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Breakthrough Cancer Pain

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ABSTRACT

Health Organization defined breakthrough pain as a temporary increase in pain from pre-existing underlying pain with moderate to severe pain intensity. Cancer patients with chronic pain experience breakthrough cancer pain during their illness. Breakthrough cancer pain caused high morbidity in patients that disrupts the quality of life of patients and their families. Until now, the causes of breakthrough cancer pain are multifactorial and subjective, therefore the assessment and management are very complex. This article aimed to provide a comprehensive and focused review from the definition to the management of breakthrough cancer pain.

Keywords: Breakthrough cancer pain, chronic pain, moderate-severe intensity.

INTRODUCTION

Pain is a complex condition that affects a person's mental and physical abilities. In general, pain is classified into two categories: acute pain (lasting less than three months and tends to be provoked by certain diseases or injuries) and chronic pain (lasting more than three months, often idiopathic). Chronic pain occurs in 2% to 40% of the adult population worldwide and is one of the most common reasons most sufferers seek medical care. One part of chronic pain is cancer pain, which is experienced by at least 35% of oncology patients when a cancer diagnosis is made. The pathophysiology of cancer pain can be caused by a primary tumor, followed by cancer-related therapies including surgery, radiation therapy, chemotherapy, targeted therapy, supportive care therapy, and/or diagnostic procedures. However, in most cases, the actual cause is unknown.[1]

Most of the pain caused by cancer can be controlled with regular long-term medical care, but some patients still experience transient pain with high intensity even with good management. This condition is known as breakthrough cancer Pain (BCP).[1]

DISCUSSION

Breakthrough pain (BTP) is commonly found in cancer patients and other non-cancerous chronic pain conditions.[2,3] The incidence of breakthrough pain varies widely from 16% to 95%. This variability may occur due to a lack of clear consensus on the definition of breakthrough pain. Breakthrough pain is generally defined as pain that occurs suddenly, lasts a short time, and intensely "breaks through (breakthrough)" analgesia to control persistent pain.[3-5]

The term BTP was originally popularized by Portenoy and Hagen (1990) who described BTP as “transient exacerbations of moderate or more intense pain occurring based on moderate or less intense pain in patients receiving chronic opioid therapy”.[5] The key word is that there must be significant underlying persistent pain before establishing BTP. Over time, other definitions have appeared in the literature (Table 1), and controversy over the best definition remains. In addition, the time from the onset of BTP to the peak of

severity is usually within 3-5 minutes with a duration of about 30 minutes and severe intensity.[3-5] Several episodes of BTP may occur daily, unexpectedly, and regardless of stimulus.[2]

Table 1. Evolution of the definition of breakthrough pain.[2,3]

Year	Definition
1990	*Transitory increase in pain to greater than moderate intensity, which occurs on a baseline pain of moderate intensity or less, in a patient receiving chronic opioid therapy*
1996	*Transitory exacerbation of pain experienced by the patient who has relatively stable and adequately controlled baseline pain*
1998	*The transitory flare of pain superimposed on an otherwise stable pain pattern in patients treated with opiates*
2005	*Transient exacerbation of pain that occurs in patients with otherwise stable baseline persistent pain*
2005	*Moderate to excruciating acute pains that occur intermittently, often on a background of well-controlled chronic pain*
2006	*Transitory increase in pain that occurs in addition to persistent pain*
2012	*Temporary increase in the severity of pain over and above the pre-existing baseline pain level*

Epidemiology

Breakthrough cancer pain has a major impact on the quality of life for patients and their families.[3,4] Pain is experienced by at least 1 in 3 cancer patients who are active in treatment and 3 out of 4 advanced cancer patients. 67% of all patients described the pain associated with cancer as misery, 36% described it as an unbearable aspect of the disease, and 32% described the pain as being so bad as to wish for death. Cancer patients consider the quality of life as important as life expectancy or survival.[4]

Pain that is not well controlled by any etiology is related to disturbances in sleep, walking, daily activities, interactions with others, and perceptions of happiness. It is also correlated with worsening anxiety and depression, dissatisfaction with opioid therapy, and poor medical outcomes. In addition, patients with BTP related to cancer or uncontrolled pain tend to use more healthcare resources, have longer hospitalization times, and increase visits to the emergency department which directly and indirectly increase treatment costs.[3,4] One study found that the total annual cost of cancer-related hospitalization and visits to emergency units and polyclinics was five times greater in patients with BTP ($12,000/patient/year) than without BTP ($2,400/patient/year).[3]

