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Analysis of the Clinical Management and Quality of Life of frail Patient's with Cancer and Breakthrough Cancer Pain in Clinical Practice

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Abstract

Purpose: The purpose of this study was to analyse the clinical management and Quality of Life (QoL) of frail patients with cancer, chronic background pain and Breakthrough Cancer Pain (BTcP) and to assess whether treatment was conditioned by their frailty status.

Methods: This was an observational study in adult frail patients with cancer, chronic background pain and BTcP. Outcomes of interest collected include clinical and sociodemographic data, Karnofsky Performance Status, quality of life (EuroQoL-5D-5L), chronic pain and BTcP characteristics, as well as treatments administered for their control.

Results: A total of 222 patients were included with a mean age of 68 years (range 24-91), 60.5% men, with a mean Karnofsky of 63.2%. The number of daily episodes of BTcP was 3.8 (95% CI 3.3-4.3), with a duration of 34.6 minutes (95% CI 28.8-40.3), and 56.8% had a gradual onset. Opioids were administered to 88.3% of patients for the chronic pain, and to 83.8% for BTcP. The treatment's daily doses administered for chronic pain and BTcP did not differ from those usually recommended. QoL was significantly worst in frail patients with cancer than EuroQol-5D-5L healthy age-matched no frail patients and was related to performance status ($p<0.001$) and to the social-familial status ($p=0.045$).

Conclusion: BTP in frail patients with cancer presents with more episodes, of a shorter duration and more gradual onset compared to other published references of patients with BTcP. QoL was seriously affected in this group of patients. No relevant differences were seen in the doses or method of administration of treatments for chronic pain and BTP in frail patients with cancer as compared to the standard recommendations for non-frail patients. Our findings support the importance of the frailty assessment in all patients with BTcP.

Keywords: Cancer • Breakthrough cancer pain • Frailty • Quality of life

Introduction

Frailty is defined as a physiologic state with increased vulnerability to stress factors, resulting from the decline in physiologic reserve or dysregulation of multiple physiologic systems [1]. It is a particularly important risk factor for patients with cancer because cancer itself and its treatment add stressors that can reduce the patient's physiologic reserve. The frequency of frailty in elderly patients with cancer is high, and approximately half of them are frail or pre-frail with a greater risk of postoperative complications, chemotherapy intolerance, disease progression, and death [2-7]. Frailty has been associated in different studies with an increased risk of chemotherapy-related toxicity and poorer tolerance to treatment [8,9]. For these reasons, many studies in patients with different types of cancer now recognize the importance of the evaluation of frailty for the stratification of risk for patients in the selection of the cancer therapy and for the decision of pharmacological or non-pharmacological treatment like radiotherapy and brachytherapy [7, 10-12]. Furthermore, the relationship between frailty and the prognosis of the tumour process has been widely demonstrated, and is, therefore, a factor that should be considered in these patients [13]. Therefore, the International Society of Geriatric Oncology (SIOG) recommends frailty assessment in all cancer patients over 70 years of age to help the oncologist make decisions about the most appropriate treatment for the patient [10].

Most patients with cancer suffer chronic pain, with prevalence between 33% and 64%, reaching over 70% in patients in advanced stages of the disease [14]. Furthermore, patients with chronic pain may experience, at some point in their course, the onset of breakthrough cancer pain, which is defined as a "transient exacerbation of pain occurring spontaneously or related to a specific predictable or unpredictable trigger, despite stable and

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adequately controlled background pain" [15-17].

The incidence of BTcP varies across studies between 23%-93% [17]. In cancer patients, the prevalence of BTcP increases as the disease progresses and can reach up to 80% in the hospice setting [14]. This frequency increases in patients with low performance status and advanced stages of the disease and is an indicator of poor prognosis [18].

Recognition of frailty status in patient with cancer conditions the decision of the type of treatment for the cancer and chemotherapy drug doses, and it is related to its prognosis. However, in the group of frail patients with chronic pain and BTcP, it is not known whether the choice of analgesic therapy is conditioned by the presence of frailty. In this regard, the objectives of this study were to analyse the clinical management and quality of life of frail patients with chronic pain and BTcP and the treatments administered for pain control in standard clinical practice.

