Italian Oncological Pain Survey (IOPS)

A Multicentre Italian Study of Breakthrough Pain Performed in Different Settings

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Objective: A survey of breakthrough pain (BTP) was performed in five palliative care units (PCU), seven oncology departments (ONC), and nine pain clinics (OPC).

Methods: A standard algorithm was used to confirm the diagnosis of BTP of patients refereed to different settings.

Results: 1,412 evaluable cancer patients were enrolled. 53.9% were males and the mean age was 63.7 ± 13.1 years. The mean intensity of background pain was 2.8 ± 0.73. Patients reported 2.4 ± 1.1 BTP episodes/day with a mean intensity of 7.37 ± 1.28. 80.6% patients reported that the BTP had a significant negative impact in everyday life. The majority of patients reported a fast onset of BTP, which was predictable in 50.7% of cases, while BTP with a gradual onset (> 10 min) was less predictable (29%) ($P = 0.001$). PCU patients were older, had lower Karnofsky levels, a lower number of BTP episodes/day, a slow onset of BTP onset, and a less predictable BTP. Cancer diagnosis was performed a mean of 23.5 months (SD ± 32.8) before the assessment. The mean duration of background pain was 3.5 months (SD ± 3.5), and the mean duration of any analgesic treatment was 2.5 months (SD ± 3). BTP started a mean of 2.2 months (SD ± 1.9) before the assessment. Characteristics of BTP were influenced by the course of disease, as well as the duration of background pain and initiation of BTP. Most patients took rapid onset opioids and were satisfied with the treatment. BTP diagnosis was prevalently made by ONC and OPC physicians, and rarely by GPs.

Conclusion: This survey performed by an Italian observatory expert review group, has confirmed that the BTP represents a clinically relevant condition with a negative impact on the patient's quality of life. BTP was detected in all settings involved. A number of factors are associated with the BTP. Also factors regarding the course of disease and setting of care have been assessed. This information may help in stratifying patients or predicting the risk of development of BTP with specific characteristics.

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The paper is dedicated to Antonio Gatti, MD, who was the head investigator and died during the project.

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Pain is a common symptom experienced by cancer patients, with wide variations from the primary diagnosis to the disease stage, the prevalence of pain being >70% in the advanced stages.[1,2] Even though available treatments are effective in maintaining an adequate analgesia for most of the day, many cancer patients develop transient flare-ups of pain. The transitory increase in pain to greater than moderate intensity that occurs in background pain of moderate to slight intensity has been reported in literature on breakthrough pain (BTP).[3] BTP negatively influences the quality of life due to a significant physical, psychological, or economic burden on patients and their caregivers.[4] The prevalence of this phenomenon in cancer patients has been variably reported in literature, ranging from 40% to 80% of cancer patients with pain, depending on the setting and the definition used to identify it.[5,6] In earlier studies, however, pain intensity peaks have been reported independently from the analgesic treatment, and in others no clear distinction between background and BTP pain intensity has been reported.[7–11] In an observational study carried out in 8 Italian palliative care centers, the prevalence and characteristics of BTP were inferred by a lack of clear distinction between background and BTP,[12] underlining the need for a more widely accepted definition and validated tools for an appropriate screening and diagnosis.[13–15] In a retrospective study conducted in 4 Italian pain clinics, the overall prevalence of BTP in cancer patients was 70.3%. However, many of these patients were not receiving appropriate treatment for this condition, probably because it was previously underdiagnosed.[16] BTP has recently been more meaningfully characterized through a diagnostic algorithm.[17–19] This is of paramount importance for prospectively adopting a clear diagnostic pathway to develop large research programs for assessing BTP. Moreover, many variables that have never been examined may also influence the characteristics of BTP.

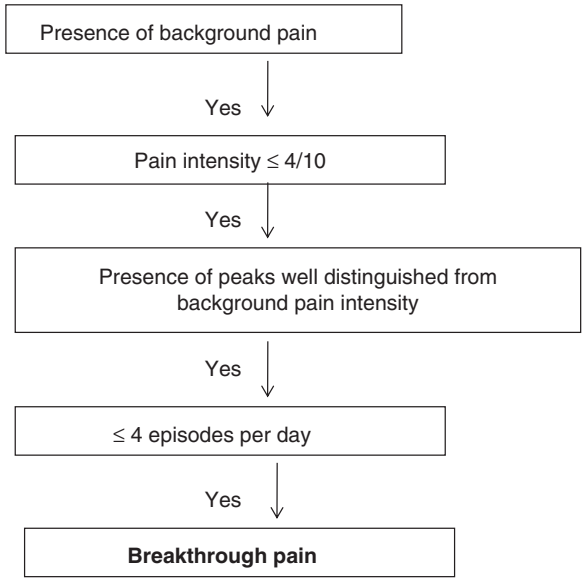

FIGURE 1. Algorithm for breakthrough pain diagnosis.

