

Evaluation of fatigue in patients with pancreatic cancer receiving chemotherapy treatment: a cross-sectional observational study

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Abstract. *Background and aim of the work:* Cancer-related fatigue (CRF) is one of the most common symptoms experienced by cancer patients (CPs) and negatively affects quality of life. Although CRF is frequently experienced, it is often underreported, underdiagnosed and undertreated. The objectives of this study were to evaluate the level of fatigue in patients with pancreatic cancer undergoing chemotherapy and to analyse its correlation with patients' demographic and clinical variables. *Methods:* A cross-sectional observational study was implemented in the Oncology Day Hospital of a Northern Italian hospital. A sample of 48 patients receiving chemotherapy were evaluated through the Brief Fatigue Inventory Italian version (BFI-I) between 1 May and 12 October 2016. Data were statistically analysed. *Results:* Most of our patients (94%) experienced fatigue. Women as well as patients with an age ≥ 65 years reported more fatigue. Anemia, pain and a weight loss of over 16 kg in the last 6 months were significantly related to the perception of fatigue. Regarding life habits, smoking was related to high global score of BFI-I. *Conclusions:* In accordance with literature, our study suggests that fatigue is a frequent symptom influenced by many constitutional, clinical and environmental factors. Our results highlight the need for an early and regular evaluation of fatigue among cancer patients, in order to implement all those pharmacological and non-pharmacological interventions with proven efficacy in attenuating this symptom.

Key words: pancreatic neoplasm, pancreatic cancer, fatigue, chemotherapy, Brief Fatigue Inventory

Background and aim

Pancreatic cancer is the seventh leading cause of cancer death (1) and, in 2017, pancreatic cancer deaths exceeded breast cancer deaths (2). In the United States, approximately 50,000 individuals are diagnosed with exocrine pancreatic cancer each year with fatal outcome for most of them (3). AIOM (Italian Association

of Medical Oncology) show that 12,500 new cases of pancreatic cancer occurred in 2015, which represented about 3% of all incident cancers (4). In Italy, pancreatic carcinoma is one of the top five causes of cancer death in males and the fourth place in females, with greater incidence in the North of Italy (5). Pancreatic ductal adenocarcinoma has the lowest five-year survival rate as compared to others cancers (6).

In literature there is no univocal definition of Cancer-Related Fatigue (CRF), however the most recurrent is that proposed by the National Comprehensive Cancer Network (NCCN) (7), which defines it as a persistent distress, a subjective feeling of physical exhaustion, related to cancer or to its treatments. The fatigue experienced by cancer patients is totally disproportionate in comparison with the physical activity undertaken, highly impacts on the performance of daily normal activities, significantly worsening the quality of life (7, 8). Fatigue can exacerbate other symptoms and negatively influence mood (9). It is different from normal fatigue since it does not find relief with rest and may persist for months or even years after the completion of chemotherapy treatment (10). CRF has been reported as the most common and, for many people, the most stressful symptom related to cancer disease by the NCCN (7). In accordance with most authors, fatigue is one of the most common symptoms related to cancer, affecting patients in many domains such as physical, emotional, cognitive and behavioral spheres. It includes subjective feeling and objective symptoms that may persist from the diagnosis of cancer to the end of life (11-13). CRF has been hypothesized as the result of a complex interaction among multiple factors related to both the disease and the side effects of the treatments. Nevertheless, it could also be influenced by other clinical or environmental factors such as malnutrition, sleep disorders, pain, anxiety and depression (14). CRF may be present for a short period or persist for years after the end of treatment and therefore it can be classified as acute or chronic. In acute fatigue, the recovery mechanisms maintain all their effectiveness, allowing the body to regain its strength and to reintegrate the consumed energy through an adequate period of rest; in chronic fatigue, the person cannot recover an adequate energy level even after prolonged rest period and/or suitable supportive therapies (13-16). The prevalence of fatigue in cancer patients during chemotherapy treatment ranges from 25% to 100% (11, 17). The different ranges reported in literature can be related to the study samples, the treatments received and the symptom evaluation methods. It can also be influenced by other concomitant pathological conditions, such as anemia and depression, conditions often present in patients with various types of cancer (18).

Patients describe fatigue as a sense of chronic tiredness, overwhelming depression, oppressive exhaustion and loss of life energy. The terms most commonly used to describe this condition are: listlessness, weakness, sluggishness, apathy, laziness, abatement, exhaustion, etc. (15). Patients are unable to concentrate and often present other associated depressive symptoms (19).

