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Characteristics of Breakthrough Pain and Its Impact on Quality of Life in Terminally Ill Cancer Patients

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Abstract

Purpose. This study aimed to characterize breakthrough pain (BTP) and investigate its impact on quality-of-life (QoL) in terminally-ill cancer patients. Similarities and differences between high and low predictable BTP were also tested. *Methods.* Secondary analysis of a multicenter longitudinal observational study included 92 patients at their end-of-life. BTP was assessed with a short form of the Italian version of the Alberta Breakthrough Pain Assessment Tool. QoL was assessed with the Palliative Outcome Scale (0-40). Patients were stratified by self-reported BTP predictability into unpredictable BTP (never or rarely able to predict BTP) and predictable BTP (sometimes to always able to predict BTP). *Results.* In all, 665 BTP episodes were recorded (median 0.86 episodes/day). A median duration of 30 minutes and a median peak intensity score of 7 out of 10 were reported. Time to peak was <10 minutes, 10 to 30 minutes, and ≥30 minutes in 267 (41.1%), 259 (39.9%), and 30 (4.6%) of the episodes, respectively. Onset of relief occurred after a median of 30 minutes. Time to peak ($P < .001$) and duration ($P = .046$) of BTP was shorter in patients with predictable pain ($n = 31$), who usually were younger than those with unpredictable pain ($P = .03$). The mean (SD) QoL score was 14.6 (4.6). No difference in QoL between patients with predictable and unpredictable BTP was found ($P = .49$). *Conclusions.* In terminally-ill cancer patients, BTP is a severe problem with a negative impact on QoL and has different characteristics according to its predictability.

Keywords

breakthrough pain, epidemiology, neoplasms, palliative care, pain assessment, patient perspective, quality of life

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Introduction

Controlling symptoms including pain in patients with poor prognosis is critical in cancer care. Two types of pain pattern have been identified in cancer patients: background pain and breakthrough pain (BTP). Whereas the former is continuous and appears quite controlled according to the 3 steps of the World Health Organization,[1] the latter emerges as a transitory exacerbation of pain to greater than moderate intensity, which occurs on a baseline pain of moderate intensity or less.[2] The BTP can occur spontaneously or in relation to a specific and predictable or unpredictable trigger despite relatively stable and adequately controlled background pain.[3] Moreover, some patients may experience a combination of both spontaneous and trigger-related episodes.[4]

The prevalence of BTP in cancer patients ranges between 40% and 80% and is associated with more advanced disease, with a wide heterogeneity across settings and patient groups.[5] At the end of life (EOL), BTP becomes an even worse distressing issue involving almost all cancer patients with a daily occurrence and high intensity.[6,7] A recent study on the circadian rhythm of BTP episodes in terminally ill cancer patients found an average of 7.2

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episodes per patient over a 7-day period with about 80% of episodes recorded between 8.00 AM and 12 AM.[6]

Patients with BTP reported poor quality of life (QoL) with low physical, psychological, and social well-being.[8,9] Moreover, BTP can place significant economic burden on both patients and their families as well as on the health care system: BTP can be associated with higher work impairment and absenteeism[8] alongside increase in emergency and hospital admission and longer in-hospital stays.[10]

Managing BTP is challenging: although there is a good evidence for managing background pain, evidence for the management of BTP is poor, likely because of its heterogeneous nature with wide variation from patient to patient and also within the same individual. A recent consensus suggested that a BTP subclassification according to pain pathophysiology may provide guidance in tailoring treatments.[11] Therefore, to allow a thorough assessment that in turn will facilitate optimal management, patients are advised to be engaged in describing their own experience with BTP. However, patients may struggle with expressing their subjective experiences, showing difficulties in finding the correct words to describe their pain.[12] Thus, the Alberta Breakthrough Pain Assessment Tool (ABPAT) was developed and validated to manage this shortcoming.[13,14] The ABPAT includes relevant characteristics of BTP, including patients in describing their BTP. However, to our knowledge, few studies adopted the ABPAT to provide a comprehensive description of BTP characteristics in patients with advanced cancer.[9,14]

Health care professionals should work with patients to capture the specific nature of BTP and maximize treatment efficacy. Therefore, this study aimed to characterize BTP using the ABPAT and investigate its impact on QoL in terminally ill cancer patients. A secondary aim was to verify similarities and differences between high and low predictable BTP.

