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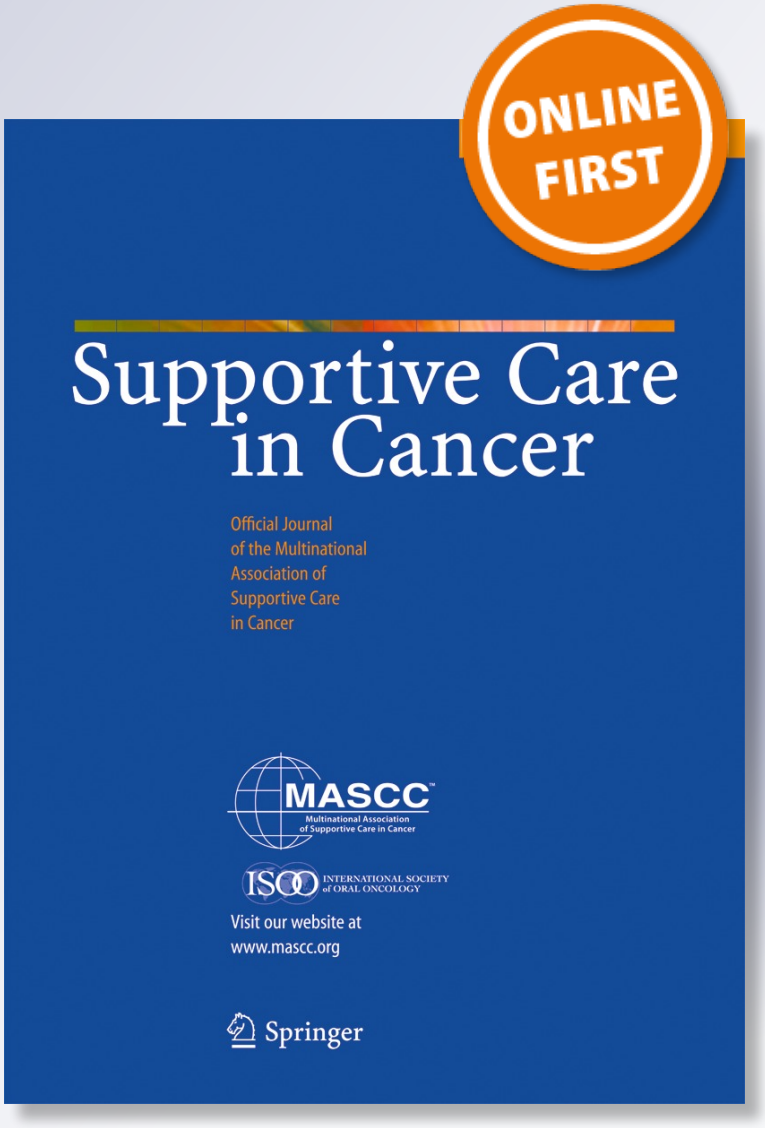

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ORIGINAL ARTICLE

Breakthrough cancer pain: a comparison of surveys with European and Canadian patients

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Abstract
Introduction Breakthrough cancer pain is defined as a transient exacerbation of pain that occurs spontaneously or in response to a trigger, despite stable and controlled background pain. Breakthrough pain often causes significant functional impairments for patients and can decrease quality of life.
Objective The objective of the study was to determine differences between breakthrough cancer pain incidence and management in Canada and Europe.
Methods Data collected from previous studies of breakthrough cancer pain in Canada and Europe was compared. A standard survey with identical inclusion/exclusion criteria was utilized for both patient populations.
Results Both groups of patients had a similar number and duration of breakthrough pain episodes, and similar pain intensity and pain interference with their daily activities. European patients reported better analgesic efficacy and satisfaction with management, and a greater percentage of European patients were prescribed a transmucosal fentanyl formulation (19.1 vs 2.9 %). More European patients (55 %) than Canadian patients (32.5 %) took their rescue medication every time they had a breakthrough pain episode.
Conclusions Breakthrough cancer pain in both Canadian and European patients greatly impacts their daily living, and both groups of patients had similar experiences with breakthrough cancer pain. Currently, this pain is not adequately managed for many patients. The role for new analgesic treatments in management of breakthrough cancer pain needs further study.