In particular, the symptoms of fatigue most commonly reported by patients are related to many domains:

- physical level: impossible to lead a normal life and to carry out usual activities; feeling of tiredness corresponds to an increased need for sleep and rest;
- psychological level: reduction of motivation and interest, feelings of sadness, frustration, irritability, loss of the ability to appreciate life and intimacy with partner, difficulty in concentrating;
- social level: loss of interest in relationships with friends and colleagues;
- professional level: difficulty in keeping a job, need to change work, request to reduce work time (20).

Commonly, fatigue is undertreated although it can represent the most debilitating symptoms with negative impact on patient and family quality of life (15). Recent research on the biological mechanisms that underlie CRF has focused on inflammation as a key pathway (21). The associations between CRF and alterations in the immune and neuroendocrine system has been documented. The same association has been observed in the Interferon-alpha therapy which predisposes to the development of fatigue (22). In particular, changes in leukocyte subsets, dysregulated cortisol rhythm, reduced glucocorticoid receptor sensitivity, and alterations in the autonomic nervous system have been correlated with the development of CRF. These systems are closely linked to inflammation and may influence fatigue by initiating or maintaining elevated inflammatory activity (21).

The management of CRF is difficult due to its uncertain and complex etiology as well as its subjective characteristics (23). The guidelines developed by the NCCN recommend early treatment of all conditions that may contribute to the onset of fatigue, which include pain, emotional disturbances, sleep disorders,

anemia, malnutrition, poor physical activity and comorbidities for all patients in active treatment, even in the long term, and at the end of life. Recommended treatments include educational and psychological interventions as well as strategies for fatigue and energy management, distraction techniques, pharmacological and non-pharmacological interventions (7).

Over the last years, the efficacy of different pharmacological approaches has been tested: antidepressants, corticosteroids, drugs for anemia and psychostimulants (24, 25). Among these drugs, only psychostimulants have been shown to improve CRF (25). Non-pharmacological interventions have the advantage of coping with multiple symptoms without inducing any side effect, which makes them particularly acceptable for cancer patients. In the last decade, research on the efficacy of non-pharmacological treatments has been increasingly implemented, with particularly promising results as evidenced by randomized controlled trials (RCT) related to the effectiveness of physical exercise (26), psycho-educational approaches (27) and energy conservation (28). A review of 57 RCTs that tested the efficacy of non-pharmacological interventions concluded that exercise and psycho-social interventions led to a similar reduction in CRF (29).

Although CRF is frequently experienced by cancer patients it is often under-recognized by health-care professionals and consequently under-treated (9).

Aim

The objective of this study is to evaluate the level of fatigue in patients with pancreatic cancer treated in an oncology day hospital and to analyze its correlation with patients' demographic variables, clinical conditions, life habits and chemotherapies.

Methods

Study design

To analyze the level of fatigue in patients with pancreatic cancer treated with chemotherapy, a cross-sectional observational study was conducted through

the administration of a questionnaire, during the period between May 1 and October 12, 2016.

Participants

In this study, we included all patients aged 18 years or over, suffered from a pancreatic cancer and treated in the Oncologic Day Hospital of a Northern Italian medical center, during the observation period of this study, with the following chemotherapy treatments: gemcitabine, gem+abraxane or folfirinox. All patients enrolled (n=48) were able to understand the questionnaire, to complete it independently and to give us their informed written consent for participation in the study, following our explanation of its purpose and design.

We excluded patients who were minors, affected by other types of cancer, treated with other chemotherapies and/or not able to give us their informed written consent due to intellectual disability, cognitive deterioration or no knowledge of Italian language.

Data were anonymously collected according to the current privacy regulations.

Instruments

To evaluate the fatigue level, we administered the Brief Fatigue Inventory (BFI), a simple scale validated in several languages (30-35), including Italian (BFI-I) (36). The validation studies of this instrument showed good acceptance by the subjects and good internal consistency (30), also in the validation studies of the Italian version (Cronbach's $\alpha=0.94$) (36).

The BFI is composed of 9 items aimed at assessing the severity and impact of fatigue on daily functioning in patients with cancer or treatment-related fatigue in the previous 24 hours. Three items ask patients to rate the severity of their fatigue at the moment of questionnaire administration at its "usual" and at its "worst" level during the previous 24 hrs using a 0-10 Likert scale, where 0 corresponds to the description "no fatigue" and 10 with "fatigue as bad as you can imagine".

