Expert Opinion

Treatment strategies for cancer patients with breakthrough pain

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Background: Breakthrough pain (BTP) is a transitory flare of pain superimposed on an otherwise stable pain pattern in patients treated with opioids. It is normally severe in intensity, has a rapid onset, has a variable duration (on average 30 min) and is considered a negative prognostic factor. *Objective*: To verify the data in the literature about therapy strategies for BTP in cancer patients. *Methods*: To find clinical trials investigating drug therapy for BTP. *Conclusion*: The treatment of BTP in cancer patients receiving opioids is principally based on the use of opioids, preferentially with a short onset. Fentanyl delivered by recently developed systems seems to be the best option to cover the temporal pattern of BTP, although the treatment should be highly personalized to provide the best in individuals, balancing patients' preferences and clinical needs. The doses to be administered is still a matter of controversy in the literature; additional studies with specific designs should be conducted to settle the question.

Keywords: breakthrough pain, cancer pain, pharmacotherapy, treatment strategies

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1. Introduction

Breakthrough pain (BTP) is a transitory flare of pain superimposed on an otherwise stable pain pattern in patients treated with opioids [1]. BTP, called episodic pain in some non-English-speaking countries, is normally severe in intensity, has a rapid onset, has a variable duration (on average 30 min) and is considered a negative prognostic factor [2,3]. BTP causes an effect of declining function [4]. An international survey evaluating 1095 patients with cancer pain from 24 countries indicates that BTP is associated with higher pain scores and more interference with function [5]. Patients with untreated BTP function less well, have greater levels of anxiety and depression and are less satisfied with their opioid therapy. Patients with BTP had more hospitalizations for uncontrolled pain, more emergency department visits and unscheduled office visits. A study examining the direct and indirect costs associated with pain in cancer patients found that the presence of BTP predicted higher direct and indirect medical expenses [6]. Precipitant factors have been identified in more than 50% of patients. There is agreement in the literature that BTP results from both predictable and unpredictable factors.

A well-understood subtype of BTP (episodic pain) is incident pain, which is due to movement and is commonly associated with bone metastases or fractures. This type of BTP limits the functional activity of these patients, and freedom of pain in motion is particularly difficult to achieve. Continuous pain may be absent or moderate on resting but may be exacerbated by different movements or positions [7]. BTP can also be idiopathic and occur spontaneously, with no obvious precipitating event. Another type of BTP is the incident non-predictive BTP such as intermittent visceral pain due to bowel adhesions.

Although, 'per definition', end-of-dose failure and pain episodes occurring during opioid titration should not be considered as BTP, they often require some treatment.

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Thus, BTP could also be an expression of opioid underdosing, regardless of time intervals of administration. In a survey of selected patients seen in an oncologic setting with predetermined uncontrolled background pain, data were reviewed 1 week after a visit. Of 70% of patients initially reporting BTP, only half of them (36%) still had BTP after pain management began, suggesting that an expert intervention may decrease the occurrence of BTP, which often is unmasked by poor efficacy of background medication [8].

The definition of BTP is not clear across the literature. For example, many epidemiological studies do not report whether patients had controlled baseline pain or not, or how this was determined. In an international survey, clinicians reported BTP in 65% of cancer patients [5]. This figure is close to the 64% prevalence reported in the first published survey of cancer patients who experienced BTP on top of well-controlled baseline pain [1].

Patients often receive basal medication for their pain, which is otherwise considered acceptable. The assessment is not easy, particularly with incident pain. One key agreement is to assess BTP as a pattern that is distinct from baseline pain. A comprehensive pain assessment is recommended which includes frequency and duration of each episode, intensity, precipitating factors, previous and current pain treatments for baseline pain, and their effectiveness. Pain assessment should also include inferred pathophysiology and origins of the pain syndrome. A patient's involvement in assessment is of paramount importance and good communication with the patient to ensure the patient's cooperation will contribute to the successful management of BTP. About 20% of patients were not taking medications prescribed for BTP and some of these underwent non-drug intervention to manage BTP. This aspect has already been reported in a previous study of a smaller sample of oncology patients [9]. Reasons for refusing BTP medication included pain that was not severe enough, pain improving before taking medication, ineffectiveness, adverse effects, concerns about adverse effects or overdosage, and practical issues. However, the treatment of patient of BTP was considered relatively good by a relevant number of patients, possibly for the same reasons discussed for background pain.

