Exploring the contribution of psychosocial factors to fatigue in patients with advanced incurable cancer

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Abstract

Objective: Fatigue is the most frequently occurring and distressing symptom in patients with advanced cancer, caused by multiple factors. Neither a specific histological diagnosis of malignancy nor the type of anticancer treatment seem to be strongly related to fatigue, which support the idea that other factors may play a role. This study investigated to what extent the model of fatigue-perpetuating factors that is known for cancer survivors was applicable for patients with advanced cancer.

Methods: Patients on active treatment for various incurable cancers were asked to complete the Checklist Individual Strength, subscale fatigue severity and physical activity, the Acceptance scale of the Illness Cognition Questionnaire, the Hospital Anxiety and Depression Scale, the Fatigue Catastrophizing Scale, the Symptom Checklist subscale sleep, and the van Sonderen Social Support List-Discrepancies.

Results: The questionnaires were filled in by 137 patients. Inappropriate coping, fear of progression, fatigue catastrophizing, discrepancies in social support, depressive mood, self reported physical activity, and sleeping problems were all related to fatigue severity in univariate analyses, of which the latter two were significant in a multivariate linear regression analysis.

Conclusion: This study tested fatigue-perpetuating factors known to be of relevance in cancer survivors, for their relation with fatigue severity in palliative patients. We demonstrated that these factors were also relevant for patients on palliative treatment. On the basis of our results, we suggest clinicians confronted with palliative patients with serious fatigue to address sleeping problems and promote physical activity. In case of persistent fatigue, personalized cognitive behavioral therapy can be considered. Copyright © 2014 John Wiley & Sons, Ltd.

Background

Fatigue is one of the most frequently occurring symptoms in patients with advanced, incurable cancer, with reported prevalence rates from 33% to 99% [1–11]. Additionally, patients describe fatigue as one of the most distressing symptoms, with a profound effect on their daily quality of life [11,12]. Fatigue in patients with advanced incurable cancer probably increases with subsequent treatment lines, and the severity seems to be associated with some types of cancer and treatment-related symptoms [12–14]. However, in another study, based on the data of this group, we did not find a relation between demographic and clinical characteristics such as tumor type or treatment modality and fatigue severity [14].

In cancer survivors, a distinction is made between the etiology of precipitating factors and fatigue-perpetuating factors [15]. When cancer patients receive treatment, the disease itself and its treatment are considered to be fatigue-precipitating factors. But when treatment is finished, these factors are no longer present and other factors

maintain the fatigue. In cancer survivors, there is evidence that fatigue is perpetuated by several behavioral and psychosocial factors [16]. These factors are poor or inappropriate coping skills, a heightened fear of disease recurrence, dysfunctional fatigue-related cognitions, dysregulatory sleep–wake cycles, dysregulatory activity patterns, insufficient social support, and negative interactions. This model of perpetuating factors was used as the basis for cognitive behavioral therapy for postcancer fatigue, which was tested in a randomized controlled trial and proved to be successful [16,17]. This individually tailored cognitive behavioral therapy intervention in survivors focuses, besides avoiding deconditioning, on elements such as coping with the consequences of having cancer, changing dysfunctional cognitions about fatigue, and restoring disturbed sleep–wake rhythm. After this successful trajectory in the curative setting, we wanted to investigate if such a model based on perpetuating factors of fatigue would also be applicable in the palliative setting.

Until now, no effective strategies or interventions have been developed to reduce fatigue in patients with

advanced incurable cancer [18]. We even do not know which factors are relevant for fatigue in palliative cancer patients. In palliative patients, the disease and treatment remain present over time, which is not the case in survivors. Nevertheless, we can learn from the existing knowledge about fatigue in cancer survivors. On the basis of the model of fatigue-perpetuating factors in cancer survivors, we explored if the aforementioned factors also contributed to fatigue severity in patients with advanced incurable cancer. The following rationales for each of these factors can be given.

Poor or inappropriate coping skills: From the curative setting, we know that poor or inappropriate coping skills can have a negative impact on the quality of life and on the severity of fatigue [16,19]. In contrast to the curative setting in which patients can remain occupied with the period of cancer treatment, which lays in the past, in the palliative setting, the cancer is a fact that will remain. We assume that poor or inappropriate coping with having cancer might be of influence on fatigue.

