

Cross Currents | in pain management

Innovations in assessment and management of breakthrough cancer pain

Neil A. Hagen, MD, FRCPC

Cancer pain is highly prevalent, with 70% to 90% of patients experiencing clinically significant pain at some time in their cancer journey.

Fortunately, for the vast majority of such patients, the application of an analgesic strategy results in good control of pain, through use of medications available at the local pharmacy. Steady, baseline cancer pain is usually managed with protocols such as the World Health Organization's analgesic ladder,¹ which calls for pain medication to be administered around the clock in a scheduled manner.

For the minority of remaining patients, the outcome may not be as good. Many of these patients have difficult pain problems that are likely to be challenging to manage. Commonly encountered difficult pain problems include neuropathic cancer pain, pain in the setting of delirium or substance abuse, pain with bulky pelvic cancer and breakthrough cancer pain.²

Breakthrough cancer pain refers to transient episodes of pain that are phenomenologically distinct from baseline, steady cancer pain. Breakthrough cancer pain is typically sudden in onset and brief in duration. It can be an abrupt worsening of the baseline cancer pain or it can be a separate pain that is entirely unrelated to the baseline pain.

Assessment of breakthrough cancer pain Classification

Breakthrough cancer pain can be spontaneous or provoked (see **Table 1**). In some patients spontaneous pain is caused by bowel activity or episodes of muscle spasm but in others it is not understood why cancer pain suddenly worsens without apparent provocation. For example, about two-thirds of patients with pain from cancer of the pancreas have transient painful episodes, but the etiology of pain from such non-moving body parts is not clear. Most patients with breakthrough cancer pain have episodes of unpredictable flares of pain.³

Patients can experience pain when their regularly scheduled pain medication wears out, a scenario called "end-of-dose failure." A common example is a circadian pattern of pain that worsens in the late evening or first thing in the morning, just prior to the next dose of slow-release opioid. As long as toxicity allows, end-of-dose failure is usually managed by increasing the regularly scheduled pain medication.

Commonly, breakthrough cancer pain is associated with movement, for example, movement-related pain caused by metastatic bone disease. Such so-called "incident" breakthrough pain can have a dramatic impact on quality of life when it interferes with functions such as activities of daily living.



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Understanding what kind of breakthrough cancer pain a patient is experiencing can guide the development of an analgesic strategy. For example, movement-related back pain due to lumbar vertebral body metastases can be improved by: use of a flexible corset-type back brace; topical application of menthol gel; heat, cold or gentle massage; and pre-emptive use of opioids, non-opioids and/or judicious use of adjuvant analgesics.

Differential diagnosis

Breakthrough cancer pain needs to be distinguished from baseline pain that is not controlled. When patients describe taking many doses of breakthrough pain medication each day, they could be experiencing multiple episodes of breakthrough cancer pain with an otherwise well-controlled baseline pain, or alternatively, baseline pain may be uncontrolled — whereby patients take supplemental doses of immediate-release opioid in order to control baseline pain. This latter situation can often be managed by increasing the regularly scheduled long-acting or slow-release opioid.

Research advances

Our group conducted the first clinical study of breakthrough cancer pain on a cohort of hospitalized patients with otherwise-controlled baseline cancer pain; about two-thirds had episodes of breakthrough pain every day.⁴ We were surprised to note how suddenly the pain appeared: the median time from onset to peak pain was three minutes, and the median duration of breakthrough pain was 30 minutes, including both patients who received treatment for the pain and those who did not. Several subsequent large surveys of cancer patients in a range of practice settings, countries and disease sites have confirmed these preliminary observations: breakthrough cancer pain is usually sudden in onset and brief in duration.

The research methodology to study breakthrough cancer pain is becoming more sophisticated. In order to undertake studies of novel approaches to managing breakthrough cancer pain, our group recognized the need for a validated assessment tool to support research in the area. The Alberta Breakthrough Pain Assessment Tool was developed for this purpose.⁵ It characterizes several specific features of a patient’s breakthrough pain, such as relationship with baseline pain, time from onset to peak, dura-

tion, effectiveness of analgesic interventions and predictability of breakthrough pain episodes. Further research in the assessment of breakthrough cancer pain is needed, however. For example, we suspect, but don’t yet know for sure, that predictability of episodes is closely linked to prognosis for pain control. No short, validated, bedside assessment tool for breakthrough cancer pain has yet been developed, although we are working on it.

