

Breakthrough cancer pain in 2020

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Structured abstract (max 200 words):

Purpose of the review: An overview on breakthrough cancer pain (BTCP), including inherent limitations of the terminology, assessment, clinical presentation, and treatment options.

Recent findings: The estimated prevalence of BTCP is dependent on the defined cutoffs for controlled background pain and the magnitude of the pain flare. In addition, pain flares outside the definition of BTCP are prevalent. In the 11th Revision of the International Classification of Diseases (ICD-11), the temporal characteristics of cancer pain are described as continuous background pain and intermittent episodic pain. BTCP should be assessed by validated methods, and the patient perspective should be included. The pain may be related to neoplastic destruction of bone, viscera, or nerve tissue and is characterized by rapid onset, high intensity, and short duration. Treatment directed towards painful metastases must be considered. Due to pharmacological properties mirroring the pain characteristics, transmucosal fentanyl formulations are important for the treatment of BTCP. Oral immediate release opioids can be used for slow-onset or predictable BTCP. For more difficult pain conditions, parenteral, or even intrathecal pain medication, may be indicated.

Summary: All clinically relevant episodic pains must be adequately treated in accordance with the patient's preferences. Transmucosal fentanyl formulations are effective for BTCP.

Abstract: 199 words (abstract subheadings included)

Keywords (3-5): Breakthrough cancer pain, episodic pain, transmucosal fentanyl formulations

Words: 2500

Bulleted references:

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3. Fallon, ESMO Guidelines

- Clinical practice guidelines for management of cancer pain, BTCP included

4. Løhre, In-hospital clinical care pathway

- The study describes a structured approach for improvement of cancer pain management

11. Davies, BTCP Guidelines

- An important contribution towards standardization of BTCP research and management

13. Løhre, Pain intensity factors

- A paper describing inherent limitations of the BTCP terminology

22. Mercadante, Factors influencing BTCP presentation

- To date, the largest survey on BTCP epidemiology

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10. Bennett, IASP classification for ICD-11

- The paper describes a classification system for cancer-related pain based on etiology and pathophysiology. The underlying logic for the classification system is that correct identification of the nature and cause of cancer pain will facilitate tailored treatment and hence optimal pain control.

