Breakthrough pain in cancer patients: prevalence, mechanisms and treatment options

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Purpose of review
The aim of this article was to examine the definition, the characteristics, and the management of breakthrough cancer pain (BTP) in cancer patients by a critical review of recent literature.

Recent findings
BTP should be more correctly defined as an episode of severe intensity in patients receiving an adequate treatment with opioids able to provide at least mild analgesia. BTP is a heterogeneous condition as episodes vary between individuals. BTP can be classified into two big distinct pictures: spontaneous-type and incident-type pain. The principal pharmacological treatment of BTP is represented by the administration of opioids as needed. Recent reviews revealed that transmucosal preparation of fentanyl provided superior and more rapid pain relief as compared with placebo in the first 30 min after dosing. Few comparison studies among fentanyl products have been performed.
Finally, although dose titration was recommended for years, a meaningful dosing according to the level of opioid tolerance may enhance the advantages of such products.

Summary
BTP represents a serious problem reported by many cancer patients despite receiving regular use of opioids. Subgroups of breakthrough pain have been identified. Different modalities of pharmacological interventions are available. Further studies are warranted to assess the net benefit of these drugs to assist decision-making by patients, clinicians, and payers according to individual clinical conditions.

Keywords
breakthrough pain, cancer pain, fentanyl preparations

INTRODUCTION

Breakthrough cancer pain (BTP) has been reported to be a relevant problem in cancer patients with pain. BTP has been variably reported in the literature, ranging in 40–80% of cancer patients with pain, depending on the setting and the definition used to identify it [1]. After many years, more information is available whereas many aspects deserve further clarification.

PREVALENCE AND DEFINITIONS

Pioneer studies defined BTP 'as a transitory increase in pain to greater than moderate intensity which occurs on a baseline pain of moderate intensity or less' [2▪▪]. This definition may sound ambiguous, as intensity of background pain and BTP may overlap making treatment choices difficult. Further definitions have been subsequently proposed, introducing a second variable, which is the use of stable doses of opioids able to maintain baseline pain control [3,4]. Unfortunately, the prevalence of this phenomenon has been often assessed without using an appropriate definition. Many epidemiological studies did not provide a definition *a priori*, so that a large variability has been reported for this phenomenon in a recent review in which papers were mixed without considering the minimal data set to describe BTP [5]. Differences in the evaluation of baseline pain and BTP episodes, and use of non-opioid analgesics have dramatically confounded the epidemiological picture [6–13].

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KEY POINTS

- About 75% of patients with adequate background analgesia have BTP episodes.
- BTP should be more correctly defined as an episode of severe intensity in patients receiving an adequate treatment with opioids able to provide at least mild analgesia.
- Breakthrough pain is a heterogeneous condition as episodes vary between individuals.
- The principal pharmacological treatment of BTP is represented by the administration of opioids as needed.
- Transmucosal preparation of fentanyl provides superior and more rapid pain relief as compared with placebo and oral opioids in the first 30 min after dosing.

Diagnostic tools have been developed in the last years to provide information for a diagnosis of BTP. They propose what a clinician should follow during a patient's examination to make a clinical diagnosis, according to some simple steps [14,15].

It is difficult to have a clear idea on a complex phenomenon without a prospective evaluation and an optimized analgesic approach. For these reasons, it is likely that BTP should be more correctly defined as an episode of severe intensity in patients receiving an adequate treatment with opioids able to provide at least mild analgesia [16,17]. It has been recently found that in patients with baseline pain of mild intensity ($\leq$4/10 on a numerical scale 0–10), the meaningful pain intensity for asking for a BTP medication was about 7/10 [18]. This aspect has obvious implications from both the epidemiological and therapeutic point of view. In a series of patients having achieved optimization of baseline analgesia with opioids, in the range of mild pain, the prevalence of BTP remained relatively high, about 75%. Thus, BTP should be more correctly defined as an episode of severe intensity in patients receiving an adequate treatment with opioids able to provide at least mild analgesia [14,15]. Of interest, in a subclass of patients with abdominal disease it has been estimated that about 55% of patients with well controlled background pain will develop BTP episodes. This percentage was higher (about 90%) in patients who presented with uncontrolled background pain, underlying the need to better characterize patients with BTP, only after a careful optimization of basal pain, as considered by the definition of BTP [19].

CHARACTERISTICS OF BREAKTHROUGH PAIN

Breakthrough pain is a heterogeneous condition as episodes vary between individuals and also within individuals. In general, breakthrough pain can be classified into two big distinct pictures. Spontaneous-type BTP is when no specific triggers are identified. Incident-type pain is when an obvious factor precipitates in the event. The spontaneous types of BTP (often named idiopathic) are unpredictable and occur without any identifiable trigger. Generally, the onset and duration may be longer [17,20▪]. In general, three to four episodes per day have been considered acceptable when most hours of the day are covered by an adequate pain relief. There are, however, some typical episodes which are triggered by several factors, for example incident pain because of bone metastases, that can occur more frequently and the focus of the treatment should be on a compromise between activity and background analgesia. Patients with incident-type pain have a shorter time to peak intensity and a shorter time duration. Most of these BTP episodes are elicited by movement in the presence of bone metastases. These episodes are potentially self-limited as it often depends on the will of maintaining an activity or of resting, that is patients' preference, although the duration of pain is unpredictable even after stopping activity. As a consequence, patients often report a relevant interference with daily living as they may prefer to limit their activity to avoid triggering BTP or use individual strategies in their daily life to prevent the occurrence of BTP.

