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Received: 26 July, 2019

Accepted: 24 August, 2019

Published: 26 August, 2019

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Keywords: Pain; BTcP; Breakthrough cancer pain; Cancer pain; Expert recommendations

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Review Article

Consensus statement on the management of breakthrough cancer pain: Assessment, treatment and monitoring recommendations

Abstract

Objective: Breakthrough cancer pain (BTcP) is still underestimated and a percentage of patients are not adequately treated, affecting their quality of life. The aim of this review was to generate a series of expert recommendations based on clinical experience and current scientific data on the management of BTcP.

Methods: An interdisciplinary group of Spanish pain experts held face-to-face meetings to review existing protocols and the relevant scientific literature on the management of BTcP, sharing their clinical experience. The outcome was a consensus document, providing practical guidelines and suggestions on the diagnosis, treatment and follow-up of BTcP patients.

Results: The following recommendations were generated to assist healthcare professionals in their therapeutic decision-making in BTcP patients: personalized evaluation of the BTcP characteristics is recommended to implement the best possible therapeutic approach; the treatment plan for BTcP should also combine preventive measures with pharmacological and non-pharmacological methods, and should be individualized according to the patient's characteristics, preferences and personal circumstances; and finally, a multidisciplinary team approach together with adequate patient health education are essential to prevent underdiagnosis and sub-optimal treatment.

Conclusions: These consensus recommendations based on recent scientific evidence will help healthcare professionals in assessing, treating and monitoring BTcP in oncology patients.

Abbreviations

BTcP: Breakthrough Cancer Pain; VAS: Visual Analogue Scale; NICE: National Institute for Health Care Excellence; ROOs: Rapid-Onset Opioids; ATC: Around the Clock.

Introduction

Pain is a complex health condition that affects both mental and physical abilities. It can be classified into acute pain (provoked by a specific disease or injury and lasting less than three months) and chronic pain (lasting more than three months, often idiopathic). Chronic pain is one of the most common reasons for seeking medical care, affecting between 2% and 40% of the adult population worldwide [1].

Cancer pain is a type of chronic pain, with 35% of oncology patients experiencing it at diagnosis [2]. Its pathophysiology is complex: it is mainly caused by the primary tumor, followed

by associated cancer therapies including surgery, radiation therapy, chemotherapy, targeted therapy, supportive care therapies, and/or diagnostic procedures [3,4]. In many cases, however, the real cause is unknown [5,6].

Most of the pain caused by cancer, known as baseline or background pain, can be controlled by long-term regular medical treatment, but even with good management, some patients still experience flares of short-term, intense pain. These transient pain events are called breakthrough cancer pain (BTcP), and are characterized by rapid onset (usually between 3 to 5 minutes), short duration (an average of 60 minutes) and moderate to high intensity (7 points on a 10-point pain Visual Analogue Scale [VAS]) (Figure 1) [7].

Regardless of recent advances in diagnosis, assessment and treatment, BTcP is still a challenge for patients and healthcare professionals alike. Therapeutic approaches differ between countries because of a lack of uniform international guidelines,

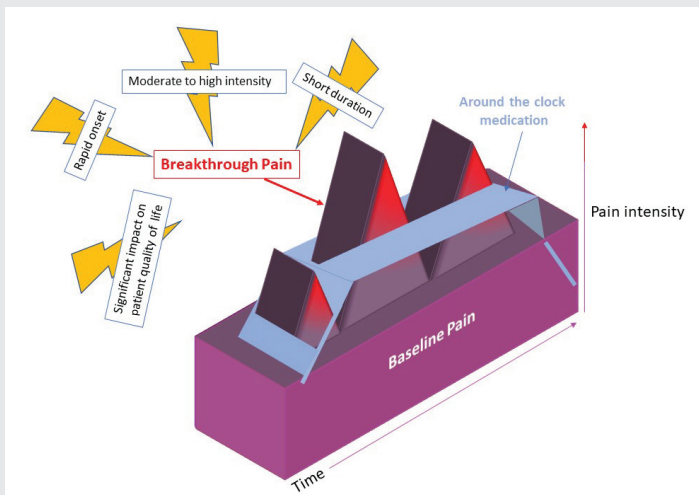


Figure 1: Characteristics of breakthrough cancer pain.

and indeed, a systematic literature review found that study designs and clinical settings were highly variable across regions. As a result, nearly 50% of patients were undertreated, affecting their daily life [8].