On March 15, 2010, the Italian government approved a new law (no. 38), requiring that physicians and nurses report the characteristics of pain in all patients' medical records. In line with these new indications from the Ministry of Health, it was mandatory to organize a national observatory of these activities by establishing an expert review group. This group of experts has focused on BTP to provide information regarding this phenomenon by developing an Italian Oncologic Pain Survey. The main aim of this study was to characterize BTP in a large number of patients in a multicenter study performed in different settings and to assess possible factors influencing its development. The secondary aim was to gather information about the diagnosis and management of BTP as well as patient satisfaction with the treatment.

PATIENTS AND METHODS

An investigational meeting was held in April 2011 to explain the intention and procedures of the survey. The study was a multicentre survey which involved 5 palliative care units (PCU), 7 oncology centers (ONC), and 9 outpatient pain clinics (OPC). The study was proposed by an expert group to 27 Italian centers representative of different settings of cancer pain, and 21 centers agreed to participate. The study was approved by each local ethics committees, and was conducted in accordance with the relevant standards for clinical research. Informed consent was obtained, after providing adequate information about the aim of the study.

The inclusion criteria were: diagnosis of cancer, age older than 18 years, regular use of analgesics with stable doses of opioids during the previous week, well-controlled background tumor-related pain (pain intensity of ≤4 on a numerical scale 0 to 10), and the presence of peaks of pain intensity well distinguished from background pain, not exceeding four episodes per day, according to a predefined BTP definition.[16–19] The algorithm for the BTP diagnosis is shown in Figure 1. The exclusion criteria were cognitive impairment and an expected survival of <2 weeks. Each center enrolled consecutive patients that met the protocol criteria.

Patient data were collected using a web-based clinical report form (CRF). The first part of the questionnaire aimed at identifying locoregional features of the primary cancer and metastases, time of diagnosis, and the Karnofsky performance scale. The second part focused on background pain to confirm that basal pain was well controlled. In this part of the questionnaire, patients were asked to characterize their background pain according to mechanisms (nociceptive, neuropathic, and mixed), duration, intensity, site of pain, analgesic treatment and dosage, and any adjuvant therapy, as well as the time of starting analgesic therapy during the course of the disease. The assessment of pain mechanisms was based on the clinical history, physical examination, and imaging studies.

The main characteristics of the BTP that were investigated included the number of events per day during the previous week, the pain intensity (using the 11-point scale—numerical rating scale), predictability (incident-type BTP), or unpredictability (idiopathic-type BTP), onset of BTP (less or more than 10 min), BTP medications, and time the BTP started during the course of the disease. Finally, information was collected regarding the BTP diagnostic methods and level of satisfaction with the

TABLE 1. Clinical Characteristics of the Study Sample, According to the Setting

	Setting		
Characteristics	**ONC 316 (22.4%)**	**OPC 840 (59.5%)**	**PCU 256 (18.1%)**
Age (y)			
Mean (SD)	61.78 ± 12.01	63.49 ± 13.60	67.06 ± 12.47
Karnofsky Index			
Mean (SD)	73.79 ± 14.59	73.79 ± 17.60	50.59 ± 16.36
Sex (n [%])			
Male	162 (51.3)	473 (56.3)	126 (49.2)
Female	154 (48.7)	367 (43.7)	130 (50.8)
Locoregional features of primary tumor site (n [%])			
Abdominal	126 (39.9)	308 (36.7)	116 (45.3)
Chest	111 (35.1)	219 (26.1)	81 (31.6)
Bone	19 (6)	114 (13.6)	22 (8.6)
Head and neck	21 (6.6)	62 (7.4)	28 (10.9)
Others	39 (12.3)	137 (16.3)	9 (3.5)
Metastases (n [%])			
With	285 (90.2)	556 (66.2)	224 (87.5)
Without	31 (9.8)	284 (33.8)	32 (12.5)
Site of metastases (n [%])			
Abdomen	142 (49.8)	216 (39)	107 (48.2)
Chest	114 (40)	175 (31.6)	92 (41.4)
Bone	170 (59.6)	379 (68.4)	127 (57.2)
Head and neck	58 (20.4)	75 (13.5)	47 (21.2)
Others	88 (30.9)	222 (40.1)	36 (16.2)