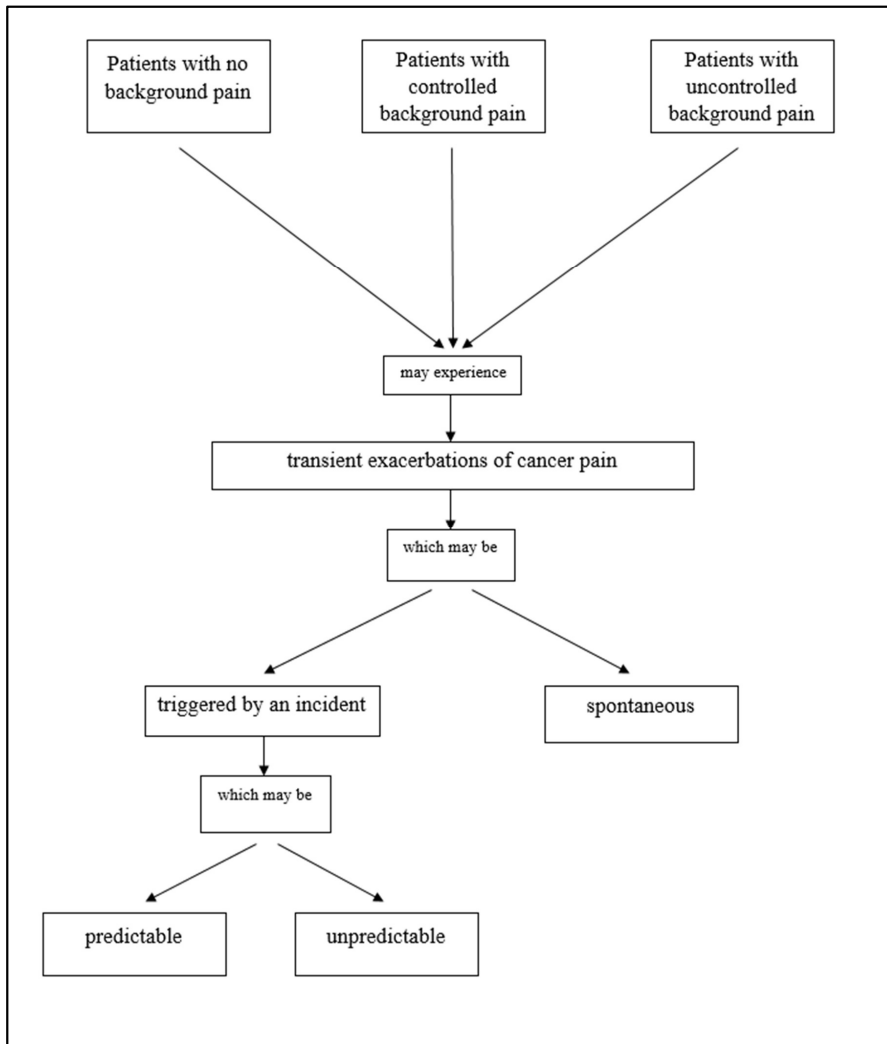
Introduction

Despite increased attention to cancer pain, pain prevalence in cancer patients has not changed significantly over the past decades (1). Cancer pain is undertreated in about one out of three patients, and deficiencies in cancer pain assessment and management may contribute to this lack of success (2). Evaluations of both background pain intensity and worst pain intensity are considered important, as information on the temporal pattern of pain is essential for adequate pain management (3). Recent research has demonstrated that structured pain assessment, reflecting available treatment options for both background pain and intermittent pain flares and including the patient perspective, can result in significantly reduced pain intensity (4). This provided the information is utilized systematically in cancer pain management based on pathophysiological pain mechanisms and evidence-based principles (4).

Breakthrough cancer pain (BTCP) is as an episode of severe pain that “breaks through” the persistent and controlled chronic pain (5). The presence of BTCP is deemed to have a negative impact on general activities and pain management (6). The reported prevalence is dependent on the population studied and ranges from approximately 40% to 80% (7). In addition, the diagnosis of BTCP is dependent on the definitional criteria (5). Almost ten years ago, the European Society for Medical Oncology (ESMO) clinical guidelines on cancer pain management stated that the lack of strict definitional criteria for BCTP may result in large prevalence variability (8). With a lowered cutoff for controlled background pain intensity (from moderate to mild) in the definition of BTCP, the reported prevalence seem to decrease (7). Participants in a previous expert Delphi study on BTCP agreed that the term episodic pain could serve as an overarching terminology for all significant transient cancer pain exacerbations (9) (Fig.). In the proposed 11th Revision of the International Classification of Diseases (ICD-11), the temporal characteristics of cancer pain are described in terms of the continuous background pain and the intermittent episodic pain, without the inclusion of the term BTCP (10). This simplified approach may represent a useful opportunity for tailored treatment of both background cancer pain intensity and worst cancer pain intensity, possibly by a combination of traditional opioids and more novel preparations and formulations (3). Furthermore, in ICD-11 chronic cancer pain is

classified by etiology and pathophysiology into bone pain, neuropathic pain and visceral pain, because correct identification of the nature and cause of cancer pain facilitates tailored treatment and hence optimal pain control (10). We believe this classification also might provide relevant information for the management of BTCP.

Fig. Transient cancer pain exacerbations regardless of background pain intensity



Definitions and terminology

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Three decades of research has not resulted in consensus on the definition and diagnostic criteria of BTCP (11). However, there is agreement that the BTCP patient must have background pain, which must be controlled, and, in addition, transient exacerbations of cancer pain (12). A review of guidelines on BTCP management found that both variable definitions and diagnostic criteria were used (11). How BTCP prevalence estimates are influenced by the definition of the condition is demonstrated (13). A change in the cutoff for controlled background pain intensity from 3 to 4 on the eleven point numeric rating scale (NRS 0-10) increased the estimated prevalence from 15% to 20%, and a cutoff for background pain intensity at NRS 6 increased the BTCP prevalence estimate to more than 30%. Moreover, the magnitude of the pain intensity increase for a transient cancer pain exacerbation to be defined as BTCP is important (13). In addition, pain flares outside the definition of BTCP are prevalent (13). We endorse the call for international consensus on strict definition and diagnosis criteria of BTCP (11). Today, a simple clinical algorithm for the diagnosis of BTCP is widely used, and it may serve as the basis for further development (3, 12). In addition, episodic pain outside the definition of BTCP must be accounted for in research and addressed in clinical practice (13).

Assessment including the patient perspective

As a minimum, patients with cancer-related pain should receive pain assessment which classifies the pain based on the proposed ICD-11 taxonomy and establishes the intensity and the impact of the pain they report (14). Moreover, it is recommended that patients with cancer pain should be assessed for the presence of BTCP, and, if identified, that this pain should be specifically assessed (11). The updated ESMO clinical practice guidelines on cancer pain describes a breakthrough pain assessment tool (BAT) validated in cancer patients (3, 15). With advances in health information technology, the use of electronic tools may further improve the ongoing symptom evaluation pivotal for modern cancer pain management (16). Electronic symptom assessment has demonstrated a potential for both

clinical benefits and improved survival in cancer care (16, 17). The introduction of a mobile application for the diagnosis and monitoring of BTCP was found useful in a study among 175 experienced physicians (18). Additionally, the study participants acknowledged the usefulness of supplementary content to guide their decision-making.

