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ORIGINAL ARTICLE

Breakthrough Pain in Patients With Abdominal Cancer Pain

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Objective: Characterization of breakthrough cancer pain (BTcP) in patients with abdominal cancer is lacking. The aim of this study was to assess the characteristics of BTcP in patients with abdominal cancer pain.

Patients and Methods: In an observational cohort study, from a consecutive sample of patients admitted to a pain relief and supportive care unit for a period of 13 months, patients with abdominal disease due to cancer, including primary cancer or metastases, were assessed for the presence of chronic abdominal pain; its mechanism, intensity of background pain, and pain flares, which were distinguishable from the baseline pain, were recorded. Patients presenting with pain flares were assessed regarding the causes and the possible factors associated with it. Patients were reassessed when background pain control was considered optimal.

Results: From a sample of 522 patients admitted to an acute pain relief and palliative care unit in a period of 13 months, 100 patients with abdominal disease were available. The mean age was 65.3 years (SD ± 11.4); of the 100 patients, 45 (45%) were males. The mean Karnofsky status was 47.7 (SD ± 11.1). At admission (T0), 67 patients (67%) had background pain with mean pain intensity of 4.9 (SD ± 1.6). Sixty-one patients of those with background pain (91%) had superimposed and well-distinguished pain flares. After analgesic optimization (T1), the mean background pain intensity was 1.7 (SD ± 1.2), and 55.2% of patients had BTcP episodes. The difference with T0 was significant ($P < 0.0005$).

Conclusions: This preliminary study provides new insights on the characteristics of BTcP in a subclass of patients with abdominal disease. It has been estimated that about 55% of patients with well-controlled background pain will develop BTcP episodes. This percentage was higher (about 90%) in patients who presented with uncontrolled background pain, underlying the need to better characterize patients with BTcP, only after a careful optimization of basal pain, as considered by the definition of BTcP.

Key Words: cancer pain, breakthrough pain, abdominal pain, epidemiology, opioids

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Abdominal pain is common in patients with cancer. In a survey on prevalence, causes, and mechanisms of pain in advanced cancer patients followed up at home, abdominal pain has been found to have an incidence of 45%. Two third of patients presented a visceral pain, although mixed pain syndromes were observed in more than half of these patients.[1] Pain may arise from different causes.[2] Primary tumors or metastases may involve luminal organs of the gastrointestinal or genitourinary tracts, the parenchymal organs, the peritoneum, or the retroperitoneal soft tissues. Obstruction of hollow viscus, including intestine, biliary tract, and ureters produces typical visceral nociceptive pain syndromes. When peritoneum, abdominal wall, pelvic organs, and retroperitoneal tissues are involved by tumor masses, mixed nociceptive and neuropathic mechanisms develop if both somatic structures and nerves are damaged. Other than the tumor involvement, oncologic treatments may cause devastating anatomic and functional changes. A number of chemotherapeutic regimens are commonly administered even in the advanced stage of disease. Neurotoxic chemotherapy, external beam radiation, radiation implants, pelvic exenteration, or other interventional procedures produce serious local problems, and pain is the most frequent symptom reported as a consequence of therapy.[1]

Breakthrough cancer pain (BTcP) has been defined as a transitory increase in pain intensity that occurs either spontaneously or in relation to a specific predictable or unpredictable trigger, despite relatively stable[3] and adequately controlled background pain.[4] BTcP is a common problem in patients with cancer and is associated with significant morbidity in this group of patients. BTcP has a negative impact on both quality of life (including activities of daily living, sleep, social relationships, and mood) and medical outcomes.[5] In different surveys, 50% to 90% of cancer patients with pain have been reported to experience intermittent flares of their pain, although using different definitions and methodology.[6] In a general population, patients with visceral neoplasms or visceral pain had a lower likelihood of BTcP.[7] However, patients with abdominal cancer may develop other mechanisms of pain. Information about epidemiology and pathophysiology of pain exacerbation in patients with abdominal cancer pain is poor and characterization of this type of BTcP is lacking.[4] The aim of this study was to assess the characteristics of BTcP in patients with abdominal cancer pain.

PATIENTS AND METHODS

From a consecutive sample of patients admitted to a pain relief and supportive care unit for a period of 7 months, patients with abdominal disease due to cancer, including primary cancer or metastases, were selected. Patients with cognitive impairment, unable to answer the questions posed for the pain assessment, were excluded. Patients who had extra-abdominal disease-producing pain, concomitant bone involvement, or patients severely ill with a survival of <2 weeks were also excluded. Patients receiving radiotherapy or who had changed their anticancer

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treatment in the previous month were excluded. Written informed consent from patients and ethical committee approval from the University of Palermo were obtained.