Role of the multidisciplinary team

Key components in the comprehensive assessment of breakthrough cancer pain are the history, physical examination with particular focus on the regional pain exam, and bedside provocative maneuvers to gently reproduce the pain that necessitated the assessment (**Table 2**, page 22). Bedside provocative maneuvers systematically aim to stress potentially pain-sensitive structures, possibly resulting in local pain being felt or referred to another region of the body. Somatic pain-sensitive structures include bone, muscle (often causing muscle spasm) and soft tissue such as the abdominal wall. Visceral pain-sensitive structures include the liver, bowels and lung. Damage to nervous tissue in nerve roots and the brachial plexus may result in neuropathic pain. Often more than one mechanism is present in the same part of the body; for example, muscle spasm is commonly present adjacent to vertebral body metastases. Identifying muscle spasm as a component of the overall pain can broaden the range of analgesic approaches to include physical measures as well as analgesic medications.⁶

From a clinical perspective, the bedside assessment of breakthrough cancer pain is easily incorporated into a clinic visit. All members of the interdisciplinary oncology care team can contribute to the comprehensive assessment and management of patients with breakthrough cancer pain. Straightforward problems do not need the same level of team-based care as tertiary-level, refractory pain problems. Nursing colleagues can initiate the history through use of validated bedside pain assessment tools. Nursing staff are often in a position to become better acquainted with the social situation of the patient and are aware of coping strategies available to the patient and family. Pharmacists can undertake medication reconciliation to document the amount of medication actually consumed, its effects and potential drug interactions. Comprehensive cancer programs routinely provide formal psychosocial oncology consultation support. “Suffering” has been defined within the medical domain as a threat to a person’s sense of intactness as a human being,⁷ and most patients with severe, chronic cancer pain have suffered greatly. Such patients and their families can benefit from multidisciplinary support, including formal psychosocial assessment and management.

Management of breakthrough cancer pain

Patients with controlled baseline pain who have brief episodes of breakthrough pain are often managed with immediate-release, orally administered analgesics, including opioids and non-opioids. The relatively slow absorption of these agents suggests that they may often be too slow in onset to be effective for most patients. No wonder breakthrough cancer pain has a poor prognosis: there is a mismatch between the sudden onset and short duration of breakthrough cancer pain and the pharmacokinetics of oral, immediate-release opioids.

TABLE 1. Classification of breakthrough cancer pain

characteristic	label
predictability	provoked breakthrough pain spontaneous breakthrough pain
relationship to regularly scheduled analgesics	end-of-dose failure
relationship to movement	incident pain
pathophysiologic mechanism	somatic pain visceral pain neuropathic pain mixed pain

It is curious that many patients do experience adequate relief of breakthrough cancer pain with oral, immediate-release opioids. There are two possible explanations for this phenomenon. First, patients who can predict they will have breakthrough pain, such as pain associated with activities of daily living, can take pre-emptive doses of opioid and wait until it is effective before becoming more active. Second, many patients experience relief of pain 15 or even 10 minutes after swallowing analgesics, long before the opioid could possibly be well absorbed (as oral opioids only begin to be absorbed after 30 minutes). How is such early-onset relief of pain possible? It could be a special placebo effect called anticipatory placebo effect; this early onset of relief is nonetheless a real and clinically important phenomenon.

Around the world, immediate-release, oral opioid is prescribed for breakthrough cancer pain beginning with 10% of a 24-hour dose, or with one-sixth of a daily dose.^{8,9} Surprisingly, there is actually very little evidence to support this widely used practice. In order to understand the range of effective breakthrough doses of opioids, our group pooled and analyzed data from three randomized controlled trials that evaluated a novel drug preparation for breakthrough cancer pain.¹⁰ In these studies, breakthrough opioid was titrated to effect. About one-third of patients did end up receiving breakthrough opioid at a dose of 10% to 20% of the daily dose of baseline opioid. But the other two-thirds of patients received either higher or lower doses. The range of effective breakthrough pain dose size was 1% to 72% of the daily baseline opioid! We concluded that 10% of a daily opioid dose is a good starting place for the breakthrough cancer pain dose, and is almost always safe, but that the dose must be individually titrated according to benefit and toxicity. Patients generally can undertake such dose titrations readily and effectively.

Toxic effects of opioids commonly include constipation, nausea, drowsiness, dry mouth and other effects. The prescribing physician should ensure prophylaxis against constipation and close monitoring for other toxicities.

