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REVIEW

Relationship between breakthrough cancer pain, background cancer pain and analgesic treatment – case series and review of the literature

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Abstract

The assessment and treatment of breakthrough cancer pain (BTcP) remain a major challenge in medicine due to its high impact on several aspects of health-related quality of life. BTcP should be carefully monitored in all cancer care settings by a multidisciplinary team to provide an appropriate and personalized clinical approach. The aim of this paper is to provide healthcare professionals involved in cancer pain management with a review of the relevant literature on the relationship between background cancer pain and BTcP which, by definition, occurs despite adequately controlled background cancer pain. The clinical cases presented contribute to a better understanding of this issue and underline its impact in daily clinical practice.

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Introduction

Cancer pain is a frequent and prevalent symptom that may arise throughout the illness and may be the first symptom of cancer, occurring during the diagnostic phase, or experienced during primary, adjuvant, maintenance, or symptomatic treatments. Unfortunately, despite the improvements in recent years, it is estimated that 39% of patients experience pain after radical anticancer treatment, 55% during treatment, and 66% in the advanced stage of cancer.[1]

Inadequate pain management is accompanied by strong negative emotional symptoms that significantly affect the physical and psychological aspects of life, contributing to the worsening of quality of life (QOL).[2] According to the WHO pain treatment ladder for pain management,[3] the correct and comprehensive assessment of the patient with cancer pain and tailored pharmacotherapy should ensure satisfactory pain control[4] and allow a reduction in healthcare costs.[5,6] Several factors still contribute to the failure to properly manage background cancer pain (BCP), and breakthrough cancer pain (BTcP) has proven to be an independent risk factor for poor pain control patients with cancer,[7] because of its high impact on daily activities, sleep, social interactions with family and friends, and overall QOL.[8–15] Fortunately, in recent years, thanks to renewed worldwide interest, the definition of BTcP has been better clarified with a strong consensus on most of its key features, and the basis for its treatment has been established.[16] Current guidelines agree on many aspects of the management of BTcP,[17,18] which requires early and proper assessment and tailored therapy with rapid onset opioids (ROOs) or immediate release (IR) opioids, selected according to patient requirements, the characteristics of BTcP and the analgesics used for background pain control.

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BCP must be well controlled with adequate baseline analgesia so that episodes of BTcP can be distinguished. However, there is still some debate as to what the characteristics of adequately controlled BCP should be, and what analgesic treatment should be used to best manage this problem.[19]

In this article, we critically review the evidence regarding the relationship between BTcP, BCP and analgesic treatment. We also present evidence for a therapeutic approach aimed at meeting the unmet needs and improving therapeutic approaches.

Methods

A literature research was performed in PubMed, Scopus, ISI-Web of Science, and Google Scholar including the key terms: "background cancer pain" and "breakthrough pain", with the search limited to humans, adults, English language and publication years 2012–2022.

Some included studies were identified from the reference lists of previous narrative reviews, systematic reviews, and meta-analyses, summarizing the results from observational studies and randomized clinical trials related to cancer pain. A hand search of the reference lists of identified papers was also performed.

The review focused on BTcP guidelines published during and after 2009 (the date of publication of guidelines by the Association for Palliative Medicine (APM) of Great Britain and Ireland).[20]

Review

Breakthrough cancer pain

The definition and classification of BTcP have been debated for several years,[17–19,21] and the persistent lack of international consensus has resulted in great discrepancies and contradictions in the reported prevalence.

The term 'breakthrough' was initially equivocal for linguistic reasons, lacking a clear correspondence in some languages, and because of the need to define whether pain exacerbations implied the existence of underlying pain.[22,23] In 2009, a task group of the Science Committee of the APM defined BTcP as an acute, transient exacerbation of severe pain occurring spontaneously or due to a specific trigger in a patient whose BCP was stable and controlled for a greater part of the time.[20] They also proposed a clinical diagnostic algorithm in order to help physicians distinguish BCP from BTcP.[17] BTcP is characterized by an acute exacerbation of severe pain of short duration (>5/10 on a Visual Analogue Scale (VAS)) suffered by a patient whose BCP is stabilized and controlled by opioids (≤3/10 on a VAS scale). It presents a substantial burden to patients, as it disrupts daily activities and QOL.[2,3] BTcP may occur spontaneously or due to a specific trigger.[2,19] In addition, studies have shown that BTcP can be either predictable or non-predictable, based on results that indicated different clusters and phenotypes of BTcP.[24,25]

