pISSN 1598-2998, eISSN 2005-9256

Cancer Res Treat. 2016;48(2):768-774

http://dx.doi.org/10.4143/crt.2015.087

Original Article

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A Korean Nationwide Survey for Breakthrough Cancer Pain in an Inpatient Setting

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Received March 2, 2015
Accepted June 21, 2015
Published Online September 15, 2015

Purpose

We evaluated the prevalence and characteristics of breakthrough cancer pain (BTcP) in Korean patients admitted with cancer pain.

Materials and Methods

In-hospital patients with cancer pain completed a questionnaire concerning severity of background cancer pain (BCP), prevalence and treatment for BTcP, sleep disorders, and satisfaction with cancer pain treatment. Medical records showing medications for BCP and BTcP were also evaluated.

Results

Total 609 patients with controlled BCP enrolled. Mean age of the patients was 59.5 years old, and 59% were male. Of all patients, 177 (29%) complained of BTcP. No clinical characteristic predicted BTcP. Of the 177 patients with BTcP, 56% did not receive treatment for BTcP. Patients with BTcP showed significant association with a sleep disorder and dissatisfaction with pain control, compared to those without BTcP ($p < 0.0001$ and $p=0.0498$, respectively). Oxycodone-immediate release was the most commonly used short-acting analgesic, followed by intravenous morphine.

Conclusion

The prevalence of BTcP was 29% in patients admitted with controlled BCP. Although the patients had well-controlled BCP, BTcP showed association with a lower quality of life in patients with cancer. More medical attention is needed for detection and management of BTcP.

Key words
Breakthrough cancer pain, Prevalence, Characteristics, Quality of life

Introduction

Pain is a significant problem in cancer patients and is often the most feared aspect of the disease; thus, effective analgesia is an essential component of pain management. Cancer patients require a comprehensive pain treatment plan that not only addresses the moderate to severe background cancer pain (BCP) but also provides adequate management of breakthrough cancer pain (BTcP) that has a separate and characteristically different presentation [1].

BTcP has different clinical and literature definitions [1]. BTcP was initially defined by Portenoy and Hagen in 1989 [2] as "a transitory flare of pain in the setting of chronic pain

managed with opioid therapy" [3]. According to more recent and comprehensive definitions, "BTcP is 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 BCP" [4]. As there is a lack of consistency in use of the term BTcP, most studies did not report the diagnostic criteria used in screening patients for BTcP or included patients with inadequately controlled BCP [3,5]. Indeed, BTcP is widely used to describe any exacerbation of pain in patients with BCP or intermittent episodes of pain in patients without BCP.

BTcP differs from BCP due to its high intensity (numerical rating score [NRS], 7), the short time interval between onset and peak intensity (median interval, 3 minutes to peak pain), short duration (median, 30 to 60 minutes), potential recurrence over 24 hours (3-4 daily episodes), and non-responsiveness to treatments for BCP [3,6-9].

BTcP impacts patient's quality of life (QoL). Because patients with BTcP are often less satisfied with their analgesic therapy, their functioning decreases due to pain, and they may also experience social and psychosocial consequences, such as increased anxiety and depression [8]. According to a large European observation study and a Canadian study, BTcP impacts daily living including normal work, mood, sleep, and walking activities [10,11].

Despite the increasing awareness of the need for evaluation and management of BTcP, only a few studies have investigated BTcP in Korea. We conducted this study to characterize the prevalence and treatments for BTcP in Korea, identify factors associated with the prevalence of BTcP, and to show the impact of BTcP on QoL.

Materials and Methods

This study was approved by the institutional review board of each participating hospital. This multicenter nationwide study was conducted from 11 September 2010, to 14 October 2010 in 78 hospitals using a patient questionnaire and retrospective review of medical records. The survey instrument was developed by the palliative care committee of the Korean Cancer Study group. Inclusion criteria were hospitalized patients whose BCP is controlled to a mild degree (NRS 3 or less), were receiving analgesic treatments, with a history of hospitalization for > 4 days. Patients aged ≥ 20 years who signed a consent form were eligible for participation. Patients who could not voluntarily participate in the survey due to clouded consciousness or who did not want to participate were ineligible.