ONC indicates oncology; OPC, outpatient pain clinic; PCU, palliative care unit.

treatment for BTP. The first recruitment started on December 1, 2011. All centers completed the recruitment on December 31, 2012.

STATISTICS

Data were collected through an electronic CRF-based Web site with standard control, validation, and security. During the analysis, all the variables considered in the CRF were evaluated, and for each of these, descriptive statistics were carried out: mean, SD, range, minimum and maximum values for continuous variables, and absolute and relative frequencies for categorical variables. The descriptive analyses were conducted for the total population and for the subgroups consisting of patients divided by sex, underlying disease, baseline pain, presence of BTP and its characteristics (intensity, number of episodes, onset [< 10 min or > 10 min]), and current therapies. In addition to analyzing the impact of certain variables on the level of pain at baseline, BTP intensity, and related pain intensities were also studied. The Student *t* test (with Bonferroni-Holm for independent and paired samples) and 1-way ANOVA (preceded by the analysis of the theoretical distribution-kurtosis and the between-group and within-group variance test) for the correct inference analysis of all possible differences. Possible interdependence between 2 or more variables, and possible associations between clinical characteristics and therapeutic interventions administered and placed in the CRF were evaluated using statistical parametric and nonparametric tests, even at a multivariate level (χ^2, binomial test). Data were processed using SPSS (IBM, Armonk, NY) version 10.0.

RESULTS

Over a period of 13 months, 1509 patients with BTP were consecutively enrolled. Data that were incomplete and any protocol violations were detected in 97 cases. Data of 1412 cancer patients with BTP were therefore analyzed.

There were 840 (59.5%), 316 (22.4%), and 256 (18.1%) patients recruited from OPC, 7 from ONC, and 5 from PCU settings, respectively. There were 761 males (53.9%); and the mean age was 63.75 (SD ± 13.16 y; range, 18 to 98 y).

The mean age was 61.78 (SD ± 12.01), 63.49 (SD ± 13.60), and 67.06 years (SD ± 12.47) in patients assessed in ONC, OPA, and PCU settings, respectively. PCU patients were older compared with patients in the other settings. The patients aged older than 65 years were 39.6%, 50.7%, and

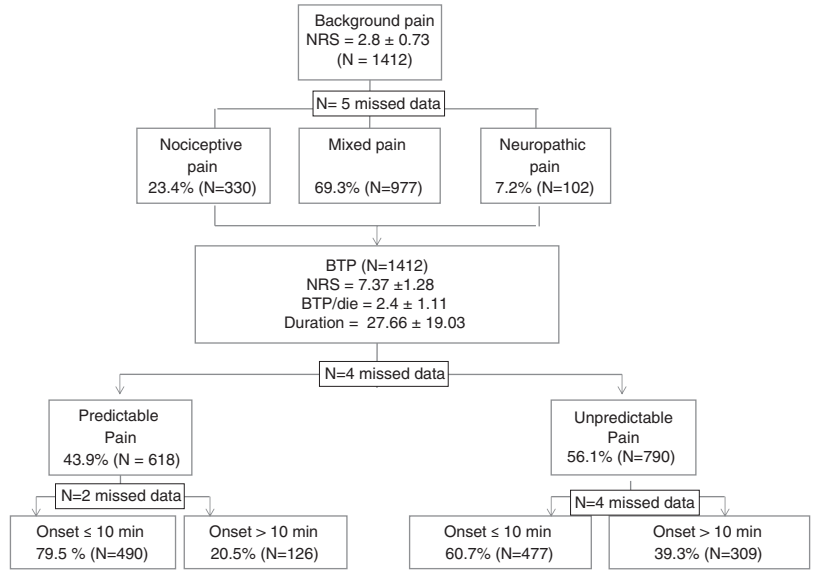

FIGURE 2. Flow chart of available data. Values are presented as mean ± SD. BTP indicates breakthrough pain; NRS, numerical rating scale.