Management of incident BTcP (predictable and related to a precipitating activity or event such as walking) is easier that of spontaneous BTcP.[3] Unrelieved BTcP substantially raises healthcare costs due to increased outpatient and emergency room visits.[3,13]

Standard of care

Diagnosis of BCP and BTcP

The concept of controlled BCP is not unanimous; it may be defined as pain at a level that allows for a QOL that is acceptable to the patient or as pain defined as tolerable by the patient,[3] assuming a highly subjective assessment. The diagnostic algorithm proposed by the APM Guidelines[20] requires that the patient with cancer reports the presence of BCP during the last week and describes it on a Verbal Rating Scale as 'none', 'mild', 'moderate' or 'severe'. According to this algorithm, if a patient has controlled BCP, it is considered as 'none' or 'mild' for >12 hours/day during the previous week. However, this intensity definition of BCP should be guided by a healthcare professional trained in cancer pain to encourage the most appropriate responses and avoid misinterpretation of the adjectives, which can assume different meanings based on specific contexts, cultures, and individual patient experiences.[19]

In later studies, BCP was defined as 'controlled' based on the measurement of pain intensity on a numerical scale; thus, BCP control requires the absence of pain or a pain intensity ≤3/10 on a numerical scale of 0–10.[20,24] The use of the numerical rating scale (NRS) or of the VAS to refer to pain intensity seems to be more objective than a verbal scale because some patients with 'moderate' BCP reported that their pain was adequately controlled.[16,19] Furthermore, in the elderly or in patients with cognitive difficulties, assessment of pain may require observational scales. Assessment of patient behaviour and discomfort in these groups of patients is usually more helpful than scales.[16]

Regarding the interaction between BCP and BTcP, some authors[11,23] have reported that severe BCP intensity is a powerful predictor of BTcP scores and is associated with more frequent BTcP episodes[26,27] or higher BTcP intensity,[26] though a recent study was unable to find a statistically significant correlation between the severe background pain score and the intensity of BTcP.[7]

On the other hand, optimization of the analgesic regimen for background pain appears to decrease the number, intensity and duration of BTcP[28] but not its prevalence.[28,29]

Almost all guidelines recommend that patients are adequately assessed to ensure that background pain and BTcP are differentiated and to avoid confusing BTcP with pain occurring during titration of opioid therapy or with 'end-of-dose failure'.[20,30]

Selection of analgesics

Regarding the pharmacological treatment of BCP, there has been no agreement for many years on whether the theoretical definition of BTcP would include the treatment of BCP with opioids alone or with other analgesics. However, most of the available literature on BTcP states that BCP needs to be treated with analgesics administered around the clock,[20] preferably by the oral route of administration based on the half-life, bioavailability and duration of action of each drug,[16] or must be well controlled with strong opioids based on the WHO analgesic ladder.[12]

The effective dose of opioids used for pain relief varies significantly amongst patients depending on their preference, acceptability and feasibility. Controlling BCP with opioids requires progressive titration to achieve effective analgesia with the lowest effective dose of opioids and without unpleasant side-effects.[31] Most specialists agree that initially the pain should be controlled with analgesics strong enough to manage the severity of pain each patient experiences. In cases of moderate or severe pain, all patients should be started with a combination of opioids, in addition to paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) in order to achieve sustained, effective and safe control of pain.[3]

Individual titration of opioids is required for all patients.[16] Although rapid titration models have been described in the literature,[17,32,33] a gradual dose adjustment for the control of moderate to severe pain in cancer patients is strongly recommended, though it usually takes several days. Moreover, even in the phase following opioid titration, many patients may experience end-of-dose pain, indicating an increase in pain at the end of a scheduled dose and before the next dose. Treatment of end-of-dose failure may include shortening the interval between doses or increasing the dose of the opioid medication.[30] For all these reasons, in most studies, patients with a pain intensity ≤4/10, for 12 hours a day, stable during the week before the evaluation of BTcP, were enrolled.[7,20,34]

All patients, who are receiving baseline analgesia, should have a rescue (breakthrough) dose to maintain analgesia in exacerbations of pain. According to the most recent European Society for Medical Oncology (ESMO) guidelines, the breakthrough dose can be equivalent to 10–15% of the 24-hour total opioid dose and if more than four doses are necessary, the baseline dose should be elevated.[16]