A heightened fear of disease progression: In the palliative phase, the disease will become progressive, as cure is not an option anymore. Brown and colleagues concluded in their review that general anxiety, not specific anxiety related to cancer, was significantly correlated with fatigue in 33 of the 35 investigated studies in patients with cancer [20]. Therefore, we wanted to explore the factor anxiety and a relation with fatigue in palliative patients.

Dysfunctional fatigue-related cognitions: Dysfunctional cognitions concerning fatigue appear to maintain fatigue in cancer survivors [16,21]. Patients experience a lack of control, feel helpless, or have catastrophic thoughts about their fatigue. We assume that these cognitions can also be relevant in palliative patients.

Sleeping Problems: It has been found that sleep–wake rhythm disorders are related to fatigue in patients with advanced cancer [22,23]. Sleeping problems, such as insomnia, together with distress co-occur with fatigue and have been found to be highly prevalent in metastatic breast cancer patients [24].

Dysregulatory activity patterns: A relation between low physical activity and fatigue has been described in several studies in cancer patients, also with advanced disease [25,26]. A pilot intervention study in patients with advanced cancer, solely aimed at increasing physical activity, seemed promising in diminishing fatigue [26]; although the findings were not confirmed in a randomized controlled trial [27]. As there seems to be a relationship between fatigue and physical activity, we find it relevant to investigate its relation and possible contribution to fatigue.

Insufficient social support and interactions: From the curative setting, we have learned that some patients perceive a discrepancy between actual support and desired support and sometimes have unrealistic expectations of others. These perceptions perpetuate the fatigue [16]. A study in 203 patients recently diagnosed with advanced cancer showed that social support was the most vital contributor to overall quality of life [28]. The fact that fatigue has a negative impact on daily quality of life underlines the importance of sufficient social support during this trajectory and legitimates taking this factor into account.

Depressive mood: Depressive mood is not a fatigue-perpetuating factor in cancer survivors. But this may be different in palliative care. Several studies have described an association between fatigue and depression in patients with cancer during active treatment [20,22,29,30]. Fatigue and depression (together with pain or insomnia) frequently co-occur in cancer patients [22,31,32]. Therefore, we wanted to add depressive mood to study its role in fatigue in the palliative phase.

To summarize, we investigated whether all of the seven aforementioned psychosocial factors are associated with fatigue in a group of cancer patients on active treatment in the palliative phase. We also investigated to what extent each factor plays a role and whether some factors are of greater or lesser importance in its contribution to fatigue. If the relationship with psychosocial factors can be confirmed, this would be a basis to develop a fatigue intervention in palliative care.

Materials and methods

Sample

Patients with advanced, incurable cancer from the department of Medical Oncology of a university and a regional hospital in the south eastern part of the Netherlands were asked to participate in this study in the period between December 2008 and June 2010. Potential eligible patients were preselected by the treating physician. Inclusion criteria were diagnosis of advanced, incurable cancer; able to receive palliative (symptom reducing or life prolonging) therapy; able to fill in and return Dutch questionnaires. Potential participants were approached by the investigator (MP). They were informed about the study by telephone, and additional written information was sent to them.

Participants from the University Medical Centre were offered the opportunity to complete the questionnaires using a computer at the outpatient clinic (in combination with a regular visit to the clinic) or a paper-and-pencil version at home. Patients from the regional hospital only received the paper-and-pencil version at home. The

questionnaires that were sent to the patients' home could be returned to the investigator by an enclosed return envelope. When a questionnaire was not returned, a maximum of two telephone calls were made by the investigator to complete the data. Although this study did not fall under the Medical Research Involving Human Subjects Act, we did obtain permission to conduct the study from the institutional review boards of both hospitals. All participants gave oral informed consent.

Instruments

General information on demographical characteristics, stage and type of cancer, and current treatment were obtained from a general questionnaire and if necessary, supplemented with data from medical records. Fatigue severity was assessed using the subscale fatigue of the Checklist Individual Strength (CIS). This subscale consists of eight items, and each item is scored on a 7-point Likert scale. Higher scores indicate more severe fatigue. The range on the fatigue subscale is from 8 to 56. The validated cutoff score of 35 or higher was used to determine severe fatigue [33,34]. This score of 35 is about two times the standard deviation above the mean score of healthy controls. The CIS is a well-validated instrument with excellent psychometric properties [35,36].