The prevalence of BTcP in a pan-European survey occurs in 50-90% of all inpatient oncological patients and 63% of patients on analgesic medication. This pain is a direct consequence of a neoplasm in 70-80% of cases and a result of anticancer treatment in 10-20% of patients. Identification of the precipitating factor can be obtained in some cases and is unknown in the rest. Although prevalence data referring to cancer pain vary depending on the geographic setting, patient age, type of treatment, and other factors, the malignancies with the greatest prevalence of pain are head and neck cancer (70%), followed by gastrointestinal cancer (59%), malignancy lung/bronchial (55%), breast cancer (54%), and urogenital cancer (52%).[4] In Indonesia, the prevalence of BTcP has never been reported, but neuropathic cancer pain is found in 31.6% of the population.[6]

Clinical

Based on information obtained from the medical history and physical examination, the BTP experienced by most patients can be categorized as one of three subtypes: incident, idiopathic or spontaneous, and late dose (Table 2).[4,7,8] The incident subtype is the most common with an incidence of up to 50% of BTP cases. BTP incident subtypes are predictable and directly related to voluntary precipitating factors (musculoskeletal movements, such as coughing or turning the bed), involuntary (which may result from contraction or spasm of visceral smooth muscle, such as bowel or bladder spasms), and procedural (diagnostic interventions or therapy such as wound care). Furthermore, the BTP subtype is idiopathic or spontaneous, has no easily identifiable cause, and usually lasts longer than the incident subtype, often more than 30 minutes. The late dose subtype occurs when a patient experiences an initial spike

of persistent pain one hour or more before scheduling to receive the next dose of pain medication and usually indicates that the dosing interval or amount of pain medication is insufficient. The cause and anatomic location of BTP are generally the same but may differ from the initial persistent pain.[3,9]

Table 2. BTP Subtypes.[3]

Subtype	Characteristic
Incident, predicted	There is a consistent relationship with precipitating factors (volunteer, involuntary, procedural)
Incident, unpredicted	There is an inconsistent relationship with precipitating factors (volunteer, involuntary, procedural)
Idiopathic or spontaneous	Not induced by an identified cause, lasts longer than the incident subtype
Late dose	Occurs before the scheduled analgesia dose ends, tends to be slow in onset with a longer duration than the incident or idiopathic subtypes

The quality of BTP is usually categorized as somatic, visceral, or neuropathic pain based on the anatomic location of the pain and the specific cause (Table 3). Somatic BTP is most often caused by low back muscle spasms, bone metastases, or osteoarthritis. Whereas liver metastases, peritoneal carcinomatosis, irritable bowel syndrome, or angina pectoris are all potential causes of visceral BTP. This type of pain can be localized to a visceral origin or referred to a distant part of the body, as in the case of left neck and facial pain due to angina pectoris. Furthermore, neuropathic pain is caused by a lesion or dysfunction in the central nervous system (e.g., brain, spinal cord) or peripheral nervous system (e.g., dorsal nerve roots, peripheral nerves).[3,4,7-9]

Table 3. BTP Quality.[3]

Pain quality	Characteristic
Somatic	Skeletal is localized to the area of the lesion; throbbing in nature, the pain increases with movement
Visceral	Derived from internal organs or on the move; generally difficult to localize; deep pain, cramps, spinning, cuts
Neuropathic	Pain due to structural changes in nerves with stimulation; shot, burned, tingling, electrocuted

In general, BTcP is characterized by rapid onset (usually between 3 to 5 minutes), short duration (average 60 minutes), moderate to high intensity (7 points on 10 points on Visual Analogue Scale [VAS] pain), and impairing quality of life sufferer.[1]