Material and Methods

Study Design

This is a secondary analysis of a multicenter, longitudinal, observational study performed from December 2012 to July 2013.[6] The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were followed to report this study.[15]

Sample and Setting

Consecutive adult cancer patients at their EOL from 2 Italian palliative care services (1 palliative home care service and 1 hospice) in the Northwest of Italy were recruited. To be included, patients had to have (*a*) histologically confirmed diagnosis of cancer, (*b*) no possibility of active oncological treatment, (*c*) a life expectancy of less than 120 days, (*d*) analgesic treatment with long-acting major opioids (ie, fentanyl transdermal, morphine intravenous/intravenous elastomer/subcutaneous/oral, oxycodone, methadone, hydromorphone, or buprenorphine), (*e*) their opioid dose assessed by previous titration, and (*f*) adequately controlled background pain (≤3/10 on the Numeric Rating Scale [NRS]). Exclusion criteria were the following: concomitant local analgesic treatment (ie, peripheral nerve ablation or spinal cord treatment) at the time of recruitment, completion of radiation therapy or radionuclide therapy within 1 month of recruitment, ascertained possibility of end-of-dose-related pain, major psychiatric disorders, and cognitive incompetence.

Procedures and Instruments

In each care setting, a palliative care nurse approached eligible patients and screened them according to the abovementioned criteria. Screening took place during the daily visit for patients receiving home palliative care services and during hospice stay for hospice patients. All patients provided written informed consent after being informed about the study and its aims. The study obtained the approval by the Ethical Committee of Azienda Ospedaliero Universitaria San Luigi (Italy) on 14 February 2013 (ethic code 3119/II/02/01).

BTP was assessed using a short form of the Italian version of the ABPAT that covers the following domains[14]: (*a*) frequency, (*b*) duration (in minutes), (*c*) time from onset to peak intensity (in minutes), (*d*) peak intensity score (on a NRS 0 = *no pain* to 10 = *worst pain possible*), (*e*) time to relief (ie, time from onset to end of episode in minutes), (*f*) relief intensity score (on NRS 0 = *no pain* to 10 = *worst pain*), (*g*) predictability of BTP on a 5-point Likert scale (1 = *never*, 2 = *rarely*, 3 = *sometimes*, 4 = *often*, 5 = *always*), (*h*) relationship with baseline pain (ie, participating patients were asked to define their BTP episodes as a brief intensification of their background pain or different from their background pain; the "I don't know" option was also available), (*i*) pain quality with specified descriptors (eg, pulsating, crampy, hot-burning), (*j*) cause of BTP (ie, triggers such as walking, eating, coughing, defecating), and (*k*) factors relieving BTP. For questions where more than one answer was possible, patients could select as many as needed, and space was provided to allow patients to write their own answer if it was not included in the list.

Patients registered onset (day and time), duration, time to peak, peak intensity score, time to relief, and relief intensity score for each BTP episode over a 7-day period using a personal diary. Nurses and family caregivers helped patients with the reporting and checked that each BTP episode was reported.

At recruitment, data on sex, age, and the following clinical characteristics were also collected: cancer site, metastasis (no vs yes and site), Eastern Cooperative Oncology Group (ECOG) performance status, around-the-clock analgesic therapy (drug and route of administration), QoL (Palliative Outcome Scale [POS]), and care setting (home care vs hospice). The ECOG identifies 5 grades of performance status: 0 = *no symptoms*; 1 = *mild symptoms*; 2 = *bedridden for ≤50% of waking hours*; 3 = *bedridden for >50% of waking hours*; 4 = *completely disabled*; 5 = *dead*. The POS assesses a patient's QoL by evaluating physical, psychological, and spiritual domains via 10 items. Eight items utilize a 5-point Likert scale, and the remaining two utilize a 3-point scale. The score for each item ranges from 0 (*no problem*) to 4 (*severe problem*). The overall POS score is obtained by summing the scores of all 10 items and, thus, ranges from 0 (*worst QoL*) to 40 (*best QoL*).[16]

