescribed. Non-opioid drugs, particularly NSAIDs, may act in a non-specific way by inhibiting the prostaglandin system, whereas opioids act centrally by targeting specific opioid receptors. Due to these differences, the combination of these two types of drugs produces an additive analgesic effect. For patients experiencing severe pain, morphine is the preferred drug due to its strength as an opioid. Paracetamol is recommended for mild to moderate pain. Morphine has a linear pharmacokinetic profile and a relatively short half-life, making it easy to titrate the dose to the patient's pain levels. Corticosteroids are frequently prescribed to cancer patients as both chemotherapeutic and analgesic agents. Multiple reviews have documented pain relief with corticosteroids in patients with epidural spinal cord compression or nerve infiltration by tumors, and in people suffering from

metastatic bone disease. The appropriate analgesic dose can provide pain relief within a reasonable time frame of four hours or more, although it may vary from patient to patient. Unlike non-opioids, weak opioids, and mixed opioid agonists-antagonists, the doses of morphine and other strong opioids can be increased indefinitely. It is important to note that this is due to the development of tolerance, rather than any inherent property of the drugs themselves [12].

The second step involves the use of medications traditionally considered as 'weak' opioids (e.g., codeine), and the third step advocates the use of stronger opioids. The fourth and final step reminds clinicians to consider non-pharmacological interventions for pain management. The World Health Organization (WHO) ladder was initially developed to guide clinicians in a systematic approach to pain management. Although these guidelines have been effective in treating cancer pain in most patients, there is still debate as to whether they are the best way to manage pain in all patients. Recent evidence indicates that patients experiencing moderate cancer pain may respond better to low-dose morphine than codeine. That raises the question of whether it is worthwhile to attempt a ''weaker'' step 2 opioid before commencing morphine to manage moderate pain, particularly given that there is no discernible difference in side effects between the two groups. While not explicitly outlined in the WHO ladder, it is necessary to consider adjunctive analgesics, integrative therapies, and interventions at each stage of pain management. Recent evidence suggests that interventions may be more effective when given in the early stages of the disease course, rather than when the pain is considered intractable with standard pharmacological management [13,14].

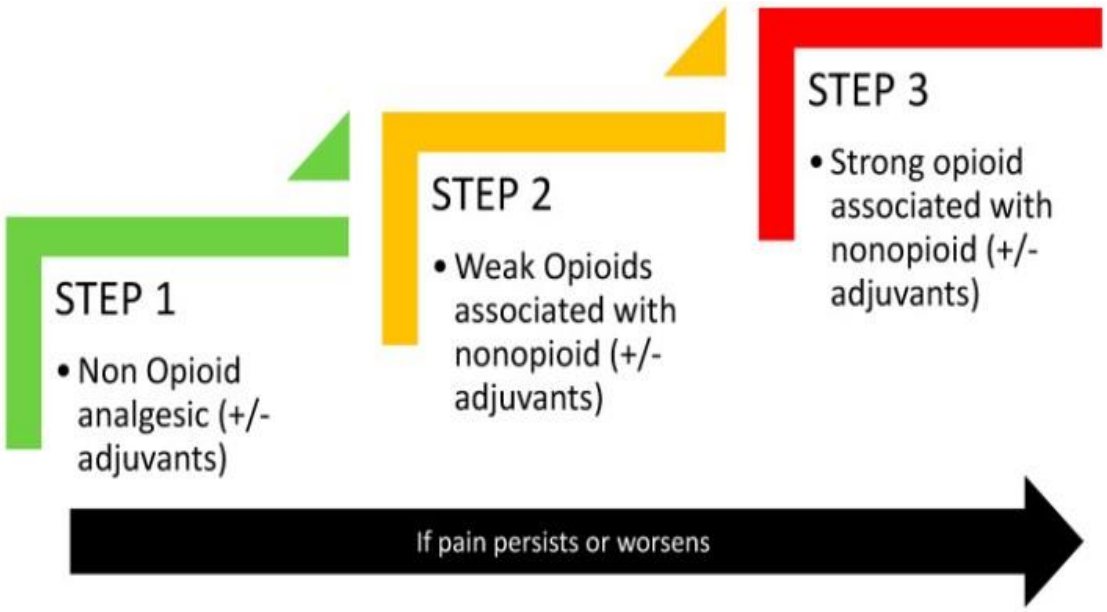

FIGURE 1 The WHO analgesic ladder for treating cancer pain. Adapted from World Health Organization (WHO) [1,15]

