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Prevalence and characteristics of breakthrough cancer pain in an outpatient clinic in a Catalan teaching hospital: incorporation of the Edmonton Classification System for Cancer pain into the diagnostic algorithm

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Abstract

Background: Breakthrough cancer pain (BTcP) is defined according to its principal characteristics: high intensity, short time interval between onset and peak intensity, short duration, potential recurrence over 24 h and non-responsiveness to standard analgesic regimes. The Edmonton Classification System for Cancer Pain (ECS-CP) is a classification tool that evaluates different dimensions of pain.

The aim of this study was to measure prevalence and the main characteristics of BTcP in a sample of advanced cancer patients and to explore the complexity observed when ECS-CP is incorporated into BTcP diagnostics algorithm.

Methods: Descriptive prevalence study (Retrospective chart review). Davies' algorithm was used to identify BTcP and ECS-CP was used to recognize appropriate dimensions of pain. The study was conducted in a sample of advanced cancer patients attending hospital outpatient clinic in Lleida, Spain. 277 patients were included from 01/01/2014 to 31/12/2015. No direct contact was made with participants. The following information was extracted from the palliative care outpatient clinic database: age, gender, civil status, cognitive impairment status, functional performance status and variables related to tumour. Only BTcP cases were included.

Results: Prevalence of BTcP was 39.34% (63.9% men). Mean of age was 68.2 years. Main diagnosis was lung cancer ($n = 154$; 31.6%). Metastases were diagnosed in 83% of the sample. 138 patients (49.8%) were diagnosed with 1 type of BTcP and 139 (50.2%) were diagnosed with more than one type of BTcP. In total, 488 different types of BTcP were recorded (mean $1.75 \pm 0, 9$), 244 of these types (50%) presented a component of neuropathic pain. Addictive behaviour, measured through CAGE test, was present in 29.2% ($N = 81$) of the patients and psychological distress was present in 40.8% ($n = 113$).

Conclusions: Prevalence of BTcP (39.34%) is similar to the one reflected in the existing literature. Study results indicate that the routine use of ECS-CP in a clinical setting allows us to detect more than one type of BTcP as well as additional complexity associated with pain (neuropathic, addictive behavior and psychological distress).

Keywords: Breakthrough cancer pain, Palliative care, ECS-CP, Neuropathic pain, Addictive behaviour, Psychological distress

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Background

In 1989, Portenoy and Hagen [1] defined breakthrough cancer pain (BTcP) as the transient exacerbation of pain occurring in a patient with otherwise stable pain in receipt of chronic opioid therapy. This pain is one of the most difficult pain syndromes to treat. The term encompasses a diverse group of transient pains that vary in their relationship to the fixed analgesic dose, temporal characteristics, precipitating events, predictability, pathophysiology, and aetiology [1, 2].

Later, BTcP was redefined as a transient exacerbation of pain that occurs either spontaneously, or in relation to a specific predictable or unpredictable trigger, despite relatively stable and adequately controlled background pain [3]. More recently, other authors [4–7] have improved BTcP definition by adding severity of intensity and the length between 30 and 60 min.

Prevalence of BTcP varies between 19 and 95% [8–11]. This is explained by the different definitions found in the literature and also depending on the area where the data are collected (inpatient or outpatient patients).

The prevalence of BTcP assessed in outpatient clinics is 39.9% and in those assessed in palliative care units, is 80.5% [12].

It is therefore difficult to diagnose BTcP. For this reason, many Scientific Societies related to cancer, palliative care and pain, work to clarify the definition and the accurate diagnosis of BTcP [13–17].

In the same way, different instruments have been defined to facilitate the diagnostic approach of BTcP. We highlight the Alberta Breakthrough Pain Assessment Tool for Cancer Patients [18], the breakthrough pain assessment tool (BAT) in cancer patients [19] and the Italian Questionnaire for Breakthrough Pain (IQ-BTP) [20].

To improve the sensitivity of the diagnosis of BTcP, several authors developed the so-called “Davies algorithm” [21], recently validated by Weber K et al. [22]. Although the use of this algorithm is widespread, it is not designed to replace clinical assessment.

Literature refers to BTcP as a single clinical entity with several possible episodes in a single patient and the fact that more than one different types of BTcP with several episodes each in the same patient has not yet been explored [16, 23, 24].

The pharmacological treatment of BTcP is based on the use of the three-step ladder of the WHO [25, 26]. Considering the characteristics of BTcP in terms of temporality and intensity, only Rapid Onset Opioids (ROOs), mainly fentanyl, have been shown to be effective [27–29]. Zeppetella and Davies [30] conclude that both oral and intranasal-Trans-mucosal fentanyl are effective for the treatment of BTcP episodes.

Early pharmacological approach is the cornerstone of the treatment of BTcP [31]. Its improvement will also

enhance both the quality of life and the functionalism of the patient [32].

The first choice of treatment is always oral and in many cases, for the treatment of BTcP, the choice is fast bioavailability treatments such as fentanyl. The rapid bioavailability of fentanyl-based ROOs may lead to episodes of abuse of these drugs; therefore it is advisable to minimize the risk with a detailed appropriately assessment [33, 34].

The Edmonton Classification System for Cancer Pain (ECS-CP) derives from the Revised Edmonton Staging System (rESS) from which construct, inter-rater reliability, and predictive validity evidence have contributed to the development of the ECS-CP. The five features of cancer pain included -Pain Mechanism (N), Incident Pain (I), Psychological Distress (P), Addictive Behavior (A) and Cognitive Function (C)- have demonstrated value in predicting pain management complexity [35, 36].

The ECS-CP is a clinically relevant systematic framework, which is able to detect differences in salient pain classification features across diverse settings and countries [37].

It is known that BTcP is difficult to diagnose and to treat. We hypothesized that if we add the ECS-CP during the diagnosis process, we find an added complexity together with the incident features of the cancer pain. This is because we can find other characteristics of pain such as the neuropathic component, addiction and psychological discomfort.

Therefore, the objectives of this retrospective review were:

1. To describe the characteristics of the population studied and the prevalence of BTcP in a sample of advanced cancer patients treated at an outpatient clinic.
2. To determine the number of different types of BTcP diagnosed in each patient, regardless the number of episodes of BTcP.
3. To explore the different pain features associated to the diagnosis of BTcP

Methods

This was a retrospective and anonymous database review of the patients attending for the first time at Palliative Care outpatient clinic, which is maintained at the Lleida University Hospital in Catalonia (Spain).

This study was approved by the Ethics Committee of the Hospital Universitari Arnau de Vilanova in Lleida. All data-analysis was performed anonymously without an additional informed consent, according to its recommendations. The administrative permissions required were obtained in order to review patient records and use the data.

This Palliative Care outpatient clinic attends advanced cancer patients early in the disease course as well as patients that are not receiving active treatment. The patients were referred to the clinic by their reference oncologist and the palliative care consultation team was the responsible organ of the pain management.

Inclusion criteria: age > 18 years, diagnosis of advanced cancer (non haematological) assisted at the outpatient clinic of the Palliative care outpatient clinic suffering, from BTcP due to cancer and without any cognitive impairment (Pfeiffer test ≥ 4 errors). End-of-dose pain was specifically excluded.

We defined BTcP according to Boceta et al. [38] as a transitory exacerbation of pain lasting less than 60 min, which occurs spontaneously or in association with a specific predictable or unpredictable trigger at some point during the day in cancer patients, despite relatively and adequately controlled background pain. BTcP was considered as those that have different characteristics in terms of localization, intensity, mechanisms that trigger it or intrinsic characteristics of pain (neuropathic vs. nociceptive). The same type of BTcP can present with several episodes (maximum 4 episodes per day). The literature review shows that there is not a broad consensus about definition of BTcP therefore, to facilitate the methodology of data collection; we included equal terms BTcP and incidental pain.

A physician, also responsible for assessing pain and other symptoms, evaluated all the patients attended in the outpatient clinic. Pain was assessed using a Visual Analogic Scale (VAS) and the cut-off value (VAS scale) of patients for their background pain was $VAS \leq 3$ during the previous 7 days. All patients who reported adequately controlled background pain ($VAS \leq 3$) in the previous week were further evaluated exhaustively. The procedure to diagnose BTcP was done following the algorithm of Davies [21] and according to the consensus recommendations from the Spanish Pain Society. The algorithm indicates that baseline pain must be adequately controlled before a diagnosis of BTcP can be considered. Each BTcP were located anatomically in the painful area and each patient could present different types of pain. For each type of BTcP, the ECS-CP test was later applied to assess additional complexity. The ECS-CP classifies the different pain features according to its origin. This way, the neuropathic and incident component of pain can be secondary to the tumor itself while the psychological discomfort and addictive behaviour can be considered personality traits. Therefore, the analysis of both the neuropathic (N) and the incident (I) component of pain was done over the total number of different types of BTcP detected and the Psychological (P) and addictive (A) traits were analysed over the total number of patients included. The Cognitive (C) component was specifically excluded.

This is the usual protocol applied in order to study pain when a patient is assessed first time at the outpatient clinic.

Data collection

The following information was extracted from the chart review: age, gender, civil status, cognitive status measured with Pfeiffer test [39, 40], functional performance status measured with Barthel test [41, 42] and with Palliative Performance Scale version 2 test (PPSv2) [43, 44]. Variables related to the tumour were obtained (primary tumour diagnosis, metastatic disease and locally advanced disease).

