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Current controversies in the assessment and management of breakthrough cancer pain

Abstract

Breakthrough cancer pain is a common phenomenon, which is associated with a significant impact on quality of life. Management of BTcP is often suboptimal, and this reflects the heterogeneous nature of BTcP, and the often standardised (rather than individualized) management of BTcP. This article reviews national / international guidelines relating to BTcP, and highlights the ongoing controversies, such as the definition, diagnosis, and management of BTcP. However, many of these guidelines agree on the fundamental aspects of the management, and specifically about the important role of so-called "rapid onset opioids".

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Introduction

Breakthrough cancer pain (BTcP) is a common phenomenon, with a reported overall prevalence of 59.2% in patients with cancer pain [1]. It has a significant impact on quality of life, which relates not only to the pain itself [2], but also to the associated physical, psychological, and social problems [3]. Equally, it has a significant impact on health systems (due to the increased use of healthcare resources) [4].

Portenoy and Hagen first described the phenomenon of BTcP over 25 years ago [5]. Since then, many papers have been published on BTcP the topic, including many contemporary national/international guidelines on BTcP [6–14]. Nevertheless, there remain a number of controversies in terms of the definition, the diagnosis, and particularly the management of this condition.

The aim of this paper is to highlight these controversies, and to review the relevant recommendations in the national/international guidelines and relevant Delphi surveys of healthcare professionals [15, 16]. The Association for Palliative Medicine of Great Britain and Ireland (APM) recommendations were used as the so-called "reference" guideline for the discussion [6].

Definition of BTcP

As discussed above, there is no consensus on the definition of BTcP [17]. The latter is important in terms of extrapolating the results of research studies, and even the recommendations of key opinion leaders.

The APM defined BTcP as "a transient exacerbation of pain that occurs either spontaneously, or in relation to a specific predictable or unpredictable trigger, despite relatively stable and adequately controlled

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background pain” [6]. This definition was derived from an earlier one proposed by Portenoy et al. [18].

Some of the national/international guidelines endorse the APM definition [7, 9, 14], whereas others have developed their own definition for BTcP [8, 11, 13]. Interestingly, a recent Delphi process on the diagnosis and management of BTcP involving Spanish healthcare professionals reported the highest level of agreement for the APM definition of BTcP [16].

Diagnosis of BTcP

The APM developed a diagnostic algorithm for BTcP (Fig. 1) [6, 19]. The algorithm was derived from an earlier one proposed by Portenoy et al [20], and enables the clinician to differentiate between patients with BTcP, patients with uncontrolled pain, and patients with intermittent/‘transitory’ pain.

Again, some of the national/international guidelines endorse the APM algorithm [7–9, 12, 14], whereas others either use other published diagnostic criteria [11] or have developed their own diagnostic criteria [13]. Interestingly, another recent Delphi process on the definition, assessment, management, and monitoring of BTcP involving Spanish healthcare professionals reported universal agreement for the APM diagnostic algorithm for BTcP [15].

Webber et al have reported that the APM algorithm has a good positive predictive value (i.e. the proportion of patients who screen positively using the algorithm and are deemed to have BTcP by a pain specialist) [21]. It should be noted that, in this study, the ‘gold standard’ for diagnosing BTcP was a comprehensive assessment by a pain specialist, i.e. an experienced consultant in pain or palliative care.

Some definitions [5], and diagnostic criteria [20] use “moderate” as the cut-off between controlled background pain and uncontrolled background pain. However, Webber et al have reported that using moderate (rather than “mild”) as the cut-off resulted in a much lower positive predictive value (i.e. 0.68 vs. 0.84) [21]. Webber et al have also reported that some patients with moderate background pain feel that their background pain is “adequately controlled” [22].