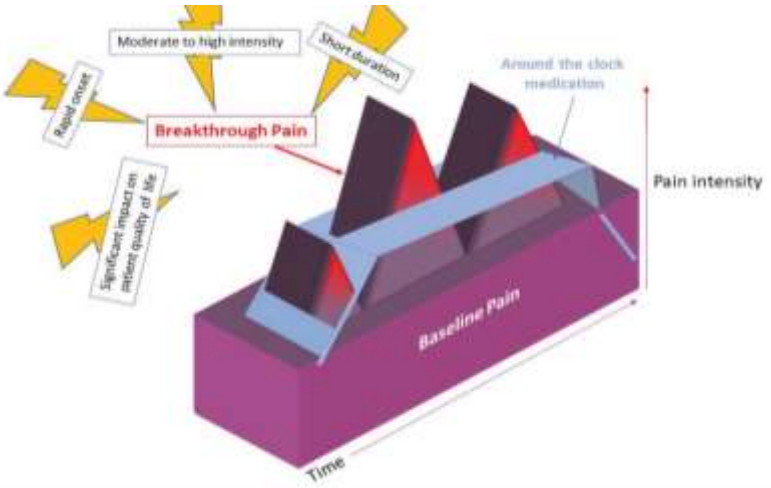

Figure 1. Characteristics of Breakthrough Pain.[1]

Pathogenesis

The underlying pathogenesis that precipitates BTcP tends to be heterogeneous and complex. Some of the underlying hypotheses are increasing stimulation and modification of the somatosensory system:[9]

- The first mechanism is associated with a temporary increase of secondary afferent stimulation to the

involving nearby tissue. Furthermore, allodynia and hyperalgesia mechanisms may be involved in this mechanism.

- The Second mechanism is an escalation of peripheral sensitization of tissue terminal, nociceptor, or ectopic sinus that formed after cancer-induced anatomical-functional alteration that lowers the threshold of nociceptor or ectopic sinus.
- The third mechanism is an increase of spinal neuron sensitization-central sensitization-following the increase of spatial-temporal afferent that originates from the peripheral receptor, not activated in normal conditions. This mechanism can happen in case sensitive input that is delivered by C fiber is increased, following involvement from "idle" nociceptor that originates in visceral organs.

Diagnosis

For cancer patients, BTP is associated with a decrease in functional status and an increase in anxiety, and depression, which tremendously affects the patient's quality of life. Furthermore, BTcP is sometimes not recognizable and often left untreated. Therefore, rapid and efficient diagnosis is extremely important.[1]

BTP diagnosis is usually made based on various resources. When the patient has a normal mental status, the self-report is the best information source to discover causes and types of breakthrough pain that have been experienced by the patient.

At the same time, when there is an alteration of mental status, BTP diagnosis is supported by evaluation from a family member or caregiver that has been experiencing direct contact with the patient. In cases where the patient does not understand the concept of BTP, the clinician needs to initiate specific questions and ask about pain episodes recently. Details about the source, severity, pattern, subtype, and etiology probability of pain episodes must be carefully documented. The physical examination can be helpful to localize pain and to identify precipitating physical characteristics. Furthermore, imaging like X-ray radiographs, *computed tomography*, or *magnetic resonance imaging* is needed.[3]

Another interactive evaluation is a unidimensional or multidimensional instrument, also needed to evaluate detailed pain characteristics. Unidimensional instruments quantitatively evaluate one pain severity dimension as the Numeric Rating Scale (NRS), Visual Analog Scale (VAS), and Wong-Baker face scale, tend to be easily used and can be solved quickly by the majority of patients.[10]

Whilst multidimensional instruments such as short pain inventories and pain diaries can provide quantitative and qualitative information, but require more time and often require help from doctors or other healthcare providers to complete it.

Besides, multidimensional instruments cannot be performed on a patient that has a cognitive impairment. However, a detailed pain diary is usually the best note about the characteristics, duration, severity, and predictability of BTP episodes in 24 hours period.[3] Other studies are using Breakthrough Assessment Tool (BAT) for pain evaluation, which contains 14 short questions about the frequency, duration, and severity, of analgesia that has been experienced so that can be facilitated better breakthrough pain management in a clinical setting.[10]

In some cases, utilization of the SF-36 pain scale and neuropathic pain diagnostic questionnaire (DN4) is often applied to support breakthrough pain diagnosis. Furthermore, the Davies algorithm is an algorithm that has been modified and is most widely used. Although as a good positive predictive value, sensitivity is still limited because of patient variability. Complete clinical evaluation is still a preferred method to diagnose BTcP.[1,8,11]

