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Breakthrough pain characteristics and syndromes in patients with cancer pain. An international survey

Augusto Caraceni, **Cinzia Martini** and **Ernesto Zecca** Neurology Unit-Pain Therapy and Palliative Care Unit, National Cancer Institute of Milan, Via Venezian 1, Milan, **Russell K Portenoy** Department of Pain Medicine and Palliative Care, Beth Israel Medical Center, New York and **a Working Group of an IASP Task Force on Cancer Pain**[1]

Breakthrough pain (BKP) is a transitory flare of pain that occurs on a background of relatively well controlled baseline pain. Previous surveys have found that BKP is highly prevalent among patients with cancer pain and predicts more severe pain, pain-related distress and functional impairment, and relatively poor quality of life. An international group of investigators assembled by a task force of the International Association for the Study of Pain (IASP) evaluated the prevalence and characteristics of BKP as part of a prospective, cross-sectional survey of cancer pain. Fifty-eight clinicians in 24 countries evaluated a total of 1095 patients with cancer pain using patient-rated items from the Brief Pain Inventory (BPI) and observer-rated measures. The observer-rated information included demographic and tumor-related data, the occurrence of BKP, and responses on checklists of pain syndromes and pathophysiologies. The clinicians reported BKP in 64.8% of patients. Physicians from English-speaking countries were significantly more likely to report BKP than other physicians. BKP was associated with higher pain scores and functional interference on the BPI. Multivariate analysis showed an independent association of BKP with the presence of more than one pain, a vertebral pain syndrome, pain due to plexopathy, and English-speaking country. These data confirm the high prevalence of BKP, its association with more severe pain and functional impairment, and its relationship to specific cancer pain syndromes. Further studies are needed to characterize subtypes of BKP. The uneven distribution of BKP reporting across pain specialists from different countries suggests that more standardized methods for diagnosing BKP are needed. *Palliative Medicine* 2004; **18:** 177–183

Key words: breakthrough pain; cancer pain; cancer pain classification; cancer pain syndromes; IASP Task Force on Cancer Pain

Introduction

Breakthrough pain (BKP), a transitory flare of more severe pain over relatively well controlled baseline pain, is a challenging clinical problem in the management of cancer pain.[1] Previous surveys indicate that BKP occurs in more than half of patients with cancer pain and is associated with a relatively more severe pain syndrome, high pain-related distress, and impaired quality of life;[2–5] BKP induced by voluntary action (incident pain) is a predictor of poor opioid responsiveness.[6–8]

Although the importance of BKP has become increasingly clear, and treatment trials have started to appear,[9–14] additional studies are needed to clarify its epidemiology, the range of pathophysiologies that underlie the condition, and potential predictors such as specific syndromes and clinicopathological correlates. Various approaches to the identification of BKP remain to be tested.

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Address for correspondence: Augusto Caraceni, Neurology Unit-Pain Therapy and Palliative Care Unit, National Cancer Institute of Milan, Via Venezian 1, Milan 20133, Italy.
E-mail: augusto.caraceni@istitutotumori.mi.it

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To evaluate the characteristics of cancer pain, a task force of the International Association for the Study of Pain (IASP) conducted an international prospective survey that involved 58 investigators in 24 countries. Using an observer-rated single item, a prevalence for BKP of 64.8% was found.[15] Subsequent analyses reported herein clarify a broad range of clinical factors associated with reporting BKP.

Methods

Survey design

The study design and assessment methodology have been described previously.[15] In brief, 100 physicians were randomly selected from among those who identified cancer pain as their main interest in the IASP membership directory. Fifty-eight physicians in 24 countries agreed to participate. Each collaborator evaluated consecutive cancer patients whose pain was significant enough to require opioid analgesics. Ten to 50 patients were recruited by each collaborator during the study period.

Measures

The investigators recorded information about patient demographics, cancer diagnosis, and extent of disease. The pain syndrome was indicated on a checklist that included 51 tumor-related pain syndromes and 18 treatment-related pain syndromes. Investigators were told to check one or more than one syndrome that best depicted the worst or only pain reported by the patient. Syndromes due to cancer were subsequently grouped into 24 major types.[15] Performance status was evaluated using the observer-rated Karnofsky Performance Status score.[16]

The investigator recorded the presence or absence of BKP, according to the following definition: 'baseline pain intensity aggravated by flaring episodes of pain of any duration'.[2] An example, incident pain due to movement, was given.

