

Research Article

Breakthrough Cancer Pain: What Role can the General Practitioner Play?

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Abstract

Background: Despite the extensive literature, Breakthrough cancer Pain (BTcP) is still under-diagnosed and under-treated. Although cancer pain affects quality of life, primary care physicians do not seem to play a role in the management of patients with BTcP.

Objectives: Point out the clinical characteristics that can help the general practitioner to identify the patient early with cancer pain and in particular with BTcP.

Methods: We studied the clinical data base of 4,016 patients enrolled in the IOPS-MS study in order to identify which clinical parameters of BTP can be early detected by primary care physicians.

Results: The results of the study show that BTcP occurs during each phase of cancer, 2.4 ± 1.4 times per day, with a duration of 43.3 ± 36.9 minutes, and it manifests 1.9 ± 5.6 months after the onset of baseline pain.

Conclusion: These data suggest that the BTcP cannot be under diagnosed if the general practitioner plans a periodic visit to each cancer patient. Therefore, the involvement of the general practitioners, through periodic screening and the use of standardised diagnostic algorithms aimed at starting the multidisciplinary care pathways in an early phase, may improve the level of satisfaction and quality of life of patients with cancer pain.

Keywords: Breakthrough pain; General practitioner

Introduction

The clinical phenomenon of Breakthrough cancer Pain (BTcP), also known as intense episodic pain, has been discussed in international literature for many years [1,2]. BTcP occurs with painful, spontaneous or triggered episodes with a relatively short duration. It affects cancer patients when the background pain (constant pain experienced for more than twelve hours a day) is already being controlled for most of the time [2]. BTcP is of considerable clinical relevance since it affects quality of life and interferes with the treatment of cancer patients [3]. Moreover, this type of pain involves a substantial consumption of healthcare resources [4]. Due to differences in definitions or research methods, various types of episodic pain have been described over the years [5]. Some studies carried out on large numbers of patients [3,6-9] suggest that the features of BTcP (intensity, duration, onset, resolution time of the painful episode) depend on the type of tumour, the existence of metastases and the Karnofsky index, and confirm the need for personalised treatment [10]. Some authors have pointed out the difficulty of the general practitioner in oncology patient management [11], and in particular of pain [12]. For this reason, we wanted to analyse the clinical aspects of

episodic pain which can be more easily detected by the general practitioner, in order to facilitate a rapid therapeutic diagnostic classification of patients with cancer pain.

Materials and Methods

This study consists in a secondary analysis of the IOPS-MS a multicentric study [13] involving 32 Italian clinical centres which, upon approval from their ethics committees, recruited patients presenting each stage of oncological disease, with a steadily controlled background pain of ≤ 4 (measured on an 11-point Numeric Rating Scale, NRS) for at least seven days, who were reporting painful episodes that were clearly distinctive from the background pain. Patients experiencing uncontrolled background pain (NRS > 4), or those who had not provided informed consent, were excluded. The clinical-medical history parameters, clinical conditions, characteristics of the baseline pain and episodic pain, treatments used and the results obtained, were collected for each patient. The episodic pain diagnosis was carried out by means of a standard diagnostic algorithm (Table 1). Thanks to the involvement of 175 investigators (oncologists, pain therapists, palliative care specialists), it was possible to enrol patients from a variety of healthcare settings (wards, day hospitals, clinics, hospices and at home care).

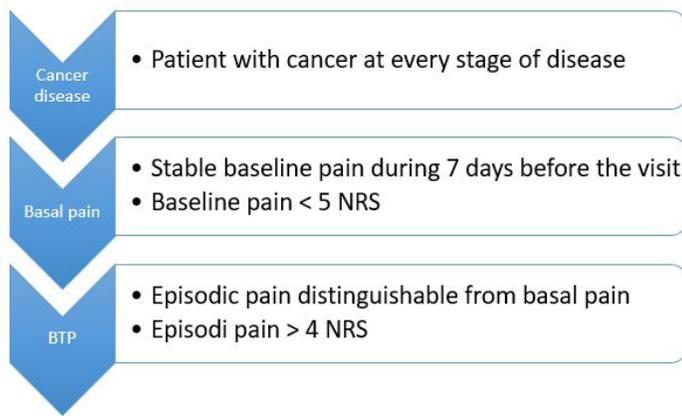


Table 1: Diagnostic algorithm used to detect episodic pain (BTP).

