CANCER-RELATED FATIGUE

a multidimensional approach

Johan de Raaf

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Energy Crisis

At first I was energized
The diagnosis shocked me into action
The clutching fear galvanized me
The details demanded attention
The family's tears called for comfort
The decisions were made
The adrenaline flowed and I was energized
But one day all the energy was gone –
Physical, psychic, emotional –
The days turned into weeks
And the weeks into months
Now I search
Each cell of my body
Each corner of my mind
For
One tiny spark
Of energy

L. Hjelmstad, 1993

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General Introduction

General Introduction

Cancer patients frequently suffer from fatigue. Although fatigue is also prevalent in the general population[1], cancer patients indicate that cancer-related fatigue differs from the tiredness they used to experience before diagnosis[2-3]. In their opinion, cancer-related fatigue is more intense, persists after adequate rest and hampers them in their daily activities[3]. These characteristics are incorporated in the definition of cancer-related fatigue as proposed by the National Comprehensive Cancer Network[4]:

"Cancer-related fatigue is a distressing persistent, subjective sense of physical, emotional and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning"

Cancer-related fatigue is experienced in all stages of the disease trajectory[5]. For example, more than 80% of the patients experience at least some fatigue during adjuvant chemotherapy for breast cancer[6]. One-third of the breast cancer survivors suffer from fatigue, even five to ten years after diagnosis[7]. In patients with advanced cancer, the estimated prevalence of fatigue is 74%, increasing up to 88% in the last two weeks of life[8].

Cancer patients indicate that fatigue is more troublesome and has a greater negative influence on quality of life and daily activities than any other cancer-related symptom, including pain, nausea and depression[5]. Fatigue forces them to change their daily routine and limits them in physical activities (e.g. walking distances), cognitive activities (e.g. concentrating) as well as social activities (e.g. taking care of the family)[5].

Qualitative studies on fatigue in cancer patients have revealed that patients describe their fatigue experiences as physical, cognitive or emotional sensations of tiredness[2-3]. These various sensations of tiredness have been called fatigue dimensions. Over the last twenty years, various multidimensional fatigue questionnaires have been developed, which are able to quantify the intensity of the separate fatigue dimensions[9]. In the development and the psychometric testing of these questionnaires, the multidimensional nature of fatigue has been reconfirmed by factor analyses[10-11]. Nowadays, the multidimensional nature of fatigue is acknowledged by experts[12], but it is unclear how many dimensions of fatigue should be distinguished. The number of dimensions measured by questionnaires varies between two (Fatigue Questionnaire[11]) and five (Multidimensional Fatigue Inventory[10]). There is consensus on the existence of at least a physical and a cognitive dimension of fatigue[12].

Several guidelines have been developed to improve the management of cancer-related fatigue, for example the guidelines of the National Comprehensive Cancer Network (United States)[4] and the Dutch Comprehensive Cancer Network[13]. These guidelines provide information on the nature of cancer-related fatigue, reflect on the mechanisms involved in its pathogenesis, provide recommendations on its assessment and give an overview of the treatment options available.

With respect to the nature of cancer-related fatigue, the guidelines refer to the multidimensional presentation of fatigue, as described above. However, many aspects of

the dimensions of fatigue have to be elucidated. First of all, it is unclear whether fatigue dimensions should be considered as expressions of one symptom (a multidimensional construct) or as phenomena which are all called 'fatigue' by patients and professionals, but are in fact separate symptoms (a multiple symptom concept). To determine whether fatigue is a multidimensional concept or a multiple symptom concept, it has to be investigated whether the various fatigue dimensions behave differently, by studying their intensity in different stages of chancer and their changes during anti-tumor therapy or during interventions aimed to relieve fatigue.

Both guidelines state that the exact pathogenesis of fatigue is still unknown[4, 13]. However, it is acknowledged that disturbances in physiological, biochemical and psychological systems are involved in the pathogenesis of fatigue[4, 13-14]. The guidelines also report that inflammation might be a potentially important mechanism underlying fatigue. Inflammatory agents can be produced by tumour cells or by inflammatory cells after their stimulation by tumour cells, anti-tumour therapy and psychological distress[15]. Inflammation might provoke fatigue by inducing anaemia, disturbances in the hypothalamic-pituitary-adrenal axis or alterations in the serotonin metabolism in the brain[16]. Nevertheless, it is unknown which fatigue dimensions are associated with inflammation and whether inflammation is a potentially important mechanism in all stages of the disease trajectory.

Concerning the assessment of cancer-related fatigue, the NCCN-guideline recommends screening for the presence of cancer-related fatigue with a 0 to 10 Numeric Rating Scale, where 0 means "no suffering" and 10 means "unbearable suffering"[4]. This way of screening is also frequently used for other symptoms, such as pain[17]. It is important to determine the clinical meaning of the scores given on the 0 to 10 NRS for the various symptoms. By using cut points, NRS scores have been categorized as none, mild, moderate and severe, or as representing clinically relevant burden or not. It is important to investigate which cut point optimally differentiates patients with clinically relevant burden from other patients.

Over the last years, many interventions to alleviate fatigue have been studied. Until now, three Cochrane reviews have been published which reported small, but significant benefits of drug therapy[18] (e.g. methylphenidate[19]), exercise[20] and psychosocial interventions[21] (e.g. psycho-education on energy conservation and activity management[22]) on fatigue intensity in cancer patients. However, few randomized controlled trials which were analyzed in these reviews included advanced cancer patients only. Therefore, the conclusions of the Cochrane reviews cannot be extrapolated to advanced cancer patients. Because current treatment options for fatigue in advanced cancer patients are scarce, we urgently need to develop new evidence-based interventions for this group of patients. Both the NCCN guideline and the Dutch guideline advise to optimize the management of accompanying physical symptoms as part of the treatment of cancer-related fatigue[4, 13]. However, this recommendation is only based on cross-sectional studies in which fatigue was associated with other symptoms, for example with pain[23-28], dyspnoea[23-30] and anorexia/cachexia[14, 23-26, 29-31], whereas evidence from randomized controlled trials is lacking.

Aims

Although both national and international guidelines have been developed to enhance the management of cancer-related fatigue, many questions regarding the nature, pathogenesis, assessment and treatment of cancer-related fatigue have to be resolved. This thesis describes research that was performed to elucidate the multidimensional nature of fatigue, the role of inflammation in the pathogenesis of fatigue, the optimal cut point on the 0 to 10 NRS for fatigue, and the possibility to relieve fatigue by optimizing treatment of accompanying symptoms. The aims of this thesis are:

1. To further explore the characteristics of the dimensions of fatigue: their intensity in different stages of cancer, their changes during antitumor therapy or by fatigue interventions and their correlates (chapters 2);
2. To investigate whether multidimensional fatigue experiences are different in various stages of cancer (chapter 3);
3. To examine the relation between inflammation and multidimensional fatigue experiences in various stages of cancer (chapter 4);
4. To investigate for fatigue and other symptoms which the optimal cut point is on a 0-10 Numeric Rating Scale (chapter 5);
5. To evaluate whether it is possible to alleviate fatigue in advanced cancer patients by optimizing treatment of other physical symptoms (chapter 6).

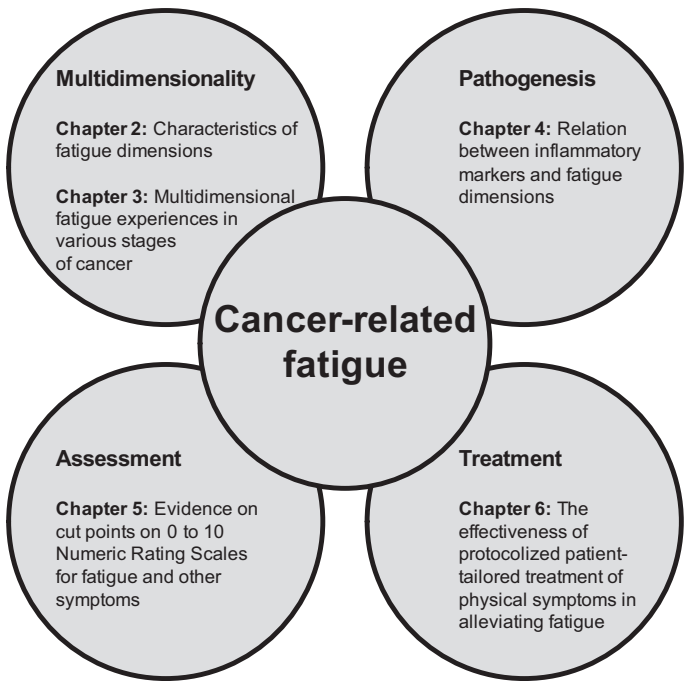

Figure 1: Outline of this thesis

Outline of this thesis

Chapter 2 describes a systematic review on the characteristics of the physical and mental dimensions of fatigue by studying: (a) their intensity in different stages of cancer; (b) their changes in intensity during anti-tumour therapy; (c) the variables to which they are related; and (d) their changes in intensity by interventions aimed to diminish fatigue (aim 1).

Chapter 3 reports the results of a comparative study on the multidimensional fatigue experiences of advanced cancer patients for whom no treatment options are available and cancer survivors who finished treatment one to five years ago (aim 2).

Chapter 4 evaluates the relation between inflammatory markers and fatigue dimensions in a subgroup of the cohorts discussed in chapter 3 (aim 3).

Chapter 5 describes a systematic review about the evidence on cut points on the 0-10 Numeric Rating Scales for the symptoms of the Edmonton Symptom Assessment Scale (ESAS) in cancer patients (aim 4).

Chapter 6 reports the results of a randomized clinical trial on the effectiveness of protocolized patient-tailored treatment of physical symptoms in alleviating fatigue in advanced cancer patients (aim 5).

Chapter 7 summarizes the key points of this thesis. Thereafter, the main conclusions are drawn and the implications for clinical practice are discussed. Finally, recommendations for future research are given.

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2

Elucidating the behavior of physical fatigue and mental fatigue in cancer patients: a review of the literature

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Abstract

Objective

Although the multidimensional nature of cancer-related fatigue is widely accepted, it could be questioned whether fatigue dimensions are expressions of one symptom (multidimensional concept) or expressions of several phenomena, which are all called fatigue but actually are separate symptoms (multiple symptom concept).

Methods

Therefore, we investigated in this review whether physical fatigue and mental fatigue behave differently in cancer patients, by studying their intensity in different stages of cancer; their changes in intensity during anti-tumor therapy; the variables to which they are related; and their changes in intensity by interventions on fatigue.

Results

In some studies, physical fatigue and mental fatigue behaved similarly: they were both more intense in cancer patients than in healthy controls and sometimes they had the same course during anti-tumor therapy or improved both during an intervention. On the contrary, there were some studies which suggested that physical fatigue and mental fatigue behaved differently: physical fatigue seemed to be more prominent than mental fatigue in some stages of the disease trajectory; several studies reported changes in physical fatigue not accompanied by changes in mental fatigue during anti-tumor therapy or by interventions aimed to relieve fatigue; and physical fatigue and mental fatigue had different correlates.

Conclusions

In conclusion, we found some studies in which physical fatigue and mental fatigue behaved differently. These findings might indicate that physical fatigue and mental fatigue are separate phenomena. To prove this multiple symptom concept, studies on the pathophysiological mechanisms leading either to physical fatigue or to mental fatigue are urgently needed.

Introduction

Fatigue is frequently experienced by cancer patients in all stages of the disease[1]. The estimated prevalence of cancer-related fatigue is 76% in patients receiving chemotherapy[2], 68% in patients receiving radiotherapy[3], 35% in breast cancer survivors[4] and 74% in patients with advanced disease[5]. Almost all fatigued cancer patients report limitations in daily activities due to fatigue[2].

In qualitative studies, both cancer patients and healthy controls described their fatigue in terms of physical, affective and cognitive sensations of tiredness[6,7]. Such sensations of tiredness are often called fatigue dimensions. The multidimensional nature of fatigue is widely accepted, evidenced by the development of many multidimensional fatigue questionnaires[8].

Although many researchers agree on the multidimensionality of fatigue, it is still unknown how many dimensions of fatigue should be distinguished. For example, the number of dimensions measured in fatigue questionnaires varies from two (Fatigue Questionnaire[9]) to five (Multidimensional Fatigue Inventory[10] and Multidimensional Fatigue Symptom Inventory[11]). On an expert meeting of the European Association for Palliative Care there was agreement on the existence of at least a physical and a cognitive, or mental, dimension of fatigue[12]. According to Smets et al., physical fatigue refers to the physical sensations of tiredness, such as feeling weak, and mental fatigue refers to the cognitive symptoms of fatigue, such as having difficulty concentrating[10]. We previously found that only the dimensions physical fatigue and mental fatigue as measured with the Multidimensional Fatigue Inventory were predictors of the overall fatigue score as given on a 0-10 Numeric Rating Scale in cancer survivors and advanced cancer patients[13].

The sensations of cancer-related fatigue have been characterized in different ways (Figure 1). There are some researchers who argue, based on factor analyses, that the physical, mental and emotional sensations of fatigue do not need to be considered separately (fatigue as a unidimensional concept)[14]. In contrast, based on qualitative studies, validation studies of multidimensional questionnaires, and consensus of experts, most researchers agree that fatigue is experienced in different fatigue dimensions. According to this multidimensional concept, the fatigue dimensions belong to one phenomenon, and are consequently supposed to have the same pathogenesis and are supposed to be treated in the same manner.

However, in our previous work, physical fatigue was more severe than mental fatigue in hospitalized advanced cancer patients. Furthermore, the various dimensions of fatigue had different correlates in these patients[15]. Therefore, it could be questioned if fatigue is one symptom which expresses itself in various dimensions (i.e. the multidimensional concept) or if there are several phenomena which are all called 'fatigue' by patients and professionals, but are in fact separate symptoms (i.e. the multiple symptom concept). If physical fatigue and mental fatigue are separate symptoms, we would expect them to behave differently. Also, if physical fatigue and mental fatigue are proven to be separate symptoms, it would be reasonable to suppose that each symptom has its own pathogenesis and might require a different treatment.

The aim of this systematic review is to investigate whether cancer-related fatigue should be considered as a multiple symptom concept. If fatigue is a multiple symptom concept, we

expect physical fatigue and mental fatigue to behave differently. We therefore explored if physical fatigue and mental fatigue differ:

(1) in their intensity in cross-sectional studies comparing various groups of patients;
(2) in the longitudinal courses of their intensity during anti-tumor therapy;
(3) in their correlated variables;
(4) in their response to interventions aimed to relieve fatigue.

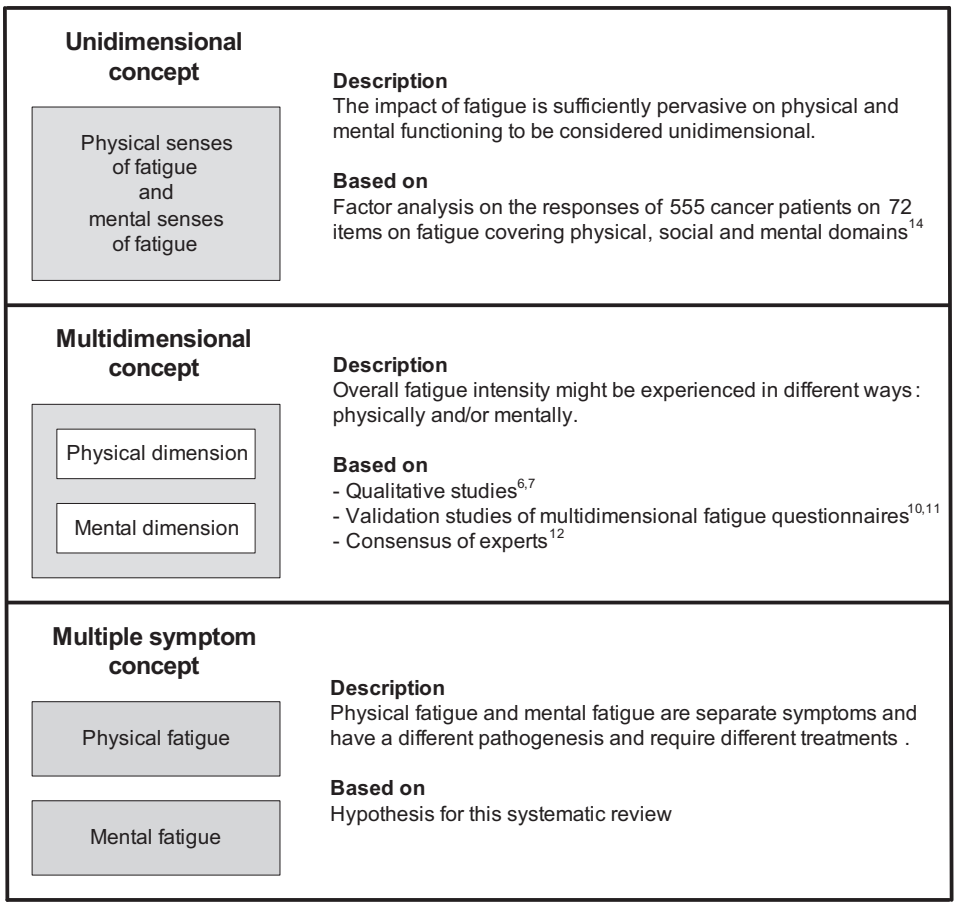

Figure 1: Three opinions of the nature of the physical and mental senses of fatigue: the unidimensional concept, the multidimensional concept and the multiple symptom concept

Methods

Relevant literature published until June 30th 2012 was searched in PubMed and PsychInfo. The search was limited to English articles. The search-string consisted of two parts, using an AND-combination. The first part consisted of the keyword 'cancer' (PsychInfo) or the Mesh-term

'Neoplasms' (PubMed). The second part included the synonyms for physical fatigue and mental fatigue and the names of the multidimensional fatigue questionnaires which measure physical and mental dimensions of fatigue: physical fatigue OR sensory fatigue OR mental fatigue OR cognitive fatigue OR Multidimensional Fatigue Inventory OR Multidimensional Fatigue Symptom Inventory OR Cancer Fatigue Scale OR Chalder Fatigue Scale OR Fatigue Questionnaire OR Fatigue Assessment Questionnaire OR Revised Piper Fatigue Scale OR Bidimensional Fatigue Scale OR Checklist Individual Strength OR multidimensional fatigue.