Materials and Methods

A cross-sectional observational study was conducted involving 29 investigators from sites in 12 Spanish provinces, including 17 medical oncology units, six pain units, three palliative care units, two geriatric departments, and one home hospitalization unit.

Patients were included from 27-June-2018 to 13-May-2019. The study was approved by the Medicinal Product Research Ethics Committee of HM Hospitales de Madrid (2-April-2018; Minutes 132).

Written informed consent was obtained from all patients. The study protocol was in accordance with the ethical standards described in the Declaration of Helsinki.

Patient selection

Patients were consecutively selected from those who attended to the clinics and who met the screening criteria, completing a single visit. No treatment was administered as a requirement of the study.

The study population consisted of frail patients with cancer with a history of controlled background chronic pain and a diagnosis of BTcP.

The Frail scale was used to identify frail patients. This is a validated scale consisting of five questions corresponding to a domain: Fatigue, Resistance, Ambulation, Illness and Weight Loss. Each domain is scored with one point. Patients were classified as frail when they scored three or more points, over five [19].

The Davies criteria and algorithm were used to diagnose BTcP [16]. This algorithm determines the existence of BTcP with: 1) Presence of baseline pain as persistent pain for 12 or more hours per day, in the week prior to the assessment (or that would exist if analgesics were not taken); 2) Adequately controlled background pain: No pain or mild pain (not moderate or severe) for 12 or more hours per day, during the week prior to the assessment; 3) Presence of transient pain exacerbations: Severe or unbearable, with a visual analogue scale score for pain intensity greater than seven points over ten points, occurring spontaneously or related to a specific, predictable or unpredictable trigger.

The inclusion criteria were: 1) Adult men and women; 2) Frail patients with ≥ 3 points on the Frail scale; 3) Patients with controlled background pain with a visual analogue scale score for pain intensity ≤ 4 over ten points. 4) Diagnosis of BTcP; 5) Patients who have signed the written informed consent to participate in the study.

Evaluation of study objectives

To assess the primary objective, the treatments received by the patient for chronic pain and BTcP and their doses and administration route were recorded.

Information was collected on age, sex, race, weight, height, Body Mass Index (BMI) and occupational status.

Social and family status was assessed using the Gijón scale [20,21]. It is a hetero-administered scale consisting of five variables (family situation, economic situation, housing, social relations, and social support), each withfive possible categories. The categories are scored from 0 to 4 points, resulting in an overall score ranging from 0 to 20 points. The cut-off point for the detection of social risk is from 16 points on.

Medical history information and the patient's performance status (Karnofsky Performance Status) was recorded. The Karnofsky scale classifies patients into ten categories (0 and 100 points).

The date of cancer diagnosis (date of diagnostic biopsy), the organ affected by cancer and the main characteristics of background pain and BTcP were recorded.

QoL was assessed using the EuroQoL-5D-5L, a generic questionnaire consisting of five questions and a visual analogue scale with values between 0-100 millimetres (EQ-VAS). Each question has five degrees and evaluates one dimension: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression [22].

Determination of sample size

The most restrictive variable for sample size determination was QoL. The reference value for EQ-VAS in the Spanish population over 18 years of age is 75.0 points (SD 0.4) [23,24]. A sample of 222 patients would allow for the description of QoL with a precision of 0.05 points and the power to find differences was 96% with a two-sided alpha error of 0.05 (Sample Power, IBM-SPSS).

Statistical analysis

A descriptive analysis was performed of frequencies and percentages for the qualitative variables, with calculation of the mean, standard deviation, minimum, maximum values, and 95% confidence intervals, for quantitative variables.

Between-group comparisons were made using the Fisher test or the Chi Square test if the variables were qualitative, and the Student's t-test or Wilcoxon test was used for quantitative variables.

A multivariate linear regression analysis was performed to explore the relationship between the EQ-VAS score and different patient characteristics: age, sex, Gijón scale score, BMI, Karnofsky Performance Status score, Frail scale score characteristics of BTcP, time since diagnosis and location of cancer. Statistical significance was considered at a value of 0.05. The IBM-SPSS version 27.0 statistical package was used throughout. The STROBE guidelines (www.strobe-statement.org) were followed to present the results of cross-sectional studies [25].

Results

A total of 222 patients were included in the study. Table 1 shows their anthropometric, sociodemographic and clinical characteristics. The percentage of patients with a Karnofsky score under 50 was 11.3% (n=25) (Table 1).

