Brief Report

Breakthrough Cancer Pain in Patients With Abdominal Visceral Cancer Pain

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Abstract

Objective. The objective of this study was to assess the characteristics of breakthrough cancer pain (BTcP) in patients with abdominal cancer pain, and the eventual factors associated with its presentation.

Methods. Patients with abdominal visceral cancer presenting BTcP were included in the analysis. Pain intensity, current analgesic therapy, number of BTcP episodes, intensity of BTcP, its predictability and triggers, onset (≤10 minutes or >10 minutes), duration, interference with daily activities, medications and doses currently used for BTcP, and time to meaningful pain relief were collected. Adverse effects imputable to a BTcP medication were recorded.

Results. Four hundred fourteen patients were included in the study. The mean background pain was 2.7 (SD 1.19) and most patients (97.6%) were receiving opioids. The mean number of BTcP episodes/day was 2.2 (SD 1.51). The mean intensity of BTcP was 7.3 (SD 1.32). BTcP onset was ≤10 minutes and >10 minutes in 271 (65.5%) and 143 patients (35.5%), respectively, and the mean duration was 52.6 minutes (SD 38.1). Interference of BTcP with daily activity was relevant for 340 patients (82%). In 122 patients (29.5%), BTcP was predictable and ingestion of food ($n = 63$, 51.6%) was the most frequent trigger. In comparison with unpredictable BTcP, postprandial BTcP had a lower intensity ($P = 0.039$), had a faster onset ($P = 0.042$), and was associated with the use of oxycodone/naloxone ($P = 0.003$), and less use of nonsteroidal anti-inflammatory drugs ($P = 0.006$).

Conclusion. Patients with abdominal visceral BTcP represent a subgroup with specific features of BTcP, particularly those with predictable BTcP. Ingestion of food was the prominent trigger for BTcP, having a faster onset and a lower intensity. This group of patients more frequently used oxycodone/naloxone or no anti-inflammatory drugs. These findings suggest consequential therapeutic decisions. J Pain Symptom Manage 2019;57:966–970.

Key Words

Breakthrough cancer pain, abdominal pain, visceral pain, opioids

Introduction

Abdominal pain is frequently reported in advanced cancer patients. In a study performed in home care patients, abdominal pain was found in 45%, and two-thirds of patients presented a pure or mixed visceral pain mechanism.[1] Visceral cancer pain includes the involvement of luminal organs of the gastrointestinal or genitourinary tracts, parenchymal organs, peritoneum, or retroperitoneal soft tissues. Obstruction of hollow viscus such as intestine, biliary tract, and ureters also causes a typical visceral pain. The involvement by tumor masses of peritoneum, abdominal wall, pelvic structures, and retroperitoneal tissues

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determines mixed nociceptive and neuropathic mechanisms as both somatic structures and nerves are damaged.[2]

Breakthrough cancer pain (BTcP) is recognized as a transitory increase in pain intensity that occurs either spontaneously or in relation to a specific predictable or unpredictable trigger, despite reporting a relatively stable and adequately controlled background pain. This phenomenon is frequent in advanced cancer patients and has a negative impact on both quality of life and medical outcomes.[3,4]

Recent data have provided insights on the characteristics of BTcP in a subclass of patients with abdominal pain. Particularly, about 55% of patients with abdominal cancer pain after optimization of background analgesia developed BTcP episodes, while the percentage was higher (about 90%) in patients who had previously an uncontrolled background pain.[5] Of interest, in the general population, optimization of background pain is able to reduce the number of BTcP episodes and possibly the intensity but is unable to decrease the prevalence of BTcP.[6] These data underline the need to better characterize patients with BTcP, only after a careful optimization of background pain. The subclass of patients with abdominal cancer pain represents an interesting sample for such suggestive implications. The aim of this study was to assess the characteristics of BTcP in patients with abdominal cancer pain with a visceral mechanism, and eventual factors associated with its presentation.

Methods

This was a secondary analysis of a multicenter study that involved 4016 patients recruited in 32 centers of oncology, pain therapy, palliative care, and radiotherapy.[7] The local ethical committees approved the protocol, and written informed consent was obtained from each patient.

