Guidelines for the Management of Breakthrough Pain in Patients With Cancer

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Abstract

The moral imperative to adequately manage pain is being increasingly recognized worldwide. A comprehensive pain management approach that addresses the various presentations of pain in patients with cancer is required, including appropriate management of breakthrough pain. Breakthrough pain commonly occurs in patients with advanced cancer and is disabling to the individual and burdensome to society, yet it is often inadequately managed. Because pain is heterogeneous, the best management of an individual’s pain, including breakthrough pain in cancer, requires a thorough assessment to tailor the treatment strategies. Recently developed guidelines support this approach and recommend treating breakthrough pain using rapid- or short-acting opioids with pharmacodynamics that mirror the rapid onset and short duration of the presenting pain. This approach should be part of a comprehensive strategy to treat pain within the context of the primary disease trajectory, offering continuity of care and access to specialized palliative care when appropriate. JNCCN 2013;11(Supp 1):S29–S36

Adequate Pain Management: A Fundamental Human Right

Recognition of the prevalence and impact of pain has spread to policymakers and health care providers worldwide. In 2010, the first International Pain Summit was held in conjunction with the International Association for the Study of Pain World Congress on Pain. More than 250 representatives from 84 countries provided input to produce the Declaration of Montreal, with the hope of heightening the awareness of the burden of unrelieved pain in the world and to declare a moral imperative for policymakers and health care providers to address this worldwide public health problem.

The Declaration of Montreal states that all people have the right to pain management by adequately trained professionals, and the right to be informed about how pain will be assessed and managed. The unnecessary suffering caused by unrelieved pain was attributed to factors such as inadequate access to appropriate analgesics, major deficits in knowledge among health care professionals regarding the mechanisms and management of pain, lack of recognition of pain medicine as a specialty, and lack of adequate national policies in most countries.

Although most countries have limited or absent consideration of pain management in their health policies, the right to pain management is beginning to attain legal status. For example, in France in June 1999 and in Italy in March 2010, laws granting all citizens legal access to palliative care and pain management were ratified by the parliaments. These laws oblige the governments and health care institutions to establish policies and systems to promote adequate pain management, and require all health care professionals to offer patients competent pain management, including regular, documented assessments of pain. In 2006 the
number of opioids prescribed in Italy was one of the lowest in Europe.2,4 Since then, the number of opioid prescriptions in the country has increased,3 as was similarly observed 10 years earlier in France.6

The Impact of Comprehensive Cancer Pain Assessment and Breakthrough Pain

Although the importance of pain management is beginning to be recognized worldwide, patients with cancer need a comprehensive treatment plan that not only addresses the moderate-to-severe background pain that occurs in many patients with advanced cancer7 but also adequately manages the separate and characteristically different presentation that is breakthrough pain. Pain assessment is an important part of this strategy, recognizing that one of the factors contributing to the undertreatment of cancer pain is the lack of standardized, appropriate pain assessment and classification methods. Some clinical factors have been associated with a relatively unfavorable outcome of analgesic treatments, and recent research data highlight the clinical relevance of incident or breakthrough pain, neuropathic pain, pain intensity, and psychological distress among the most relevant indicators of the complexity of the pain syndrome at the individual patient level.8,9 The need for guidelines for accurate diagnosis and treatment of breakthrough pain in cancer is therefore the focus of this article.

The Definition of Breakthrough Pain

Breakthrough pain has been defined in recent guidelines as “transitory exacerbations of pain that occur on a background of stable pain otherwise adequately controlled by around-the-clock opioid therapy”7 or 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 background pain.”10 Background pain that is uncontrolled or poorly controlled near the end of a dose period because of the decreasing concentration of analgesic is generally not considered breakthrough pain; rather this is referred to as “end-of-dose failure.”10,11

Breakthrough pain can have various pathophysiologies (nociceptive, neuropathic, mixed) and different and multiple causes, such as cancer, cancer treatment, or comorbidities.12 Breakthrough pain is generally categorized as “spontaneous” when unpredictable, or “incident” when it is associated with an identifiable cause.10 Although the clinical characteristics of breakthrough pain vary, typically it has a rapid onset (median interval of 3 minutes to peak pain), short duration (median, 30–60 minutes), and high severity.12-15 Studies have reported that the number of daily episodes of breakthrough pain range from 1 to greater than 10, with a median of 4 episodes per day.12-14 Compared with patients without breakthrough pain, patients who experience it have significantly greater pain-related functional impairment16 and psychological distress, such as depression and anxiety (P<.001),13 and a significantly reduced quality of life (P<.001).17 Unrelieved breakthrough pain can be debilitating to individuals and burdensome to the health care system, with high costs of care from increased emergency and medical visits, more hospital admissions, and longer in-hospital stays.18

