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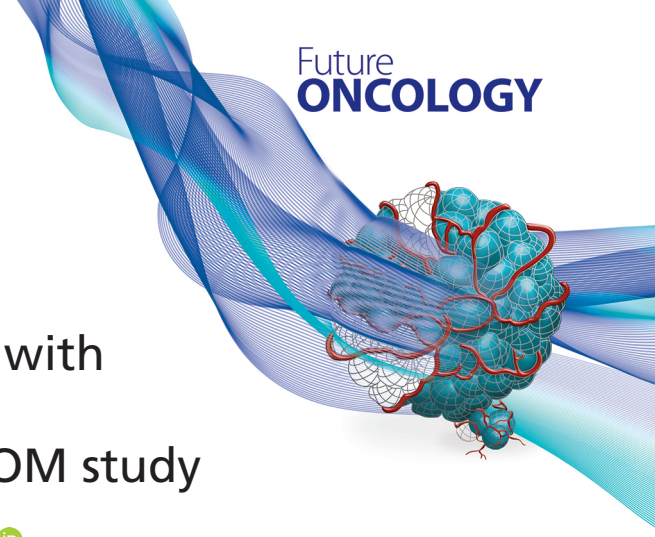

Increased quality of life in patients with breakthrough cancer pain after individualized therapy: the CAVIDIOM study

Paula González Villarroel[1], Josep Gumà Padró[2], Gloria Marquina[3], Noelia Martínez Jáñez[4], Emilio Esteban González[5], Antonio Antón[6], Miguel Berzosa Sánchez[7], Alberto Rodrigo Cáceres[8], Rafael López-López[9], Roberto Escala Cornejo[10], Pablo Borrega García[11], Raquel Marse Fabregat[12], Beatriz Castelo Fernández[13], Cristina López Bermudo[14] & Carlos Camps*[,15]

[1]Department of Medical Oncology, Hospital Álvaro Cunqueiro, Vigo, Spain
[2]Department of Medical Oncology, Hospital Universitari de Sant Joan de Reus, URV, IISPV, Tarragona, Spain
[3]Department of Medical Oncology, Hospital Clinico Universitario San Carlos. Department of Medicine, School of Medicine, Universidad Complutense de Madrid (UCM), IdISSC, Madrid, Spain
[4]Department of Medical Oncology, Hospital Universitario Ramón y Cajal, Madrid, Spain
[5]Department of Medical Oncology, Hospital Universitario Central de Asturias, Asturias, Spain
[6]Department of Medical Oncology, Hospital Universitario Miguel Servet, IIS Aragón, Zaragoza, Spain
[7]Department of Medical Oncology, Hospital Virgen de La Cinta de Tortosa, Tarragona, Spain
[8]Department of Medical Oncology, Hospital Universitari Arnau de Vilanova de Lleida, Lleida, Spain
[9]Department of Medical Oncology & Health Research Institute, Hospital Clínico Universitario de Santiago de Compostela, CIBERONC, Santiago de Compostela, A Coruña, Spain
[10]Department of Medical Oncology, Hospital Universitario de Salamanca, Salamanca, Spain
[11]Department of Medical Oncology, Hospital San Pedro de Alcántara, Cáceres, Spain
[12]Department of Medical Oncology, Hospital Universitario Son Espases, Palma, Spain
[13]Department of Medical Oncology, Hospital La Paz, Madrid, Spain
[14]Department of Medical, Angelini Pharma España SLU
[15]Department of Medical Oncology, Hospital General Universitario de Valencia, Department of Medicine, Universidad de Valencia; CIBERONC, Spain
*Author for correspondence: camps_car@gva.es

Aim: To evaluate the quality of life (QoL) in patients with breakthrough cancer pain (BTcP) in Spanish medical oncology departments. **Patients & methods:** In a prospective, observational, multicenter study, we assessed QoL using the EQ-5D-5L instrument at baseline and after 15 and 30 days of individualized BTcP therapy, as well as BTcP characteristics and treatment. **Results:** Patients (n = 118) were mainly women, over 64 years old and with advanced cancer. QoL improved at 15 (p = 0.013) and 30 days (p = 0.011) versus baseline. Individualized BTcP therapy consisted mostly of rapid-onset opioids (transmucosal fentanyl at doses of 67–800 μg) according to the physician evaluation. BTcP improved, including statistically significant reductions in intensity, duration, number of episodes in the last 24 h and time to onset of BTcP relief. **Conclusion:** QoL increased after individualized pain therapy in patients with advanced cancer and BTcP in medical oncology departments.

Plain language summary: Cancer patients can experience flares of pain, called breakthrough pain (BTcP), despite treatment with painkillers. Although BTcP can be excruciating, its intensity and other characteristics depend on several factors, including its treatment. However, even if treated, BTcP can impair quality of life for cancer patients. We assessed quality of life in 118 patients with advanced cancer and BTcP treated in 13 medical oncology departments across Spain. We treated BTcP with individualized therapy, taking into account both pain-related and patient-related factors. We also measured quality of life using a specific, widely-used questionnaire at the study visits: at onset of individualized pain therapy and after 3, 15 and 30 days' treatment. At each visit, flare-up pain therapy was adjusted or maintained as necessary. Throughout the study, quality of life and sleep quality improved for all participants. Furthermore, there was a greater reduction in intensity, duration and frequency of BTcP. The most common treatments for flare-ups were low doses of rapid-onset opioids (fentanyl given by

sublingual, buccal or nasal administration), which were much better tolerated than high-dose opioids. Overall, the study showed that quality of life in patients with advanced cancer and BTcP increased after individualized pain therapy, mainly with low doses of rapid-onset opioids.

Tweetable abstract: CAVIDIOM study: increased quality of life after individualized therapy with low-dose rapid-onset opioids in patients with advanced cancer and breakthrough cancer pain treated in medical oncology departments in Spain.

Clinical Trial Registration: NCT03435120 (ClinicalTrials.gov)

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Breakthrough cancer pain (BTcP) is common, but there is not a universally accepted definition [1]. It is considered as a transitory exacerbation of pain in cancer patients, but its intensity and the characteristics and treatment of background pain are controversial [2]. Different definitions have been proposed, such as that of the European Society of Medical Oncology (ESMO) [3]. However, an expert panel established a consensus on BTcP and defined it as 'an acute exacerbation of high-intensity pain of short duration and rapid onset, suffered by a patient whose baseline pain is stabilized and controlled by opioids' [2]. BTcP prevalence ranges from 19 to 95%; this wide interval is due to the different BTcP definitions and clinical settings in the analyzed studies [2]. Among 3765 patients with cancer in Spain, 1117 (30%) had cancer-related pain and 539 (48%) of them had BTcP. However, BTcP prevalence varied depending on the hospital department or unit, with the highest rate in palliative care units (61%) [4]. According to a Delphi survey of Spanish medical oncologists, BTcP prevalence ranged from 20 to 80% [2].