2. Management of breakthrough pain

2.1 General recommendations

Clinicians have recognized the importance of interventions to minimize the occurrence of BTP events for their impact on quality of life and on the chances of pain control. Many strategies have been developed to manage transitory pain flares [7]. Special consideration should be given to primary treatment of the underlying etiology, when indicated or available, according to the clinical stage of disease. Cognitive and behavioral approaches may be useful in specific conditions. Patients may prefer to take less medication if friends are visiting or if they are going to physical therapy. Moreover, it is important to recognize precipitating or alleviating factors that help prevent or reduce the occurrence of pain exacerbations. Patients or family caregivers may help handle an episode of BTP; changing position, applying heat or cold, massag ing the painful area and using relaxation techniques can help a patient while waiting for relief from medication. Miscellaneous other treatment was effective, including defecation, flatus, suppression of cough, antacids, sleeping or squeezing the painful region, mainly provided by patients themselves. It is important to outline the emerging role of kyphoplasty in incident spine pain [1]. However the likelihood that pain may remit spontaneously after a short time may reduce the meaning of benefits attributed to specific interventions by patients.

It is essential to optimize around-the-clock (ATC) analgesia by an appropriate opioid titration to obtain the best balance between analgesia and adverse effects, also using different sequences of opioids, and combining analgesics and adjuvants when necessary. A careful titration may improve the analgesia while limiting the adverse effects. If BTP occurs because the dose of ATC medication is insufficient (end-of-dose failure), increasing the dose of ATC medication or decreasing the interval between the doses can provide fast relief. Data from a recent study indicate that optimization of basal opioid therapy should be attempted in cancer patients with bone metastases, presenting incident pain, who apparently have a well-controlled pain condition at rest, but probably have hypersensitivity to some innocuous stimuli, such as movement, requiring pre-emptive higher doses of basal opioid medication to reduce the occurrence of an increased pain input [10].

On the other hand, an increase in dose may often result in unacceptable toxicity, mostly sedation, during the period between incident pain episodes. Doubling opioid doses in 6 days resulted in a better pain control, although methylphenidate was used to assist opioid titration in patients with incident pain [11].

Patients with intermittent visceral pain due to bowel adhesions complicating surgery or radiation should be amenable to interventions, if feasible and not contraindicated by an advanced clinical status. The role of antisecretive-antispastic or anti-inflammatory agents as analgesics in conditions of bowel obstruction is not yet well defined [7]. States of intestinal subobstruction are challenging when using opioids, as one of the most striking pharmacological features of opioid drugs is their ability to induce constipation. An intermittent use of opioids adjusted for fluctuating pain levels may enable patients to take the lowest opioid doses that will have sufficient effect, with a consequently lower risk of intestinal adverse effects. Nociceptive pain tends to respond well to opioids and NSAIDs, while neuropathic pain will more likely require adjuvant analgesics. Another possible research area could be that of pre-emptive analgesia provided by bisphosphonates [12,13]. These drugs have been shown to be effective in reducing bone pain and prevent skeletal events. According to that, their regular use in the presence of metastatic bone pain

could reduce the development of incident pain, which is the most difficult condition, limiting patients' quality of life. The economic burden, however, has never been evaluated in terms of cost-benefit and should be assessed in future studies with appropriate design.

Radiotherapy provides an effective symptomatic treatment for local bone pain causing transitory events. As protracted courses of radiotherapy are difficult to perform in advanced cancer patients with a limited life expectancy and poor performance status, treatment with single fractions may be more convenient and equally effective in terms of pain relief [14]. Compared with external beam irradiation, radioisotopes are more imprecise in delivering specific dose irradiation: their advantages include less toxicity, easy administration and effectiveness in subclinical sites of metastases. Strontium-89 and other recent bone-seeking radioisotopes with a shorter half-life, such as 186-rhenium and 153-samarium, are clinically used [15]. However, the extent of pain relief, particularly incident pain, has been quantified in a small number of patients [15,16].

