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Breakthrough Cancer Pain: Ten Commandments

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ABSTRACT

The term "breakthrough cancer pain" (BTcP) was introduced about 25 years ago. Peaks of pain intensity reported in patients with cancer had been invariably examined in the past years, providing relevant information for a better knowledge of this phenomenon and its treatment. The aim of this critical review was to provide the golden rules, namely, the 10 commandments, for a correct diagnostic pathway of BTcP and a consequent personalized pharmacological treatment. These are as follows: 1) assessment of background analgesia, 2) drugs used for background analgesia, 3) BTcP is a frequent phenomenon, 4) characteristics of BTcP, 5) diagnosis of BTcP, 6) continuous assessment, 7) tailored pharmacological treatment of BTcP, 8) selection of BTcP medication, 9) dosing BTcP medications, and 10) education. These steps may help clinicians to recognize and treat BTcP adequately.

Keywords: breakthrough cancer pain, cancer pain, opioids.

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Introduction

The term "breakthrough cancer pain" (BTcP) was introduced about 25 years ago [1]. This pioneer study suggested that there is a temporal variability in pain intensity with peaks interrupting a state of adequate analgesia. At that time, the variability of pain had already been considered because some tools designed for pain assessment tried to explore this condition by measuring pain at its "worst," "least," "average," and "now" [2,3]. This concept has changed the way of managing cancer pain. Patients with cancer pain were traditionally treated with oral opioids, namely, immediate-release morphine at regular intervals (every 4 hours), providing the same dose when the pain got severe [4], particularly during opioid dose titration, until achieving an adequate analgesia. It was implicit that the same dose could be given every time the pain worsened. Doses were then increased on the basis of the average or worst pain. This approach was frequently associated with the prevalence of central adverse effects. Portenoy et al. [1,5] suggested that pain could be adequately controlled for most hours of the day with analgesics given at regular intervals, whereas the peaks of pain intensity could be separately treated with other therapeutic options providing fast and short analgesia. These peaks of pain intensity reported in patients with cancer had been invariably examined in the past years, providing relevant information for a better knowledge of this phenomenon and its treatment. The aim of this critical review was to provide the golden rules, namely, the 10 commandments, for a correct diagnostic pathway of BTcP and a consequent personalized pharmacological treatment. Table 1

First Commandment: Background Analgesia

Background analgesia should be carefully assessed. Studies have invariably considered BTcP as a transitory increase in pain to greater than moderate intensity that occurs on a baseline pain of moderate intensity or less. This definition, however, could be ambiguous because background pain and BTcP may overlap and then cannot be easily distinguished. Moderate pain is often worthwhile of treatment or therapeutic refinements because of its interference with most quality-of-life issues [6]. Indeed, most epidemiological surveys did not provide a definition a priori, and so a large variability has been reported for this phenomenon [7]. Literature has reported several surveys in which BTcP was analyzed in patients who did not have an appropriate background analgesia, that is, the preliminary criterion for a diagnosis of BTcP. Patients were undertreated or had insufficient analgesia. Indeed, optimization of background pain is mandatory before taking BTcP into consideration [8]. End-of-dose failure, initially constituting a subtype of BTcP [1], is no longer considered as such, but is rather a form of uncontrolled pain requiring some adjustment of opioid therapy [9,10]. Thus, before considering BTcP, the intensity of background pain should be mild for most

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hours of the day and most efforts should be dedicated to optimize basal pain control [8,9,11].

Second Commandment: Drugs Used for Background Analgesia

In the subsequent years a more meaningful definition of BTcP was proposed, which included the introduction of a second variable—the use of stable doses of opioids that are able to maintain baseline pain control [5,12]. In many studies, the use of nonopioids or opioids for moderate pain for background analgesia resulting in poor pain control has dramatically confounded the epidemiological picture of this phenomenon [13–20]. It is likely that *BTcP* should be more correctly defined as an episode of severe pain intensity in patients receiving an adequate treatment with opioids that are able to provide at least mild background analgesia [9–11].

Third Commandment: Breakthrough Pain Exists!

Different BTcP prevalence rates, ranging from 30% to 90%, have been reported in literature. As mentioned earlier, many epidemiological studies did not provide a definition a priori, and so in a recent review a large variability has been reported for this phenomenon, in which articles were mixed without considering the minimal data set to describe BTcP [7]. According to the first two commandments, differences in the evaluation of baseline pain and BTcP episodes and the use of nonopioid analgesics have dramatically confounded the epidemiological data [13–20]. Nevertheless, the phenomenon exists and involves three-fourth of patients, even when receiving optimized opioid therapy that provides mild background analgesia [9]. Some studies have shown that the prevalence and characteristics of BTcP may change through the course of disease [21,22]. In patients with advanced cancer with a lower performance status, the prevalence of BTcP could be lower, possibly because of a reduced incident pain component, given the limited physical activity [23].

