Original Article

Breakthrough Pain in Oncology: A Longitudinal Study

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Abstract

Context. Existing studies on breakthrough pain (BP) have reported different prevalence rates because of different settings, populations, and assessment methods. These studies have used cross-sectional designs, and the relationship of BP with analgesic treatment has not been evaluated.

Objectives. The aim of this study was to longitudinally assess BP in cancer patients admitted to oncology units.

Methods. A consecutive sample of patients admitted to oncology centers was selected. At admission (T0), three months after admission (T3), and six months after admission (T6), data on background pain and BP were recorded. BP was assessed in terms of its intensity, duration, number of episodes, onset with movement, spontaneous relief after stopping activity, limitation of physical activity, and effectiveness of analgesics.

Results. Three hundred two patients completed the study. At T0, T3, and T6, 39%, 38%, and 33% patients, respectively, had continuous pain ($P = 0.294$). Pain intensity significantly decreased ($P = 0.004$ and 0.027 at T3 and T6, respectively). Most patients had BP at T0 (87.1%), T3 (80.9%), and T6 (73.2%), and there was a significant decrease in the prevalence of BP over time ($P = 0.016$). Of 149 patients with BP, pain on movement was recorded in 43.6%, 43.4%, and 32.4% at T0, T3, and T6, respectively ($P = 0.228$). Pain spontaneously decreased or ceased when stopping physical activity in 66%, 56%, and 62% at T0, T3, and T6,

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respectively ($P = 0.537$). Pain on movement strongly limited physical activity in most patients.

Conclusion. These data expand current information about BP and underline the need for a longitudinal assessment of a phenomenon that is invariably dependent on stage of disease, patient, and therapeutic factors. J Pain Symptom Manage 2010;40:183–190.

Key Words
Cancer pain, breakthrough pain, epidemiology, oncology

Introduction

In the cancer population, breakthrough pain (BP) is a transitory flare of pain superimposed on an otherwise stable pain pattern in patients treated with opioids.[1] Several cross-sectional studies have reported a variable prevalence, dependent on the setting, such as hospice admission, oncology inpatient, or pain clinic. In an international survey performed in a wide range of patients with pain severe enough to be treated with opioids, a BP prevalence of about 65% was found, and BP was associated with poor pain control and functional impairment.[2] In advanced cancer patients followed by palliative care physicians in different settings, including hospice and home care, BP had a prevalence of 86%–93%,[3–5] whereas in other studies with a mixed population, a lower prevalence (41%–51%) was found.[6,7] In an outpatient pain clinic, BP was found in 39% of patients.[8] All these data occur in the context of chronic pain; oncology outpatients and inpatients admitted with uncontrolled pain have an overall prevalence of 70%.[9]

It is likely that different settings, populations, and assessment methods may produce different results in surveys of BP. Moreover, existing studies are cross-sectional, and no study has assessed changes in BP over time during the course of disease and the possible relationship with the analgesic treatment. For example, one type of BP, incident pain because of movement in patients with bone metastases, may be influenced by physical activity, which is dependent on the stage of disease or response to oncologic treatment. Moreover, patients receive an analgesic treatment that can be either effective or insufficient, and the outcome strongly influences the feature of BP. In other words, the entity of BP is strictly linked to the clinical scenario, rather than a phenomenon of pain, independent from other variables.

Patients with cancer pain can be placed at two extremes, with a large variability between these points: patients who are receiving oncologic treatment are quite different from advanced cancer patients with a short survival followed at home. Because of the dynamic course of cancer disease and analgesic regimen, it is likely that changes in these components influence BP.

The aim of the present project was to longitudinally assess BP in different settings according to the different stages of disease and treatments. The present study assessed patients in oncology units longitudinally followed over a period of six months during the course of disease. Data regarding advanced cancer patients who were followed at home have been the subject of a concomitant study with a similar but shorter design.

Patients and Methods

This survey was a prospective, longitudinal, observational study. An investigator meeting was held to explain to each responsible center participating in the study the procedures for assessing BP and other details of the study. Informed consent and approval of ethics committees were obtained.