58.2% in ONC, OPA, and PCU patients, respectively (χ^2 test, $P < 0.0001$).

Characteristics of the Disease and the Patients

The mean duration of the oncologic disease was 23.4 months (SD ± 32.8). The majority of patients (n = 1065, 75.4%) had metastases in 1 or more locations, and the most frequently affected sites were the abdomen (43.8%), thorax (35.9%), lumbar (32.9%), and the sacral area (21.1%). The mean Karnofsky index, which was 69.6 (SD ± 18.9), was worse in females (68.5 ± 19.2) than in males (70.5 ± 18.7) ($P = 0.05$). No differences were found in age ($P = 0.079$) (Table 1). The mean Karnofsky index was lower ($P < 0.0001$) in PCU patients (50.59 ± 16.36, median = 50) than ONC patients (73.79 ± 14.59) and OPC patients (73.79 ± 17.60). In PCU, 59.3% of patients had a Karnofsky index of ≤50, whereas in ONC and OPC, the percentage of patients with such low values was 12.4% and 20.5%, respectively ($P < 0.0001$).

Background Pain

In the 1392 patients who provided an answer, the most frequent sites of pain were in order of rank: abdomen (n = 527, 37.3%), lumbar (n = 397, 28.5%), thoracic wall (n = 341, 24.5%), sacral area (n = 257, 18.5%), lower extremities (n = 155, 11.1%), and pelvis (n = 138, 9.9%). Twenty patients did not provide the site of pain (Fig. 2).

The background pain started at a mean of 104.93 days (SD ± 107.42) before the assessment. The mean intensity of background pain in the last week was 2.8 ± 0.7. No differences were found in sex ($P = 0.650$), presence of metastases ($P = 0.274$), pain mechanism ($P = 0.290$), Karnofsky index ($P = 0.233$), or age ($P = 0.356$). Pain intensity was statistically lower in ONC ($P = 0.003$, ANOVA test).

The type of background pain was more frequently mixed (n = 977, 69.2%). The pain mechanism was nociceptive and neuropathic in 330 (23.4%) and 102 patients (7.2%), respectively. No differences were observed in sex ($\chi^2 = P = 0.725$), but the neuropathic pain mechanism was reported more frequently in younger patients ($P = 0.026$). Patients with a higher Karnofsky index had more frequent mixed pain mechanisms ($\chi^2 = P < 0.0001$). A different pain mechanism distribution was also observed among the 3 settings (χ^2 test, $P = 0.0001$): mixed pain, nociceptive pain, and neuropathic pain were more frequently observed in PCU, OPC, and ONC, respectively (Table 2).

TABLE 2. Characteristics of Background Pain According to the Setting

	Setting		
Characteristics	ONC 316 (22.4%)	OPC 840 (59.5%)	PCU 256 (18.1%)
Numerical rating scale			
Mean (SD)	2.67 ± 0.85	2.84 ± 0.59	2.81 ± 0.96
Type (n [%])			
Nociceptive	88 (27.9)	139 (16.6)	103 (40.2)
Neuropathic	44 (14.0)	54 (6.4)	4 (1.6)
Mixed	183 (58.1)	645 (77.0)	149 (58.2)
Site of background pain (n [%])			
Bone	275 (87.5)	588 (71.5)	171 (67.3)
Abdomen	127 (40.4)	298 (36.2)	102 (40.2)
Chest	67 (21.3)	212 (25.7)	62 (24.4)
Head and neck	46 (14.7)	113 (13.7)	35 (13.8)
Other	22 (7.0)	67 (8.1)	4 (1.6)

ONC indicates oncology; OPC, outpatient pain clinic; PCU, palliative care unit.

TABLE 3. Opioid Used for Background Pain (Multiple Choice)

Drugs	N.
SR oxycodone-naloxone	390
TD fentanyl	328
Hyodromorphone	152
TD buprenorphine	89
Tapentadol	31
SR morphine	82
SR oxycodone	224
Oxycodone-paracetamol	69
Tramadol	67
Tramadol-paracetamol	32
Methadone	4
Parenteral morphine	13

28% of patients used also anti-inflammatory drugs.