Studies were included in this review if they measured fatigue in cancer patients and published results of both physical fatigue and mental fatigue. Reviews, validation studies and articles on childhood cancer or survivors of childhood cancer were excluded from this review. Cross-sectional studies which did not compare fatigue experiences between two groups of patients were also excluded. Finally, due to the high risk of bias, we excluded uncontrolled intervention studies, randomized controlled trials which did not perform an analysis on the differences between the groups over time, and studies which only univariately assessed the relation between fatigue dimensions and other variables. Articles were reviewed independently by two authors (PJdR and CdK). We found 215 articles through the original search of which 34

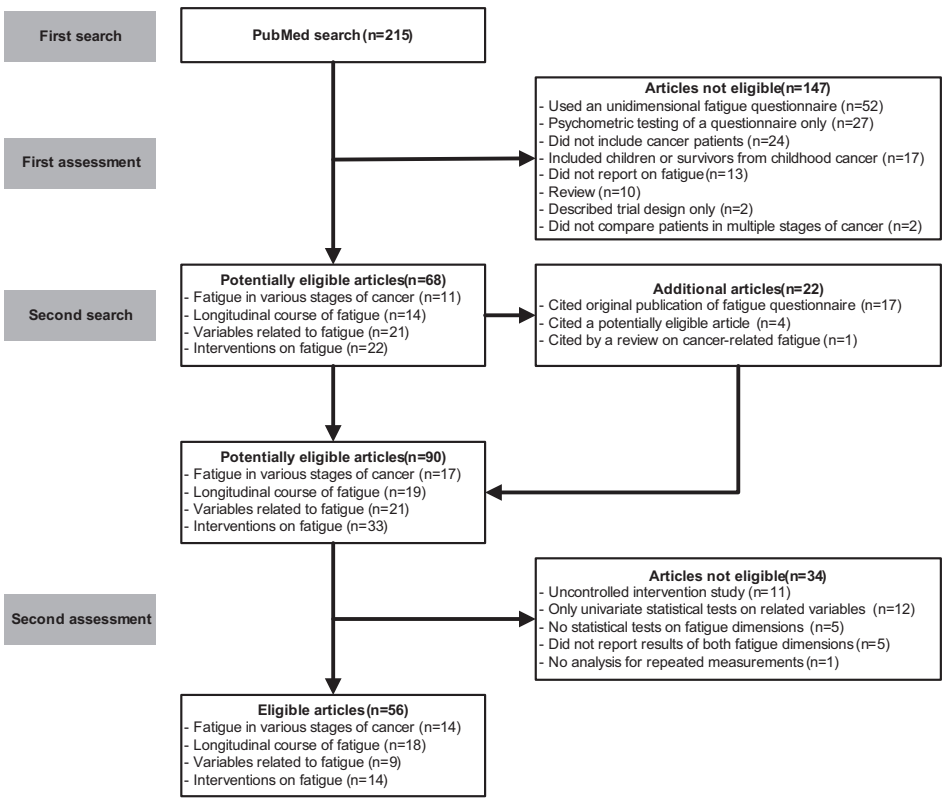

Figure 2: Flowchart of the review process

met the inclusion and exclusion criteria. Additionally, we checked the reference list of each potentially relevant article, the articles referring to potentially relevant articles, articles referring to the original publications on the multidimensional fatigue questionnaires and the citations in reviews on cancer-related fatigue. This resulted in 22 additional relevant publications (Figure 2).

Group differences in the intensity of physical fatigue and mental fatigue or in the course of physical fatigue and mental fatigue during interventions were quantified by calculating the effect sizes (Cohen's d). The effect size is the difference in the mean intensity of fatigue between the groups divided by the pooled standard deviation[16]. If an article did not provide sufficient information for this calculation, the first author was contacted to get additional data.

Results

General

We found 56 articles which met our inclusion and exclusion criteria: twenty-four cross-sectional observational studies[4,15,17-38], eighteen longitudinal observational studies[39-56], and fourteen randomized controlled trials[57-70]. Six different multidimensional questionnaires were used in these studies: Multidimensional Fatigue Inventory (MFI)[15,19-21,26,29,32-34,36,38,39,41,42,44,45,48,51,52,56,57,60-62,65,66,68,70], Fatigue Questionnaire (FQ)[18,23-25,27,28,31,37,53,54,58,59,64,67], Revised Piper Fatigue Inventory (R-PFI)[40,43,55,63], Cancer Fatigue Scale (CFS)[17,22,30,35], Multidimensional Fatigue Symptom Inventory (MFSI)[4,49,50,69] and Fatigue Assessment Questionnaire (FAQ)[46,47].

Intensity of physical fatigue and mental fatigue in various stages of cancer and healthy controls

Fifteen studies were identified which compared fatigue experiences between cancer patients and healthy controls[4,18-21,25,28,31,33,34,37,38] or compared fatigue experiences between two groups of cancer patients[24,27,29]. Three different groups of cancer patients could be distinguished: 1) patients undergoing curative treatment, i.e. patients undergoing any cancer treatment aiming to cure the disease rather than to postpone death; 2) cancer survivors, i.e. patients treated for cancer in the past without any evidence of disease at the moment of inclusion; and 3) advanced cancer patients, i.e. patients with incurable disease (Table 1).

Eight out of ten studies which compared fatigue experiences between cancer survivors and healthy controls found statistically significant higher levels of both physical fatigue and mental fatigue in the cancer patients[4,18,19,21,25,28,31,37].

The two studies which compared fatigue experiences between cancer patients on curative treatment and healthy controls had contradictory results[20,33]. Cancer patients on hormonal therapy had similar levels of physical fatigue and mental fatigue as healthy controls[33]. On the contrary, cancer patients on chemotherapy had statistically significant higher levels of both physical fatigue and mental fatigue than healthy controls[20]. However, in the subgroup of cancer patients on chemotherapy with mild anemia, the difference in physical fatigue between cancer patients and healthy controls was greater than the difference in mental fatigue (effect size 1.49 vs. 0.37)[20].

The only study which compared the fatigue experiences of cancer patients on treatment and cancer survivors, reported a higher intensity of physical fatigue in the patients who still

received adjuvant hormonal therapy for prostate cancer than in prostate cancer survivors, whereas levels of mental fatigue were similar in the two groups[27].

Two studies compared fatigue experiences of advanced cancer patients and patients in other stages of cancer[24,29]. In one study, advanced cancer patients had both more physical fatigue and mental fatigue than patients receiving curative radiotherapy, but the difference in physical fatigue was more pronounced than the difference in mental fatigue (effect size 1.39 vs. 0.27)[29]. In the other study, advanced cancer patients referred for palliative radiotherapy had higher levels of physical fatigue than cancer survivors, with comparable levels of mental fatigue[24].

In summary, cancer patients experienced both more physical fatigue and mental fatigue than healthy controls. Additionally, few studies compared fatigue experiences between different stages of the disease trajectory. Physical fatigue was more prominent than mental fatigue in patients with advanced cancer as compared to patients undergoing curative treatment or cancer survivors. Furthermore, physical fatigue was more prominent in patients undergoing curative treatment than in cancer survivors.

Longitudinal course of physical fatigue and mental fatigue in relation to anti-tumor therapy

Eighteen studies were identified which reported about the longitudinal course of physical fatigue and mental fatigue (Table 2). De Jong et al. reported their results on the course of physical fatigue and mental fatigue during adjuvant chemotherapy for breast cancer in a single group of patients in two separate papers[41,42]. Fleer et al. reported on the longitudinal course of fatigue in two different groups of patients[44].

The studies included patients during curative treatment[39,40,43,49,52-54], after curative treatment[44,47,48] or both during and after curative treatment[41,42,44-46,50,51,55,56]. The anti-tumor therapy provided was chemotherapy[41-44,48,49], radiotherapy[39,40,45-48,51,52,54,56], hormonal therapy[53], immunotherapy[55] or surgery[44]. Generally, physical fatigue statistically significantly increased during anti-tumor therapy (in 11/15 studies)[39,41,43-46,49,51,53-55] and statistically significantly decreased thereafter (in 7/11 studies)[41,44-46,48,51,56]. The results on the longitudinal course of mental fatigue were contradictory: during anti-tumor therapy 5/15 studies found a statistically significant increase [39,46,49,51,53] and one of these 15 studies measured a statistically significant decrease in mental fatigue[42]. After completion of treatment 3/11 studies reported a statistically significant decrease of mental fatigue[46,48,51] and in one study mental fatigue statistically significantly increased [47].

Comparing the course of physical and mental fatigue, both physical fatigue and mental fatigue changed significantly with parallel courses in six studies[39,46,48,49,51,53]. In five studies, only a significant change in the intensity of physical fatigue was found, without changes in mental fatigue[43,45,54-56]. In three studies, neither physical fatigue nor mental fatigue did change significantly over time[40,44,52]. In the two studies which reported about the same sample of women undergoing adjuvant chemotherapy for breast cancer an increase in physical fatigue, but a decrease in mental fatigue was found during treatment[41,42]. One study, which compared fatigue intensities 2.5 years after completing radiotherapy with pre-treatment intensities of fatigue, reported an increase in mental fatigue, without changes in the intensity of physical fatigue[47].

Table 1: Studies which reported about differences in physical fatigue and mental fatigue between various groups of cancer patients or between cancer patients and healthy controls

Author	Group 1		
	Patients	*n*	*Tumor*
Studies which compared fatigue experiences between cancer survivors and healthy controls			
Broeckel, 1998[4]	Cancer survivors (3-36mo after adjuvant CT)	61	Breast cancer
Hoftijzer, 2008[19]	Cancer survivors (0.3-42yr after treatment)	153	Thyroid cancer
Smets, 1998[34]	Cancer survivors (9mo after RT)	154	Various cancers
Howell, 2000[21]	Cancer survivors (≥1yr after CT)	66	Hematological malignancies
Loge, 1999[28]	Cancer survivors (≥2yr after treatment)	442	Hodgkin's disease
Knobel, 2000[25]	Cancer survivors (≥3yr after CT+SCT)	33	Malignant lymfoma
Hjermstad, 2004[18]	Cancer survivors (≥3yr after treatment)	128	Hematological malignancies
Orre, 2008[31]	Cancer survivors (≥4yr after treatment)	1431	Testicular cancer
Caravati, 2011[38]	Cancer survivors (5y, 10y, or 15y after diagnosis)	542	Colorectal cancer
Vistad, 2007[37]	Cancer survivors (≥6yr after treatment)	79	Cervical cancer
Studies which compared fatigue experiences between cancer patients on curative treatment and healthy controls			
Schilder, 2009[33]	Cancer patients on HT (after CT)	80	Breast cancer
Holzner, 2002[20]	Cancer patients on CT without anemia	15[2]	Various cancers
Holzner, 2002[20]	Cancer patients on CT with mild anemia	40[2]	Various cancers
Studies which compared fatigue experiences between cancer patients on curative treatment and cancer survivors			
Kyrdalen, 2010[27]	Cancer patients (still on HT, 1yr after RT)	82	Prostate cancer
Kyrdalen, 2010[27]	Cancer patients (still on HT, 1yr after RT)	82	Prostate cancer
Studies which compared fatigue experiences between two groups of cancer patients in different stages of the disease			
Lundh Hagelin, 2009[29]	Advanced cancer patients referred for palliative care	228	Various cancers
Knobel, 2003[24]	Advanced cancer patients on RT for bone metastasis	238	Solid malignancies

[1] Calculated by the authors (PJdR and CdK independently), using the data published in the article
[2] Data not mentioned in the article, but provided by first author
PF = Physical Fatigue; MF = Mental Fatigue
FQ = Fatigue Questionnaire; MFI = Multidimensional Fatigue Inventory; MFSI = Multidimensional Fatigue Symptom Inventory
CT = chemotherapy; SCT = stem cell transplantation; RT = radiotherapy; HT= hormonal therapy

Group 2			Recruitment group 2	Matching or adjustment	Ques-tion-naire	Intensity of PF (group 1 vs. group 2)		Intensity of MF (group 1 vs. group 2)	
Patients	*n*	*Tumor*				*Intensity*	*Effect size*	*Intensity*	*Effect size*
Healthy controls	59	-	Primary analysis	Age, sex	MFSI	↑	0.58[1]	↑	0.52[1]
Healthy controls	336	-	Group 2 secondary analysis	Age, sex, SES	MFI	↑	0.57[1]	↑	0.43[1]
Healthy controls	139	-	Primary analysis	-	MFI	=	0.20[1]	=	-0.31[1]
Healthy controls	44	-	Group 2 secondary analysis	Age, sex	MFI	↑	?	↑	?
Healthy controls	2186	-	Group 2 secondary analysis	-	FQ	↑	0.47[1]	↑	0.42[1]
Healthy controls	1786	-	Group 2 secondary analysis	-	FQ	↑	?	↑	?
Healthy controls	1806	-	Group 2 secondary analysis	Age, sex	FQ	↑	?	↑	?
Healthy controls	1080	-	Group 2 secondary analysis	Sex	FQ	↑	0.26[1]	↑	0.14[1]
Healthy controls	1181	-	Primary analysis	Age, sex and residence area	MFI	=	?	=	?
Healthy controls	237	-	Group 2 secondary analysis	Age, sex	FQ	↑	0.47[1]	↑	0.32[1]
Healthy controls	48	-	Secondary analysis	Age, sex, IQ	MFI	=	0.28	=	0.29
Healthy controls	120	-	Primary analysis	Age, sex	MFI	↑	0.89	↑	0.72
Healthy controls	120	-	Primary analysis	Age, sex	MFI	↑	1.49	↑	0.37
Cancer survivors (6mo after finishing HT, 1yr after RT)	157	Prostate cancer	Secondary analysis	-	FQ	↑	0.55[2]	=	0.26[2]
Cancer survivors (1-3yr after RT)	184	Prostate cancer	Secondary analysis	-	FQ	↑	0.44[2]	=	0.02[2]
Patients on curative RT within the trunk	81	Various cancers	Primary analysis	-	MFI	↑	1.39[1]	↑	0.27[1]
Cancer survivors (3-5yr after CT+SCT)	128	Hematological malignancies	Secondary analysis	-	FQ	↑[1]	1.02[1]	=[1]	0.00[1]

SES = socioeconomic status; IQ = Intelligence quotient
↑ (statistically significant higher levels in group 1); = (no significant differences between group 1 and group 2); Effect size = degree of difference in fatigue between group 1 and group 2. Positive effect size: fatigue levels higher in group 1 than group 2, negative effect size: fatigue levels higher in group 2 than group 1.

Table 2: Studies which reported about the longitudinal course of physical fatigue and mental fatigue during and after anti-tumor therapy

Author	Patients			Questionnaire
	n	*Tumor*	*Treatment*	
Studies which assessed fatigue during anti-tumor therapy only				
El-Banna, 2004[43]	27	Lymphoma	Autologous PBSCT	R-PFS
Liu, 2005[49]	63	Breast	CT (adjuvant or neoadjuvant)	MFSI-SF
Stone, 2000[53]	62	Prostate	HT (neo-adjuvant or palliative)	BFS
Stone, 2001[54]	69	Breast and prostate	RT (adjuvant or curative)	BFS
Smets, 1998[52]	250	Mixed	RT (adjuvant or curative)	MFI
Ahlberg, 2005[39]	60	Uterine	RT (adjuvant)	MFI
Beach, 2001[40]	74	Lung	RT (curative or adjuvant)	R-PFI
Studies which assessed fatigue both during and after anti-tumor therapy				
De Jong, 2004-2005[41,42]	157	Breast	CT (adjuvant)	MFI
Fleer, 2005[44]	37	Testicular	CT	MFI
Prue, 2010[50]	65	Gynecological	Curative treatment	MFSI-SF
Trask, 2004[55]	16	Melanoma	HD-IFN (adjuvant)	R-PFS
Visser, 1998[56]	250	Mixed	RT (adjuvant or curative)	MFI
Purcell, 2010[51]	210	Mixed	RT (adjuvant or curative) ± CT	MFI
Geinitz, 2001[46]	41	Breast	RT (adjuvant)	FAQ
Fürst, 2001[45]	81	Mixed	RT (curative)	MFI
Studies which assessed fatigue after anti-tumor therapy only				
Heutte, 2009[48]	935	Hodgkin's lymphoma	CT ± RT or RT alone	MFI
Fleer, 2005[44]	15	Testicular	Orchidectomy	MFI
Geinitz, 2004[47]	38	Breast	RT (adjuvant)	FAQ

[1] Data not mentioned in the article, but provided by first author
[2] Level of significance not mentioned in the article, but calculated by the first author (PJdR) using the data presented in the article
PF = Physical Fatigue; MF = Mental Fatigue
BFS= Bidimensional Fatigue Scale; FAQ = Fatigue Assessment Questionnaire; MFI = Multidimensional Fatigue Inventory; MFSI-SF = Multidimensional Fatigue Symptom Inventory-Short Form; R-PFS = Revised Piper Fatigue Scale; RT = radiotherapy; CT = chemotherapy; HT = hormonal therapy; PBSCT = Peripheral blood stem cell transplantation; HD-IFN = high dose interferon
↑ (statistically significant increase); ↓ (statistically significant decrease); = (no significant difference);