Statistical Analysis

Descriptive and inferential statistics were used. Categorical variables were computed as sums and percentages, whereas continuous variables were expressed as means and SDs and/or range and median and interquartile range (IQR). The Shapiro-Wilk test was used to test the normality of the variables. The χ^2 test, *t* test, or Wilcoxon rank sum test were used to test differences according to the nature of the variable.

Patients were also stratified by predictability of BTP episodes into the unpredictable BTP group (1 to 2 on the Likert scale) and predictable BTP group (3 to 5 on the Likert scale). Difference in daily frequency, duration, peak intensity score, time to peak of BTP episodes, and QoL scores between unpredictable and predictable BTP groups was tested.

All statistical computations were performed using R version 3.4.0.[17] The level of statistical significance was set at a 2-tailed α level of $\leq .05$.

Results

Patient Characteristics

A total of 92 patients was involved. The mean age was 72.2 (±12.0) years, and men accounted for 44.6% of the sample. Lung cancer (n = 16, 17.5%) was the most prevalent diagnosis followed by large-bowel (n = 14, 15.2%), breast (n = 12, 13.0%), and urogenital (n = 11, 12.0%) cancer. Bone (n = 30, 32.6%), liver (n = 20, 21.7%), lung (n = 18, 19.6%), and lymph nodes (n = 16, 17.4%) were the most frequent sites of metastasis. Transdermal fentanyl was the most frequent around-the-clock analgesic used (n = 34, 37%), followed by intravenous morphine (n = 23, 25%) and oral oxycodone (n = 14, 15.3%; Table 1).

A total of 61 (66.3%) patients reported that they were never or rarely able to predict the onset of their BTP episodes (unpredictable BTP group), whereas 31 (33.7%) patients were sometimes or often able to predict the onset of their BTP episodes (predictable BTP group). No patients reported that they were always able to predict their BTP episodes.

Patients with predictable BTP episodes were younger (mean age = 68.4 vs 74.1 years, $P = .03$) than patients whose BTP episodes were unpredictable. Differences in the around-the-clock analgesic therapy were found between patients with predictable BTP episodes and those with unpredictable BTP episodes, with the former being prescribed oral morphine more frequently than the latter ($P = .021$, Table 1).

Frequency, Duration, Intensity, Time to Peak, and Time to Relief of BTP Episodes

In all, 665 BTP episodes were recorded, with a median (IQR) number of 0.86 (0.43-1.32) BTP episodes per day. Median duration was 30 minutes, and median peak intensity score was 7 out of 10. Time to peak was <10 minutes in 267 (41.1%) episodes, 10 to 30 minutes in 259 (39.9%) episodes, and more than 30 minutes in 30 (4.6%) episodes. Patients did not know the time to peak in about 1 of 6 episodes (n = 94, 14.5%). Onset of relief occurred after a median of 30 minutes, with a drop in the pain intensity score to a median of 2 out of 10 (Table 2).

Patients with predictable BTP episodes had a lower median duration (30 vs 40 minutes, $P = .02$) and a more rapid time to peak (<10 minutes in 51.8% of episodes vs 43.3% of episodes, $P < .001$) of BTP than patients with unpredictable BTP episodes (Table 2). No difference was found in daily frequency ($P = .17$), peak intensity score ($P = .49$), time to relief ($P = .67$), and relief intensity score ($P = .38$).