If more than one type of baseline pain was noted, the investigators were told to focus on the worst pain for the subsequent questions. This pain was designated as caused by the tumor, tumor treatment, or factors unrelated to tumor or treatment. Pain duration and treatments were recorded, and there were specific queries about the administration of analgesic drugs. The pathophysiology of the pain was described as nociceptive somatic, nociceptive visceral, neuropathic, or psychogenic. More than one definition could be checked if, in the judgment of the investigator, this most appropriately described the pain.

All patients completed language-appropriate pain intensity scales. If the Brief Pain Inventory (BPI)[17] was validated in the patient's language ($n = 436$: English, French, Spanish, Filipino, or Italian), the short-form of this instrument was used. The four 0 to 10 numeric pain intensity scales are anchored by 'no pain' and 'pain as bad as you can imagine,' and assess pain 'right now,' pain 'at its worst' during the past day, pain 'at its least' during the past day, and pain 'on average' during the past day, respectively. If a language-appropriate BPI was not available, the four numeric scales were translated into the language appropriate to the patient.

The 436 patients who completed a language-appropriate BPI also scored the instrument's seven items assessing pain-related interference with functioning. These items measure the degree to which pain interferes with general activity, mood, walking, normal work, relations, sleep, and life enjoyment, respectively, using separate 0 ('does not interfere') to 10 ('completely interferes') scales.

Statistical analysis

Bivariate contingency tables were created to analyze the association between the presence or absence of BKP and potentially related variables. These tables were evaluated using odds ratios (OR) and their 95% confidence intervals (95% CI). The OR has a value higher or lower than 1 and indicates that, for patients in a given category, the likelihood of having BKP is higher or lower, respectively, than patients in a reference category. The association between a variable and BKP is likely to be significant if the 95% CI of the OR does not include 1. The association between BPI scores and the presence of BKP also was studied by means Wilcoxon rank sum test. These analyses were followed by a logistic regression model, which used the presence or absence of BKP as the dependent variable and modeled all the variables that were significantly associated with BKP in the bivariate analyses. Patients whose data were missing from any variable were not included in the analyses involving that variable. All tests were two tailed and $P < 0.05$ was considered significant.

In an earlier analysis, we observed that BKP was reported at relatively higher frequencies by investigators in English-speaking (USA, Canada, Australia, New Zealand) and northern European countries.[15] To further explore this difference, we arbitrarily subdivided the centers located in non-English-speaking countries and evaluated the patient sample in five groups: English-speaking [$n = 223$], northern and western Europe [$n = 380$], southern and eastern Europe [$n = 172$], South America [$n = 60$], and Asia [$n = 260$].

Table 1 Demographic and baseline clinical variables

Age Mean = 58.2 (SD = 14.6)	*n (%)*
Gender	
Male	554 (50.6)
Female	541 (49.4)
Missing	0
Diagnosis	
Lung	197 (18.1)
Breast	146 (13.4)
Head and neck	111 (10.2)
Pancreas, stomach, esophageal	105 (9.6)
Colon–rectum	103 (9.5)
Uterus	72 (6.6)
Prostate	65 (6.0)
Leukemia, lymphoma	43 (3.9)
Other	247 (22.7)
Missing	6
Pain cause (each patient may have more than one)	
Pain due to tumor	1007 (92.5)
Pain due to tumor treatment	226 (20.8)
Pain unrelated to tumor or treatment	25 (2.3)
Pain duration – months	
Mean (SD)	5.9 (10.5)
Missing	30
BKP	
Yes	615 (64.8)
No	334 (35.2)
Missing	146

Results

There were 1095 patients from 24 countries. Demographics and tumor-related characteristics were highly variable (Table 1).[15] Most patients had metastatic solid tumors and pain was generally severe and had been present for a period of months.

Prevalence and impact of BKP

The prevalence of BKP was 64.8% (Table 1). Considering the 1095 patients, among those with BKP, the median worst pain was 8 and the lower and upper quartiles [Q1–Q3] of worst pain intensity were 6 and 9, respectively; among those without BKP, the median worst pain was 7 and the Q1–Q2 was 5–8 ($P = 0.0001$ for the difference between the BKP and non-BKP groups). Average pain intensity was also higher for patients with BKP (median = 5, Q1–Q3 = 4–6) when compared to patients without BKP (median = 4, Q1–Q3 = 3–6) ($P = 0.0001$). Least pain intensity and pain right now were not different between groups.