	Assessment				PF		MF	
	Frequency	*Baseline*	*Fatigue maximum*	*End follow-up*	*During treatment*	*After treatment*	*During treatment*	*After treatment*
	5	Before start CT	7d after PBSCT	14d after PBSCT	↑		=	
	8	Before start CT	1st wk of 4th cycle CT	3rd wk of 4th cycle CT	↑[1]		↑[1]	
	2	Before start HT	3 mo after start HT	3 mo after start HT	↑		↑	
	2	Before start RT	1st wk after RT	1st wk after RT	↑		=	
	2	2 wk before start RT	2wk after RT	End RT	=		=	
	3	0-2w before start RT	End RT (5-6wk after start RT)	End RT	↑		↑	
	3	Before start RT	4th wk of RT	End RT	=		=	
	5	Before start CT	Dependent on CT regimen	12wk after CT	↑	↓	↓	=
	3	Before start CT	End CT (12wk after start CT)	1yr after start CT	↑[2]	↓[2]	=[2]	=[2]
	13-21	Before start CT or RT	Month 1-2 (during treatment)	12mo after start CT or RT	?	?	=	=
	6	Before start HD-IFN	2mo after HD-IFN	6mo after HD-IFN	↑	=	=	=
	3	2w before start RT	2wk after RT	9mo after RT	=	↓	=	=
	3	First day RT	End RT	6mo after RT	↑	↓	↑	↓
	7	Before start RT	End RT	2mo after RT	↑	↓[1]	↑	↓[1]
	4	Before start RT	End RT	3mo after RT	↑	↓	=	=
	6	0-6 mo after treatment	0-6mo after treatment	>4y after treatment		↓		↓
	3	Within 1m after surgery	1mo after surgery	13mo after surgery		=[2]		=[2]
	3	<9d before start RT	2.5yr after RT	2.5yr after RT		=		↑

Table 3: Studies which reported on correlates of physical fatigue and mental fatigue found in multivariate analyses

Author	Patients (n)	Tumor	Questionnaire	Dimension	*Age*	*Sex*	*Tumor type*	*Performance status*	*On hormonal therapy*	*Physical symptoms*	*Pain*	*Dyspnea*
Studies on cancer survivors												
Sugawara, 2005[35]	79	Breast	CFS	PF	-			-	-			
				MF	-			-	-			
Knobel, 2001[23]	92	M. Hodgkin	FQ	PF	-	-						
				MF								
Okuyama, 2000[30]	134	Breast	CFS	PF	+						-	+
				MF	-						-	+
Kuhnt, 2009[26]	646	Mixed	MFI	PF	+	-					+	+
				MF	+	+					-	-
Studies on cancer patients during curative treatment												
Purcell, 2010[32]	210	Mixed	MFI	PF	-	-	-	+			-	
				MF	-	-	+	-			-	
Studies on advanced cancer patients												
Inagaki, 2008[22]	46	Mixed	CFS	PF	-	-						
				MF								
Echteld, 2007[15]	100	Mixed	MFI	PF	-						-	+
				MF	-						+	-
Studies on cancer patients in various disease stages												
Van Weert, 2006[36]	72	Mixed	MFI	PF	-	-	-			-		
				MF	-	-	-			+		
Haghighat, 2003[17]	112	Breast	CFS	PF	-				+		+	-
				MF	-				-		+	-

+ Statistically significant relationship in multivariate analyses; **-** no significant relationship in multivariate analyses
PF = Physical Fatigue; MF = Mental Fatigue
FQ = Fatigue Questionnaire; MFI = Multidimensional Fatigue Inventory; CFS = Cancer Fatigue Scale

Variables not related to either physical fatigue or mental fatigue in either univariate or multivariate analyses: marital status[17,26,32,35], household size[30,35], educational level[17,26,32,35], employment[26,32,35], disease stage[17,23,26], tumour load[15], presence of lymph node metastasis[35], time since diagnosis[26,36], time since treatment[36], disease recurrence[36], appetite loss[15,30,35], weight loss[15,32], weight[22], vomiting[15,32], diarrhoea[15,26,32], constipation[26], hiccups[15], itch[15], red blood cells[35], haemoglobin level[15,35], white blood cells[35], creatinine[15], albumin[15], bilirubin[15], LDH[15], ASAT[15], TSH[23], previous surgery[32], type of surgery[17,30,35], days after surgery[35], chemotherapy[15,17,26,32,35,36], days after chemotherapy[35], number of chemotherapy lines received[15], radiotherapy[15,17,26,35,36], immunotherapy[15], treatment to the brain[32], treatment to the abdomen[32], psychological symptoms[36], psychiatric condition[32], extraversion[35], perception of disease recurrence[35], comorbidity[32], blood transfusions[32], attending a concurrent fatigue program[32], taking nutritional supplements[32], opioids[15], anti-emetics[15], benzodiazepines[15,30], anti-depressants[15], corticosteroids[15], neuroleptics[15], lean body mass[36], muscle force upper extremity[36], muscle force lower extremity[36], perceived physical functioning[36], perceived mental functioning[36], daily activities[32], moderate activity[32], carer hours[32], self efficacy[36].

Nausea	*Sleep problems*	*Depression*	*Anxiety*	*Menstruation pattern*	*Adjustment to illness*	*Role limitations*	*Social support*	*Neuroticism*	*Anti-convulsant use*	*ALAT*	*IL-6*	*Gas transfer impairment*	*Exercise*	*Vigorous activity*	*Maximal workload*	*Walking*	*Productive hours*
	-	-	-	-				+					-				
	-	-	-	+				+					-				
												+			-		
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	-	+	-				+										
	-	+	-		+		-										
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Generally, physical fatigue increased during anti-tumor therapy and decreased afterwards. In the studies that found significant changes in mental fatigue over time, the course of mental fatigue nearly always was the same as the course of physical fatigue.

Correlates of physical fatigue and mental fatigue

We found nine studies which investigated correlates of physical fatigue and mental fatigue in multivariate analyses[15,17,22,23,26,30,32,35,36] (Table 3). The studies varied considerably in the variables investigated. Most studies investigated demographic characteristics[15,17,22,23,26,30,32,35,36], physical symptoms[15,17,26,30,32], sleep problems, anxiety and depression[15,17,26,30,32,35].

Four studies included cancer survivors[23,26,30,35]. In the largest study physical fatigue and mental fatigue were correlated with different sets of variables[26]. In the three smaller studies

incongruence was found for only a minority of the correlates of physical fatigue and mental fatigue[23,30,35]. One of these studies focused on correlates not investigated by the other studies[23].

In the only study which included cancer patients during curative radiotherapy, different sets of correlates were found for physical fatigue and mental fatigue[32]. This was also the case in the largest of the two studies which recruited advanced cancer patients[15]. The smaller study focused on cytokines and did not investigate the variables included in the other studies[22]. Two studies enrolled cancer patients in various disease stages[17,36]. Both found different correlates for physical and mental fatigue.

In summary, although studies differed with respect to the included patient populations, most studies found different sets of correlates for physical fatigue and mental fatigue.

Course of physical fatigue and mental fatigue during interventions on fatigue

Fourteen randomized controlled trials reported about the effect of interventions on physical fatigue and mental fatigue[57-70] (Table 4). Eight studies included patients receiving curative treatment[58-60,63-65,68,70], four studies included cancer survivors[61,62,66,69], one study included advanced cancer patients[67], and one study included patients undergoing curative or palliative chemotherapy[57]. Two randomized controlled trials had a three-arm design; therefore, sixteen comparisons were made in fourteen articles. Only six studies reported a power analysis and sample size calculation[57,58,60,63,67,68].

The effect of complementary and alternative medicine interventions was evaluated in four studies including patients during curative treatment[58,59,63,65]. Acupuncture and acupressure statistically significantly alleviated physical fatigue, but not mental fatigue[65]; multivitamins[59] and Guaraná[58] were not effective in relieving any fatigue dimension; and relaxation breathing exercises caused statistically significant improvements in both physical fatigue and mental fatigue[63].

The studies which investigated the effect of psychological interventions showed contradictive results: a study on cognitive behavioral therapy for insomnia in cancer survivors found a statistically significant improvement in mental fatigue only[69], a study which investigated the effectiveness of cognitive behavior therapy in cancer patients in various disease stages reported a statistically significant improvement in physical fatigue only[57] and a study on education and behavioral therapy in patients undergoing curative radiotherapy did not find any improvement in either physical fatigue or mental fatigue[68].

A study on testosterone administration in cancer survivors[62] reported statistically significant improvements in physical fatigue but not in mental fatigue.

The results of the studies on physical exercise were heterogeneous. In cancer survivors one study found a decrease in physical fatigue only[61], whereas another study found a decrease in both physical fatigue and mental fatigue, although the effect size for physical fatigue was larger than the effect size for mental fatigue[66]. One study in patients during curative treatment found no decrease for any dimension[60], whereas the other study in patients during curative treatment reported a statistically significant improvement in physical fatigue, but not in mental fatigue[70]. One study investigated the effects of physical exercise in advanced cancer patients and did not find any improvements in physical fatigue or mental fatigue[67].

In two studies, multimodal interventions were investigated[64,66]. Physical exercise combined with cognitive behavioral therapy in cancer survivors resulted in improvements in physical fatigue only[66], while a combination of education, physical exercise and relaxation in patients during curative treatment was not effective in improving any fatigue dimension[64].

In summary, if fatigue decreased during an intervention, it was usually a decrease in physical fatigue. A decrease in mental fatigue occurred less frequently and was nearly always accompanied by a similar or even greater decrease in physical fatigue.

Discussion

The concept of the multidimensionality of fatigue is largely based on qualitative studies in which patients expressed fatigue as physical, cognitive or emotional sensations of tiredness[6,7]. In this review, we chose to focus on physical fatigue and mental fatigue, because these dimensions were acknowledged by the expert group of the European Association for Palliative Care[12]. We aimed to investigate whether physical fatigue and mental fatigue behave differently to determine whether the multiple symptom concept is preferable above the multidimensional concept (Figure 1).

In this review, we found some studies in which physical fatigue and mental fatigue behaved differently in cancer patients, which is in favor with the multiple symptom concept. There were some studies which found a changing intensity of physical fatigue during anti-tumor therapy or during an intervention aimed to relieve fatigue but a stable intensity of mental fatigue. Moreover, a study in cancer survivors found an increase in mental fatigue as compared to pre-treatment levels, but a stable intensity of physical fatigue[47], whereas another study reported a decrease in mental fatigue, but an increase in physical fatigue[41,42]. Also, physical fatigue had different correlates than mental fatigue. On the other hand, some studies supported the multidimensional concept: cancer survivors had both higher levels of physical fatigue and mental fatigue as healthy controls and there were a lot of studies that reported the same course for physical fatigue and mental fatigue over time.

In conclusion, the different behavior of physical fatigue and mental fatigue in some situations might suggest that physical fatigue and mental fatigue are separate phenomena and that further research on the multiple symptom concept is justified. To prove the multiple symptom concept, the pathogeneses of physical fatigue and mental fatigue have to be elucidated. Also, it should be investigated whether there are specific situations which effect mental fatigue but not physical fatigue, which could be expected if physical fatigue and mental fatigue are indeed separate phenomena.

This review reveals important gaps in the research on cancer-related fatigue. Although the multidimensionality of fatigue is widely accepted, we identified only 90 potentially eligible articles in which physical and mental fatigue were distinguished as separate dimensions of cancer-related fatigue. This is a rather small number compared to the yearly amount of publications about cancer-related fatigue. Furthermore, only five out of the 56 studies which fitted the inclusion and exclusion criteria of this review included advanced cancer patients; none of these studies reported about the course of fatigue over time and only one study

Table 4: Randomized controlled trials which reported about the course of physical fatigue and mental fatigue during interventions on fatigue

Author	n	Intervention group	Control group	Questionnaire
Complementary and alternative medicine				
Molassiotis 2007[65]	32	Acupressure	Sham acupressure	MFI
Molassiotis 2007[65]	31	Acupuncture	Sham acupressure	MFI
Da Costa Miranda 2009[58]	36	Guaraná (herbal medicine)	Placebo controlled randomized cross-over trial	ChFS
De Souza Fêde 2007[59]	35	Multivitamins	Placebo controlled randomized cross-over trial	ChFS
Kim 2005[63]	42	Relaxation breathing exercise	Standard care	R-PFS
Psychological interventions				
Ritterband 2012[69]	28	Cognitive behavioral therapy for insomnia	Wait list control	MFSI-SF
Armes 2007[57]	55	Cognitive behavioral therapy	Standard care	MFI
Purcell 2011[68]	110	Education and behavioral therapy	Standard care	MFI
Pharmacological interventions				
Howell, 2001[62]	35	Testosterone transdermal	Placebo patches	MFI
Physical exercise				
Heim 2007[61]	63	Physical exercise (more structured than standard rehabilitation program)	Rehabilitation program	MFI
Van Weert 2010[66]	133	Physical exercise	Waiting list	MFI
Haines 2010[60]	89	Multimedia physical exercise program	Multimedia flexibility and relaxation program	MFI
Wiskemann 2011[70]	105	Physical exercise	Social contact and regular physio-therapy	MFI
Oldervoll 2011[67]	231	Physical exercise	Standard care	FQ
Combined interventions				
Van Weert 2010[66]	138	Physical exercise + Cognitive behavioral therapy	On a waiting list for oncological rehabilitation	MFI
Lindemalm 2008[64]	41	Supportive group intervention (education, physical exercise, relaxation)	Standard care	FQ

PF = Physical Fatigue; MF = Mental Fatigue
[1] Active control condition (sham intervention) [2] Randomized cross-over trial [3] Effect sizes based on comparison CAN-FIT program vs. usual care [4] ≥3 findings (physical complaints, reduced physical capacity, psychological problems, increased fatigue, sleep disturbances, coping problems)
MFI = Multidimensional Fatigue Inventory; ChFS = Chalder Fatigue Scale; CFS = Cancer Fatigue Scale ;

Patients			Prerequisite on fatigue level	Follow up	Power analysis	PF		MF	
Tumor	*Stage*	*Tumor treatment*				*Effect*	*Effect size*	*Effect*	*Effect size*
Mixed	Curative treatment	Mixed	NRS-fatigue ≥5/10	4wk	-	↓	-0.47	=	+0.11
Mixed	Curative treatment	Mixed	NRS-fatigue ≥5/10	4wk	-	↓	-0.89	=	-0.10
Breast	Curative treatment	RT	-	4wk	+	=	?	=	?
Breast	Curative treatment	RT	-	4wk	-	=	?	=	?
Hematological malignancies	Curative treatment	Allogeneic SCT	-	6wk	+	↓	-2.75	↓	-2.10
Mixed	Survivors	-	Poor sleep >6m, ≥3 nights/week	9wk	-	=	-0.47	↓	-0.66
Mixed	Mixed	CT	Report "significant fatigue"	9mo	+	↓	-0.86	=	-0.19
Mixed	Curative treatment	RT	-	6wk post-RT	+	=	0.47[3]	=	0.14[3]
Hematological malignancies	Survivors	-	-	15mo	-	↓	?	=	?
Breast	Survivors	-	NRS-fatigue ≥4/10	3mo after rehabilitation	-	↓	?	=	?
Mixed	Survivors	-	≥3 findings[4]	12wk	-	↓	-0.55	↓	-0.30
Breast	Curative treatment	Mixed	-	6mo	+	=	-0.02	=	-0.04
Hematological malignancies	Curative treatment	Allogeneic SCT	-	6-8wk after discharge	-	↓	-0.76	=	0.24
Mixed	Advanced cancer	Mixed	-	8wk	+	=	-1.12	=	-0.50
Mixed	Survivors	-	≥3 findings[4]	12wk	-	↓	-1.16	=	-0.25
Breast	Curative treatment	RT ± CT	?	12mo	-	=	0.06	=	0.44

FQ = Fatigue Questionnaire; R-PFI = Revised Piper Fatigue Scale; MFSI-SF = Multidimensional Fatigue Symptom Inventory ; FQ = Fatigue Questionnaire; NRS = Numeric Rating Scale
RT = radiotherapy; CT = chemotherapy; SCT = stem cell transplantation
↓ (statistically significant decrease); = (no significant difference);
Effect size = degree of difference between the groups in the effect of the intervention

reported on the effect of interventions on fatigue in these patients. Moreover, there were few studies which compared fatigue experiences of patients in different stages of cancer, whereas we previously found that advanced cancer patients and cancer survivors had different fatigue experiences[13]. Also, we found few studies investigating fatigue in short-term survivors and long-term survivors simultaneously. Furthermore, only a few studies reported on correlates of physical and mental fatigue (Table 3), which is necessary to generate hypothesis on the pathogenesis of the separate fatigue dimensions. Also, only a minority of the randomized controlled trials on cancer-related fatigue reported in literature assessed the effects of the intervention on physical fatigue and mental fatigue separately.

An important limitation of this review is the heterogeneity of the questionnaires used in the included studies. Although all multidimensional fatigue questionnaires have subscales referring to the physical and mental sensations of tiredness, the items of the subscales differ greatly between the questionnaires. For example, the Mental Fatigue subscale of the Multidimensional Fatigue Inventory only asks questions about the ability to concentrate[10], whereas the Mental Fatigue Subscale of the Fatigue Questionnaire asks questions about concentration, memory, finding correct words and slips of the tongue[9]. Therefore, it is unknown whether all these questionnaires are measuring exactly the same aspects of fatigue, limiting the comparability of the studies included in this review. We limited our literature search to English articles, which is another limitation, because we cannot exclude that valuable articles are published in other languages and from other cultures.

Despite the heterogeneity in the quality of the studies included in this review we did not perform a quality assessment, which is another limitation of this review. However, there is no well-validated quality assessment tool for observational studies[71]. We decided not to do a quality assessment with a non-evidence based tool as this might have introduced selection bias. Nevertheless, we tried to avoid adopting false-positive results from studies by excluding uncontrolled intervention studies, randomized controlled trials which did not perform an analysis on the differences between the groups over time, and studies which only univariately assessed associations between fatigue and other variables. Furthermore, several aspects concerning study quality (e.g. sample size, power analysis, type of control sample) were described in the tables.

In conclusion, we found some studies in which physical fatigue and mental fatigue behaved differently. These findings might indicate that physical fatigue and mental fatigue are separate phenomena and that fatigue should be considered as a multiple symptom concept. However, to prove the multiple symptom concept, we have to investigate the pathogenesis of physical fatigue and mental fatigue separately. A different pathogenesis is a strong argument for the multiple symptom concept. If the multiple symptom concept is proven, a paradigm shift in the management of fatigue is needed: physical fatigue and mental fatigue should be investigated separately in research and should be assessed separately in daily practice. Also, if they are separate phenomena, it is reasonable to suppose that physical fatigue and mental fatigue need different treatments. Therefore, in randomized controlled trials on interventions to alleviate fatigue, fatigue dimensions should be included as outcome variables, to assess which interventions are effective against which type of fatigue. In our opinion, such approach is a prerequisite for inventing effective treatments for a multi-causal symptom like fatigue.