Patients' Self-report About Characterization of BTP

BTP was described as a brief flare-up of the background pain (n = 50, 54.3%) or as a pain different from the background pain (n = 21, 22.8%); 21 (22.8%) patients were not sure about how to describe their BTP. Patients described their BTP using multiple descriptors in the ABPAT, most commonly with nociceptive characteristics (Table 3) such as shooting (n = 35, 38%), sharp (n = 32, 34.8%), stabbing (n = 20, 21.7%), and aching (n = 18, 19.6%); less often, patients described neuropathic pain characteristics such as crampy (n = 9, 9.8%) and hot-burning (n = 9, 9.8%) or psychological pain characteristics such as terrible/cruel (n = 9, 9.8%), tiring/exhausting (n = 7, 7.6%), and fearful (n = 5, 5.4%).

Table 1. Patient Characteristics at Recruitment According to the Predictability of BTP Episodes (n = 92).

Patient Characteristics	Unpredictable BTP Group (n = 61, 66.3%), n (%)	Predictable BTP Group (n = 31, 33.7%), n (%)	*P*
Male sex	26 (42.6)	15 (48.4)	.76
Age, years			
Mean (SD)	74.1 (12.9)	68.4 (9.1)	.03
Range	41-97	48-84	
ECOG			.60
0	0 (0.0)	1 (3.2)	
1	9 (14.8)	3 (9.7)	
2	4 (6.6)	3 (9.7)	
3	18 (29.5)	10 (32.3)	
4	30 (49.1)	14 (45.1)	
Site of the primary tumor			.10
Lung	9 (15.3)	7 (24.1)	
Large bowel	12 (20.3)	2 (6.9)	
Breast	11 (18.6)	1 (3.4)	
Urogenital	4 (6.8)	7 (24.1)	
Gynecological	6 (10.2)	1 (3.4)	
Head and neck	5 (8.5)	2 (6.9)	
Pancreas	4 (6.8)	2 (6.9)	
Stomach	3 (5.1)	3 (10.5)	
Other	5 (8.4)	4 (13.8)	
Site of metastasis[a]			.28
Bone	15 (17.0)	15 (29.4)	
Liver	12 (13.6)	9 (17.6)	
Lung	13 (14.8)	4 (7.8)	
Lymph nodes	17 (19.3)	8 (15.7)	
Brain	2 (2.3)	3 (5.9)	
Other	29 (33.0)	12 (23.6)	
Around-the-clock analgesic therapy (route of administration)			.02
Fentanyl (transdermal)	26 (34.7)	8 (18.2)	.055
Morphine (intravenous)	12 (16.0)	13 (29.5)	.080
Oxycodone (oral)	12 (16.0)	2 (4.5)	.061
Morphine (intravenous elastomer)	4 (5.3)	4 (9.1)	.429
Morphine (oral)	2 (2.7)	6 (13.6)	.021
Methadone (oral)	2 (2.7)	0 (0.0)	.275
Others	17 (22.6)	11 (25.1)	.772

Abbreviations: BTP, breakthrough pain; ECOG, Eastern Cooperative Oncology Group.
[a]The sum is higher than the number of patients because several patients had more than 1 metastasis.

Table 2. Frequency, Duration, Intensity, Time to Peak, and Time to Relief of BTP Episodes (n = 665).

	Overall (n = 92)	Low BTP Predictability Group (n = 61, 66.3%)	High BTP Predictability Group (n = 31, 33.7%)	*P*
Daily frequency, median (IQR)	0.86 (0.43-1.32)	0.86 (0.43-1.29)	1.00 (0.57-1.64)	.17
Duration, minutes, median (IQR)	30.0 (30.0-60.0)	40.0 (30.0-60.0)	30 (30.0-60.0)	.046
Peak intensity score (NRS 0-10), median (IQR)	7 (6-8)	7 (6-8)	7 (6-8)	.49
Time to peak (n = 650), n (%)				<.001
<10 Minutes	267 (41.1)	137 (34.3)	130 (51.8)	<.001
10 To 30 minutes	259 (39.9)	167 (41.9)	92 (36.7)	.187
>30 Minutes	30 (4.6)	21 (5.3)	9 (3.6)	.321
Do not know	94 (14.5)	74 (18.5)	20 (8.0)	<.001
Time to relief, minutes, median (IQR)	30 (20-30)	30 (20-30)	30 (15-30)	.67
Relief intensity score (NRS 0-10), median (IQR)	2 (1-3)	2 (1-3)	2 (2-3)	.38

Abbreviations: BTP, breakthrough pain; IQR, interquartile range; NRS, Numeric Rating Scale.

