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REVIEW ARTICLE

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Breakthrough pain in cancer patients

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ABSTRACT

Breakthrough pain is a brief episode of severe pain occurring in patients undergoing analgesic procedures in the course of cancer. It affects about 70% of patients and significantly influences their quality of life. It is important to identify specific types of pain and inducing factors. Treatment is based on modification of pain management including use of immediate-release drug formulations.

Key words: breakthrough pain, cancer, fentanyl

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Pain is one of the most common clinical symptoms associated with malignant diseases. Although it can occur at every stage of cancer, 30–40% of patients suffer from pain at diagnosis [1]. Among actively treated patients the percentage is even higher and accounts for 50%, and in advanced disease it is found in up to 90% patients [2]. Despite intensive treatment of pain, some patients experience short-term exacerbation of pain of very high intensity, known as breakthrough pain.

In this publication the pathogenesis, diagnosis, and treatment of breakthrough pain are presented based on a review of currently available literature data.

The causes and evaluation of pain related to cancer

According to the definition by the International Association for the Study of Pain (IASP), pain is an unpleasant feeling and emotional experience related to preexisting or potential injury of the tissues. It is believed that pain contains physical, psychosocial, emotional, and spiritual components. However, this is always a subjective sensation. The pathogenesis of pain in cancer is very complex. It could result from infiltration of tissues (40–90% of patients), asthaenia and cancer cachexia (10–30% of patients), or it can be a consequence of active anticancer treatment (10–20% of patients), but in some patients the real cause remains unknown [3, 4].

Intensity of pain should be assessed at every visit, and in order to do this there are different scales based on a variety of criteria. The most commonly used is the numerical rating score (NRS) with the level of pain intensity assessed from 0 to 10 — 0 represents a lack of pain ("no pain") and 10 reflects the most extreme pain ("the strongest pain you can imagine"). The visual analogue score (VAS) is also frequently used; patient describes pain intensity on a numerical scale of 100 mm length (0 — no pain, 100 — the strongest pain imaginable). The descriptive Likert scale ("no pain", "mild pain", "moderate pain", "strong pain", "severe pain") is the least accurate, but it is often the easiest to understand by the patient.

Breakthrough pain

Cancer can be accompanied by baseline as well as breakthrough pain. Baseline pain is consistent and long-lasting (most commonly 12 hours or longer), and is usually controlled by long-term drug administration. It can have somatic, visceral, or neuropathic background.

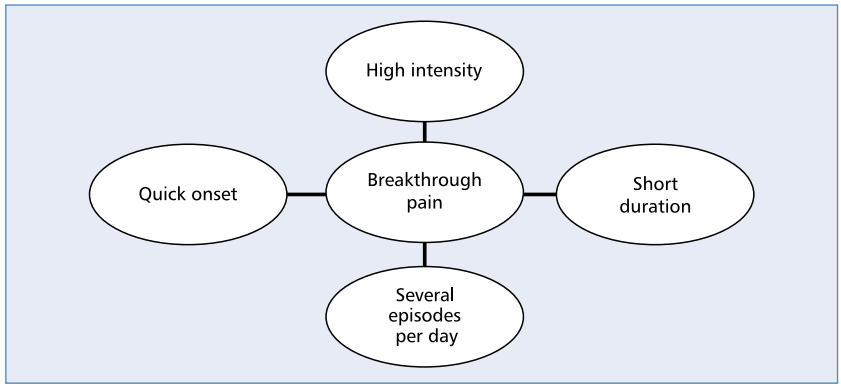

Figure 1. Characteristics of breakthrough pain

The treatment should be conducted according to the guidelines developed by the World Health Organization (WHO). The WHO analgesic ladder allows sufficiently controlling pain in 70–90% of patients [5].

Despite good control of baseline pain some patients experience short-term, transient episodes of strong pain. This is called breakthrough pain and has been described in literature for the last 25 years [6]. No single, valid definition of breakthrough pain has been established to date. A large, multicentre clinical trial involving 1095 patients treated in 24 countries confirmed that the incidence of breakthrough pain as well as treatment methods were significantly determined by the breakthrough pain definition adopted by investigators [7].

Breakthrough pain is most frequently defined as transient, exacerbating pain, which appears during baseline cancer pain, and is sufficiently controlled with long-acting opioid drugs. It was estimated that breakthrough pain affects 40–80% of cancer patients [8]. The incidence is different depending on cancer stage, and similarly to baseline pain it increases along with advancement of disease. Among patients with advanced disease, breakthrough pain concerns nearly 90% of cases [8].