Table 1. Sociodemographic and clinical data of frail patients with cancer and breakthrough pain.

Sociodemographic or clinical variable (n=222)		% (n) or mean (95% CI)
Age		68.2 (66.6-69.8)
Gender	Male	135 (60.8)
	Female	39.2 (87)
Race	Caucasian	80.2 (178)
	Hispanic	19.4 (43)
	Black	0.4 (1)

Employment status	Employee	2.3 (5)
	Temporary work disability	12.6 (28)
	Permanent work disability	15.8 (35)
	Retirees	69.3 (154)
Gijón Scale	Overall score (0-20)	4.9 (4.5-5.3)
	No social-familial risk (<16)	99.6 (221)
	With social-familial risk (≥16)	0.4 (1)
Body Mass Index (kg/m^2)		25.1 (24.2-25.7)
Classification according to body mass index (BMI)	Cachexic (BMI <20 kg/m^2)	14.9 (33)
	Normal (BMI ≥ 20 and	37.4 (83)
	<25 kg/m^2)	
	Overweight (BMI ≥ 25 and	31.1 (69)
	<30 kg/m^2)	
	Obese (BMI ≥ 30 kg/m^2)	16.6 (37)
Karnofsky performance status		63.2 (61-65.4)
Time since cancer diagnosis (months)		33.9 (27.3-40.5)
Primary cancer location	Lung	33 (73)
	Gastrointestinal	23.5 (52)
	Breast	7.2 (16)
	Prostate	5 (11)
	Other	31.5 (70)

Two hundred and fifteen patients (96.8%) received treatment for some comorbidity. About 79.7% (n=177) of the patients were receiving treatment for cancer. The median time since cancer diagnosis was 14.7 months. The most common primary tumor was lung (73, 33.0%), followed by gastrointestinal (52, 23.5%) and breast (16, 7.2%).

Chronic pain was caused by spinal problems in 5% (n=11), osteoarthritis in 2.3% (n=5), peripheral neuropathy in 1.8% (n=4), trauma in 0.5% (n=1), and other causes in 4.1% (n=9). Chronic pain was mixed in 34.7% of patients (n=77), somatic in 28.8% (n=64), visceral in 23% (n=51), and neuropathic in 13.5% (n=30).

Table 2 describes the main characteristics of the BTcP. The first episode was explored in 60 patients (26%) at the study visit.

Table 2. Characteristics of breakthrough pain in frail patients with cancer.

Characteristics of breakthrough pain		**% (n) or mean (95% CI)**
Number of daily episodes		3.8 (3.3-4.3)
Duration of episodes (minutes)		34.6 (28.8-40.3)
Location	Lumbar	30.2 (67)
	Abdomen	22.5 (50)
	Chest	21.2 (47)
	Head	11.7 (26)
	Other	14.4 (32)
Onset	Gradual	56.8 (126)
	Sudden	43.2 (96)
Intensity	Mild	3.2 (7)
	Moderate	34.2 (76)
	Severe	45.5 (101)
	Unbearable	17.1 (38)
Incidental	No	52.5 (116)
	Yes	47.5 (105)
Predictable	No	64.9 (144)
	Yes	35.1 (78)
Time of day when it appears	At night	12.6 (28)
	During the day	36.9 (82)
	Unrelated	50.5 (112)
Type of pain	Somatic	27.5 (61)
	Visceral	24.8 (55)
	Neuropathic	16.7 (37)
	Mixed	31.1 (69)

Frailty

All patients were frail, with a mean score on the Frail scale of 3.9 points (95% CI 3.8-4). There were no significant differences in the scores per cancer location (Figure 1).