Patients completed a questionnaire including (1) average pain intensity for the last 24 hours; (2) prevalence, frequency, and treatments for BTcP; (3) time interval between onset and treatment of breakthrough pain; (4) sleep disorder; and (5) satisfaction with pain treatment for the last week. Sleep disorder was defined as the frequency of unexpected awakening from sleep.

Patients' medical charts were reviewed with respect to pain management until the date the patient entered the study. The following information was obtained from medical records: patient characteristics (age, sex, diagnosis, stage, current treatment, and type of facility), Eastern Cooperative Oncology Group performance status (ECOG PS), and treatments for background pain and BTcP.

The patient's demographic and pain characteristics were summarized by a number of subjects (percentage). Association between the patient characteristics and presence of BTcP was examined using the chi-square test. A multiple logistic regression model was used to determine factors affecting BTcP. Degrees of difference in patient's QoL (in terms of sleep disorder and satisfaction with pain control) between patients with and without BTcP were examined using crude odds ratios and 95% confidence intervals. All analyses were performed using SAS ver. 9.4 statistical software (SAS Institute Inc., Cary, NC). A p-value of < 0.05 was considered significant.

Results

1. Patient demographic characteristics

Of the 1,841 patients with BCP, 496 (26.9%) complained of high NRS pain, and 736 patients (40%) complained of moderate NRS pain. The remaining 609 patients (33.1%) who complained of pain ≤ 3 NRS were analyzed. Of the 609 patients, 29.1% complained of BTcP. Percentage of patients ≤ 65 years was 63% and that of males was 59%. Most patients (86%) were admitted to the general ward, and most were diagnosed with a solid cancer (87%). Of all patients, 67% were receiving chemotherapy during the study. Approximately 80% of patients had stage IV cancer, and 84% were ECOG PS < 3 (Table 1).

2. Predictors for BTcP

Patients with BTcP were more frequently admitted to the hospice ward and were less frequently treated with chemotherapy compared to those without BTcP (p=0.0397 and p=0.0642, respectively) (Table 1). However, the results of multivariate analysis showed no significant predictors of

Table 1. Demographic characteristics of the study subjects

Variable	Breakthrough pain[a]		Total (n=609)	p-value[b]
	Yes (n=177)	No (n=432)		
Age (yr)				
≤ 65	117 (67)	262 (61)	379 (63)	0.1375
> 65	57 (33)	169 (39)	226 (37)	
Sex				
Male	104 (59)	253 (59)	357 (59)	0.9049
Female	72 (41)	179 (41)	251 (41)	
Ward				
Hospice	32 (19)	51 (12)	83 (14)	0.0397
Non-hospice	138 (81)	364 (88)	502 (86)	
Diagnosis				
Solid cancer[c]	151 (87)	365 (87)	516 (87)	0.7043
Hematologic malignancy	21 (12)	55 (13)	76 (13)	
Chemotherapy				
Yes	106 (61)	287 (69)	393 (67)	0.0642
No	67 (39)	128 (31)	195 (33)	
Stage				
I/II/III	17 (13)	57 (17)	74 (16)	0.2497
IV	115 (87)	274 (83)	389 (84)	
ECOG PS				
0, 1, 2	104 (76)	276 (81)	380 (80)	0.2477
3, 4	32 (24)	64 (19)	96 (20)	

ECOG PS, Eastern Cooperative Oncology Group performance status. [a]Values are presented as numbers of subjects (%), [b]p-values by chi-square test, [c]Solid cancer included epithelial originating (lung, stomach, colorectal, breast, esophagus, etc.) and mesenchymal originating cancer.

Table 2. Risk factors for predicting breakthrough cancer pain (BTcP)

Variable[a]	Coefficient	S.E.	aOR	95% CI (aOR)	p-value[b]
Age (≤ 65 yr)	0.3429	0.2418	1.409	0.88-2.26	0.1561
Female sex	0.0313	0.2337	1.032	0.65-1.63	0.8936
Department (non-hospice)	0.0253	0.3602	1.026	0.51-2.08	0.9439
Diagnosis (solid cancer)	0.5427	0.5745	1.721	0.56-5.31	0.3448
Current treatment (no)	0.2967	0.2601	1.345	0.81-2.24	0.2541
Stage (IV)	0.2259	0.3346	1.253	0.65-2.42	0.4997
ECOG PS (3-4)	0.3761	0.2977	1.457	0.81-2.61	0.2065

S.E., standard error; aOR, adjusted odds ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status. [a]Reference: age (> 65 years), sex (male), department (hospice), diagnosis (hematological malignancy), current treatment (yes), stage (I/II/III), ECOG PS (0, 1, and 2), [b]p-values by multiple logistic regression analysis.