Poor or inappropriate coping skills were measured by the subscale Acceptance of the Illness Cognition Questionnaire for chronic diseases. This subscale consists of six items on a 4-point scale from 1 (do not agree) to 4 (completely agree). (e.g., 'I can handle the problems related to my illness') [37]. The Illness Cognition Questionnaire is a self-report instrument with three subscales (acceptance, helplessness, and perceived benefits). It has shown good reliability with Cronbach's alpha coefficient range from 0.84 to 0.91 in patients with chronic diseases.

As a proxy of heightened fear of disease progression, the subscale anxiety of the Hospital Anxiety and Depression Scale (HADS) was used to measure the level of anxiety [38–40]. This subscale consists of seven items with a 4-point Likert scale. The HADS is an extensively validated and used instrument. A score of 8 or more is used as the cutoff; the subscale anxiety has 78% sensitivity and 74% specificity for detecting clinical anxiety [41,42].

Dysfunctional fatigue-related cognitions were measured with the Fatigue Catastrophizing Scale. This scale consists of 10 items, measuring the relation of catastrophizing to fatigue on a 5-point scale from 1 (never true) to 5 (all of the time true) (e.g., 'I imagine the fatigue becoming even more intense and exhausting') [21,43]. Higher scores are indicative for more fatigue catastrophizing. A total score is derived by computing the mean of 10 ratings (Cronbach's alpha = 0.85).

Sleeping problems were measured by the sleep subscale of the Symptom Checklist [44,45]. This subscale consists of three items on a 5-point scale from 1 (not at all) to 5 (very much) and scores range from 3 to 15. Higher scores indicate lower quality of sleep. Patients were asked if they (a) slept well, b) had difficulty with falling asleep, and (c) woke up early in the morning, during the last month. This subscale is widely used and has a good reliability with a Cronbach's alpha of 0.73.

Level of physical activity was measured by the subscale physical activity of the CIS. This subscale consists of three items, and each item is scored on a 7-point Likert scale (e.g., 'I get little done'). Higher scores are indicative for a lower level of physical activity [35,36,46]. The Cronbach's alpha for this subscale is 0.87 [33].

Insufficient social support and interactions were measured by the van Sonderen Social Support List-Discrepancies (SSL-D) [47,48]. The subscale SSL-D consists of eight items on a 4-point scale and measures discrepancies between the amount of received social support and the desired amount of social support (e.g., 'What is your opinion about the extent to which people: Stand by you?'). Scores for the SSL-D range from 8 to 32. Higher scores are indicative for a higher discrepancy. This instrument has a good reliability with a Cronbach's alpha of 0.95 [48].

Depressive mood was measured with the subscale depression of the HADS [38,39]. This subscale consists of seven items with a 4-point Likert scale. The HADS is a well-validated instrument [49]. When using a cutoff score of 8 or more, this subscale has 82% sensitivity and 74% specificity for detecting major depressive disorder [41,42].

Statistical methods

We analyzed our data using SPSS software version 20 (SPSS Inc, Chicago, IL, USA). For sample characteristics, descriptive statistics and frequencies were generated. To explore the association between fatigue severity and the seven psychosocial factors of fatigue, Pearson correlations were performed. To further explore the contribution of the different factors of fatigue to its severity, we performed a linear regression analysis, enter-method. For all analyses, a p value of <0.05 was considered statistically significant.

Results

Two-hundred patients with advanced cancer were approached for this study. One hundred and sixty-two patients agreed to participate. One hundred and thirty-seven patients (69%) filled in the questionnaires. Only three of them completed the questionnaires on the computer at the hospital, all others preferred the paper-and-pencil version at home. Nonparticipants ($N = 63$) did not differ from the participants with regard to gender,

Table I. Demographical and cancer-related characteristics (N = 137)