Diagnosing Breakthrough Pain

In the Western world, management of cancer pain is often oversimplified by reliance on the WHO analgesic ladder,19,20 which actually encompasses a small portion of the WHO guideline. Assessment and treatment of the underlying cancer condition are 2 critical and underrecognized aspects of adequate pain management. Oncology patients are often not systematically assessed. Without the proper diagnosis, treatment will likely be suboptimal (eg, underestimating the role of palliative radiation therapy for pain control); reassessment of pain and cancer stage is an essential aspect of ongoing patient care.10

Assessment is also a key step toward adequately managing breakthrough pain in cancer, which is an extraordinarily heterogeneous condition involving different underlying diseases, clinical features, and natural histories.10 Hence, a thorough assessment is required to identify tailored treatment strategies that are necessary to best manage an individual’s pain. A few key questions can be used to determine whether a patient is experiencing breakthrough pain. An algorithm for diagnosing patients with breakthrough pain is presented in Figure 1.10 The algorithm indicates that baseline pain must be adequately controlled.
before a diagnosis of breakthrough pain can be considered. Strategies needed to improve baseline pain control include opioid titration, the use of adjuvant analgesics, and other interventions.7,11

The initial assessment should endeavor to identify the pain’s origin (cancer, treatment, and/or comorbidities) and pathophysiology (nociceptive, neuropathic, or mixed), and any factors that would affect treatment. In the guidelines on managing breakthrough pain in cancer created by a group of palliative care specialists under the auspices of the Association for Palliative Medicine of Great Britain and Ireland, the first recommendation is to conduct an assessment to differentiate uncontrolled background pain from controlled background pain with episodes of breakthrough pain10; this recommendation is also the keystone of the French Breakthrough Cancer Pain guidelines.21 These 2 different clinical scenarios require different approaches to treatment. Subsequently, the outcomes of treatment are critical to assess and reassess, including whether the patient is consistently taking the treatment as prescribed, and if not, determining why, and if so, determining how effective and tolerable the treatment is.

Overall, the assessment of breakthrough pain in cancer is the same as that of other types of pain. Patient history is the primary source of information about breakthrough pain and therefore this evaluation should be thorough. Additionally, a physical examination and relevant testing can provide other important information supporting a differential diagnosis. Assessment must be focused on relevant aspects of breakthrough pain. Key questions used to characterize this pain are detailed in Table 1.10 All information obtained during assessment should be recorded in the patient’s medical history, including a record of episodes of breakthrough cancer pain. An assessment tool can also be an effective way to probe and document the characteristics of a patient’s breakthrough pain.

The special difficulties associated with reliably diagnosing breakthrough pain in cancer have been demonstrated in an international study of cancer pain characteristics and syndromes. Therein, the prevalence of breakthrough pain in cancer varied according to the nationality of the researcher.22 Similarly, variability in the clinical criteria used by physicians to identify breakthrough pain in cancer was also observed in a second multicenter national survey study. The authors found that the identified prevalence of breakthrough pain in cancer differed depending on whether the diagnosis was made through physician evaluation (73%) or with an assessment tool (the Questionnaire for Intense Episodic Pain [QUDEI], 66%).23

**Assessment Tools for Breakthrough Pain**

A systematic review of the literature in 2010 conducted on behalf of the European Palliative Care Research Collaborative identified 10 tools to assess breakthrough pain, 7 of which were discussed but have not been made available and have only been used in 1 publication.11

The Breakthrough Pain Questionnaire (BPQ) was the first tool developed to assess breakthrough pain and is the tool most frequently used.11 The BPQ was designed to assess breakthrough pain in patients with cancer,12 and then later modified for use with patients who have chronic noncancer pain and have been prescribed opioids long term.24 The tool assesses the temporal characteristics of breakthrough pain and its severity, location, pathophysiology, cause, precipitating and palliative factors, and relationship to the regularly scheduled analgesic through

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**Table 1**

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<tr>
<th>Step</th>
<th>Question</th>
<th>Answer</th>
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<tr>
<td>1</td>
<td>Does the patient have background pain?</td>
<td>YES (If no, patient does not have breakthrough pain)</td>
</tr>
<tr>
<td>2</td>
<td>Is the background pain adequately controlled?</td>
<td>YES (If no, patient does not have breakthrough pain)</td>
</tr>
<tr>
<td>3</td>
<td>Does the patient have transient exacerbations of pain?</td>
<td>YES (If no, patient does not have breakthrough pain)</td>
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and Hagen questionnaire (the QUDEI) combined with an algorithm versus physician clinical judgment. One limitation of this study was that patients with moderate baseline pain intensity (a score of 6 on a 0–10 numeric rating scale) could be diagnosed as having breakthrough pain. This is, however, an operational definition; the pain intensity score for considering that baseline pain is controlled could be set at less than 6, a more demanding level, without changing the characteristics and the validity of the questionnaire.