Breakthrough pain is characterised by rapid onset, usually developing within a few minutes or even seconds (approximately three minutes on average), is stronger than baseline pain, and can reach 7 points on a 10-point scale, and moreover lasts for a very short time (30 minutes on average). The number of breakthrough pain episodes varies; usually there are a few during a day (Figure 1) [1].

In the majority of cases there are no prodromal symptoms of breakthrough pain.

Breakthrough pain could have either receptor (somatic or visceral) or neuropathic pathogenesis. Receptor pain accounts for approximately 30–40% of cases; it results from irritation of neural ends by tissue damaging factors, and is transmitted as an impulse to the central nervous system (CNS). Neuropathic pain in 25–35% of cases results from irritation or injury of nervous system structures (nerves, roots, spinal cord). In some patients (approximately 20%) breakthrough pain has a mixed nature [9, 10]. Usually the mechanism and location of breakthrough pain are the same those of baseline pain.

Breakthrough pain can be either predictable, e.g. induced by particular stimulus (position changes, touch, cough, breathing, therapeutic factors, care procedures), or is difficult to anticipate [6]. The relation with circadian rhythm was observed; breakthrough pain is more frequent during the day (10:00 AM–06:00 PM — 60% of patients) [11]. In the majority of cases (70–80%) cancer is the direct cause of breakthrough pain, less frequently it is due to an anticancer treatment (10–20%), and in less than 10% of patients breakthrough pain is not connected with any of the mentioned factors [9].

Breakthrough pain should be differentiated from so-called "end-of-dose pain", which is observed within the last hours of action of extended release opioid drugs. The intensity of "end-of-dose pain" increases slowly and indicates a time correlation with the used treatment.

Diagnostics

Assessment of pain is an essential part of physical examination of cancer patients. Taking into consideration the high percentage of patients with concomitantly occurring breakthrough pain, the additional questions have a special value, giving a more comprehensive clinical picture. Table 1 presents some questions prepared based on one of the questionnaires available in the literature, which assess breakthrough pain (Alberta Breakthrough Pain Assessment, ABPAT) [8]. Another questionnaire has also been published, validated in patients with different solid tumours (BAT, Breakthrough Pain Assessment Tool) [12]. Nevertheless, the tools for diagnostics and assessment of treatment efficacy need additional evaluation in future prospective clinical trials.

Table 1. Questionnaire for assessment of breakthrough pain (based on [8])

1. How was the intensity of baseline pain during last days?
2. What analgesic drugs are taken permanently? What are the doses of drugs?
3. Is pain control satisfactory during the majority of the day?
4. Do episodes of rapidly increasing pain occur?
5. What is the average intensity of those additional pain episodes?
6. How many episodes do occur per day/week?
7. How quickly do the symptoms increase and how long do they last?
8. Are their features the same as the characteristics of baseline pain?
9. Do they appear either spontaneously or related to any factor?
10. Do they appear regularly before taking baseline analgesic drugs?
11. How do they affect daily life?
12. Do any drugs that are taken relieve the additional, severe pain? Are any other methods efficacious?
13. What are those drugs and in what doses are they taken?

Table 2. Influence of breakthrough pain on quality of life [13]

	All patients	Patients with specific factor	Patients with idiopathic pain	p
General activity	7	7	7	0.124
Mood	7	6	7	0.016
Mobility	7	8	6	< 0.001
Work	8	9	8	0.001
Interpersonal relations	5	5	5	0.297
Sleep	5	5	6	< 0.001
Life satisfaction	7	7	7	0.995

Clinical implications

Similarly to baseline pain, breakthrough pain significantly affects patient's quality of life (QoL) [13, 14].

Davies at al. published the results of a multicentre clinical trial involving 1000 patients treated in 28 specialised palliative care units between 2008 and 2011 in 13 European countries [13]. The patients were classified as eligible to participate in the trial based on a questionnaire of five questions. In 44% of patients breakthrough pain was induced by particular factors, in 41.5% it was an idiopathic symptom, and in 14.5% the aetiology was mixed. It was revealed that mobility problems and difficulties with basic daily activities were more frequent among patients with breakthrough pain induced by specific factors, whereas patients with idiopathic pain more commonly reported changes of mood and sleep problems (Tab. 2) [13].