BTcP characteristics are variable and are influenced by several factors, including disease course, duration of background pain and BTcP treatment [5]. Its diagnosis is usually based on the algorithm of Davies *et al.* [6]. BTcP therapy should be individualized, taking into account both pain-related and patient-related factors, as recommended by guidelines such as those of the European Society of Medical Oncology [3] and the Spanish Society of Medical Oncology [7]. However, even when treated, BTcP is associated with an impairment in the quality of life (QoL) of patients with cancer [8–12]. Although health professionals caring for patients with cancer are aware of the impact of pain on QoL [13], underdiagnosis and undertreatment of cancer pain still occur [14].

Health-related QoL includes those aspects of QoL related to physical or mental health [15]. There is not a widely accepted definition, but health-related QoL is a complex and multidimensional concept that, unlike QoL, can comprise subjective and objective points of view [16]. It is of increasing importance, as well as the patient-reported outcomes instruments [17]. New evidence has been recently published regarding QoL in patients with BTcP in radiation oncology [10] and palliative care units [11,12]. In this context, we conducted the CAVIDIOM study, named after an acronym for the Spanish words meaning 'quality of life in patients with breakthrough cancer pain treated in medical oncology services'. The study's main objective was to assess QoL in patients with BTcP in the medical oncology setting. As secondary objectives, we evaluated the clinical and demographic characteristics of patients, including background pain, BTcP characteristics, social functioning, cancer progression, comorbidities, sleep quality and anxiety and depression status, as well as potential relationships between these factors and QoL. We also assessed caregiver burden, quality of care received by patients with BTcP in medical oncology departments, patients' and physicians' perception of global improvement, and safety of BTcP treatments.

Patients & methods

Study design & population

We performed an observational, prospective, multicenter study of cancer patients with BTcP recruited at 14 medical oncology departments in Spain. Inclusion criteria were: age ≥18 years; histologically confirmed cancer (at any site and stage); clinically estimated life expectancy >3 months; background cancer pain controlled with opioids; and diagnosis of BTcP using the Davies algorithm [6]. Exclusion criteria consisted of: no opioid treatment for background pain; intolerance to opioids; severe psychiatric disorder or any disease or condition that prevented the collection of study data; and addiction to opioids, alcohol or other drugs.

Data collection & analyzed variables

Data were recorded in a specifically designed electronic case report form. Investigators filled out the form based on data obtained during the study visits, with clinical history consultation when necessary, and by means of the corresponding questionnaires. Visit planning included visits at baseline (V0) and after 3 (V3), 15 (V15) and 30 (V30) days. All visits were in person except that on day 3, which could be done by phone. Study variables were measured at V0, V3, V15 and/or V30. The efficacy population was defined as patients who completed V15, V30 or both.

At V0, after diagnosing BTcP based on the Davies algorithm [6], we collected demographic data (sex, age, weight and height), functional status according to the Eastern Cooperative Oncology Group performance status (ECOG PS) scale [18], characteristics of the cancer process (location, stage, metastases and current therapy) and comorbidities (Charlson Comorbidity Index [CCI]) [19].

We assessed QoL using the Spanish version of the five-level EQ-5D (EQ-5D-5L) instrument [20,21] at V0, V15 and V30. The EQ-5D-5L is a patient-reported instrument that was developed by the EuroQol group to assess health-related QoL [22]. It consists of the EQ-5D descriptive system and the EQ visual analog scale (EQ VAS). In the descriptive system, patients rated five domains (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) at one of five levels (no problems, slight problems, moderate problems, severe problems and extreme problems). Patients also rated their health status in the EQ VAS, from 0 (worst health) to 100 (best health) [20,21]. In addition, the EQ-5D index was calculated and its value could range between 1 (best health status) and 0 (death) [23].

Furthermore, we also recorded the characteristics of background pain (intensity and management) and BTcP (intensity and duration of episodes, number of episodes per day during the last week and since the previous visit, triggering factors, etiology, and pain location and management). We evaluated the intensity of background pain and BTcP through different visits using a VAS from 0 (no pain) to 10 (worst imaginable pain). Background pain was considered 'controlled' if the VAS score was $\leq$4. Drugs used for opioid therapy were also registered. Regarding BTcP, its intensity was defined according to the VAS score as 'mild' if it was $\leq$4; 'moderate' if it was between 5 and 6 and 'severe' if it was >6. Other BTcP characteristics collected were: mean number of episodes per day in the last week and in the last 24 h; time to maximum BTcP peak intensity; mean duration of episodes; pain location and irradiation; and type of pain by triggering factors and by pathophysiology. For BTcP treatment, drugs were classified as rapid-onset opioids (ROOs), strong opioids, weak opioids and analgesic non-opioids. Data on the selected opioid and its dose, time to onset of pain relief, and adjuvant analgesic non-opioid drugs were collected.

We assessed social functioning with the Gijón Social-Familial Evaluation Scale [24]. This instrument was developed in Spain and therefore we considered it was adequate to evaluate social issues in this study. The scale includes five dimensions: family status, economic status, place of residence, social relationships and social network support. If the total score (the sum of all dimension scores) is higher than 16, the person is considered to be at sociofamilial risk.

To assess the quality of sleep, we used the Medical Outcomes Study Sleep Scale (MOS-SS). This instrument has six subscales (sleep disturbances, snoring, waking up with shortness of breath or headache, amount of sleep, daytime adequacy and sleepiness) with scores from 0 to 100. The higher the score, the higher the intensity of the parameter evaluated [25,26]. Moreover, we estimated the depression and anxiety status of patients using the Goldberg anxiety and depression scale, which includes two subscales (anxiety and depression), each one with nine dichotomous questions (yes or no). In the corresponding subscales, anxiety is suggested by a score $\geq$4, while a score $\geq$2 indicates depression [27]. We also used the Caregiver Burden Index, which consists of 13 dichotomous questions (yes or no) posed to the caregiver by the interviewer. The total score ranges between 0 and 13 points, suggesting a high level of burden if it is $\geq$7 [28,29].

Regarding quality of care as perceived by the patients with BTcP in the medical oncology departments, we used a modified specific questionnaire from the Spanish Ministry of Health. This instrument is composed of 11 questions that can be scored according to a Likert scale from 1 (very satisfied) to 7 (very unsatisfied) [30].

