Assessment and Management of Breakthrough Pain in Cancer Patients: Current Approaches and Emerging Research

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Cancer pain is highly prevalent and often severe. Fortunately, most cancer pain can be readily managed, with up to 90% of patients responding well to standard interventions. However, breakthrough cancer pain—brief flares of severe pain superimposed on baseline pain—is common, difficult to manage, and often negatively impacts patients' quality of life. Breakthrough cancer pain is traditionally managed with oral, immediate-release opioids. However, because of its sudden onset and severity, oral opioids often fall short of providing adequate control. Research into novel approaches to pain management has identified several innovative strategies for this difficult cancer pain problem. We describe current approaches to assess, define, characterize, and treat breakthrough cancer pain, and summarize recent clinical research on novel agents, novel routes of drug delivery, and other advances in its management.

Introduction

Cancer pain is highly prevalent. Depending on the clinical circumstances, such as type of cancer, extent of disease, and other important clinical variables, pain is present in 30% to 70% of patients early in their disease course and becomes more prevalent and severe as the disease advances. Fortunately, most cancer pain can be readily managed by interventions available at local pharmacies, with up to 90% of patients responding well to simple interventions such as the World Health Organization's analgesic ladder [1]. However, some cancer pain problems are predictably more difficult to manage. Specific pain syndromes or clinical scenarios that have been associated with a poorer prognosis include cancer-related neuropathic pain, pelvic pain, pain in patients with delirium, pain in patients with a history of substance abuse, breakthrough pain, and several others [2]. Breakthrough cancer pain can have a good outcome but requires a separate set of strategies from those usually used to assess and manage chronic cancer pain.

The Definition of Breakthrough Pain

Breakthrough pain was originally defined as a transitory increase in pain to greater than moderate intensity (that is, to an intensity of "severe" or "excruciating"), which occurs on a baseline pain of moderate intensity or less (that is, no pain or pain of "mild" or "moderate" intensity) [3]. Existing terminology characterizing the phenomenology of breakthrough pain reflects its several clinically important dimensions. Because wide variations in reported prevalence rates of breakthrough pain are likely in part due to different meanings or understandings of the concept of breakthrough pain [4], there is a need for widely accepted and validated pain terminology. Vocabulary surrounding breakthrough pain has been a topic of considerable debate and was the subject of a major consensus meeting of an expert working group of the European Association for Palliative Care [4]. The group recommended the use of a broader, simpler term such as "episodic" or "transient" pain, as the English term "breakthrough" has no literal translation in many other languages. Although experts and clinicians in the field have grappled with standardized definitions of pain, to date no such universal taxonomy is available; at present the term "breakthrough pain" remains widely used, and hence, the title of this article.

One recent effort to characterize patients' experience of breakthrough pain involved the development of

Table 1. Consensus definitions for breakthrough pain–related terms

Baseline pain	Pain that is almost always present and may be described as continuous, steady, or constant. It can be partly or completely masked if controlled by analgesic management.
Breakthrough pain	A transitory exacerbation of pain experienced by a patient who has relatively stable and adequately controlled baseline pain. Breakthrough pain can be an exacerbation of the baseline pain OR it can be a pain with a different cause from that of the baseline pain. Breakthrough pain can be evoked, spontaneous, predictable, or unpredictable. It is difficult to characterize breakthrough pain when baseline pain is not controlled.
Controlled baseline pain	Baseline pain that is managed with scheduled (around-the-clock) opioids, nonopioid analgesics, or nondrug analgesic interventions. The patient describes the intensity of his/her baseline pain on average as "mild" or less on a verbal rating scale (response categories: none, mild, moderate, severe) or as a score of ≤ 4 on a numeric rating scale (anchors: 0 [no pain] and 10 [worst possible pain]) during the past 24 hours.
Somatic pain	Pain arising from, or thought to arise from, skin, subcutaneous tissue, mucosa (eg, oral, nasal, auditory, genital, or anal), or tissues of the musculoskeletal system (eg, bone, cartilage, fascia, ligament, muscle, or tendon).
Visceral pain	Pain arising from, or thought to arise from, internal organs of the circulatory, digestive, urinary, respiratory, or other systems (eg, the heart, esophagus, stomach, liver, gallbladder, pancreas, colon, rectum, spleen, kidney, bladder, uterus, lung, and parts of the peritoneum and pleura).
Neuropathic pain	Pain resulting from damage to or dysfunction of the central nervous system (brain, brainstem, or spinal cord) or peripheral nervous system (nerve roots, plexus, cranial or spinal nerves).
Mixed pain	Pain resulting from more than one of somatic, visceral, or neuropathic pain.
	Breakthrough pain can be somatic, visceral, neuropathic, or mixed, and baseline pain may have the same classification or a different classification. Patients can have more than one kind of baseline pain and several discrete breakthrough pain syndromes.