The mean duration of the analgesic treatment was 75.3 days (SD ± 90.2), with males receiving analgesic treatment for a longer period (80.6 ± 95.2 d) than women (69.2 ± 83.6 d) ($P = 0.0017$). All patients were receiving opioids and 28% and 89% of patients were using anti-inflammatory drugs and adjuvants, respectively. The analgesic drugs administered for background pain are listed in Table 3.

Adverse Effects Reported With Background Analgesia

The following adverse effects were reported in order of rank: constipation (n = 445), nausea (n = 160), mental confusion (n = 88), drowsiness (n = 61), vomiting (n = 38), gastric pain (n = 16), pruritus (n = 13), and headache (n = 9). Some adverse events were prevalently reported by patients over 65. The longer the duration of opioid therapy, the less frequency of adverse effects (Table 4).

Characteristics of BTP

The site most affected by BTP was the abdomen, with overlapping data regarding persistent pain (Table 5). Patients reported a mean of 2.4 (SD ± 1.1) episodes of BTP per day, with a mean intensity of 7.4 (SD ± 1.28). A lower intensity of episodes of BTP ($P = 0.001$) was found in PCU patients, and in patients with lower Karnofsky level ($P = 0.018$), but intensity was higher in patients with immediate onset of BTP ($P = 0.0001$). The intensity of BTP was not influenced by sex ($P = 0.097$), age ($P = 0.624$), or predictability ($P = 0.722$). A total of 1137 (80.6%) patients reported that the BTP had a significant negative impact on their everyday life: BTP influenced daily life completely or very much in 18.8% and 61.8% of patients, respectively, and minimally or not at all in 18% and 0.5%, respectively.

Number of BTP Episodes

The number of daily BTP episodes tended to increase with the increase in the background pain intensity (ANOVA test and LSD post hoc analysis $P < 0.0001$). A lower number of BTP events per day was detected in the PCU (ANOVA test, $P = 0.002$), in patients 65 years and younger ($P = 0.007$), in patients with a lower Karnofsky index ($P = 0.009$), and when the onset of BTP was gradual

TABLE 4. Adverse Events Reported With Opioids

	Age		Duration of Opioid Treatment	
Adverse Events	**≤65 y**	**> 65 y**	**≤45 d**	**> 45 d**
Headache	55.5% (n = 5)	44.4% (n = 4)	66.7% (n = 6)	33.3% (n = 3)
Confusion	37.5% (n = 33)	62.5% (n = 55)	52.3% (n = 46)	47.7% (n = 42)
Gastralgia	43.8% (n = 7)	51.2% (n = 9)	68.8% (n = 11)	31.3% (n = 5)
Nausea	38.8% (n = 62)	61.2% (n = 98)	71.3% (n = 112)	18.7% (n = 45)
Pruritus	53.9% (n = 7)	46.1% (n = 6)	38.5% (n = 5)	61.5% (n = 8)
Constipation	40.2% (n = 179)	59.8% (n = 266)	57.2% (n = 250)	42.8% (n = 187)
Vomiting	31.6% (n = 12)	68.4% (n = 26)	81.6% (n = 31)	18.4% (n = 7)
All	38.0% (n = 222)	62.0% (n = 366)	59.0% (n = 339)	41.0% (n = 236)

(≤10 min) ($P = 0.000$). No differences were observed in sex ($P = 0.472$) or predictability ($P = 0.111$).

Onset of BTP

The onset of BTP was gradual (>10 min) and immediate (≤10 min) in 437 patients (31.1%) and 969 patients (68.9%), respectively (Fig. 2). In 6 patients, this information was unavailable. No differences were observed in sex.

The immediate onset of BTP was more frequent in patients with higher Karnofsky levels (71.1%) than in patients with lower values (62.8%) ($\chi^2 = P = 0.004$). Adult patients had a higher percentage of gradual BTP (56.5%), compared with more elderly patients who had a higher percentage of immediate BTP (52.3%) ($\chi^2 = P = 0.002$).

Patients with gradual-onset BTP had a lower BTP intensity ($P < 0.0001$) and a lower number of episodes per day than patients with immediate-onset BTP ($P < 0.0001$). PCU patients had a higher percentage of gradual BTP (39.8%) (χ^2 test, $P = 0.004$) than in ONC (28.3%) or OPA patients (29.5%).