At admission (T0), information with regard to the presence of chronic abdominal pain, its mechanism, intensity of background pain, and pain flares, which were clearly distinguishable from the baseline pain, were obtained. This information was based on the previous 24 hours before admission. Pain mechanisms were diagnosed according to the clinical history, presentation, and imaging studies; pain intensity was assessed using a numerical scale from 0 to 10. Characteristics of patients were recorded, including age, sex, primary cancer, site of pain, intensity of background pain, and analgesics used for background pain. Patients presenting with pain flares were assessed regarding the causes and the possible factors associated with it. Data regarding characteristics, causes, and frequency of BTcP, as well as onset, duration, intensity, medications used for BTcP, and level of satisfaction with this treatment (poor, acceptable, good, and very good) were recorded. Patients were treated according to the department policy. According to the modality and characteristics of BTcP presentation, an analgesic treatment was planned, including the optimization of basal opioid therapy with the aim to achieve an adequate analgesia. After establishing an around-the-clock opioid medication able to produce an acceptable analgesia, with a pain intensity $\leq 4/10$, without relevant adverse effects, patients were encouraged to call when their pain got severe and when superimposed episodes of BTcP occurred. The choice of opioids for background pain and BTcP was on the basis of clinical judgment, according to different factors, including the patient's characteristics, clinical needs, patients' compliance, and preference. Written orders for BTcP, including drugs and doses to be administered when pain gets severe enough are routinely mentioned in the therapy chart. Department policy suggests that the dose to be given is proportional to the dose administered for background analgesia.[6] Patients were reassessed when background pain control was considered optimal (T1), mainly the day before discharge.

Statistics

The initial part of the study included 50 patients in a period of 7 months. This period was considered insufficient for recruiting a large number of subclass of patients with abdominal cancer disease. A sample of 100 patients was deemed to be appropriate for the purpose of this study, to have a sufficient epidemiological value, and the study was prolonged with this purpose. The sample size of 100 patients was able to detect a 30% difference in intragroup pain intensity score at a significance level of α type 1 error of 0.05, considering β type 2 error = 0.8. The within-group SD is assumed to be 3 with a percentage of missing data of 20%.

All continuous data are expressed as a mean ± SD of the mean. Statistical analysis of quantitative data, including descriptive statistics, was performed for all the items. Frequency analysis was performed using the Pearson χ^2 test and the McNemar test, as needed. The paired samples The Student *t* test and the paired Wilcoxon signed-rank test were used to compare parametric and nonparametric variables, respectively, at different intervals. Data were analyzed by the Epi Info software, version 3.2.2 (Centers for Disease Control and Prevention) and by SPSS Software 14.0 version (SPSS Inc., Chicago, IL). All *P* values were 2-sided, and *P* values <0.05 were considered statistically significant.

RESULTS

From a consecutive sample of 522 patients admitted to an acute pain relief and palliative care unit in a period of 13 months, 100 patients with abdominal disease were available for the study assessment. The epidemiological characteristics of the selected population are described in Table 1.

At admission (T0), 67 patients (67%) had background pain. The mechanisms were: 30 pure visceral pain, 11 visceral-neuropathic pain, and 26 visceral somatic pain. At admission, the mean intensity of background pain intensity was 4.9 (SD ± 1.6). Fifty-four (80.6%) patients were receiving analgesic drugs for background analgesia (Table 2).

The causes of BTcP identified at T0 are described in Table 3. Sixty-one patients of those with background pain (91%) had superimposed and well-distinguished pain flares with a mean intensity of 8.0 (SD ± 0.9). The background pain intensity in this group of patients was 5.1 (SD ± 1.5). The difference between BTcP intensity and background pain intensity reported in all patients was significant ($P = < 0.0005$). The mean number of episodes per day was 2.6 (SD ± 1.0). In 13 patients, the onset was <1 minute, in 28 patients the onset was 1 to 5 minutes, in 14 patients was 5 to 10 minutes, and in 6 patients the onset was >10 minutes. The duration of BTcP was <5 minutes in 1 patient, 5 to 10 minutes in 18 patients, 10 to 30 minutes in 22 patients, >30 minutes in 19 patients, and not evaluable in 1 patient. The identified causes of BTcP are listed in Table 2. Fifty-four patients were using analgesics for BTcP. Analgesics used for pain flares are reported in Table 4. The satisfaction with BTcP medication was good in 3 patients, acceptable in 13 patients, and poor in 38 patients.