Six items focused on how much fatigue had interfered with aspects of the patient's life during the previous 24 hours. Interference items include general activity, mood, walking ability, normal work (which in-

cludes both work outside the home and daily chores), relations with other people, and enjoyment of life. These items are measured on a 0-10 Likert scale where 0 means “does not interferes” and 10 “completely interferes”. A global BFI score is calculated as the mean of all nine questions, and higher scores correspond to more severe fatigue. Patients who could answer at least five of the questions were included. The level of fatigue can be divided into “mild” (1-3), “moderate” (4-6) and “severe” (7-10) in accordance with literature (30, 37-39).

Statistical analyses

Descriptive statistical analyses were performed: means and standard deviations for continuous data, and percentages for categorical data, while t-test and ANOVA were applied to identify significant differences among continuous data. Categorical variables were calculated through the contingency tables and the differences were detected through the Chi-square. We analyzed both the total mean score of BIF-I as a continuous variable and the four levels of questionnaire score as categorical variables in order to apply a sort of sensitivity analysis, in accordance with other studies (34, 36, 38). Cronbach's Alfa allowed us to determine the internal consistency of the questionnaire items. The statistical analysis was performed using the SPSS software.

Results

Our sample consisted of 48 patients: 29 males (60.4%) and 19 females (39.6%). 62.6% of them were ≥ 65 years old. The most frequent comorbidity was represented by cardiovascular diseases (45.8%); smoking was the most frequent life habit (22.9%). Most of the interviewed patients were treated with gem-abraxane (85.4%) (Table 1).

The internal consistency of the scale was very good: Cronbach $\alpha=0.905$.

We divided the fatigue into four level groups according to the BFI-I score: absent (score=0), mild (score range=1-3), moderate (score range=4-6) and severe (score range=7-10). 94% of patients experienced

Table 1. Constitutional and clinical variables of our sample

Variables	N	%
Gender		
Females	19	39.6
Males	29	60.4
Age (years)		
18-50	9	18.7
51-64	9	18.7
≥ 65	30	62.6
Comorbidities		
Cardiovascular	22	45.8
Endocrine	6	12.5
Neurological	1	2.1
Musculoskeletal	2	4.2
Urogynecological	3	6.3
Infectious	3	6.3
Unknown	7	14.5
No comorbidity	4	8.3
Life habits and correlated disorders		
Smoking	11	22.9
Substance abuse	1	2.1
Eating disorders	5	10.4
Normal	30	62.5
Unknown	1	2.1
Chemotherapies		
Gem-Abraxane	41	85.4
Gemcitabina	6	12.5
Folfirinox	1	2.1

fatigue according to BFI-I score, mostly mild (n=26) and moderate (n=18).

As shown in Table 2, many constitutional and clinical variables are statistically significantly correlated with the four level groups of fatigue: females ($\chi^2=8.723$, $p=.033$), patients with age ≥ 65 years ($\chi^2=14.521$, $p=.024$), patients affected by cardiovascular comorbid diseases ($\chi^2=62.262$, $p<.001$), patients with smoking habit ($\chi^2=31.077$, $p=.002$) presented statistically significant higher levels of fatigue. Both mild and severe anemia were frequently associated with fatigue whereas only a weight decreased from 6 to 15 kg in the last 3 months was associated with severe fatigue. The other variables selected, chemotherapy drugs, depression and pain, did not present any statistically significant correlation with fatigue (Table 2).

Table 2. The constitutional and clinical variables correlated with the BFI-I score groups