a comprehensive clinical research tool [5•]. Through an iterative, organized discussion, several definitions for breakthrough pain–related terms were agreed to by international experts on the topic (Table 1) [5•]. With time and further input, these definitions will likely continue to evolve; for now, they help to simplify the area.

Types of Breakthrough Pain

In general, breakthrough pain can be characterized as incident pain, spontaneous pain, or end-of-dose pain [3,6]. Incident pain refers to physical activities such as weight-bearing in a patient with bone metastases, or dressing changes that can be predicted to worsen pain. Incident pain can include events that are volitional, such as pain with voluntary movement, or nonvolitional, such as breakthrough pain caused by a bowel motion in a patient with bulky pelvic cancer. End-of-dose failure is another predictable kind of breakthrough pain that is related to pharmacokinetic factors, in which the baseline pain increases before the next scheduled dose of analgesic. The interval between the onset of end-of-dose failure and the next scheduled pain medication can give the clinician an idea of the degree of baseline medication underdosing. Breakthrough pain can also occur without any clear antecedent cause, for reasons that are difficult to fully understand. An example of spontaneous breakthrough pain is a circadian flare of pain, with pain that predictably worsens in the afternoon or evening.

The Prevalence of Breakthrough Pain

The demographics of cancer-related breakthrough pain have been characterized in a range of clinical situations and a variety of patient populations. An early study of hospitalized cancer pain patients found that about two thirds of patients with otherwise well-controlled baseline pain had episodes of breakthrough pain each day [3]. Other studies conducted in different countries and practice settings have described breakthrough pain prevalence ranging from 40% to upwards of 80%, depending on the setting [4]. Most patients with cancer of the pancreas will have spontaneous flares of pain, although the mechanism is not understood [7]; a recent report has highlighted the high prevalence of spontaneous, unpredictable episodes of breakthrough pain in many kinds of cancer [8].

Assessment of Breakthrough Pain

The pain history should include key elements that characterize the salient clinical features of breakthrough pain (Fig. 1), in addition to standardly described approaches to the cancer pain history [6]. Clinicians have often implemented routine use of several validated pain tools to complement the pain history, including one or more of the following: the Brief Pain Inventory, Neuropathic Pain Scale, Edmonton Symptom Assessment Scale, Edmonton Classification Scale, Memorial Pain Assessment Card, Memorial Pain Assessment Scale, McGill Pain Questionnaire, visual analogue scales, numerical scales, and