The BPI functional interference items were completed by 436 patients. BKP was associated with greater interference with general activity, walking and working ability (Table 2). In this subgroup, BKP also was associated with higher scores for both worst and average pain intensity.

BKP and other variables

Age, gender, pain duration and other characteristics were not associated with the presence of BKP. BKP was associated with a group of visceral neoplasms (i.e., pancreatic, gastric and esophageal cancers), which had a lower likelihood of BKP (OR = 0.68, CI = 0.56–0.81).

BKP was significantly associated with the presence of metastases, worse performance status, neuropathic and somatic pain pathophysiologies, more than one pain, and the use of nonopioid analgesic and adjuvant treatments (Table 3). Several pain syndromes were also associated with BKP (Table 4). These included pain syndromes due to vertebral lesions; lesions in the pelvis, long bones or joints; radiculopathy; and plexopathy. In contrast, visceral pain pathophysiology and some visceral pain syndromes were associated with a lower chance of developing BKP.

The extent to which the item assessing BKP was not completed by investigators varied geographically. The percentage of patients with missing data on BKP was: English-speaking (8.5%), northern and western Europe (10%), South America (25%), southern and eastern Europe (27%), and Asia (30%). Nationality and linguistic grouping also had a strong impact on BKP reporting. English-speaking and northern and western European centers reported BKP more often than other centers (Table 5).

The logistic regression model evaluated all the pain variables and other clinical variables that were significantly associated with BKP in the bivariate analyses. The model revealed that nationality, presence of more than one pain, vertebral pain syndrome, and plexopathy retained independent associations with BKP (Table 6).

Table 2 Impact of BKP on BPI scores (the patients for whom the whole BPI was available are a subsample of the study group, $n = 436$)

Variable	Median (lower–upper quartile) BKP present	Median (lower–upper quartile) BKP absent	P*
Worst pain	8 (6–9)	7 (5–8)	0.0001
Least pain	2 (1–4)	2 (1–4)	n.s.
Average pain	5 (4–6)	4 (3–6)	0.0001
Pain right now	4 (2–6)	3 (2–6)	n.s.
Pain relief	60% (30–80)	60% (40–80)	n.s.
General activity	8 (5–10)	7 (3–8.5)	0.002
Mood	7 (4–8)	6 (2–8)	n.s.
Walking activity	7 (3–9)	5 (2–8)	0.0012
Normal work	10 (7–10)	9 (5–10)	0.0443
Relations	5 (1.5–7)	5 (1–7)	n.s.
Sleep	5 (2–8)	5 (1–8)	n.s.
Life enjoyment	7 (4–9)	7 (3–9)	n.s.

* Wilcoxon rank sum test.

Table 3 Associations between BKP, and disease and pain-related variables

Variable	BKP% and n	OR (CI)
Metastasis		
No	57.1 (132)	1
Yes	67.1 (425)	1.53 (1.12–2.08)
Performance status		
>60	59.6 (280)	1
≤ 60	67.8 (273)	1.42 (1.07–1.88)
More than one pain		
No	59.0 (371)	1
Yes	80.7 (167)	2.90 (2.00–4.02)
Somatic pain		
No	57.5 (142)	1
Yes	67.4 (417)	1.52 (1.13–2.06)
Visceral pain		
No	69.6 (382)	1
Yes	55.8 (177)	0.55 (0.41–0.73)
Neuropathic pain		
No	59.0 (310)	1
Yes	73.0 (249)	1.8 (1.4–2.52)
Bone pain syndrome		
No	56.9 (264)	1
Yes	72.8 (281)	2.03 (1.52–2.70)
Visceral pain syndrome		
No	69.0 (411)	1
Yes	53.1 (135)	0.51 (0.38–0.69)
Neurological syndrome		
No	59.2 (348)	1
Yes	76.1 (194)	2.19 (1.58–3.04)
Post-treatment syndrome		
No	63.2 (505)	1
Yes	79.3 (46)	2.23 (1.18–4.22)
Nonopioids		
No	57.6 (151)	1
Yes	67.4 (388)	1.57 (1.12–2.05)
Adjuvants		
No	62.1 (328)	1
Yes	69.4 (195)	1.38 (1.02–1.88)
Other analgesics		
No	62.4 (413)	1
Yes	76.2 (93)	1.93 (1.24–3.00)

Discussion

The interpretation of these data is constrained by the limitations in the survey methodology. All patients were referred to self-identified pain specialists and the study required pain to be severe enough to be treated with opioid analgesics. This referral bias may limit generalizability of the data. Furthermore, BKP was assessed using an observer-rated item, which referred to published experience,[2] but has not been validated.