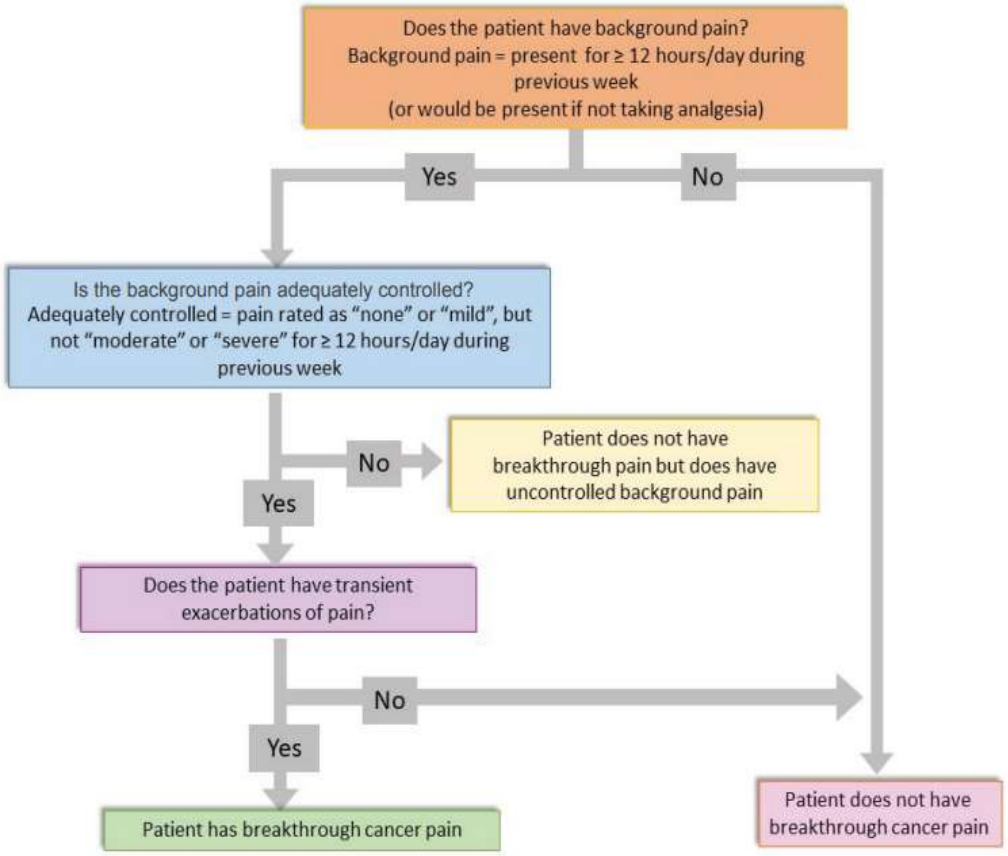

Figure 2. BTcP diagnostic flow through the Davies algorithm. [1,8,11]

Therapy

Some guidelines suggest that 3 to 4 episodes of BTcP per day is an acceptable outcome if pain during the rest of the day can be controlled. BTcP is considered to be very complex and heterogeneous because it is highly dependent on comorbidities and patient activity level, therefore the effectiveness of treatment depends on the individual patient's perspective regarding activity and the use of initial analgesia and the reliability of BTcP therapy currently used.[7]

Given the wide inter- and intra-individual variability that characterizes BTcP patients, it is critical to perform a full initial individual evaluation to provide the best management approach. In addition to the underlying etiology, mandatory BTcP management is multimodal by combining preventive measures with pharmacological and non-pharmacological methods. Support from family and health professionals will also be important for the best results.[1]

- **Non-pharmacological**

  Initial treatment of BTcP should be started before or simultaneously with pharmacological therapy.[1,3] The actions included in this type of therapy are lifestyle changes to limit or accelerate physical activity; and regular exercise. Cognitive behavioral techniques (ie, hypnotic and relaxation methods) or alternative medical therapies such as acupuncture or hypnosis may be very beneficial in some patients either alone or in addition to opioid therapy.[3]

- **Pharmacological**

  The goal of pharmacological therapy is to reduce the frequency and intensity of BTP with drugs that have a rapid onset and relatively short duration of action. There are 4 basic principles in administering pain medication in the form of 4A (Analgesia, Life Activities, Adverse effects (drug side effects), and Aberrant drug-taking behaviors (drug use behavior)). Various types of opioid

and non-opioid drugs (corticosteroids, antidepressants, anticonvulsants) are available to assist BTcP therapy, so pharmacodynamic and pharmacokinetic considerations play a major role in the effectiveness of therapy.[3]