The main objective of this review was to present the current evidence on the management of BTcP, and to provide an action protocol to properly diagnose, treat and follow-up BTcP patients based on practical experience, to help healthcare specialists in making therapeutic decisions, thereby improving patient quality of care.

Methods

This paper is the result of a consensus document produced by a group of 12 Spanish experts in cancer pain therapy, based on their daily clinical experience and critical assessment of the current literature. The expert panel was composed of oncologists, pharmacists, pain specialists, radiation oncologists, in-home care physicians and emergency care doctors with extensive experience in treating cancer patients. A review of the existing literature was performed to obtain practical protocols for the management of BTcP. In order to identify as much information as possible, we searched the main international databases (MedLine/PubMed, Cochrane Library, ISI WOK [ISI Web of Knowledge], and SCOPUS), including Google scholar, for pertinent articles published in English and Spanish during the last 10 years; however, our search was unsuccessful.

The present consensus statement is the result of multiple face-to-face meetings where the panel experts discussed existing guidelines and relevant scientific studies on the management of BTcP. It includes a series of practical recommendations for the diagnosis, treatment and follow-up of BTcP, in order to aid other health professionals in making therapeutic decisions.

Results

Considerations on the definition of BTcP

Breakthrough cancer pain was first defined by Portenoy et

al. in 1990 [7], as ‘a transitory exacerbation of pain experienced by patients undergoing long-term opioid treatment for cancer-related pain whose baseline pain is adequately controlled’, but there has been controversy with respect to this definition over the past two decades. Some international guidelines recommend the definition of BTcP derived from the original by Portenoy [9–12], whereas others have established their own definition [13–15]. The main discrepancy is the fact that BTcP can also occur in the absence of background cancer pain and regardless of opioid treatment [16,17]. So far, there has been no global agreement on the definition of BTcP [18]. This lack of consensus has generated different criteria for diagnosing cancer pain, which explains the large variability found in BTcP prevalence rates, ranging from 12% to 93%, depending on the study [8,19–22].

In 2012, an association of Spanish medical doctors, composed of palliative care, pain specialists, oncologists and radiation oncology experts, produced a consensus document with a series of guidelines to properly diagnose and treat BTcP patients. BTcP at that time was defined as ‘a transient, highly intense exacerbation of pain of short duration (less than 20–30 minutes) appearing through a stable pain baseline that can be controlled by opioid treatment’[13]. Although this definition is still valid, some clarifications are needed. First, how exactly is stable baseline pain defined? Some specialists consider that baseline pain is stable when the intensity is very low or there is no pain at all for more than 12 hours, but it can also be interpreted as pain with stable intensity for at least 48 hours, or when there are no more than five daily BTcP episodes. Second, we also need to delimit the length of a ‘transient episode’. BTcP episodes are extremely variable, both between and within individuals, and, although it is generally considered that the average duration of a BTcP event is around 30 minutes, it can last more than 1 hour [23]. Lastly, one should distinguish between BTcP and end-of-dose pain. End-of-dose pain occurs just before the next scheduled dose of opioid treatment, indicating an inadequate dose or too prolonged interval between subsequent administrations.

All medical specialties involved in the management of BTcP should agree on a practical definition for BTcP, identifying all possible variables and drawing up an international consensus for the proper diagnosis and management of BTcP.

Recommendations for the treatment of BTcP

The following recommendations were generated with the goal of assisting healthcare professionals in their therapeutic decision-making in patients with cancer pain.

Diagnostic criteria

For patients with cancer, BTcP is associated with decreased functional status and increased levels of anxiety and depression, greatly affecting the patient’s quality of life [24]. In fact, a study by the American Pain Foundation showed that living with pain negatively influences emotional health and causes suffering in 82% of patients [25]. However, despite its prevalence and

impact on patients, BTcP is sometimes unrecognized and often undertreated [26–28]. Prompt and efficient diagnosis is therefore essential.