TABLE 5. Characteristics of BTP

	Setting		
Characteristics	**ONC 316 (22.4%)**	**OPC 840 (59.5%)**	**PCU 256 (18.1%)**
NRS			
Mean (SD)	7.33 ± 1.51	7.46 ± 1.16	7.11 ± 1.32
BTP episodes/d			
Mean (SD)	2.45 ± 1.29	2.44 ± 0.96	2.17 ± 1.30
Duration (min)			
Mean (SD)	20.03 ± 16.19	31.46 ± 19.97	24.33 ± 15.40
Type (n [%])			
Predictable	87 (27.6)	42.6 (50.9)	105 (41.0)
Unpredictable	228 (72.4)	411 (49.1)	151 (59.0)
Onset (n [%])			
≤10 min	226 (71.7)	590 (70.5)	153 (60.2)
> 10 min	89 (28.3)	247 (29.5)	101 (39.8)
Site of BTP pain (n [%])			
Bone	258 (81.7)	619 (73.6)	167 (65.2)
Abdomen	108 (34.2)	270 (32.1)	89 (34.8)
Chest	60 (19.0)	189 (22.5)	52 (20.3)
Head and neck	41 (12.9)	110 (13.1)	39 (15.3)
Other	17 (5.4)	104 (12.4)	4 (1.6)

BTP indicates breakthrough pain; ONC, oncology; OPC, outpatient pain clinic; PCU, palliative care unit.

Predictability of BTP

BTP was predictable and unpredictable in 618 (43.9%) and 790 patients (56.1%), respectively. In 4 patients, this information was unavailable. No differences in sex ($\chi^2 = P = 0.242$) were observed (Fig. 2).

Patients with unpredictable BTP had a lower Karnofsky level than patients with predictable BTP (Student t test $P = 0.000$). In patients with immediate-onset BTP, this was predictable in 50.7% of cases, whereas in patients with gradual-onset BTP, it was only predictable in 29% of cases ($\chi^2 = P = 0.001$). These differences were confirmed in all the settings examined. The cohort of patients aged under 65 years had more unpredictable pain (61.5%) than the group aged over 65 (50.6%)($\chi^2 = P < 0.0001$). A significant different distribution of predictable and unpredictable events of BTP was observed among the 3 different settings (ONC, OPA, PCU) ($\chi^2 = P < 0.0001$) (Table 6).

Duration of BTP

The mean duration of untreated episodes of BTP was 27.6 minutes (SD ± 19). The distribution of duration frequency, expressed as intervals, is reported in Table 7. The most frequent range of BTP duration was 21 to 30 minutes. No differences were observed in sex ($P = 0.705$), predictability ($P = 0.556$), or BTP onset ($P = 0.664$). The duration of BTP was 20.03 (SD ± 16.19), 31.46 (SD ± 19.97), and 24.33 minutes (SD ± 15.40) in ONC, OPA, and PCU, respectively.

Course of the Disease and at BTP Characteristics

Cancer diagnosis was performed 23.5 months (SD ± 32.8) before the assessment. The background pain duration was 3.5 months (SD ± 3.5), and the mean duration of any analgesic treatment was 2.5 months (SD ± 3). BTP started 2.2 months (SD ± 1.9) before the assessment. Thus, BTP started about 1 month after the onset of background pain.

TABLE 6. Predictability of BTP in Different Settings

Settings	Predictable BTP (%)	Unpredictable BTP (%)
ONC	27.6	72.4
OPC	50.9	49.1
PCU	41.0	59.0

BTP indicates breakthrough pain; ONC, oncology; OPC, outpatient pain clinic; PCU, palliative care unit.

TABLE 7. Frequency of the Mean Intervals of BTP Duration (Untreated Episodes)

Intervals (min)	n (%)
0-10	242 (17.4)
11-20	352 (25.4)
21-30	472 (34.1)
31-40	141 (10.3)
41-60	146 (10.5)
> 60	27 (2.3)
Total	1380

BTP indicates breakthrough pain.

A moderate but not significant temporal relationship was reported between the onset time of background pain and BTP (Pearson correlation 0.541). These data does not seem to be influenced by the other variables taken into consideration. No differences were observed in sex ($P = 0.097$) or predictability ($P = 0.722$).