We also extracted the information related to BTcP as following:

- Related Factors: predictable, unpredictable or idiopathic (volitional, non-volitional or idiopathic).
- Cause of pain: tumour, treatments received or idiopathic cause.
- Intensity of pain: measured through a VAS scale. Minimum and maximum intensity were recorded. The difference between VAS minimum intensity (VAS min) and VAS maximum intensity (VAS max) should be ≥ 3 points measured with scale from 0 to 10.

The ECS-CP was applied in order to detect additional pain features other than incident pain in the same patient. The neuropathic component of pain was assessed through the Doleur Neuropathique-4 questionnaire (DN4) [45, 46] altogether with the clinical examination. For the psychological distress we followed the Clinical Practice Guidelines in Oncology (NCCN) and a $VAS \geq 4$ in either anxiety or depression was the cut-off point [47]. Regarding the addictive behaviour only the addiction to alcohol was collected and measured through Cut down, Annoyed, Guilty and Eye-opener questionnaire (CAGE) [48]. Two or more “yes” responses indicated the possibility of alcoholism.

For each pain features detected by the ECS-CP (NIPAC), one point was given.

Even if the number of BTcP episodes were specifically registered in the patients files, they were not included in the data analysis.

Data analysis

The data included all patients attending the outpatient clinic of the Catalan University Hospital Arnau de Vilanova of Lleida between 2014 and 2015. The information for the study was extracted between June and October 2016.

The study was carried out in two separate phases; in the first phase the data analyzed was related to the total number of patients with pain included consecutively in the study and this sample was further studied according to the number of different types of pain found (1 types vs. > 1 type

of pain). In the second phase, data analyzed was related to the total number of different types of BTcP individualized after having used the ECS-CP in the diagnostic algorithm and the sample was also further analyzed depending of the pain intensity. We considered mild and moderate pain if the VAS < 7 and severe pain included VAS ≥ 7.

Statistical analyses were conducted using SPSS Statistics 20 (IBM Corporation) and Microsoft Excel (Microsoft Corporation) software [49]. 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. Statistical significance was assumed at a 0.05 level ($P < 0.05$).

Results

The palliative care team visited a total of 1276 patients for the first time at the University Hospital Arnau de Vilanova in Lleida, Catalonia (Spain) between January 2014 and December 2015. 704 of them (55.17%) attended the outpatient clinic. 303 patients had pain, and 277 were diagnosed of BTcP and included to the chart review study. Mean age was 68.2 ± 13 years while men accounted for 67.9% of the sample. Lung cancer (31%) was the most prevalent cancer diagnosis and metastatic disease was found in 83% of the sample.