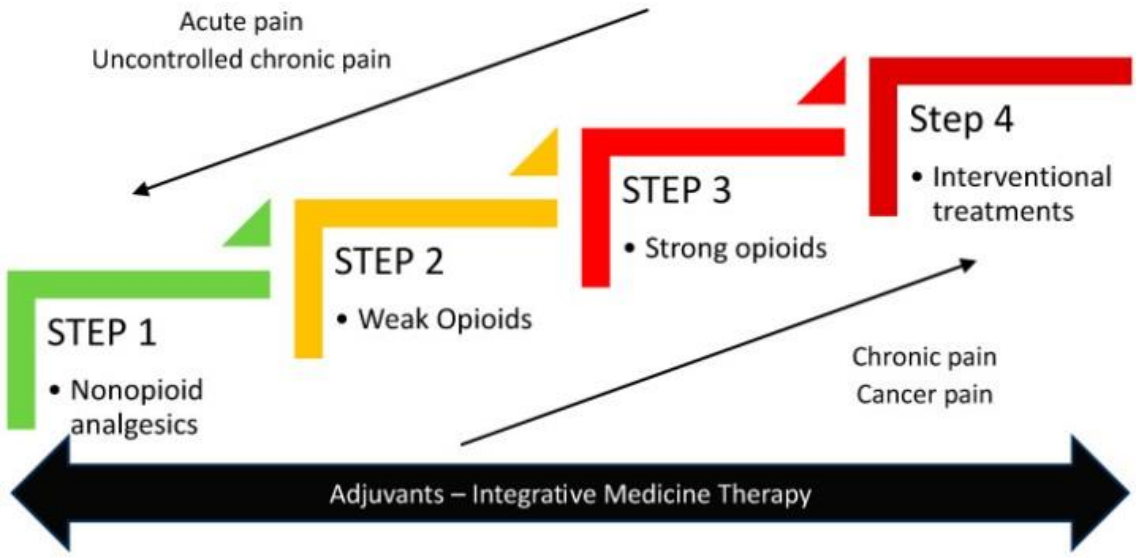

FIGURE 2 Modified WHO analgesic ladder [1,13]

TABLE 3 Essential analgesic drugs [13]

Drugs Class	Examples
Simple analgesia	Paracetamol
	Non-steroidal anti-inflammatory drugs (NSAIDs) including coxibs
Opioids	*Opioids for moderate intensity pain:*
	Codeine, dihydrocodeine, and tramadol
	Opioids for moderate to severe intensity pain:
	Immediate release opioids as oral and injectable formulations (morphine, oxycodone, and hydromorphone); sustained release opioids as oral (morphine, oxycodone, tapentadol, and hydromorphone) and transdermal (fentanyl, buprenorphine) formulations,
	Opioids for specialist use only
	Rapid onset transmucosal fentanyl based formulations Methadone
Antidepressants	Amitriptyline, imipramine, duloxetine, and venlafaxine
Antipileptics	Gabapentin, pregabalin, and carbamazepine
Corticosteroids	Prednisolone and dexamethasone
Bisphosphonates	Pamidronate and Zoledronate
Monoclonal antibodies	Denosumab and Tanezumab
Other	Topical lidocaine and ketamine (*specialist use only*)

Treatment of breakthrough pain with opioids

Various options exist for treating breakthrough cancer pain (BTcP), including pharmacological and non-pharmacological treatments. The primary pharmacological treatment involves administering opioids as required [10]. Opioids are commonly used to treat cancer pain. Concerns about their efficacy, safety, and potential for abuse; however, have evolved, with some decades being associated with overly restrictive attitudes to opioid use and reluctance to prescribe the drugs even for severe cancer pain, and other decades being associated with a push for more expansive acceptance of support for these regimens [16]. Opioids are essential and useful for people with advanced cancer and severe pain. Unfortunately, they may not be appropriate for most people with cancer who do not have active cancer [17].