Currently, no tool exists for assessing breakthrough pain that has undergone independent clinical validation, although the Alberta Breakthrough Pain Assessment Tool underwent a validation process during its development.²⁷ However, a new clinical assessment tool for breakthrough pain, the Breakthrough Pain Assessment Tool, was recently developed and validated (A. Davies, oral communication, 2012).

Management of Breakthrough Pain: Recent Guideline Recommendations

In oncology, recommendations for treatment are stratified according to tumor type and then tailored appropriately. Pain is less easily subdivided but just as heterogeneous, thereby posing a significant challenge for expert groups assembling guidelines. Pain is a changing and evolving symptom, and therefore treatment should be dynamic, be optimized to the changing needs and responses of an individual, and involve ongoing monitoring. Although breakthrough pain varies both interindividually and intra-individually, it is commonly rapid in onset and short in duration. The pharmacotherapies used to treat this type of pain are taken as required rather than on a regular basis (eg, at the onset of spontaneous breakthrough pain or preceding predictable incident pain) and are called “rescue medications.”²⁹ Ideal rescue medications would be tailored to the unique presentation of breakthrough pain, with pharmacodynamics mirroring those of the pain being treated: with quick onset and short duration.³⁰ Historically, treatment of breakthrough pain has involved supplementation with oral opioid doses of 5% to 20% of the total daily dose of the opioid already being taken to relieve background pain.³¹ In the past decade, treatments with pharmacodynamics that mirror the
pattern of breakthrough pain have been specifically developed and rigorously tested, developing an evidence base that has been recognized in international guidelines. After a rescue medication is selected, it should be titrated to an effective, tolerable dose for each patient.29

Authors of many of the most recent national and international guidelines on managing breakthrough pain in cancer have recognized its unique presentation, reviewed the evidence base for its treatment, and tailored their recommendations to reflect their findings. Many of these guidelines recommend similar approaches to managing breakthrough pain in cancer, even though the development processes of these guidelines varied. International guidelines differ particularly in the methodology and rigor used to develop them, and in the composition of the expert groups and the intended use.

EAPC Guidelines
The European Association for Palliative Care (EAPC) guideline on managing cancer-related pain is an international consensus of a multidisciplinary and multiprofessional organization representing all of Europe, and was therefore developed to be flexible enough to be used and adapted by the many diverse users in different circumstances.7 A Delphi consensus was used to establish and identify new content and revise the previous guidelines after comparison with other guidelines.12 As a result, the EAPC published a new set of guidelines on managing cancer-related pain in 2012, of which a portion focused on managing breakthrough pain.7 The available data supported the EAPC’s strong recommendation that around-the-clock opioid therapy must be appropriately titrated before potent rescue opioid analgesics are considered. Uncontrolled background pain should be treated with additional doses of immediate-release oral opioids. Only after background pain has been controlled can breakthrough pain be effectively managed with buccal or intranasal fentanyl preparations. Immediate-release oral opioids can also be used as first-line treatment, and transmucosal fentanyl preparations reserved for when a more rapid onset of action and shorter duration of effect are necessary. Furthermore, the EAPC weakly recommends that immediate-release formulations of opioids with short half-lives can preemptively treat predictable episodes of breakthrough pain in cancer when administered 20 to 30 minutes before the provoking procedure.7

French Guidelines
French guidelines were created by a similar methodology involving adaptation of available guidelines for cancer pain and systematic reviews of the literature. The French guidelines, however, were tailored for the health needs and drug availability within France. The French Society for the Study and Treatment of Pain, the French Society for Accompaniment and Palliative Care, and the French Association for Supportive Care in Oncology21 collaborated to develop and endorse a single guideline with an expert panel that included specialists in pain, palliative care, supportive care, and oncology. The French guideline provides specific information on treating breakthrough pain in cancer and provides recommendations for integrating 5 new transmucosal fentanyl formulations available in France from 2001 to 2011 into clinical practice.21 The French guideline aligns closely with the EAPC recommendations7 on breakthrough pain; however, although the EAPC weakly recommends administering immediate-release opioids with short half-lives to preemptively treat breakthrough pain, the French guideline recommends only transmucosal fentanyl for managing induced procedural pain in patients already receiving an opioid for chronic pain.21 Because of formulation and absorption site differences, the transmucosal products are not dose interchangeable, and the French expert panel recommended methods for dose titration unique to each formulation, in keeping with the original studies of each individual product.21 Although the regulations issued by the French High Authority for Health (Haute Autorité de Santé)23 echoed the restrictions imposed in the original clinical studies of the transmucosal fentanyl formulations, which involved a minimum 4-hour period before further readministration, the French expert panel permitted the use of additional doses within a shorter period for patients with continued pain if they are closely monitored.21 Notably, the pharmacokinetics of fentanyl warrant caution when considering repeated administration, and the French expert panel recommended monitoring for drowsiness, sedation, and reduced respiratory rate.21