Table 3. Characterization of BTP, and Triggering and Relieving Factors According to Patients' Self-report.

Descriptors of BTP,[a] n (%)	
Shooting	35 (38.0)
Sharp	32 (34.8)
Stabbing	20 (21.7)
Aching	18 (19.6)
Heavy/Squeezing	17 (18.5)
Throbbing	13 (14.1)
Gnawing	11 (12.0)
Crampy	9 (9.8)
Hot-burning	9 (9.8)
Sickening	9 (9.8)
Terrible/Cruel	9 (9.8)
Tiring/Exhausting	7 (7.6)
Fearful	5 (5.4)
Something else	15 (16.1)
Triggering factors,[a] n (%)	
Movement in bed	36 (39.1)
No specific trigger	23 (25.0)
Coughing	13 (14.1)
Sitting	11 (12.0)
Standing	11 (12.0)
Walking	11 (12.0)
Touching skin areas	10 (10.9)
Bowel movement/Urinating	10 (10.9)
Not sure	7 (7.6)
Breathing	5 (5.4)
Scheduled pain medication wearing off	5 (5.4)
Swallowing	5 (5.4)
Eating	3 (3.3)
Vomiting	1 (1.1)
Something else	21 (22.6)
Relieving factors,[a] n (%)	
As needed BTP medications	73 (79.4)
Scheduled pain medications	62 (67.4)
Sleeping	13 (14.1)
Lying down/Sitting/Rolling up	13 (14.1)
Applying heat/Cold	5 (5.4)
Massage	5 (5.4)
Bowel movement/Urinating	4 (4.4)
Moving	4 (4.4)
I don't know	4 (4.4)
Avoiding coughing	3 (3.3)
Breathing	1 (1.1)
Something else	16 (17.4)

Abbreviation: BTP, breakthrough pain.
[a]The sum is higher than the number of patients because several patients reported more than 1 descriptor, or triggering or relieving factors for their BTP.

The most commonly identified triggers of BTP were "movement in bed" (n = 36, 39.1%) and "coughing" (n = 13, 14.1%); one-fourth (n = 23) of the patients reported no specific trigger, and in 7 cases, the precipitant was not identified with certainty (Table 3). The most common relieving factor was "as needed BTP medications" (n = 73, 79.4%), and 62 (67.4%) achieved relief through scheduled pain medications. The most common nonpharmacological strategies used to reduce pain flares included sleeping (n = 13, 14.1%) and lying down/sitting/rolling up (n = 13, 14.1%; Table 3).

Health-Related Quality of Life

In all, patients reported mean (SD) scores on the POS of 14.6 (4.6). No difference was found with regard to the QoL between patients with predictable BTP episodes and those with unpredictable BTP episodes (mean POS score 14.1 [SD = 3.8] vs 14.8 [SD = 5.0]; $P = .49$).

Discussion

This study describes the main characteristics of BTP episodes in terminally ill cancer patients and tests similarities and differences in the nature of BTP between patients with predictable BTP and those with unpredictable BTP. The results document that BTP is sudden, short in duration, and severe in intensity and has a negative impact on QoL in a terminally ill cancer population. Moreover, BTP predictability influences pain characteristics.

The prevalence of unpredictable BTP was double that of predictable BTP, confirming previous data,[18,19] although some authors found a lower proportion of unpredictable pain.[4,7] However, our patients were terminally ill with almost half having an extremely low performance score, thus being less likely to be engaged in volitional activities such as walking that may trigger the pain episode.[20]

The time to peak intensity was less than 10 minutes, which is consistent with that reported in previous studies.[4,7,9,18,19] The median duration was 30 minutes, which is in keeping with some previous studies,[7,8] although somewhat shorter than that reported in other studies.[4,18,19]