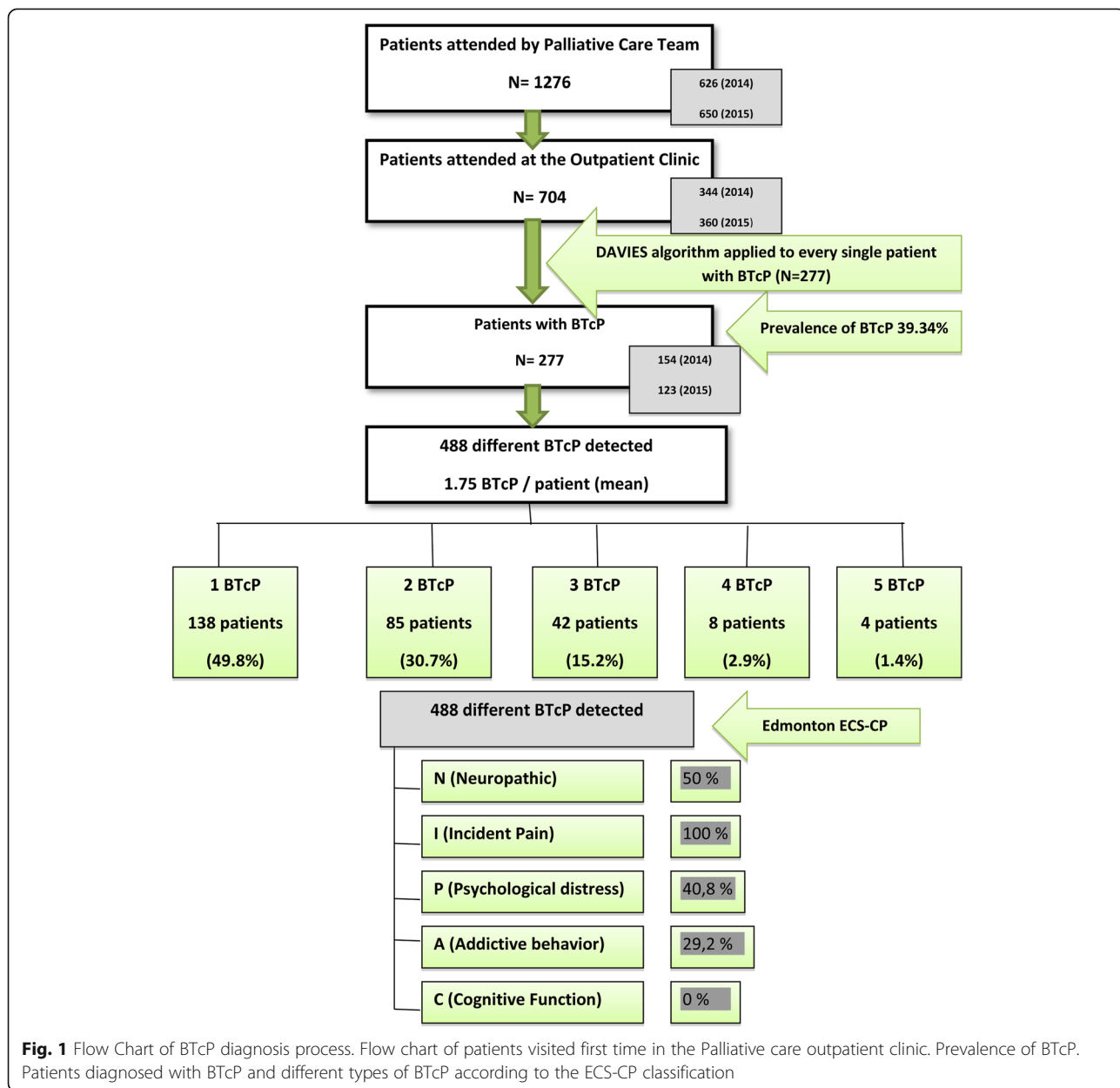


Fig. 1 Flow Chart of BTcP diagnosis process. Flow chart of patients visited first time in the Palliative care outpatient clinic. Prevalence of BTcP. Patients diagnosed with BTcP and different types of BTcP according to the ECS-CP classification

A prevalence of 39.34% of BTcP (277/704 patients) was found. A total of 488 different types of BTcP were detected (mean of 1.75 ± 0.9 types of BTcP per patient). Up to 5 different types of BTcP were found among the patients and 50,2% of patients ($N = 139$) accounted for ≥ 2 types of BTcP (Fig. 1).

Main characteristics of the population studied are showed in Table 1. Addictive behavior was detected in 29.2% of the sample and the psychological discomfort was detected in 40.8%. This table also shows the results according to two groups of patients (1 type vs > 1 type). The group of patients with > 1 type was younger (66 ± 12 , $p = 0.002$), had more metastatic disease (90.6%, $p = 0.001$) and presented with more psychological discomfort (47.5%, $p = 0.023$). Patients with 1 type of BTcP presented addictive behavior (CAGE) (34.8%, $p = 0.043$).

In Table 2, the analysis was performed taking into account the number of different types of BTcP detected ($N = 488$). The use of the ECS-CP tool on each type of BTcP allowed us to detect that, together with the incident feature of pain, 50% ($N = 244$) had a neuropathic component. Non-volitional component of BTcP was detected in the 63.7% of the sample. The sum of the different pain features detected by the ECS-CP (NIPAC) when applied on the sample of 488 different types of BTcP is 2.2 ± 1 .

Discussion

This retrospective study was designed to determine several outcomes related to BTcP in a sample of advanced cancer patients who attended the outpatient clinic of a University hospital during a two-year period (2014–2015).

We identified a prevalence of 39.34% of BTcP in the sample of patients screened for the study. The application of Davies algorithm and a close clinical examination were the cornerstone for defining pain. This result is consistent with Deandrea et al. [12] who after a bibliographic research, stated a prevalence of BTcP of 39.9% for cancer patients attended at the outpatient clinic. Similar outcome data are reported by Margarit et al. [50] who, after reviewing data from the *American Pain Foundation*, show a prevalence of 35% for those cancer patients seen on an ambulatory regime.

To our knowledge, this study provides the first data regarding the fact that a single patient can present with more than one type of BTcP. Previous studies only address this subject as a single patient having different episodes of the same BTcP. On the current study, we found that a total of 488 different types of BTcP were assessed in a sample of 277 patients. Each patient had an average of 1.75 BTcP. We remark that more than half of the patients (139/277) were found to report more than one type of BTcP. Up to 12 patients presented with 4 or 5 different types of BTcP (4.3%) while

Table 1 Sociodemographic and medical characteristics of the patients ($N = 277$) in relation to the number of BTcP