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3

Differences in fatigue experiences among patients with advanced cancer, cancer survivors, and the general population

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Abstract

Context

Fatigue is a multidimensional symptom experienced physically, cognitively and emotionally. Research on fatigue experiences in various stages of cancer might help to elucidate the nature of cancer-related fatigue.

Objective

To compare fatigue experiences in patients with advanced cancer (ACPs), cancer survivors (CSs), and controls from the general population (GenPop).

Methods

Sixty-three ACPs (no antitumour therapy in the last month and no options for future therapy) were matched for age, sex and diagnosis with 63 CSs (last treatment one to five years ago) and 315 controls. Fatigue was measured unidimensionally with the Numeric Rating Scale (NRS) and multidimensionally with the Multidimensional Fatigue Inventory.

Results

All fatigue levels (general fatigue, physical fatigue, reduced activity, reduced motivation, mental fatigue) were higher in ACPs than in CSs and controls ($p<0.01$), whereas fatigue levels were not different between CSs and controls. NRS scores in ACPs and CSs were significantly predicted by the fatigue dimensions physical fatigue and mental fatigue only. Although physical fatigue and mental fatigue were strongly related in the GenPop, the relation was weaker in CSs and not significant in ACPs. In multivariate analyses, only physical fatigue differentiated ACPs from CSs and controls ($p<0.01$)

Conclusion

ACPs experience fatigue more intensely than CSs and controls when fatigue is measured multidimensionally. Although mental and physical dimensions of fatigue contribute to the overall experience of fatigue in both groups of cancer patients, physical fatigue best differentiated ACPs from both CSs and controls.

Introduction

Healthy people's fatigue is a normal phenomenon, helping them to schedule their lives[1], whereas cancer patients describe their fatigue as a chronic, unpleasant, distressing and activity-limiting tiredness throughout the day[1-2]. Cancer-related fatigue has more negative impact on daily activities and quality of life than other cancer-related symptoms, such as depression, pain and nausea[3].

Both cancer patients and healthy individuals express their experiences of fatigue as physical, affective and cognitive feelings of tiredness, which suggests that fatigue is a multidimensional phenomenon[1]. Although the multidimensionality of fatigue is widely accepted, it is still unclear how many dimensions fatigue has and which dimensions significantly contribute to the experience of fatigue, often measured by unidimensional instruments such as the zero to ten Numeric Rating Scale (NRS). An expert group of the European Association for Palliative Care reached consensus on the existence of at least a physical dimension and a cognitive dimension of fatigue[4].

Few studies have compared multidimensional fatigue experiences in different stages of cancer. A study that compared fatigue levels in advanced cancer patients (ACPs) and cancer patients receiving curative radiotherapy found both higher levels of physical fatigue and mental fatigue in the ACPs[5]. Another study, which compared ACPs and cancer survivors (CSs), found higher levels of physical fatigue in ACPs but similar levels of mental fatigue in both[6]. However, in both studies the two study populations differed greatly in age, tumour type, and treatment received; and one study did not perform statistical tests[6]. Eight studies reported higher levels of both physical and mental fatigue in CSs than in age-matched controls[7-14]. Most of these studies included CSs younger than 60 years only.

In conclusion, most studies on the multidimensionality of cancer-related fatigue did not make a comparison with properly matched patients in another stage of cancer. Consequently, it remains unclear whether patients at different stages of the disease have different fatigue experiences. A better understanding of possible differences in fatigue between patients in different stages of cancer may help to elucidate the characteristics of cancer-related fatigue, which is essential to formulate new hypothesis about the pathogenesis of cancer-related fatigue.

The aim of this study was to examine whether ACPs, CSs, and the general population (GenPop) experience fatigue differently. The study groups were matched for age, sex and diagnosis (if applicable). We investigated:

1. Differences in the intensity of separate fatigue dimensions among the groups.
2. The contribution of these separate fatigue dimensions to the overall fatigue experience in ACPs and CSs.
3. Which of the dimensions contributing to the overall fatigue experiences differentiate best between the studied groups.

Based on a previous study[15] and on clinical experience, we expected physical fatigue to be more prominent in ACPs.

Patients and methods

Study population

ACPs admitted to the palliative care unit or having an appointment at the outpatient clinic of the Erasmus MC Daniel den Hoed Cancer Centre were invited to participate in this study. They were eligible if systemic anti-tumour therapy was considered to be no longer appropriate and if they had not received any systemic antitumour therapy in the last four weeks.

For every ACP, a CS matched for age (± five years), sex, and diagnosis was recruited at the outpatient clinic. CSs were eligible if their last treatment had been received one to five years ago and if there was no evidence of disease at the moment of inclusion. Patients still receiving adjuvant hormonal therapy for breast cancer were eligible for inclusion. The Medical Research Ethics Committee of the Erasmus MC granted ethical permission for this study, and all patients gave written informed consent.

Additionally, for each ACP, five age- and sex-matched controls were randomly drawn from a database with scores of a sample of the German GenPop on the Multidimensional Fatigue Inventory (MFI)[16]. Because there are no major cultural differences between Germany and The Netherlands, we considered that it was justified to extrapolate these norm values to the Dutch situation.

Measurements

Data on demographic characteristics and disease characteristics of ACPs and CSs, including tumour type and anticancer therapy received, were collected from the electronic medical record.

The cancer patients rated the severity of their fatigue unidimensionally with the NRS. They had to indicate their intensity of fatigue in the last week on an 11-point scale, ranging from 0 ("no fatigue") to 10 ("the worst fatigue you can imagine"). A score of four or higher was used as a cutoff score for clinically relevant fatigue, as suggested by the National Comprehensive Cancer Network[2].

To measure the various dimensions of fatigue, cancer patients completed the MFI, a multidimensional, self-report questionnaire that comprises 20 statements. Patients had to indicate to what extent each statement applied to them on a five-point Likert-scale. The MFI covers five dimensions: 1. general fatigue, general remarks about feelings of tiredness; 2. physical fatigue, remarks on the physical sensations of tiredness; 3. reduced activity, remarks about a decrease in level of activity; 4. reduced motivation, referring to the lack of motivation to do things; and 5. mental fatigue, referring to difficulty in concentrating[17]. The items and dimensions of the MFI have been postulated based on patient interviews and its five-dimensional structure has been confirmed by factor analysis[18]. Subscale scores range from four to 20. The higher the scores, the greater the fatigue[17]. The psychometric properties of the MFI in terms of internal consistency, discriminant validity, and convergent validity are satisfactory[19]. Schwarz et al. provided norm values for the MFI from a GenPop in Germany[16]. We selected our age- and sex-matched controls from this dataset as described previously.

Data analyses

Our primary endpoint was the difference in physical fatigue between ACPs and CSs. To detect a clinically relevant difference (Cohen's d of 0.50) in our primary endpoint, with a two-tailed α value of 0.05 and a power of 0.80, the sample size required was 63 per group.

Table 1: Patients' characteristics

	Advanced cancer patients	Cancer survivors	General population
	(n=63)	(n=63)	(n=315)
Age – mean (SD)	59 (12)	59 (11)	59 (12)
Sex – n (%)			
Male	28 (44%)	28 (44%)	140 (44%)
Female	35 (56%)	35 (56%)	175 (56%)
Hospitalized – n (%)			
Yes	35 (56%)		
No	28 (44%)	63 (100%)	
WHO performance – n (%)			
0	1 (2%)	38 (61%) ‡**	
1	24 (39%)	23 (37%)	
2	17 (27%)	1 (2%)	
3	16 (26%)	0 (0.0%)	
4	4 (7%)	0 (0.0%)	
Cancer diagnosis – n (%)			
Breast	18 (29%)	18 (29%)	
Gastro-intestinal	16 (25%)	16 (25%)	
Urogenital	11 (18%)	11 (18%)	
Other	18 (29%)	18 (29%)	
Treatment – n (%)			
Surgery			
Total	46 (73%)	61 (97%) **	
Curative	45 (71%)	61 (97%) **	
Palliative	15 (24%)		
Chemotherapy			
Total	50 (79%)	36 (57%) **	
Curative	25 (40%)	36 (57%) *	
Palliative	44 (70%)		
Radiotherapy			
Total	41 (65%)	29 (46%) *	
Curative	24 (38%)	29 (46%)	
Palliative	28 (44%)		
Hormonal therapy			
Total	15 (24%)	17 (27%)	
Curative	7 (11%)	17 (27%) *	
Palliative	13 (21%)		
Time since last treatment (months) – mean (SD)	36 (17.4)	4 (5.6) **	

* p<0.05 ** p<0.01
‡ overall difference between groups

Differences in treatment and disease characteristics between ACPs and CSs were calculated using Chi-square tests. Survival of the ACPs was calculated using the Kaplan-Meier method.

Depending on the normality of the distribution of the scores, the differences between the ACPs, CSs and GenPop in the intensity of the primary endpoint physical fatigue and the other fatigue measurements were determined using the Mann-Whitney-U test or the independent Student's t-test. We calculated for both groups of cancer patients the Spearman's correlations between the NRS and the MFI dimensions. To investigate which fatigue dimensions determined the overall experience of fatigue as rated on the NRS in ACPs and CSs, we performed a backward linear regression analysis for each group, with the NRS score as the dependent variable and the scores on the dimensions physical fatigue, reduced activity, reduced motivation and mental fatigue as the independent variables. We excluded the MFI dimension general fatigue from these analyses because general fatigue is considered to be a unidimensional measure of fatigue[17]. Therefore, we expected no relevant insight from the relation between general fatigue and the NRS. Thereafter, we calculated in each group the Spearman's correlation coefficient between the dimensions significantly predicting the NRS scores. Finally, to examine which of these dimensions differentiated best among ACPs, CSs and GenPop, we performed backward multivariate logistic regression analyses with the group of cancer patients as dependent variable and the dimensions of the MFI that significantly predicted NRS scores as independent variables. All analyses were performed using SPSS for Windows version 17.0 (SPSS, Inc., Chicago, IL).

Results

Between October 2008 and October 2010, we included a total of 63 ACPs and 63 CSs. These cancer patients were compared with 315 individuals from the German GenPop. Patient characteristics are presented in Table 1. As a result of the matching of patients, the distribution of age, sex, and cancer diagnosis was comparable in the groups. ACPs had a lower physical performance score than CSs. Nineteen percent of ACPs had been diagnosed with incurable disease at the first presentation and, therefore, these patients had not received any treatment aimed at cure. The median survival of ACPs was 93 days (interquartile range 26-199), whereas all CSs were alive in October 2010.

In ACPs, the unidimensionally measured fatigue was more severe than in CSs (mean 5.7 ± 2.5 standard deviation [SD] vs. mean 3.5 ± 2.6 SD, $p < 0.001$). Clinically relevant fatigue, as defined by an NRS score of four or higher, was experienced by 80% of ACPs and 53% of CSs ($p < 0.01$). The intensity of fatigue as measured with the MFI in ACPs, CSs, and GenPop is shown in Figure 1. ACPs reported more fatigue on all fatigue dimensions than CSs and GenPop (all p-values ≤ 0.01). In these univariate analyses, there were no significant differences in the intensity of fatigue between CSs and the GenPop.

To explore the relation between the NRS and the MFI dimensions in the cancer patients, correlation coefficients were calculated for ACPs and CSs separately (Table 2). In the ACPs, only reduced motivation was not correlated to the NRS, whereas all MFI dimensions were significantly correlated with the NRS scores in the CSs. Linear regression analyses revealed that, in ACPs as well as in CSs, physical fatigue and mental fatigue significantly predicted the NRS scores (Table 3). However, the percentage of explained variance in the NRS scores was lower in

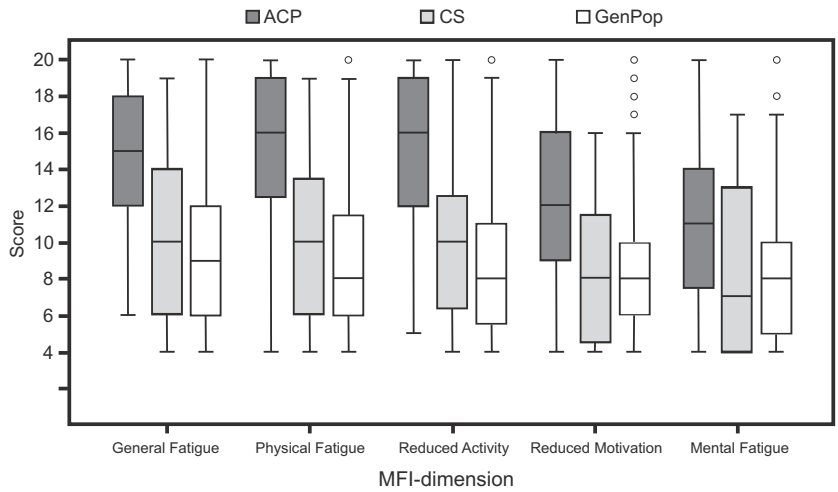

Figure 1: Boxplot of the scores of ACP, CS, and the GenPop on the dimensions of the MFI. Horizontal line = median; bar = interquartile range; t-bar = range (except outliers); dots = outliers; ACP = advanced cancer patients; CS = cancer survivors; GenPop = general population; MFI = Multidimensional Fatigue Inventory

Table 2: Spearman's correlation coefficients between the NRS and the MFI-dimensions for advanced cancer patients and cancer survivors

	Correlation with the NRS	
	Advanced cancer patients	**Cancer survivors**
General Fatigue	0.56**	0.88**
Physical Fatigue	0.43**	0.79**
Reduced Activity	0.29*	0.60**
Reduced Motivation	0.20	0.46**
Mental Fatigue	0.39**	0.48**

* p <0.05
** p <0.01

Table 3: Backward multivariate linear regression analyses to predict NRS-scores of advanced cancer patients (ACP) and cancer survivors (CS), based on the intensity of Physical Fatigue, Reduced Activity, Reduced Motivation and Mental Fatigue

	Standardized regression weights (β)	**p**	**Percentage explained variance (R^2)**	**Variance Inflation Factor**
ACP[1]			0.32	1.06
Physical Fatigue	0.40	<0.01		
Mental Fatigue	0.34	<0.01		
CS[1]			0.62	1.18
Physical Fatigue	0.67	<0.01		
Mental Fatigue	0.23	0.01		

[1] Variables not in the equation: Reduced Activity and Reduced Motivation

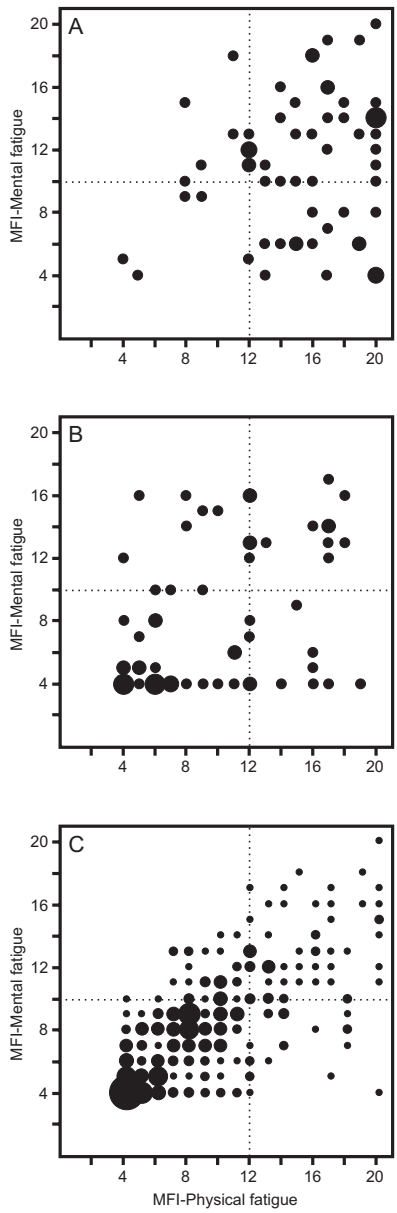

Figure 2: Individual scores on physical fatigue and mental fatigue for A) ACP, B) CS, and C) GenPop.
Dotted lines: p75 of the matched 315 GenPop. The size of the dots reflects the number of patients with that particular score.
ACP = advanced cancer patients; CS = cancer survivors; GenPop = general population; MFI = Multidimensional Fatigue Inventory.

ACPs than CSs (32% vs. 62%). No indication of multicollinearity was found.

To explore the relationship between physical fatigue and mental fatigue, scores of the individual patients were plotted for each group separately (Figure 2). In ACPs, physical fatigue and mental fatigue were not correlated ($r = 0.15$, not significant). Seventy-five percent of ACPs had a score on physical fatigue in the upper quartile of the scores of the GenPop, with various levels of mental fatigue. In CSs, physical fatigue and mental fatigue were slightly correlated ($r = 0.35$, $p<0.01$). The distribution of scores on physical fatigue and mental fatigue was heterogeneous in the CSs: 11% had a score in the upper quartile of physical fatigue only, 19% had a score in the upper quartile of mental fatigue only, and 16% had a score in both upper quartiles of physical fatigue and mental fatigue. In the GenPop, physical fatigue and mental fatigue were significantly correlated ($r = 0.68$, $p<0.01$).

Multivariate logistic regression analyses revealed that only the levels of physical fatigue differentiated between ACPs and CSs and between ACPs and GenPop (Table 4). We did not perform a multivariate analysis to differentiate between CSs and GenPop because there were no significant differences in the dimensions of the MFI in the univariate tests.

Exploratory analyses

We retrospectively divided the CSs and the GenPop in a group aged younger than 60 years and a group aged 60 years or older. In the group aged younger than 60 years, the CSs had significantly higher fatigue scores than the GenPop on all dimensions of the MFI, except reduced motivation ($p<0.05$). On the contrary, in the group aged 60 years or older, the CSs had significantly lower scores on mental fatigue and reduced motivation than the GenPop ($p<0.05$), without significant differences in the other dimensions.