Variables	Absence fatigue n=3	Mild fatigue n=26	Moderate fatigue n=18	Severe fatigue n=1	Total n=48	Statistical test Probability
Gender, n (%)						
Females	--	7 (26.9)	11 (61.1)	1 (100)	19 (39.6)	$\chi^2=8.723$ p=0.033
Males	3 (100)	19 (73.1)	7 (38.9)	--	29 (60.4)	
Age (years), n (%)						
18-50	3 (100)	4 (15.4)	2 (11.1)	--	9 (18.8)	$\chi^2=14.521$ p=0.024
51-64	--	5 (19.2)	4 (22.2)	--	9 (18.8)	
≥65	--	17 (65.4)	12 (66.7)	1 (100)	30 (62.5)	
Comorbidities, n (%)						
Cardiovascular	--	15 (57.7)	6 (33.3)	1 (100)	22 (45.8)	$\chi^2=62.262$ p<0.001
Endocrine	--	4 (15.4)	2 (11.1)	--	6 (12.5)	
Neurological	--	1 (3.8)	--	--	1 (2.1)	
Musculoskeletal	--	--	2 (11.1)	--	2 (4.2)	
Urogynecological	3 (100)	--	--	--	3 (6.3)	
Infectious	--	1 (3.8)	2 (11.1)	--	3 (6.3)	
Unknown	--	--	4 (22.2)	--	4 (8.3)	
No comorbidity	--	5 (19.2)	2 (11.1)	--	7 (14.6)	
Life habits and correlated disorders, n (%)						
Smoking	--	6 (23.1)	5 (27.8)	--	11 (22.9)	$\chi^2=31.077$ p=0.002
Substanceabuse	--	1 (3.8)	--	--	1 (2.1)	
Eatingdisorders	3 (100)	2 (7.7)	--	--	5 (10.4)	
Normal	--	17 (65.4)	12 (66.7)	1 (100)	30 (62.5)	
Unknown	--	--	1 (5.6)	--	1 (2.1)	
Chemotherapies, n (%)						
Gem-Abraxane	3 (100)	20 (76.9)	17 (94.4)	1 (100)	41 (85.4)	$\chi^2=3.474$ p=0.747
Gemcitabina	--	5 (19.2)	1 (5.6)	--	6 (12.5)	
Folfirinox	--	1 (3.8)	--	--	1 (2.1)	
Pain, n (%)						
Absent	3 (100)	18 (69.2)	6 (33.3)	1 (100)	28 (58.3)	$\chi^2=8.856$ p=0.182
Mild	--	7 (26.9)	11 (61.1)	--	18 (37.5)	
Severe	--	1 (3.8)	1 (5.6)	--	2 (4.2)	
Weight, n (%)						
Unchanged	3 (100)	16 (61.5)	3 (16.7)	--	22 (45.8)	$\chi^2=30.374$ p=0.011
Increased	--	3 (11.5)	4 (22.2)	--	7 (14.6)	
Decreased from 1 to 15 kg in the previous month	--	1 (3.8)	3 (16.7)	--	4 (8.3)	
Decreased from 6 to 15 kg in the previous 3 months	--	6 (23.1)	5 (27.8)	--	11 (22.9)	
Decreased by over 16 kg in the previous 6 months	--	--	2 (11.1)	1 (100)	3 (6.3)	
Unknown	--	--	1 (5.6)	--	1 (2.1)	
Anemia, n (%)						
Haemoglobin ≥ 11g/dl	3 (100)	16 (61.5)	5 (27.8)	--	24 (50)	$\chi^2=8.940$ p=0.030
Haemoglobin 8-10g/dl	--	10 (38.5)	13 (72.2)	1 (100)	24 (50)	
Depressive disorders, n (%)						
Yes	--	4 (15.4)	2 (11.1)	--	6 (12.5)	$\chi^2=2.478$ p=0.871
No	3 (100)	22 (84.6)	15 (83.3)	1 (100)	41 (85.4)	
Unknown	--	--	1 (5.6)	--	1 (2.1)	

The global score of BFI-I showed higher values among the patients aged from 51 to 64 ($M=3.02$, $SD=1.66$) and ≥ 65 ($M=2.91$, $SD=1.92$), with a statistically significant difference between the two genders: males had a mean score of 2.18, $SD = 1.66$ and females one of 3.71, $SD=1.78$ ($t=3.043$, $p=.004$).

As shown in Table 3, the mean scores of BFI-I statistically significantly differed among respondents regarding the following variables: comorbidities ($F=2.782$, $p=.019$), life habits ($F=2.98$, $p=.029$), pain ($F=4.710$, $p=.014$), weight ($F=4.419$, $p=.003$) and anemia ($F=12.835$, $p=.001$). In particular, the BFI-I scores showed high level of fatigue among patients affected by musculoskeletal comorbidities (4.2%), smoking

population (22.9%), patients with mild pain (37.5%), patients who decreased weight by over 16 kg in the last 6 months (6.3%), patients with Hb values ranged between 8-10 g/dL (50% of our sample) (Table 3).