Differently from previous studies that assessed the characteristics of BTP without selecting patients with a specific diagnostic algorithm, recent surveys, by using a clear definition of BTP, have shown a more meaningful picture of BTP, with its variable components. In a large study of 1412 ppatients, 80.6% patients reported that the BTP had a significant negative impact on everyday life. The mean number of episodes was 2.4 per day with a mean intensity 7.4/10. The onset of BTP was more often rapid ($\leq$10 min) (about 69%) than gradual ($>$10 min). In patients reporting a fast onset of BTP, this was predictable in about half of cases, whereas BTP with a gradual onset ($>$10 min) was less predictable. The mean duration of untreated episodes of BTP was about 30 min [20▪]. These characteristics may change during the course of disease. For example, patients receiving palliative care were older, had lower Karnofsky levels, a lower number of BTP episodes per day, a slow onset of BTP onset, and a less predictable BTP, in comparison with patients assessed in a pain clinic or oncological

ward. Other large epidemiological studies have shown that the mean time to peak intensity is about 10 min, although pain on movement may have a shorter onset and a duration of 60 min [17].

TREATMENT OPTIONS

The principal pharmacological treatment of BTP is represented by the administration of opioids as needed. Oral opioids, particularly oral morphine, have been the mainstay approach for the management of BTP. In particular, oral morphine has been given for years in doses proportional to opioid doses used for background analgesia [21]. The onset and duration of action of oral opioids such as morphine or oxycodone may, however, not be suitable for treating many episodes of BTP which are of short onset and duration. Pharmacokinetic studies have suggested a poor correlation of their analgesic effect with the dynamics of a typical BTP episode [22]. Nevertheless, NICE guidelines (website: www.nice.org.uk/cg140) suggest using oral morphine as first-line drug, according to the low differences reported in comparison studies with rapid onset opioids (ROOs). There are many methodological reasons to explain these minimal differences reported in comparative studies (see below). For instance, BTP duration is often limited in time, as most episodes should auto-resolve, oral opioids are expected to provide some pain relief after 30–45 min [22], and differences are unlikely to be found at these intervals, when most episodes vanish spontaneously. Of interest, no study has ever tested oral opioids in BPT, other than as a comparator in studies with fentanyl preparations (see below). Recent reviews revealed that the ROOs provided superior pain relief as compared with placebo in the first 30 min after dosing, whereas oral morphine performed slightly better than placebo [23,24].

With most BTP episodes peaking in intensity within a few minutes and lasting for 30–60 min, the speed of analgesic onset is crucial for an effective pain management. Different technologies have been developed to provide fast pain relief with potent opioid drugs such as fentanyl, delivered by noninvasive routes. Fentanyl is a potent and strongly lipophilic drug, which matches the characteristics to favour the passage through the mucosa and then across the blood–brain barrier to provide fast analgesia.

Different generations of transmucosal preparations of fentanyl, each with its particularities and availabilities, have been introduced in the market. These products provide a rapid effect clinically observable 10–15 min after drug administration. As these products have been tested in opioid-tolerant patients, all the studies performed with ROOs have recommended that these drugs should be administered to patients receiving doses of oral morphine equivalents of at least 60 mg. The characteristics of opioids used for BTP are listed in Table 1.

Oral transmucosal fentanyl citrate (OTFC) was the first product approved for BTP. A dosage unit resembles a lollipop or lozenge on a stick, and consists of a fentanyl impregnated sweetened lozenge on a plastic handle. The lozenge is gently rubbed against the buccal mucosa until it has completely dissolved (which should take no longer than 15 min, if appropriately used). Second-generation products have been shown to be superior to placebo and oral morphine. The fentanyl buccal tablet facilitates rapid absorption of fentanyl through the oral mucosa using an enhanced effervescent absorption technology [25]. A sublingual formulation of fentanyl which dissolves in minutes was developed. This formulation involves a small tablet made of a mix of active drug particles and water-soluble carrier particles coated with a mucoadhesive agent. A

Table 1. Characteristics of opioids used for BTP

	Analgesic onset	Availability	Dwell time
Oral morphine	30–45′	30	NA
Oral oxycodone	30–45′	40–50	NA
OTFC	15–30	50	15
FBT	15	65	15
SLF	10–15	70	2
FBSF	15	65	2–5
INFS	5–10	80–90	NA
FPNS	5–10	70	NA

BTP, breakthrough cancer pain; FBSF, fentanyl buccal soluble film; FBT, fentanyl buccal tablet; FPNS, fentanyl pectyn nasal spray; INFS, intranasal fentanyl spray; OTFC, oral transmucosal fentanyl cytrate; SLF, sublingual fentanyl.

sublingual spray has been recently developed. Finally, a buccal soluble film has been marketed. This is characterized by a bioerodible muco-adhesive delivery technology [25].