A specific chart was designed to gather study information from patients at time of inclusion and for the following assessments (visit or telephone). A consecutive sample of patients admitted to different oncology centers in Italy

during two days of the first week of October 2007 was recruited. Patients could be in the day hospital, inpatient units, or outpatient clinic. The patients who gave their informed consent to participate in the study were assessed and surveyed for a period of six months. Patients were excluded if they had a survival expectation of less than six months or were cognitively impaired or too unwell to provide reliable answers to questions regarding data collection.

After the screening, common epidemiologic data, the presence of continuous pain and its intensity (on a numerical scale from 0 to 10), and the presence of BP were recorded. If BP was reported, it was assessed according to intensity (on a numerical scale from 0 to 10), duration, number of episodes, whether induced by movement, and whether there was spontaneous relief after stopping activity. The severity of limitation of physical activity because of pain on movement was graded as none (0), lightly (1), severely (2), and completely (3). Patients were asked information about the analgesic regimen for continuous pain and its effectiveness, as well for BP, graded as none (0), poor (1), moderate (2), and good (3), and the use of bisphosphonates also was recorded. Data were collected by treating physicians responsible for the study at each center.

After the initial assessment, patients received analgesics for background pain and BP, as well as symptomatic treatment usually provided at each oncology center, according to local policies and protocols, without changing routine activity. They continued their oncologic treatments as per protocol. At three- and six-month intervals (T3 and T6, respectively), the same data collected at admission (T0) were recorded. When patients were unavailable for a visit, they were contacted by phone.

Statistical Analysis

Data collected in the charts were computerized and analyzed by SPSS Software (v.14.0, SPSS, Inc., Chicago, IL). Statistical analysis of quantitative data, including descriptive statistics, was performed for all the items. The paired Wilcoxon signed-rank test and the paired samples Student's *t*-test were used to compare the differences in pain intensity scores and other parameters at the time intervals. All *P*-values were two-sided, and *P*-values less than 0.05 were considered to indicate statistical significance.

Results

Four hundred thirty-five of 750 patients initially screened during the two days of the first week of October 2007 were recruited from six oncology centers in Italy and surveyed for this study. Two hundred sixty-five were excluded according to the criteria described in the protocol or because they did not give their consent. The characteristics of patients are described in Table 1. Mean Eastern Cooperative Oncology Group (ECOG) value at study entry was 1 and remained stable for the entire period of study (Table 2). Data regarding 65 and 133 patients were unavailable at T3 and T6, respectively. Forty-two patients and 100 patients had died by T3 and T6, respectively. Ten patients and four patients moved to other hospitals by T3 and T6, respectively. Data were missing in 13 and 29 patients at T3 and T6, respectively.

At admission (T0), 171 (39%) patients had continuous pain, with a mean (standard deviation) pain intensity of 5.6 (1.9). No significant changes were observed at T3 and T6 (38% and 33%, respectively; $P = 0.294$). Pain intensity significantly changed at T3 and T6 ($P = 0.004$ and 0.027, respectively), as well as the effectiveness of background analgesia ($P < 0.0005$ at T3 and T6). At T0, 126 (73.7%) patients were satisfied (moderate to good) with the background analgesia. At T3 and T6, 133 (93%) patients and 92 (91%) patients,

Table 1
Characteristics of Surveyed Patients

Characteristic	Value
No. of participants	435
Mean age	62.9 (95% CI: 61.7–64.0)
Gender	
Male	201
Female	234
Primary tumor	
Lung	65
Breast	100
Gastrointestinal	111
Urogenital	94
Liver	20
Other	45

CI = confidence interval.

Table 2
Reason for Admission and Data Regarding Continuous Pain at the Different Time Intervals

	T0	T3	T6
n	435	370	302
ECOG score	1.0 (±0.9)	1.0 (±1.0)	1.0 (±1.0)
Reason for admission			
CH DH	267	140	99
CH admission	31	20	20
Symptom control or other reason	137	210	183
Continuous pain (y/n)	171/304 (39%)	142/279 (38%)	101/228 (33%)
Intensity	5.6 (±1.9)	4.9 (±2.2)	4.8 (±2.0)
Use of strong opioids	88 (51.4%)	79 (55%)	59 (54%)
Bisphosphonates (y/n)	57	52	29
Satisfaction with treatment[a]			
0	20	2	1
1	25	7	8
2	69	53	29
3	57	80	63

CH DH = chemotherapy in day hospital; CH admission = chemotherapy during admission.
[a]Satisfaction graded as 0 = none, 1 = poor, 2 = moderate, and 3 = good.

respectively, were satisfied with the background analgesia. No change in the use of strong opioids and bisphosphonates was observed (Table 2).