The impact of fatigue on all daily activities was prevalently absent or mild, with severe influence only on two dimensions, mood and enjoyment of life, as shown in Figure 1.

Discussion

The findings of our study revealed that 94% of our participants experienced CRF during the course of

Table 3. The constitutional and clinical variables correlated with mean global score of BFI-I

Variables	BFI-I Mean (\pm SD)	Confidence interval 95%	Statistical test Probability
Comorbidities			
Cardiovascular	2.66 (1.95)	1.80-3.53	
Endocrine	2.57 (1.22)	1.28-3.85	
Neurological	0.55 (0.0)	-	F=2.782
Musculoskeletal	5.16 (1.17)	-5.42-15.75	p=0.019
Urogynecological	0.07 (0.12)	-0.24-0.39	
Infectious	3.81 (1.32)	0.52-7.10	
Unknown	2.77 (1.43)	1.44-4.10	
No comorbidity	4.44 (1.18)	2.55-6.33	
Life habits and correlated disorders			
Smoking	3.29 (1.33)	2.39-4.18	
Substance abuse	3.00 (0.0)	-	F=2.986
Eating disorders	0.68 (0.95)	-0.49-1.86	p=0.029
Normal	2.84 (1.90)	2.12-3.55	
Unknown	6.00 (0.0)	-	
Pain			
Absent	2.15 (1.83)	1.44-2.87	F=4.710
Mild	3.75 (1.51)	3.00-4.51	p=0.014
Severe	2.88 (2.04)	-15.46-21.24	
Weight			
Unchanged	1.89 (1.44)	1.26-2.53	
Increased	3.04 (2.10)	1.10-4.99	F=4.419
Decreased from 1 to 15 kg in the previous month	3.63 (1.88)	0.64-6.63	p=0.003
Decreased from 6 to 15 kg in the previous 3 months	3.03 (1.45)	2.05-4.00	
Decreased by over 16 kg in the previous 6 months	5.62 (1.50)	1.88-9.37	
Unknown	6.00 (0.0)	-	
Anemia			
Haemoglobin ≥ 11 g/dl	1.93 (1.58)	1.26-2.59	F=12.835
Haemoglobin 8-10 g/dl	3.64 (1.73)	2.91-4.38	p=0.001