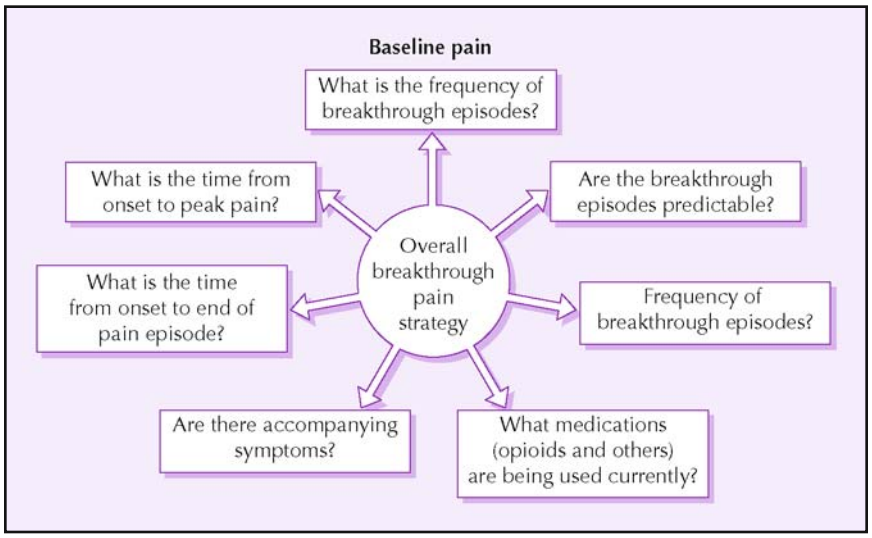

Figure 1. Key elements characterizing the clinical features of breakthrough pain.

others. However, these tools have more limited use in the assessment of breakthrough pain. At present, no widely used clinical tool is available to assess breakthrough pain. In an effort to improve and support research in the area of breakthrough pain, we have developed the Alberta Breakthrough Pain Assessment Tool for research purposes, which has undergone content and construct validity testing and is now available for use [5•]. Figure 1 depicts the key elements for assessment of the patient with cancer-related breakthrough pain, which provided the foundation for the development of the Alberta Breakthrough Pain Assessment Tool.

Interference with function is one of the key ways that breakthrough cancer pain negatively impacts quality of life [8]. Patients may report good control of pain while at rest, only to have severe pain with movement. The extent of pain's interference with function has been captured in a variety of quality-of-life instruments such as the Brief Pain Inventory and, from a pragmatic perspective, may be one of the most important dimensions of the overall pain experience that patients can relate to clinicians.

The physical examination is an essential component of the clinical assessment process to ensure a thorough understanding of the cancer pain experience [6]. Most authorities agree that the physical examination of the cancer pain patient includes a general physical examination based on a systems approach; an oncologic examination to assess extent of disease; and a regional pain examination to identify pathology in the area of pain. Bedside provocative maneuvers have been shown to accurately reproduce cancer pain in most cases and can lead to a more accurate pain diagnosis [9]. This assessment technique may be useful in characterizing pain and can guide selection of treatment options. However, bedside provocative maneuvers are not as able to reproduce certain specific pain syndromes: spontaneous, paroxysmal spells of pain, some kinds of neuropathic pain, and some clinical situations of steady headache.

Management of Cancer-Related Breakthrough Pain

As described earlier, breakthrough pain is commonly quite sudden in onset. One study identified a median time from onset to peak pain of only 3 minutes [3]. Further, breakthrough pains are often brief in duration and have been described to have a median duration of about 30 minutes [3,10]. Because of its sudden onset, severity, and brief duration, an analgesic ideal for breakthrough pain would have very rapid onset and brief duration of analgesic effect. A widely cited approach to managing cancer-related breakthrough pain is the use of oral immediate-release opioids. However, oral immediate-release morphine first appears in the blood close to half an hour after it is ingested [11]. In fact, in a recent study evaluating the analgesic effectiveness of several breakthrough pain rescue medications among hospice patients taking oral preparations (including morphine, oxycodone, or hydromorphone), the average time to meaningful pain relief was greater than 30 minutes, whereas the average duration of breakthrough pain in these patients was only 35 minutes [10]. There appears to be a critical mismatch between the early pharmacokinetics of oral immediate-release opioids and the sudden onset and brief duration of breakthrough pain.