Statistical Analysis

Clinical information was collected using an electronic clinical report form. Data were checked and validated before being analysed. Descriptive statistics were carried out: average and SD for continuous variables, absolute and relative frequencies

for categorical variables. Descriptive analyses were carried out for all patients and all subgroups. A Chi-squared test, a Student’s t-test (using the Bonferroni-Holm method) and a 1-way ANOVA (preceded by analysis of the theoretical distribution-kurtosis and the between-group and within-group variance test), were performed in order to obtain a correct inference analysis of all possible differences. Statistical parametric and non-parametric tests were used to assess possible interdependence between 2 or more variables and the possible associations between clinical characteristics and therapeutic interventions administered and entered in the clinical report form. The Chi-squared test (with calculation of the odds ratio when the bivariate 2x2), the Student’s t-test and the variance analysis (F Fisher and post-hoc LSD test), were carried out to identify the factors correlated to BTcP. The data were processed by using SPSS (IBM, Armonk, NY) version 10.0.

Results

In the period from March 2013 to November 2015, a total of 4,056 patients were enrolled in the IOPS-MS a multicentric study [13], of which, 4,016 were evaluable, and 78.0% had recently been or currently under cancer treatment (Table 2).

Cancer site	Gastro Intestinal & Liver (N=785)	Pancreas (N=344)	Lung (N=978)	Breast (N=474)	Head & Neck (N=150)	Urogenital (N=620)	Other cancer (N=665)	N= 4016
Metastasis %	89.5%	82.0%	84,50%	96.4%	56.7%	91.1%	68.6%	84,00%
Anticancer treatment %	77,10%	71,10%	73,10%	92,70%	81.5%	84,90%	71,80%	78,00%
Karnofsky Index	61±19,7	63,3±18,9	61,9±18,2	62,9±18,1	67,4±18,6	61,0±18,5	61,9±19,4	61,8±18,7
intensity of basal pain NRS (mean±SD)	2.9±1.1	2.9±1.1	3.1±1.0	3.0±1.0	3.0±1.1	3.0±1.1	2.9±1.1	3.0±1.1
BTP onset (<10min) %	71,70%	66,00%	71,00%	64,50%	69,00%	65,00%	71.0%	68.9%
Duration of BTP, min (mean±SD)	42,7±35,1	52,8±42,0	41 +/- 33	41,1±37,7	44±41	47±41	39±35	43,3±37,7
BTP non predictable %	74%	75%	67%	65%	61%	71%	68%	70%

Table 2: Site of the tumor, the average performance status (Karnofsky Index), the baseline pain intensity, duration, predictability and time at which the breakthrough pain reaches its highest intensity.

3,188 (79.4%) patients reported episodic pain clearly distinguishable from basal pain with an intensity of 7 to 10, while the remaining 828 (20.6%) reported episodic pain, clearly distinguishable from baseline pain, with moderate intensity (NRS 5 or 6; average NRS of 5.7 ± 0.4) (Table 3).

BTP Characteristics, mean (95% CI) or n (%)	BTP Moderate	BTP severe	P
	(NRS 5-6)	(NRS ≥ 7)	
	(N=828)	(N=3188)	
Number of BTP/die	2.0 (1.9, 2.1)	2.5 (2.4, 2.5)	p<0.0001
Intensity	5.7 (5.7, 5.8)	8.0 (7.9, 8.0)	p<0.0001
Onset ≤ 10 min	535 (64.6%)	2234 (70.1%)	p=0.003
Onset >10 min	293 (35.4%)	954 (29.9%)	
Duration (min)	41.0 (36.1, 46.0)	43.7 (41.4, 46.0)	p=0.34
Predictable	291 (35.1%)	934 (29.3%)	p=0.001
Non predictable	537 (64.9%)	2254 (70.7%)	

Table 3: Characteristics of moderate (NRS 5-6) and intense BTP (NRS>7).

30.6% of enrolled patients reported basal pain with an intensity of NRS 0 to 2, while 69.4% reported intensity of NRS 3 to 4 (Table 4).