At the last visit, patients answered the Patient Global Impression of Improvement (PGI-I) scale [31], while physicians fulfilled the Clinical Global Impression of Improvement (CGI-I) scale [32]. PGI-I and CGI-I are Likert scales of 7 points, from 0 or 'very much improved' to 7 or 'very much worse' [31,32].

We also recorded adverse events (AEs). We classified them by severity as grades 1 (mild), 2 (moderate), 3 (severe), 4 (life-threatening) or 5 (death).

Statistical analysis

We calculated the sample size according to the primary objective of the study, which was to assess the QoL of patients with BTcP in medical oncology departments using the EQ-5D-5L tool. The EQ-5D-5L index was considered applicable to perform the sample calculation. In order to detect differences of 0.05 points [33] in the mean EQ-5D-5L index score between baseline and final visit, and considering a power of 80%, an α of 0.05 and a standard deviation of 0.2, we needed to include 128 patients in the study. However, assuming 15% losses, 152 patients should be included. Sample size was calculated with one-sample t-test power analysis.

We performed a descriptive analysis of all the variables for both primary and secondary objectives. Furthermore, analysis of the answers to the EQ-5D-5L questionnaire was carried out using specific analysis methods, obtaining the score for each component of the EQ-5D-5L index, the overall VAS score and the instrument dimensions. The EQ-5D-5L index and VAS score were reported at V0, V15 and V30 using mean and standard deviation, and scores at V15 and V30 were compared with baseline using the Student t-test for related samples. The dimensions of the EQ-5D-5L index were reported by frequency and percentages at all visits, and results at V15 and V30 were compared with baseline using the $\chi 2$ test. In addition, analysis of variance repeated measure analysis was performed to analyze differences at V0, V15 and V30 for EQ-5D-5L index and VAS score, and *post hoc* tests were performed to evaluate which time points had statistically significant differences from baseline.

Regarding secondary objectives, besides descriptive analysis, background pain and BTcP characteristics were compared at V0, V15 and V30 using the Student t-test; variables related to BTcP typology were analyzed using the $\chi 2$ test. Changes at V15 and V30 from baseline in sleep quality (MOS-SS) and Goldberg anxiety and depression subscales were analyzed using the Student t-test. Percentages of patients with total score ≥ 4 points in the anxiety subscale or ≥ 2 points in the depression subscale at V15 and V30 were compared with baseline using the $\chi 2$ test. Finally, other additional analyses were performed, with continuous variables described by mean and standard deviation, and categorical variables described by frequency distribution and percentage; contrast methods used were the Student t-test, $\chi 2$ test and analysis of variance.

We performed all statistical analyses using SPSS® Statistics v. 22.0 (IBM Corp., NY, USA), and p-values < 0.05 were considered statistically significant.

Results

Clinical & demographic characteristics

From March 2018 to January 2020, 121 patients were recruited at 13 of 14 planned medical oncology departments. Three patients were excluded due to screening failures and so the analysis population included 118 patients. Ninety-seven patients (82.2%) completed the study; the other 21 patients (17.8%) were lost to follow-up because of death (n = 7), consent withdrawal (n = 1) or other reasons (n = 13). After a further 14 patients were excluded due to no availability of EQ-5D-5L results at baseline and/or later visit, 104 patients constituted the efficacy population. Of them, 90 patients completed the study (Supplementary Figure 1).

Most patients were women (60.2%), the mean age was 63.9 ± 14 years and 66.1% of patients were ≥60 years old. Regarding clinical data, 75.4% of patients had an ECOG PS of 0 or 1 and more than 80% of patients had one or two comorbidities, the most common ones being diabetes (20.6%) and chronic pulmonary disease (7.1%). Patients tended to have long-term evolving disease, as the mean time from cancer diagnosis was 54.2 ± 75.9 months, although in 15 patients this period was longer than 10 years. The most frequent types of cancer were breast (20.3%), colorectal (17.8%), lung (11.9%) and genitourinary (11.9%). Also at baseline, most patients (83.9%) had stage IV cancer, with bones (48%), liver (35%) and lungs (33%) being the main metastasis locations. Moreover, 71.2% of patients were receiving some cancer treatment and most of them were treated with chemotherapy alone (44.9%) or in combination with other therapies (6.7%). However, around 29% of patients were not receiving any antineoplastic treatment. Details of demographic and clinical characteristics at baseline can be found in Supplementary Table 1.

Quality of life

EQ-5D-5L index increased from 0.55 ± 0.30 at V0 to 0.61 ± 0.28 at V15 and 0.61 ± 0.27 at V30. Differences between V0 and V15 or V30 were statistically significant (p = 0.013 and p = 0.011, respectively). EQ VAS score was 51.8 ± 19.2 at V0, 55.6 ± 20.2 at V15 and 55.5 ± 23.4 at V30, without statistically significant differences.

Scores of EQ-5D-5L dimensions were also recorded during the study. Statistically significant differences were found only in the pain/discomfort dimension between V0 and V15 ($p < 0.001$) and V30 (p = 0.006) (Table 1).

Table 1. Comparison of scores of EQ-5D-5L dimensions at baseline and at 15 and 30 days.

Dimension	Comparison	p-value
Mobility	Baseline vs V15	0.940
	Baseline vs V30	0.740
Self-care	Baseline vs V15	0.464
	Baseline vs V30	0.370
Usual activities	Baseline vs V15	0.229
	Baseline vs V30	0.559
Pain/discomfort	Baseline vs V15	0.000
	Baseline vs V30	0.006
Anxiety/depression	Baseline vs V15	†
	Baseline vs V30	0.587

†The test could not be performed in an r × c contingency table.
V15: Visit at day 15; V30: Visit at day 30.

Characteristics & evolution of background pain & BTcP

Mean intensity (VAS score) of background pain decreased from 4.1 ± 2.5 at V0 to 2.8 ± 2.2 at V15 and to 2.7 ± 2.1 at V30 ($p < 0.001$ for both comparisons). Most patients had their background pain controlled (VAS score ≤4), but in at least 20% of patients this control was not achieved during the study. As for treatments for background pain, almost 50% of patients were treated with transnasal fentanyl. However, there was a high variability in fentanyl doses, from 12.5 to 75 µg/h, with the most common dose being 25 µg/h (in 21 patients; 17.8%) (Table 2). At each visit, 24% of patients needed a change in their opioid therapy, usually a dose increase.