Even more curious are the early pharmacodynamics of opioids in breakthrough pain (ie, the onset of analgesic effect over time). Studies have identified an apparent placebo phenomenon, whereby there is an onset of analgesic effect of oral opioids or other agents much earlier than could be accounted for by the anticipated increase in blood levels [12,13]. The phenomenon is of major clinical effect within about 20 minutes after ingestion of analgesics but has been described to occur as early as 10 minutes after administration. Although neither studied nor named, it could be described as an anticipatory placebo effect. Despite the presence of this earlier-than-expected effect of immediate-release analgesics, cancer-related

Table 2. Conventional and emerging treatments for cancer-related BTP*

Treatment	Findings/notes	Studies
Oral agents		
SR vs IR oral morphine	In randomized controlled trials, the incidence of BTP, or use of supplemental morphine for BTP, did not differ between treatment with IR morphine every 4 hours and SR morphine every 12 hours.	[18,19]
Effervescent morphine	In this uncontrolled, open-label study, the mean time to sufficient pain relief was shorter with effervescent morphine (13 ± 5.6 min) than IR morphine (27 ± 4.4 min).	[20]
Sustained-release oxycodone	This uncontrolled, open-label safety study describes the management of cancer pain by SR oxycodone. Half of the study patients took < 1 dose of rescue medication/day.	[21]
ER hydromorphone†	This uncontrolled, open-label study describes a regimen by which patients can be converted from prior opioid therapy and titrated to an effective dose of ER hydromorphone. Patients who were successfully titrated required a mean of < 2 daily doses of rescue medication.	[22]
Oral methadone	In this uncontrolled, open-label pilot study, 3 of 6 patients experienced an onset of BTP relief within 10 min of oral methadone ingestion.	[23]
TD agents		
TD fentanyl	These open-label studies describe the use of TD fentanyl plus IR morphine (as needed) to manage cancer pain (including rescue morphine requirements).	[24,25]
TD buprenorphine†	In a randomized, controlled trial, patients given TD buprenorphine plus sublingual buprenorphine (as needed) had a 49% greater reduction in BTP rescue medication use vs patients given a placebo patch. In a follow-up study of patients continuing active treatment, most (66%) managed their pain with ≤ 1 BTP rescue dose/day.	[26,27]
IV agents		
IV morphine	In two open-label studies, BTP intensity was reduced by ≥ 50% within 15 min of IV morphine administration in most treated BTP episodes. In a comparative study, BTP intensity at 15 min after administration was significantly lower for IV morphine vs OTFC. Among pediatric oncology patients treated with IV morphine, the mean incidence of BTP was < 1 episode per patient per day.	[28–31]
IV hydromorphone	In this randomized, controlled trial, the mean number of rescue morphine injections for BTP did not differ between patients given IV vs SC hydromorphone.	[32]
SC agents		
SC hydromorphone vs SC morphine	In a randomized, controlled trial, patients given SC hydromorphone required more analgesia for BTP in the first 24 hours of the study, vs patients given SC morphine. Doses were increased in both groups at 24 hours, after which there were no differences between groups in BTP analgesia requirements.	[33]
SC morphine, SC hydromorphone, and SC sufentanil	In two small pilot studies, patients self-administered SC morphine, hydromorphone, or sufentanil for BTP using an injection pen. Across all three analgesics, efficacy was rated as "good" by 84% of patients.	[34]

*Unless otherwise specified, the patient population under study consisted of adults with cancer-related pain.
†These treatments were evaluated in patients with malignant and nonmalignant pain syndromes.
BTP—breakthrough pain; ER—extended release; FBT—fentanyl buccal tablets; IR—immediate release; IV—intravenous; OTFC—oral transmucosal fentanyl citrate; PK—pharmacokinetic; SC—subcutaneous; SL—sublingual; SR—sustained release; TD—transdermal.

breakthrough pain remains a difficult-to-manage pain syndrome, and more effective interventions with faster onset could potentially be of great benefit.