Spanish Guidelines
Although no national cancer institute exists and Spain has neither accepted nor established a national guideline for managing cancer pain, several Spanish guidelines are available that include recommendations on managing breakthrough pain in cancer. The most recent guideline is the one endorsed by the Spanish Society for Palliative Care, the Spanish Society of Medical Oncology, the Spanish Society of Radiotherapeutic Oncology, and the Spanish Society of Pain.34–36 This guideline was originally created in 2002 and then updated in 2012 by a multidisciplinary group of medical oncologists, radiothera-
Caraceni et al

peutic oncologists, palliative care specialists, and pain specialists. Each one of the statements and recommendations within the Spanish consensus statement was graded based on the strength of the supporting evidence. The Spanish consensus statement recommends that analgesic treatment of breakthrough cancer pain be specific and not replace the treatment of baseline pain. It also recommends that breakthrough pain treatment should be opioid-based and prescribed to all patients to complement the opioid treatment used to control their baseline pain. Patients with cancer with breakthrough pain treated in this manner must be tolerant to opioids to prevent overdose and opioid toxicities. Short-acting opioids were considered useful in preventing volitional or procedural incident breakthrough pain in cancer, because this pain can be anticipated and avoided by administering the drug 30 minutes before its anticipated occurrence. However, nonvolitional and idiopathic breakthrough cancer pain, which are unpredictable in occurrence, are considered ideally managed with rapid-onset opioids, such as rapid-onset fentanyl formulations.

US Guidelines

In the United States, the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Adult Cancer Pain are a continually evolving source of recommendations for practitioners who manage cancer pain (to view the most recent version of these guidelines, visit NCCN.org). The NCCN revises their guidelines every year and conducts teleconferences with their experts to make minor changes as needed in light of new developments or data. Originally the guidelines had been developed to be a resource for oncologists, and then they evolved into comprehensive cancer pain guidelines accessible to all practitioners. The guidelines are created based on consensus from representatives of several cancer institutes and contain recommendations regarding comprehensive approaches to treatment, including pharmacologic and procedural. The 2011 NCCN Guidelines recommend administering a rescue dose of the same opioid being used to control background pain at 10% to 20% of the 24-hour dose, however, transmucosal fentanyl formulations can be considered for opioid-tolerant patients with pain flares not from end-of-dose failure, beginning with the lowest dose of the formulation and titrated to effect.

Discussion and Conclusions

Creating a comprehensive approach that addresses the varied presentations of cancer-related pain is essential. A thorough assessment of pain is a key step toward adequate management. Assessment should therefore enable clinicians to accomplish these steps:

- Recognize the specific pain syndrome to explain how cancer or its treatment is causing the pain.
- Evaluate the pain within the context of the cancer disease stage and trajectory, along with the individual patient’s psychological and social conditions. The continuity of care and a gradual transition to palliative care should always be considered in the presence of advanced disease and significant symptom burden.
- Describe in full the pain characteristics, including intensity and other clinically important features.
- Review the analgesic history to evaluate how pain has been managed and how it responded to previous and present analgesic regimens. Each pain component should be individually evaluated.
- Establish a treatment strategy applying clinical guidelines. Guidelines are important sources of current clinical strategies on management and can be useful for creating a standard for comparison with one’s own clinical practice, placing it in the context of the general formulation for practice and establishing benchmarks to support local clinical practice when adhering to administrative, regulatory, and political policies.

All of the evidence-based guidelines on managing idiopathic breakthrough pain in cancer include rapid-acting opioids as a treatment option, most of which also include fentanyl formulations. However, it is important not to overuse rapid-acting opioids for pain that could be managed with around-the-clock opioid titration and with the careful and well-established use of immediate-release oral opioids or other therapeutic strategies.

More research on preemptive use of analgesics for procedural breakthrough pain in cancer and head-to-head comparative trials are needed to provide evidence-based guidance on the use of fentanyl formulations for predictable pain flares and on specific formulation superiority.
References


31. Hagen NA, Fisher K, Victorino C, et al. A titration strategy is needed to manage breakthrough cancer pain effectively:


