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ORIGINAL RESEARCH

Breakthrough Cancer Pain: Preliminary Data of The Italian Oncologic Pain Multisetting Multicentric Survey (IOPS-MS)

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ABSTRACT

Introduction: An ongoing national multicenter survey [Italian Oncologic Pain multiSetting Multicentric Survey (IOPS-MS)] is evaluating the characteristics of breakthrough cancer pain (BTP) in different clinical settings. Preliminary data from the first 1500 cancer patients with BTP enrolled in this study are presented here.

Methods: Thirty-two clinical centers are involved in the survey. A diagnosis of BTP was performed by a standard algorithm. Epidemiological data, Karnofsky index, stage of disease, presence and sites of metastases, ongoing oncologic treatment, and

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characteristics of background pain and BTP and their treatments were recorded. Background pain and BTP intensity were measured. Patients were also questioned about BTP predictability, BTP onset (≤10 or >10 min), BTP duration, background and BTP medications and their doses, time to meaningful pain relief after BTP medication, and satisfaction with BTP medication. The occurrence of adverse reactions was also assessed, as well as mucosal toxicity.

Results: Background pain was well controlled with opioid treatment (numerical rating scale 3.0 ± 1.1). Patients reported 2.5 ± 1.6 BTP episodes/day with a mean intensity of 7.5 ± 1.4 and duration of 43 ± 40 min; 977 patients (65.1%) reported non-predictable BTP, and 1076 patients (71.7%) reported a rapid onset of BTP (≤10 min). Higher patient satisfaction was reported by patients treated with fast onset opioids.

Conclusions: These preliminary data underline that the standard algorithm used is a valid tool for a proper diagnosis of BTP in cancer patients. Moreover, rapid relief of pain is crucial for patients' satisfaction. The final IOPS-MS data are necessary to understand relationships between BTP characteristics and other clinical variables in oncologic patients.

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Keywords: Breakthrough pain; Cancer pain; Pain assessment; Rapid-onset opioid

INTRODUCTION

Pain is common in cancer patients, particularly in the advanced stage of disease when the prevalence is estimated to be more than 70% [1]. Adequate pain control is achieved in most patients with available analgesic therapies [2].

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However, despite adequate pain control for most hours of the day, patients may develop transient flares of pain throughout the day. This phenomenon is known as breakthrough cancer pain (BTP) [3]. BTP has been reported to produce a negative impact on quality of life and is associated with a significant physical, psychological, and economic burden [4]. Several studies have assessed the epidemiology of this phenomenon, reporting largely variable data in different settings by using different definitions and methodologies, e.g., without an a priori definition of BTP, without clearly distinguishing background pain intensity and BTP intensity, or without considering the level of opioids used for background analgesia [5–7]. In recent years, BTP has been more meaningfully characterized through a diagnostic algorithm. Moreover, some attempts to better characterize this phenomenon according to a number of variables have been made. Recently, an expert consensus suggested that a BTP subclassification according to the characteristics of BTP may provide tailored treatment [8].

In the previous Italian Oncologic Pain multiSetting (IOPS) study, performed in various settings in a large number of patients, several factors influencing the development and characteristics of BTP were assessed [9]. From this data, the IOPS expert group planned a new multicenter survey, with the aim of providing further information on BTP and the factors influencing its characteristics in a large number of patients, diagnosed according to a specific algorithm. The use of BTP medications and factors interfering with administration of transmucosal opioids, commonly used for the management of BTP because their PK profile fits with BTP onset and duration, were also evaluated [5]. Reported here is a preliminary analysis of data from the first 1500 patients of

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4056 patients globally enrolled in this second IOPS study.

METHODS

This preliminary analysis included the first 1500 patients recruited in a national, observational, multicenter Italian study. An investigator meeting was held to present and comment on the project with the representatives of each center that participated. Subsequently, each center received an IOPS Multicentric Survey (IOPS-MS) investigator manual.

Thirty-two centers were involved. Each center consecutively enrolled patients for 24 months after obtaining local ethic committee approval and the patients' informed consent. Patients were recruited in the most common care settings where cancer patients are assessed for pain, including oncology, outpatient pain therapy, palliative care, and radiotherapy settings. The place of assessment was also recorded, including outpatient clinic, day hospital, home care, hospice, and inpatient ward.

Inclusion criteria were age greater than 18 years, cancer diagnosis at any stage, stable background pain in the last week with an intensity of at most 4 on a numerical scale from 0 to 10, and episodes of BTP with an intensity of 5 or more, clearly distinguished from background pain. A standard algorithm to diagnose BTP was followed according to the following definition: BTP is a transitory exacerbation of pain of moderate to severe intensity that occurs spontaneously or predictably [8–11], and is well distinguished from background pain of mild intensity [6, 12]. Exclusion criteria were the absence of a cancer diagnosis, uncontrolled background pain (>4 on a numerical scale of 0 to 10), or no relevant increases in pain intensity (<5) which could be interpreted as BTP episodes. Patients unable to provide information about the data required for the study, as a result of either cognitive failure or terminal disease, were also excluded. Patients meeting the inclusion criteria and assessed at each center were consecutively surveyed.

Epidemiological data, Karnofsky index, stage of disease, presence and sites of metastases, ongoing oncologic treatment, and characteristics regarding background pain and BTP and their treatments were recorded. Type of pain was registered according to routine clinical practice (neuropathic, nociceptive, or coexistent mechanism), and background and BTP intensity were measured on a numerical scale from 0 to 10. Patients were also questioned about BTP predictability, BTP onset ($\leq$10 or >10 min), BTP duration, background and BTP medications and their doses, time to meaningful pain relief after BTP medication, and satisfaction with BTP medication (a four-point scale was used by physicians: very satisfied, satisfied, not satisfied, and neither satisfied nor dissatisfied) [9, 10]. The occurrence of adverse reactions was also assessed, and mucosal toxicity was graded according to the World Health Organization (WHO) criteria [13]. The presence of candidiasis and xerostomia was also recorded. Each patient followed local policy and therapeutic protocols, and no specific treatment for BTP was assigned. To guarantee good quality of the data, these were entered in a web-based clinical report form. Each center had an individual password to enter their data into the system, and the study monitors could check records by local and remote monitoring.

Statistics

Data from the first 1500 patients were preliminarily examined. Continuous variables were summarized as means and standard deviations (SD). Categorical variables were summarized as percentages (absolute numbers). Univariate analysis was

performed using the Wilcoxon or Chi square test without correction for continuity for comparison among groups of continuous and categorical variables, respectively. Multivariate analysis was based on generalized linear models, with suitable link function chosen according to the characteristics of the response variable: identity for continuous and logit for binary or proportional-odds ordered categorical variables. All variables considered were entered into the model as they were, without any transformation or cutoff. The nonlinear effect of covariates was modeled by means of a restrictive cubic spline function, and its significance was assessed by means of the χ^2 Wald test. The model strategy was determined by following a backward selection strategy among variables reaching a level of at least 0.25 on univariate analysis. Model fit was considered significantly improved on the basis of the Akaike information criterion (AIC) applied backward for each model at a significance level of 0.05. To avoid inflation in type I error due to multiplicity of testing, subgroup analysis was conducted by introducing interaction terms into the main multivariate model, and its significance assessed by means of AIC. Multivariate models were depicted as nomograms. To evaluate the goodness of fit of the models, cross-validation and bootstrap (1000 runs) techniques were applied by the use of Somer's D_{xy}. Statistical significance was set at $p \leq 0.05$. The R-System statistical package and the Harrell regression modelling strategies libraries were used for analysis.

Compliance with Ethics Guidelines

Each of the 32 centers involved in the study obtained local ethics committee approval. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. Informed consent was obtained from all patients for being included in the study.

RESULTS

Patient Characteristics

Of the first 1500 patients recruited in IOPS-MS, most had metastatic disease and were receiving anticancer treatment (Table 1). The most common care settings were oncology and pain therapy, and patients were seen most often in outpatient clinics (37%) and inpatient wards (33%). No differences in gender were found among the different settings ($p = 0.989$). A lower and a higher Karnofsky index were found in the palliative care and radiotherapy settings, respectively [39.4 ± 10.8 vs 70 ± 18.2; $F = 86.7$; degrees of freedom ($d.f.$) = 3.519; $p < 0.001$]. Finally, older patients (mean ± SD age 73.9 ± 12.5 years) were over-represented in the palliative care setting ($F = 27.1$; $d.f. = 3.519$; $p < 0.001$).

BTP Characteristics

The initial diagnosis of BTP was most often performed by oncologists ($n = 616$ diagnoses, 41%) and pain physicians ($n = 583$, 39%), followed by palliative care physicians ($n = 241$, 16%), nurses ($n = 18$, 1%), general practitioners ($n = 15$, 1%), other healthcare providers ($n = 15$, 1%), and radiotherapists ($n = 9$, 0.6%). In three cases, data were unavailable. Patients in hospices had a longer time from diagnosis of BTP in comparison with outpatient settings ($p = 0.0123$). The percentages of patients with baseline pain and the characteristics of BTP are presented in Fig. 1.

Table 1 Baseline patient characteristics

Characteristic	$N = 1500$
Mean ± SD age, years	64.8 ± 12.3
Gender, *n* (%)	
Male	810 (54)
Female	690 (46)
Karnofsky index score, mean ± SD	61.1 ± 18.2
Place of assessment, *n* (%)	
Outpatient clinic	549 (37)
Day hospital	171 (11)
Home care	232 (15)
Hospice	47 (3)
Hospital inpatient ward	501 (33)
Primary tumor site, *n* (%)	
Lung	352 (22)
Urogenital	254 (17)
Gastrointestinal	276 (18)
Breast	201 (13)
Pancreas	129 (8)
Liver	16 (1)
Head and neck	97 (6)
Others	241 (15)
Disease, *n* (%)	
Locoregional	250 (17)
Metastatic	1250 (83)
Previous anticancer treatment, *n* (%)[a]	1154 (79)
Care setting, *n* (%)	
Palliative care	289 (19)
Oncology	672 (45)
Pain therapy	526 (35)
Radiotherapy	13 (1)

All values are presented as mean ± SD or number of patients (proportion of patients)
SD standard deviation
[a] Data available in 1464 patients

The mean number of BTP episodes/day was 2.5 ± 1.6 (data available for 1499 patients). In patients with higher Karnofsky index and with prostate cancer the number of BTP episodes was significantly higher than in patients with other primary diagnoses ($p < 0.001$). BTP onset was ≤10 and >10 min in 1076 (71.7%) and 424 (28.3%) patients, respectively.

The mean duration of untreated BTP was 43 ± 40 min (data available for 504 patients). Variables significantly associated with a longer BTP duration were metastatic disease ($p = 0.03$), head and neck cancer ($p = 0.04$) and pancreatic cancer, and receiving anticancer therapy ($p = 0.05$; Table 2). In the multivariate analysis, a significant association with background pain intensity was found, with a linear effect of 10.9 min [95% confidence interval (CI) 9.3–12.5].

The distribution of BTP mechanisms in the different care settings is reported in Table 3. A mixed mechanism of BTP was found to be more represented in oncology and pain therapy settings than in radiotherapy and palliative care settings. Conversely, a nociceptive mechanism was more frequently found in palliative care and radiotherapy settings than in oncology and pain therapy settings.

Predictable BTP

BTP was unpredictable in 977 patients (65.1%) and predictable in 523 patients (34.9%). Predictable BTP was associated with age ($p = 0.008$), pain mechanism ($p < 0.001$, lower risk with mixed mechanism), place of assessment ($p < 0.001$), care setting ($p = 0.002$), background pain ($p = 0.004$), diagnosis of prostate cancer ($p = 0.030$), Karnofsky index ($p = 0.046$), and oral mucositis ($p < 0.001$). In

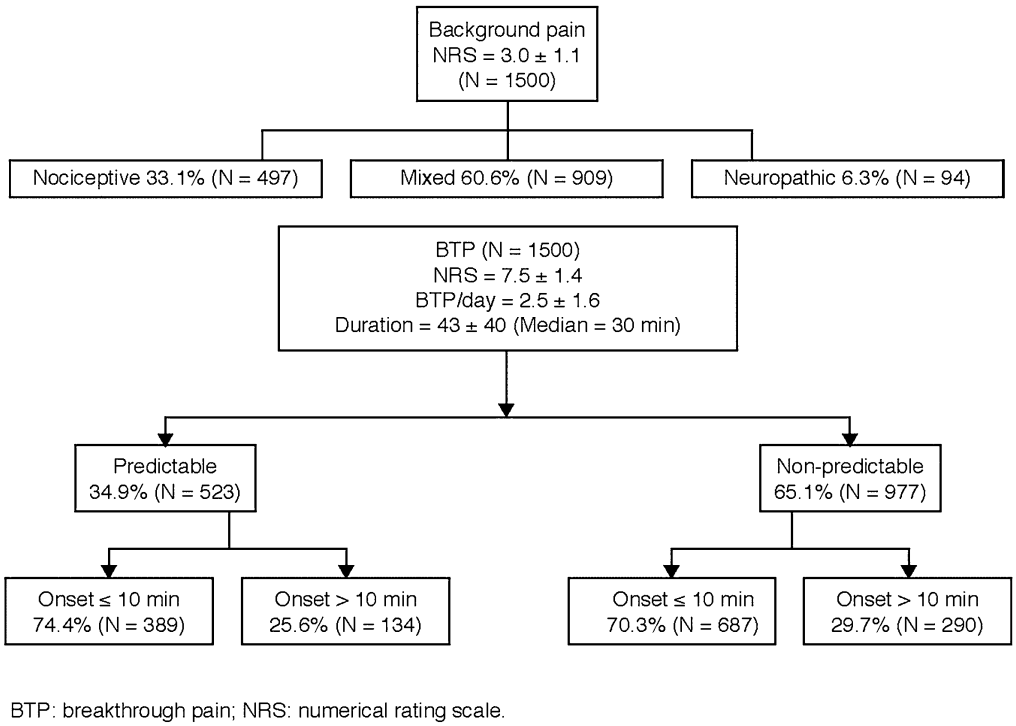

Fig. 1 Percentages of patients with baseline pain and characteristics of BTP

the multivariate analysis, lower Karnofsky, lower BTP intensity, and rapid onset of BTP were significantly associated with predictable BTP. The radiotherapy setting was strongly associated with predictable BTP (odds ratio [OR] 9.05). The main trigger for predictable BTP was activity-movement ($n = 349$, 67%), followed by swallowing ($n = 80$, 15%), cough ($n = 54$, 10%), procedure ($n = 39$, 7%), and bowel movement ($n = 31$, 6%).

Intensity of Background Pain and BTP

The mean intensity of background pain on assessment and the average pain in the previous week were both 3.0 ± 1.1. The mean doses of oral morphine equivalents (OME) used for background pain were 69.8 ± 139.7 mg/day. The mean intensity of BTP was 7.5 ± 1.4. Rapid-onset BTP and high levels of background pain intensity were associated with a higher BTP intensity. Conversely, a slow-onset BTP was associated with a lower BTP intensity. No differences in BTP intensity among the care settings and triggers of predictable BTP were found. Using mixed pain mechanism as a reference, BTP intensity was higher for neuropathic pain ($p = 0.0248$) and lower for nociceptive pain ($p = 0.0257$). BTP was of lower intensity in older patients ($p = 0.0002$), in patients with higher Karnofsky status ($p = 0.0016$), and in patients with breast cancer ($p = 0.04$). Finally, mucositis was associated with higher BTP intensity ($p = 0.0083$).

BTP Medications

A total of 1263 (84%) patients were receiving opioid drugs for the management of BTP, including fentanyl pectin nasal spray (FPNS,

Table 2 Patient characteristics associated with duration of breakthrough pain

Characteristic		*n*	Mean duration of BTP, min	SD	*p* value
Disease	Locoregional	109	36.54	34.54	
	Metastatic	395	44.64	41.34	0.03
Primary tumor	Other	90	36.00	36.59	
	Gastrointestinal/liver	89	42.36	38.99	
	Pancreas	56	55.09	46.35	
	Lung	99	42.26	40.41	
	Breast	68	38.18	33.75	
	Head and neck	16	50.38	58.09	0.04
	Urogenital	86	45.74	39.70	
Anticancer treatment	No	97	37.24	32.97	
	Yes	388	45.06	42.22	0.05

BTP breakthrough cancer pain, *n* number of patients, *SD* standard deviation

Table 3 Frequency of breakthrough pain according to care setting

	Care setting					*p* value
	Palliative care	Oncology	Radiotherapy	Pain therapy	All	
N	289	672	13	526	1500	
Type of BTP experienced, *n* (%)						
Mixed	113 (39)	411 (61)	6 (46)	364 (69)	894 (60)	<0.001
Neuropathic	8 (3)	63 (9)	0 (0)	15 (3)	86 (6)	
Nociceptive	168 (58)	198 (29)	7 (54)	147 (28)	520 (35)	

23%), oral morphine (OM, 17%), fentanyl buccal sublingual tablet (FBST, 15%), fentanyl buccal tablet (FBT, 11%), oral transmucosal fentanyl citrate (OTFC, 5%), subcutaneous morphine (SC-M, 4%), intravenous morphine (IV-M, 3%), and intranasal fentanyl spray (INFS, 1%). The mean ± SD doses of each drug were 178 ± 144 μg (FPNS), 13 ± 11 mg (OM), 227 ± 169 μg (FBST), 261 ± 207 μg (FBT), 490 ± 330 μg (OTFC), 11 ± 5 mg (SC-M), 9 ± 9 mg (IV-M), and 109 ± 59 μg (INFS). No differences in BTP medication according to the characteristics of BTP were found. FPNS was less frequently used in radiotherapy and pain therapy settings ($p = 0.008$), while SC-M was more frequently used in oncology and palliative care settings ($p = 0.004$). There was a significant relationship between OME and opioid doses for BTP (correlation 0.42, 95% CI 0.37–0.46).

Time to Meaningful Pain Relief After Drug Administration

The mean time for achieving meaningful pain relief after BTP medication was 17 ± 14 min. In Table 4, the variables associated with the time

Table 4 Time to meaningful pain relief by treatment and other variables

	Mean ± SD time to pain relief, min	*p* value
BTP treatment		
FBST	16.15 ± 14.3	
FBT	13.78 ± 11.0	
FPNS	10.99 ± 8.6	0.012
INFS	10.64 ± 5.2	0.012
IV-M	13.44 ± 8.6	0.012
SC-M	15.36 ± 10.2	
OM	18.84 ± 12.1	
OTFC	12.97 ± 5.4	
Other	27.73 ± 18.1	
Place of assessment		
Outpatient clinic	23.08 ± 18.0	
Day hospital	14.95 ± 10.8	
Home	16.24 ± 13.0	
Hospice	14.82 ± 8.0	
Inpatient ward	14.05 ± 11.0	<0.001
Primary tumor site		
Gastrointestinal–liver	15.29 ± 11.7	
Pancreas	13.93 ± 10.8	0.0193
Lung	16.11 ± 16.0	
Breast	23.02 ± 18.9	
Head and neck	14.33 ± 10.7	0.0193
Urogenital	19.60 ± 12.9	
Other	16.87 ± 13.0	

BTP breakthrough pain, *FBST* fentanyl buccal sublingual tablet, *FBT* fentanyl buccal tablet, *FPNS* fentanyl pectin nasal spray, *INFS* intranasal fentanyl spray, *IV-M* intravenous morphine, *OM* oral morphine, *OTFC* oral transmucosal fentanyl citrate, *SC-M* subcutaneous morphine, *SD* standard deviation

for meaningful pain relief are presented (data were available for 810 patients). In the multivariate analysis, factors associated with shorter meaningful pain relief were assessment in the inpatient ward ($p < 0.001$), drug therapy (INFS, FPNS, and IV-M, $p = 0.012$), and pancreas and head and neck cancers ($p = 0.0193$).

Satisfaction with BTP Medication

Patients were very satisfied, satisfied, not satisfied, and neither satisfied nor dissatisfied with their BTP medication in 154 (11%), 765 (55%), 262 (19%), and 211 (15%) cases (data available in 1392 patients). The level of satisfaction was significantly associated with the use of FPNS ($p = 0.0002$). Also, the outpatient clinic ($p = 0.04$), care in the oncology setting ($p = 0.0011$), and receiving anticancer treatment ($p = 0.0166$) were associated with patients' satisfaction (Table 5).

Adverse Effects of BTP Medications

Adverse reactions attributed to BTP medications were reported in 53 out of 1500 (4%) patients and were constipation ($n = 18$), dizziness ($n = 18$), nausea ($n = 5$), headache ($n = 2$), vomiting ($n = 1$), and other unspecified adverse effects ($n = 9$). The intensity was mild in 46 patients (88%) and moderate in 6 patients (12%). In 38 patients (83%) no specific therapeutic change was required, while in the remaining 8 cases (17%) it was deemed necessary to treat the adverse effects or discontinue the BTP medication. No association was found between adverse reactions and choice and dosage of opioids used for BTP ($p = 0.843$). Finally, no medication abuse was reported.

Oral Mucositis

Two hundred and twelve patients (14%) presented with different levels of oral

Table 5 Multivariate model for dissatisfaction

	OR (95% CI)	*p* value
BTP treatment		0.0002
Other vs FPNS	1.98 (1.42–2.76)	
FBST vs FPNS	1.51 (1.03–2.21)	
FBT vs FPNS	1.31 (0.86–1.99)	
INFS vs FPNS	0.41 (0.14–1.24)	
IV-M vs FPNS	0.47 (0.22–1.00)	
SC-M vs FPNS	0.99 (0.50–1.94)	
OM vs FPNS	1.35 (0.93–1.95)	
OTFC vs FPNS	1.65 (0.95–2.88)	
Place of assessment		0.04
Day hospital vs outpatient clinic	0.71 (0.45–1.13)	
Home care vs outpatient clinic	0.29 (0.10–0.85)	
Hospice vs outpatient clinic	0.52 (0.15–1.72)	
Inpatient vs outpatient clinic	0.72 (0.51–1.03)	
Previous anticancer treatment vs no previous anticancer treatment	1.41 (1.06–1.87)	0.0166
Care setting		0.0011
Palliative care vs oncology	0.84 (0.29–2.44)	
Radiotherapy vs oncology	1.58 (0.54–4.59)	
Pain therapy vs oncology	0.53 (0.38–0.74)	

95% CI 95% confidence interval, *BTP* breakthrough pain, *FBST* fentanyl buccal sublingual tablet, *FBT* fentanyl buccal tablet, *FPNS* fentanyl pectin nasal spray, *INFS* intranasal fentanyl spray, *IV-M* intravenous morphine, *OM* oral morphine, *OR* odds ratio, *OTFC* oral transmucosal fentanyl citrate, *SC-M* subcutaneous morphine

mucositis. Of them, 134 patients had oral aching/erythema, 56 had oral erythema/ulcer/solid diet tolerated, 17 patients had oral ulcers/only liquid diet tolerated, and in 5 patients oral feeding was impossible (from level 1 to level 4, respectively). Head and neck cancer was positively associated with the severity of oral mucositis (OR 5.42; 95% CI 2.70–10.86; $p < 0.001$). Of interest, the grade of mucositis was positively associated with BTP on swallowing (OR 4.85; 95% CI 2.79–8.40). No association was found between levels of oral mucositis and choice of drugs for BTP and their doses. Candidiasis and xerostomia were detected in 90 (6%) and 280 (19%) patients, respectively.

DISCUSSION

Preliminary data for the first 1500 patients of the IOPS-MS survey suggest that, in general, in patients with BTP, older patients and patients with a lower Karnofsky index were most frequently followed in a palliative care setting. This information is consistent with data collected in the previous IOPS survey [9] and in other surveys performed either in oncology or in palliative care settings [14, 15], confirming that the patients' characteristics differ among the settings of care, particularly in patients with the highest morbidity under the care of palliative care physicians. Data suggest that higher prevalence rates of BTP are reported in studies performed in the hospice setting [9, 16, 17].

Results of this survey suggest that the diagnosis of BTP was performed more frequently by oncologists than by palliative care physicians. Conversely, a longer time for diagnosis of BTP was reported in the hospice setting. Oncologists generally have more opportunities to make an early diagnosis of BTP, as they see patients more often through the course of disease [18], whereas physicians in palliative care see patients later in the course of their disease, which may explain this result. Another explanation could be that oncologists

have improved their pain assessment skills in the years since large surveys showed worrying data, suggesting a great need for continuing education programs in pain management among oncologists [19, 20]. However, it is important to note that these findings may not adequately represent the situation, particularly as the differences in the number of patients with BTP in oncology versus palliative care setting may simply be due to the sampling design. Further investigation is warranted.

In this preliminary survey, prostate cancer, a tumor commonly associated with multiple bone metastases, significantly produced more episodes of BTP, potentially representing a risk factor for this phenomenon (see below, predictable BTP). This observation should be confirmed by the complete analysis of the IOPS-MS data. In a European survey, patients had a median of 3 BTP episodes/day. Of interest, patients were included whether they had just 1 episode/month or up to 24 episodes/day [10]. Patients who had a better Karnofsky index were more likely to have more BTP episodes. It is likely that more physical activity may produce more episodes of BTP. Alternately, one can argue that the management of background pain of these patients could be better optimized. This observation confirms previous data, in which very advanced and bedridden patients had fewer BTP episodes with longer onset [9].

The mean duration of untreated BTP was about 40 min, reflecting data from many epidemiological studies that describe a variable duration of 30–60 min [9, 10, 21]. BTP duration has been reported to be longer in spontaneous unpredictable BTP than in patients with incident-type BTP [10]. It should be considered that BTP duration in untreated BTP is more difficult for patients to properly assess, and not all patients are able to do so.

To facilitate the patients' orientation, a dichotomous measure was chosen for BTP onset ($\leq$10 or >10 min). BTP onset was rapid in 71.7% of patients and slower in 28.3% of patients. Similar values, with a median of 10 min, were found in a multicenter European survey [10] and an Italian survey [9], where they were lower with incident-type BTP.

BTP predictability is an important clinical factor with obvious therapeutic consequences for timing and choice of available BTP medications. Moreover, incident-predictable BTP has been considered to be a negative factor for cancer pain management [17, 22, 23]. This is due to the difficulties in balancing analgesia at rest and pain on movement, which often results in attempts to improve basal analgesia with a possible occurrence of opioid-induced adverse effects. Predictable BTP has a faster onset, typically observed in patients with bone metastases, triggered by physical activity or movement. In this survey, about 35% of patients had predictable BTP, and physical activity was the most frequent trigger.

Some factors were independently associated with predictable BTP and included lower Karnofsky index, lower BTP intensity, and faster BTP onset. Predictable BTP has been previously found to be associated with a faster onset of BTP [9, 10]. Pain induced by movement in patients with bone metastases occurs rapidly and is clearly predictable. A worse performance status was associated with predictable BTP. This is in contrast to a previous finding and probably due to the different care setting distribution in the first IOPS study [9]. It is reasonable to hypothesize that patients with a lower Karnofsky index have lower background pain intensity at rest for most daytime hours, but develop predictable BTP on movement. These data should be confirmed in a larger number of

patients with complete analysis the IOPS-MS study. Furthermore, the relationship between predictable BTP and BTP intensity is complex. Patients with a higher BTP intensity had less predictable BTP. This could be explained by patients' attitudes in limiting a sustaining trigger that induced a predictable BTP, thus avoiding a higher peak of pain intensity.

Of interest, predictable BTP was more frequently observed in the radiotherapy setting, which could be explained by the fact that patients are commonly referred to these specialists for the treatment of bone metastases.

Among the other trigger factors for predictable BTP, swallowing was associated with oral mucositis. Thus, mucosal damage, commonly reported in patients who have received or are still receiving toxic agents [24], is more likely to produce a predictable BTP on swallowing. As expected, mucositis was associated with head and neck cancer, possibly due to previous anticancer treatment. The presence of mucosal damage was also associated with higher levels of BTP intensity. Mucositis is a typical example of BTP occurring with swallowing only. Moreover, the presence of oral mucositis has obvious clinical consequences in terms of route of administration when considering the possible use of transmucosal agents such as rapid-onset opioids, prejudicing reliable absorption of oral transmucosal agents [5]. This suggests that physicians should pay more attention to the diagnosis of mucositis, but also to xerostomia and candidiasis, for optimal selection of BTP therapy.

The relationship between background analgesia and BTP intensity is fundamental in describing the phenomenon of BTP, particularly from a therapeutic perspective. It has been reported that a meaningful cutoff of these levels of pain intensity, as reported in the real world by patients instructed in BTP, is about double [12]. In this survey these levels were maintained on average (3 and 7.5 for background pain and BTP intensity, respectively), suggesting that the standard algorithm used in this study allows an appropriate diagnosis of BTP in cancer patients. Of interest, younger patients, higher background pain intensity, a short BTP onset, the level of mucositis, and neuropathic mechanisms were also independently related to BTP pain intensity. These aspects are worthy of further evaluation with the complete data.

The relationship between background pain and BTP intensity is problematic. Some patients, for example, avoid taking a medication because BTP intensity is not considered high enough. On the other hand, in a recent Delphi survey, experts in the field of BTP suggested that transient pain exacerbations can occur independently of background pain level and ongoing pain medication, and the phenomenon includes several subgroups of BTP types [8].

In our survey, a large number of patients were receiving opioids for the management of BTP, particularly transmucosal fentanyl, in relatively similar or proportional doses, according to the fentanyl availability of different delivery systems. Of interest, a highly significant relationship between the doses of BTP opioid medications and opioid doses for background pain was found. This finding reflects the growing evidence suggesting that a dose proportional to the basal opioid regimen is both safe and effective [25–28], regardless of recommendations suggesting titrating the dose against the effect [29]. Moreover, adverse reactions attributed to BTP medications were limited and of mild intensity in most cases, and were independent of the drug and dose used. This observation confirms that opioid

medications given in doses proportional to background opioid dose are relatively safe [25, 26]. This aspect deserves further analysis.

Nasal administration of fentanyl provided faster analgesia relative to other fentanyl products [30]. Patient-reported satisfaction with pain treatment is an important outcome measure when assessing both background pain and BTP [8]. Of interest, the use of FPNS and IV-M, home care assessment, pain therapy setting, and the absence of anticancer treatment were associated with the highest level of satisfaction. Therefore, faster analgesia and patients' satisfaction should be strongly considered in order to prescribe optimal treatment. These aspects deserve further research and will be better explored with the complete data of IOPS-MS.

There are some limitations to this survey, mainly due to the inherit nature of the study design. Firstly, caution must be taken when interpreting some of the outcomes because of the retrospective nature of the survey. Furthermore, for some outcomes, data are missing.

CONCLUSIONS

Overall, the number of patients allows a preliminary analysis only. Although preliminary, these data provide interesting information that will be developed with the complete IOPS-MS survey. BTP diagnosis was performed according to strict criteria, including stable background analgesia achieved with analgesics given around the clock. BTP intensity was clearly distinguished from basal pain, confirming the validity of the algorithm used for the diagnosis of BTP. These aspects allow us to better evaluate the BTP phenomenon. The characteristics of BTP, including the number of episodes, predictability, onset, intensity, duration, and time from diagnosis, were influenced by the many variables taken into consideration. From a therapeutic point of view, opioids, particularly fentanyl products, were largely given for BTP management. The analgesic effect of BTP medications was dependent on a number of variables. Satisfaction with BTP medications was relatively good, particularly in specific settings and with fentanyl preparations. Tolerability was acceptable in most cases, independently of the medication used. Despite the presence of oral mucositis, there was no association with specific drugs or delivery systems. Further data from IOPS-MS should provide a more complete picture of BTP in patients with different cancer types receiving various anticancer treatments, to finally understand this "phenomenon".

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Compliance with Ethics Guidelines. Each of the 32 centers involved in the study obtained local ethics committee approval. All procedures followed were in accordance with the ethical

standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. Informed consent was obtained from all patients for being included in the study.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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