Conventional and Emerging Treatments for Breakthrough Pain

Standard approaches to management of breakthrough pain include recommendations for immediate-release oral opioid, representing 10% to 20% [14], 5% to 15% [15], or one sixth of the total daily dose of opioids [1]. However, recent research suggests that the effective dose of opioids is only poorly related to the total daily dose of opioid. In a large study of 188 cancer patients with breakthrough pain, the effective breakthrough opioid dose ranged from 10% to 20% of the daily dose of opioid about one third of the time; the dose was outside of that range in the remaining two thirds. The effective breakthrough opioid dose

Table 2. Conventional and emerging treatments for cancer-related BTP* ***(Continued)***

Treatment	Findings/notes	Studies
SL agents		
SL methadone	In this small pilot study, significant relief of BTP occurred, with a median onset of 5 min after administration of SL methadone.	[35]
SL sufentanil	This case study describes the management of episodic BTP in one cancer pain patient using 25 μg of SL sufentanil solution.	[36]
SL fentanyl	In a small pilot study of SL fentanyl for BTP, 82% of patients had a reduction in BTP intensity within 15 min after administration. In a subsequent PK study, plasma fentanyl was first detected between 8–11 min after SL fentanyl administration.	[37,38]
SL buprenorphine	See entry for TD buprenorphine.	[27]
SL ketamine	This pilot study describes the management of BTP with 25 mg SL ketamine in 3 cancer patients. Effective pain control was achieved within 10 min for each of 12 BTP episodes evaluated.	[39]
Transbuccal agents		
FBT	Randomized, controlled trials of FBT for BTP report an onset of analgesia within 10–15 min after FBT administration.	[40,41•]
OTFC	Randomized, controlled trials of OTFC for BTP report significantly greater reductions in BTP intensity and better pain relief with OTFC vs usual rescue medications (including IR morphine) 15 min after administration.	[12,13,42,43]
Intranasal agents		
Intranasal morphine	Uncontrolled, open-label studies evaluating intranasal morphine (5–80 mg) for BTP report an onset of pain relief within 5 min of administration.	[44,45]
Intranasal fentanyl	In a small pilot study, 7 of 12 patients had reductions in BTP pain scores within 10 min of taking intranasal fentanyl citrate (20 μg).	[46]
Inhaled agents		
Nitrous oxide	In this small pilot study involving 7 patients, there was no significant effect of nitrous oxide on mean or median peak BTP intensity scores, compared with treatment with placebo gas.	[47]

*Unless otherwise specified, the patient population under study consisted of adults with cancer-related pain.
†These treatments were evaluated in patients with malignant and nonmalignant pain syndromes.
BTP—breakthrough pain; ER—extended release; FBT—fentanyl buccal tablets; IR—immediate release; IV—intravenous; OTFC—oral transmucosal fentanyl citrate; PK—pharmacokinetic; SC—subcutaneous; SL—sublingual; SR—sustained release; TD—transdermal.

size was as small as 1% of the total daily dose of opioid and as much as 71% of the total daily dose of opioid. The authors concluded that breakthrough opioid dosage should be titrated individually for each patient, and with a titration strategy separate from that of the baseline cancer pain medication [16]. However, starting with about 10% of daily opioid dose seems safe in most clinical circumstances and has been widely accepted [17].

Although oral immediate-release opioids are often effective for breakthrough pain, a range of other routes, drugs, and drug delivery systems have been evaluated partly to identify ways to achieve faster relief of pain. Studies have evaluated transdermal, intravenous, subcutaneous, sublingual, transbuccal, intranasal, and inhaled routes of administration of analgesics for breakthrough pain. Table 2 highlights key publications selected from a large, emerging body of literature. The most extensively studied novel route for breakthrough medication is transbuccal (ie, cheek mucosal membrane), using the oral transmucosal fentanyl citrate (OTFC) lozenge; to date, four controlled trials of OTFC for cancer pain have been published (Table 2). Its onset of action is faster than oral opioids. However, the agent is expensive. Subcutaneous infusions have been widely used for breakthrough pain and may be preferred by patients over intravenous or intramuscular routes of drug administration [1]. Rectal suppositories of acetaminophen or immediate-release opioids can be used when the oral route is not feasible [1]. Rarely, patients with gastrointestinal disease have self-administered slow- and immediate-release opioids via the vaginal route, with good effect. A small pharmacokinetic study described absorption of fentanyl administered in a vaginal suppository [48].