Protection with orthotic devices may be useful for upper extremity bone lesions. The lower extremities are hardly amenable because of the high degree of load. Loss of the ability to walk frequently occurs in the presence of bone involvement of lower extremities. A physiatric approach should be started and adequate training is necessary to improve the patient's functionality and compliance. Mobility aids, bracing of the painful part, instruction in ergonomic principles and adaptation of the patient's home may be more productive than a pharmacologic approach. Orthopedic intervention may be indicated to restore mobility in bed-bound patients [15]. Impeding fractures require surgical stabilization using fixation devices or prosthetic reconstruction. Surgical stabilization of the spine and extremities may dramatically improve the quality of life, decrease the incident pain and prevent complications associated with immobility. Risks should be balanced against the benefits of such interventions.

2.2 Specific treatment of breakthrough pain

Depending on the setting, patients' characteristics, and compliance, there are different modalities to deliver opioids for the management of BTP. The availability of supplemental doses of oral opioids in addition to the continuous analgesic medication is the main treatment suggested to manage pain flares. Current dosing recommendations for BTP generally suggest that the effective dose of BTP medication must be a percentage of the patient's total daily opioid dose [17]. Whenever possible, the rescue dose should be the same opioid as the patient is taking around the clock for baseline pain. Using the same drug makes it easier to identify the source of any potential side effect. In the case of morphine, the EAPC recommends one-sixth (17%) of the daily dose as a starting point [17]. However, an oral dose of morphine, oxycodone or hydromorphone can take a longer time to relieve pain, with peak concentrations achieved within 30 – 45 min. On the other hand, the slow analgesic peaks achieved with oral opioids could be useful in other circumstances, for example administered 15 – 30 min before starting physical activity in patients with predictable incident pain, or during opioid titration phase.

As pain relief is usually required urgently, routes of administration designed to deliver drugs rapidly are often chosen. A shorter onset of effect is commonly obtainable only with parenteral administration of opioid analgesics. Intravenous morphine (IV-MO) has been found to be highly effective and safe, as only a low intensity of opioid-induced adverse effects has been observed, even when administering large doses [18]. A recent confirmatory study of a large sample of patients confirmed that IV-MO administered for the management of BTP in doses proportional to the basal opioid regimen, even given in older patients or relatively large doses, did not result in life-threatening adverse effects while being effective for patients in most cases [19]. While IV-MO is feasible in acute units, it is not favored in some other centers. At home, injections are not easily manageable and the subcutaneous route is commonly preferred in settings such as hospices and home care.

2.3 New generations of non-invasive, fast-delivery systems

Administration of opioids via the nasal or oral mucosa provides a non-invasive mechanism for more rapid drug absorption and more rapid onset of pain relief compared with oral dosing. Lipophilic drugs are well suited for nasal or oral mucosal delivery. Fentanyl, sufentanil and methadone cross the blood–brain barrier quickly. The respiratory track and mouth provide a large mucosal surface for drug absorption allowing them to enter the systemic circulation directly, bypassing the gastrointestinal tract and first-pass metabolism in the liver. Transmucosal administration of lipophilic substances has gained a growing popularity in the last years, owing to the rapid effect clinically observable 10 – 15 min after drug administration. New delivery systems for fentanyl are or will be available, including inhalatory delivery systems, nasal sprays, sublingual tablets and fentanyl effervescent buccal tablets [20-22].

The first studies of oral transmucosal fentanyl cytrate (OTFC) have shown that this approach produces a faster onset of relief and a greater degree of pain relief than oral morphine, at 15, 30 and 60 min [23-26], with a meaningful pain relief obtained within 15 min. A lack of relationship between the effective OTFC dose and fixed schedule opioid regimen, regardless of the opioid used, was observed, suggesting the need to titrate the dose of OTFC. This observation contradicted the anecdotal assumption that the effective dose as needed is a percentage of the opioid daily dose. The reasons for these findings are not clearly explained. Similar findings have been recently reported with effervescent buccal tablets of fentanyl (EBTF) in a study with a similar design [27].