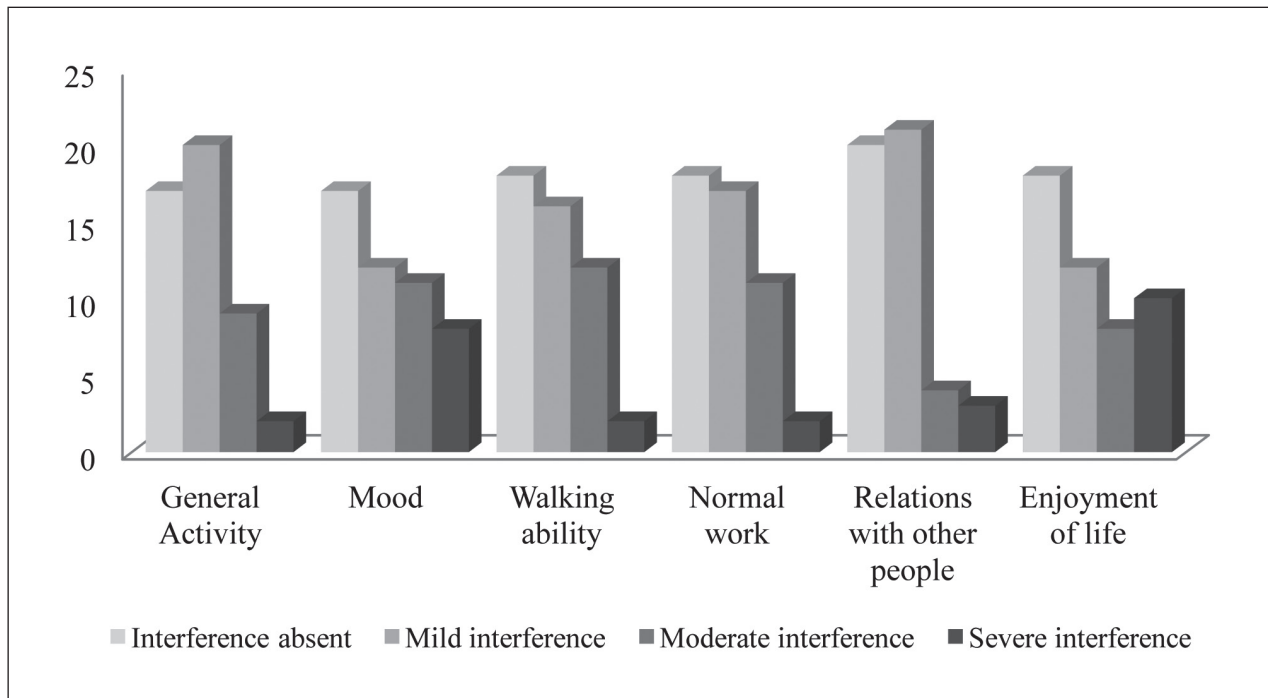


Figure 1. The impact of fatigue on daily activities, mood and relationships

treatment. This result is in line with the highest prevalence rates of fatigue reported by other studies, which ranged CRF between 25 to 100% during the course of chemotherapies (11, 17, 39-42). The prevalent constitutional factors associated with fatigue were represented by female gender and older age, in accordance with recent research (17, 42-46). Among clinical variables, anemia, loss of weight and pain were associated with the highest scores of BFI-I in our study. This result overlaps literature and clinical experience concerning the close relationship between fatigue and physical impairment induced by both cancer and chemotherapies. In particular, low hemoglobin levels are associated with greater fatigue in cancer patients (9, 18, 39, 40, 42, 47, 48) as well as pain symptoms in accordance with most reports (14, 17, 40, 49). Weight loss is a significant symptom in this type of cancer, often associated with neoplastic cachexia. Our analysis shows that a weight loss >16 kg in the previous six months is related to higher mean score of fatigue. As highlighted by other authors, an important weight loss can be considered a factor that affects the perception of fatigue

in many patients (50). From our analysis, we can infer that fatigue can be a consequence of both chemotherapies and cancer but not of other comorbidities, since we found higher levels of fatigue in patients who did not have any concomitant disease in comparison with others who did. We have to put in evidence that, among the comorbidities reported by our patients, the ones most correlated with fatigue were cardiovascular and musculoskeletal diseases, a result that is in line with another study (40). Smoking has also proved to be a factor that affects the perception of fatigue: smoking patients reported higher mean score of fatigue than non-smokers in our study as in others (17, 51). Although the treatment with Gemcitabine+Abiraterone, to date the elective treatment for metastatic pancreatic cancer, has been strongly associated with fatigue as a prevalent side effect (52), we did not find any significant correlation between this treatment and fatigue.

The BFI-I has shown to be a questionnaire easy to administer and simply to answer. The internal consistency of the scale was very good, similar to the value obtained in the BFI Italian validation study (36).

Conclusions

We observe that the majority of our participants experienced mild and moderate fatigue. Several factors influenced the perception of fatigue: gender, pain, important weight loss, anemia and smoking. These data highlight how fatigue is frequently present as a consequence of cancer and its treatments, placing importance on CRF diagnosis and recognition to implement early on all those pharmacological and non-pharmacological interventions with proven efficacy in reducing it.

This study has many limitations, in particular its limited sample size, insufficient to draw definitive conclusions. Another limitation is represented by the period of BFI-I administration from May to October, concomitant with the warmest part of the year, which can exacerbate the perception of fatigue. In addition, other relevant risk factors for fatigue as reported in literature (41), physical activity, sleep disorders and clinical stage of cancer, were not investigated.

We can conclude by suggesting that fatigue is a multidimensional symptom which can be influenced by a variety of constitutional and clinical factors. It represents one of the most prevalent and debilitating conditions observed in cancer, for which we can suggest a holistic therapeutic approach, based on the active involvement of the person in care and treatment for fostering clinical recovery with respect for patient dignity (53, 54). Education about fatigue should be offered in a tailored way to all patients with cancer, in particular to those beginning potential fatigue-inducing treatments (7, 9). Moreover, professionals should give their psychological support to patients, reassuring them that fatigue can be overcome or reduced concomitantly with the treatment implementation. In this regard, only an empathic attitude can help professionals to better understand the level of fatigue suffered from patients in order to help them to face their fear of disease progression.

Further studies focused on fatigue and its multi-factor aspects are recommended in patients with pancreatic cancer who undergo chemotherapy.

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