Table 4: Backward multivariate logistic regression analyses using Physical Fatigue and Mental Fatigue to predict group

	ACP vs. CS			ACP vs. GenPop		
	Odds ratio[1]	*p*	R^2	*Odds ratio*[2]	*p*	R^2
Physical Fatigue	1.28 (1.16-1.40)	<0.01	0.32	1.34 (1.25-1.44)	<0.01	0.36
Mental Fatigue	-	0.16		-	0.85	

[1] Reference = CS
[2] Reference = GenPop

Discussion

In this study, we show that ACPs experience fatigue differently from CSs. First, the ACPs experienced more fatigue than the CSs and the GenPop in all dimensions studied. Second, although physical fatigue and mental fatigue were the relevant dimensions of fatigue in both ACPs and CSs, these dimensions seem to be separate symptoms in the ACPs, where no correlation was found between these dimensions. Finally, in multivariate analyses, only physical fatigue discriminated between ACPs and both CSs and the GenPop, which indicates that the physical aspects of fatigue are more prominent in these patients.

No significant differences were found in the fatigue intensity between CSs and the GenPop. However, there was more heterogeneity in the relationship between physical fatigue and mental fatigue among CSs. Therefore, it is impossible to characterize one pattern of fatigue for the whole group, but there might be subgroups with different patterns of fatigue in the CSs: only physically fatigued, only mentally fatigued and both physically and mentally fatigued.

Our results are in agreement with Hagelin et al. who found higher levels of both physical and mental fatigue in ACPs than in patients in another stage of cancer[5]. They are in contrast to the study of Knobel et al., who found similar levels of mental fatigue in ACPs and CSs[6]. However, Knobel et al. recruited ACPs still receiving treatment, whereas we included ACPs without treatment options. Futhermore, we matched the groups on age, sex and diagnosis, whereas Knobel et al. did not. Our results were also in contrast with the studies that found higher levels of both physical fatigue and mental fatigue in CSs than in healthy controls[7-14]. However, in most of these studies, the CSs included were much younger than our cancer survivors[8-13]. In our exploratory analyses, we found that especially young CSs (younger than 60 years) experienced more fatigue than their peers, but we did not find an excess in fatigue in the older cancer survivors (60 years or older).

In our study, of the five dimensions of the MFI, only physical fatigue and mental fatigue were significantly related to the fatigue scores on an NRS. Remarkably, the explained variance in NRS was much higher in the CSs than in the ACPs. This indicates that there must be unknown factors in the ACPs which influenced the scoring on the unidimensional NRS.

Furthermore, we do not know how the scores on fatigue dimensions change with increasing levels of fatigue. The different relation between physical fatigue and mental fatigue between ACPs and CSs might be caused by different underlying pathofysiological mechanisms. However, another explanation might be that the relation between the physical

and mental dimensions of fatigue is dependent on the intensity of fatigue. In that case, the differences we found between the advanced cancer patients and cancer survivors are caused by a difference in prevalence of clinically relevant fatigue rather than by different pathogeneses between the groups.

A limitation of the study is that we do not know whether a certain fatigue score represents fatigue of the same severity in both groups. It is known that personal experience of extreme fatigue affects patients' judgment of their fatigue levels and causes them to assign lower fatigue scores[20]. This phenomenon, which is called response shift, might contribute to the findings of similar fatigue intensities in the CSs and the GenPop.

Another limitation of our study is the completion of the MFI in various languages: the cancer patients completed the original Dutch version and the GenPop the German version. This might have led to measurement nonequivalence. However, the German version of the MFI was translated by two independent persons in collaboration with the first author of the Dutch version[16], which makes measurement non-equivalence less likely.

Finally, an additional limitation of our study is the heterogeneity of the included patients. Although the patients were matched for age, sex, and diagnosis, we still expect the groups to differ in many ways, for example, in the use of medication. Furthermore, because of the inclusion of patients with different tumor types, we also expect a great intragroup variability, especially in tumor load in the ACPs and in the intensity of received treatment in the CSs. This heterogeneity should be kept in mind when interpreting the results of our study.

Despite these limitations, we have shown that ACPs have other fatigue experiences than CSs and the GenPop. As expected, the ACPs with progressive disease without treatment options mainly suffered from the physical sensations of fatigue. We were not able to show unequivocally that CSs experienced more fatigue than the GenPop, although response shift cannot be excluded. Surprisingly, mental fatigue was not related to the physical senses of tiredness in the ACPs. Among fatigued CSs, the pattern of fatigue seems to be heterogeneous, with some CSs reporting about physical fatigue, others about a difficulty to concentrate and others experiencing both kinds of fatigue.

These results imply that physical fatigue and mental fatigue also may represent different phenomena and, therefore, should be studied separately in future research. In intervention studies, separate fatigue dimensions should be measured to determine if the intervention is effective on the physical senses of fatigue, on problems with concentrating or on multiple dimensions of fatigue. Because of the heterogeneous presentation of fatigue in CSs, it is especially important to measure fatigue multidimensionally in this group, to clarify which kind of fatigue they suffer from. It should be investigated whether different pathways are involved in the pathogenesis of the various fatigue dimensions. Insight regarding these pathways may stimulate the development of patient-tailored interventions based on individual fatigue experiences.

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4

Inflammation and fatigue dimensions in advanced cancer patients and cancer survivors: an explorative study

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Abstract

Background

Inflammation may underlie cancer-related fatigue; however, there are no studies that assess the relation between fatigue and cytokines in patients with advanced disease versus patients without disease activity. Furthermore, the relation between cytokines and the separate dimensions of fatigue is unknown. Here, association of plasma levels of inflammatory markers with physical fatigue and mental fatigue was explored in advanced cancer patients and cancer survivors.

Methods

A total of 45 advanced cancer patients and 47 cancer survivors completed the subscales Physical Fatigue and Mental Fatigue of the Multidimensional Fatigue Inventory. Plasma concentrations of C-reactive protein (CRP), interleukin-1 receptor antagonist (IL-1-ra), interleukin-6 (IL-6), interleukin-8 (IL-8), and neopterin were measured. Nonparametric tests were used to assess differences in fatigue intensity and levels of inflammatory markers and to determine correlation coefficients between the fatigue dimensions and inflammatory markers.

Results

Compared with cancer survivors, patients with advanced cancer had higher levels of physical fatigue (median 16 vs 9, $p<0.001$) and mental fatigue (median 11 vs 6, $p=0.01$). They also had higher levels of all cytokines ($p<0.01$). In advanced cancer, CRP ($r=0.49$, $p=0.001$), IL-6 ($r=0.43$, $p=0.003$), IL-1-ra ($r=0.32$, $p=0.03$), and neopterin ($r=0.25$, $p=0.10$) were correlated with physical but not with mental fatigue. In cancer survivors, only IL-1-ra was related to both physical fatigue ($r=0.24$, $p=0.10$) and mental fatigue ($r=0.35$, $p=0.02$).

Conclusions

In advanced cancer, inflammation seems to be associated with physical fatigue, but not to mental fatigue. In cancer survivors, there was no convincing evidence that inflammation plays a major role in fatigue.

Introduction

Fatigue is one of the most frequent and pervasive symptoms among cancer patients. Patients in all stages of the disease trajectory, from before diagnosis to years after treatment, experience fatigue, which has a greater negative impact on quality of life and daily functioning than any other cancer-related symptom[1]. Patients describe their feelings of fatigue as physical, cognitive, and affective senses of tiredness, which indicates that fatigue is a multidimensional phenomenon[2].

Although the exact pathogenesis of fatigue is still unknown, there is not much doubt about the multicausality of fatigue[3]. Inflammation has been hypothesized to be one of the causes of cancer-related fatigue[3-6]. In a review that pooled correlation coefficients between fatigue and cytokine serum levels of individual studies, a statistically significant positive association was found between fatigue and circulating levels of interleukin-6 (IL-6), interleukin-1 receptor antagonist (IL-1-ra), and neopterin[5]. These inflammatory markers may be produced by tumor cells or by inflammatory cells after their stimulation by antitumor treatment, tumor cells or psychological distress[6]. They may provoke cancer-related fatigue by inducing anemia, disturbances in the hypothalamic-pituitary-adrenal axis or alterations in brain serotonin metabolism[4].

Although a statistically significant association between inflammation and fatigue has been found in cancer patients at various stages of the disease trajectory[5], there are no studies that compared different groups of patients, ie, patients with advanced disease and cancer survivors, with respect to this association. Nevertheless, because tumor load, antitumor therapy, and distress are known to affect cytokine levels[6], it seems reasonable to suppose a different role of inflammation at various time points along the disease trajectory. Furthermore, most studies on cytokines and fatigue measured fatigue as a single symptom, whereas fatigue is known to have both physical and cognitive dimensions. These dimensions of fatigue might have different etiologies. For that reason, it is important to investigate whether inflammation is associated with all dimensions of fatigue or only with a single dimension.

In contrast to previous studies, we explored the association between fatigue and inflammation in patients with advanced cancer and in cancer survivors and for the physical and mental dimensions of fatigue separately. Based on the review of Schubert et al, we decided to measure plasma concentrations of IL-6, IL-1-ra and neopterin, because these markers were found to be significantly correlated with fatigue[5]. Furthermore, we measured C-reactive protein (CRP), because it is considered to be a surrogate marker of IL-6 activity[4] for which routine measurements are available in clinical practice. We also measured interleukin-8 (IL-8), because we previously found an increase in the concentration of this cytokine after infusion of taxanes, which are known to cause major fatigue (unpublished data). In these exploratory analyses, we aimed to identify inflammatory markers possibly involved in the pathogenesis of cancer-related fatigue, which should be studied in greater detail in subsequent studies. Therefore, we determined in both advanced cancer patients and cancer survivors:

1. which inflammatory markers are related to physical fatigue and mental fatigue.
2. whether inflammatory markers that are associated with fatigue are related to each other.

Materials and methods

Study population

Patients included in this study originated from an observational study on differences in fatigue experiences between advanced cancer patients and cancer survivors[7]. Advanced cancer patients admitted to the palliative care unit or having an appointment at the outpatient clinic of the Erasmus MC Daniel den Hoed Cancer Centre, Rotterdam, the Netherlands, were invited to participate in the study. They were eligible when systemic anticancer therapy was no longer available and when they had not received any systemic anticancer therapy in the last 4 weeks.

For every advanced cancer patient, a cancer survivor matched for age, sex, and cancer diagnosis was recruited at the outpatient clinic. If feasible, they were also matched for treatment received for the primary tumor. These cancer survivors were eligible if their last treatment had been received 1 to 5 years ago and if there was no evidence of disease at the moment of inclusion. Patients still receiving adjuvant endocrine therapy for breast cancer were eligible for inclusion.

Patients for whom regular laboratory examinations were planned by their physician were asked permission for taking 1 extra blood sample for research on the relationship between fatigue and inflammatory markers. Here, data are published for the patients who both provided a blood sample and completed the fatigue questionnaire.

The Research Ethics Committee at the Erasmus MC granted ethical permission for this study, and all participants gave informed consent before data collection.

Procedures

All eligible participants were given oral and written information by the first author and were asked to give written consent. Venous blood samples, anticoagulated with ethylene diamine tetraacetic acid, were taken between 8am and 12noon in order to minimize the effects of diurnal fluctuations in cytokine levels[8]. Plasma was harvested within 2 hours from collection, and stored in aliquots at -80°C until analysis. Patients were requested to complete the fatigue questionnaire on the same day as the laboratory examination.

Questionnaire

Data on demographic characteristics and disease characteristics, including tumor type and anticancer therapy received, were collected from the electronic medical record.

The dimensions of fatigue were measured with the physical fatigue and mental fatigue subscales of the Multidimensional Fatigue Inventory (MFI). The subscale physical fatigue consists of 4 statements referring to the physical sensations related to subjective fatigue, and the subscale mental fatigue consists of 4 statements referring to cognitive symptoms (Table 1). Patients have to indicate to what extent each statement applied to them on a 5-point Likert scale. Both subscale scores range from 4 to 20, with higher score indicating more severe fatigue[9]. Schwarz et al provided reference values for the MFI, determined in a sample of 2037 German representatives from the general population[10].

Table 1: Items of the subscales Physical Fatigue and Mental Fatigue of the Multidimensional Fatigue Inventory[9]

Physical Fatigue	Mental Fatigue
1. Physically I feel only able to do a little	1. When I am doing something, I can keep my thoughts on it
2. Physically I can take on a lot	2. I can concentrate well
3. Physically I feel I am in a bad condition	3. It takes a lot of effort to concentrate on things
4. Physically I feel I am in an excellent condition	4. My thoughts easily wander

Measurement of inflammatory markers

Plasma concentrations of CRP, IL-1-ra, and neopterin were measured by enzyme-linked immunosorbent assays using commercially available kits (CRP: Assay Pro, St Charles, Mo; IL-1-ra: R&D Systems, Minneapolis, Minn; neopterin: IBL International, Hamburg, Germany) according to manufacturer instructions. IL-6 and IL-8 plasma concentrations were determined by the Cytometric Bead Arrays (BD Bioscience, San Diego, Calif) according to the manufacturer instructions. Samples were tested in duplicate and related to the standard curves for each assay. The lowest detection limit per assay was 0.25 ng/mL for CRP; 1.35 nmol/L for neopterin; 15.6 pg/mL for IL-1-ra; 5.0 pg/mL for IL-6 and 2.5 pg/mL for IL-8. If the level of an inflammatory marker was undetectable, the detection limit for that cytokine was imputed in the dataset.

Data analyses

Because this study is a secondary analysis of a previous study, we did not perform a power analysis. Because of the explorative character of this study, p-values were not corrected for multiple testing and associations with $p<0.10$ are considered to be important to investigate in further research. Differences in patients' and disease characteristics between advanced cancer patients and cancer survivors were assessed with the chi-square test. Differences between advanced cancer patients and cancer survivors in the intensity of fatigue, and the levels of the inflammatory markers were determined with the Mann- Whitney U test. For both advanced cancer patients and cancer survivors, Spearman correlation coefficients were calculated to explore the relationships between fatigue measurements and concentrations of inflammatory markers.

Results

We included a total of 63 advanced cancer patients and 63 cancer survivors in the original study between October 2008 and October 2010. Eighteen advanced cancer patients and 16 cancer survivors did not provide a blood sample, because their physician had not planned a regular laboratory examination. In this study, we present the data of the 45 advanced cancer patients and the 47 cancer survivors who both completed the questionnaire and provided a blood sample. In this analysis, 12 advanced cancer patients and 14 cancer survivors were unmatched because their match did not provide a blood sample, 22 pairs of patients were matched for age,

sex, and diagnosis, and 11 pairs of patients were matched for age, sex, diagnosis, and treatment of primary tumor. Patients' characteristics and fatigue scores are presented in Table 2. There were no significant differences between the groups in age, sex, or tumor diagnosis. Advanced cancer patients had a significantly lower physical performance than cancer survivors (p<0.01). Advanced cancer patients had undergone primary surgery less frequently than cancer survivors (<0.01), because 18% of advanced cancer patients already had advanced disease at the time of diagnosis. Advanced cancer patients had been treated with chemotherapy and radiotherapy more frequently than cancer survivors (p<0.05). Compared to cancer survivors, advanced cancer patients had higher levels of physical fatigue (median 16 vs 9, p<0.001) and mental fatigue (median 11 vs 6, p=0.01).

Levels of inflammatory markers for advanced cancer patients and cancer survivors are shown in Figure 1. Levels of all inflammatory markers were higher in advanced cancer patients than in cancer survivors (p<0.01). A total of 93% of advanced cancer patients and 21% of cancer survivors had at least 1 marker above the upper limit of the normal range (p<0.001). Seventy-three percent of advanced cancer patients and 6% of cancer survivors had at least 1 marker at 2 times higher than the upper limit of the normal range (p<0.001).