In clinical practice, other than presenting a shorter onset of analgesia, EBTFs do not require any further intervention by the patient after drug dissolution, different from OTFC self-administration, requiring an active effort, which may be

boring, particularly in patients with weakness. On the other hand, different from experience with OTFC suggesting that the use of the stick can be discontinued as sufficient analgesia is produced, EBTFs do not have such 'flexible' off-label properties [28].

The choice of the opioid dose to be prescribed for BTP remains controversial. The need for titrating opioid doses for BTP may make the day-to-day practical use of OTFC difficult, particularly at home or in outpatients. Moreover, using different pieces of OTFC for treating each episode may be time consuming and may exceed the spontaneous duration for BTP which can spontaneously subside, as evidenced by successful placebo-treated patients. Most patients may be reluctant to try the dose and avoid using OTFC, preferring traditional oral dosing of morphine [9]. OTFC, given in doses proportional to the basal opioid regimen, for example 200 µg in patients receiving daily doses of 60 mg of oral morphine equivalents, has been found quite effective and, above all, safe, avoiding the need to titrate the dose, which is considered boring for patients, reducing their compliance with the treatment [29-31]. This observation confirms data gathered with IV-MO and contrasts with almost all studies of OTFC. The latter data require some comment. For example, many patients on higher doses of original medication generally required larger doses of OTFC, and 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 relationship 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. However, only 19% of the variability of the final dose of OTFC was explained by basal doses of opioids, according to the low-R-square vale of the model used [24]. Finally, recent observations from data pooled from trials of OTFC showed a statistically significant relationship between the breakthrough dose and ATC dose, despite a relevant interindividual variability in patients' dose requirements for BTP [29]. It is likely that patients receiving high doses of opioids as basal analgesic regimen will not be candidates for titration with minimal doses of opioids, as they are opioid-tolerant, and the process would be time consuming. Thus, a reliable compromise between the different opinions could be to start with relatively higher doses of opioids in highly-tolerant patients, until more information will be available to settle the question. A task group of the Science Committee of the Association for Palliative Medicine of Great Britain and Ireland (APM) made a series of 12 recommendations about certain generic strategies; these are reported in **Table 1** [32].

3. Conclusion

The treatment of BTP in cancer patients receiving opioids is principally based on the use of opioids, preferentially with a short onset. Fentanyl delivered by recently developed systems seems to be the best option to cover the temporal pattern of BTP, although the treatment should be highly personalized to provide the best in individuals, balancing each patient's preferences and clinical needs. The doses to be administered are still a matter of controversy in the literature, and additional studies with specific designs should be conducted to settle the question.

4. Expert opinion

The term 'breakthrough pain' has been progressively adopted in many countries to define the temporal pattern of this event. Available data indicate that fentanyl delivered by recently developed systems seems to be the best option to cover the temporal pattern of BTP. Given the paucity of existing data, other specific recommendations remain below a standard level of evidence. Specifically, the opioid dose to be administered for BTP still remains controversial and deserves some comment. From a historical perspective, dosing recommendations have been based for years on anecdotal experience; they suggest that the effective dose of BTP medication is a percentage of the patient's total daily opioid dose with one-sixth (17%) of the daily dose as a starting point [17]. On the other hand, all the trials with transmucosal fentanyl (OTFC) have contradicted this assumption drawn from practical experience, suggesting a lack of a relationship between the effective OTFC dose and ATC opioid dose [23-26]. According to these studies, the dose of opioid for BTP should be determined by individual titration. A better critical analysis may help interpreting existing data, as these clinical trials have never specifically examined this issue, and the information gathered is just consequential to the study design aimed to demonstrate superiority of OTFC over placebo, oral morphine or usual oral opioids, or to evaluate the safety and efficacy of ascending doses of OTFC in dose-finding studies. Indeed, observations from data pooled from the same trials of OTFC showed a statistically significant relationship between the BTP and ATC opioid dose, despite a large interindividual variability in patients' dose requirements [31].