Pain levels can currently be evaluated using different scales and questionnaires, including a visual analogue scale (VAS), the SF-36 pain scale and a neuropathic pain diagnostic questionnaire (DN4) [29,30]. There are different tools for the diagnosis of BTcP [31–33], although the standard one used is the Davies algorithm. Figure 2 shows the most widely used algorithm, modified from the original published in 2009 [23,34,35]. Although it has a good positive predictive value, its sensitivity is still limited due to patient variability. A complete clinical evaluation is still the preferred method to diagnose BTcP [36].

should know and consider the use of interventional, non-pharmacological methods in the management of BTcP. These include:

- Palliative radiotherapy
- Orthopedic surgery
- Spinal reinforcement measures
- Analgesia techniques, including local infiltrations and nerve block.
- Physical measures

Pharmacological approaches: The management of BTcP is primarily based on pharmacological treatment. Treatment options include:

- Addition of co-analgesics such as antidepressant and anticonvulsant medication, corticosteroids and others.
- Increase the daily basal analgesic dose (25% to 50%), to minimize the intensity and number of BTcP episodes [40]. Previous studies on patient tolerability and adverse events at higher levels of basal analgesics should be performed before applying this measure.

- Prescription of opioid analgesics as rescue medication for BTcP. Strong opioids, such as immediate-release morphine, have traditionally been used to treat BTcP [41], and indeed it is still the first treatment option for some scientific societies, including the National Institute for Health and Care Excellence (NICE) [42]. However, the pharmacokinetic/pharmacodynamic profiles of opioids do not always follow the temporal characteristics of most breakthrough pain episodes [43]. Oral opioids need around 30–40 minutes to take effect, while the maximum pain intensity of BTcP is reached very fast (often in less than 10 minutes) [44]. Rapid-onset opioids (ROOs), specifically fentanyl formulations, are the current gold standard in BTcP treatment because they act very quickly, and are very effective [45,46]. In fact, the European Society for Medical Oncology (ESMO) guidelines for the management of cancer pain recommends the use of fentanyl forms for the treatment of BTcP (level of evidence I, degree of recommendation A), whilst morphine is given a level of evidence of II and degree of recommendation of B [34]. Moreover, fentanyl forms are also generally better tolerated, which is particularly important in patients with renal and hepatic disease, since they cannot tolerate strong opioids due to known accumulation of toxic metabolites [47]. Thus, fentanyl formulations are presently the first option in the treatment of BTcP recommended by most medical oncology societies [34,48].

Fentanyl selection: Administration options and dose titration procedure

As previously mentioned, rescue treatment for BTcP involves taking an extra dose (usually at 5%–20% of the total

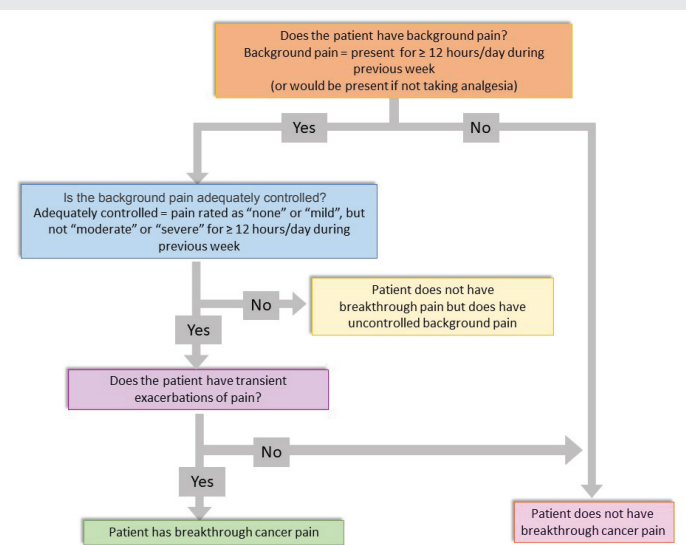


Figure 2: Adapted Davies algorithm.