The decision to use a specific opioid preparation for breakthrough pain management should be based on the characteristics of pain (onset, duration), the product characteristics (pharmacokinetics, pharmacodynamics and how clinical status can influence a patient), previous response to certain opioids, and on the patient's preference for an individual preparation or route of administration.[3] The pharmacokinetic/pharmacodynamic profiles of oral opioids as stated in the WHO guidelines, do not always mirror the temporal characteristics of most BTcP episodes, and are not considered the 'gold standard' of treatment of BTcP, though they have a role in some patients.[3] Oral IR opioids, especially morphine, have been the gold standard approach for the management of BTcP for many years; however, the pharmacokinetics of morphine do not allow pain control in many patients because it results in late occurring analgesia and ongoing adverse reactions.[16] The APM favours ROOs to manage BTcP, due to their rapid onset of action and a route of administration that minimizes the first-pass hepatic metabolism to provide high bioavailability.[12]

However, there are some patients who, for several reasons, cannot use them, including patients with limited access to several forms of opioids, or patients who not adequately respond to some categories of rescue opioids for pharmacokinetic or pharmacodynamic reasons.[17] ESMO guidelines also state that there are still indications for IR oral opioids in BTcP management, which mainly include a slower onset BTcP or a pre-emptive administration of opioids before the event.[16]

The WHO guidelines for cancer pain management[3] suggest that, for patients who receive therapy with strong opioids, transmucosal fentanyl could be used starting from the lowest dose in opioid-tolerant patients who are already on a strong opioid for cancer pain for at least 1 week. Transmucosal IR fentanyl formulations (oral, buccal, sub-lingual and intranasal) have a rapid and predictable onset of action. The minimum dose of baseline opioid should be morphine 60 mg/24 hours per os, fentanyl 25 µg/hour/transdermal, hydromorphone 8 mg/24 hours per os, oxycodone 30 mg/24 hours per os, or an equivalent dose of any strong opioid. Although one study suggested that transmucosal fentanyl products can be tolerated by patients receiving less than 60 mg/day of OME,[35] the FDA requires a risk evaluation and mitigation strategy for IR fentanyl to ensure that transmucosal IR fentanyl drugs are only prescribed and dispensed to opioid-tolerant patients. This strategy is part of the efforts to avoid inappropriate prescription of opioid-intolerant

patients and to help mitigate the risks of accidental exposure, misuse, dependence and overdose.[36]

Finally, of note, pain intensity needs to be part of a comprehensive assessment, considering the characteristics of the patient and the progression of the disease. BTcP management should always be individualized and the literature suggests that proper treatment certainly improves the health-related QOL of patients.[37,38]

Pain aetiology and multimodal analgesia

Identification of the specific aetiology of the syndrome can guide therapeutic interventions and clarify the prognosis of pain.[28,39–48] The characteristics of pain are related to the kind of tumour and the therapy received by the patient (surgery, radiotherapy, chemotherapy, alone or in combination) as well as its location and proximity to nerves or bones. In clinical practice, we believe it is important to adequately consider all these factors. Regardless of whether cancer pain is of nociceptive or neuropathic in origin, the therapeutic regimen for establishing analgesia should be dynamic, following the progression of the disease and its therapies.

These goals and a potential opioid-saving effect could be achieved by adding other specific pharmacological (NSAIDs or steroids in inflammatory pain, bisphosphonates in bone metastases pain, spasmolytics in visceral pain, etc.) and non-pharmacological treatments.[49]

The treatment of neuropathic pain, which is quite common in cancer patients,[50] is based on pharmacotherapy with adjuvants such as anticonvulsants (pregabalin and gabapentin) and antidepressants (tricyclic antidepressants such as amitriptyline or selective serotonin-norepinephrine reuptake inhibitors such as duloxetine and venlafaxine). We report the cases of two patients with neuropathic pain (cases 2 and 3). In case 3, the occurrence of such pain, especially after the second cycle of radiotherapy,[51] may have been responsible for the rapid escalation of adjuvants and opioid doses, which ultimately did not lead to an improvement in pain control.[52,53]

Multimodal analgesia combining various analgesics with different mechanisms of action is used in chronic cancer pain management,[54] but there is a lack of studies investigating the possible role of adjuvant drugs combined with opioids in BTcP. Only one study, including patients with pancreatic cancer, evaluated the addition of pregabalin, demonstrating that patients who received combination therapy had a significant decrease in the duration of BTcP; however, there was no difference in numbers and severity of BTcP episodes.[55] Further studies are needed to better evaluate the effect of tailored multimodal therapy on the control of BCP and BTcP.