To affirm scientifically the need of titration, a randomized trial should compare efficacy and safety in groups of patients titrated versus groups non-titrated, and this has not been the case. The risk of overdosage and, consequently, the occurrence of adverse effects is claimed to justify titration. Some open-label studies reflecting daily practice have shown that intravenous morphine (IV-MO) used at doses proportional to the ATC dose provided prompt analgesia and was effective in most cases, without evident risks even in the aged population [18,19]. As IV-MO has the highest intrinsic risk for serious adverse event, one could argue that other drugs should be at least similarly safe. In a controlled study, OTFC used in a similar way, that is at a dose proportional to the basal opioid regimen, was safe in all patients experiencing pain exacerbation, even though administered at starting doses of 1600 µg in highly tolerant patients [29]. In daily

Table 1. Recommendations for the management of cancer-related breakthrough pain from task group of the Science Committee of the Association for Palliative Medicine of Great Britain and Ireland (APM) [32].

Patients with pain should be assessed for the presence of breakthrough pain (Grade of recommendation: D)
Patients with breakthrough pain should have this pain specifically assessed (D)
The management of breakthrough pain should be individualized (D)
Consideration should be given to treatment of the underlying cause of the pain (D)
Consideration should be given to avoidance/treatment of the precipitating factors of the pain (D)
Consideration should be given to modification of the background analgesic regimen/'around-the-clock medication' (D)
Opioids are the 'rescue medication' of choice in the management of breakthrough pain episodes (D)
The dose of opioid 'rescue medication' should be determined by individual titration (B)
Non-pharmacological methods may be useful in the management of breakthrough pain episodes (D)
Non-opioid analgesics may be useful in the management of breakthrough pain episodes (D)
Interventional techniques may be useful in the management of breakthrough pain (D)
Patients with breakthrough pain should have this pain specifically reassessed (D)

Grades of recommendation: (A) Strong research-based evidence – multiple relevant, high-quality scientific studies with homogeneous results; (B) Moderate research-based evidence – at least one relevant, high-quality study or multiple adequate studies; (C) Limited research-based evidence – at least one adequate scientific study; (D) No research-based evidence – information that does not meet the criteria for scientific evidence.
Reproduced with permission from [32].

practice, the dose of oral opioids used as rescue medication was 18% of the ATC opioid dose, whereas for OTFC, titrated to determine the effective dose, the rescue dose was about 35% of the ATC dose [33], suggesting that the titration process mostly provides even higher doses that those expected by using proportional doses to ATC regimen. A titration process starting with 200 µg of OTFC is likely to produce minimal effects in patients who are receiving high doses of opioids regularly. This practice may discourage patients, particularly outpatients, to continue titration in daily activity. The need of titration has probably limited the use of OTFC and probably will be the same with other new delivery systems, despite the superiority over oral morphine. Many patients will continue to prefer the conventional use of oral morphine, even though most of the episodes will evanish spontaneously [9] and an uneventful burst of morphine will be gratuitously given.

Other factors could influence the outcome, namely the different pain intensity of each episode or the type of BTP, which potentially should require titration for each episode, unfeasible in clinical practice. For example, incident pain due to movement is a challenge as it is strongly dependent from physical activity and may spontaneously evanish, stopping movement. Previous preliminary studies have shown that, in patients receiving opioids for chronic cancer pain, the risks of administering about 20% of the daily dose of opioids with rapid modalities, intravenously or transmucosally, are minimal, going back to previous recommendations, based on clinical experience [17]. This can be explained by the protective effect offered by opioid tolerance in patients chronically receiving relevant opioid doses for the management of cancer pain. A reliable compromise between the different opinions could be to start with relatively higher doses of opioids in highly tolerant patients skipping some steps of dose titration, until more information will be available to settle the question. Randomized studies with an appropriate design comparing advantages and disadvantages of titration versus fixed doses proportional to ATC opioid doses could reveal the truth.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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