In the IASP classification of pain, temporal characteristics are highlighted (Axis III).[18] In the only study that applied the IASP temporal classification to a cohort with cancer pain,[19] transitory changes in pain intensity, which could be potentially labeled BKP, were noted in two-thirds of the patients; specifically, pain was categorized as continuous with fluctuations in 36%, sustained with paroxysms in 12% and paroxysmal in 1%. Other surveys have specifically isolated BKP through a series of questions that elicit the experience of transitory pains. These surveys have described the experience of BKP in 63%,[2] 51.2%,[3] 89%[4] and 70%,[5] respectively. Similarly high prevalence rates have been found in studies that have applied other definitions of BKP (prevalences of 86% and 41%, respectively[20,21]), or definitions of episodic pain flares (prevalence 93%[22]), or transitory pains (prevalence 39%[23]). The variation in these rates is presumably related to differences in the study populations, the applied definitions of the phenomena, and the degree to which the specific survey methodology encouraged clinical recognition of BKP. The present study found a prevalence of 64.8% among mostly ambulatory patients referred to pain specialists.

It is unlikely that the variation in BKP reporting by collaborators in different parts of the world is due to actual differences in BKP prevalence. Patient self-report of pain intensity did not vary geographically,[15] and it is probable that BKP, which is linked to pain severity, also has a base rate that is similar across the regions. If this is the case, the variation in reporting suggests poor inter-rater reliability in the response to the BKP item. The limitations in the survey methodology acknowledged previously could potentially explain this, and suggests that the findings of the study overall should be interpreted cautiously. Equally likely, however, is the possibility that cultural differences in describing pain and reporting it to health care professionals may play a role.[24] Although recent data show substantial cross-cultural validity of some elements of pain measurement, including the items assessed by the BPI,[17] other aspects of the pain experience, such as BKP, may be more difficult to assess in non-English-speaking areas of the world or nonwestern cultures. It is also possible that some terms used in clinical practice are heavily influenced by the predominant use in scientific writing of the English language, and may be not as familiar to pain specialists for whom English is not the first language. It is important to underline that 'breakthrough pain' as an English term has no literal translation in many languages (Italian, Spanish and French at least). Even in English, the term has been variably defined as pain that 'breaks through' ongoing analgesic therapy[25] or any pain exacerbation over a relatively milder baseline pain.[26] A recent commentary by an international expert group defined it as 'transitory exacerbation of pain that occurs in addi-

Table 4 Associations between BKP and cancer pain syndromes

Syndrome*	BKP% and n	OR (CI)
Skull		
No	64.6 (525)	1
Yes	57.8 (26)	n.s.
Vertebral lesions		
No	60.7 (442)	1
Yes	84.6 (110)	3.56 (2.21–5.72)
Pelvis, long bones, joint lesions		
No	62.3 (468)	1
Yes	78.3 (83)	2.18 (1.35–3.51)
Generalized bone pain		
No	63.4 (476)	1
Yes	69.0 (69)	n.s.
Chest wall pain due to rib lesion		
No	64.1 (511)	1
Yes	66.6 (40)	n.s.
Fracture		
No	63.6 (517)	1
Yes	77.3 (34)	n.s.
Esophageal		
No	64.2 (534)	1
Yes	68.0 (17)	n.s.
Liver/spleen syndromes		
No	65.2 (514)	1
Yes	53.1 (37)	0.61 (0.37–1.01)
Epigastric pain (RRS)		
No	66.0 (519)	1
Yes	44.3 (31)	0.41 (0.25–0.67)
Abdominal pain		
No	64.5 (515)	1
Yes	61.1 (33)	n.s.
Suprapubic perineal pain		
No	65.5 (500)	1
Yes	54.3 (50)	0.69 (0.41–0.97)
Ureteral obstruction		
No	64.1 (541)	1
Yes	76.9 (10)	n.s.
Mucous oral membrane skin lesions		
No	64.7 (507)	1
Yes	59.4 (44)	n.s.
Soft tissue infiltration in chest, abdominal wall and limbs		
No	65.4 (501)	1
Yes	54.9 (50)	0.64 (0.41–0.99)
Soft tissue infiltration in the head and neck		
No	63.9 (518)	1
Yes	70.2 (33)	n.s.
Retroperitoneal lesion		
No	64.4 (529)	1
Yes	61.1 (22)	n.s.
Pleural lesion		
No	64.8 (516)	1
Yes	57.4 (35)	n.s.
Peripheral nerve lesion		
No	63.5 (499)	1
Yes	71.4 (50)	n.s.
Radiculopathy/cauda equina		
No	62.9 (499)	1
Yes	81.7 (49)	2.62 (1.37–5.02)
Plexus lesion		
No	62.1 (459)	1
Yes	78.2 (90)	2.19 (1.38–3.47)
Cranial neuropathy		
No	64.4 (541)	1
Yes	57.1 (8)	n.s.
CNS lesion		
No	64.2 (542)	1
Yes	81.8 (9)	n.s.