Patients were included if they were ≥18 years, had a diagnosis of cancer, had a stable and controlled background pain (intensity ≤4 on a 0−10 numerical scale), and had BTcP episodes of intensity clearly distinguished from the level of background pain (moderate-severe intensity), according to a predefinite algorithm.[8,9] Patients were excluded if they had no cancer diagnosis, an unstable condition of background pain (>4/10); had extra-abdominal disease-producing pain, concomitant bone involvement; did not have significant peaks in pain intensity (<5/10); or were incapable to be assessed. Patients who met the inclusion criteria were consecutively surveyed. Patients with abdominal cancer pain and a visceral pain mechanism were selected from this sample.

General data were recorded and included age, gender, setting and place of the visit, primary diagnosis, extent of the disease (locoregional or metastatic), anticancer treatments, and Karnofsky status. Average pain intensity (0−10) in the last week, opioids used for background pain, expressed as oral morphine equivalents were recorded,[10] as well other analgesic drugs. The mean daily number of BTcP episodes in the last week, the mean intensity of BTcP (on a numerical scale 0−10), BTcP predictability and factors able to trigger the episode, time to achieve the maximum pain intensity (≤10 minutes or >10 minutes), mean duration of untreated episodes, interference with daily activities (on a scale from 0 to 3, none and very much, respectively), medications and doses currently used for BTcP, and time to meaningful pain relief after taking medication were recorded. Finally, adverse effects imputable to BTcP medication were recorded.

Statistical Analysis

Descriptive statistics have been provided and frequency distributions have been explored. The analysis focused on detecting statistical association among variables performing χ^2 tests where necessary. If needed, a component analysis of the contingency tables has been performed. Pairwise comparisons of continuous variables have been carried out using independent-samples t-tests, Tukey's adjusted for multiple comparisons setting at the onset a 5% first-type error. The analysis has been carried out using the statistical software STATA (version 14 StataCorp, College Station, TX).

Results

Of 4016 patients screened in the original study, 1239 patients had background abdominal pain; 50 patients (4.0%) had a neuropathic pain mechanism, and 719 (58.1%) a somatic or mixed pain syndrome. Four hundred seventy patients (37.9%) presented a visceral background pain as main prevalent mechanism. Of these, five (1.1%) and 51 patients (10.8%) had a BTcP with neuropathic and mixed mechanism, respectively. Thus, 414 patients (88.1%) had a visceral BTcP. The characteristics of these patients with a pure abdominal visceral BTcP are presented in Table 1. Data collection was performed by the visiting physician experienced in cancer pain and palliative care.

Background Pain

The mean background pain was 2.7 (SD 1.19). Four hundred four patients (97.6%) were receiving opioids for background pain (see Table 2). The mean oral morphine equivalent dose was 90.82 mg (SD 84.1,

Table 1
Characteristics of Patients With Abdominal Visceral BTcP

Age (yrs), mean (SD)	65 (13), range 28–97 yrs
Gender (M/F)	205 (49.5%)/209 (50.5%)
Karnofsky mean (SD)	57 (SD), range 10–100
Primary tumor	
Gastrointestinal	142 (34.3%)
Pancreas	100 (24.1%)
Liver	36 (8.7%)
Gynecologic	31 (7.5%)
Urological	19 (4.6%)
Breast	18 (4.3%)
Others	24 (5.8%)
Disease	
Locoregional	52 (12.6%)
Metastatic	362 (87.4%)
Anticancer treatment	
Disease-oriented	268 (64.7%)
Palliative care	107 (25.8%)
Place of visit	
Hospital inpatient	170 (41.1%)
Home care	140 (33.8%)
Outpatients	69 (16.2%)
Hospice	18 (4.3%)
Day-hospital	17 (4.1%)
Setting	
Oncology	193 (46.6%)
Palliative care	159 (39.4%)
Pain therapy	62 (15.0%)
Radiotherapy	0
Mean background pain intensity last week	2.7 (SD 1.2), range 0–4
Mean opioid doses (expressed as oral morphine equivalents)	90.82 mg/day (SD 84.1), range 1–645

BTcP = breakthrough cancer pain.

range 1–645 mg). One hundred forty-four patients (34.8%) were also receiving nonopioid analgesics (27 and 117 patients receiving nonsteroidal anti-inflammatory drugs and paracetamol, respectively); 250 patients (60.4%) were receiving adjuvant drugs: benzodiazepines (n = 66, 15.9%), anticonvulsants (n = 40, 9.7%), antiemetics (n = 79, 19.1%), laxatives (n = 85, 20.5%), corticosteroids (n = 157, 37.9%), and antidepressants (n = 27, 6.5%).