BTcP frequency (Table 2).

The frequency of BTcP per day was 73 patients complained once, 62 complained twice, 25 patients complained three times, 11 patients complained four times, and six patients complained more than five times. The mean and median frequencies of BTcP were 1.95 and 2, respectively.

Table 3. Associations between breakthrough cancer pain (BTcP) and quality of life

Variable	Breakthrough pain[a]		Total (n=609)	p-value[b]	cOR (95% CI)
	Yes (n=177)	No (n=432)			
Sleep disorder					
1 or under	125 (71)	393 (91)	518 (85)	< 0.0001	1.0
2 or more	52 (29)	37 (9)	89 (15)		4.42 (2.77-7.05)
Pain control					
Dissatisfaction	23 (13)	34 (8)	57 (9)	0.0498	1.74 (1.00-3.06)
Satisfaction	154 (87)	397 (92)	551 (91)		1.0

cOR, crude odds ratio; CI, confidence interval. [a]Values are presented as numbers of subjects (%), [b]p-values by chi-square test.

Table 4. Associations between long-acting and short-acting analgesics

Long-acting analgesics	Short-acting analgesics	Breakthrough pain[a]		Total (n=609)	p-value[b]	cOR (95% CI)
		Yes (n=177)	No (n=432)			
Morphine	Morphine	3 (38)	2 (9)	5 (17)	0.1020	6.00 (0.78-46.14)
	No morphine	5 (63)	20 (91)	25 (83)		1.0
Fentanyl patch	Actiq	0	3 (2)	3 (1)	0.5528	-
	No actiq	80 (100)	157 (98)	237 (99)		-
Hydro-morphone	Hydromorphone IR	2 (15)	1 (4)	3 (8)	0.2421	4.73 (0.39-57.70)
	No hydromorphone IR	11 (85)	26 (96)	37 (92)		1.0
Oxycodone	Oxycodone IR	18 (31)	20 (13)	38 (18)	0.0038	2.85 (1.38-5.90)
	No oxycodone IR	41 (69)	130 (87)	171 (82)		1.0
Tramadol	Tramadol	0	1 (4)	1 (3)	1.0000	-
	No tramadol	6 (100)	23 (96)	29 (97)		-

cOR, crude odds ratio; CI, confidence interval; IR, immediate release. [a]Values are presented as numbers of subjects (%), [b]p-values by Fisher exact test.

3. Impact of BTcP on QoL

Patients with BTcP 4.42 times more frequently complained sleep disorder, which caused patients to wake up two or more times during sleep, compared to those without BTcP ($p < 0.0001$) (Table 3). And they were 1.74 times more unsatisfied with their pain control than patients who did not have BTcP (p=0.0498) (Table 3).

4. BTcP treatment

According to the patient questionnaire results, 77% of patients with BTcP answered that they were treated with a short-acting analgesic during an attack. A total of 110 patients answered that they were treated with a short-acting analgesic within 10 minutes, 29 patients within 11 to 20 minutes, five patients within 11 to 20 minutes, three patients within 31 to 60 minutes, and six patients after 60 minutes.

According to the medical records, 77 of 177 patients (44%) with BTcP were prescribed short-acting analgesics on the day of their enrollment in this study. Thirty-six patients were treated with oxycodone-immediate release (IR), 30 patients with morphine (29 intravenous morphine and one S-morphine), six patients with tramadol, three with hydromorphone, one with Actiq, and one with acetaminophen. There was no clinical predictor for the reason why patients did not take and short-acting analgesics. Concordance between long-acting and short-acting analgesics was analyzed. A cognate short-acting analgesic, such as oxycodone-IR, was more frequently prescribed for patients treated with oxycodone as a long-acting analgesic (p=0.0038) (Table 4).