Keywords Breakthrough pain · Cancer · Patients' perspectives

Introduction

Pain is a common symptom and side-effect of treatment in patients with cancer, with over 50 % of cancer patients reporting some type of pain [1]. In order to effectively address the unmet pain needs of cancer patients, the World Health Organization (WHO) has implemented a 3-step pain ladder for adult cancer patients. The first step is to manage pain with non-opioid treatment, followed by opioids for mild to moderate pain ("weak opioids") and then opioids for moderate to severe pain ("strong opioids") [2].

Cancer pain can emerge as continuous and/or episodic. Continuous, or background pain, is consistently experienced by the patient and often can be controlled with standard pain medication, in accordance with the 3-step ladder of the WHO [2]. Breakthrough cancer pain (BTCP) has been defined as "a transient exacerbation of pain that occurs either spontaneously, or in relation to a specific and predictable or unpredictable trigger, despite relatively stable and adequately controlled background pain" [3]. Breakthrough pain has been documented by 40–80 % of cancer patients, and is a cause of great morbidity [4]. It can cause physical impairment, psychological distress, and decrease in social well-being, all of which can severely diminish quality of life [5].

In terms of pain management, patients should be prescribed pain medications of increasing strength based on their pain needs. Oral formulations of opioids, such as morphine, oxycodone, and hydromorphone, are the most common treatment

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for background cancer pain [3]. BTCP is more difficult to manage due to its rapid onset, increased severity, and shorter duration, necessitating the need for rescue medications in response to BTCP [6, 7]. Current rescue medication treatments consist of immediate-release preparations such as immediate-release morphine, oxycodone, and hydromorphone. However, pharmacokinetic studies have demonstrated that these oral opioids can have a delayed onset of effect and long duration, resulting in a number of side-effects. Therefore, administration of rapid-release opioids, such as transmucosal administration of fentanyl or sufentanil, may be useful in managing BTCP as pain relief is experienced only 10–15 min after administration [7].

Inter-individual and intra-individual variation often exists with BTCP, as timing and severity of pain differs both between patients and between individual patient episodes [3]. In order to successfully manage cancer pain, and specifically BTCP, a thorough assessment of the patient is required and an individualized treatment plan must be created [3]. In order to best understand the patient's experience with severity of pain, a patient must be able to describe their pain to their health care provider. Patients, however, struggle with finding the correct words to accurately describe their pain, which can impact both the understanding of pain state by the health care provider as well as care [5]. Health care providers need to be cognizant of possible misinterpretation of pain. Providers must work with patients to determine the pain severity and characteristics in order for optimal management.

A number of studies have determined the safety and efficacy of various medications for the treatment of BTCP in cancer patients; however, only a small number of studies have been published analyzing the perspectives of patients experiencing BTCP and undergoing treatment for this pain. We have previously published data on the patient perspectives of BTCP in subsets of European and Canadian patients [8, 9]. The purpose of this study is to explore the similarities and differences in patient experiences and management of BTCP between Canadian and European cancer patients.

Methods

This was a non-interventional study conducted in the palliative care programs at 4 cancer centers across Canada and 28 centers across 13 European countries (Austria, Czech Republic, Denmark, Finland, Germany, Greece, Italy, The Netherlands, Republic of Ireland, Spain, Sweden, and the UK). A number of items were qualitatively compared between the two patient groups. The results of the individual Canadian [8] and European [9] studies have previously been reported.

To be eligible for the study, patients were required to be at least 18 years of age, have a diagnosis of cancer, be using prescription medication for background pain, and have breakthrough cancer pain of any degree. A standard one time survey questionnaire was utilized for both patient groups. The first section was comprised of screening questions to identify patients with breakthrough pain, while the second section asked questions about the characteristics of breakthrough pain. The questionnaire included demographic questions, questions on background and breakthrough pain characteristics as well as management, quality of life (through the use of modified Brief Pain Inventory—Short Form interference subscales), management of breakthrough pain, opinions towards alternative routes of analgesic administration, and a question on the important features new pain treatments should encompass.