Regarding BTcP (Table 2), its mean intensity (VAS score) was 8.5 ± 1.4 at V0, with a mean number of 3.6 ± 2.0 episodes/day during the last week and a mean duration of 37.6 ± 34.3 min. At baseline, we obtained data of BTcP trigger factors and pathophysiology from 116 patients. BTcP was spontaneous in nearly 60% of patients, without any specific trigger factor. In terms of pathophysiology, BTcP had a neuropathic component in 67.3% of patients, with mixed pathophysiology in 44% of patients. BTcP had only nociceptive features in 32.7% of patients. Moreover, mixed pathophysiology was more common in spontaneous BTcP than in incident BTcP. These BTcP characteristics remained until V30. At V0, the main locations of BTcP were back (35.6%), abdomen (30.5%) and thorax (10.2%).

Most patients received ROO therapy (fentanyl at doses of 67–800 µg), alone or in combination, to treat BTcP episodes, according to the physician evaluation. At V0, 44.1% of patients received ROO, and this proportion was increased at V3 (77.8%) and V15 (74.1%). At V30, still 70.0% of patients were receiving ROOs (fentanyl), while the use of strong opioids slightly increased and that of weak opioids and non-opioid analgesics diminished, as well as the percentage of patients not receiving BTcP treatment. Low-dose ROOs (fentanyl: 67, 100 and 133 µg/h) were the most used treatment for BTcP, according to the physician evaluation, and increased from 28% of patients at baseline to 43.3% of patients at V30 (Table 3). More than 30% of patients did not receive any adjuvant analgesic drug at V0 or during the study. The adjuvant analgesic drugs were corticosteroids, benzodiazepines, analgesics/anticonvulsants and NSAIDs, alone or in combination.

BTcP of severe intensity (VAS >6) was reported by almost 95% of patients at V0, but by less than 70% at V30 (Figure 1). When comparing BTcP characteristics during the study (Supplementary Table 2), statistically significant differences were found between V0 and V3, V15 and V30 for a series of variables. The mean BTcP intensity (VAS) was reduced compared with baseline ($p < 0.001$ for each visit), as well as the mean duration of BTcP episodes between baseline and V3 ($p = 0.003$), V15 ($p = 0.044$) and V30 ($p = 0.006$). Equally, the mean number of BTcP episodes in the last 24 h decreased ($p < 0.001$ for each visit), as did the mean time to onset of BTcP relief between V0 and V3 ($p = 0.003$), V15 ($p < 0.001$) and V30 ($p = 0.002$). Moreover, the mean number of BTcP episodes per day during the last week diminished between V0 and V3 ($p < 0.001$), but not between V0 and V15 or V30. No statistically significant differences were found either in the time to maximum BTcP intensity peak or in the mean number of BTcP episodes/day in the last week between V0 and V3, V15 and V30. However, there were statistically significant differences in BTcP intensity (VAS) between the different BTcP treatments at V30 ($p = 0.006$), but not at V3 or V15.

Table 2. Characteristics of background pain and breakthrough cancer pain at baseline.

Background pain	
Intensity (VAS), mean ± standard deviation	
Baseline	4.1 ± 2.5
V15	2.8 ± 2.2
V30	2.7 ± 2.1
Controlled at baseline (VAS ≤4), n (%)	66 (60.6)
Opioid treatment at baseline, n (%)	
Fentanyl	57 (48.3)
Morphine	27 (22.9)
Oxycodone/naloxone	15 (12.7)
Tapentadol	6 (5.1)
Buprenorphine	6 (5.1)
Oxycodone	4 (3.4)
Tramadol	2 (1.7)
Methadone	1 (0.8)
Patients with change in opioid treatment during the study, n (%)	
At V15	30 (26.5)
At V30	25 (25.8)
BTcP	
Episodes/day last week (n)	3.6 ± 2.0 (n = 91)
Intensity (VAS)	8.5 ± 1.4 (n = 104)
Episodes/day last week in patients with controlled BTcP at baseline (n)	2.8 ± 1.1 (n = 70)
Time to maximum BTcP intensity peak (min)	13.1 ± 17.0 (n = 72)
Duration of BTcP episode (min)	37.6 ± 34.3 (n = 72)
Number of BTcP episodes in the last 24 h	3.1 ± 2.4 (n = 84)
Time to onset of pain relief (min)	24.7 ± 25.5 (n = 65)
Location of pain, n (%)	
Back	42 (35.6)
Abdomen	36 (30.5)
Thorax	12 (10.2)
Pelvis	10 (8.5)
Arm	4 (3.4)
Bones	2 (1.7)
Other	11 (9.3)
No pain	–

BTcP: Breakthrough cancer pain; ROO: Rapid-onset opioid; VAS: Visual analog scale; V15: Visit at day 15; V30: Visit at day 30.

Other results related to QoL

Social functioning & QoL

Most patients were not at sociofamilial risk, as expressed by an overall score of the Gijón Socio-Familial Evaluation Scale <16 for 93 patients (95.9%). Only four patients had an overall score ≥6. In relation to the subscales, most patients lived with a partner of similar age, did not have a risky economic situation, lived in a place suitable for their needs, had social relationships not limited to relatives and neighbors and received support from family and neighbors. There were no statistically significant differences in mean overall score on this scale between the categories of the different dimensions of the EQ-5D-5L scale at V30.

Cancer progression, comorbidity & QoL

At V30, 17 patients (17.5%) had cancer progression, 33 patients (34%) had neither responded to prescribed cancer treatment nor had stable disease, and nine patients (9.3%) had responded to prescribed cancer treatment. The remaining 38 patients (39.2%) were not evaluable due to the short follow-up period of the study. In relation to QoL, there was a statistically significant relationship at V30 between the mean VAS score on EQ-5D-5L and cancer

Table 3. Evolution of breakthrough cancer pain treatment during the study.