The causes of BTcP after analgesic optimization (T1) are described in Table 3. The mean background pain intensity was 1.7 (SD ± 1.2). The difference in comparison with T0 was significant ($P < 0.0005$). Thirty-seven of 67 patients (55.2%) had BTcP episodes. The difference with T0 was significant ($P < 0.0005$). In this group of patients, the mean background pain intensity was 2.2 (SD ± 0.9). The mean pain intensity of BTcP was 7.1 (SD ± 1.0). Fifteen patients had 1 episode per day, 17 patients had 2 episodes per day, 4 patients had 3 episodes per day, and 1 patient had 4 episodes per day. The onset was <1 minute in 7 patients, 1 to 5 minutes in 24 patients, 5 to 10 minutes in 4 patients, and >10 minutes in 2 patients. The duration of BTcP was <5 minutes in 6 patients, 5 to 10 minutes in 20 patients, 10 to 30 minutes in 8 patients, and >30 minutes in 3 patients. Analgesics used for pain flares are reported in Table 4. The level of satisfaction with BTcP medication was good (23 patients) or very good (13 patients) and

TABLE 1. Epidemiological Characteristics of Patients

Patients surveyed	522
Patients selected	100
Age (mean) (y)	65.3 (SD ± 11.4)
Sex (male/females)	45/55
Karnofsky status (mean)	47.7 (SD ± 11.1)
Primary tumor (n [%])	
Pancreas	32 (32)
Colon	19 (19)
Liver	11 (11)
Genitourinary	11 (11)
Others	27 (27)

TABLE 2. Analgesics Used for Background Analgesia

	T0		T1	
Analgesic Drugs	**n**	**Mean Doses (± SD) (mg)**	**n**	**Mean Doses (± SD) (mg)**
Transdermal fentanyl	13	1.6 (± 1.4)	25	1.1 (± 1.2)
CO-PA	10	111 (± 40.0)		
Tramadol	4	81.2 (± 33.1)		
Oxycodone-naloxone	9	33.9 (± 19.3)	4	43.7 (± 26.9)
Oxycodone	4	40 (± 23.1)	3	40 (± 20.0)
Oxycodone-paracetamol	1	60	1	20
Hydromorphone	2	32 (± 22.6)	8	52.0 (± 83.6)
Paracetamol	1	3000		
Oral morphine			2	70.0 (± 28.2)
Transdermal buprenorphine			9	0.7 (± 0.3)
Transdermal fentanyl-morphine			2	
Tapentadol	2	350 (± 70.7)	6	241.7 (± 168.6)
Hydromorphone-morphine			1	24/24
CO-PA + OX-NA	1	180/20		
CO-PA + oxycodone	1	90/20		
Parenteral morphine	2	15 (± 7.1)		
OX-NA + paracetamol	1			
Tramadol-NSAIDs	1			
Tramadol-paracetamol	1			
NSAIDs	1			

CO-PA indicates codeine-paracetamol; NSAIDs, nonsteroidal anti-inflammatory drugs; OX-NA, oxycodone-naloxone.

acceptable in one patient. The difference in comparison with T0 was significant ($P < 0.0005$).

DISCUSSION

Although incident pain associated with bone metastases has been commonly recognized as one of the most relevant type of BTcP and its incident factors, like movement or burden, are well established,[8,9] abdominal BTcP has never been categorized. In this study, the characteristics of patients with abdominal cancer disease were assessed. Moreover, we tried to distinguish the epidemiology of this event as a possible condition of undertreatment, such as it was expected at admission, and after optimizing the background analgesia. The findings were quite interesting. Although some temporal characteristics, such as onset and duration, resemble data reported for BTcP observed in general population,[10–14] causes and frequency of BTcP were quite different, at least at admission, when patients were likely to be undertreated.

TABLE 3. Identified Causes of BTcP at T0 and T1 (See Text)

	T0	T1
Idiopathic—possibly UT	27	
Possibly UT	7	
Idiopathic—possibly UT—eating	5	
Idiopathic—possibly UT—supine position	1	
Idiopathic—possibly UT—deambulation	1	
Idiopathic—possibly UT—visceromegaly	1	
Idiopathic	9	36
Idiopathic + deambulation	2	1
Idiopathic + orthostatism	1	
Idiopathic + constipation	1	
Idiopathic + eating	1	
Possibly UT + deambulation	1	
Possibly UT + sitting position	1	
Possibly UT + defecation—eating	1	
Possibly UT + eating	2	

BTcP indicates breakthrough cancer pain; UT, undertreatment.