The questionnaire was specifically developed for the purposes of the Canadian and European patient studies. For most questions, patients were to select an answer from a list of options. For questions were more than one answer was possible, patients were allowed to select as many as needed, and there was also space for patients to write their own answer if not included in the list. Limitations to this questionnaire included the fact that for questions where patients were able to fill in their own answer, analysis of the answers became more difficult as there were a wider variety of answers. Further information on this questionnaire can be found in the Canadian and European studies [8, 9].

Patients were recruited during clinic visits or during treatment by a clinical research associate. The questionnaire was completed by the patient while in the clinic. Patients were recruited consecutively from both the inpatient and outpatient populations.

Results

This study compared data between 1,000 European cancer patients and 94 Canadian cancer patients with BTCP. Demographic characteristics between the Canadian and European patient groups were compared (Table 1). The European population had a balanced number of males and females, while the Canadian population included more females (57 %). Age was similar between the two groups, with a median age falling between 60 and 69 years. There were a variety of primary cancer sites for both patient groups. The European group mostly included patients with primary cancers of the gastrointestinal tract (26.4 %), lung (17.2 %), urological origin (16 %), and breast (12.5 %). The Canadian group mostly included patients with primary cancers of the lung (21.3 %), breast (21.3 %), gastrointestinal tract (11.7 %), and urological origin (10.6 %).

The two patient groups were then compared on the basis of their breakthrough pain and analgesic characteristics. Analgesic characteristics were different between the two patient groups. A greater number of European patients than

Table 1 Patient demographics

Characteristic	European	Canadian
Gender	51 % male 49 % female	43 % male 57 % female
Age	62 years (median)	60–69 years—26 %
Primary cancer	Breast—12.5 % GI—26.4 % Gynecological—7.2 % Head and neck—6.5 % Hematological—3.5 % Lung—17.2 % Melanoma—2.5 % Neurological—0.8 % Sarcoma—3.4 % Unknown/not stated—4.0 % Urological—16 %	Breast—20.3 % GI—11.7 % Gynecological—2.1 % Head and neck—5.3 % Hematological—5.3 % Lung—21.3 % Melanoma—1.0 % Neurological—1.1 % Sarcoma—2.1 % Unknown—2.1 % Urological—10.6 % Other—16.8 %

Canadian patients were prescribed opioids to manage their background pain (99.7 vs. 86 %, respectively). Similarly, there were also more European patients prescribed opioids for breakthrough pain (97.4 vs. 90 %). In addition, European patients were more likely to be prescribed fentanyl for breakthrough cancer pain (19.1 vs. 2.9 %) (Table 2).

Patients were questioned as to how satisfied they were with the amount of pain relief they obtained from pain medications. Although there were relatively few European patients obtaining complete relief of their pain due to medications (20 %), 75 % of these patients said they were "satisfied" with their rescue medication. Similarly, 75 % of Canadian patients said they were "satisfied"; however, only 19 % of Canadian patients had very good relief of their pain with their BTCP medications.

Both patient groups experienced very similar BTCP characteristics (Table 3). The majority of patients' BTCP was incident related, with more Canadian (64.9 %) than European (44 %) patients reporting incident pain. In the European population, 43 % of patients experienced 2–3 BTCP episodes per day, and 39 % experienced more than 3 episodes, while in the Canadian population, 27.2 % experienced 2–3 episodes while 37 % of patients experienced more than 3 episodes a day. Both patient groups experienced a median time of 10 min to peak intensity for their BTCP. If left untreated, the duration of a BTCP episode would last over 60 min for half of Canadian patients, and for 37 % of European patients. It is important to note that not all European patients answered this question, 37 % of the 505 patients who responded to this question had an episode duration of greater than 60 min.

Pain greatly interfered with European and Canadian patients' daily activities. Canadian and European patients alike rated their pain interference with general activity as 7 out of 10, and pain interference with their work as 8 out of 10.