Therapeutic management

Given the wide inter- and intra-individual variability that characterizes BTcP patients [12,23], it is crucial to perform an individualized and very exhaustive initial evaluation to provide them with the best possible management approach. The etiology of the cancer pain will determine the best treatment option. However, regardless of the treatment, therapeutic management should be multimodal, combining preventive measures with both pharmacological and non-pharmacological methods. Support from family and health professionals will also be essential for a successful outcome.

Non-pharmacological approaches: Interventional strategies can be used prior to or alongside pharmacological therapy. Specialists have traditionally followed the original analgesic stepladder algorithm (WHO), in which pharmacological measures are first applied and non-pharmacological techniques are used only when the analgesic ladder fails [37,38]. More recently, though, some clinicians are advocating the early application of non-pharmacological techniques, arguing that it could be beneficial for pain control [39]. Regardless of the time of application, professionals

daily dose) of the opioid used around-the-clock (ATC) to relieve baseline pain [47,49,50]. This approach, which is based on years of clinical experience, might not always work because the pharmacokinetics of ATC opioids might not match the onset of the BTcP episode [43]. For this reason, ROOs, specifically fentanyl formulations, are the treatments of choice at present.

Clinicians should take into consideration different variables to choose the correct transmucosal fentanyl form from among buccal, sublingual or intranasal preparations [51]. Patient preferences and personal circumstances should first be considered (Table 1). For instance, in the case of patients with frequent vomiting or mucositis, intranasal or sublingual forms of fentanyl administration are recommended. Patients taking buccal tablets or films are advised not to eat or drink anything until the medication has completely dissolved inside the buccal cavity. Having a dry mouth, as well as breaking or sucking the tablets, will decrease their clinical efficacy. Previous moisturization of the oral mucosa has been proven to effectively improve fentanyl absorption [52]. Additionally, the pain specialist should also evaluate the drug pharmacokinetic characteristics and possible contraindications, especially in polymedicated patients.

For adequate BTcP analgesia, it is important for fentanyl forms to be titrated over time to meet the patient's individual needs [35,53]. To do so, physicians should consider their clinical needs, age, presence of comorbidities and appearance of adverse events upon treatment initiation. The final aim is to provide individually tailored BTcP treatment by identifying the optimum fentanyl dose and minimizing the risk of side effects.

The fentanyl dose should be gradually adjusted starting with the lowest concentration possible, as indicated in the Summary of product characteristics. The algorithm for fentanyl dose-titration is shown in Figure 3. If, for any reason, patients do not obtain sufficient relief, the concentration

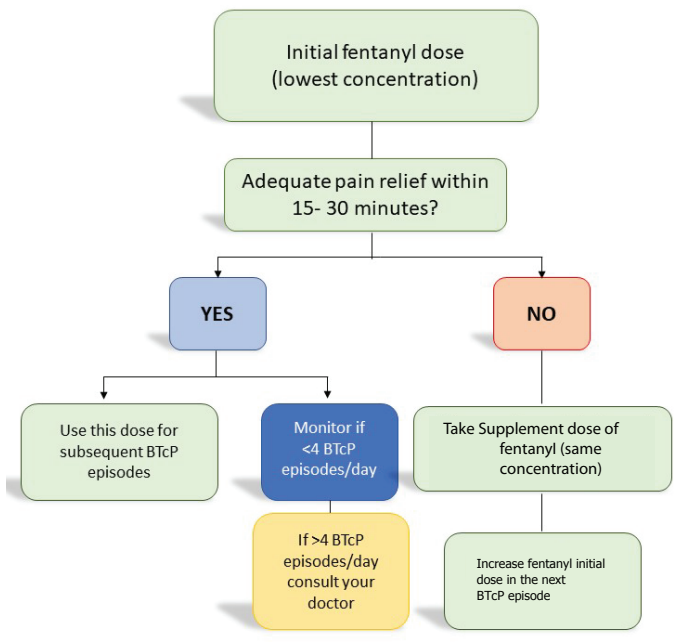


Figure 3: Fentanyl dose-titration algorithm.