Many epidemiological studies of BTcP are inferred by the inclusion of patients with uncontrolled background pain or receiving inadequate basal analgesia.[7,10–14] However, according to the prevalent definitions,[3–5] end of dose failure or undertreatment should be excluded, per definition, as a cause of BTcP.[6,15] The need to reassess patients after achieving a good background analgesia is of paramount importance in such epidemiological studies, as reported in a previous survey where a decrease in BTcP frequency was observed after adequate analgesia was obtained by a careful dose titration of opioids.[16] This is confirmed by the finding of this study where the frequency of BTcP significantly decreased after optimization of background analgesia, also changing the pattern of factors identified as triggers for BTcP by patients, leaving the idiopathic nature of BTcP as the leading cause.

Another controversial point is the duration of episodes of BTcP, often reported in the literature. Although it is possible to measure this parameter in patients with untreated BTcP, after adequate training, patients take their medication for BTcP, and duration of BTcP becomes dependent on the onset of the analgesic medication, rather than the natural duration of the BTcP. For this reason, we did not report the duration after optimization of basal therapy when it is expected that patients receive adequate medications as needed.

The amount of opioids for background pain and the appropriateness of drugs administered for BTcP significantly changed in comparison with drugs received before admission, which often included nonopioid drugs or opioids for moderate pain. After a comprehensive approach in an acute ward, patients were receiving higher doses of opioids for background analgesia, as well as more rapid onset opioids for BTcP, which should be considered the goal standard because of their capacity to overlap an episode of BTcP for both onset and duration, irrespective of

TABLE 4. Analgesic Drugs Used for BTcP at T0 and T1

	T0		T1	
Analgesic Drugs	**n**	**Range of Doses**	**n**	**Range of Doses**
Anti-inflammatory drugs-paracetamol	22		1	
Codeine-paracetamol	5	30/500 mg		
OTFC	8	200-800 μg	3	200-600 μg
FBT	4	100-800 μg	9	100-2000 μg
FNS	2	100-400 μg	2	100 μg
Oxycodone-paracetamol	4	5 mg		
SLF	1	200 μg	8	100-400 μg
PFNS	2	200 μg	4	100-400 μg
Antispasmodics	2			
Oral morphine			2	15-50 mg
Parenteral morphine	1	2 mg	4	2-15 mg
Oral morphine	2	10-14 mg	3	6-10 mg
Oxycodone-naloxone	1	20 mg		
Tramadol			1	50

BTcP indicates breakthrough cancer pain; FBT, fentanyl buccal tablet; FNS, fentanyl nasal spray; OTFC, oral transmucosal fentanyl citrate; PFNS, pectin fentanyl nasal spray; SLF, sublingual fentanyl.

their cost.[15,17] In fact, the level of satisfaction with regard to pain medication for BTcP significantly improved.

It has been anecdotally reported that transient visceral pains initiated by volitional activity may benefit from preemptive therapies or specific therapies targeted at the underlying mechanisms.[18] Oral opioids have been proposed to be administered about 30 minutes before the pain is triggered by a predictable pain trigger,[19] for example, eating in patients with pancreatic cancer pain.[20] According to the finding of this study, this clinical feature is often associated with an analgesic undertreatment and tends to disappear after optimization of background analgesia.[10] In a concomitant study performed in a general population, including all cancers and not only abdominal pain distribution, the same approach was effective in reducing the number, duration, and intensity of BTcP but was unable to change the prevalence of BTcP.[21]

Limitations of the study are linked to the lack of a controlled design and the number of patients enrolled in the study. These problems are inherent to many studies of cancer patients. A placebo effect cannot be excluded, without any comparison. Hospital stay and the specific setting may in part influence the outcome. This issue is strongly debated in palliative care, where there is a need for controlled studies providing the best evidence. In contrast, a control group is difficult to conceive in the context of patients' suffering. In this case, patients with uncontrolled pain would have been treated with a placebo, raising ethical and practical concerns. For instance, such information should be considered as preliminary and should be confirmed in future studies.

The number of patients recruited may be another limitation. After conducting the first part of the study, we were aware of the need to increase the sample size to provide more consistent information. Of interest, most studies of BTcP, which include a treatment, were approximately performed in a similar amount of patients. Findings of this study should be confirmed in larger multicenter studies and in different settings.

In conclusion, this preliminary study provides new insights on the characteristics of BTcP in a subclass of patients with abdominal disease. It has been estimated that about 55% of patients with well-controlled background pain will develop BTcP episodes, which positively respond to an individualized treatment. This percentage was higher (about 90%) in patients who presented with uncontrolled background pain, underlying the need to better characterize patients with BTcP, only after a careful optimization of basal pain, as considered by the definition of BTcP.

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