Discussion

Recent surveys have reported BTcP prevalence of 28%-71% for in-patients with cancer [1]. Here, we reported prevalence of 29% among hospitalized cancer pain patients. This is a lower percentage than previously reported [12-14], although Hagen et al. [15] reported that 28% of patients with cancer pain have BTcP. Nationwide surveys conducted in Korea between 2001 and 2006 reported BTcP incidence of 35% [12]. One explanation for the discrepancy may be different inclusion criteria. Two surveys conducted in 2001 and 2006 enrolled cancer pain patients who visited the outpatient clinic or were admitted in hospital. These also included patients with uncontrolled BCP, and patients with advanced stage cancer and poor PS [12]. In comparison with previous studies, the current survey, conducted in 2010, only enrolled hospitalized patients with controlled BCP, as the exact definition of BTcP.

Actually, prevalence of BTcP varies in different settings. The lowest prevalence rates were detected in studies conducted in out-patient clinics and the highest were reported in studies conducted in the hospice ward [1]. Hospitalized patients who maintained generally good PS and received chemotherapy were enrolled in this study. This setting could explain the lower prevalence of BTcP. Another possible explanation for the lower prevalence of BTcP in the current study is that patients might have recall bias. As a matter of fact, 77% of our patients answered that they have received short-acting analgesics for BTcP but the medical records reported that only 44% of the patients were treated with short-acting analgesics. Thus, patients with BTcP may not have reported their pain because of difference between patients' memory of pain and the medical record of the study day. In addition, as no validated BTcP assessment tool was available at the time of this study, we could not reliably determine the prevalence of BTcP only by asking patients to describe the frequency, intensity, and duration.

BTcP affects patient's QoL. Bedard et al. [11] reported that BTcP impacts daily living activities of European and Canadian patients and Raj et al. [13] reported that patients with BTcP have more mood and sleep disturbances and are less able to keep up with normal work. We also found that BTcP was related to dissatisfaction with pain control and sleep disorders. However, there was no available clinical predictor to distinguish patients with and without BTcP. Thus, successful management of BTcP depends on a combination of adequate assessment and appropriate treatment. A systematic review of the literature in 2010 identified 10 tools for assessment of BTcP, seven of which were discussed but have not been made available and have only been used in one study [14]. Portenoy and Hagen [3] developed the Breakthrough Pain Questionnaire (BPQ) specifically for assessment of BTcP. This tool assesses the severity, location, pathophysiology, cause, and precipitating and palliative factors for BTcP, as well as its relationship to scheduled analgesic use through patient's self-report. Although the BPQ has been used in epidemiological and pharmaceutical studies, it has not been validated [14]. Hagen et al. [15] developed the Alberta Breakthrough Pain Assessment Tool (ABPAT), using the Delphi process, specifically for assessment of BTcP. This tool was developed for research purposes and was formally validated for clinical use in 2014 [16]. The Episodic Pain Documentation Sheet [17] and a modified version of the original Potenoy and Hagen questionnaire [18] were also developed for assessment of BTcP. However, only the ABPAT has been clinically validated for independent assessment of BTcP.

Oral IR opioid preparations are recommended as first-line therapy for BTcP [19]. Their advantages include easy administration, relatively rapid onset, and extensive experience in use. Morphine, oxycodone, and hydromorphone are available as oral IR preparations in Korea. Most patients were also treated BTcP with an oral or intravenous opioid. Concordance was observed between oxycodone as a long-acting analgesic and oxycodone IR as a short-acting analgesic because physicians had more experience in prescribing oxycodone as an oral preparation and it could be easily titrated. Many recent studies have suggested that buccal, sublingual, or oral/nasal transmucosal formulations of fentanyl are effective for BTcP [9,20,21]. Fentanyl is a highly lipophilic synthetic opioid, which shows rapid diffusion across the blood brain barrier to elicit a rapid pain response [22]. A recent study demonstrated that physicians are more aware of the benefits of fentanyl, as a higher proportion of patients are prescribed this agent for control of BTcP [11]. Fentanyl (Actiq) was only prescribed to 1.2% of patients in our study. In 2010, Korean physicians had limited options for treatment of BTcP. Actiq was first available for use in Korea in 2008 and Fentora and Abstral became available in 2014. Therefore, nowadays, with an established definition of BTcP, different assessment tools, and many treatment options for BTcP, this result did not coincide exactly with treatment of BTcP. However, this study might be useful in showing the state of epidemiology and clinical significance of BTcP and help support further studies in Korea.