Opioids are frequently used in the treatment of moderate to severe cancer-related pain, often in combination with adjunctive therapies, to achieve sufficient pain reduction in various cancer pain syndromes. Essential opioids for controlling somatic pain include oxycodone, morphine, hydromorphone, and fentanyl. Anticonvulsants, such as gabapentin and pregabalin, are among the pharmacological options for neuropathic pain. Besides, typical side effects include fatigue, drowsiness, nausea, indigestion, and constipation [18].

Oral opioids

Immediate-release oral opioid formulations have been available for the management of BTcP for decades. It is worth noting that they have been the principal approach in this field. Oral morphine is administered traditionally in doses comparable to the dose of opioids used for analgesia. According to the guidelines set forth by the National Institute for Health and Care Excellence (NICE), oral morphine is suggested as the primary medication option. However, oral opioids are not always suitable for managing many BTcP episodes which are characterized by a distinctive temporal pattern due to their onset and duration of action. From a pharmacokinetic perspective, it could be argued that there is a weak correlation that exists between the analgesic effect of oral opioids and the dynamics of typical BTcP episodes. It is essential to emphasise that the duration of BTcP is often limited in time (approximately 30-40'), and the analgesic effects of oral opioids are thought to occur within 30-45 minutes, when most episodes disappear spontaneously. It should be noted that there is currently a lack of studies on the use of oral opioids in the management of BTcP, with the exception of a comparative study of fentanyl preparations. It has been observed that intravenous morphine, when administered in doses comparable to the basal opioid regimen, can provide rapid and effective analgesia within 5-15 minutes. However, it is important to consider that this may not be a feasible option for the majority of patients [10].

Biomarkers for the evaluation of cancer pain treatment in chronic cancer pain

Biomarkers are characteristics that are objectively measured and used to indicate normal biological processes, pathogenic processes or pharmacological responses to therapeutic interventions. They are not assessments of how an individual feels, functions, or survives, which are more appropriately defined as clinical endpoints [19]. Composite biomarker signatures as shown in Table 4, which combine evidence from various research areas, are being developed to improve the objective assessment and effective treatment of chronic pain. These signatures aim to capture the multidimensional and subjective nature of pain, which is not easily captured by a single biomarker [20,21].

The development of biomarkers for chronic pain is considered crucial in reducing healthcare costs. It has the potential to lead to the creation of drug regimens for disease-modifying pain and to improve the accuracy of diagnosis. However, it is important to acknowledge that biomarker discovery is challenging due to the complexity of chronic pain and the frequent co-morbid diagnoses of depression and anxiety [22].

TABLE 4 Functional biomarkers of pain test panel [22]

Biomarker	Abnormal Result Indicates	Biomarker Class
Methylmalonic acid	Intracellular Vitamin B12 deficiency	Nerve health
Xanthurenic acid	Intracellular Vitamin B6 deficiency	Nerve health
Homocysteine	Deficiencies of Folate, Vitamin B6 or B12	Nerve health
3-HPMA	Acrolein exposure	Nerve health
Quinolinic acid	Brain Kynurenine pathway and NMDA agonization	Inflammation
Kynurenic acid	Aids interpretation of Xanthurenic acid and Quinolinic acid	Inflammation
Pyroglutamate	Glutathione response capacity	Oxidative stress
Hydroxymethylglutarate	Coenzyme Q10 deficiency	Oxidative stress
Ethylmalonic acid	Carnitine and/or Vitamin B2 deficiency	Oxidative stress
5-Hydroxyindoleacetate	Serotonin turnover	Neurotransmiter status
Vanilmandelate	Epinephrine & Norepinephrine turnover	Neurotransmiter status