	Total ($n = 277$)	BTcP		p^b
		BTcP (1 type) $N = 138$	BTcP (> 1 type) $N = 139$	
Age (years) ^a	68.2 ± 13	70.4 ± 13	66 ± 12	0.002
Gender (men) (%)	67.9	73.2	62.6	0.059
Civil Status (%)				0.854
Married/couple	71.1	69.6	72.7	
Single	6.5	5.8	7.2	
Separated/divorced	7.6	8	7.2	
Widowed	10.8	11.6	10.1	
Missing	4	5.1	2.9	
Type tumor (%)				0.508
Lung	31	31.2	30.9	
Upper digestive	19.9	21	18.7	
Lower digestive	19.1	18.8	19.4	
Ear-Nose and Throat	8.7	10	7.2	
Genitourinary male	8.7	6.5	10.8	
Genitourinary female	4	2.2	5.8	
Other	8.7	10.1	7.2	
Metastatic disease (%)	83	75.4	90.6	0.001
Pfeiffer Test ^a	0.8 ± 1	0.9 ± 1	0.6 ± 1	0.068
Barthel Test ^a	87 ± 17	87 ± 18	87 ± 15	0.409
PPSv2 Test ^a	64 ± 12	64 ± 12	63 ± 11	0.131
Pain features				
Addictive	29.2	34.8	23.7	0.043
Psychological	40.8	34.1	47.5	0.023
Number of BTcP types ^a	1.75 ± 0.9			

^amean ± standard deviation

^bComparison between groups with the χ^2 test and for continuous variables with the Mann-Whitney test

127 patients (45.9%) presented with 2 or 3 different types of BTcP.

Younger patients and those presenting with metastatic disease variables were found statistically significant.

The classification ECS-CP provides further insight into several characteristics of pain like neuropathic, psychological distress and addictive behavior features. As the Incident component of pain is already included in the ECS-CP, all types of pain found in our study had a BTcP component. The addictive behaviour (A) was sensibly higher (29.2%) than the found in the literature. Parsons et al. [51] and Dev et al. [52] found in their studies a prevalence of addictive behaviour of 17% in cancer patients attending an outpatient clinic while Chow et al. [53] found a poor 7% prevalence rate in an

Table 2 Characteristics of episodes of incidental pain ($n = 488$) according to intensity (maximum VAS ≥ 7)

	SAMPLE ($n = 488$)	VAS MAX < 7 ($n = 305$)	VAS MAX ≥ 7 ($n = 183$)	p^b
Due to Tumour	93,0	91,8	95,1	0,168
Due to treatment	8,0	8,5	7,1	0,575
Volitional	36,3	36,7	35,5	0,789
Non volitional	63,7	64,1	35,9	0,618
Neuropathic condition	50,0	45,4	63,0	0,001
Σ NIPAC	2,2 \pm 1	2,2 \pm 1	2,3 \pm 1	0,044
Type tumor				0,007
Lung	31,6	35,4	25,1	
Upper digestive	18,0	18,7	16,9	
Lower digestive	20,1	20,3	19,7	
ENT	7,6	6,9	8,7	
Genitourinary male	8,4	8,9	7,7	
Genitourinary female	5,1	4,3	6,7	
Other	9,2	5,6	15,3	

Values as percentage

^amean \pm standard deviation

^bComparison between groups with the de χ^2 test and for continuous variables with the Mann-Whitney test

outpatient palliative radiotherapy clinic. Even if all studies screened the addictive behaviour using the CAGE questionnaire, differences found can be explained by the fact that we recorded the CAGE in current or former drinkers.

The sample of 488 different types of pain found was further divided according to pain intensity. Only neuropathic nature of pain, the summation of the ECS-CP and the type of cancer showed significant statistical differences.

The ECS-CP has demonstrated its utility in routine clinical practice. Arthur et al. [54] found that neuropathic pain and psychological distress were associated with higher pain intensity. Also a higher sum of ECS-CP features was associated with higher pain intensity. More recently the same author found that increasing sum of ECS-CP features was not predictive of pain management complexity. Our study shows that a higher sum of ECS-CP features was found among the group of types of BTcP with a VAS intensity ≥ 7 .

However the study has limitations; first, the study was carried out in a single institution and data available from medical records were recorded by a single physician during clinical interviews. Second, data from addiction behaviour only included alcohol screening through the CAGE questionnaire.

Our study did not aim to analyse any specific pharmacological treatment the patients received. Our study shows a high prevalence of the neuropathic component of BTcP, further studies have to address this finding.

The strengths and limitations of this study are the following:

- This is a retrospective study and prevalence rates are reported from a single institution and a single physician recorded the data available from medical records during clinical interviews.
- This study includes BTcP and incidental pain in equal terms.
- Data from addiction behaviour only included alcohol screening through the CAGE questionnaire.
- This study included a large cohort of patients who had BTcP.
- This study supports the hypothesis that a single patient can present more than one type of BTcP.
- This study supports the use of screening tools to better categorize diagnose of Cancer pain.

Conclusions

Our study provides data regarding prevalence of BTcP in a palliative care outpatient clinic in a single Teaching Hospital and the result of 39.94% is similar to those found in the literature.