Some recommendations for treatment selection in cases of BTcP include:

- Addition of analgesic drugs such as antidepressants and anticonvulsants, corticosteroids, and others.[1]
- Increase the daily dose of basal analgesics (25-50%), to minimize the intensity and number of BTcP episodes, while evaluating patient tolerance and side effects of the therapy administered.[1]
- Administration of opioid analgesics by considering pharmacokinetics and pharmacodynamics, as well as previous medical history.[12] In the latest guidelines, the use of rapid-onset opioids (ROOs), particularly fentanyl formulations, is the gold standard in the treatment of BTcP because is rapid onset, effective, and has tolerance in patients with kidney or liver disease.[1]

Selection of Opioids

Some characteristics of opioids used in cancer pain are shown in table 4. Immediate Release (IR) oral opioid formulations generally have a broad cross-first effect as well as have higher hydrophilic properties thus slowing the onset of analgesia. Whereas, nasal fentanyl provides a faster onset of analgesia and the achievement of clinically relevant pain relievers. This therapy was rated superior compared to the placebo in the first 30 minutes after administration, while oral morphine worked only slightly better than the placebo.[8]

Table 4. Characteristic of opioids.[8]

	IR opioid	The onset of analgesia (minutes)	Duration of effect (hours)	Advantages (A)/disadvantages (D)	
Hydrophilic	Morphine (oral)	30-40	4	A D	available in multiple dosage forms, liquid concentrate slow onset of analgesia for idiopathic BTcP
	Oxycodone (oral)	30	4	Same as morphine	
	Hydromorphone (oral)	30	4	D	no liquid concentrate, slow onset of analgesia far idiopathic BTcP
	Methadone (oral)	10-15	4-6	A D	faster onset of analgesia in one small study complex pharmacology, pharmacokinetics
Lipophilic	Fetanyl (transmucosal)	5-10	1-2	A D	Fastest to onset of analgesia Requires ongoing patient cooperation in the use

For adequate BTcP analgesia, it is important to select the type of fentanyl (Table 5) that will be titrated over time to meet the patient's individual needs, considering the patient's clinical needs, age, the presence of comorbidities and the appearance of side effects at initiation of treatment. The ultimate goal is to provide individually tailored BTCP treatment by identifying the optimal fentanyl dosage and minimizing the risk of side effects. The dose of fentanyl should be adjusted gradually starting with the lowest possible concentration (Figure 3).[1]

Table 5. Characteristics of fentanyl products used for BTcP.[7]

Type of Fentanyl	Analgesic Onset	Availability	T max (minute)
Oral Transmucosal Fentanyl Citrate	15-30	50	40
Fentanyl Buccal Tablet	15	65	45
Sublingual Fentanyl	10-15	70	40
Fentanyl Buccal Soluble Film	15	65	60
Intranasal Fentanyl Spray	5-10	80-90	20
Fentanyl Pectyn Nasal Spray	5-10	70	20