	Basal pain NRS				
	0	1	2	3	4
No. of pts	149	186	895	1145	1641
Oral Equivalent Morphine, mean (95% CI) [N]	112.1	100.4	92.0	97.0	103.6
	(93.1, 131.2) [N=141]	(83.4, 117.5) [N=179]	(85.1, 98.9) [N=867]	(91.3, 102.7) [N=1111]	(97.7, 109.6) [N=1593]
BTP intensity, mean (*)	6.8 ± 1.4	7.0 ± 1.4	7.1 ± 1.2	7.5 ± 1.2	7.8 ± 1.2
(95% CI)	(6.6, 7.1)	(6.8, 7.2)	(7.0, 7.2)	(7.4, 7.6)	(7.8, 7.9)
Number of BTP/Die, mean (*)	1.5	1.8	2.0	2.4	2.7
(95% CI)	(1.3, 1.7)	(1.6, 2.0)	(1.9, 2.1)	(2.3, 2.5)	(2.6, 2.8)

Table 4: Intensity of the BTP and the number of BTP/day based on baseline pain. (*) ANOVA p<0.0001 for both intensity and number of BTP.

The number of episodes per day, the duration and the intensity of the BTcP did not seem to be influenced by the stage of the tumour, calculated according to the Classification of Malignant Tumours (TNM) (p=0.7) or to the presence of metastases (p=0.4), while the intensity of the BTcP increased significantly with a reduction in KI (p=0.0001).

It was found that patients reported the occurrence of BTcP 56.6 (51.3, 61.8) days, after the onset of baseline pain (Pearson 0.685 p <0.0001), while the onset of pain occurred on average

after 43.3 (40.5, 46.1) days in those having ongoing treatment for baseline pain.

It was found that patients taking pain relievers reported that episodic pain arose on average 2.9 (2.4, 3.4) months earlier than under other treatment conditions (p=0.0001).

Finally, patients experiencing both intense and moderate BTcP reported a higher level of satisfaction (p=0.042 and p=0.000, respectively) when taking ROO through intranasal administration (Table 5).

BTP Therapy	Meaningful time for pain relief in min, mean (95% CI)		Morphine equivalent dose in mg/day,	Mean dose (mcg)/day per BTP	% of pts satisfied
	onset	onset	mean	mean	
	≤ 10min	> 10min	(95% CI)	(95% CI)	
ROO Trans mucosal Nasal	10.0	12.7	102.7	163.9	705/835 (84.4%) (*)
(N=847)	(9.4, 10.5)	(11.6, 13.7)	(95.3, 109.9)	(155.6, 172.2)	
	p<0.0001				
ROO Trans mucosal Oral	13.1 (12.3, 13.9)	15.3 (14.2, 16.5)	127.4 (120.6, 134.2)	OTFC: 393.5_(345.5, 441.4) [N=130]	833/1111 (75.0%)
(N=1134)				FBT: 237.1 (219.9, 254.4) [N=434]	
				FBST: 230.5 (216.7, 244.4) [N=570]	
				total oral ROO: 251.7 (240.3, 263.1)	
	p=0.001				
Oral morphine (N=563)	18.0 (15.6, 20.5)	20.3 (17.8, 22.7)	88.7 (81.6, 95.8)	12.1 (11.4, 12.7) [N=563]	413/551 (75.0%)
(\$): 4 patients used both; ROO: Trans mucosal Nasal and ROO Trans mucosal Oral; 15 patients ROO Trans mucosal Nasal and Oral morphine; 20 patients ROO Trans mucosal Oral and Oral morphine.					

Table 5: Satisfaction reported by patients receiving morphine or fentanyl (oral and nasal trans mucosal) (\$). (*) p<0.0001.