Finally, it must be noted that in every case, patients should be adequately monitored regarding pain relief and possible side-effects. Telemedicine might have a role in patients who cannot easily reach a pain management unit due to distance, health reasons, or absence of carers. Studies support the use of telemedicine or hybrid medical assessment (combination of visits with internet-based appointments), keeping in mind that in this case very slow titration rates must be suggested, as well as frequent assessment of patients' pain intensity and characteristics, renal and hepatic function, and cognition.[56–59]

Case reports

Three clinical cases are described, with the intent to exemplify the patient management and describe how BTcP might be approached. All the data referring to the patients are published after informed consent, in anonymous way, without any details allowing reidentification of the patient, and in accordance with the World Medical Association Declaration of Helsinki.

Case 1

A 58-year-old woman was diagnosed with adenocarcinoma of the left lung pT1NxMxG2R0 (IA), underwent upper left lobectomy in 2009, and right lung adenocarcinoma T1N0M0 (IA) operated by wedge excision in 2014. She also complained about neck pain with C5–C6 irradiation, due to cervical column abnormality with a neuropathic component, previously submitted to C5–C7 arthrodesis by neurosurgeons. The patient was referred to the multidisciplinary pain team in November 2017 because of severe chest pain (VAS >6) and neck pain with C6 irradiation (VAS >5), both with neuropathic characteristics. She was already being treated with tapentadol (100 mg BID) and diazepam 5 mg. Due to severe pain, tapentadol was increased to 150 mg BID combined with an osmotic laxative, and pregabalin 50 mg BID was prescribed, with adequate pain control.

She maintained adequate pain control and good tolerance during regular follow-up until December 2018, when she was urgently assessed for uncontrolled BCP and BTcP episodes, both spontaneous and following physical efforts. Pregabalin was discontinued by the patient. She was prescribed a buprenorphine transdermal system 52.5 µg/hour, 2 times/week, amitriptyline 10 mg, and a stimulant laxative (bisacodyl) as needed. BCP was well controlled (VAS ≤3) but 2–3 episodes/day of BTcP with short duration and intensity of ≥5 in VAS persisted. Sub-lingual fentanyl 133 µg up to four times a day was prescribed, and the patient reported significant relief of BTcP for 1 year.

In April 2019, she was diagnosed with right lung recurrence (cT3N0M0) treated with chemotherapy and radiotherapy, and buprenorphine was gradually increased to 70 + 35 µg/hour along with an increase of sub-lingual fentanyl to 267 µg.

The patient's pain was under control until August 2021, when she presented with a skin allergy to buprenorphine transdermal therapy and was switched to fentanyl transdermal system 75 µg/hour/72 hours, maintaining sub-lingual fentanyl 267 µg as needed, and amitriptyline 10 mg. In February 2022, the patient underwent selective right C5 and C6 ganglion blocks because of relapse of the cervical pain with good results. By May 2022, she reported satisfactory pain control using the same analgesic medication since August 2021.

This case highlights the high prevalence of lung cancer pain and BTcP, the mixed pain origin (cancer and neuropathic) because of comorbidities (column pathology), and the difficulties in management as well as the importance of adjuvant analgesics and multimodal therapy and the suitable pharmacological characteristics of ROOs for the treatment of BTcP.

Case 2

A 48-year-old female patient with invasive breast cancer was diagnosed in 2019 (cT1cN0M0, triple negative), and treated with neoadjuvant chemotherapy, brachytherapy (ypT1cN0-sn) and radiotherapy. In February 2022, she developed brain parenchymal and meningeal metastases that were treated with radiotherapy and she participated in a clinical trial (atezolizumab).

The patient reported left shoulder pain (NRS 5) radiating to the neck with a mixed somatic and neuropathic component. Due to the mixed nature of the pain, the patient was treated with oxycodone slow release (SR) titrated to 20 mg BID and NSAIDs. She was recommended to take a rescue dose of morphine sulfate IR (10 mg as needed), and pregabalin was titrated to 75 mg BID.

Owing to depressed mood and sleep disorders, duloxetine 30 mg was added along with oral dexamethasone 4 mg BID to manage consciousness disturbances due to the presence of metastatic lesions in the central nervous system. The patient also reported paroxysmal BTcP episodes approximately two to four times per day, on the left shoulder region with radiation to the left upper limb and neck, accompanied with sensation of numbness and described as electrical shock-like pain; BTcP was treated with a sub-lingual formulation of transmucosal IR fentanyl at the dose of 133 µg, up to four times per day.