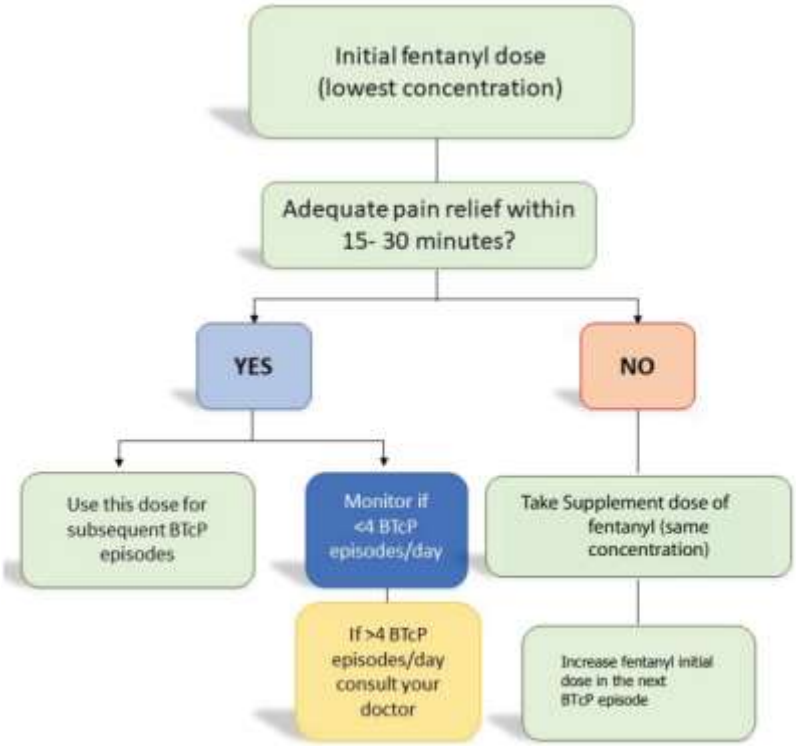

Figure 3. Fentanyl dose algorithm.[1]

CONCLUSION

Breakthrough cancer pain is a complex and clinically challenging condition defined as a transient increase in moderate-to-severe intensity pain, which occurs based on moderate or less intense pain in patients receiving chronic opioid therapy. BTcP conditions require special attention because it has the potential to reduce a patient's quality of life. Appropriate assessment taking into account the etiology, subtype, and degree of pain helps in establishing a better diagnosis and targeted treatment.

Declaration by Authors

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REFERENCES

1. Alarcón MDL, Estevez FV, Triado VD, Segura PB, Comes GH, Jaime AB, et al. Consensus statement on the management of breakthrough cancer pain: Assessment, treatment and monitoring recommendations. Open Journal of Pain Medicine. 2019 Aug 26;3(1):008–14.
2. Oostendorp LJ, Rajapakse D, Kelly P, Crocker J, Dinsdale A, Fraser L, et al. Documentation of breakthrough pain in narrative clinical records of children with life-limiting conditions: Feasibility of a retrospective review. J Child Health Care. 2019 Dec;23(4):564–78.
3. Payne R. Recognition and diagnosis of breakthrough pain. Pain Med. 2007 Jan-Feb;8 Suppl 1:S3–7.
4. Margarit C, Juliá J, López R, Anton A, Escobar Y, Casas A, et al. Breakthrough cancer pain - still a challenge. J Pain Res. 2012 Nov 19;5:559–66.
5. Portenoy RK, Hagen NA. Breakthrough pain: definition, prevalence and characteristics. Pain. 1990 Jun;41(3):273–81.
6. Riyanto Sofyan H, Aninditha T, Kwandou L, Odilo J, Andriani R. Prevalensi nyeri neuropatik pada pasien dengan nyeri kanker di RSUPN Dr Cipto Mangunkusumo dan PKN RS Dharmais. Majalah Kedokteran Neurosains Perhimpunan Dokter Spesialis Saraf Indonesia. 2020 Jun 1;37(3).
7. Mercadante S, Portenoy RK. Breakthrough cancer pain: twenty-five years of study. Pain. 2016 Dec;157(12):2657–63.
8. Vellucci R, Mediati RD, Gasperoni S, Mammucari M, Marinangeli F, Romualdi P.

Assessment and treatment of breakthrough cancer pain: from theory to clinical practice. J Pain Res. 2017 Sep 12;10:2147–55.
9. Zucco F, Bonezzi C, Fornasari D. Breakthrough cancer pain (BTcP): a synthesis of taxonomy, pathogenesis, therapy, and good clinical practice in adult patients in Italy. Adv Ther. 2014 Jul;31(7):657–82.
10. Webber K, Davies AN, Zeppetella G, Cowie MR. Development and validation of the breakthrough pain assessment tool (BAT) in cancer patients. J Pain Symptom Manage. 2014 Oct;48(4):619–31.
11. Caraceni A, Davies A, Poulain P, Cortés-Funes H, Panchal SJ, Fanelli G. Guidelines for the management of breakthrough pain in patients with cancer. J Natl Compr Canc Netw. 2013 Mar;11 Suppl 1:S29–36.
12. Narain L, Naeem R, Nemala A, Linder D, Sun Z, Young L. Conceptualizing breakthrough pain. J Nurs Educ Pract. 2021 Aug 9;11(12):46.

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