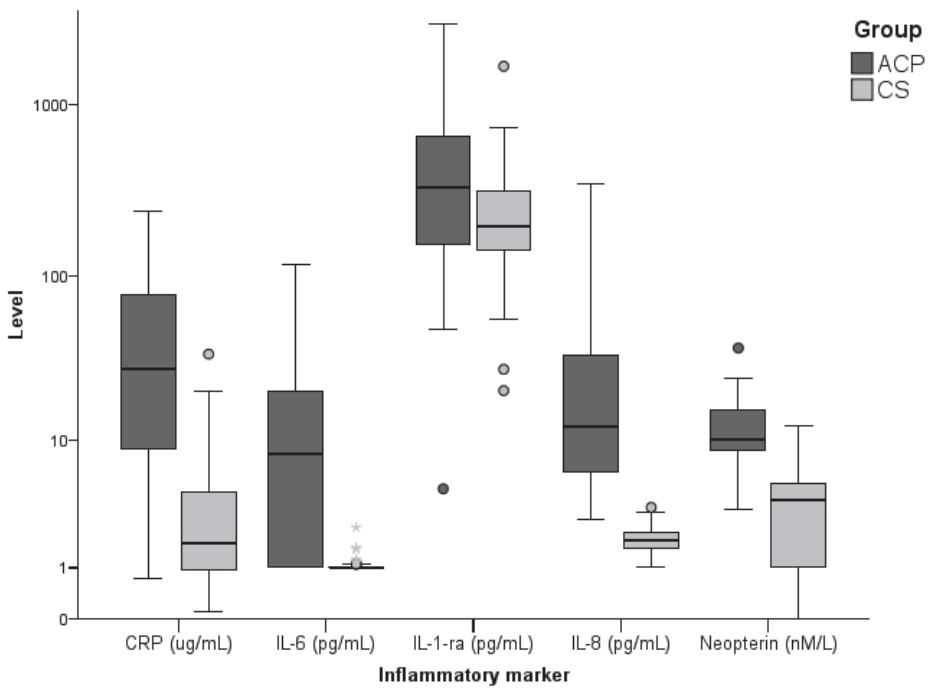

Figure 1: Boxplot of plasma concentrations of C-reactive protein (CRP), Interleukin-6 (IL-6), Interleukin-1 receptor antagonist (IL-1-ra), Interleukin-8 (IL-8) and Neopterin in advanced cancer patients (ACP) and cancer survivors (CS). Horizontal line indicated median; box is interquartile range; whiskers indicate range (without outliers); dots indicate outliers (>1.5 times interquartile range above 75th or below 25th percentile)

Table 2: Patient characteristics

	Advanced cancer patients (n=45) *n (%)*	**Cancer survivors (n=47)** *n (%)*
Age (mean, range)	58 (22-81)	57 (36-77)
Sex		
Male	18 (40%)	19 (40%)
Female	27 (60%)	28 (60%)
WHO performance***		
0	1 (2%)	29 (62%)
1	16 (36%)	17 (36%)
2	17 (39%)	1 (2%)
3	8 (18%)	
4	2 (5%)	
Cancer diagnosis		
Breast	15 (33%)	15 (32%)
Gastro-intestinal	11 (24%)	14 (30%)
Urogenital	9 (20%)	8 (17%)
Other	10 (22%)	10 (21%)
Treatment received		
Surgery		
Total	33 (73%)	46 (98%)***
Curative	32 (71%)	46 (98%)***
Palliative	11 (24%)	
Chemotherapy		
Total	37 (82%)	30 (64%)**
Curative	17 (38%)	30 (64%)**
Palliative	31 (69%)	
Radiotherapy		
Total	33 (73%)	24 (51%)**
Curative	19 (42%)	24 (51%)
Palliative	22 (49%)	
Hormonal therapy		
Total	13 (29%)	14 (30%)
Curative	6 (13%)	14 (30%)
Palliative	12 (27%)	
Months since last treatment[1] **(median, IQR)**	2.5 (1.0-7.0)	28.0 (20.0-47.0)
Fatigue scores (median, IQR)		
Physical Fatigue	16 (13-19)	9 (5-12)**
Mental Fatigue	11 (6-15)	6 (4-12)**

[1] Surgery, chemotherapy or radiotherapy.
IQR = Inter-quartile range
** p <0.05
*** p <0.01

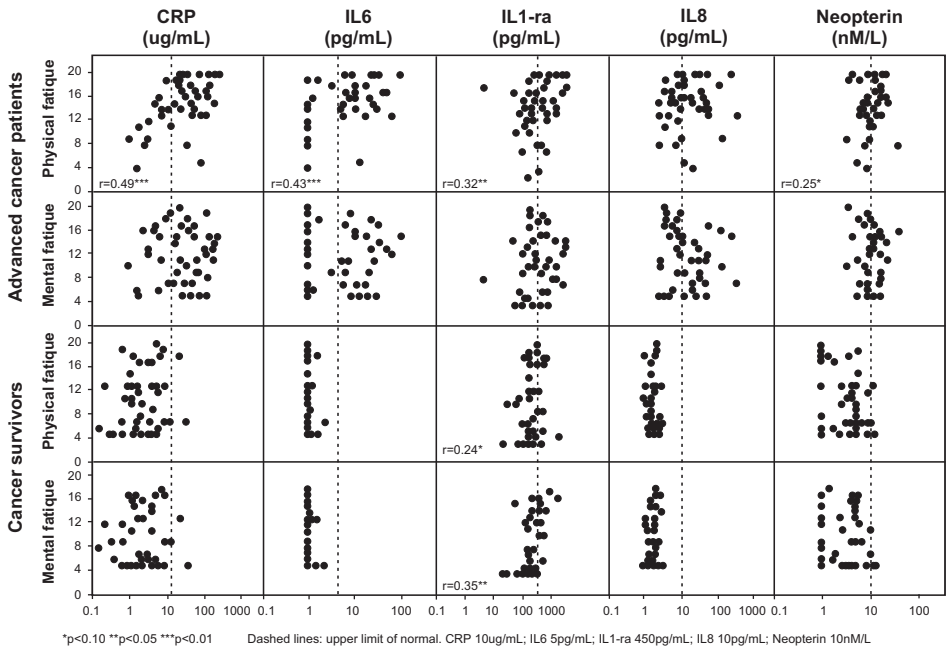

Figure 2: Scatter plots of the fatigue scores and plasma concentrations of inflammatory markers of individual patients. The Spearman correlation coefficient is presented for significant correlations.

The relationships between fatigue measurements and levels of inflammatory markers for both advanced cancer patients and cancer survivors are shown in Figure 2. In the advanced cancer patients, physical fatigue was positively correlated with the levels of CRP (r=0.49, p=0.001), IL-6 (r=0.43, p=0.003), IL-1-ra (r=0.32, p=0.03), and, to a lesser extent, neopterin (r=0.25, p=0.10). No inflammatory markers were related to mental fatigue in the advanced cancer patients. In the cancer survivors, IL-1-ra was related to both physical fatigue (r=0.24, p=0.10) and mental fatigue (r=0.35, p=0.02). In this group, no associations were found for any other soluble factors assessed with either physical or mental fatigue.

Table 3: Spearman correlations between inflammatory markers significantly associated with physical fatigue in the advanced cancer patients

	IL-6	IL-1-ra	Neopterin
CRP	0.82***	0.50***	0.35**
IL-6	-	0.58***	0.36**
IL-1-ra		-	0.27*
Neopterin			-

* p <0.1
** p <0.05
***p <0.01

All inflammatory markers that were associated with physical fatigue in the advanced cancer patients were positively correlated with each other as detailed in Table 3.

Discussion

In this study, we explored whether fatigue dimensions were associated with inflammatory markers in different groups of cancer patients. In the advanced cancer patients, CRP, IL-6, IL-1-ra, and neopterin were significantly associated with physical fatigue, but not with mental fatigue. These findings suggest that physical fatigue and mental fatigue have different underlying pathogeneses in these patients. On the contrary, in the cancer survivors, both physical fatigue and mental fatigue were associated with IL-1-ra only, which indicates that the pathogenesis of physical and mental fatigue might differ between advanced cancer patients and cancer survivors.

Four other studies have previously investigated the relation between at least 1 of these inflammatory markers and fatigue in advanced cancer patients[11-14]. The only study that measured fatigue multidimensionally in terminally ill advanced cancer patients also found the IL-6 concentrations to be related to physical fatigue and not to mental fatigue[11]. The 3 other studies measured fatigue as 1 symptom (unidimensionally) and their results were in contrast with our findings[12-14]. Two of these studies investigated the relation between IL-6 and fatigue in advanced cancer patients and could not find a significant relation[13-14]. However, these patients had a better performance than our patients (93%[14] and 75%[13] Eastern Cooperative Oncology Group performance status [ECOG PS] ≤1 vs. 38% ECOG PS ≤1 in our study). Therefore, our patients were more vulnerable and might have experienced more fatigue. The third study investigated the relation between CRP and symptom clusters in patients with advanced cancer of the lung or pancreas. Fatigued patients had similar CRP concentrations as non-fatigued patients. Furthermore, in this study, hardly any patient had a CRP concentration above the upper limit of the normal range (10 mg/mL)[12]. No studies assessing the relationship between fatigue and IL-1-ra, IL-8, or neopterin in advanced cancer patients have been published thus far.

In the advanced cancer patients, all inflammatory markers that were associated with physical fatigue were positively intercorrelated. CRP is an acute-phase protein produced by hepatocytes after stimulation by IL-6, which is reflected by a strong correlation between CRP and IL-6 in our study[15]. IL-6 production is stimulated by IL-1b[16]. Both IL-1b and IL-6 stimulate the production of IL-1-ra, an anti-inflammatory cytokine that antagonizes IL-1 activity[17]. Therefore, of the markers that were correlated with fatigue in our study, IL-6 in particular might play an important role in the fatigue-inducing cytokine cascade. Subsequently, the elevated levels of both CRP and IL-1-ra in this study could be caused by increased IL-6 activity. Interestingly, in the treatment of the IL-6-mediated Castleman's disease, both blockade of IL-6 production by IL-1-ra administration[18] and blockade of IL-6 activity by administration of anti-IL-6 antibodies[19] were highly effective in decreasing disease activity and in alleviating fatigue. Furthermore, there are some data from phase 1 and phase 2 clinical trials which suggest that anti-IL-6 antibody treatment in patients with advanced lung cancer might alleviate fatigue[20].

The association between inflammatory markers and fatigue in cancer survivors was investigated previously in 6 studies[21-26]. In the only study that measured fatigue multidimensionally,

IL-1-ra was associated with physical fatigue but not with mental fatigue, whereas we found an association with both physical and mental fatigue. Furthermore, this study found a significant correlation between CRP and physical fatigue, whereas we did not[25]. The 5 other studies in cancer survivors measured fatigue only unidimensionally[21-24, 26]. In a study on breast cancer survivors, CRP was associated with fatigue, in contrast to our results[26]. Similar to our results, there was no relation between IL-6 and fatigue in other studies on cancer survivors[22-26]. The results of the studies on IL-1-ra and fatigue and on neopterin and fatigue in cancer survivors were contradictory. Some studies found an association between fatigue and IL-1-ra[21-22], or neopterin[23, 25-26], whereas other studies did not find an association between fatigue and IL-1-ra[23, 26] or neopterin[21]. The association between IL-8 and fatigue has never been studied before in cancer survivors.

The clinical meaning of the solitary association of IL-1-ra and fatigue in the cancer survivors remains unclear. Because this relation is congruent with the literature[21-22, 25], it seems unlikely that the statistical significant correlation we found is caused by chance, because of multiple testing. On the other hand, if inflammation is one of the important causes of fatigue in the cancer survivors, we would have expected more inflammatory markers to be related to fatigue, because they are not independent factors, but part of complex, collaborating pathways.

There are several limitations to this study, hindering the interpretation of the results. Because of the cross-sectional study design, we were not able to prove causality between inflammation and physical fatigue. Longitudinal measurements of both fatigue severity and concentrations of inflammatory markers are needed to confirm the causal relationship between them. Furthermore, despite our matching advanced cancer patients and cancer survivors to minimize intergroup heterogeneity, there is a great intragroup variability in age, diagnosis, and intensity of treatment. Finally, in this explorative study, we did not control for other variables that are known to influence fatigue, such as depression. Depression has been reported to be correlated with both physical and mental fatigue in advanced cancer[27] as well as cancer survivors[28]. Also, behavioural symptoms like depression have been hypothesized to be related to cytokine release[29]. However, a recent study in breast cancer patients who completed curative chemotherapy recently failed to find a correlation between depression and inflammatory activity; whereas unidimensionally measured fatigue was correlated with both inflammation and depression[30]. These results further substantiate the multicausality of cancer related fatigue and the need for large prospective studies unravelling the etiologic mechanisms.

Nevertheless, the novelty of this study lies in the simultaneous measurement of the relation between inflammation and fatigue dimensions in different groups of cancer patients. We showed that inflammation seems to be associated to physical fatigue, but not to mental fatigue in the advanced cancer patients, whereas there were no strong indications that inflammation plays a major role in cancer survivors' fatigue. In future research, longitudinal studies controlling for important confounders are needed to prove the causal relationship between inflammation and fatigue. Furthermore, if it should be proven that cytokines cause fatigue, it has to be investigated which pathogenetic pathways lead from elevated concentrations of inflammatory markers in plasma to subjective complaints of fatigue. Hopefully, the identification of the important inducers of cancer-related fatigue will finally lead to novel targets of treatment, for example by blockade of IL-6 production or IL-6 activity.

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5

Cut points on 0-10 Numeric Rating Scales for symptoms included in the Edmonton Symptom Assessment Scale in cancer patients: a systematic review

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Abstract

Context

To improve the management of cancer-related symptoms, systematic screening is necessary, often performed by using 0-10 numeric rating scales. Cut points are used to determine if scores represent clinically relevant burden.

Objectives

The aim of this systematic review was to explore the evidence on cut points for the symptoms of the Edmonton Symptom Assessment Scale.

Methods

Relevant literature was searched in PubMed, CINAHL®, EMBASE, and PsychINFO®. We defined a cut point as the lower bound of the scores representing moderate or severe burden.

Results

Eighteen articles were eligible for this review. Cut points were determined using the interference with daily life, another symptom-related method, or a verbal scale. For pain, cut point 5 and, to a lesser extent, cut point 7 were found as the optimal cut points for moderate pain and severe pain, respectively. For moderate tiredness, the best cut point seemed to be cut point 4. For severe tiredness, both cut points 7 and 8 were suggested frequently. A lack of evidence exists for nausea, depression, anxiety, drowsiness, appetite, well-being, and shortness of breath. Few studies suggested a cut point below 4.

Conclusion

For many symptoms there is no clear evidence as to what the optimal cut points are. In daily clinical practice, a symptom score ≥4 is recommended as a trigger for a more comprehensive symptom assessment. Until there is more evidence on the optimal cut points, we should hold back using a certain cut point in quality indicators and be cautious about strongly recommending a certain cut point in guidelines.

Introduction

Cancer patients suffer from many physical and psychological symptoms, negatively affecting quality of life and daily activities[1]. To improve the management of these cancer-related symptoms, it is necessary to screen for these symptoms systematically. Many screenings instruments measure the intensity of symptoms on a 0-10 numeric rating scale (NRS), in which 0 means "no suffering" and 10 means "unbearable suffering"[2-4].

Before being able to interpret the results of these measurements, it is important to determine the clinical meaning of the scores given on the 0-10 NRS for the various symptoms. NRS scores have been categorized as none, mild, moderate, and severe[5] or as representing clinically relevant burden or not[6]. When studies categorize NRS scores as none, mild, moderate, and severe, they report two cut points: one cut point for the boundary between mild and moderate burden and another cut point for the boundary between moderate and severe burden. In case articles report one cut point for clinically relevant burden, they describe it as a clinically significant cut point, an optimal single cut point, or a cut point for significant burden. The cut point for clinically relevant burden is considered to be equivalent to the cut point between mild and moderate burden[6].

Cut points are frequently used in research and in daily clinical practice. For example, cut points are frequently used in inclusion criteria and in the definition of endpoints of clinical trials. Furthermore, they are used in quality indicators to measure the quality of care. In addition, cut points are recommended in guidelines as a starting point for the initiation of treatment and for the evaluation of the treatment[7] (e.g. National Comprehensive Cancer Center Network [NCCN] guidelines[8-9]).

For various symptoms, cut points on the NRS have been proposed, especially for pain and fatigue[6, 10]. However, there is heterogeneity in the cut points being recommended. For example, the NCCN proposed a cut point ≥4 for fatigue[8], whereas an expert group of the European Association for Palliative Care suggested the cut point ≥5[11]. Despite this lack of uniformity, as mentioned before, cut points are advised in guidelines and quality indicators, which has consequences for the treatment of the symptoms and the assessment of the quality of care.

Therefore, it is important to define evidence-based cut points that are proven to distinguish between NRS scores with clinically relevant burden or not. The aim of this review was to explore the evidence on cut points for the respective symptoms of the Edmonton Symptom Assessment Scale (ESAS) in cancer patients and whether it is possible to recommend an optimal cut point per symptom or to recommend one cut point for all symptoms of the ESAS.

Methods

We conducted a systematic review on cut points for the symptoms of the ESAS: pain, tiredness, nausea, depression, anxiety, drowsiness, appetite, well-being, and shortness of breath. We searched for studies that measured these symptoms on an NRS or an equivalent instrument, that it, a visual analogue scale (VAS)[12], the Brief Pain Inventory (BPI)[13], the Brief Fatigue Inventory (BFI)[14], the ESAS[2], the M.D. Anderson Symptom Inventory[3], the Fatigue Symptom Inventory[15], or the Symptom Monitor[4].

Relevant literature was searched in PubMed, using the search strategy: "Neoplasms"[Mesh] AND (cut OR cut-off OR "cut off" OR cutpoint* OR "*symptom* severity") AND (*symptom* OR VAS OR "Visual Analogue Scale" OR "Visual Analog Scale" OR "Visual Scale" OR NRS OR "Numeric Rating Scale" OR BPI OR "Brief Pain Inventory" OR BFI OR "Brief Fatigue Inventory" OR ESAS OR "Edmonton Symptom Assessment Scale" OR FSI OR "Fatigue Symptom Inventory" OR "M.D. Anderson Symptom Inventory" OR "symptom monitor"). We used this strategy for the nine symptoms of the ESAS and also included the synonyms used by the revised ESAS[16]: pain, tiredness (including fatigue and lack of energy), nausea, depression (including feeling sad), anxiety (including nervousness and feeling nervous), drowsiness (including sleepiness and feeling sleepy), appetite (including loss of appetite, lack of appetite, poor appetite, and anorexia), well-being, and shortness of breath (including dyspnea, and breathlessness).

The search was limited to English articles published until July 2011 and to original articles. Studies were included in this review if they were performed in cancer patients, measured one or more symptoms of the ESAS on a 0-10 NRS, and performed statistical tests to determine the optimal cut point. To identify supplementary studies, we studied the reference list of the selected articles and we searched for cross-references. We conducted an additional search in CINAHL®, EMBASE, and PsychINFO® using the same search strategy.

Articles were reviewed for eligibility independently by two authors (W.H.O. and P.J.d.R.). The results were summarized, and conclusions were independently drafted by these two authors. If the reviewers disagreed about a conclusion, the assumptions leading to the conclusion were discussed until consensus was reached.

Per study, we reported patient characteristics (e.g., disease stage, antitumor treatment), inclusion criteria with respect to symptom scores, methodological characteristics, and quality criteria (e.g., prospective or retrospective design, if a primary or secondary analysis was performed, sample size), specification of the type of symptom intensity asked for (e.g., usual, worst), the method used to determine the cut point, and the number of optional cut points explored. We studied which NRS scores were tested as possible cut points for the various symptoms and which scores were finally selected as the most optimal cut points.

In some articles, the reported cut point reflected the lower bound of a category[14], whereas in other studies the reported cut point represented the upper bound of a category[5]. We chose to report the lower bound of a category as the cut point. For example, when we report cut points 5 and 7 (CP57), we mean that mild burden is defined with scores 1-4, moderate burden is defined with scores 5-6, and severe burden is defined with scores 7-10.