Characteristics	Participants *n* (%)
Participants	137
Female gender	84 (61)
Male gender	53 (39)
Mean age, years (range)	59 (30–79)
Female	58 (32–78)
Male	61 (30–79)
Education level	
Lower education (≤4)	89 (65)
Higher education (>4)	48 (35)
Marital status	
Married	111 (81)
Single (unmarried, divorced, and widowed)	26 (19)
Employment status	
Work outside home	27 (20)
Voluntary work	14 (10)
Disablement insurance act	25 (18)
Partial disablement insurance act	6 (4)
Sick leave	30 (22)
Retired	39 (29)
Type of cancer	
Breast	41 (30)
Gastro-intestinal	41 (30)
Urogenital	15 (11)
Gynecological	13 (9.5)
Bone and soft tissue	13 (9.5)
Other	14 (10)
Treatment modalities	
Chemotherapy	72 (53)
Oral targeted therapy	21 (15)
Hormonal therapy	20 (15)
Chemo-targeted therapy	19 (14)
Radiotherapy	2 (1)
Chemo-radiotherapy	1 (1)
No actual treatment	2 (1)
Treatment line	
First-line	92 (67)
Second-line	28 (20)
Third-line	12 (9)
Fourth-line	5 (4)

age, and cancer diagnosis as has been reported elsewhere [14]. Table 1 gives additional demographic and cancer-related information of the participants. This table shows that almost 30% of all participants were retired and that 20% still participated in regular labor. Another 10% was involved in voluntary work. The mean score of fatigue was 32 (13.2). Sixty-four of all participants (47%) were severely fatigued.

The mean scores of seven psychosocial factors are shown in Table 2. This table also shows that all seven psychosocial factors correlated significantly with fatigue severity. The linear regression (Table 3) shows that the seven investigated psychosocial factors together predicted 64% of the variance on fatigue severity. The factors sleeping problems and physical activity each had a significant contribution to fatigue (beta 0.244 and 0.676, respectively).

Discussion

In this study, seven plausible psychosocial factors, identified by their effect on fatigue in cured cancer patients or by literature, were explored for their potential relationship with fatigue severity in patients with advanced incurable cancer. All seven factors correlated significantly with fatigue. A linear regression showed that fatigue severity was most strongly associated with sleeping problems and self-reported low physical activity. Six of the seven psychosocial factors were chosen as they were components of an effective fatigue intervention in cancer survivors [16]. The current study demonstrated that such a model may be relevant for advanced cancer patients too. However, some critical remarks should be made. Although we found significant relations, only two factors showed independent correlation by linear regression. This might be due to the instruments we used to operationalize the seven psychosocial factors. Some of them were more generic in nature and not always directly

Table 2. Mean scores and correlations between fatigue severity and seven psychosocial factors

Factors	Mean score (SD)	Min	Max	Pearson correlation	*p* value
Poor or inappropriate coping skills					
Acceptance (ICQ)	17 (4.3)	7	24	−0.309	<0.001
Anxiety					
Anxiety (HADS)	6 (4.3)	0	18	0.359	<0.001
Dysfunctional fatigue-related cognitions					
Catastrophizing (FCS)	18 (17.3)	10	40	0.433	<0.001
Sleeping problems					
Sleep quality (SCL-90)	6 (2.9)	3	15	0.356	<0.001
Level of physical activity					
Physical activity (CIS)	13 (5.6)	3	21	0.735	<0.001
Insufficient social support					
Discrepancies (SSL-D)	9 (2.4)	8	24	0.187	0.030
Depressive mood					
Depression (HADS)	4 (3.6)	0	19	0.455	<0.001

All correlations are significant.
SD, standard deviation; ICQ, Illness Cognition Questionnaire; HADS, Hospital Anxiety and Depression Scale; FCS, Fatigue Catastrophizing Scale; SCL-90, Symptom Checklist; CIS, Checklist Individual Strength; SSL-D, van Sonderen Social Support List-Discrepancies.

Table 3. Linear regression to predict fatigue severity

| | Dependent variable: CIS-fatigue | | | |
| | | 95% CI for B | | |
Independent variables	Beta	Lower bound	Upper bound	*p* value
Poor or inappropriate coping skills				
Acceptance (ICQ)	0.073	−0.265	0.747	0.347
Anxiety				
Anxiety (HADS)	−0.026	−0.646	0.472	0.759
Dysfunctional fatigue-related cognitions	0.154	−0.004	0.577	0.054
Catastrophizing (FCS)				
Sleeping problems	0.244	0.587	1.749	<0.001
Sleep quality (SCL-90)				
Level of physical activity	0.676	1.285	1.900	<0.001
Physical activity (CIS)				
Insufficient social support	−0.050	−1.226	0.493	0.400
Discrepancies (SSL-D)				
Depressive mood				
Depression (HADS)	−0.066	−0.324	0.831	0.386

Adjusted $R^2 = 0.642$.