Relationship to background pain

Breakthrough pain can only exist in the presence of background pain (see above) [6]. Nevertheless, patients with cancer may experience transient episodes of pain in the absence of background pain [23]. Recently, the term “episodic” pain has been suggested to describe these (and other) transient episodes of

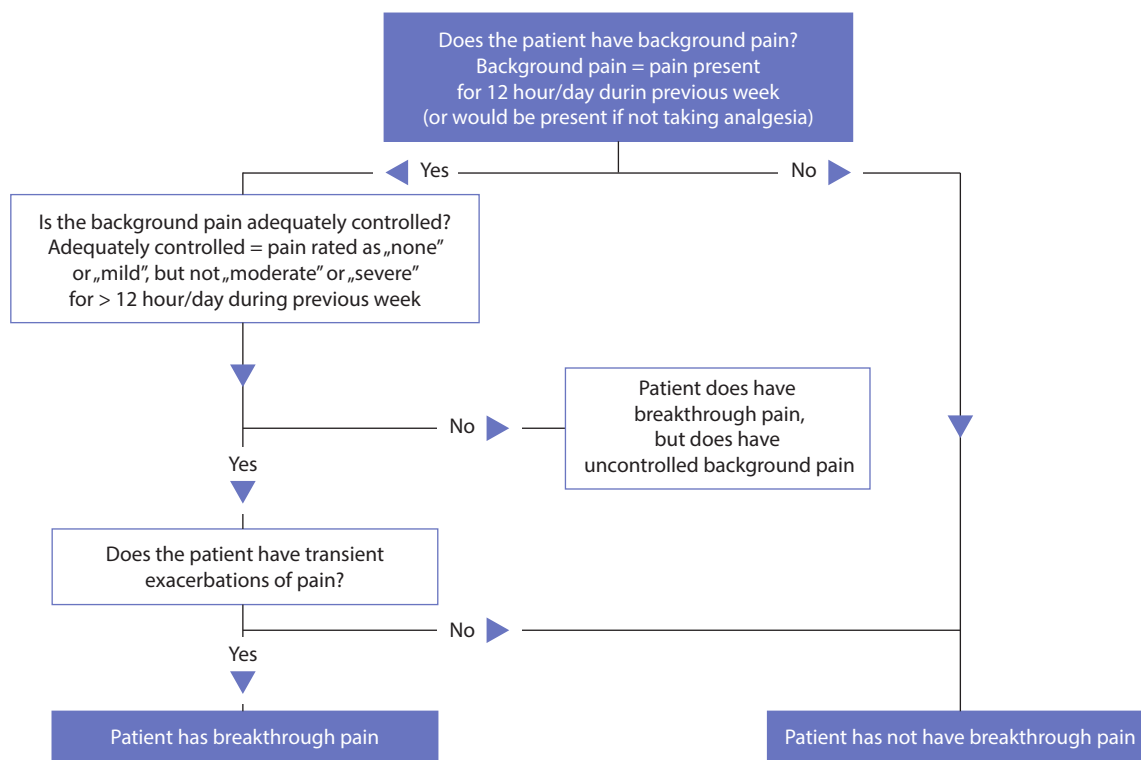


Figure 1. Association for Palliative Medicine of Great Britain and Ireland (APM) diagnostic algorithm for breakthrough cancer pain [6, 19]

pain that do not meet the diagnostic criteria for BTcP [24]. However, the choice of the term episodic pain is somewhat perplexing, because episodic pain has been used as a surrogate for BTcP in the past [25, 26].

Relationship to background medication

In 1990, Portenoy and Hagen defined BTcP as “a transitory exacerbation of pain that occurs on a background of otherwise stable pain in a patient receiving chronic opioid therapy” [5]. However, it was realised that the stipulation about background opioid medication was too restrictive [23], and so the definition was later amended to exclude any reference to background opioid medication [18].

The Spanish BTcP guideline’s definition of BTcP includes the use of opioid to control background pain [8]. However, the two Spanish Delphi surveys agreed that the prescription of a regular opioid was not required to make the diagnosis of BTcP [15, 16].

Frequency of BTcP episodes

Some authors have suggested that BTcP should be defined by the number of episodes per day, and that patients with more than four episodes per day should be considered to have uncontrolled pain, or should be treated in a different manner (i.e. modification of background medication rather than use of rapid-onset opioids) [9, 16]. It appears that the number four relates to the recommended dose frequency of so-called “rapid-onset opioids” (see later), rather than to any scientific rationale or data from clinical trials.