Portenoy et al. assessed the influence of breakthrough pain on QoL using the Beck Depression Inventory (BDI) questionnaire, the Beck Anxiety Inventory (BAI) questionnaire, and by measurement of baseline pain intensity based on the VAS scale. Among 178 patients with well-controlled baseline pain two groups of patients were extracted and evaluated, depending on whether or not they had breakthrough pain. In 65% of patients breakthrough pain resulted from cancer, and in the remaining cases it was connected with the treatment used. In patients with breakthrough pain the baseline pain was more intense (34.2 vs. 16.7 in VAS scale — $p < 0.01$). Moreover, it was assessed how the pain influenced mood, work, sleep, mobility, social relations, and life satisfaction. Every aspect was evaluated on a numerical scale from 0 to 10 (0 — no influence, 10 — entire influence). In cases of BDI and BAI scales the patients responded to 21 questions, graded from 0 to 3 (0 represents no symptoms and 3 the highest intensity of symptoms) (Tab. 3) [14].

Of note, breakthrough pain could negatively affect prognosis [15], and also adversely influence duration of cancer treatment [16]. Precise diagnosis of the type of pain and early introduction of appropriate treatment should be sought.

Management

The management of breakthrough pain is primarily based on pharmacological treatment, but in some cases it is also possible to use surgical procedures (blockades, neurolysis, TENS) or aetiotropic treatment (e.g. pallia-

Table 3. The influence of breakthrough pain on quality of life [14]

	Patients without BP	Patients with BP	p
Activity	2.7	4.0	< 0.001
Mood	2.5	3.6	< 0.001
Mobility	2.3	3.5	< 0.001
Work	2.5	3.9	< 0.001
Social relations	1.9	2.9	< 0.001
Sleep	2.2	3.2	< 0.001
Life satisfaction	2.7	3.7	< 0.001
Cumulatively	16.7	24.8	< 0.001
BDI	12.8	18.2	< 0.001
BAI	9.9	17.9	< 0.001

BP — breakthrough pain; BDI — Beck Depression Inventory; BAI — Beck Anxiety Inventory

tive irradiation of bone lesions, use of bisphosphonates). It is also essential to identify and prevent the action of the factors inducing breakthrough pain (e.g. excessive physical effort, persistent cough, constipation). Before making a therapeutic decision, the level of baseline pain control should be assessed; in cases of more than four episodes of breakthrough pain per day increasing the dose of permanently administered analgesic drugs could be justified [17].

Simple analgesics (effervescent tablets of paracetamol or metamizole) could be effective in pharmacotherapy of breakthrough pain [18]; however, patients who continue to take opioid drugs of modified release most commonly demand introduction of opioids. The choice of treatment should be based on both the type of breakthrough pain (incidental, idiopathic) as well as the type of the drug previously used for treatment of baseline pain [17].

Taking into consideration the dynamics of breakthrough pain, its rapid increase, and short duration, it seems to be optimal to use drugs of immediate release, demonstrating an analgesic effect within a few minutes after administration and maintaining their action for a moderately long time, to minimise the adverse effects of therapy.

For a long time, orally administered morphine in immediately released formulations was the drug of choice in the treatment of breakthrough pain (the recommended dose is 10–15% of daily dose of baseline opioid); however, the pharmacokinetic features of oral morphine are not optimal. After oral administration of hydrophilic opioids (morphine, oxycodone) maximum serum concentration is reached within 30–80 minutes (the drug is absorbed only in the proximal part of the small intestine) [19]. Analgesic effect appears approximately 30 minutes after drug administration, which makes those drugs inappropriate in the treatment of breakthrough pain. An exceptional case is incidental breakthrough pain that can be predicted by the patient. In this situation it is reasonable to take an opioid drug dose of immediate release 30–45 minutes before the activity that could cause the pain [19].

The pharmacotherapy of idiopathic breakthrough pain comprises some challenges because this pain is difficult to predict and lasts for a relatively short time, but its intensity is high and increases within minutes. Thus, the activity of an optimal drug should be characterised by similar dynamics, with concomitant acceptable safety profile. The efficacy of a few formulations of fentanyl (a lipophilic drug, penetrating well through mouth mucosa and easily crossing the blood-brain barrier) in the treatment of breakthrough pain in patients continuously taking the opioid drugs was assessed in randomised clinical trials [20]. Pharmacokinetic features of fentanyl allow quick absorption of the drug into the circulation and faster analgesic effect. There are different formulations of fentanyl available: buccal tablets, lollipops, and intranasal aerosol.