Due to mild renal impairment, oxycodone (40 mg/day) was replaced with a buprenorphine patch (transdermal therapeutic system) at a dose of 35 µg/hour, whilst transmucosal fentanyl was considered safe and administered at the same dose (133 µg). Pregabalin was reduced to 75 mg at night and duloxetine was discontinued. The patient also required intravenous hydration and diuretics. When the patch was changed twice, the analgesic effect of steady-state buprenorphine was evaluated as satisfactory, and the patient rated the pain as two on the NRS. Episodes of BTcP occurred with varying frequency and intensity, approximately twice per day, and were well controlled with sub-lingual fentanyl, without any modification of the initial dose.

This case focuses on the mixed origin of the BCP, the comorbidities (renal impairment, central nervous system metastasis) that necessitate adjustment of therapy and the efficacy of the transmucosal fentanyl on BTcP.

Case 3

A 66-year-old patient diagnosed with a tumour of the right lung apex (Pancoast' tumour) and dissemination to the mediastinal lymph nodes was started on palliative radiotherapy (30 Gy). Four months after the completion of radiation therapy, the patient was referred to the palliative care specialist due to pain in the right shoulder and arm (NRS 3–5). Pain was described by the patient as burning, intermittent cold, and freezing (depending on the position of the head and movement of the limb), radiating throughout the limb to the elbow joint area, as well as toward the neck and the right shoulder blade. The pain worsened at night (NRS 6–7) and led to sleep disruption. Weakness and impaired function of the right upper limb were also confirmed. The pain was considered as neuropathic after radiotherapy and the patient underwent multimodal pain pharmacotherapy with oral oxycodone SR gradually increased to 40 mg BID, pregabalin 75 mg BID, venlafaxine 75 mg BID, and dexamethasone 4 mg once daily.

One month after the second cycle of radiotherapy, the patient visited the Outpatient Clinic again because of a rapid increase in severe pain (mean NRS 5–7) in the same previous localization and characteristics, despite the increased doses of analgesics and the addition of new medications.

On admission, the patient was administered oxycodone SR 200 mg BID, methadone 8 mg BID, pregabalin 300 mg BID, venlafaxine 75 mg BID, and dexamethasone 1 mg once daily, and all medications were administered orally. The patient used oral morphine IR 60 mg four to six times per day for pain flares.

Physical examination revealed severe pain (mean NRS 8–9) of a mixed, predominantly neuropathic nature in the upper thoracic spine region, neck, shoulders, and arms, with restricted mobility. All complaints were described by the patient as lancinating and burning, with significant hypersensitivity and mechanical allodynia. The patient was sleepy, easily distracted, had difficulty engaging in conversations and did not remember recent facts. Nocturnal rest was disturbed by breakthrough pain. The patient suffered from great effort and pain on defecation and reported more frequent episodes of dyspnoea. The patient moved with difficulty, mainly using a wheelchair, and fell a few days prior to admission. An adjustment of the analgesic therapy was considered necessary, and oxycodone and methadone were discontinued.

The patient was started on the following oral medications: morphine sulfate controlled release 100 mg BID (also due to dyspnoea), tapentadol 250 mg BID, pregabalin 300 mg BID, duloxetine increased to 60 mg once per day, naproxen 250 mg BID, dexamethasone increased to 8 mg BID, and sub-lingual fentanyl was added at a dose of 267 µg in case of breakthrough pain. Medications for other concomitant diseases were used, such as laxatives (lactulose), diuretics, and protective treatment for the gastric and duodenal mucosa. Complex decongestive physiotherapy was then administered. Very good pain control was achieved with one or two episodes of BTcP per day (NRS maximum up to 7) relieved by transmucosal fentanyl.

The case described reflects the complexity and difficulties with the proper diagnosis and subsequent treatment of chronic pain in patients with cancer. This case highlights that radiotherapy-induced neuropathic pain is very difficult to adequately manage and contributes significantly to BTcP. Furthermore, there is a need for opioid rotation in order to achieve the proper dose and formulation for the management of pain at various stages of the illness along with close monitoring and continuous assessment of the patient with cancer for the early identification of adverse events (side-effects) of the analgesic therapy.

Conclusion

BTcP must be clearly differentiated from underlying BCP, as it demands a different approach to diagnosis and treatment. Pain exacerbations should be closely monitored, and it is therefore necessary to differentiate BTcP from variations occurring during titration of opioid therapy, end-of-dose failure, and circadian fluctuations. Although many guidelines and recommendations have emerged during the past decade regarding the terminology, diagnosis, and treatment of BTcP, it seems that there are still many issues to be resolved. Early diagnosis, close monitoring of pain intensity and aetiopathogenetic characteristics, as well as proper assessment of the exact types of pain are required. It is advisable to manage pain with a multimodal analgesic plan to achieve optimal pain control and a better QOL for patients with cancer.

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