ICQ, Illness Cognition Questionnaire; HADS, Hospital Anxiety and Depression Scale; FCS, Fatigue Catastrophizing Scale; SCL-90, Symptom Checklist; CIS, Checklist Individual Strength; SSL-D, van Sonderen Social Support List-Discrepancies.

related to the experience of having advanced incurable cancer or experiencing fatigue. For example, the factor anxiety: As a proxy, we used the subscale anxiety of the HADS. This subscale measured anxiety as a mood disorder but gives no information on fear related to the disease, which we intended to measure. To our knowledge, at that time there was no specific questionnaire available in Dutch to measure specifically the anxiety for progression. Such a questionnaire, which recently has been validated, would have probably been more suitable [50]. Furthermore, we measured sleeping problems with the subscale sleep of the Symptom Checklist. Some studies have reported that an irregular sleep–wake cycle is related to fatigue [22–24]. We did not take this into account.

Fatigue catastrophizing had a borderline significance in the multivariate analyses. As over 50% of our patients did not experience severe fatigue, this might have resulted in an underestimation here. Although in our group as a whole, not all factors contributed significantly to fatigue; they should not be precluded in advance in an individual patient. Clinical experience in cancer survivors showed us that at individual level, each factor can play a unique role. We have no reason to assume that this is different in the palliative phase.

We explored seven factors in the current study, but this does not preclude other psychosocial factors from contributing to fatigue in patients with advanced cancer. Moreover, it is difficult to extrapolate our results to an individual patient. In severely fatigued cancer survivors, not all fatigue-perpetuating factors are present in each patient, and this may also be the case in fatigued patients with advanced cancer [16]. Additionally, the advanced

cancer and its treatment cannot be ruled out as a precipitating factor combined with perpetuating factors for fatigue in this palliative setting.

A limitation of our study is its cross-sectional design. In this study, we included patients at one time point but at various moments in their palliative trajectory. Most participants in this study were at the beginning of the palliative phase, as 67% of them received first-line treatment. Also, the fact that 20% were still active in regular labor could be seen as an indication that our group of participants could be considered as a relatively fit group. In another study based on the data of this group of patients, we found a significant difference in fatigue severity between patients at first treatment line and patients at further treatment line [14]. Also, other studies reported that most cancer-related symptoms increase when the disease progresses and a cumulative effect of several treatment lines cannot be precluded [13,51–53].

This study is to our knowledge the first in which a specific model of perpetuating psychosocial factors of fatigue in cancer survivors was investigated for its applicability in the palliative phase. Although we did not test this model, our results confirmed the correlations of seven factors with fatigue severity in the patients with advanced incurable cancer. This study could therefore be considered a step forwards in obtaining more insight in the multifactorial symptom fatigue in the palliative phase and the development of an intervention. However, new studies, preferably longitudinal, are warranted to confirm our findings. Such an intervention should probably be individually tailored because at individual level, each factor may play a unique role such as in cured cancer patients. For now, for health

care professionals in daily practice, it seems advisable to focus on sleeping problems and physical activity as options to reduce fatigue.

Conclusion

The main aim of this study was to explore the extent to which seven psychosocial factors contributed to fatigue and its severity. Although all investigated factors were significantly correlated to fatigue severity, only sleeping problems and low physical activity level contributed independently. Our finding that the investigated psychosocial factors together explained 64% of the variance in

fatigue severity gives support to the suggestion that a model of fatigue-perpetuating factors is also relevant in the palliative setting. Such a model could lead to a starting point for developing a cognitive behaviorally oriented intervention for fatigue. Currently, in daily practice, health care professionals could focus on sleeping problems and physical activity as options to reduce fatigue, as they seem to be the most common and relevant aspects related to fatigue in patients with advanced cancer.

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