The importance of the patient perspective is emphasized in modern medicine (16). The use of patient-reported outcome measures and a shared decision-making process can facilitate patient involvement in treatment planning (16). Evaluation of self-reported pain intensity is the first step towards effective and individualized treatment of cancer pain (3). The patient-reported pain site provides important diagnostic information, and the classic perception that BTCP often occurs at the same location as the background pain, and represents a brief flare-up of the background pain, is also confirmed in recent research (19, 20). Additionally, data from a pilot study suggest that patients use qualitatively similar pain descriptors for background pain and BTCP (21).

Clinical presentation

BTCP may occur in patients with cancer growth affecting bone, soft tissue, viscera, and the nervous system (22, 23). Up to 50% of the patients experience two or more types of BTCP, which in approximately one third of the patients is predictable (22, 24). A neuropathic pain mechanism is associated with more unpredictable pain flares and a longer time to achieve stable pain control (22, 23). Time to maximum pain intensity is less than ten minutes in about two thirds of the patients, and the mean duration of an untreated BTCP episode can be up three quarters of an hour (22). Mean pain intensity is often > NRS 7 (22, 25), and the pain flares may follow a circadian rhythm (26). These pain characteristics emphasize the importance of knowledge of the treatment principles for cancer pain due to various pathophysiological pain mechanisms, and availability of opioids and routes of administration suitable to relieve the transient cancer pain exacerbations.

Genetic polymorphisms and opioids

The genetics of pain is subject to research, and more than 400 genes are currently considered potential pain modulators (27). Normal genetic and pharmacokinetic variability may result in individual differences in both treatment responses and adverse effects of opioids (28). So far, the available knowledge on gene polymorphisms affecting opioid responses has little impact on clinical cancer pain guidelines and practice (28). Still, there is strong evidence to support individualization of pain treatment due to individual differences in opioid receptors and opioid metabolism (28). Therefore, unexpected opioid effects and side effects in cancer pain management should call for considerations on genetic variability.

Treatment alternatives

BTCP should be treated with a rescue medicine, and opioids are the medication of choice for exacerbations of cancer pain (11, 29). Oral morphine is often recommended as first line therapy for moderate to strong cancer pain, with oral oxycodone or oral hydromorphone as effective alternatives (3, 27). For severe cancer pain requiring rapid pain relief, parenteral approaches should be applied, with intravenous administration providing the most immediate effect (27). Parenteral opioids may also be administered by the patients, with the use of a patient-controlled analgesia device (30). Oral opioids, and oral immediate release morphine in particular, have traditionally been the standard treatment approach for transient cancer pain exacerbations (3). However, with a peak analgesic activity approximately one hour after intake, oral immediate release morphine may not be an ideal treatment option for a typical BTCP episode (22, 27).

Fentanyl is a lipid-soluble, synthetic opioid analgesic, up to 100 times more potent, and crossing the blood-brain barrier more quickly, than morphine (31). Fentanyl is metabolized by cytochrome enzymes, and any drug that induces or inhibits cytochrome P-450 can affect its metabolic conversion (31). Guidelines emphasize the important role of transmucosal fentanyl formulations for the treatment

of BTCP, and placebo-controlled randomized controlled trials have demonstrated the efficacy of the available transmucosal fentanyl formulations (3, 11). Fentanyl for BTCP may be administered intranasally or intraorally by different formulations like spray, soluble tablets, films, or lozenges (31, 32). The different formulations are not compared head-to-head in double-blinded randomized trials, and there is no evidence for the superiority of any particular formulation (3, 32, 33). Hence, before selecting the most suitable formulation, the pros and cons of each formulation should be discussed with the patient (32). [The presence of mucositis or xerostomia may be relevant aspects of the discussion \(31, 32\).](#) Due to differences in absorption profiles and bioavailability, the different products cannot be compared on a microgram-to-microgram basis (31). The products are tested in opioid-tolerant patients and recommended only for patients receiving at least 60 mg oral morphine equivalents per day (3). Additionally, a careful dose titration is recommended (3). Advantages of transmucosal fentanyl formulations are the rapid onset of effect and short duration, mirroring the clinical presentation of a BTCP episode (3, 31, 32, 34). On the other hand, the potency and rapid onset also raise concerns about misuse and overdoses (31). Furthermore, a long titration phase may result in a period of inadequate pain management for the patient (32, 34). Age, comorbidity, and cancer-related or cancer treatment-related factors may limit the possibilities for correct use of the transmucosal fentanyl formulations, which also may cause both systemic and local side effects (31).