Most of these patients had BP at T0 (87.1%), and there was a moderate decrease at T3 (80.9%), more importantly at T6 (73.2%) ($P = 0.016$). Intensity of BP did not change at these time intervals ($P = 0.635$ and 0.991, respectively). Duration of pain episodes was mostly less than 60 minutes, and most patients had fewer than four episodes per day. No significant changes were observed over time in pain duration ($P = 0.262$) or number of episodes ($P = 0.637$) (Table 2).

Of 149 patients with BP, the cause was incident pain on movement related to bone metastases in 43.6%, 43.4%, and 32.4% of patients, at T0, T3, and T6, respectively ($P = 0.228$). The intensity of incident pain did change significantly after six months ($P = 0.368$ and 0.011 at T3 and T6, respectively).

Pain decreased spontaneously or ceased when stopping physical activity in 66%, 56%, and 62%, at T0, T3, and T6, respectively ($P = 0.537$). Pain on movement strongly limited physical activity in most patients, without change over time, and cessation of physical activity decreased pain on movement in about 60% of patients, also without change over time ($P = 0.537$) (Table 3).

One hundred twenty-six (84.5%), 96 (85%), and 59 (79%) patients were prescribed a medication for BP at T0, T3, and T6, respectively ($P = 0.033$), although 23 (18.2%), 19 (19.7%), and 15 (25%), respectively, were not taking BP medication, despite having a prescription. One hundred nine (86.5%) patients who were prescribed a BP medication were satisfied with the treatment, and a similar number continued to be satisfied at T3 and T6 (Table 3), attaining a significant change at T6 ($P = 0.027$). Seventy (55.5%) patients were receiving strong opioids as BP medication, mainly transmucosal fentanyl and oral morphine in a similar proportion, and a similar number continued to receive strong opioids for BP at the subsequent intervals.

There was a correlation between ECOG values and basal pain intensity ($P = 0.013$), BP intensity ($P < 0.0005$), and pain on movement ($P = 0.003$). No correlation between the use of bisphosphonates and pain intensity was found.

Discussion

This survey was performed in oncology centers representative of common units providing care for the cancer population in Italy, and it is the first time that a longitudinal approach was applied to gather information about the subject of BP and its treatment in this population.

Data at Admission

At inclusion in the study, about 40% of patients with a mean good performance status

Table 3
BP and BP on Movement, Limitation of Physical Activity, and Effectiveness of BP Medications at the Different Intervals

	T0	T3	T6
BP (y/n)	149/171 (87.1%)	115/142 (80.9%)	74/101 (73.2%)
Intensity	6.7 (±2.0)	6.5 (±1.8)	6.5 (±1.9)
Duration			
≤30	85	69	46
>30–60	41	30	20
60–120	16	7	2
>120	7	9	6
Number of episodes			
1	85	65	46
2–4	47	45	23
>4	17	5	5
BP on movement (y/n)	65/149 (43.6%)	50/115 (43.4%)	24/74 (32.4%)
Intensity	7.2 (±1.9)	6.9 (±1.6)	6.8 (±1.6)
Cessation after stopping movement	43/65 (66.1%)	28/50 (56%)	15/24 (62.5%)
Duration			
≤30	34	28	14
30–60	18	17	10
60–120	10	5	0
>120	3	0	0
Grade of limitation of physical activity[a]			
0	9	2	2
1	6	5	3
2	35	35	15
3	15	8	4
Analgesic treatment of BP	126/149 (80.5%)	96/115 (82.6%)	59/74 (79.7%)
Satisfaction[b]			
0	6	3	0
1	11	7	5
2	55	42	23
3	54	44	31

[a]Graded as 0 = none, 1 = lightly, 2 = severely, and 3 = completely.
[b]Graded as 0 = none, 1 = poor, 2 = moderate, and 3 = good.

were reporting continuous pain requiring background analgesia. A recent large survey performed in oncologic centers in Italy revealed similar figures, with a 34% pain prevalence,[10] confirming what happens in the context of an oncology ward.