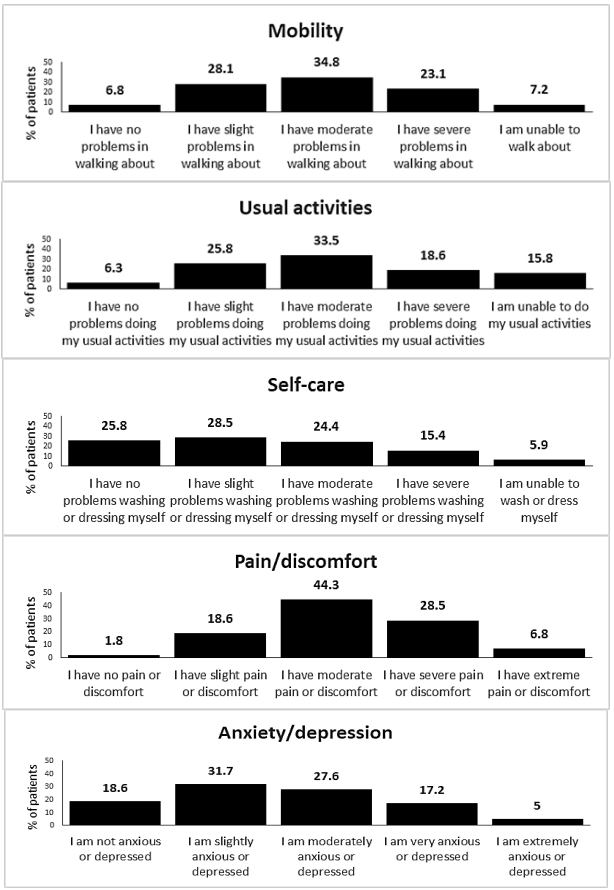

Figure 1. Distribution of patients in the categories of the five dimensions of the EuroQoL-5D-5L health-related quality of life questionnaire in frail patients with cancer and breakthrough cancer pain.

Quality of life

The mean EQ-VAS score was 51.3 mm (95% CI 48.5-54), with a median of 50 mm. Figure 1 shows the distribution of patients in the categories of the five dimensions of the QoL questionnaire. No significant differences were observed in the EQ-VAS score between frail patients or according to the cancer location (Figure 2).

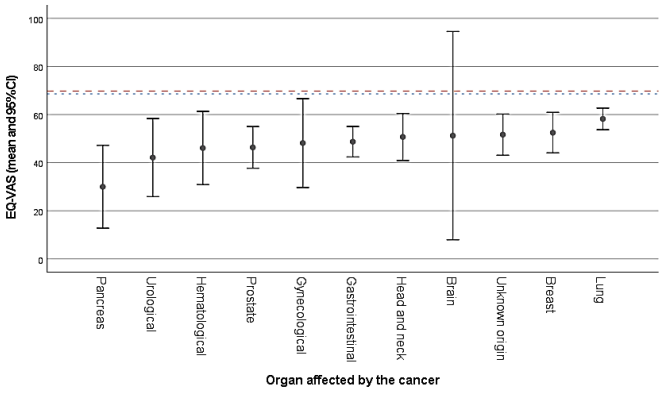

Figure 2. Mean score of the quality-of-life EQ-VAS in frail patients with cancer and breakthrough cancer pain. Comparison by cancer location and with the general healthy population for the same age group.

Note: (– – –) Mean EQ-VAS score in the general healthy population of the 65-74 years-old age group. (– – –) Mean EQ-VAS score for patients with cancer. EQ-VAS: EuroQoL-5D-5L health-related quality of life questionnaire visual analogue scale; Value 0 means worst quality of life and value 100 means the best quality of life.

Treatments for pain

For the treatment of background pain, 27 different drugs were administered in 215 patients with a total of 316 administrations. Table 3 details the drugs used and summarizes the mean daily doses administered to patients by compound and route of administration. A total of 65.8% of the active substance administered were opioids (208/316) and they were administered to 196 patients (88.3%).

The drugs used for the treatment of BTcP, the doses administered, and the administration routes are described in Table 4. A total of 11 different active substances were administered in 196 patients with a total of 219 administrations of which 196 (89.5%) were opioids administered to 83.8% of patients (186/222).

Factors related to QoL

In multivariate regression analysis, the higher the Gijón social-familial evaluation scale score (plus social exclusion), the EQ-VAS quality of life score worsened in a statistically significant manner (p=0.045), so that one point higher on the Gijón scale represented a reduction in quality of life of 0.9 mm (95% CI 0.02-1.8). It was also seen that the lower the Karnofsky score, the quality-of-life score in EQ-VAS significantly worsened manner (p<0.001), so that ten points lower on the Karnofsky scale implied a 4 mm impairment in quality of life (95% CI 0.2-0.5).

Table 3. Drugs administered to frail patients with cancer and breakthrough pain for the treatment of chronic pain.

Active ingredient for chronic pain	Administration route	Daily frequency	Daily dose	
			Nº	Mean
Aceclofenac	Oral	Every 12 h	1	200 mg
Amitriptyline	Oral	Every 24 h	1	10 mg
Baclofen	Oral	Every 24 h	1	10 mg
Butylscopolamine	Parenteral	Every 6 h	1	40 mg
Buprenorphine	Topical/Transdermal	Every 72 h	2	36.8 µg
Clonazepam	Oral	Every 8 h	1	1.5 mg
Dexketoprofen	Oral	Every 12 h	1	50 mg
		Every 8 h	3	75 mg
	Parenteral	Every 8 h	1	75 mg
Dexamethasone	Oral	Every 24 h	11	3.4 mg
		Every 12 h	1	8 mg
		Every 8 h	1	12 mg
	Parenteral	Every 24 h	1	12 mg
		Every 8 h	2	12 mg
Duloxetine	Oral	Every 24 h	2	45 mg
Eslicarbazepine	Oral	Every 24 h	1	800 mg
Etoricoxib	Oral	Every 24 h	2	90 mg
Fentanyl	Respiratory/inhaled	Every 8 h	1	300 µg
		Every 3 h	1	500 µg
	Topical/Transdermal	Every 24 h	37	65.5 µg
		On demand	10	56.3 µg
		Every 48 h	1	50 µg
		Every 72 h	64	14.6 µg
Gabapentin	Oral	Every 24 h	1	600 mg
		Every 8 h	7	1,200 mg
Ibuprofen	Oral	Every 8 h	1	1,800 mg
Lacosamide	Oral	Every 12 h	1	200 mg
Methadone	Oral	Every 8 h	1	15 mg
Metamizole	Oral	Every 12 h	1	0.8 mg
		Every 8 h	18	1,826 mg
	Parenteral	Every 8 h	3	6 mg

Morphine	Oral	Every 24 h	2	65 mg
		Every 12 h	31	85.5 mg
		Every 8 h	5	486 mg
	Parenteral	Every 24 h	6	108.5 mg
		On demand	2	55 mg
Naproxen	Oral	Every 12 h	2	700 mg
Oxycodone	Oral	Every 12 h	5	68 mg
		Every 8 h	2	22.5 mg
		Every 6 h	1	20 mg
Oxycodone/Naloxone	Oral	Every 24 h	2	6.3 mg
		Every 12 h	12	42.5 mg
		Every 8 h	1	90 mg
Paracetamol	Oral	Every 8 h	20	2,797 mg
		Every 3 h	1	5,000 mg
	Parenteral	Every 8 h	5	2,400 mg
Paracetamol/codeine	Oral	Every 8 h	1	3,000 mg
Prednisone	Oral	Every 24 h	1	5 mg
Pregabalin	Oral	Every 24 h	4	43.8 mg
		Every 12 h	10	160 mg
		Every 8 h	1	75 mg
Tapentadol	Oral	Every 24 h	2	150 mg
		Every 12 h	10	155 mg
Tramadol	Oral	Every 12 h	1	150 mg
		Every 8 h	6	156 mg
		Every 6 h	1	400 mg
	Parenteral	Every 12 h	1	200 mg
Tramadol/paracetamol	Oral	Every 8 h	1	225 mg

Note: a. N: number of patients with the treatment, patients received one or more treatments.

Table 4. Drugs administered to frail patients with cancer for the treatment of breakthrough pain.