BTcP treatment, n (%)	Baseline (n = 118)	V3 (n = 117)	V15 (n = 112)	V30 (n = 97)
ROO	52 (44.1)	91 (77.8)	83 (74.1)	68 (70.1)
Low dose	33 (28.0)	60 (51.3)	52 (464)	42 (43.3)
Medium dose	15 (12.7)	26 (22.2)	26 (23.2)	23 (23.7)
High dose	4 (3.4)	5 (4.3)	5 (4.5)	3 (3.1)
Strong opioid	14 (15.2)	13 (11.1)	18 (16.1)	19 (19.6)
Weak opioid	23 (25)	1 (0.9)	0 (0.0)	0 (0.0)
Non-opioid analgesic	14 (17.2)	4 (3.4)	7 (6.3)	6 (6.2)
No BTcP treatment	26 (22.0)	8 (6.8)	4 (3.6)	4 (4.1)
Changes in BTcP treatment, n (%)	**Baseline (n = 118)**	**V3 (n = 116)**	**V15 (n = 112)**	**V30 (n = 97)**
Changes		47 (40.5)	24 (21.4)	15 (14.5)
ROO dose	–	2 (1.7)	3 (2.7)	–
ROO dose and treatment type	–	1 (0.9)	–	2 (6.8)
ROO dose and ROO type	–	1 (0.9)	3 (2.7)	3 (3.1)
Onset of ROO treatment	–	17 (14.7)	2 (1.8)	–
Treatment type	–	25 (21.6)	15 (13.4)	9 (9.3)
Onset of strong opioid	–	1 (0.9)	1	–
Dose change (no ROO)	–	–	–	1 (1.0)
No changes	–	69 (59.5)	88 (78.6)	82 (84.5)

BTcP: Breakthrough cancer pain; ROO: Rapid-onset opioid; V3: Visit at day 3; V15: Visit at day 15; V30: Visit at day 30.

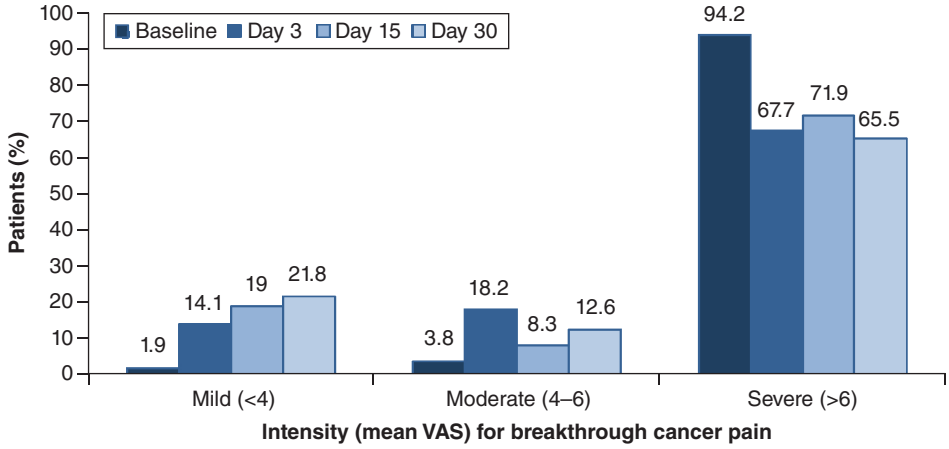

Figure 1. Changes in breakthrough cancer pain intensity in patients with individualized pain therapy for 30 days.
VAS: Visual analog scale.

progression (p = 0.040): VAS score was higher, with a better perception of healthy status, in patients without disease progression (56.3) than in patients with it (42.5). Furthermore, there were statistically significant differences in the dimensions of self-care (p = 0.009), discomfort (p = 0.001) and anxiety/depression (p = 0.002) of the EQ-5D-5L at V30.

Comorbidities were assessed in 112 patients. The mean CCI score was 5.8 ± 1.9, which indicates a high mortality prediction (>85%) and it was consistent with cancer stage of the patients at baseline, when most of them had stage IV cancer. No statistically significant differences were found between CCI score and the categories of the different dimensions of the EQ-5D-5L scale at V30.

Sleep & QoL

Sleep quality improved from V0 to V30. Patients evaluated with the MOS-SS showed that they had mild but not severe problems with sleep and rest. There were statistically significant differences in the sleep disturbance and the sleep problems index I & II dimensions of the MOS-SS between baseline and V15 ($p < 0.001$, p = 0.032 and

p = 0.005, respectively) and V30 (p = 0.003, p = 0.020 and p = 0.012, respectively). There were also statistically significant differences in the snoring and sleep quantity subscales between V0 and V30 (p = 0.023 and p = 0.01, respectively).

In relation to QoL, there was a statistically significant relationship between the sleep problems index II dimension and pain/discomfort (p = 0.008) and depression/anxiety (p = 0.028), with a lower score on the sleep problems index II meaning better QoL. Furthermore, statistically significant relationships were found between three EQ-5D-5L dimensions (mobility, pain/discomfort and anxiety/depression) and several MOS-SS dimensions. The mobility dimension of EQ-5D-5L was related to adequacy (p = 0.041), somnolence (p = 0.025) and sleep problems index I (p = 0.028). In turn, the pain/discomfort dimension was related to disturbance (p = 0.046), adequacy (p = 0.011), somnolence (p = 0.013), sleep problems index I (p = 0.004) and sleep problems index II (p = 0.002). Finally, the anxiety/depression dimension was related to disturbance (p = 0.034), shortness of breath (p = 0.032), sleep problems index I (p = 0.038) and sleep problems index II (p = 0.022).

Anxiety & depression & QoL

The results of the Goldberg anxiety and depression scale showed that most patients did not feel anxious (anxiety score <4 in 64.2% of patients at V0 and 70.7% at V30), but they felt depressed (depression score ≥2 in 76.5% of patients at V0 and 82.6% at V30) in all visits. There was a slight tendency to improvement from baseline at V15 and V30, but without statistically significant differences.

In relation to QoL according to the EQ-5D-5L, at V30 higher scores of the Goldberg anxiety and depression scales seemed possibly to correlate with more problems in some dimensions of the QoL questionnaire. For the mean Goldberg anxiety scale, statistically significant differences were found in the EQ-5D-5L dimensions of self-care (p = 0.016), usual activities (no problems vs severe problems: p = 0.015) and anxiety/depression (no problems vs moderate problems: p = 0.06; no problems vs severe problems: p = 0.010). Likewise, for the mean Goldberg depression scale, there were statistically significant differences in the EQ-5D-5L dimensions of usual activities (no problems vs severe problems: p = 0.019) and anxiety/depression (no problems vs all: p < 0.001). For both the anxiety and depression scales, higher scores seemed possibly to correlate with a higher level of anxiety/depression in the EQ-5D-5L.

Caregiver burden

The mean score of the Caregiver Burden Index was 3.5 ± 3.3 at V0; there was an improvement at V30 with a decrease in the score to 3.1 ± 3.3, pointing to a decreased burden. The majority of caregivers (70/83; 84.3%) had a score <7 at V0. Nevertheless, the percentage of caregivers with high burden increased from V0 (15.7%) to V30 (20.4%). No statistically significant differences were observed between baseline and V30.