The intranasal administration of fentanyl may have some advantages, for example in patients with mucosal damages or salivary dysfunction. Two formulations of nasal fentanyl have been developed, an aqueous solution (INFS) as well as a pectin-based drug delivery system in the form of a gel designed to be applied to mucosal surfaces to optimize absorption [25].

Comparison studies among fentanyl products are lacking. In a recent survey, OTFC was relatively underscored for modality of administration and time for pain relief [26]. OTFC, formulated as self-administration of a solid drug matrix on a handle, requires patient discipline and focus, which may limit compliance, particularly in patients with weakness, a common symptom in advanced stage of disease. On the other hand, experience with OTFC suggests that the use of this product can be discontinued when sufficient analgesia is produced as the unit is easily removed from the mouth with the handle. Such flexibility is not available with administration of the other ROOs. This off-label use has never been assessed in a scientific way. Furthermore, this approach requires skilled patients and cannot be proposed in old or severely ill patients. The other ROOs were well accepted by patients in terms of easiness and modality of administration, palatability, and overall impression. Regardless of the efficacy, which has been examined in controlled trials of BTP [25], the second generation of ROOs seems to have more favourable characteristics for some practical issues. This is a fundamental aspect regarding the use of these medications, as patients' education and compliance are the most important factors for an appropriate use of these agents [26].

Only two comparative studies among ROOs exist. INFS was superior to OTFC in terms of onset and efficacy [27]. INFS and PFNS provided similar analgesic profiles when given at presumably equianalgesic doses, despite differences in availability [28].

DOSING

The dose of an ROO to be prescribed as needed still remains debated in the literature. It has been recommended that the dose should be titrated against the effect starting with the lowest available dose [29]. The reasons for these findings are not clearly explained, considering that the presence of tolerance should suggest a dose proportional to those used for background analgesia, as for the traditional use of oral opioids [21]. From a practical point, the use of different pieces or spray of ROOs for treating each episode may be time-consuming exceeding the spontaneous duration for BTP which can spontaneously subside, as evidenced by successful placebo-treated patients [30,31]. Moreover, dose titration may make the practical use of ROOs difficult in the daily activity, particularly at home or in outpatients. Most patients may be reluctant to try the dose and avoid to use these drugs, preferring, at the end, traditional oral dosing of morphine [26].

Data reported in the literature need accurate interpretation. The indication to titrate the doses derives from studies designed for other purposes, for example to compare fentanyl products with placebo or oral opioids. Of interest, in successful patients the regular rescue dose was a moderate predictor of the effective OTFC dose. In one of the controlled studies of OTFC, a relation between the OTFC dose and the fixed scheduled opioid had been already found, and regular rescue dose was a moderate predictor of the effective OTFC dose. Only 19% of the variability of the final dose of OTFC was, however, explained by basal doses of opioids, according to the low-*R*-square value of the model used [30,31]. Furthermore, data pooled from trials of OTFC showed a statistically significant relationship between the breakthrough dose and around-the-clock dose, despite a relevant interindividual variability in patients' dose requirements for BTP [32]. These studies had an enriched design, which excluded patients who did not respond to dose titration or when maximum doses were achieved. From a pure scientific point of view, there is no evidence of the need of titration, as this statement is consequent to the secondary observation that there was no correlation between the basal opioid regimen and the successful dose of ROO after titration. In other words, the need to titrate has never been determined on the basis of a real comparative study between titration strategy and no titration strategy. Rather, a few existing comparative studies have shown that ROO doses proportional to the basal opioid regimen are more effective than titration strategy without determining high risk of adverse effects [33].

These studies have confirmed preliminary and confirmatory surveys have shown the safety of this approach in a large number of patients with no life-threatening adverse effects occurring even in older patients or receiving high doses of opioids [27,28,33–39]. Respiratory depression, which is the most feared adverse effect, has never occurred, and no emergency call was needed [36]. On the other hand, in a real life study, patients receiving a mean oral morphine dose of 132 mg required 800 μg of OTFC [10], suggesting that the titration

process may provide even higher doses than those expected by using proportional doses to basal opioid regimen.

From a clinical point of view, patients receiving high doses of opioids as basal analgesic regimen could have detrimental effects with dose titration with minimal initial doses of ROOs, as they are opioid-tolerant. This process could be time-consuming and able to decrease patients' compliance. While waiting to settle this controversial issue in further studies with this aim, a reliable compromise could be to start with relatively higher doses of ROO in highly tolerant patients, until more information will be available to settle the question.

CONCLUSION

BTP represents a serious problem reported by about 70% of cancer patients despite receiving regular use of opioids and having a well controlled background pain. There are different modalities of pharmacological interventions which will depend on individual characteristics and preference. Further studies are warranted to assess the net benefit of ROOs to assist decision-making by patients, clinicians, and payers according to individual clinical conditions [33]. A meaningful dosing, according to the level of opioid tolerance may enhance the advantages of such products, as this approach may produce better and rapid efficacy, without adding relevant risks. The risk of opioid addiction with long-term use of these products should be better assessed in future studies.

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