In this population of patients, the incidence of BP was relevant and about 87% reported it. Most patients had BP for a duration of less than 60 minutes. Most patients had one to four episodes per day. No changes over time were observed in these characteristics. In a concomitant study performed in advanced cancer patients followed at home, the frequency of BP was found to be lower (about 50%).[11] Experiences in cross-sectional studies performed in different settings report variable figures, ranging from 39% to 86%.[2–8] It is unclear whether the duration of BP, reported in most epidemiologic studies of BP, is spontaneous or the consequence of a medical intervention. This issue should be better defined and appropriately debated.

More than 40% of episodes were produced by movement in patients with bone metastases, with a significant decrease six months after initial evaluation. It was not possible to recognize whether the effects were because of oncologic treatment or a decrease of physical activity because of the progression of disease. There were no relevant changes over time in the use of strong opioids for background analgesia, and a significant relationship between a worse ECOG and background pain intensity, BP intensity, and pain on movement were observed. This confirmed previous data from the cancer population showing that worst levels of ECOG were associated with higher levels of pain intensity.[10]

Incident pain strongly dependent on physical activity ceased or decreased after stopping physical activity (about 60% of patients). Consequently, many patients limited their physical activity to prevent pain occurrence. This finding may explain how patients with BP of

incident origin may have a greatly reduced quality of life. Paradoxically, this group of patients may present no episodes of BP if they stay at rest. For example, home care patients with minimal physical activity, particularly when they are close to death, are likely to have less incident pain.[11] Furthermore, if not separately assessed, incident pain may confound the results of many studies performed with drugs of rapid onset, such as transmucosal or effervescent fentanyl, where different kinds of BP were included. Evaluation of drug effectiveness in incident pain should be assessed according to the possibility that many of these episodes may disappear without any intervention, just stopping activity, and this may complicate efforts to adjust for the placebo effect in studies.[12]

A large number of patients were receiving some BP medication at study entry. Different figures were reported in a previous study of hospice admissions, where 43% of patients were prescribed no rescue medication.[4] In contrast, the rate of BP medication, mainly oral morphine, was very high in patients surveyed in Catalonia.[6] As for background pain, in advanced cancer patients discharged from hospital to home care, a low number of patients were receiving medication for BP, but the percentage of patients prescribed BP medication doubled after one month of treatment at home.[11] Of interest, about 20% of patients were not taking medications prescribed for BP. This aspect already has been reported in a previous study of a smaller sample of oncology patients.[13] Reasons for refusing BP medication included pain that was not severe enough, pain improving before taking medication, ineffectiveness, adverse effects, concerns about adverse effects or overdosage, or practical issues. However, the treatment of BP was considered relatively good by a majority of patients, possibly for the same reasons discussed for background pain.

In a survey performed in selected patients seen in an oncology setting with predetermined uncontrolled background pain, data were reviewed one week after a visit. Of 70% of patients initially reporting BP, only half of them (36%) still had BP after pain management began, suggesting that an expert intervention may decrease the occurrence of BP unmasked by the poor efficacy of background medication. Of interest, duration of BP, a median of 15 minutes, did not change despite prescription of rescue medication, presumably based on oral morphine, which was otherwise considered effective by 83% of patients.[9]

Changes Over Time

After three and six months, 370 (85%) and 302 (69.4%) patients, respectively, were available for analysis. Despite the survival expectations and good performance status, a certain number of patients died, and possibly some patients at study completion were particularly advanced, also explaining the preservation of the same ECOG level in survivors.