Treatment challenges

Different pain etiologies and pathophysiological mechanisms may call for different treatment modalities. Single-fraction radiotherapy may relieve pain from bone metastases, as adjuvant drugs and nerve blocks may relieve pain from cancer-related neuropathic and visceral pain (3). Still, BTCP may occur at the respective pain localizations and require specific attention. A predictable pain flare, induced by e.g. eating or movement, may be handled by a planned administration of immediate release oral opioids prior to the activity (3, 22). Then, the delayed onset of analgesic effect must be taken into consideration (3, 35). However, a rapid-onset predictable BTCP may be more adequately handled with

the use of transmucosal fentanyl formulations or patient-controlled parenteral analgesia (3, 27, 35). The unpredictable nature of pain flares with a neuropathic pain component demands pain management providing rapid symptom relief (22). For patients with episodic pain triggered by an incident, but otherwise not satisfying the criteria for BTCP and using less than 60 mg oral morphine equivalents per day, transmucosal fentanyl formulations are currently not recommended (3, 12). However, in a pilot study nasal fentanyl was successfully administered to opioid naïve cancer patients (36). In older patients, the inherent frailty of the population must be acknowledged (37). Hence, a more cautious dose adjustment, following the principle “start low and go slow”, is recommended (36). For severe cancer pain, parenteral administration of opioids may be necessary (27). In the case of refractory pain, the indication for invasive pain management, like intrathecal drug delivery, should be evaluated (3).

Current guidelines

A paper reviewing international and national guidelines on BTCP management, reported good general agreement between the guidelines (11). The disparities represented opinions rather than research evidence, but the evidence supporting the guidelines was low grade (11). Moreover, as generic cancer pain guidelines often advocate the use of oral opioids as rescue medication, the specific BTCP guidelines endorse the use of transmucosal opioids as rescue medication (3, 11). The ESMO clinical practice guidelines on cancer pain in adult patients recommend the use of immediate release opioids to treat BTCP in opioid-responsive patients (3). Transmucosal fentanyl formulations have a role in unpredictable and rapid-onset BTCP (3). There are indications for immediate release oral opioids for slow-onset BTCP and pain flares triggered by known events, provided the opioid is administered early enough to supply pain relief (3). The World Health Organization Guidelines for the pharmacological and radiotherapeutic management of cancer pain in adults and adolescents suggest a rescue dose of immediate release morphine equivalent to 50-100% of the regular 4-hourly dose (29). This is similar to the ESMO guidelines’ recommendation of a breakthrough dose equivalent to 10–15% of the daily

opioid dose (3). For transmucosal fentanyl formulations, a low initial dose followed by a dose titration is recommended (3).

Tailored treatment

Standards for pain management may improve outcomes and reduce quality variations, both on a general and individual level (14). A pain management plan, explaining the causes and prognosis of the pain and the multimodal treatment options, should be developed in agreement with the patient (14). Considerations must be put into factors like age, previous history, organ function, and potential drug interactions (27). In addition, pain characteristics, pharmacologic properties of the envisaged drug(s), and the patient perspective are necessary to address (27).

Most guidelines endorse individualized treatment of BTCP (11). A thorough evaluation of the around the clock opioid regimen and pain characteristics is paramount when treating BTCP, as well as other clinically relevant episodic pains (38). Furthermore, the pain flares must be treated by opioids with pharmacological properties suitable for the pain characteristics (39). In addition, patient preferences are important when deciding on BTCP medication (38). Dosing recommendations are formulated for the transmucosal fentanyl products as a group (3, 11). Recent research suggest both effectiveness and safety of doses proportional to opioid doses used for background pain (3, 34, 40).

Management recommendations

Cancer pain assessment should include evaluations of both background pain intensity and worst pain intensity. The patient perspective should be an integral part of the assessment, and satisfaction with the pain treatment is a natural aspect of the patient perspective. Based on the pathophysiological pain mechanisms, specific interventions like single-fraction radiotherapy for painful bone metastases should be considered, as this may have a positive impact on both background pain intensity and worst pain intensity. Around the clock opioid medication should be adjusted to maximize effect and

minimize side effects. A need for more than four rescue doses per day usually calls for adaption of the baseline opioid regimen (3). In addition, independent of an uncontrolled, controlled, or absent background pain, the episodes of worst pain that “breaks through” a stable situation must be treated adequately. The drug and administration route of choice should provide pharmacological effects mirroring the clinical presentation of the pain intensification. Transmucosal fentanyl formulations are recommended for BTCP. For opioid naive patients, slow onset pain episodes, and before activities causing pain, immediate release oral opioids may provide pain relief. However, the relatively slow onset of effect must be considered when preparing a pain management plan. For refractory cancer pain, parenteral and invasive pain management is recommended.

Conclusion

Clinically significant transient cancer pain exacerbations should be adequately treated. International consensus on the definitional criteria of BTCP might facilitate the achievement of this goal.

Transmucosal fentanyl formulations are important in the treatment of BTCP, but other interventions such as oral opioids, parenteral opioids or neuroaxial analgesia may be indicated in selected patients.

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