Global impression of improvement, quality of care perceived & safety

The PGI-I scale was completed by 88 patients and the CGI-I scale results were available from 80 patients. Results reported by patients and clinicians were similar. Among patients, 70.5% perceived some improvement (very much better, much better, a little better), 14.8% did not perceive any change and 14.7% reported a worsening (a little worse, much worse). Among physicians, 63.8% perceived an improvement (much better, a little better), 23.8% did not find any change and 12.6% considered that there was a worsening (a little worse, much worse) (Figure 2).

In terms of quality of care perceived by patients, the mean scores on the questionnaire were between 1 and 2 for all questions except question 9 ('Time elapsed from the time you were given an appointment until you went into the consultation'), which had a mean score of 3.2 ± 2.2. There were statistically significant differences among study sites, but only 72 patients answered the questionnaire and sample sizes by individual study site were low.

Safety was evaluated in all patients (n = 118). During the study, 66 AEs (33.9% of the patients) were reported. By severity, 15 AEs (22.7%) were mild, 21 (31.5) were moderate, 13 (19.7%) were severe, four (6.0%) were life-threatening and seven (10.6%) were fatal. The majority of AEs (n = 43; 57.6%) were not related to any treatment. Only 23 AEs (42.4%) were treatment-related: 11 related to a non-opioid treatment, six induced by a ROO, three induced by strong opioids (non-ROO), one caused by a combination of a ROO and a strong opioid, and two caused by combinations of opioids (one of them not specified). Regarding AEs related to opioid treatment, the majority were induced by high-dose ROO treatment, and the most frequent opioid-related AEs were gastrointestinal events.

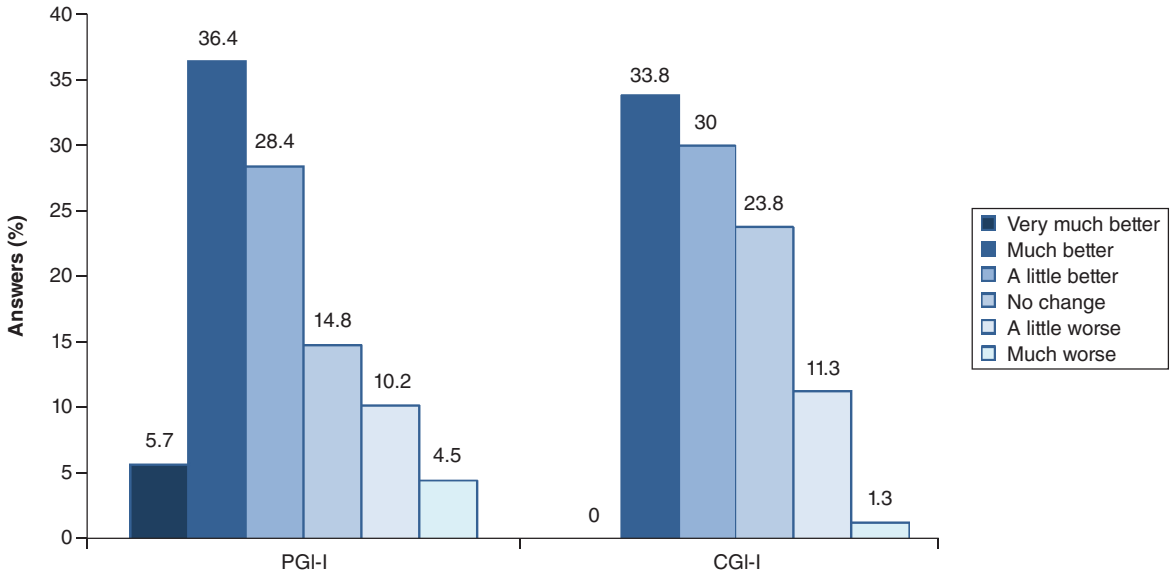

Figure 2. Results from the Patient Global Impression of Improvement (n = 88) and Clinical Global Impression of Improvement (n = 80) questionnaires at the final visit.
CGI-I: Clinical Global Impression of Improvement scale; PGI-I: Patient Global Impression of Improvement scale.

Discussion

The CAVIDIOM study provides data on QoL and BTcP in patients with advanced cancer treated in medical oncology departments. In Spain there are 106 hospitals with medical oncology departments, distributed all over the country in the 17 autonomous regions. Most hospitals are included in the NHS [34], which is universal and free, although citizens can additionally pay for private health insurance. Our study was performed in 13 public tertiary hospitals from nine autonomous regions.

Patients included were old (age ≥60 years) and had cancer in advanced stage, long-term disease, at least one comorbidity and an ECOG PS score ≤2. These characteristics are frequent in our clinical practice and are similar to those reported in other Spanish studies on QoL and BTcP [10,11]. The typical profile of the patients treated for cancer pain is of someone with long-term cancer, often breast cancer, with incident pain of severe intensity and with neuropathic pathophysiology (mixed or pure). As specified in the Edmonton classification of BTcP [35], the neuropathic component determines poor results of pain management. Therefore BTcP with a neuropathic component is a type of pain that is difficult to manage.

Quality of life

We used the EQ-5D-5L instrument to assess QoL because it is a Spanish validated tool developed by the EuroQol Group (www.euroqol.org) and is a fast, generic and standardized questionnaire to describe and assess health-related QoL. After 1 month of follow-up with dose adjustment or drug switching if necessary at V3 and V15, our results showed an improvement in QoL. Specifically, there were changes in the pain/discomfort domain of the EQ-5D-5L instrument: from V0 to V30, the percentage of patients in the worst categories (moderate and severe problems) decreased from 75.0 to 51.1%, while the percentage of patients in the best categories (no problems and slight problems) increased from 23.1 to 47.8%. In the subanalysis of QoL by treatment type and intensity of pain at baseline, no statistically significant differences were observed. It would seem that these factors do not markedly influence the QoL, but the low sample size of treatment groups did not allow such a conclusion to be firmly stated.