Active ingredient for breakthrough pain	Route	Unit dose			Unit dose in the Mercadante study [26]
		Nº	Mean	(95% CI)	Mean dose (SD)
Dexketoprofen	Oral	2	25 mg	-	-
Duloxetine	Oral	1	30 mg	-	-
Fentanyl	Oral	8	190 µg	(71.1-309)	234.6 (183.1) µg
	Sublingual	81	161.7 µg	(139-184)	231.4 (171.1) µg
	Nasal with pectin	59	155.9 µg	(130-182)	167.7 (125.7) µg
	Nasal without pectin	1	100 µg	-	100 (50.7) µg
	Transdermal	3	29 µg	(19-77)	-
Ibuprofen	Oral	1	400 mg	-	-
Metamizole	Oral	5	231.2 mg	(159-621)	-
	Parenteral	4	2 mg	(2-2)	-
Metamizole/Scopolamine	Parenteral	1	2,500/20 mg	-	-
Morphine	Oral	12	11.7 mg	(8-15)	11.8 (8.2) mg
	Parenteral	17	10.7 mg	(7-14)	8.2 (6.1) mg
Oxycodone	Oral	6	9.2 mg	(2-20)	-
Oxycodone/Naloxone	Oral	1	10 mg	-	-
Paracetamol	Oral	6	683.3 mg	(288-1,078)	-
	Parenteral	3	1,000 mg	(1,000-1,000)	-
Tramadol	Oral	6	54.2 mg	(44-65)	-

Discussion

This observational study provides, for the first time, an overview of the clinical, social-health, and quality of life characteristics of frail patients with cancer, chronic pain and BTcP together with their management in real life in Spain. It also evaluated the analgesic treatment received by patients for chronic pain and BTcP and whether their choice was conditioned by the patients' own frailty status.

Characteristics of BTcP in frail cancer patients have not been described previously. However, Mercadante, et al. published in 2018 a large study in 4,016 patients with cancer and BTcP [26]. A comparison between our study and the latest encountered interesting results. Frail patients reported significantly greater mean number of BTcP episodes per day than those in the reference study, 3.8 (95% CI 3.3-4.3) versus 2.4 (SD 1.4). The duration of BTcP episodes reported by frail patients was shorter, 34.6 minutes (95% CI 28.8-40.3) versus 43.3 minutes (SD 36.9). The onset of BTcP was sudden (short onset) in 43.2% of our frail patients, while this type of onset was seen in 68.9% of patients in the reference study. Even though the assessment of the BTcP intensity was measured differently in both studies, we observed severe or unbearable BTcP in 17.1% of our frail patients, and Mercadante, et al. reported a mean intensity of 7.5 over 10 points [26]. Furthermore, in another study conducted in 1,000 cancer patients, Davies, et al reported severe BTcP in 62.4% of patients. Similar results were observed among frail patients (62.6%) in our study [27].

Predictable BTcP was found in 35.1% of our frail patients, alike data (30.5%) described by Mercadante, et al. [26]. Difference on BTP mechanism was observed in both populations. Neuropathic pain was more frequently observed among our frail patients (16.7% vs. 8.1%), while mixed pain was more common in those cancer patients of the referred study (71.8%, vs. 31.1%) [26].

The higher the number of BTcP episodes, the shorter the duration and the more gradual onset seen in frail patients. A pathophysiological process related to frailty status might underly these observations since a greater frequency of BTcP episodes has been reported in patients with worse performance status [27]. Interestingly, the performance status of patients observed in both studies was similar, 63.2 (95% CI 61-65.4) versus 61.8 (SD 18.73) [26].

Among our frail patients, 79.7% of them were in active treatment for cancer, likewise 78% of patients in the reference study. This situation should be considered, since receiving this type of treatment could condition the administration of other treatments, such as, for example, for background pain and BTcP [26].

Drugs for the treatment of BTcP and chronic pain administrated to frail patients did not substantially differ on their doses and the frequency of administration, to the standard treatment for chronic pain (Table 3). Regarding BTcP treatment, in our study, 83.8% of frail patients with cancer received opioid treatment for BTcP control, just as patients with cancer included in other studies [26,27]. Transmucosal immediate release fentanyl, treatment of choice for BTcP in cancer patients was administered to 68.5% of frail patients with cancer [14]. The doses of the treatments were within the range recommended in their prescribing information (Table 4). On the other hand, our attention was caught by the fact that 10 patients used drugs that are not usually indicated for BTcP but for basal pain therapy in standard practice, such as dexketoprofen, ibuprofen, metamizole or paracetamol, frequently complementary to the opioids administrated for the background chronic pain. In the Table 4 the number of administrations for such treatments was 28, but only 6 patients received only these drugs.