Breakthrough Cancer Pain

The mean number of BTcP episodes/day was 2.2 (SD 1.51, range 1–10). Twenty-five (6.0%), 89 (21.5%), and 300 patients (72.5%) had more than five episodes/day, three to four episodes/day, and one to two episodes/day, respectively. The mean intensity of BTcP was 7.3 (SD 1.32, range 5–10).

Table 2
Opioids Used for Background Analgesia

Weak opioids (codeine, tramadol)	41 (10.1%)
Transdermal fentanyl	153 (37.9%)
Oxycodone/naloxone	102 (25.2%)
Oxycodone	41 (10.1%)
Parenteral morphine	25 (6.2%)
Morphine	13 (3.2%)
Hydromorphone	7 (1.7%)
Tapentadol	7 (1.7%)
Methadone	2 (0.5%)

Table 3
Predictability of BTcP and Main Trigger Factors

Unpredictable BTcP	292 (70.5%)
Predictable BTcP	122 (29.5%)
Ingestion of food	63 (51.6%)
Movement	53 (43.4%)
Defecation	10 (8.2%)
Procedures	7 (5.7%)

BTcP = breakthrough cancer pain.

Patients with unpredictable and predictable BTcP, as well the triggers for predictable BTcP, are presented in Table 3.

BTcP onset was ≤10 minutes and >10 minutes in 271 (65.5%) and 143 patients (35.5%), respectively. The mean duration of BTcP was 52.6 minutes (SD 38.1, range 2–180).

Interference with daily activity was mild, much, and very much in 68 (16.4%), 233 (56.3%), and 107 patients (25.8%), respectively. In one patient only, BTcP did not have any interference with daily activity.

Three hundred eighty-one patients (92%) were receiving a BTcP medication, whereas 33 patients (8.0%) were receiving no medication for BTcP; 325 patients (85.3%) were prescribed strong opioids (see Table 4). No correlation was found between the choice of BTcP medication and BTcP duration ($P > 0.09$), gender ($P = 0.385$), age ($P > 0.097$), and use of disease-oriented therapy ($P = 0.836$).

In patients receiving BTcP medications, the grade of satisfaction was as follows: not satisfied, neutral, satisfied, and much satisfied in 13 (4.0%), 53 (16.5%), 207 (64.3%), and 49 (15.2%) of cases, respectively. The mean meaningful time for pain relief was 14.9 minutes (SD 12.83, range 2–120). Only two patients (0.85%) reported adverse effects (nausea and confusion of mild intensity). No severe adverse effects were reported.

BTcP After Ingestion of Food

In 63 patients (51.6%), predictable BTcP was triggered by ingestion of food. This subgroup of patients was then reanalyzed because the data were largely

Table 4
Opioids Given for BTcP

Fentanyl pectin nasal spray	122 (37.5%)
Oral morphine	55 (16.9%)
Sublingual fentanyl	54 (16.6%)
Parenteral morphine	46 (14.1%)
Fentanyl buccal tablet	32 (9.8%)
Oral transmucosal fentanyl citrate	10 (3.1%)
Intranasal fentanyl	6 (1.8%)

BTcP = breakthrough cancer pain.

different from the entire population of the original study.[7]

In comparison with the other causes of predictable BTcP, postprandial BTcP was not found to be related to age ($P = 0.232$), gender ($P = 0.769$), metastatic disease ($P = 0.209$), disease-oriented therapy ($P = 0.174$), and background pain intensity ($P = 0.137$). Postprandial BTcP was associated with pancreatic cancer (36.1%, χ^2 tests, $P = 0.039$). No relationship with the use of opioids used for background analgesia was found, unless for oxycodone/naloxone (75% vs. 25%, $P = 0.003$). Patients with postprandial BTcP were less frequently receiving nonsteroidal anti-inflammatory drugs (16.7% vs. 83.3%, $P = 0.006$). No differences in doses of opioids were found ($P = 0.408$). Of interest, in comparison with the group of patients having other predictable causes of BTcP, patients reporting postprandial episodes had a lower intensity (6.9, SD 1.24 vs 7.4, SD 1.33) ($P = 0.039$), a faster onset (60.5% vs 39.5%, $P = 0.042$), and a shorter duration (45.8 minutes [SD 36.70] vs. 70.4 minutes [SD 49.95]; $P = 0.021$) of BTcP.