In order to relieve BTCP, patients were prescribed breakthrough pain medications. In comparison to Canadian patients, European patients were more likely to take their BTCP medication every time they had an episode (55 vs. 32.5 %). Both groups of patients had similar reasons for non-adherence, such as pain was not always severe, pain was not long-lasting, medications were not effective, and medications had side-effects, worry of addiction, and worry of tolerance (Table 3). In European patients, it has been documented that adherence was influenced by the frequency of BTCP; patients who experienced fewer episodes were more likely to take their rescue medication for every episode. This was not analyzed in the Canadian patient group. A small number (3.5 %) of European patients also utilized non-pharmacological and complementary therapies to help with their BTCP. These therapies included acupuncture, aromatherapy, homeopathy, praying, tea and coffee, hypnosis, and alcohol. This information was not documented for Canadian patients.

Discussion

BTCP negatively affects a large portion of cancer patients. A literature review by Deandrea et al. has recently been published, which aimed to conduct a pooled analysis of the prevalence of breakthrough cancer pain [10]. This study demonstrated the wide variety of breakthrough cancer pain, with large between-study heterogeneity. Individual study prevalence of BTCP ranged from 33.3 to 95.0 %, with outpatient clinic studies demonstrating lower prevalence rates [10]. Overall, through a pooled analysis, it was determined that approximately 53.8 % of cancer patients experience BTCP. These findings confirm the need for BTCP to be further investigated. Current treatments should be utilized more effectively, and new treatments developed in order to relieve the breakthrough pain felt by patients.

This is the first comparison of European and Canadian patient perspectives on BTCP. It is evident from this comparison that breakthrough cancer pain in both the European and Canadian cohorts is currently not optimally managed. European and Canadian patients alike struggle with BTCP on a daily basis, and the majority require breakthrough pain medications, most of which do not negate their pain.

European patients are more often prescribed fentanyl, a fast-acting opioid indicated for the treatment of BTCP. Fentanyl is a highly lipophilic synthetic opioid, which allows it to rapidly diffuse across the blood brain barrier to elicit rapid pain response [11]. Patients who were not prescribed fentanyl were treated most often with an oral opioid for pain relief. Most opioids typically take at least 20 min for the initial onset of pain relief [12, 13]. It appears that European physicians are more aware of the benefits of fentanyl, as a higher proportion

Table 2 Analgesia characteristics

Characteristic	European	Canadian
Background analgesia	Opioid—997 patients (99.7 %) Non-opioid—571 patients (36 %)	Opioid—78 patients (86 %) Non-opioid—13 patients (14 %)
Breakthrough analgesia	Opioid—974 patients (97.4 %) Non-opioid—289 patients (23 %)	Opioid—70 patients (90 %) Non-opioid—8 patients (10 %)
Fentanyl	19.1 % received fentanyl	2.9 % received fentanyl

European patients could document an opioid as well as a non-opioid medication, whereas Canadian patients' medications were classified as either opioid or non-opioid

of their patients were prescribed this agent to control BTCP. In addition, more European patients were receiving opioids for BTCP treatment. Nevertheless, both patient groups still experienced large amounts of uncontrolled BTCP.