The relationship between BTP predictability and some variables, including duration of background pain, start, onset and duration of BTP, sex, age, Karnofsky index, and setting are reported in Table 5. Interestingly, in patients with a background pain duration of >180 days (n = 213, 15.2%), the start of BTP was significantly faster (83.1%). Patients with recent background pain reported a shorter duration of BTP and a more gradual onset (57%) (ANOVA test and LSD post hoc analysis $P < 0.0001$). Furthermore, when the background pain was recent ($\leq$30 d), BTP was unpredictable in 61.9% of cases (χ^2 test, $P < 0.0001$).

Relieving Factors

Relieving factors were identified by 1115 patients. Drugs were used mostly for relieving BTP (n = 994, 89.1%). Patients took rapid-onset opioids (76.5%), short-acting opioids (13%), and NSAIDs (4.4%) as indicated in Table 8. Other relieving factors included rest (n = 418, 37.5%), massages (n = 86, 7.7%), and others (n = 72, 6.2%).

Satisfaction With BTP Treatment

Data regarding satisfaction with BTP treatment were unavailable in 35 patients. A total of 1035 patients (73.3%) were satisfied with the treatment, whereas 342 (24.2%) were unsatisfied.

TABLE 8. Drugs Used for BTP, as Reported by Patients (Some Patients Were Taking >1 Drug)

Drugs	N
Nasal products of transmucosal fentanyl	620
Oral products of transmucosal fentanyl	493
Morphine immediate release	144
NSAIDs	61
Acetaminophen	41
Tramadol	27
Oxycodone + acetaminophen	24
Codeine + acetaminophen	15
Morphine slow release	13
Parentalmorphine	13
Tramadol + acetaminophen	4
Transdermal fentanyl	2
Oxycodone slow release	1
Methadone	1
No therapy	12

BTP indicates breakthrough pain.

TABLE 9. Physicians Who Made the First Diagnosis of BTP

Physicians	n (%)
Oncologist	312 (32.5)
Palliative care physician	182 (19)
Pain physician	458 (47.7)
General practitioner	8 (0.8)

BTP indicates breakthrough pain.

Diagnosis and Awareness of BTP

A total of 532 (61%) and 862 (39%) patients were aware or unaware of the BTP diagnosis, respectively. Data were unavailable for 18 patients. Data regarding the physicians who diagnosed BTP are reported in Table 9.

DISCUSSION

This survey is part of an observatory activity, which is relevant in terms of number of patients performed in different settings, including ONC, OPC, and PCU. By adopting a clear definition of BTP, this survey showed that BTP is observed in all the settings involved, and that this form of pain affects every stage of the oncological disease.

This survey confirmed the importance of having well-controlled basal pain to assess BTP. Unlike many other epidemiological studies,[7–12] patients were recruited according to a specific diagnostic algorithm for excluding patients with false BTP,[16–18] commonly due to undertreatment of cancer pain. A recent observation has shown that a suboptimal background treatment produces more frequent, severe, and long-lasting episodes of BTP, although the prevalence does not change.[19]

Several general epidemiological issues need to be addressed. The PCU patients were older and had a lower Karnofsky index, with more frequent mixed pain syndromes, possibly corresponding to the advanced stage of the disease. The pain intensity of background pain was lower in ONC patients. Pain mechanisms were distributed differently, with younger patients and ONC patients reporting more frequently neuropathic pain. These findings were expected and reflect the real-world, suggesting that the clinical history and care setting may influence the interpretation of data.

All patients were receiving opioids for their background pain. The observation that the longer the duration of opioid therapy, the less frequent the adverse effects, is explainable by the tendency to develop tolerance with prolonged opioid use. Data indicating that an elderly population is more at risk of developing adverse effects confirm available information about tolerability of opioid therapy in the elderly.[20] Interestingly, males were receiving analgesic treatment with opioids for longer periods of time. This disparity with females may be due to cultural influences or other factors, and deserves further research.