The widely evaluated formulation is oral transmucosal citrate fentanyl (OTCF), applied in the form of "lollipops" (unavailable in Poland). Its efficacy was compared with placebo as well as morphine in formulations of immediate release [20–22]. It was shown that fentanyl with this route of administration significantly decreases the symptoms in approximately 75% of patients, the analgesic effect is faster than after morphine (approximately 10 minutes), and the treatment is in general quite well tolerated; the most common adverse events include nausea, dizziness, and constipation. Some inconvenience was reported by patients because of necessity to maintain an applicator with the drug in the mouth until the lozenge is entirely dissolved. For some patients the bitter taste of the drug and its form of application were the disadvantages of such therapy.

An alternative is tablet form, which, after placing in the posterior part of mouth between gum and cheek, releases the dose of the drug (100, 200, 400, 600, or 800 μg of fentanyl). Approximately 55% of the dose is

Table 4. Response rates after administration of varied formulations of fentanyl in different time periods

	Compared drugs	RR (%) 10 min.	RR (%) 15 min.	RR (%) 30 min.
Mercadante 2009 [25]	INF vs. OTFC	50 vs. 20	70 vs. 40	90 vs. 80
Kress 2009 [24]	INF vs. placebo	58	ND	80
Portenoy 2006 [22]	FBT vs. placebo	ND	13	48
Slatkin 2007 [29]	FBT vs. placebo	16	30	51

RR — response rate; INF — intranasal fentanyl; OTFC — oral transmucosal citrate fentanyl; FBT — fentanyl buccal tablets; ND — no data

absorbed through mucous membrane and the dissolving of the lozenge takes just a few minutes (14–25 minutes on average). The efficacy of such a formulation was compared to placebo. In patients treated with fentanyl the pain intensity was reduced by 3.2 points in an 11-point scale, compared to 1.8 points in the control group ($p < 0.0001$) [22]. Furthermore, patients treated with fentanyl statistically significantly more rarely demanded add-on analgesic drugs, and within 30 minutes after drug administration 24% of patients reported symptoms of relief by 50% (16% in the placebo group). The treatment was well tolerated. The most common adverse events included nausea, dizziness, and fatigue [22]. Ulceration in the area application was noted in 2% of patients in the experimental group. Relatively long time of drug absorption (15–25 minutes) and necessity of keeping the tablet under the cheek for the whole time could be perceived as inconvenient.

A very interesting form of fentanyl use in breakthrough pain is intranasal aerosol. In 2009 this formulation was approved in European Union (EU) countries. There are a few dosage forms (50, 100, and 200 μg/dose), which makes it easier to set a proper dose for a particular patient. Titration should be started from the dose of 50 μg, and in case of lack of efficacy this dose could be repeated after 10 minutes. It is estimated that maximum serum concentration of fentanyl is reached approximately 13 minutes after application and the analgesic effect is observed after just seven minutes [23]. The safety and efficacy of such a form of fentanyl in the treatment of breakthrough pain were evaluated in several randomised clinical trials.

In a group of 120 patients it showed significant benefit, which was measured by reduction of pain intensity 10 minutes after drug application (decreasing by 2.36 points in the VAS scale compared to 1.1 points in the placebo group) [24]. Additionally, there were no major toxicities, and the most common adverse events included nausea and dizziness.

Intranasal fentanyl was also compared with transmucosal formulations. In the group of 139 patients with breakthrough pain intranasal fentanyl was titrated and subsequently also OTFC was administrated in the same pattern [25]. The time until decreasing pain intensity and the percentage of patients who rated that response to the drug as "meaningful" were assessed. The results favoured the intranasal formulation [analgesic effect after 11 minutes as compared with 16 minutes for oral formulation, decreasing of pain intensity by 33% within 5 minutes after drug administration in 25% of patients comparing to 6.8% ($p < 0.001$) for oral formulation, easier application as well as better tolerance of treatment] (Tab. 4) [25].