This study had some limitations related to the methods used for classification of patients with BTcP. The study was designed to describe the epidemiology and pain management strategy for patients with cancer in Korea with special emphasis on the prevalence and treatment patterns for cancer pain in 2010. The variables and measurements used were most appropriate for BCP, not BTcP. Therefore, this study did not report subtypes of BTcP such as spontaneous or incidental type or the impact of BTcP on daily living. In

addition, we rely solely on patient self-reporting techniques, which can be inaccurate, as patients are not always specific when reporting their pain, and we did not use a BTcP-specified assessment tool, as no validated assessment tool for BTcP was available at the time of the study. Neverthless, this study presents the first report about BTcP in Korea based on a valid definition of BTcP.

Conclusion

In summary, approximately 30% of hospitalized patients with adequately controlled BCP complained of BTcP. Unfortunately, there were no clinical factors predicting the presence of BTcP, and BTcP impacted QoL of cancer patients with controlled BCP. Therefore, physicians should perform more appropriate evaluation, and provide adequate management of BTcP in cancer patients with controlled BCP.

This is the first study to show the prevalence and clinical characteristics of BTcP in Korea based on a valid definition of BTcP. Further advances in BTcP diagnosis and treatment, as well as knowledge of predictors will continue to inform us about the evolving, complex nature of cancer pain classification and management.

Conflicts of Interest

This research was supported financially by grants from the Johnson & Johnson family of companies, whose role was restricted and did not involve providing assistance to the investigators in the conception, conduct, and analysis of the study.

Acknowledgments

We thank all institutions and physicians participating in this survey. Participating institutions are listed as follows.

Ajou University Medical Center, Asan Medical Center, Baptist Hospital, Bobath Memorial Hospital, Bohun Hospital (Daegu), Bohun Hospital (Gwangju), Bohun Hospital (Seoul), Bundang CHA Hospital, Bundang Jesaeng Hospital, Busan Medical Center, Busan St. Mary's Hospital, Cheongju St. Mary's Hospital, Chonbuk National University Hospital, Chonnam National University Hwansun Hospital, Chosun University Hospital, Chung-Ang University Hospital, Chungbuk National University Hospital, Chungnam National University Hospital, Daegu Fatima Hospital , Daegu Catholic University Medical Center, Dankook University Hospital, Dong-A University Hospital, Dongguk University Ilsan Hospital, Gyeongsang National University Hospital, Eulji University Hospital (Daejeon), Eulji University Hospital (Seoul) Medical Center, Ewha Womens University Mokdong Hospital, Gachon University Gil Hospital, Good Samaritan Hospital, Korea Cancer Center Hospital, Hanil Hospital, Hallym University Medical Center, Hanyang University Hospital, Inha University Hospital, Inje University Haeundae Paik Hospital , Inje University Sanggye Paik Hospital, Inje University Seoul Paik Hospital, Inje University Busan Paik Hospital, Kangbuk Samsung Hospital, Keimyung University Dongsan Medical Center, Konkuk University Medical Center, Konyang University Hospital, Korea University Anam Hospital, Korea University Guro Hospital, Kosin Universiy Gospel Hospital, Kyung Hee University Hospital at Gangdong, Kyungpook National University Hospital, Medi-Yin Hospital, Myongji Hospital, National Health Insurance Servive Ilsan Hospital, Pusan National University Hospital, Pusan National University Yangsan Hospital, SAM Anyang Hospital, Saemyung Hospital, Samgsung Medical Center, Seoul Medical Center, Seoul Metropolitan Seobuk Hospital, Seoul National University Bundang Hospital, Severance Hospital, SMG-SNU Boramae Medical Center, Soonchunhyang University Hospital, Soonchunhyang University Bucheon Hospital, Soonchunhyang University Cheonan Hospital, St. Carollo Hospital, The Catholic University of Korea Bucheon St. Mary's Hospital, The Catholic University of Korea Daejeon St. Mary's Hospital, The Catholic University of Korea Incheon St. Mary's hospital, The Catholic University of Korea Seoul St. Mary's Hospital, The Catholic University of Korea Yeouido St. Mary's Hospital, The Catholic University of Korea St. Paul's Hospital, The Catholic University of Korea Uijeongbu St. Mary's Hospital, Wonju Christian Hospital, Wonkwang University Hospital, Yeungnam University Hospital.

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