Although this survey confirmed previous observations, it also provided new insights into the interpretation of BTP and its characteristics. The number of BTP episodes was associated with higher limits of what is considered well-controlled background pain. This observation was often reported,[12] but it was related to poor pain control. Indeed,

the number of daily BTP was relatively higher with the increase in background pain intensity, even in patients with well-controlled pain. This point raises an important question about the definition of well-controlled pain, regardless of the scales used for assessing pain intensity.[13] For instance, a relationship has been found between background cancer pain, BTP, and analgesic treatment.[18]

Despite well-controlled background pain, BTP interfered with everyday life in the majority of patients, justifying the great amount of attention to this phenomenon over recent years in medical literature. In about 80% of patients, BTP had an impact on daily life, in any setting, and at any stage of the disease, as reported in several studies.[3,14,16]

Characteristics of BTP: Onset, Predictability, Duration

The setting or stage of the disease may also influence the characteristics of BTP. In PCU patients, who were older and had lower Karnofsky levels, the number of BTP episodes was lower, BTP onset occurred more gradually, and was less predictable. It could be argued that this population has a low level of activity inducing BTP, in comparison, for example, with OPC patients who are more likely to be outpatient subject, confirming some preliminary observations reported in advanced cancer patients followed at home and in oncologic wards.[5,6] In general, the prevalence of unpredictable (idiopathic-type) BTP was relatively higher than predictable (incident-type) BTP. In a recent observational study the percentage of incident-type and idiopathic BTP was quite similar. However, no distinction between PCU and OPC patients was made, and ONC patients were not included.[17] Data of the present study reflect the experience of a large cohort of cancer patients recruited in different settings, and representing the entire oncology population. The onset of BTP reported by the cohort of patients assessed in this survey was prevalently immediate. Some variables taken into considerations, including higher levels of BTP intensity, higher Karnofsky levels, and care setting, were the principal factors associated with an immediate onset of BTP. These findings suggest that patients with better physical activity could have a BTP induced by movement in an apparently well-controlled pain state, which could potentially be improved, confirming the observations reported above.

Similar considerations regarding BTP predictability reflect clinical situations commonly observed in the real-world. BTP predictability was more often observed in patients with immediate BTP onset, commonly associated with physical activity, irrespective of the setting. Conversely, the lower levels of physical activity in older patients, patients with a lower performance score, or PCU patients, explain the prevalence of unpredictable BTP.

The duration of BTP episodes was about 30 minutes on average. This information confirms previous data,[7,9,11,14,17,18,21] and no specific variables influenced BTP duration.

Some aspects have never been assessed in studies of BTP. A relationship between the BTP, the course of the disease, and treatment are additional relevant aspects that need to be investigated. In ONC patients and patients with longer periods of background pain, BTP occurred earlier. Moreover, predictable BTP was more frequently reported in patients with long-lasting periods of background pain and BTP. Therefore, the characteristics of BTP may be influenced by the course of the disease, as well as at the onset of background pain and BTP.

The use of analgesic drugs was the main relieving factor. Interesting, unlike other studies,[11,17,22,23] a large number of patients were using rapid-onset opioids, and the majority of patients were satisfied with the treatment. Although recent guidelines fail to supply any evidence to suggest that fentanyl products were more effective than oral morphine for the management of BTP (http://www.nice.org.uk/cg140), this class of drugs provided effective and rapid analgesia in comparison with oral opioids in most studies.[24,25] Thus, the National Institute for Health and Clinical Excellence directives were based on the economic burden of rapid-onset opioids rather than on their efficacy.

Finally, >60% of patients were aware of the diagnosis of BTP. This aspect is of paramount importance, as it has obvious implications for the patients' expectations and the impact of psychological factors. Unfortunately, no data are yet available and this finding should prompt further research. The diagnosis was mainly performed by oncologists and pain physicians. This is an apparent paradox, given that PCU physicians should be expert in making a diagnosis of BTP. However, from the temporal point of view, patients are referred to PCU physicians late in the course of the disease. Interestingly, the BTP diagnosis was practically never made by GPs. According to these findings, it is evident that GPs need to acquire more in-depth knowledge about the recognition and management of BTP.

CONCLUSIONS

This survey performed by an Italian observatory expert group, has confirmed that BTP represents a clinically relevant condition with a negative impact on the patient's quality of life. BTP was detected in all the settings involved, where the use of a diagnostic algorithm and a standardized CRF facilitated the diagnosis and classification of BTP. The principal finding of this study was that a number of factors are able to influence the development and characteristics of BTP, particularly regarding the course of the disease and the care setting. This information may help in stratifying patients or predicting the risk of developing BTP with specific characteristics in future studies. A systematic assessment of the types of BTP may also help in establishing more appropriate pharmacological treatment.

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