Table 1: Practical recommendations for selecting the fentanyl formulation.

Problem	Recommendations
Frequent vomiting and dysphagia	Do not drink or eat anything until transmucosal fentanyl has been completely absorbed
	Use of antiemetics in conjunction with opioids
	Wait 30 minutes before another fentanyl dose to see if there is pain relief. Determine if fentanyl was absorbed before vomiting
Constipation is a common symptom in patients treated with opioids	Use intranasal or sublingual fentanyl formulations
	Use of laxatives in conjunction with opioid treatment. For persistent constipation, consider PAMORAs (peripherally acting mu-opioid receptor antagonists)
Presence of mucositis	Use intranasal or sublingual fentanyl formulations
Patients with renal or hepatic failure	Continue using fentanyl as analgesia but closely controlling the dose
Opioid-related complications	Closely monitor patients at greater risk of developing complications including patients with any of the following conditions: Severe comorbidities, advanced age, polymedication, hepatic and/or renal dysfunction, situation of social risk, cognitive impairment and history of drug abuse.

should be gradually increased until the pain is adequately controlled without side effects, with an interval of at least two hours between doses of sublingual fentanyl tablets and four hours in other fentanyl forms. In older adults, the method for trialing the opioid treatment is not exactly the same [54]. These patients are usually more susceptible to the medication effects, and many analgesic guides recommend a “start slow and go slow” approach [55]; however, this dosing strategy is often misinterpreted as “start low, stay low”, entailing the risk of inadequate analgesia [56]. To avoid excess sedation, it is recommended to use half the starting dose used for younger adults and proceed with smaller dose increments when needed [56]. If patients of any age present adverse effects or tolerability issues, it is advised to change to another fentanyl formulation. In these cases, a new dosage adjustment protocol should be drawn up, because each fentanyl preparation has different absorption profiles.

To evaluate treatment efficacy and tolerability, patients should be advised to keep track of their in-home fentanyl use by keeping a daily diary [13]. They should record all the variables that could affect medication performance, as summarized in Table 2. Keeping this pain diary can be helpful to reinforce patient treatment adherence. Ultimately, the objective is that the patients identify the most appropriate dosage of analgesic therapy by themselves, according to their individual characteristics and type of pain. Patients should be closely supervised until the optimal dose of BTcP analgesia is achieved.

Follow-up

Physicians should do an early assessment by telephone 48 hours after treatment initiation [11,57]. It is also recommended that patients contact their specialist if they have more than four BTcP episodes per day. Subsequent follow-up can be done

Table 2: List of recommended annotations in a patient daily diary for in-home fentanyl titration.

Time of each BTcP episode
Frequency of daily episodes
Duration and intensity (score) of the pain episodes
Fentanyl dose administered (concentration)
Number of daily fentanyl doses
Pain relief level obtained
Time to feel relief
Need to add extra dose of fentanyl to get relief
Adverse events
BTcP: breakthrough cancer pain

through scheduled visits or appointments at the patient's request.

Optimal cancer pain management will require continuous monitoring and patient reevaluation. Physicians should check for the following factors:

- Treatment efficacy.
- Any kind of change in the BTcP profile.
- Duration, frequency and intensity of BTcP episodes.
- Rescue medication dose.
- Pain relief level and duration after treatment.
- Side effects.
- Patient functionality.

Treatment withdrawal should start when patients achieve complete remission. Furthermore, patients with hard-to-control BTcP events should be referred to a pain specialist or to palliative medicine.

The need for a multidisciplinary approach

Cancer pain can be extremely difficult to manage because it is very heterogeneous and can vary significantly from one patient to another [12,23]. It is essential that patients and their families receive appropriate health education. Physicians should focus on explaining the different treatment options and the importance of early treatment initiation, to prevent low adherence rates to medication due to lack of confidence in the treatment or fear of possible side effects.