This retrospective chart review allows determining the number of different types of BTcP diagnosed in each patient, regardless the number of episodes of BTcP. This is possible with the routine use of the ECS-CP in tandem with the Algorithm of Davies when exploring BTcP in cancer patients.

This study explores the different pain features associated to the diagnosis of BTcP. Clinicians have to take into account several pain features such as the neuropathic nature of pain, psychological distress and addictive behaviour, as the optimal therapeutic approach can change.

The existence of more than one type of BTcP in each patient adds more complexity to the pain assessment.

Abbreviations

A: Addictive Behavior; BAT: Breakthrough pain assessment tool; BTcP: Breakthrough Cancer Pain; C: Cognitive Function; CAGE: Cut down, annoyed, guilty and eye-opener questionnaire; DN4: Doleur neuropathique-4 questionnaire; ECS-CP: Edmonton Classification System for Cancer Pain; ENT: Ear, Nose and Throat; I: Incident Pain; IQ-BTP: Italian Questionnaire for Breakthrough Pain; N: Pain Mechanism; NCCN: Clinical Practice Guidelines in Oncology; P: Psychological Distress; PPSv2: Palliative Performance Scale version 2 test; rESS: Revised Edmonton Staging System; ROOs: Rapid Onset Opioids; SD: standard deviations; VAS max: VAS maximum intensity; VAS min: VAS minimum intensity; VAS: Visual analogic Scale

Authors' contributors

JCS participated in the design of the work, carried out the study and had the main responsibility for writing the manuscript and for the final approval, EBG participated in conceiving the study, writing the manuscript and participated in the final approval of the version to be published, PJJ revised it critically and approved of the version to be published, JTC supported data analysis and writing the manuscript. NAT, RGR and MRG participated in the interpretation of data for the work and JCS, PJJ, EBG and JTC have made significant contributions to this topic in the field of palliative care. All authors read and approved the final manuscript and have assumed accountability for all aspects of the work.

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Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was approved by the local ethics authorities (Ethics Committee of the University Hospital Arnau de Vilanova in Lleida, No 1611). All data-analysis was performed anonymously without an additional informed consent, according to the local ethical recommendations.

Competing interests

The authors declare that they have no competing interests.

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References

- Portenoy R, Hagen N. Breakthrough pain: definition and management. *Oncology*. 1989;3:25–9.
- Portenoy R, Payne D, Jacobsen P. Breakthrough pain: characteristics and impact in patients with cancer pain. *Pain*. 1999;81(1):129–34.
- Davies AN, Dickman A, Reid C, Stevens AM, Zeppetella G. Breakthrough cancer pain. *BMJ*. 2008;337(7681):1252.
- Burton B, Zeppetella G. Assessing the impact of breakthrough cancer pain. *Br J Nurs*. 2011;20(Sup5):S14–9.
- Payne R. Recognition and diagnosis of breakthrough pain. *Pain Med*. 2007; 8(suppl 1):S3–7.
- Porta-Sales J, Garzón Rodríguez C, Julià Torras J, Casals Merchán M. Dolor irruptivo en cáncer. *Med Clin (Barc)*. 2010;135(6):280–5.
- Zampi M, Morabito A, Salvato F, Vinciguerra A. Breakthrough pain: the importance of baseline analgesic regimen with opioids. *Transl Med UniSa*. 2012;3:62–6.
- Mercadante S, Zagonel V, Breda E, Arcara C, Gebbia V, Porzio G, et al. Breakthrough pain in oncology: a longitudinal study. *J Pain Symptom Manag*. 2010;40(2):183–90.
- Greco MT, Corli O, Montanari M, Deandrea S, Zagonel V, Apolone G. Epidemiology and pattern of care of breakthrough cancer pain in a longitudinal sample of cancer patients: results from the Cancer pain outcome research study group. *Clin J Pain*. 2011;27(1):9–18.
- Mercadante S, Costanzo BV, Fusco F, Buttà V, Vitrano V. Breakthrough pain in advanced cancer patients followed at home: a longitudinal study. *J Pain Symptom Manag*. 2009;38(4):554–60.
- Davies A, Buchanan A, Zeppetella G, Porta-Sales J, Likar R, Weismayr W. Breakthrough cancer pain: an observational study of 1000 European oncology patients. *J Pain Symptom Manag*. 2013;46(5):619–28.
- Deandrea S, Corli O, Consonni D, Villani W, Greco MT, Apolone G. Prevalence of breakthrough cancer pain: a systematic review and a pooled analysis of published literature. *J Pain Symptom Manag*. 2014;47(1):57–76.
- Haugen D, Hjermstad MJ, Hagen N, Caraceni A, Kaasa S. Assessment and classification of cancer breakthrough pain: a systematic literature review. *Pain*. 2010;149(3):476–82.
- Porta-Sales J, Pérez C, Escobar Y, Martínez V. Diagnosis and management of breakthrough cancer pain: have all the questions been resolved? A Delphi-based consensus assessment (DOIRON). *Clin Transl Oncol*. 2015;18(9):945–54.
- Boceta J, De la Torre A, Samper D, Farto M, Sánchez-de la Rosa R. Consensus and controversies in the definition, assessment, treatment and monitoring of BTcP: results of a Delphi study. *Clin Transl Oncol*. 2016;18(11):1088–97.
- Løhre ET, Klepstad P, Bennett MI, Brunelli C, Caraceni A, Fainsinger RL, et al. From "breakthrough" to "episodic" Cancer pain? A European Association for Palliative Care Research Network Expert Delphi Survey toward a common terminology and classification of transient Cancer pain exacerbations. *J Pain Symptom Manag*. 2016;51(6):1013–9.
- Working Group Nientemale DEI, Vellucci R, Fanelli G, Pannuti R, Peruselli C, Adamo S. What to do, and what not to do, when diagnosing and treating breakthrough Cancer pain (BTcP): expert opinion. *Drugs* 2016;76(3):315–330.
- Hagen NA, Stiles C, Nekolaichuk C, Biondo P, Carlson LE, Fisher K, et al. The Alberta breakthrough pain assessment tool for cancer patients: a validation study using a delphi process and patient think-aloud interviews. *J Pain Symptom Manag*. 2008;35(2):136–52.
- Webber K, Davies AN, Zeppetella G, Cowie MR. Development and validation of the breakthrough pain assessment tool (BAT) in cancer patients. *J Pain Symptom Manag*. 2014;48(4):619–31.
- Samolsky Dekel BG, Remondini F, Gori A, Di Nino G, Melotti RM. Development, validation and psychometric properties of a diagnostic/prognostic tool for breakthrough pain in mixed chronic-pain patients. *Clin Neurol Neurosurg*. 2016;141:23–9.
- Davies A, Dickman A, Reid C, Stevens A, Zeppetella G. The management of cancer-related breakthrough pain: recommendations of a task group of the science Committee of the Association for palliative medicine of Great Britain and Ireland. *Eur J Pain*. 2009;13:331–8.
- Webber K, Davies AN, Cowie MR. Accuracy of a diagnostic algorithm to diagnose breakthrough cancer pain as compared with clinical assessment. *J Pain Symptom Manag*. 2015;50(4):495–500.
- Daeninck P, Gagnon B, Gallagher R, Henderson J, Shir Y, Zimmermann C. Canadian recommendations for the management of breakthrough cancer pain. *Curr Oncol*. 2016;23(2):96–108.
- Hjermstad M, Kassa S, Caraceni A, Loge J, Pedersen T, Haugen D, et al. Characteristics of breakthrough cancer pain and its influence on quality of life in an international cohort of patients with cancer. *BMJ Support Palliat Care*. 2016;6(3):344–52.
- Potter MB. Opioids for management of breakthrough pain in cancer patients. *Am Fam Physician*. 2006;74(11):1855–7.
- William L, MacLeod R. Management of breakthrough pain in patients with cancer. *Drugs*. 2008;68:913–24.
- Lavery D. Treating cancer-related breakthrough pain: the oral transmucosal route. *Int J Palliat Nurs*. 2007;13(7):326–31.
- Mercadante S, Radbruch L, Davies A, Poulain P, Sitte T, Perkins P, et al. A comparison of intranasal fentanyl spray with oral transmucosal fentanyl citrate for the treatment of breakthrough cancer pain: an open-label, randomised, crossover trial. *Curr Med Res Opin*. 2009;25(11):2805–15.
- Grape S, Schug SA, Lauer S, Schug BS. Formulations of fentanyl for the management of pain. *Drugs*. 2010;70(1):57–72.
- Zeppetella G, Davies AN. Opioids for the management of breakthrough pain in cancer patients. In: *Cochrane database of systematic reviews*. Wiley-Blackwell; 2013.
- Escobar Y, Mañas A, Juliá J, Gálvez R, Zaragoza F, Margarit C, et al. Optimal management of breakthrough cancer pain (BCP). *Clin Transl Oncol*. 2012; 15(7):526–34.
- Davies A, Kleeberg UR, Jarosz J, Mercadante S, Poulain P. Improved patient functioning after treatment of breakthrough cancer pain: an open-label study of fentanyl buccal tablet in patients with cancer pain. *Support Care Cancer*. 2015;23(7):2135–43.
- Núñez-Olarte JM, Alvarez-Jiménez P. Emerging opioid abuse in terminal cancer patients taking oral transmucosal fentanyl citrate for breakthrough pain. *J Pain Symptom Manag*. 2011;42(6):e6–8.
- Granata R, Bossi P, Bertulli R, Saita L. Rapid-onset opioids for the treatment of breakthrough cancer pain: two cases of drug abuse. *Pain Med*. 2014; 15(5):758–61.
- Nekolaichuk CL, Fainsinger RL, Lawlor P. A validation study of a pain classification system for advanced cancer patients using content experts: the Edmonton classification system for Cancer pain. *Palliat Med*. 2005;19(6):466–76.
- Fainsinger RL, Nekolaichuk CL. A «TNM» classification system for cancer pain: the Edmonton classification system for Cancer pain (ECS-CP). *Support Care Cancer*. 2008;16(6):547–55.
- Nekolaichuk CL, Fainsinger RL, Aass N, Hjermstad MJ, Knudsen AK, Klepstad P, et al. The Edmonton classification system for Cancer pain: comparison of pain classification features and pain intensity across diverse palliative care settings in eight countries. *J Palliat Med*. 2013;16(5):516–23.