Emerging treatments for unmet pain needs

A group of patients remains that is not able to achieve adequate relief of breakthrough pain with oral, immediate-release opioids, with other analgesics such as anti-inflammatories, with increased baseline opioid dose, or with non-drug interventions such as a back brace for movement-related back pain. For such patients, new ways to manage breakthrough cancer pain are greatly needed.

A range of alternative routes of opioid administration and novel preparations has been described in the literature. Alternative routes of opioid administration include subcutaneous, intravenous, epidural, vaginal, transbuccal and sublingual routes.¹¹ Our group investigated sublingual drops of methadone, as this drug is known to be rapidly and well absorbed through the sublingual route. Methadone appears to result in rapid and effective management of breakthrough pain, however, further research is needed.¹²

The past few years have seen the development of novel preparations of opioids specifically designed to be rapidly absorbed. These include intranasal, sublingual and transbuccal mucosal routes. Intranasal fentanyl has been studied in a large, randomized, multicentre European clinical trial.¹³ Sublingual or transbuccal wafers of fentanyl dissolve promptly but can require some intraoral moisture to initiate the dissolution. Another transbuccal product known as BEMA — BioErodible MucoAdhesive — binds firmly to the buccal mucosa until the fentanyl has been well absorbed.

TABLE 2. Bedside or clinic assessment of breakthrough cancer pain

domain	questions to ask the patient
control of baseline pain (controlled generally means ≤ 4 out of 10)	What is the average pain intensity during the past 24 hours, on a scale of 1–10?
presence of breakthrough pain	Do you have brief flares of severe pain? How often — every day?
predictability of breakthrough pain	Are your brief flares of pain caused by anything, or do they happen just out of the blue?
adequacy of regularly-scheduled pain medication (end-of-dose failure?)	How is the pain just before your regularly scheduled pain medication is due?
effectiveness of current breakthrough pain medication	How quickly does your current breakthrough pain medication work? Are you satisfied with how well it works?
interference with function by pain	Do pain flares prevent you from doing the things you need and want to do?
impact on quality of life	How much does this pain interfere with your quality of life?
non-drug interventions	Have you tried heat, cold, massage, a back brace, etc.?
pain diagnosis: somatic, visceral, neuropathic or mixed	History, physical examination and bedside provocative maneuvers to gently reproduce the pain.

All of the above preparations have several features in common: relief of pain is superior to oral opioid at the 15-minute mark or even earlier; medication-related toxicity is generally mild and is dose-related; local irritation from the product is generally mild; and importantly, the dose needs to be individually titrated according to effect. **Table 3** summarizes features of an ideal breakthrough pain medication. For example, the dosage for each episode of break-

through pain for the BEMA product begins at 200 mcg. If the first episode of breakthrough pain is inadequately managed, the dose is titrated upward in a stepwise manner until the effective dose is identified. Effective initial doses have ranged between 200 mcg and 1200 mcg. It is essential that the breakthrough dose not be calculated from the baseline opioid 24-hour dose. Instead, for each patient, dosing should start at 200 mcg and be titrated upward to effectiveness — both for patients who are receiving oral opioids and those who are receiving transdermal fentanyl.

The effective dose of breakthrough opioid correlates only poorly with the baseline dose of opioid. This is a key safety issue, as some patients on large doses of baseline opioid require only small doses of breakthrough opioid. In summary, there needs to be an individual approach to upward dose titration, and also patient and family education about pain management.

Looking forward

Breakthrough pain is a highly prevalent and difficult-to-manage cancer pain syndrome. It has traditionally been managed with oral, immediate-release analgesics such as opioids, which are often too slow in onset to fully meet patients' needs. Fortunately, substantial efforts to develop new approaches to managing breakthrough cancer pain have yielded novel products that allow rapid absorption of fast-onset opioids such as fentanyl. Some of these preparations are anticipated to become available in Canada over the coming months and next few years. ■

Disclosure

Dr. Hagen reports being on advisory boards of Valeant and Cephalon and being a consultant for Nycomed.

TABLE 3. Features of the ideal breakthrough pain medication

domain	characteristics
onset of analgesic effect	within a few minutes
duration of effect	gone quickly
range of dosing	wide range of dosing sizes to facilitate upward titration
ease of administration	non-invasive, rapidly administered and discrete
risk of diversion	in a formulation that is difficult to divert

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