Table 3 Breakthrough cancer pain characteristics

Characteristic	European	Canadian
Type of pain	Incident—44 % Spontaneous—41.5 % Combination—14.5 %	Incident—64.9 % Spontaneous—6.4 % Combination—28.7 %
Number of episodes a day	Less than 1 episode—7 % 1 episode—11 % 2–3 episodes—43 % 3+ episodes—39 %	Less than 1 episode—14.1 % 1 episode—17.4 % 2–3 episodes—27.2 % 3+ episodes—37.0 % Do not know—4.3 %
Time to peak intensity	10 min (median)	10 min (median)
Duration of untreated episode	<10 min—15 %[a] 10–30 min—25 %[a] 30–60 min—23 %[a] >60 min—37 %[a]	<10 min—16.6 % 10–30 min—15.2 % 30–60 min—15.2 % >60 min—50 % Not sure—3 %
Intensity	Mild—3.6 % Moderate—33.7 % Severe—61.8 % No data—0.9 %	Mean—7.8/10 Median—8/10
Pain interference	Degree of interference (0–10 scale) General activity—7/10 Mood—7/10 Walking—7/10 Work—8/10 Relations with others—5/10 Sleep—5/10 Enjoyment of life—7/10	Degree of interference (0–10 scale) General activity—7/10 Mood—7/10 Walking—7/10 Work—8/10 Relations with others—5/10 Sleep—6/10 Enjoyment of life—7/10
Rescue medication	55 % took all the time	32.5 % took all the time 32.5 % took most of the time 3.75 % took half of the time 28.8 % took occasionally 2.5 % never took
Non-adherence reasons[b]	Not always severe—44.5 % Not long-lasting—37.4 % Not effective—16.3 % Side effects—20.6 % Worried about addiction—27.9 % Worried about tolerance—19.7 % Limits set on usage—7.7 %	Not always severe—36.7 % Not long-lasting—16.7 % Not effective—18.3 % Side effects—6.7 % Worried about addiction—11.7 % Worried about tolerance—23.3 % Limits set on usage—1.7 %

[a] Data based off responses from 505 patients

[b] Patients were allowed to select more than one answer

It is important to note that neither the Canadian nor the European study correlated satisfaction with pain management with the use of a transmucosal opioid. Any benefit of the transmucosal administration is purely speculative. Head to head studies of regular release opioids versus transmucosal opioids are required to determine the correlation between the two. This should be further investigated in future studies.

Although the majority of patients from both groups have indicated that they are satisfied with their medications, they still experienced a number of debilitating BTCP episodes daily. Severe pain often resulted in decreased function and increased amounts of functional interference, thereby resulting in decreased quality of life [14]. It is evident that there is room for improvement in the BTCP management of both patient groups.

This study also demonstrates the need for patient education in terms of addiction and medication tolerance. Only 53 % of European patients and 32.5 % of Canadian patients reported taking their BTCP medication when they needed them. Fears of addiction and medication tolerance are two reasons for non-adherence that could potentially be avoided if patients are properly educated when given BTCP medication. Cancer pain education is imperative for patients and their families in order for them to understand their situation [15]. Patients should also be given adequate time to ask questions to their physician in order to disprove any unnecessary worry the patient may have in regards to their BTCP and BTCP medications. Having a greater number of open conversations with patients may be able to reduce the non-adherence that we have seen in this study. As breakthrough cancer pain varies considerably between patients and even between a single patient's episodes, it needs to be addressed on an individual basis [3].

Ultimately, it is imperative for physicians to effectively control BTCP through the use of medications and other treatments in order to prevent patients from experiencing unnecessary pain. In addition, controlling BTCP from its early manifestations will allow patients to maintain their quality of life as well as daily functioning. In the future, medications and treatments that can more effectively and promptly manage BTCP than current standards should be investigated and developed.

There are a few limitations with the methods that were carried out in this study. This study relied solely on patient self-reporting techniques, which can often be inaccurate as patients are not always precise in reporting their pain. For example, patients are often reluctant to report pain and their concern about medication side effects due to a variety of well-documented reasons, such as fear of addiction and side effects [16]. Pain is also a subjective experience, which makes it hard to quantify, and therefore report. In addition, this comparison had a large European sample size (n=1,000), and a much smaller Canadian sample size (n=94). The large difference in sample sizes may have had an impact on eventual comparisons, which relied purely on descriptive rather than inferential statistics.

Conclusion

There does not appear to be a large difference between the characteristics of BTCP in Canadian and European patients. For both patient groups, improvement in treatment of BTCP is warranted, and new treatments should be developed to better address this debilitating symptom of cancer. In addition, patients and physicians alike require further education about BTCP and management strategies. BTCP has a major impact on patients' quality of life, thus research into new treatments and alternative treatment administration routes should be investigated.

Conflict of interest None.

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