Results

General

We found 1524 articles through the original search, of which 14 were relevant. The additional search produced four supplementary articles. In total, we found 18 relevant articles that determined cut points for symptoms covered by the ESAS questionnaire (Figure 1). The main characteristics and the quality aspects of these articles are summarized in Tables 1 and 2. The majority of the studies included patients with various stages of cancer; five studies only included

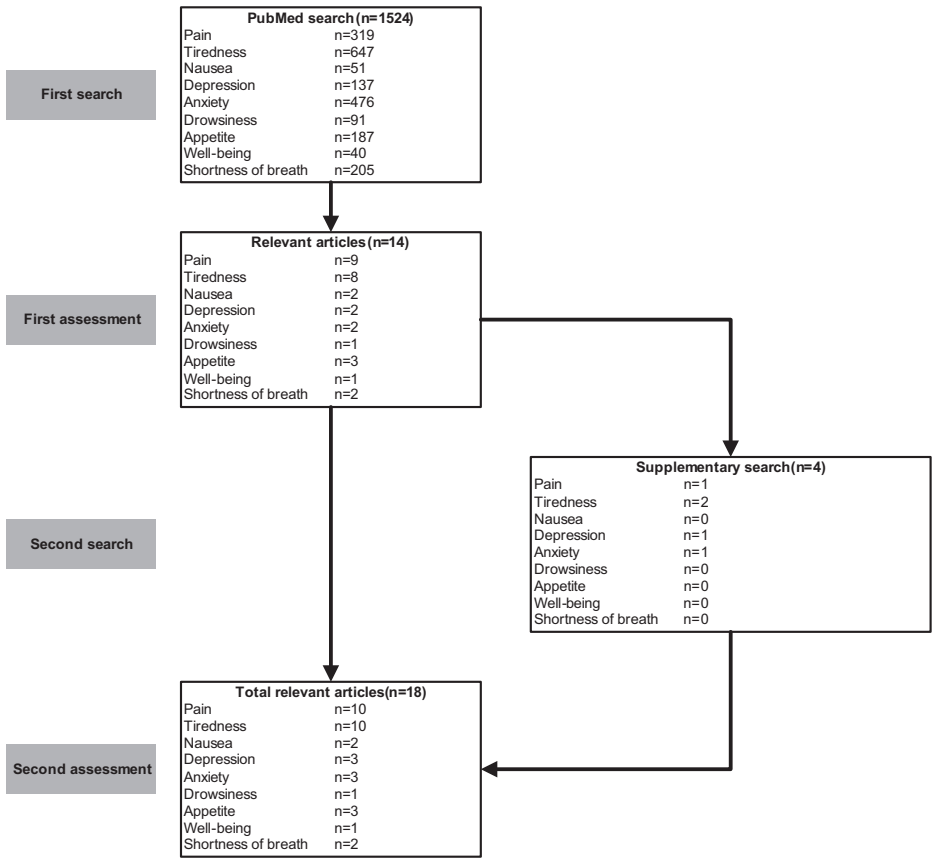

Figure 1: Flowchart of the review process

patients with advanced cancer[5, 10, 17-19]. In seven articles, patients were only eligible when they met a certain inclusion criterion on symptom burden[5-6, 19-23]. Four articles determined cut points for multiple symptoms[6, 10, 21, 24]. Six studies were primary designed to calculate cut points[6, 10, 23, 25-27]. All studies measured the symptom on a 0-10 NRS, and no studies used a VAS. For pain, all studies defined the type of symptom intensity (e.g., worst or usual) they asked for. Four out of 10 studies on fatigue[10, 18, 21, 26] and all studies on the other symptoms did not define the type of symptom intensity (Table 2). The recall time of the question about symptom intensity varied between "right now"[10] to "last week"[5]. Seven studies did not describe the recall time[17, 19-21, 23-24, 26].

Methods used to determine cut points

Fifteen studies determined the cut point for a certain symptom using the interference of that symptom with daily life as reference[5-6, 14, 17-23, 25, 27-30]. Three studies used another symptom-related questionnaire as reference[6, 24, 26], and one study assessed the cut point using the severity of that particular symptom on a verbal scale (none, mild, moderate, severe) as reference[10] (Table 2).

Table 1: Overview of the characteristics of the included studies

Author and year	Symptoms	Study design	Type of analysis	Patient population			
				n	*Disease stage*	*Treatment*	*Symptom burden in inclusion criteria*
Serlin 1995[5]	Pain	Retrospective	Secondary	1897	Metastatic (100%)	?	Worst pain >0
Mendoza 1999[14]	Fatigue	Prospective	Secondary	305	Advanced (85%) Early (15%)	CT (100%)	-
Okuyama 2001[18]	Fatigue	Prospective	Secondary	157	Advanced lung cancer	-	-
Hwang 2002[25]	Fatigue	Prospective	Primary	180	NED (7%) Localized (5%) Locally advanced (21%) Advanced (67%)	CT (17%) RT (10%) CRT (4%) HT (22%) None (47%)	-
Okuyama 2003[30]	Fatigue	Prospective	Secondary	252	Recurrence (36%) Metastatic (50%)	Surgery (2%) CT (22%) RT (2%)	-
Paul 2005[19]	Pain	Retrospective	Secondary	160	Metastatic (100%)	CT (46%) HT (32%) RT (18%) BT (3%) None (12%)	Average pain ≥2.5
Temel 2006[26]	Fatigue	Prospective	Primary	574	?	?	-
Vignaroli 2006[24]	Depression, anxiety	Retrospective	Secondary	216	?	?	?
Chang 2007[27]	Fatigue	Prospective	Primary	150	I (10%) II (9%) III (23%) IV (58%)	Surgery (15%) CT (66%) RT (27%) None (21%)	-
Li 2007[17]	Pain	Retrospective	Secondary	199	Metastatic (100%)	RT (100%)	-
Butt 2008[6]	Pain, Fatigue, Appetite loss	Prospective	Primary	148	Local (27%) Regional (24%) Metastatic (42%) N/A (7%)	?	NRS ≥4 on ≥1/4 symptoms
Given 2008[21]	Pain, fatigue, nausea, depression, anxiety, poor appetite, dyspnea	Retrospective	Secondary	588	Early (15%) Late (85%)	CT (100%)	NRS ≥2 on ≥1/16 symptoms
Kalyadina 2008[28]	Pain	Prospective	Secondary	148	I or II (7%) III (52%) IV (35%) Recurrent disease (6%)	?	-
Valeberg 2008[23]	Pain	Prospective	Primary	210	Metastatic (41%)	?	Average pain ≥0
Utne 2009[22]	Pain	Retrospective	Secondary	225	Metastatic (70%)	?	Opioid treatment
Mendoza 2010[29]	Fatigue	Prospective	Secondary	206	?	?	-

Table 1: Overview of the characteristics of the included studies

Author and year	Symptoms	Study design	Type of analysis	Patient population			
				n	*Disease stage*	*Treatment*	*Symptom burden in inclusion criteria*
Selby 2010[10]	Pain, tiredness, nausea, depression, anxiety, drowsiness, loss of appetite, well-being, shortness of breath	Prospective	Primary	400	Advanced	?	-
Ferreira 2011[20]	Pain	Prospective	Secondary	143	Metastatic (66%)	None (100%)	Chronic cancer-related pain

NED = No evidence of disease; N/A = not applicable (i.e., patients with hematologic malignancies); CT = chemotherapy; HT = hormonal therapy; RT = radiation therapy; CRT = Chemoradiation therapy; BT = biotherapy; NRS = Numeric Rating Scale

Twelve studies described two cut points: a cut point for mild/moderate burden and a cut point for moderate/severe burden[5, 10, 14, 17, 19-21, 25, 27-30]. The other studies assessed one cut point for clinically relevant burden[6, 18, 22-24, 26] (Table 2).

Studies used regression models or a receiver operating characteristic (ROC) curve to determine the optimal cut point(s). The studies using regression models (multivariate analyses of variance [MANOVA] or general linear model [GLM]) studied multiple cut points or combinations of cut points to categorize NRS scores by symptom severity (clinically relevant/not clinically relevant or mild/moderate/severe). The cut point or combination of cut points that best differentiated the symptom severity categories with respect to the level the symptom interfered with daily life, as measured with the reference questionnaire, was considered to be the optimal cut point. The number of possible options explored for a single cut point varied from one[25] to seven[17].

The studies using an ROC curve predefined per patient if a symptom was present, using a reference questionnaire. Thereafter, for each possible cut point on the NRS, the sensitivity and specificity were calculated. The sensitivity was defined as the proportion of the patients suffering from that particular symptom (as predefined using the reference questionnaire) with an NRS-score on that possible cut point or higher. The specificity was defined as the proportion of the patients not suffering from that particular symptom (according to the reference questionnaire) with an NRS-score below that possible cut point. The optimal cut point is the cut point with the optimal ratio between sensitivity and specificity.

Optimal cut points per symptom

Pain

Ten studies assessed cut points on an NRS for pain[5-6, 10, 17, 19, 21-23, 28]. Pain was asked as present pain[10, 17], average pain[17, 19, 21, 23], or worst pain[5-6, 17, 19-20, 22, 28]. Seven studies used a MANOVA[5, 17, 19-20, 22-23, 28] and one study a GLM[21], both with the interference items of the BPI as reference. In the seven studies that used MANOVA statistics[5, 17, 19-20, 22-23, 28], multiple models were tested to determine cut points, with Li et al. testing most extensively[17]. Two other studies used an ROC curve with the interference items of the BPI[6] or a verbal scale[10] as a reference. Thirteen cut points were calculated for moderate pain or clinically relevant pain (range CP2-CP5), with CP5 most frequently being recommended as the optimal cut point[5, 10, 17, 19-20, 22-23, 28]. Ten cut points were suggested for severe pain (range CP5-CP8), with CP7 presented as the optimal cut point most frequently[5, 10, 17, 28] (Table 2).

We found no clear differences in cut points between studies asking for different types of pain intensity (present, average, or worst pain) (Table 2).

Tiredness

Ten studies published cut points on an NRS for tiredness[5-6, 14, 18, 21, 25-27, 29-30]. The question on tiredness was formulated as worst fatigue[6, 14, 25, 27, 29-30], usual fatigue[25, 27], fatigue[18, 21, 26] or tiredness[10]. Six studies used a MANOVA[6, 14, 25, 27, 29-30] and one study a GLM[21] with the interference items of the BFI as reference. In all studies that determined the cut point using a MANOVA[6, 14, 25, 27, 29-30], conclusions on the optimal cut point were based on the analyses of two possible cut points only (Table 2). The other studies used an ROC-curve with the Functional Assessment of Cancer Therapy-Fatigue subscale (FACT-F)[6, 26], the interference items of the BFI[18], or a verbal scale[10] as a reference. Twelve cut points were proposed for moderate tiredness or clinically relevant tiredness (range CP2-CP6)[6, 10, 14, 18, 21, 25-27, 29-30], with CP4 being found as the optimal cut point most frequently[14, 26-27, 29-30]. Nine cut points were proposed for severe tiredness (range CP5-CP8)[10, 14, 21, 25, 27, 29-30], with CP7[14, 25, 29] and CP8[10, 27, 30] being recommended as the optimal cut points most frequently. We could not investigate if there were differences in cut points between studies asking for different types of tiredness intensity (i.e., usual or worst fatigue), because only two studies asked for usual fatigue.

Nausea

Two studies assessed cut points on an NRS for nausea, using an ROC curve[10] or a GLM[21]. The study that used the severity of nausea expressed on a verbal scale as reference reported CP4 for moderate nausea and CP5 for severe nausea[10]. The other study, which determined the cut point using the interference of nausea in daily life, found CP4 and CP7 to be the optimal cut points for moderate and severe nausea, respectively[21] (Table 2).

Depression

Three studies published cut points on an NRS for depression[10, 21, 24]. Two studies used an ROC curve with the depression subscale of the Hospital Anxiety and Depression Scale[24] or a verbal scale[10] as a reference. One other study calculated the cut point using the interference of

Table 2: Cut points per symptom

Author and year	n	Source of NRS	Question	Recall time	Reference			Statistical method	NRS score									
					Type	*Question-naire*	*Cut point*		*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*
Pain																		
Li 2007[17]	199	BPI	Pain (present)[1]	Now	Interference	BPI-I	-	MANOVA			Mo*	Mo*^	Mo*^	Mo*^	S*^	S*^	S*^	S^
Selby 2010[10] 2010	400	ESAS	Pain (present)	Now	Verbal Scale	VRS	Mo or S	ROC-curve					Mo	Mo	S	S	S	S
Paul 2005[19]	160	BPI	Pain (average)	?	Interference	BPI-I	-	MANOVA				*	Mo*	Mo*^	Mo^	S	S	S
Li 2007[17]	199	BPI	Pain (average)[1]	?	Interference	BPI-I	-	MANOVA			*	*^	Mo*^	Mo*^	S*^	S*^	S*^	S^
Given 2008[21]	588	7-item[3]	Pain (average)	?	Interference	BPI-I[5]	-	GLM		Mo	Mo	Mo	S	S	S	S	S	S
Valeberg 2008[23]	210	BPI	Pain (average)	?	Interference	BPI-I	-	MANOVA				*	CR*	CR*	CR*	CR*	CR*	CR
Serlin 1995[5]	1897	BPI	Pain (worst)	7 d	Interference	BPI-I	-	MANOVA				*	Mo*	Mo	S^	S^	S	S
Paul 2005[19]	160	BPI	Pain (worst)	?	Interference	BPI-I	-	MANOVA				*	Mo*	Mo*^	Mo^	S^	S	S
Li 2007[17]	199	BPI	Pain (worst)[1]	?	Interference	BPI-I	-	MANOVA			*	*^	Mo*^	Mo*^	S*^	S*^	S*^	S^
Butt 2008[6]	148	4-item[4]	Pain (worst)	3 d	Interference	BPI-I	BPI-I ≥45	ROC curve				CR	CR	CR	CR	CR	CR	CR
Kalyadina 2008[28]	148	BPI	Pain (worst)	24 h	Interference	BPI-I	-	MANOVA				*	Mo*	Mo	S^	S^	S	S
Utne 2009[22]	225	BPI	Pain (worst)	24 h	Interference	BPI-I	-	MANOVA				*	CR*	CR*	CR*	CR	CR	CR
Ferreira 2011[20]	143	BPI	Pain (worst)	?	Interference	BPI-I	-	MANOVA				*	Mo*	Mo*^	Mo^	S^	S	S
Tiredness																		
Selby 2010[10]	400	ESAS	Tiredness	Now	Verbal Scale	VRS	Mo or S	ROC curve						Mo	Mo	S	S	S
Okuyama 2001[18]	157	1-item	Fatigue	24 h	Interference	BFI-I	≥1 item ≥1	ROC curve			CR	CR	CR	CR	CR	CR	CR	CR
Temel 2006[26]	574	1-item	Fatigue	?	Symptom Scale	FACT-F	FACT-F <30	ROC curve				CR	CR	CR	CR	CR	CR	CR
Given 2008[21]	588	7-item[3]	Fatigue	?	Interference	BPI-I[5]	-	GLM		Mo	Mo	Mo	S	S	S	S	S	S
Hwang 2002[25]	180	BFI	Fatigue (usual)[2]	24 h	Interference	BFI-I	-	MANOVA			Mo*	Mo	Mo	Mo^	S^	S	S	S
Chang 2007[27]	150	BFI	Fatigue (usual)[2]	24 h	Interference	BFI-I	-	MANOVA			*	Mo*	Mo	Mo	Mo^	S^	S	S
Mendoza 1999[14]	305	BFI	Fatigue (worst)	24 h	Interference	BFI-I	-	MANOVA				Mo*	Mo*	Mo	S^	S^	S	S
Hwang 2002[25]	180	BFI	Fatigue (worst)[2]	24 h	Interference	BFI-I	-	MANOVA				*	Mo*	Mo	S^	S	S	S
Okuyama 2003[30]	252	BFI	Fatigue (worst)	24 h	Interference	BFI-I	-	MANOVA				Mo*	Mo*	Mo	Mo^	S^	S	S
Chang 2007[27]	150	BFI	Fatigue (worst)[2]	24 h	Interference	BFI-I	-	MANOVA			*	Mo*	Mo	Mo	Mo^	S^	S	S
Butt 2008[6]	148	4-item[4]	Fatigue (worst)	3 d	Symptom Scale	FACT-F	FACT-F ≤42	ROC curve					CR	CR	CR	CR	CR	CR
Mendoza 2010[29]	206	BFI	Fatigue (worst)	24 h	Interference	BFI-I	-	MANOVA				Mo*	Mo*	Mo	S^	S^	S	S

Table 2: Cut points per symptom (continued)

Author	Year	n	Source of NRS	Question	Recall time	Reference			Statistical method	NRS score									
						Type	*Question-naire*	*Cut point*		*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*
Nausea																			
Given 2008[21]		588	7-item[3]	Nausea/ vomiting	?	Interference	BPI-I[5]	-	GLM				Mo	Mo	Mo	S	S	S	S
Selby 2010[10]		400	ESAS	Nausea	Now	Verbal Scale	VRS	Mo or S	ROC-curve				Mo	S	S	S	S	S	S
Depression																			
Vignaroli 2006[24]		216	ESAS	Depression	?	Symptom Scale	HADS	HADS-D ≥8	ROC-curve		CR	CR	CR	CR	CR	CR	CR	CR	CR
Given 2008[21]		588	7-item[3]	Depression	?	Interference	BPI-I[5]	-	GLM		Mo	Mo	S	S	S	S	S	S	S
Selby 2010[10]		400	ESAS	Depression	Now	Verbal Scale	VRS	Mo or S	ROC-curve				Mo	Mo	Mo	S	S	S	S
Anxiety																			
Vignaroli 2006[24]		216	ESAS	Anxiety	?	Symptom Scale	HADS	HADS-A ≥8	ROC-curve		CR	CR	CR	CR	CR	CR	CR	CR	CR
Given 2008[21]		588	7-item[3]	Anxiety	?	Interference	BPI-I[5]	-	GLM				Mo	Mo	S	S	S	S	S
Selby 2010[10]		400	ESAS	Anxiety	Now	Verbal Scale	VRS	Mo or S	ROC-curve					Mo	Mo	S	S	S	S
Drowsiness																			
Selby 2010[10]		400	ESAS	Drowsiness	Now	Verbal Scale	VRS	Mo or S	ROC-curve					Mo	Mo	S	S	S	S
Appetite																			
Butt 2008[6]		148	4-item[4]	Appetite loss	3 d	Severity	FAACT-A	FAACT-A ≤21	ROC-curve						CR	CR	CR	CR	CR
Given 2008[21]		588	7-item[3]	Poor appetite	?	Interference	BPI-I[5]	-	GLM				Mo	Mo	Mo	S	S	S	S
Selby 2010[10]		400	ESAS	Loss of appetite	Now	Verbal Scale	VRS	Mo or S	ROC-curve					Mo	Mo	S	S	S	S
Well-being																			
Selby 2010[10]		400	ESAS	Wellbeing	Now	Verbal Scale	VRS	Mo or S	ROC-curve						Mo	S	S	S	S
Shortness of breath																			
Given 2008[21]		588	7-item[3]	Dyspnea	?	Interference	BPI-I[5]	-	GLM			Mo	Mo	Mo	Mo	S	S	S	S
Selby 2010[10]		400	ESAS	Shortness of breath	Now	Verbal Scale	VRS	Mo or S	ROC-curve				Mo	Mo	S	S	S	S	S

* Optimal lower bound cut points tested to define a symptom as of moderate burden (only for studies using MANOVA)
^ Optimal lower bound cut points tested to define a symptom as of severe burden (only for studies using MANOVA)
[1] Authors recommended to ask for worst pain, which better predicted interference scores than average pain or present pain
[2] Authors recommended to ask for usual fatigue, which better predicted interference scores than worst fatigue
[3] The authors questioned for the intensity of pain, fatigue, nausea, depression, anxiety, poor appetite and dyspnea simultaneously, each on a 0-10 NRS
[4] The authors questioned for the intensity of pain, fatigue, distress and appetite loss simultaneously, each on a 0-10 NRS
[5] The authors used 4 interference items from the Brief Pain Inventory: enjoyment of life, social relationships, general daily activities and emotions
Mo = moderate; S = severe; CR = clinically relevant
NRS = Numeric Rating Scale; BPI-I = Interference-items Brief Pain Inventory; BFI-I = Interference-items Brief Fatigue Inventory; FACT-F = Functional Assessment of Cancer Therapy-Fatigue subscale; HADS = Hospital Anxiety and Depression Scale; HADS-D = Hospital Anxiety and Depression Scale – Depression subscale; HADS-A = Hospital Anxiety and Depression Scale – Anxiety subscale; FAACT-A = Functional Assessment of Anorexia/Cachexia Treatment-Anorexia subscale; VRS = verbal rating scale. MANOVA = Multivariate analysis of variance; ROC = Receiver Operating Characteristics; GLM = Generalized Linear Model

depression with daily life in a GLM[21]. Cut points for moderate/clinically relevant depression were CP2[21, 24] or CP4[10]. Severe depression was represented with CP4[21] and CP7[10] (Table 2).