Choice of rescue medication

The APM recommendations state that opioids are the rescue medication of choice for BTcP, and that “the decision to use a specific opioid preparation should be based on a combination of the pain characteristics (onset, duration), the product characteristics (pharmacokinetics, pharmacodynamics), the patient’s previous response to opioids (efficacy, tolerability), and particularly the patient’s preference for an individual preparation” [6].

The APM guidelines highlighted that “the pharmacokinetic/pharmacodynamic profiles of oral opioids do not tend to mirror the temporal characteristics of most breakthrough pain episodes” [6].

A number of “rapid-onset opioids” are now available to treat BTcP (i.e. intranasal formulations, buccal formulations, sublingual formulations). Research suggests that they are very effective, and are more

effective than oral opioids [27, 28]. Moreover, research suggests that they are generally very well-tolerated.

However, the rapid-onset opioids are not a panacea for BTcP. For example, some pains are opioid poorly responsive, some pains are ultra-short in duration (which limits the efficacy of most pharmacological interventions), some patients are intolerant of fentanyl, and some patients have difficulty using specific rapid-onset opioids (e.g. patients with xerostomia may have difficulty with oral transmucosal formulations).

Recent BTcP guidelines support the preferential use of rapid-onset opioids (rather than oral opioids) [8, 11, 13, 14], and the recent Delphi processes involving Spanish healthcare professionals both reported high levels of agreement for the use of rapid-onset opioids to manage BTcP [15, 16].

It should be noted that some generic cancer pain guidelines continue to recommend the use of oral opioids to manage BTcP [29, 30]. One of the reasons for the continued promotion of oral opioids is the need to use as-required medication in patients with uncontrolled background pain (i.e. during opioid initiation/titration): these flares of pain are often still inappropriately referred to as breakthrough pain. However, the treatment of choice in this situation is invariably an oral opioid (not a rapid-onset opioid). Another reason for the continued promotion of the use of oral opioids is monetary (i.e. the higher cost of rapid-onset opioids vs the cost of oral opioids) [30], although the use of ineffective medication will lead to increased use of healthcare resources (and thus to higher costs) [4].

Titration of rescue medication

The APM recommendations state that the dose of rescue medication should be determined by individual titration. This advice was based upon data from several randomized controlled trials) [31–34], and mirrors the advice in the prescribing information (Summary of Product Characteristics [SmPC]) for all rapid-onset opioids [35]. It should be noted that, although most of the data on titration relate to rapid-onset opioids, there is analogous data on titration of oral opioids (i.e. oral morphine) [32]. This recommendation for titration is endorsed by most of the other guidelines [7–9, 11, 14].

Nevertheless, the view has been expressed by one key opinion leader that ‘fixed’ doses of rescue medication should be used rather than dose titration of rescue medication. Thus, it is suggested that the dose of rescue medication administered should be a proportion of the dose of the background (‘around the clock’) medication administered [36, 37]. Interestingly, however, the Italian BTcP guidelines

recommend a hybrid method of rapid titration in “highly (*opioid*) tolerant patients” (i.e. missing out some steps/doses) [13].

Frequency of rescue medication

The Summary of Product Characteristics (SmPC) of most rapid-onset opioids state that they should be used to treat no more than four BTcP episodes per day, which reflects the maximum usage in the relevant pivotal clinical studies [35]. However, there is no pharmacologic reason to restrict the use of rapid-onset opioids to four times daily and, indeed, clinicians do so without any problems in selected patients [11].

Abuse/addiction of rescue medication

In many countries, restrictions have been imposed on the prescribing of rapid-onset opioids due to concerns about abuse/addiction. However, although opioid addiction is a major problem throughout the world, it does not appear to be a major problem in patients treated for cancer pain [38], or in those treated for BTcP with rapid-onset opioids [39].

Conflict of interest

Dr. Andrew Davies has received honoraria for speaking at satellite symposia from Angelini, Menarini, Prostrakan, Takeda, and Teva; honoraria for attending advisory boards from Grunenthal, MEDA, Nycomed, Prostrakan, and Teva; and unrestricted research grants from Cephalon, Prostrakan, and Takeda.

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