Quality of life & breakthrough cancer pain

In the last years, new studies focusing on QoL in cancer patients have been published. In another Spanish observational study (the CAVIDIOPAL study), 99 patients with advanced cancer and BTcP assisted by palliative care departments were included. QoL was assessed with the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire at baseline and after 28 days of individualized BTcP therapy, mainly with transmucosal fentanyl at low doses. Almost all subscales of EORTC QLQ-C30 significantly improved ($p < 0.001$)

at the end of the study. Therefore this study showed that individualization of treatment with fentanyl (ROO) improved QoL as well as some BTcP characteristics (intensity, duration and number of BTcP episodes) [11,12]. In an observational study in pain units and palliative care departments in Spain, the QoL of 152 patients with BTcP was assessed [36]. Fentanyl was the BTcP treatment in 81.2% of patients, but doses were not reported. After 1 month of follow-up, global health status and all functional and symptoms dimensions of EORTC QLQ-30 improved ($p < 0.001$) [36]. In a similar Spanish study, albeit conducted in radiation oncology departments in Spain (CAVIDIOR study), QoL was evaluated with the 12-item Short-Form Health Survey (SF-12) in 79 patients with BTcP who were receiving or planning to receive palliative radiation therapy. Transmucosal fentanyl was the BTcP therapy in 65.2% of patients. At the end of the study, the mental component improved ($p < 0.001$), meaning improvements in social functioning, role-emotional status, mental health and vitality [10]. In this study, patients received mainly ROOs (low doses of transmucosal fentanyl) as BTcP treatment.

The relationship between BTcP control and QoL improvement in cancer patients with BTcP has been shown in other recent studies. In an observational, multicenter Italian study in palliative care departments, oncology departments and pain clinics, 154 patients with BTcP were included. Individualized treatment of BTcP with transmucosal fentanyl improved almost all physical and emotional components of QoL in the EORTC QLQ-C15-PAL, with statistically significant differences from baseline [37]. Additionally, in a Japanese study of 44 outpatients with cancer pain treated with opioids, there was a statistically significant relationship between BTcP intensity and QoL [38].

All these studies highlight the impairment of QoL in patients with cancer and BTcP. They also point to the relevance of BTcP control to improve physical and emotional components of QoL in our patients.

Background pain

In this study, uncontrolled background pain (VAS >4) was reported by 40% of patients at baseline, suggesting an inadequate or incomplete diagnosis. Therefore it is necessary to implement diagnostic procedures as well as evaluation of pain characteristics according to current guidelines [3,7]. Treatments for background pain were opioids, mainly transdermal fentanyl (48.3%) and morphine (22.9%). Statistically significant decreases in background pain intensity ($p < 0.001$) were observed at V15 and V30, but this improvement was slightly smaller than that in the CAVIDIOPAL study [11]. In both studies, background pain was assessed with an 11-point VAS. Mean VAS score for background pain was reduced from 4.0 to 2.0 in the CAVIDIOPAL study and from 4.1 to 2.7 in this study. Control of pain seems to be better in palliative care departments (CAVIDIOPAL study) [11] than in medical oncology departments (our study). This difference might be due to higher awareness of cancer pain by palliative care teams, along with more expertise in opioid use and in a comprehensive approach to oncological patients, as was found in a national survey of medical oncologists and palliative care specialists in the USA [39].

BTcP characteristics

Regarding BTcP characteristics, the mean time to maximum peak at baseline (13.1 min) was longer than that stated in the Spanish consensus document on BTcP (3–5 min); however, according to that document, this time is highly variable, from seconds to hours [40]. Furthermore, this time can be longer in patients with breast and gynecological cancers [41], who represent 31.3% of our study population. In relation to results, statistically significant improvements were observed in pain intensity, number of episodes in both the last week and the last 24 h, duration of BTcP episodes, and onset of pain relief at V15 and V30. At all study visits, no trigger factor was identified in at least 60% of patients, and the most common pathophysiology was the mixed type (in at least 40% of patients). BTcP intensity (VAS) was reduced during the study, from 8.5 (severe intensity) to 6.0 (moderate intensity); this was a statistically significant difference. However, a high number of patients still had BTcP episodes of severe intensity. In addition, the results relating to BTcP intensity were worse than in the CAVIDIOPAL [11] and CAVIDIOR [10] studies, both also using a 11-point VAS scale. In the CAVIDIOPAL study the decrease in BTcP intensity was from 8 ± 1.0 at baseline to 4.6 ± 2.4 at day 28 and 4 ± 2.4 at day 90 [11]. In the CAVIDIOR study, this reduction was from 8.2 ± 1.3 at baseline to 4.7 ± 3.5 at the final visit [10]. As commented above, it is possible that pain management may be better in palliative care departments. In addition, these better results in radiation oncology departments might be attributed to the fact that radiation oncology specialists know that radiotherapy causes pain by itself. Therefore, probably they are more aware of this problem.

BTcP therapy

BTcP therapy must be individualized. In addition, the involvement of multidisciplinary teams could be beneficial for patients [42]. According to the result of a Delphi survey among Spanish experts, rapid-onset fentanyl formulations should be the preferred therapy [2]. In our study (CAVIDIOM), ROOs (transmucosal fentanyl) were prescribed to 44.1% of patients at baseline and to 70.1% at V30. This use of ROOs (transmucosal fentanyl) at baseline was less than in the CAVIDIOPAL (67.1% of patients [11,12]) and CAVIDIOR (93.9% of patients [10]) studies. These variations in the level of use of ROO therapy might account for the differences in the decrease of BTcP intensity between these three studies. With regard to ROO doses, medium and high doses of ROOs are used in the treatment of BTcP. In the present study, low doses of ROOs provided equal or better pain control than higher doses, along with a longer-term effect with progressive improvement as the treatment continued. In addition, low doses can prevent short-term tolerance, whereas high doses cannot. Therefore, in this study, low doses of ROOs prevented dose-related AEs, dependence and possible tolerance effects associated with opioids. In the CAVIDIOPAL study, most patients were treated with low doses of sublingual fentanyl (67 and 133 μg; 52.6 and 48.4%, respectively), according to the physician evaluation. Decrease of BTcP intensity was faster in patients treated with low doses and there was a twofold reduction of pain score. Moreover, there were statistically significant improvements in the role-emotional, cognitive and social functioning dimensions of QoL in patients treated with low doses of fentanyl, but not in those treated with higher doses [12]. In the present study, all reported AEs were expected taking into account the type of patients and the results of previous studies.

QoL, sleep & mental health

Among the other study results, changes in the MOS-SS instrument pointed to a sustained improvement in the quality of sleep during the study. Furthermore, there were statistically significant relationships between sleep and QoL. When patients had problems sleeping and were tired and sleepy during the daytime, it seemed that they had more problems with mobility, more pain/discomfort and more anxiety/depression, with statistically significant relationships; that is, the worse the value in the MOS-SS dimension, the worse the value in the EQ-5D-5L dimension. Therefore, the more sleep problems, the lower the QoL. These statistically significant relationships have also been found in other studies of patients with cancer using different instruments to assess sleep quality, mobility and anxiety/depression [43]. Another result also related to mental health in our patients was that they felt depressive more than anxious. Although there was a mild tendency to improvement during the study, no statistically significant differences were found between V0 and V15 or V30. However, we suggest that this result may be due to the short period of evaluation of the study.