* For detailed description of syndromes see Caraceni *et al.*[15]

tion to otherwise stable persistent pain'.[1] The present study demonstrates the need for better and validated definitions of pain terminology in general and the availability of translations of evaluation tools and taxonomies to facilitate communication and encourage multicenter international trials.

Notwithstanding these limitations in assessment, the data confirm the association between BKP and higher ratings on the worst and average pain scales, and higher pain interference with function. BKP was not associated with any cancer diagnosis. Although it was slightly more frequent with metastatic disease, worse performance status, and treatment-related pain, these associations were small and the confidence intervals are barely significant.

On univariate analysis, BKP was positively associated with the diagnosis of both somatic and neuropathic pain, and inversely associated with visceral pain. It also was associated with vertebral and other bone pain syndromes involving weight-bearing structures, and with radiculopathies and plexopathies (Table 4). In the multivariate model, pain caused by vertebral lesions and plexopathies predicted BKP.

The observation that BKP is associated with some pain syndromes, such as vertebral pain, may be relevant therapeutically. Bone pain due to cancer has always been postulated to be a major source of BKP, and is likely to be the major cause of pain induced by movement or posture (incident pain). In the present survey, vertebral pain syndromes (13.5%) and pelvis and long bones lesions (10.6%) were among the most prevalent pain syndromes.[15] Of the patients with these syndromes,

Table 5 Associations between BKP with and location of collaborators

Group	BKP yes, n (%)	OR (CI)
English-speaking	144 (80.1)	1
South America	023 (54.8)	0.28 (0.14–0.58)
Northern and western Europe	211 (69.4)	0.53 (0.34–0.83)
Southern and eastern Europe	086 (63.7)	0.41 (0.25–0.69)
Asia	095 (45.9)	0.20 (0.12–0.32)

English-speaking = Australia, Canada, New Zealand, USA.
Northern and western Europe = France, Germany, Scandinavia, The Netherlands.
Southern and eastern Europe = Greece, Israel, Italy, Portugal, Russia, Spain.

84.6% and 78.2%, respectively, also had BKP. In another study of cancer patients, bone pain on movement was the most important predictor of poor pain relief.[6]

The diagnosis of BKP in nerve lesions also may have therapeutic implications. Specific subtypes of these BKPs may benefit from the addition of adjuvant analgesics to an opioid-based analgesic regimen. In one study brief transitory pains were associated with neuropathic pain pathophysiology.[23]

The observation that BKP is associated with relatively worse pain and more frequent use of nonopioid and adjuvant analgesics might suggest that this type of pain is often more difficult to control and requires the use of polypharmacy. Another potential explanation could relate to the association with bone and nerve lesions, which may particularly benefit from coanalgesic therapy.

As a corollary to the observed association between BKP and specific cancer pain syndromes, it is likely that there are important subtypes of BKP, such as BKP due to bone lesions and BKP due to neurological lesions. Further studies are needed to characterize these syndromes.

Table 6 Multivariate model predicting the presence of BKP from all possible explanatory variables

Variable	OR (95% CI)	P (Wald statistics)
English-speaking		
Yes	1	0.0001
No	0.43 (0.19–0.65)	
More than one pain		
No	1	0.0015
Yes	2.44 (1.34–4.82)	
S2 vertebral pain		
No	1	0.0041
Yes	2.54 (1.34–4.82)	
S20 plexopathy		
No	1	0.012
Yes	2.52 (1.22–5.2)	

As an indicator of a more severe pain syndrome, BKP should be considered an important covariate in clinical trials aimed at the control of cancer pain. Interestingly, the presence of BKP affected the intensity of worst and average pain, but not present pain (Table 2), suggesting that present pain assessment may be an insufficient measure of the pain problem in patients with BKP. This is further evidence of the need for improved operational definitions of BKP,[1,23,26–28] which link the phenomenon to the patient and caregiver perception of treatment needs.

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