We observed BTcP interference with daily activities in 93.7% of frail patients (Figure 1) while Mercadante, et al. reported that in 86% of their patients [26]. Furthermore, they found that age, Karnofsky, BTcP severity, short onset, and longer duration of breakthrough pain significantly interfered with daily activities of cancer patients. In our study, we were able to relate a poorer QoL score (EQ-VAS) to a worse Karnofsky score in frail patients, already described in different studies [26,28,29]. In addition, our study found a significant association between QoL and social exclusion in frail patients with cancer but due to the cross-sectional design we cannot know which one was the first event.

The EuroQoL-5D-5L questionnaire conducted in healthy Spanish population revealed that the 65–74-year-old age group reported problems with mobility (29.3%), self-care (10.4%), daily activities (19.1%), pain (43%), and anxiety or depression (20%) [30]. According to our study, frail cancer patients with BTcP seem to be more impaired, as 93.2% of frail patients experienced greater mobility problems, 74.2% self-care problems, 93.7% interference with daily activities, 98.2% pain, and 81.4% anxiety or depression (Figure 1). Meanwhile, data observed in a review of 32 studies in patients with cancer shows impairment rates for mobility ranging from 2-60%, self-care 2-50%, daily activities 15-100%, pain 12-80%, and anxiety or depression 13%-100% i.e.there is greater deterioration in frail patients in our study in three of the five dimensions [31].

The mean EQ-VAS score, as a measure of patient-perceived quality of life, was 51.3 mm (95% CI 48.5-54) in frail patients with BTcP in our study, values well below those seen in the general Spanish population of the same age group, 69 mm (Figure 2) [23]. In addition, this value is much more affected than in cancer patients, analysed in a review of 32 studies, who presented a value of 68.6 mm [31].

It is known that the occurrence of BTcP has a significant impact on patient quality of life [32-33]. In the case of patients in our study, the low quality of life levels observed could be due to both BTP and frailty status, or to the interaction of both factors.

In Spain, the prevalence of frailty has been studied in six cohort studies, ranging from 2.4% to 27.3% in patients over 65 years of age [24]. However, in the setting of our study, conducted mainly in medical oncology units and in some pain and geriatric units, the prevalence of frailty is much higher, so the results of this study are relevant to standard clinical practice in these units [7,10,13].

This study has several limitations inherent to the cross-sectional observational design, which prevents causal relationships from being established. Patients were classified as frail using the Frail scale following national recommendations, so frail patients could be classified differently from other classification scales not based on the Fried criteria [1,19,24]. As this is a cross-sectional study, patients were included at different follow-up times after the onset of BTcP. For this reason, we could not analyse which were the first treatments for BTcP in frail patients or their doses, which could differ at the start, and then be adjusted. Other treatments for patients with cancer such radiotherapy and brachytherapy play an important role in this setting of patients for the treatment of pain with many advantages in elderly and frail patients, but not collected in our study that was focused on pharmacological treatment [11,12].

Conclusion

This study concluded that some characteristics of BTP in frail patients with cancer differ from those reported in other studies in patients with cancer. In addition, it has been seen that the treatments used for both chronic pain and BTcP in frail patients are like those commonly prescribed in non-frail patients. QoL in frail patients has also been found to be severely impaired as compared to the reference population of patients with cancer and was related to a poorer performance status of the patient and poorer social-familial status. This relationship between frailty and impaired quality of life highlights the importance of the frailty assessment in all patients with BTcP.

Declarations

Ethics approval and consent to participate

The study was approved by the Medicinal Product Research Ethics Committee of HM Hospitales de Madrid (2-April-2018; Minutes 132).

Written informed consent was obtained from all patients. The study

protocol was in accordance with the ethical standards described in the Declaration of Helsinki, and all participants' privacy rights were respected.

Consent for publication

Not applicable.

Availability of data and material

The study data is available upon reasonable request to the corresponding author.

Competing interest

GSG, JPC and SFS received payment from Kyowa Kirin Farmacéutica, S.L. for their participation in the design and coordination of the study. AJJL, ACA and IHG are employees at Kyowa Kirin Farmacéutica, S.L. BSL was contracted by Kyowa Kirin Farmacéutica, S.L. for project management. The rest of the authors declare that they have no conflicts of interest with the study results.

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Author's contributions

GSG, JPC, SFS, contributed to the study concepts, the study design, data acquisition and manuscript review. AJJL, ACA and IHG contributed to the study concepts and design and the manuscript review. BSL contributed to the study design, quality control of data, statistical analysis, and manuscript preparation.

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