In comparison with all patients having unpredictable episodes ($n = 292$), postprandial BTcP was associated with pancreatic cancer (36.1% vs. 63.9%, $P = 0.038$). Postprandial BTcP was less frequent in metastatic disease (15.7% vs. 84.3%) ($P = 0.009$). No relationship with age ($P = 0.191$), gender ($P = 0.273$), background pain intensity ($P = 0.363$), disease-oriented therapy ($P = 0.484$), use of anti-inflammatory drugs ($P = 0.508$), and type of opioids, unless for oxycodone/naloxone (71.3% vs. 28.7%) ($P = 0.001$), was found. Intensity of postprandial BTcP was lower (6.9 [SD 1.24] vs. 7.5 [SD 1.31]; $P = 0.003$), and its onset was faster (77.8% vs. 64.4%; $P = 0.041$). Finally, no differences were found in duration of BTcP (45.8 minutes, SD 36.7, vs. 49.6 minutes, SD 34.7, $P = 0.315$).

Discussion

The findings of this secondary analysis provided new and interesting findings, also suggesting therapeutic perspectives. The most relevant finding is that in patients who had predictable BTcP, the most frequent trigger was the ingestion of food, that is, a postprandial BTcP, a phenomenon that has not assessed in literature. Postprandial BTcP had a faster onset and a lower intensity, either in comparison with other causes of predictable BTcP and unpredictable BTcP.

Indeed, this aspect has obvious implications on the nutritional status and quality of life because patients may avoid to eat owing to the fear of evoking BTcP. This BTcP subtype could be eventually prevented by an appetizer, that is, a preemptive BTcP medication, for example, a fentanyl preparation just few minutes before eating or oral morphine given half an hour before food ingestion.[11] In a recent study, a prophylactic rescue dose of oral opioids was effective and did not add risks of toxicity in patients with postprandial BTcP.[12] Of interest, although in general population optimization of background analgesia has been reported to reduce the number and the intensity of BTcP episodes, but not to eliminate the phenomenon,[5] in patients with abdominal visceral pain, the optimization of basal opioid regimen produced a disappearance of BTcP in about half of patients.[6] Postprandial pain has been reported for a long time as a common feature in patients with pancreatic pain.[13] This study confirms that patients with abdominal visceral cancer may present this subtype of BTcP, and a further refinement of background analgesia may prevent the occurrence of BTcP episodes. This suggests to reevaluate what is the level of good pain control even in patients having a pain intensity which is commonly considered optimal when it is $\leq 4/10$.

There is another interesting information regarding the use of medications for background analgesia. One could argue that oxycodone/naloxone may provide limited background analgesia or a lower threshold for BTcP in patients with abdominal visceral cancer pain, thus determining more episodes of predictable postprandial BTcP. Similarly, patients who were not receiving nonsteroidal anti-inflammatory drugs seemed to be more susceptible to postprandial BTcP. These hypotheses should be confirmed in studies with an appropriate design in a larger number of patients with this subtype of BTcP.

This study presents some limitations. This was a secondary analysis of a large sample of patients participating in a study assessing the factors associated with BTcP presentation. Moreover, the distinction of this subtype of BTcP was performed on clinical examination, available documentation, and anamnesis. Second, at the moment, no instrument has been completely validated often remaining on an empirical basis. Indeed, any instrument is circularly validated by a clinical examination. Participating centers have a long experience with cancer patients and their assessment should be considered reliable. On the other hand, the strict criteria for diagnosing BTcP were based on a shared algorithm in a prestudy investigator meeting[7,8] and on a continuous monitoring of data via Web. This should guarantee about the quality of data gathered from the primary study. A final concern may regard the recall bias at the time of visit. This is inevitable for such studies.

Conclusion

This study showed that in patients with abdominal visceral BTcP, ingestion of food is the prominent trigger for predictable BTcP. This subtype of BTcP has a faster onset and a lower intensity and was more likely to occur in patients receiving oxycodone/naloxone or no anti-inflammatory drugs. These data suggest possible therapeutic decisions, including a preemptive BTcP medication and/or the optimization of background analgesia.[11,12,14] Further studies should be performed to clarify these aspects.

Disclosures and Acknowledgments

The original study was sponsored by Molteni, Italy. Data were independently analyzed by the IOPS MS Scientific Committee. Data for secondary analysis were independently managed by authors.

The authors declare no conflict of interest.

The data sets generated during and/or analyzed during the present study are available from the corresponding author on request.

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