During the study period, the proportion of patients with background pain did not change. Pain intensity decreased, possibly as a consequence of treatments, oncologic and/or analgesic, and pain treatment was considered moderately or completely effective by most patients, although the mean value of pain intensity suggests that pain was still of moderate intensity, possibly requiring some adjustment of analgesic therapy. Also, strong opioid consumption did not change. The discrepancy between patient satisfaction and pain intensity frequently has been reported, possibly because of patient compliance or their specific relationship with the same professionals who are caring for their disease. This contradiction also was observed in a previous survey.[10] Research on the correlates of satisfaction with general pain treatment indicates that patients tend to report high levels of satisfaction, even when pain severity remains relatively high. Different factors may influence patient satisfaction with treatment other than the analgesic therapy, including perceived support, high levels of internal locus of control, various aspects of the patient-health care provider relationship, communication, and confidence or trust in the treatment provider.[14] Of interest, in a survey performed in advanced cancer patients with a limited survival, a high number of patients were unsatisfied with the previous analgesic treatment prescribed in hospital at time of referral to home care, when they were visited by a subsequent professional, namely a palliative care physician.[11]

The incidence of BP significantly decreased after six months. Similarly, satisfaction with BP medication improved during the same

interval. These findings could be because of the anticancer treatment received in the meantime, as a consequence of the natural history of cancer and its treatment, and/or an improvement in analgesic therapy of background pain and BP. The latter consideration seems unlikely considering that the pain intensity of background pain and the use of strong opioids for background pain did not change. Alternatively, as mentioned above, reduced physical activity in patients close to death may have influenced the outcome. However, the number of episodes, the BP pain intensity, and duration did not change significantly, and the number of patients with a BP prescription did not change. Moreover, the pattern of BP medication did not change, with strong opioids, including oral transmucosal fentanyl citrate, oral morphine, and oxycodone used in about 50% of patients. Of interest, regardless of the prescription of BP medication, 25% of patients were not using BP medication six months after recruitment into the study. Given that the worst ECOG was associated with a worsening pain situation, it is likely that the changes observed in the study period are consequent to oncologic treatment. This should be better addressed in subsequent studies with an appropriate design. It is worthwhile to report that no changes in the use of strong opioids for both background and BP pain were reported during the study period, underlining the educational need around pain management for oncologists.

Despite generally good satisfaction, pain control was not optimal in most patients. This suggests a relevant role for efforts to improve the patient-health care provider relationship, confidence, trust in the treatment provider, or even dependency,[14] and raises an important question for future research. For instance, when referring to home palliative care physicians, most patients are dissatisfied with the previous pain management provided by oncologists.[11,15,16]

An important limitation to this study was the dropout rate over time. Less than one-third of patients dropped out before the conclusion of the study. This finding was expected because of the duration of the study and related lack of adherence or compliance. Many patients did not respond to phone calls at the time of the interview some months after, or changed setting, and for about 30% of them, it was verified that they died (about one-sixth of the dropouts). This information, however, is imprecise because no information for patients who were not reached was available.

Another limitation of this study was the lack of assessment of the specific oncologic therapies and their possible effects on pain.[17] Moreover, the lack of interrater reliability testing, lack of validated measures, and the limited information about study dropouts, factors commonly related to the nature of a multicenter observational study, may limit the generalizability of data.

Conclusions

Data regarding BP remain quite controversial in the literature, mainly because of different settings, influence of the treatment, and lack of longitudinal perspective in assessing cancer patients. This study showed the change in BP prevalence over time in a cancer population followed in a typical clinical scenario where disease and its treatment, as well as pain and its treatment, interact. Paradoxically, this phenomenon should be studied in patients who are receiving no analgesic treatment, which is ethically unacceptable and unrealistic and contradicts the original definition of BP, or in different conditions where patients are receiving analgesics with no, partial, or adequate pain relief. In other words, it is difficult to have a clear idea about a complex phenomenon, and a prospective evaluation may help in understanding what happens in an individual patient. For example, one can assume that the incidence of BP, particularly movement-related pain, may decrease with the worsening of disease, as a consequence of a reduced level of activity or because patients stop even minimal activity after feeling an increase in pain intensity. Alternatively, a better analgesic approach may limit the occurrence of BP episodes. The change in physical activity, as well as analgesic regimen, modifies the general view about BP when longitudinally examined. This feature underlines the need for a longitudinal assessment of a phenomenon that is invariably dependent on stage of disease, patient, and therapeutic factors. In other words, this phenomenon is impossible to assess as a pure event, which in any case is influenced

by activity or analgesic regimen. This approach reflects what happens in clinical practice, in oncology centers, where the analgesic treatment could not be optimal. Further studies should examine more specifically how and how much oncologic treatments are able to influence the natural history of cancer pain during the progression of disease, in a very large sample of patients divided into several subclasses.

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