38. Boceta J, De la Torre A, Samper D, Farto M, Sánchez-de la Rosa R. Consensus and controversies in the definition, assessment, treatment and monitoring of BTcP: results of a Delphi study. *Clin Transl Oncol*. 2016;18(11):1088–97.
39. Martínez De La Iglesia J, Herrero RD, Vilches MCO, Taberné CA, Colomer CA, Luque RL. Adaptación y validación al castellano del cuestionario de Pfeiffer (SPMSQ) para detectar la existencia de deterioro cognitivo en personas mayores de 65 años. *Med Clin (Barc)*. 2001;117(4):129–34.
40. Pfeiffer E. A short portable mental status questionnaire for the assessment of organic brain deficit in elderly patients. *J Am Geriatr Soc*. 1975;23(10):433–41.
41. Mahoney FI, Barthel DW. Functional evaluation: the Barthel index. *Md State Med J febrer*. 1965;14:61–5.
42. Cid-Ruzafa J, Damián-Moreno J. Valoración de la discapacidad física: el índice de Barthel. *Rev Esp Salud Publica*. 1997;71(2):127–37.
43. Ho F, Lau F, Downing MG, Lesperance M. A reliability and validity study of the palliative performance scale. *BMC Palliat Care*. 2008;7(1):10.
44. Barallat E, Nabal M, Canal J, Trujillano J, Gea-Sánchez M, Larkin PJ, et al. The Spanish adaptation of the palliative performance scale (version 2) among Cancer patients at the end of life: psychometric properties. *J Pain Symptom Manag*. 2017;54(4):570–7.
45. Bouhassira D, Attal N, Alchaar H, Boureau F, Brochet B, Bruxelle J. Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). *Pain*. 2005;114(1–2):29–36.
46. Perez C, Galvez R, Huelbes S, Insausti J, Bouhassira D, Diaz S, et al. Validity and reliability of the Spanish version of the DN4 (Douleur Neuropathique 4 questions) questionnaire for differential diagnosis of pain syndromes associated to a neuropathic or somatic component. *Health Qual Life Outcomes*. 2007;5:66.
47. National Comprehensive Cancer Network Guideline for Patients. Distress. 2017 on: <https://www.nccn.org/patients/guidelines/distress/files/assets/common/downloads/files/distress.pdf>. Accessed 7 Jan 2018.
48. Mayfield D, McLeol G, Hall P. The CAGE questionnaire: validation of a new alcoholism screening instrument. *Am J Psychiatr*. 1974;131(10):1121–3.
49. IBM Corp. IBM SPSS Statistics for Windows v. 20.0. Armonk, NY: IBM Corp; 2011.
50. Margarit C, Juliá J, López R, Anton A, Escobar Y, Casas A, et al. Breakthrough cancer pain - still a challenge. *J Pain Res*. 2012;5:559–66.
51. Parsons H, Delgado-Guay M, El Osta B, Chacko R, Poulter V, Palmer J. Alcoholism screening in patients with advanced cancer: impact on symptom burden and opioid use. *J Palliat Med*. 2008;11(7):964–8.
52. Dev R, Parsons H, Palla S, Palmer J, Del Fabbro E, Bruera E. Undocumented alcoholism and its correlation with tobacco and illegal drug use in advanced cancer patients. *Cancer*. 2011;117(19):4551–6.
53. Chow E, Connolly R, Wong R, Franssen E, KW F, Harth T. Use of the CAGE questionnaire for screening problem drinking in an out-patient palliative radiotherapy clinic. *J Pain Symptom Manag*. 2001;21(6):491–7.
54. Arthur J, Yennurajalingam S, Nguyen L, Tanco K, Chisholm G, Hui D. The routine use of the Edmonton classification system for Cancer pain in an outpatient supportive care center. *Palliat Support Care*. 2015;13(5):1185–92.

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