Fourth Commandment: Characteristics of BTcP

Several studies have shown that BTcP is not a unique entity, but a heterogeneous condition because episodes vary between individuals and also within individuals. Two large subclasses have been identified. Spontaneous-type BTcP, often named idiopathic, is when BTcP occurs with no identifiable cause or precipitant event. Generally, the onset and duration of this BTcP subtype may be longer [23,24]. Predictable incident-type pain is when BTcP is triggered by an identifiable event, typically the movement in patients with bone metastases or swallowing in patients with oral mucositis. The onset of this subtype of BTcP is rapid and the duration is shorter [23,24]. 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 [5]. Nevertheless, the modalities of BTcP development may be different even in these subcategories. There are some typical episodes that are triggered by several factors, for example, incident pain due to bone metastases, which can occur more frequently. Most of these BTcP episodes are elicited by physical activity in the presence of bone metastases. Stopping the physical activity or the movement inducing pain may spontaneously subside the episode. In some cases, pain develops every time the patient tries to move and is potentially self-limited because it often depends on the will of maintaining an activity or resting. In other cases, this kind of pain can persist, lasting even after the patient stops the activity. This status corresponds to a relevant interference with daily living because patients may prefer to limit their activity to avoid triggering BTcP or use individual strategies in their daily life to prevent the occurrence of BTcP.

Thus, the focus of the treatment should be to find a compromise between activity and background analgesia. It is of interest that in a subclass of patients with abdominal disease, it has been estimated that about 55% of the patients with well-controlled background pain will develop BTcP episodes. This percentage was estimated to be higher (about 90%) in patients who presented with uncontrolled background pain, underlying the need to better characterize patients with BTcP only after a careful optimization of basal pain, as considered by the definition of BTcP [25].

The characteristics of BTcP can change during the course of disease. Patients with advanced cancer in a setting of palliative care were older, had lower Karnofsky levels, a lower number of BTcP episodes per day, a slower onset of BTcP, and a less predictable BTcP than did patients assessed in a pain clinic or an oncological ward [21–23].

Fifth Commandment: Making a Diagnosis, the Loop of Commandments 1 to 4

It is difficult to have a clear idea of a complex phenomenon without a prospective evaluation and an optimized analgesic approach for baseline pain. Thus, it is likely that *BTcP* be more correctly defined, according to the previous commandments, as an episode of severe pain intensity in patients receiving an adequate treatment with opioids that are able to provide at least mild analgesia [9–11]. A clear distinction between levels of pain intensity commonly considered to be acceptable ($\leq$4 on a numerical scale of 0–10) and BTcP, which is a severe episodic pain ($\geq$7 on a numerical scale of 0–10), is needed. It has recently been found that in patients with baseline pain of mild intensity ($\leq$4 on a numerical scale of 0–10), the meaningful pain intensity for asking for a BTcP medication was about 7 or more [9,11]. Although there might be variations in individuals, these levels of pain intensity are widely used for defining mild pain ($\leq$4 on a numerical scale of 0–10) and severe pain ($\geq$7 on a numerical scale of 0–10) [6]. This aspect has obvious implications from both the epidemiological and the therapeutic points of view.

Sixth Commandment: Assessment

A specific assessment should be performed in individuals to provide further information for a specific treatment. Several tools to assess patients' experience of BTcP have been proposed, but only a minority have been partially validated [26].

Some questionnaires have been developed to assess BTcP. A Delphi instrument was developed, followed by patient pretesting on the clarity and feasibility of completing the instrument, and submitted to a panel of national and international experts to provide indications to screen BTcP, attempting to group the principal items commonly used in the clinical setting. Key issues included the relationship with baseline pain, the last time when BTcP was experienced, frequency, intensity of pain at peak, location, quality, time from onset to peak intensity, duration, causes, predictability, general relief, relief from BTcP medication, satisfaction with BTcP medication, onset of pain relief, and satisfaction with onset of pain relief. Other items completed by professionals included etiology of BTcP and inferred pathophysiology of BTcP [27]. More recently, a new assessment tool for BTcP has been developed. This instrument provides information on how BTcP and the efficacy and toxicity of BTcP medications may interfere with daily life. Reliability and validity of the tool tested on a group of patients was reasonably good [28].

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