Lesions of the mucous membrane, resulting from oncology treatment or underlying disease, are very important factor, that should be considered during choosing transmucosal fentanyl formulation for treatment of breakthrough pain. One of these problems is a dry mouth, which could affect up to 80% of patients with advanced malignant disease [26]. It makes dissolving of buccal tablets very difficult, increases discomfort, and decreases the efficacy of the treatment. Another complication is concomitant presence of mucosal inflammation. The pharmacokinetics of the drug were assessed in patients with common cold as well as allergic rhinitis, demanding use of oxymetazoline [27, 28]. Whilst common cold did not change the pharmacokinetics, administration of oxymetazoline significantly prolonged the absorption time of fentanyl from the mucosa. However, it should be remembered that in cases of epistaxis or ulceration of nasal mucosa it is recommended that the treatment with intranasal formulation be stopped and another form of therapy introduced.

A meta-analysis published by Zeppatella et al. showed that transmucosal fentanyl formulations allow better pain control in a shorter time period as compared to placebo or to oral morphine of immediate release [30].

ESMO recommendations regarding management of breakthrough pain indicate the necessity of appropriate treatment of baseline pain. Oral morphine formulations of immediate release are recommended for the treatment of predictable episodes of breakthrough pain, when the drug could be taken at least 20 minutes before the action of the triggering factor. In other cases of breakthrough pain fentanyl is recommended in the form of buccal tablets or intranasal aerosol [31].

The recommendations of the Polish Society of Clinical Oncology (PTOK, Polskie Towarzystwo Onkologii Klinicznej) reflect the ESMO guidelines [32]. Table 5 presents the drugs recommended in the treatment of breakthrough pain.

Table 5. Opioids used in the treatment of breakthrough pain [32]

Drug	Posology	Maximum dose
Fentanyl buccal tablets	Individual dosage through titration starting from 100 or 200 μg per dose	800 μg per dose/per episode
Fentanyl intranasal spray	Individual dosage through titration starting from 50 μg per dose Do not exceed two doses, with interval between doses of at least 10 minutes	Up to four episodes per day
Fentanyl sublingual tablets	Individual dosage through titration starting from 100 μg per dose	800 μg per dose/per episode
Morphine tablets of immediate release	1/6 of daily dose of opioid drugs using in the treatment of baseline pain	Maximum dose not defined

Summary

Pain treatment is an integral part of management in patients with cancer. Despite active treatment, in some patients pain control remains unsatisfactory, which also applies to breakthrough pain. A lack of unambiguous definition as well as a validated tool for assessment of pain still significantly impedes the diagnostics and treatment of breakthrough pain. Management is based on modification of the treatment of baseline pain, considering opioid drugs of immediate release, used in 1/6 of baseline drugs' daily dose. Transmucosal opioids ensure faster analgesic effect than other oral formulations, and intranasal aerosol seems to be currently the most beneficial route of administration.

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Comment on the paper *Breakthrough pain in cancer patients*

The incidence of breakthrough pain determines its' importance in patients with malignant diseases. At least 30% of patients experience breakthrough pain during anticancer treatment, and in patients with advanced disease the incidence is as high as 70% [1]. Currently in Poland cancer is diagnosed in approximately 150,000 patients annually [2] — therefore, the problem of pain treatment is quite important, at least from an epidemiological point of view. Pain in cancer patients is associated with underlying disease as well as anticancer treatment, but also it could result from different concomitant medical conditions. The pathophysiology of pain differs, due to a variety of mechanisms and clinical features of nociceptive and neuropathic symptoms. Effective pain treatment requires understanding of conditions mentioned above as well as an individualised approach, which should consider also the type of cancer.

Specific diagnostic and therapeutic challenges are connected with so-called breakthrough pain, which affects at least 50% of cancer patients [3]. It is characterised by periodic and usually short-term (approximately 30 minutes) exacerbation of pain in patients with baseline symptoms generally well controlled with opioids. The management should be based on the type and pathomechanism of breakthrough pain — it is recommended to use "salvage" opioids of rapid-onset and short-term activity [3]. Frequent episodes of breakthrough pain should lead to analysis of the value of analgesic treatment compared to preexisiting symptoms, and they also have some relevance in classification of general intensity of pain [4].

Pain management should be an integral part of supportive care in oncology because effective analgesic treatment is very often one of the most important measures of quality of life in cancer patients. The complexity of breakthrough pain in cancer patients as well as its' high frequency of this symptom justifies the need for the education of all physicians taking care of patients with malignant diseases. It should also be underlined that effective pain treatment demands the integrity of all therapeutic modalities, especially palliative radiotherapy. The effectiveness and side effects of pain management should be carefully monitored, considering the risk of adverse drug-drug interactions and other drugs used by patients. Well established interpersonal contact with the patient and family members is of high importance.

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