Although not the focus of this review, it is worth noting that several of these emerging treatments for breakthrough pain have been evaluated in populations of patients with nonmalignant pain syndromes. Transdermal fentanyl has been used to treat pain from acute pancreatitis [49], and intranasal ketamine was effective in treating patients with chronic, nonmalignant pain [50]. Random-

ized controlled trials evaluating fentanyl buccal tablet effectiveness have reported decreases in breakthrough pain intensity within 10 minutes of administration among patients with chronic low back pain [51] and chronic noncancer neuropathic pain [52]. Similarly, OTFC has been shown effective in treating chronic noncancer pain [53] and migraine pain [54].

In order to identify interventions that are more rapid in onset, investigators have considered not only the route of administration but also the speed and magnitude of analgesic effect once the drug has been ingested. Some agents can be predicted to have more rapid onset of analgesic effect than traditional opioids. For example, intravenous bolus morphine has an onset of analgesic effect of about 5 minutes after administration, with a lag of the peak effect beyond 20 minutes [55]. The peak effect occurs about 1 hour after injection of intramuscular morphine [56]. The peak effect of oral morphine is close to 2 hours after ingestion [56]. Intravenous bolus hydromorphone has a rapid initial effect similar to that of intravenous morphine, with a faster peak analgesic effect of between 10 and 20 minutes after injection [55].

The onset and peak of opioid analgesic effect is influenced by several well-defined factors; of these, lipid solubility is one of the most important. Fat-soluble opioids include fentanyl series agents (fentanyl, sufentanil, and alfentanil), methadone, and others. Oral methadone in particular appears to have an onset of action within 10 minutes [23], and published evidence suggests it may have a faster onset of action than oral morphine in cancer patients [10]. With this in mind, in a preliminary study of the early pharmacodynamics of sublingual methadone, a highly fat-soluble opioid, investigators found evidence that it may have an analgesic effect as short as 5 minutes after administration [35]. However, further work with this approach is needed before widespread use. Other studies involving sublingual sufentanil and fentanyl [36–38] also suggest a very rapid onset of these lipid-soluble opioids.

A range of nonopioid analgesic medications have also been evaluated. Sublingual ketamine for breakthrough pain was evaluated in three cancer patients receiving spinal analgesics; effective pain control was achieved within 10 minutes for each of 12 breakthrough pain episodes evaluated [39]. Inhaled nitrous oxide use by seven patients with cancer-related incident pain resulted in a nonsignificant reduction in pain change scores (baseline to peak pain), compared with inhaled placebo gas in a crossover design over 2 consecutive days [47].

Conclusions

Breakthrough cancer pain is highly prevalent and negatively impacts quality of life. A wide range of treatments are standardly available, and ongoing research holds the promise for more effective agents over the coming years. A reasonable approach to manage cancer-related breakthrough pain is with the use of oral immediate-release opioids, beginning with approximately 10% of the daily dose of opioid. The breakthrough pain medication should be titrated upward or downward according to effect. When pain is predictable, oral immediate-release opioids should be taken well in advance (eg, 30 minutes or longer before the expected pain). For breakthrough pains that are sudden in onset and severe, alternative routes (eg, intranasal or sublingual) and medications (eg, fentanyl or sufentanil) should be considered. Continuity of care is the key to providing the best possible outcome, along with careful attention to the underlying mechanisms of pain and effective treatment of the causes whenever possible.

Disclosures

No potential conflicts of interest relevant to this article were reported.

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