Patients with predictable pain had a shorter time to peak intensity and a shorter duration of BTP episodes, confirming previous literature.[4,7,21] Moreover, they were younger compared to those with unpredictable pain; it could, therefore, be argued that this population had higher levels of physical activity inducing BTP.[7]

Patients reported BTP to be severe by referring a median peak intensity score of 7 out of 10,[9,19,22] whereas relief generally occurred 30 minutes after the onset of the episode. Time to relief confirmed previous data,[9] although other authors reported relief to be achieved more quickly.[19]

Patients generally described their BTP as a brief flare-up of their background pain,[9] by adopting nociceptive adjectives such as shooting or stabbing, whereas adjectives referring to neuropathic (eg, crampy) or psychological (eg, fearful) characteristics were less frequently used.[8,9] This is not surprising because BTP has been suggested to

be mostly sustained by a nociceptive mechanism and only to a lower extent having a neuropathic or psychological nature.[18,19,23] However, the mechanism underlying BTP is usually mixed.[18,19]

The main triggering factor for predictable BTP was movement, whereas nonvolitional activities such as coughing or vomiting were ranked much lower.[8,9,18,19] In contrast to a previous research,[9] the aspects related to end-of-dose failure were not noteworthy because only 5 patients attributed their pain to medication wearing off. This suggests attention by palliative care teams in the assessment of pain intensity and dosage of pain medications, which may be also sustained by the patients' acknowledged terminal condition and the desire to guarantee an EOL without suffering. The most common intervention to relieve BTP was as-needed BTP medication followed by scheduled pain medications, confirming previous data.[7,9] Among the nonpharmacological treatments, sleeping and resting were the most common strategies adopted.[4,7,8]

Our data confirm previous literature that extensively documents poor QoL in patients with cancer-related BTP. Patients complain of negative consequences on both physical and psychological well-being, with interference in daily activities, lowered mood, sleep disorders, loss of life enjoyment, and disrupted social relationships.[4,7,8,18] We found no difference in QoL between patients with predictable BTP and those with unpredictable BTP, differently from Davies et al,[4] suggesting that patients with predictable BTP are more likely to report interference with activities of daily living, whereas sleep and mood are more affected in patients with unpredictable BTP. However, we assessed QoL by merging all the items of the POS, and data for each item that could have provided a more in-depth understanding of the affected QoL dimensions according to the nature of BTP are not available.

This study relies only on patient self-report, which can be inaccurate because patients may not be always precise in reporting their pain. Second, the generalizability of our findings is limited by the small sample size, although the data collection on 2 different series of patients (patients in a palliative home care service and hospice patients) reduced the possibility of a result occurring by chance. Additionally, the small sample size prevented meaningful analyses of BTP characteristics and relieving factors according to BTP predictability. Future research on larger samples is warranted to more fully examine the characteristics of BTP in this population. However, the study offers a picture of BTP in an understudied terminally ill population, with almost half of the included patients having an ECOG performance status of 4, whereas only 3% had an ECOG performance status of 0. Moreover, the findings are strengthened by the use of a validated and well-accepted assessment tool[14] and reporting according to STROBE guidelines.[15]

Conclusions

Our findings confirm that BTP is a severe problem with a negative impact on QoL in terminally ill cancer patients and that it may appear with nociceptive, neuropathic, or psychological features. Moreover, we found that time to peak intensity and duration of BTP was shorter in patients with predictable pain who usually were younger than those with unpredictable pain. This suggests that BTP characteristics may vary and be influenced by functional status. Therefore, improving the assessment of BTP with specific focus on pain features to identify the nature of BTP is mandatory. In addition, BTP therapy should be tailored to the patient's clinical conditions and characteristics of BTP to optimize pain management and thereby QoL.

Rescue medications may be used prophylactically for predictable pain or as soon as pain starts for unpredictable pain; moreover, BTP with a slow onset and lasting for an hour or more may respond best to oral opioids, whereas BTP of rapid onset and short duration may mostly benefit from transmucosal opioids. In addition, specific treatments such as drugs active on the central nervous system and anxiolytics should be used to address those BTP episodes with neuropathic and psychological features.

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