Discussion

In this study 828 patients reported moderate BTcP with an intensity of 5 to 6. These subjects reported a lower average basal pain than the patients with intense BTcP, 2.48 ± 1.2 and 3.1 ± 1.0 respectively. We can assume that subjects experiencing moderate BTcP and controlled baseline pain could be more easily underestimated if not properly investigated. Furthermore, we observed that when patients are experiencing baseline pain with an intensity of 0 to 2 or 3 to 4, 65% and 85% of patients, respectively, are likely to have BTcP with an NRS >7. As confirmation of this, we also observed a linear correlation ($p=0.0001$) between the intensity of BTcP and the intensity of baseline pain. Furthermore, our data confirm [14] that, even if patients have well-controlled basal pain (NRS=0) they still complain of episodic pain (1.5 ± 1.1 BTcP/day with an intensity of 6.8 ± 1.4). These results suggest that an average difference of 3 or 4 points between the baseline pain and episodic pain may be a useful clinical marker in raising suspicion about the occurrence of BTcP. This variable, if confirmed by further studies, could constitute an alarm signal for the general practitioner, who will then see the usefulness of a diagnostic investigation into the pain.

Our analysis highlights that patients experience painful crises for between 20 and 76 hours per month, with a resulting negative impact on their quality of life. Therefore, patients with cancer should be periodically surveyed with a diagnostic algorithm that takes into account the basic episodic pain even outside the oncologic pathway of care. The IOPS-MS study was designed to investigate the features of oncological BTcP reported by the patients interviewed, using a standard diagnostic algorithm (Table 1) which was applied in various healthcare settings (hospital wards, hospices or home care). As with other instruments [15,16], the algorithm used in the IOPS-MS study has been confirmed as a practical diagnostic tool to detect BTcP [3,6,9,10,13] and it could be also used in the primary care setting between the various specialist

follow-ups. Considering also the temporal relationship between the onset of baseline pain and BTcP (1.9 ± 5.6 months, $p=0.001$), our data confirm that cancer patients reporting pain should undergo at least one investigation per month [13] with the active participation of general practitioners in order to reduce the time lag between the onset of pain and the start of analgesic therapy.

Finally, we observed that patients taking oral trans mucosal rapid onset opioid need a higher average dose of opioids than those using nasal rapid onset opioid. Also for periodic monitoring of opioid-based therapy the GP should play a priority role.

Conclusions

Although many recommendations have been published, there is no international consensus on the diagnosis and treatment of BTcP [15]. The management of the cancer patient, and in particular of the symptoms in palliative care, can cause discomfort in the general practitioners [16,17]. But the role of GP remains crucial to reducing the number of cancer-related hospitalizations for pain [18].

From a practical point of view, our analysis indicates that patients assessed thoroughly using a standard algorithm, report that they can clearly distinguish between baseline pain and episodic pain, that BTcP also occurs even when the baseline pain is steadily controlled, and that the level of satisfaction varies according to the treatment strategy adopted.

BTcP can arise at every stage of cancer disease and therefore an active participation of the GP for early detection of this form of pain can induce substantial benefits (Table 6). We believe that health authorities should invest more to create care pathways where general practitioners, oncologists and other professionals work together to promptly identify patients in need of supportive care. Finally, guidelines should be more calibrated for home-based clinical practice.

Clinical alert	Action	Advantages for patients	Advantages for Health Authorities
Cancer disease	Administer an algorithm to identify the BTP	Early identification of the patient at risk of pain Reduction of latency between pain and start of analgesic therapy Appropriate path of care Satisfaction improvement Early estimation of supportive and palliative care needs Raising awareness against pain	Reduction of unscheduled hospital access Resource optimization Early implementation of appropriate multidisciplinary care pathways Possibility of measuring results on a large scale (audit)
Lack of periodic medical control			
Basal pain NRS < 5 or Episodic pain NRS > 4 or Any pain report from the caregiver or Periodic check even if the basic pain is completely controlled or Patient with baseline analgesia without rescue dose for BTP			
Variation of therapeutic response Dissatisfaction with therapy Drug interactions Higher opioid dose needs Opioid intake for a long time			
Depression or other pain-related disorders or Sleep disorders			
Lack of adherence to therapies			
Change in the cure setting or cancer stage			
Any conditions that alters the absorption of drugs (i.e. mucositis, xerostomia, mycosis, etc.)			

Table 6: Suggestions for the General Practitioner: some (non-exhaustive) situations in which it is appropriate to apply a diagnostic algorithm for BTP.

Ethical Dimension

The 32 centres involved in the study were granted approval from the local ethics committee. All procedures were followed in accordance with the ethical rules for clinical trials and in accordance with the Declaration of Helsinki of 1964, amended in 2013. Informed consent was obtained from all patients included in the study.

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19. Abstract