The most successful way to diagnose, treat and monitor patients suffering from BTcP is to establish a multidisciplinary approach. Since cancer pain occurs throughout the course of the disease, it is essential that all specialists who treat cancer patients are familiar with its detection and management. Close collaboration between medical specialists, nurses and primary care physicians will result in a more accurate diagnosis and optimal management of BTcP to the benefit of patients and their families. Primary care health professionals and nurses

are in the best position to identify problems and plan care accordingly. They have a crucial role in patient follow-up and in improving their quality of life, providing them with psychological support.

Discussion

Breakthrough cancer pain affects a large proportion of cancer patients, decreasing their quality of life. However, management of the disease is often unsatisfactory because it is based on old definitions and treatment algorithms. A European nursing survey performed in 2014 [58] showed that there is still high variability in the definition of BTcP used in different countries, resulting in poor patient management. A standardized, global consensus definition of BTcP and its symptomatology is needed to help doctors to correctly diagnose it. Similarly, treatment and monitoring guidelines should be standardized to provide patients worldwide with the best possible care. At present, different tools have been created to facilitate the correct diagnosis of BTcP [31–33]. Nonetheless, these instruments have only been validated in some countries, and need to be further approved to be introduced in other populations. There is therefore still a long way to go in order to standardize procedures, and to have a universal action protocol for the management of BTcP.

Although some controversy remains, enough clinical data has been generated to suggest that ROOs, specifically fentanyl formulations, should be the analgesic of choice for the pharmacological treatment of BTcP. However, they must be titrated carefully according to the patient's needs, age or presence of comorbidities in order to minimize the risk of clinically significant adverse effects. Many countries, including Spain, have national programs and guidelines for the safe use of ROOs [59]. Moreover, patients, doctors and pharmacists must receive proper education to be aware of all their possible risks.

Conclusions

In this paper, a group of Spanish experts in BTcP provide a series of practical recommendations to assist practitioners and clinicians in the current management of BTcP, based on a critical review of the evidence and their own extensive clinical experience. These recommendations include: performing a personalized initial evaluation of the patient, treating cancer pain by combining preventive measures with both pharmacological and non-pharmacological methods based on the patient's individual circumstances, and providing them with adequate health education from a multidisciplinary team.

Conflict of Interest

M^a Dolores López Alarcón has received payments for consultancies and lecture fees from Kyowa Kirin, Takeda, Gebro Pharma, Lab Esteve, Teva and Grünenthal. Francisco Villegas declares that he has received honoraria scientific advice from Esteve and acted as speaker for Takeda, Gebro Pharma, Grünenthal, Teva, Mylan, and Kyowa Kirin. Vicente Domingo Triadó reports having received payments for consultancies

and lecture fees from Kyowa Kirin and Grunenthal. Ana Blasco Cordellat declares that has collaborated with Kyowa Kirin, Takeda and Bristol-Myers Squibb as a consultant. Jorge Pastor Peidro has received payments for consultancies and advisory role from Grünenthal, Astellas Pharma, GP Pharm and Janssen Cilag. Carlos Ferrer Albiach has received payments for consultancies and lecture fees from Astellas Pharma, Janssen Cilag and Kyowa Kirin. Alfonso Berrocal reports having received consulting fees from Bristol-Myers Squibb, Novartis, Roche, Pierre Fabre, Pfizer, Merk, MSD, Amgen, Sanofi and acted as speaker for Bureau and Bristol-Myers Squibb. Almudena Ruiz, Genoveva Hernández Comes, Manuel Hernández Peris, Jose López Torrecilla and Pilar Blasco Segura have no conflicts of interest to declare.

Medical writing and editing services were provided by Medical Statistics Consulting S.L. (MSC) and funded by a grant from Kyowa Kirin Farmacéutica S.L.U.

All authors, as members of the scientific committee, were responsible and participated in data collection and interpretation and had access to full data and reports. In addition, all authors revised the manuscript versions and approved the final draft.

Acknowledgements

The authors thank Lucía Perez Carbonell and Vanessa Marfil Vives at MSC S.L. (Valencia, Spain) for editorial support in writing of this manuscript.

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