Cancer progression

Another secondary objective was related to cancer progression. The majority of patients did not report cancer progression between V0 and V30, but the short study length was inadequate to observe any disease progression.

Impression of global improvement

We also assessed the impression of global improvement using the PGI-I and CGI-I questionnaires, with similar results in patients and clinicians. The response 'much better' was chosen by 36% of patients and 34% of clinicians, while 'a little better' was the answer given by 27% of patients and 30% of clinicians. However, in the CAVIDIOPAL study, this result was different, with a greater proportion of physicians (around 80%) considering that the improvement was significant in comparison with 60% of patients [11]. In the CAVIDIOR study the difference was even bigger, with almost more than double the number of physicians (81.9%) giving a positive answer compared with patients (43.6%) [10]. These results show that impressions of improvement between patients and physicians are more similar in medical oncology departments than in palliative care units and radiation oncology departments. The reason for this difference could be that we medical oncologists are able to follow up patients from diagnosis and for a long time, even for years in some patients, such as those with breast or colon cancer.

Strengths & limitations of the study

The main strength of the study was that we assessed the QoL of patients with BTcP all over Spain using standardized and validated instruments, in particular the EQ-5D-5L. Furthermore, characteristics of the study patients coincided with those of patients in our clinical practice. As for quality of data, several steps were taken in the planning and implementation of this study to ensure that the data collected were accurate, consistent, complete and reliable.

Despite the controls performed during and after the study, there were some limitations: sample size, study duration, site variability, diversity of patients, some unusual questionnaires, some issues at inclusion and missing data. The evaluable sample size was lower than calculated. The sample size was calculated at 152 patients to detect differences of 0.05 points [32] in the mean of the EQ-5D-5L index score between the baseline and final visit, considering a power of 80%, an α of 0.05 and a standard deviation of 0.2, and assuming 15% losses. However, the evaluable sample size was 104 patients, which reduced the power of the study to 71.4%, taking into account the same assumptions as in the original sample calculation. This limitation affected above all the subgroup analyses. Regarding study duration, in some objectives and additional analysis there were not statistically significant differences between periods or treatment received due to a short evaluation period. As for site variability, clinical practice is different between study sites and oncology services and the type of patient recruited is also different. Patients were widely diverse; although all had cancer, clinical and demographic characteristics were different. Therefore some results of the objectives analyzed are widely distributed. With regard to measurement instruments, some questionnaires are not usually used in clinical practice, so their interpretation by physicians and/or patients can be difficult. Quality controls were established to avoid loss of data integrity; nevertheless, some study incidences could affect data integrity and thus affect the analysis and interpretation of results. Issues related to inclusion criteria were that nine (7.6%) patients were prescribed a ROO for background cancer pain, when this type of treatment is indicated for BTcP. Moreover, 43 (39.4%) patients reported uncontrolled pain (mean VAS pain intensity >4) at baseline, when the inclusion criteria specified only patients with controlled pain. Furthermore, any change of ROO was at physician discretion. Finally, there were missing data in the information related to treatment and study questionnaires between visits, and consequently the numbers of patients with information available were different between visits and some results can be distorted.

Suggestions for future research & interventions

From the study results, two measures for improving cancer pain management can be suggested. The first measure is related to BTcP definition and diagnosis. Some patients were included at baseline with uncontrolled background pain (VAS >4) and others had more than four BTcP episodes. There were no established criteria for the diagnosis of BTcP in the medical oncology departments in clinical practice. Possible consequences of the misdiagnosis are underdosage or inappropriate drug prescription. Therefore a universal BTcP definition should be established and medical departments might implement strategies to improve BTcP diagnosis according to the current guidelines.

The second measure refers to individualized BTcP treatment. As this study showed, there is a need to reduce the intensity of BTcP episodes. A possible solution is to optimize BTcP treatment according to patient characteristics and to perform a close follow-up of patients. A multidisciplinary approach might be useful, working in collaboration with palliative care experts or other specialists to achieve integrated care of our patients. It would be necessary to review the compliance with dose management guidelines, as well as searching for a more specific patient profile to relate to a specific and individualized treatment.

Therefore, in our opinion, future oncological pain research could focus on establishing a single universally accepted BTcP definition, gaining better knowledge of individualized BTcP treatment and the role of low-dose ROOs, and refining the multidisciplinary approach to BTcP.

Conclusion

In patients with advanced cancer and BTcP treated in medical oncology departments, QoL could increase with careful follow-up and individualized management of pain. However, some aspects still have to be improved, including BTcP diagnosis, follow-up and opioid dose.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/fon-2022-0758

Author contributions

C Camps was the study coordinator and was involved in study design, protocol, case report form elaboration and data analysis. C López Bermudo was involved in study design and interpretation of data results. All authors except C Camps and C López Bermudo contributed to data collection. All authors read and approved the final manuscript.

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Ethical conduct of research

The study was approved by the relevant independent ethics committees from each participating center and its corresponding autonomous community. It was conducted according to the International Conference on Harmonization Guideline for GCP, the Declaration of Helsinki, the guidelines for Good Pharmacoepidemiology Practices, the Spanish Data Protection Directive and all local requirements. We anonymized data by identifying patients with numbers. Furthermore, patients should provide a signed and dated informed consent document before data collection. The study was registered at ClinicalTrials.gov (Identifier NCT03435120).

Summary points

- Breakthrough cancer pain (BTcP) is common in patients with advanced cancer, but underdiagnosis and undertreatment of cancer pain still occur. Moreover, pain impacts on the quality of life (QoL) of patients with cancer.
- The relationship between QoL and BTcP was assessed in patients with advanced cancer treated at medical oncology departments in Spain.
- Study patients received individualized BTcP treatment.
- QoL improved during the study, with statistically significant differences between mean score of the EQ-5D-5L questionnaire at baseline and at days 15 and 30.
- Intensity of background pain was reduced, from a mean visual analog scale score of 4.1 at baseline to 2.7 at the final visit.
- Intensity of BTcP was also reduced, from a mean visual analog scale score of 8 at baseline to 6 at the final visit. Mean duration of BTcP episodes was 37.6 min at baseline but 28.2 min at the final visit.
- The most frequent treatment for BTcP were rapid-onset opioids, mainly transmucosal fentanyl at low doses.

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