Tetrahydrobiopterin pathway as a target for evaluation of cancer pain treatment

Tetrahydrobiopterin, or BH4, is an important cofactor for the activity of several enzymes that play a critical role in physiological and metabolic functions, including three types of nitric oxide synthase (neuronal, inducible, and endothelial), alkylglycerol monooxygenases, and aromatic amino acid hydroxylases such as phenylalanine, tryptophan, and tyrosine hydroxylase. Through the action of these enzymes, BH4 is required for the formation of nitric oxide, ether lipid metabolism, phenylalanine catabolic processes, as well as the synthesis of neurotransmitters such as noradrenaline, adrenaline, serotonin, and dopamine. BH4 can be produced through three different pathways: the de novo pathway, the salvage pathway, and recycling, with the de novo pathway being the main pathway for its synthesis. The increased production of tetrahydrobiopterin (BH4) that occurs in injured sensory neurons contributes to increased pain sensitivity and prolongs the sustainability of that pain [23,24].

The first study that established a connection between chronic pain and BH4 metabolism was based on the identification of a single nucleotide polymorphism at the GTPCH1 locus. This polymorphism was found to be associated with reduced sensitivity to experimental and clinical persistent pain. It is worth noting that the homozygous haplotype in humans is linked to the down-regulation of GTPCH1 upon inflammatory stimulation, but it does not completely eliminate GTPCH function, which helps to maintain baseline BH4 concentrations. It is known that this human protective pain haplotype only affects the nociceptive threshold after pain sensitization. Moreover, expression and functional profiling in rodents suggest that increased transcription and activity of BH4 biosynthetic enzymes in sensory neurons and immune cells leads to increased BH4 levels, resulting in greater chronic pain hypersensitivity [24,25].

Researchers have found that reducing BH4 levels using GTP cyclohydrolase 1 (GCH1) inhibition enhances the analgesic effects of morphine in mice with cancer pain. This finding suggests that BH4 regulation may play a part in cancer pain mechanisms. It was observed that rodents that underwent SNI and CCI exhibited analgesia as a result of the pharmacological inhibition of GTPCH activity. The mechanical and cold hypersensitivity that was induced by nerve injury was reversed by the use of 2,4-diamino-6-hydroxypyrimidine (DAHP), which is a GTPCH inhibitor. Furthermore, the DAHP treatment resulted in

a reduction of tumor-evoked microglial activation in the spinal cord and cancer-induced systemic hyperalgesia in mice. The initial data suggests that targeting the flux of this metabolic pathway could open up new possibilities in the clinical management of chronic pain. However, it is important to consider that GTPCH activity is essential for BH4 production. Therefore, any pharmacological approaches should aim to reduce exacerbated BH4 levels back to basal levels, without compromising its physiological roles in endothelial function and the metabolism of neurotransmitters, lipids, and nitric oxide [24,26].

Conclusion

Pain related to cancer is a major problem and one of the main symptoms reported by cancer patients. Breakthrough Cancer Pain (BTcP) is a definition of an exacerbation of pain in patients with controlled chronic pain. It has a high prevalence in all cancer types and stages. The most appropriate treatment for chronic pain is a combination of pharmacological and non-pharmacological therapies. The primary pharmacological treatment for breakthrough cancer pain (BTcP) is often the administration of opioids as needed. It is important to ensure adequate pain management to avoid potential negative consequences such as longer hospital stays, decreased productivity, functional deficits, reduced life expectancy, and increased use of healthcare resources.

The modulation of tetrahydrobiopterin levels has been found to have an impact on the sensitivity of the pain system. This can affect the response of healthy individuals to noxious stimulation as well as the susceptibility of patients to the development of persistent neuropathic pain. It is expected that examining the production of the tetrahydrobiopterin pathway will aid in the treatment evaluation for chronic pain in cancer patients.

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Conflict of Interest

The authors declare that there is no conflict of interest with respect to the study, authorship, and/or publication of this article.

Ethics Approval

There is no ethics approval. This article is the result of a literature review and does not involve direct research on human subjects, animal treatment, or other ethical violations.

Orcid:

Ardhian Wardana:*
https://orcid.org/0009-0000-9841-3636
Christrijogo Sumartono Waloejo:
https://orcid.org/0000-0001-6234-0842
Herdiani Sulistyo Putri:
https://orcid.org/0000-0002-3839-9147
Wiwiek Indriyani Maskoep:
https://orcid.org/0009-0005-8676-8153

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