Anxiety

Three studies assessed cut points on an NRS for anxiety[10, 21, 24]. Two studies calculated the sensitivity per cut point using the anxiety subscale of the Hospital Anxiety and Depression Scale (clinically relevant CP2)[24] or using a verbal scale (moderate CP5)[10], whereas the third study determined the optimal cut point using the interference of anxiety with daily life in a GLM (moderate CP4)[21]. Severe anxiety was indicated with CP6[21] or CP7[10] (Table 2).

Drowsiness

One study determined a cut point on an NRS for drowsiness based on the severity of drowsiness as measured with a verbal scale. Moderate drowsiness was reflected best by CP5, and severe drowsiness was indicated by CP7[10] (Table 2).

Appetite

Three studies reported cut points on an NRS for appetite[6, 10, 21]. The question on appetite was formulated as "appetite loss"[6], "loss of appetite"[10] or "poor appetite"[21].

Two studies calculated the sensitivity per cut point using the Functional Assessment of Anorexia/Cachexia Therapy (clinically relevant CP6)[6] or using a verbal scale (moderate CP5)[10], whereas the other study calculated the optimal cut point using the interference of poor appetite with daily life in a GLM (moderate CP4)[21]. Two studies that determined a cut point for severe appetite loss reported CP7[10, 21] (Table 2).

Well-being

Only one study determined a cut point on an NRS for well-being using an ROC curve with a verbal scale as reference. Moderate impairment of well-being corresponded best with an NRS score of 6 and severe impairment of well-being corresponded best with NRS score of 7 or higher[10] (Table 2).

Shortness of breath

Two studies assessed cut points on an NRS for shortness of breath[10, 21]. The study that used the severity of shortness of breath expressed on a verbal scale as reference, reported CP4 for moderate shortness of breath and CP6 for severe shortness of breath[10]. The other study, which determined the cut point using the interference of dyspnea in daily life in a GLM, found CP3 and CP7 to be the optimal cut points for moderate and severe dyspnea, respectively[21] (Table 2).

Discussion

Based on this review, there is not sufficient evidence for recommending the same cut point for all symptoms of the ESAS questionnaire. The level of evidence of the optimal cut point differs per symptom. The most evidence exists for cut points for pain and tiredness. Concerning pain, there is consensus for CP5 as the cut point for moderate pain and, to a lesser extent,

for CP7 as the cut point for severe pain. This implies that mild pain is reflected by NRS-scores 1-4, moderate pain by NRS-scores 5-6, and severe pain by NRS-scores 7-10. For moderate tiredness, CP4 seems to be the most appropriate cut point. For severe tiredness, the evidence is ambiguous; both CP7 and CP8 are suggested frequently. There is conflicting evidence for cut points on the symptoms depression, anxiety and appetite. For these symptoms we found three or four studies with inconsistent results per symptom. A lack of evidence exists for cut points for nausea, shortness of breath and well-being. Possible cut points for these symptoms were only studied once or twice.

Determination of the optimal cut point depends on the purpose of the test in a specific context, as well as the costs of misses and false alarms. In research and quality assessment of care, one usually aims for optimal accuracy when using a screening measure such as the NRS. In daily practice, clinicians who screen for cancer-related symptoms in their patients generally aim to minimize the amount of false-negative test results. In this context, symptom screening with a brief, easy-to-administer screening tool is usually followed by a more comprehensive symptom history to identify patients who actually experience clinically relevant burden. The present review showed that few existing studies have recommended a cut point below 4. Therefore, we argue that using CP4 as cut point for further screening of symptoms will result in identifying most patients with clinically relevant burden.

The interpretation of the results of this review is hampered by the limited comparability of the studies included because the patients in these studies varied greatly in tumor type, disease stage, and received treatment. The comparability of the studies is also limited by the heterogeneity in the symptom assessment questionnaires used, which, for instance, differed in the wording of the probe question and recall time. In addition, the studies varied in the type of symptom intensity asked for (e.g., worst, usual, or current) or they did not specify this (Table 2). Besides this, the studies differed in the reference questionnaire used, the cut point used on the reference questionnaire, the number of possible cut points explored, and the method to determine cut points (Tables 1 and 2).

The interpretation of the results of this study is also complicated by differences in the quality of the included studies. For example, several studies explored only one optional cut point for a distinction between two categories of pain or fatigue and we can not rule out that the potential cut point above[5, 25, 27-28] or below[14, 25, 29-30] the studied cut point has better characteristics. Unfortunately, there are no quality assessment tools for observational studies that are sufficiently validated[31]. Moreover, there are no quality assessment tools available that contain criteria on prerequisites for a reliable assessment of optimal cut points. Therefore, we decided to describe several aspects of study quality in the Results section and in Tables 1 and 2 instead of performing a quantitative quality assessment with a non-validated tool.

In this review, we identified three methods to determine cut points: based on daily interference, based on another symptom-related questionnaire, and based on verbal rating of symptom severity (Table 3). Every method had its advantages and disadvantages, and it is not clear which method is most suitable to determine the optimal cut point. In the future, thinking aloud studies[32] have to be performed to investigate whether patients rate their symptom intensity on the NRS mainly on the basis of perceived disabilities caused by that particular

Table 3: Advantages and disadvantages of the various methods to determine cut points

Determination of cut points using	Advantages	Disadvantages
Daily interference	Gives insight in symptom-related impairments in daily activities No cut point needed on reference questionnaire	Difficult for patients to discriminate which symptom causes impairments in daily life in case of suffering from multiple symptoms Does not take patients' opinion on acceptability of certain symptom scores into account
Other symptom-related questionnaire	Sensitivity and specificity of cut points can be calculated Facilitates comparison with other questionnaires	Assumption needed on cut point on reference lists, because of lack of gold standards Does not take patients' opinion on acceptability of certain symptom scores into account Does not give insight in symptom-related impairments in daily activities
Symptom intensity on verbal rating scale (none, mild, moderate, severe)	Professionals' prejudices not needed for determination of cut points Fits with the subjective nature of symptoms	Does not give insight in symptom-related impairments in daily activities

symptom (daily interference), or by word descriptors of the symptom intensity (mild/moderate/severe). More insight in the cognitive processes underlying the scores on the questionnaires will help to determine whether cut points should be determined based on the inference of a certain symptom with daily life or based on the subjective severity on a verbal scale. Also, we must investigate whether various approaches to determine cut points in the same population result in different cut points.

Most importantly, in future research, cut points should be reported unambiguously. Fourteen of the 18 included articles described the cut points as boundaries of the created categories. The four other articles reported the ranges of the categories created[18, 27, 29-30], without mentioning the actual cut point. Six articles, all pain literature, described upper boundaries of a category[5, 17, 19-20, 22-23], whereas eight articles reported the lower boundaries of a category[6, 10, 14, 21, 24-26, 28]. Uniformity in reporting cut points is important to avoid confusion. For example, the NCCN guideline "Adult Cancer Pain" categorized mild pain as 1-3[9] referring to Serlin et al[5]. In the original study however, Serlin et al. categorized mild pain as 1-4[5].

Little is known about the validity of cut points in different situations, for example in the different stages of cancer or for inpatients and outpatients. Besides this, it is possible that the type of symptom intensity asked for (e.g., worst, usual, or current) will affect the cut points. Moreover, cut points could differ depending on the pathophysiology of the symptom (e.g., nociceptive pain and neuropathic pain; physical fatigue and mental fatigue). Furthermore, it is unclear whether cut points are stable over time. It is conceivable that cut points change after a long duration of suffering of a certain symptom. Prospective studies are needed to determine the factors that influence the cut points.

In conclusion, cut points are frequently used in clinical practice and scientific research. In this review, we found some evidence on cut points for pain (moderate pain CP5 and severe

pain CP7) and fatigue (moderate fatigue CP4). Until there is more evidence on the optimal cut points, we should hold back in using a certain cut point in quality indicators and be cautious to strongly recommend a cut point in guidelines. In daily clinical practice, symptom scores ≥4 should trigger a more comprehensive symptom assessment to properly identify the patients with clinically relevant symptom burden.

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6

Systematic monitoring and treatment of physical symptoms to alleviate fatigue in patients with advanced cancer: a randomized controlled trial

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Abstract

Purpose

Several guidelines on the treatment of cancer-related fatigue recommend optimizing treatment of accompanying symptoms. However, evidence for this recommendation from randomized clinical trials is lacking. We investigated whether monitoring and protocolized treatment of physical symptoms alleviates fatigue.

Patients and methods

In all, 152 fatigued patients with advanced cancer were randomly assigned to protocolized patient-tailored treatment (PPT) of symptoms or care as usual. The PPT group had four appointments with a nurse who assessed nine symptoms on a 0 to 10 Numeric Rating Scale (NRS). Patients received a nonpharmacologic intervention for symptoms with a score ≥1 and a medical intervention for symptoms with a score ≥4. Fatigue dimensions, fatigue NRS score, interference of fatigue with daily life, symptom burden, quality of life, anxiety, and depression were measured at baseline, and after 1, 2 and 3 months. Differences between the groups over time were assessed by using mixed modeling.

Results

Seventy-six patients were randomly assigned to each study arm. Mean age was 58±10 years, 57% were female, and 65% were given palliative chemotherapy. We found significant improvements over time in favor of PPT for the primary outcome General Fatigue (P=0.01), with significant group differences at month 1 (p=0.007, effect size 0.26) and month 2 (p=0.005, effect size 0.35). Improvements in favor of PPT were also found for the following secondary outcomes: fatigue dimensions Reduced Activity and Reduced Motivation, fatigue NRS, symptom burden, interference of fatigue with daily life and anxiety (all P≤0.03).

Conclusion

In fatigued patients with advanced cancer, nurse-led monitoring and protocolized treatment of physical symptoms is effective in alleviating fatigue.

Introduction

Cancer-related fatigue is a common symptom in palliative care, with an overall prevalence of 74%[1]. Fatigue is considered to be a multidimensional symptom, consisting of physical, emotional, and cognitive dimensions[2-3]. The pathogenesis of cancer-related fatigue is still unclear, but disturbances in physiologic, biochemical and psychological systems seem to be involved[4].

Because of this multicausal pathogenesis, a variety of interventions for cancer-related fatigue have been studied. So far, three Cochrane reviews have been published that reported small but significant benefits of drug therapy[5] (e.g. methylphenidate[6]), exercise[7], and psychosocial interventions[8] (e.g. psycho-education on energy conservation and activity management[9]) on fatigue intensity in patients with cancer. However, few randomized controlled trials (RCTs) analyzed in these reviews included only patients with advanced cancer. Therefore, the conclusions of the Cochrane reviews cannot be extrapolated to patients with advanced cancer. Because current treatment options for fatigue in patients with advanced cancer are scarce, we urgently need to develop new evidence-based interventions for this population.

Some guidelines advise optimizing management of other physical symptoms as part of the treatment of fatigue in patients with cancer[10]. However, this recommendation is based only on cross-sectional studies in which fatigue was associated with other symptoms such as pain[11-16], dyspnea[11-18], lack of appetite[11-14,17-19] and nausea[11-12]. Therefore, in this RCT we investigated whether monitoring and protocolized treatment of physical symptoms coordinated by a nurse have a more favorable effect on the severity of fatigue than the symptom management included in the standard oncological care of patients with advanced cancer. We also investigated whether this intervention is more effective than standard care in decreasing symptom burden, interference of fatigue with daily life, anxiety, and depressed mood and in improving quality of life.

Methods

Patients

From October 2007 to March 2011, we included fatigued ambulatory patients with advanced cancer in a nonblinded RCT on the effectiveness of protocolized patient-tailored treatment (PPT) of physical symptoms as compared with care as usual (CAU). This study was performed at the outpatient clinic of the Department of Medical Oncology of the Erasmus Medical Center-Daniel den Hoed Cancer Center in Rotterdam, the Netherlands.

Patients were eligible to participate if they had a solid malignancy, received treatment with palliative intention, gave a fatigue score ≥ 4 on a 0 to 10 Numeric Rating Scale (NRS), had an ECOG performance status ≤2, had a life expectancy ≥ 4 months, and were able to write and speak Dutch. Patients were not eligible if they had received any experimental drug in the last 4 weeks, their oncologist considered that their anxiety and/or depressive symptoms reached levels requiring psychiatric consultation, had severe comorbidity causing fatigue (e.g. symptomatic heart failure or symptomatic chronic obstructive pulmonary disease), lived in nursing homes, or were cognitively impaired.

Design

Patients were invited to participate in the trial by medical staff. These health care providers were encouraged to offer study participation to all eligible patients, but the investigators did not systematically screen all patients for eligibility.

Eligible patients who provided written informed consent and completed the baseline questionnaire were randomly assigned to either PPT or CAU in a 1:1 ratio. The randomization was based on a computer-generated randomization procedure with a variable block length (one-four repetitions per block).

Patients randomized to the PPT arm had four appointments with a nurse specialist during the trial: within 1 week after random assignment, after 2 to 4 weeks, after 5 to 7 weeks, and after 8 to 10 weeks.

Participants received questionnaires from the investigators at baseline and via mail 1, 2, and 3 months after random assignment. Patients completed the questionnaires without help from the investigators.

The local Medical Research Ethics Committee had granted permission to perform this study, which has been registered in the Dutch Trial Register (number NTR1170).

Intervention

The nurse specialist coordinated a complex intervention regarding the following physical symptoms: pain, nausea, vomiting, constipation, diarrhea, lack of appetite, shortness of breath, cough and dry mouth.

During meetings with the nurse specialist at the outpatient clinic, patients were asked to rate the intensity of these symptoms in the last week on a 0 to 10 NRS, where 0 represents 'no suffering' and 10 represents 'unbearable suffering'. When patients rated a certain symptom higher than 0, they received a nursing intervention, which comprised education on the importance of drug adherence and non-pharmacological interventions for that particular symptom. In addition, when patients rated a certain symptom ≥4[20-21], the nurses asked the oncologist to determine the cause of that symptom and to start an appropriate treatment by using protocols, based on the guidelines for palliative care developed by the Dutch Comprehensive Cancer Centers. The level of evidence for most recommendations in these guidelines is comparable to NCCN Category 2A evidence, which is based on lower-level evidence but uniform consensus. The medical interventions consisted of changes in disease-related treatment, starting or adjusting medication for symptom control, referral to other specialists, invasive interventions (e.g. pleural drainage), further diagnostic examinations, or admission to the hospital for the treatment of the respective symptoms. A summary of the interventions for each symptom is given in the Appendix.

In case of suffering of multiple physical symptoms, nurse specialists were instructed to manage as many symptoms as possible, starting with the symptom most troublesome in the patients' opinion. The nurses were also instructed to focus on the nine physical symptoms only and not to educate patients on fatigue itself.

The symptoms of the patients in the CAU group were not monitored systematically, and the treatment they received was not guided by a protocol, but was based on the initiative, knowledge, and experience of their own oncologists. They did not have planned appointments

with the nurse specialists for symptom control, although they received the standard nursing care, e.g. during hospital stays or while visiting the day care clinic.

Measurements

Fatigue was measured by using the Multidimensional Fatigue Inventory (MFI), which consists of 20 statements covering five dimensions of fatigue: General Fatigue, Physical Fatigue, Reduced Activity, Reduced Motivation and Mental Fatigue. Patients indicated their agreement with each statement on a five-point Likert-scale. Therefore, the subscores per dimension vary between 4 and 20; higher scores indicate more fatigue[3]. The internal consistency, discriminant validity, and convergent validity of the MFI are satisfactory[22]. Fatigue was also measured by using a 0 to 10 NRS that asked for average fatigue in the last week[10].

The severity of each of the nine physical symptoms over the last week was measured on a 4-point verbal scale in accordance with the EORTC QLQ-C30[23]. We calculated a total score for symptom burden with a possible range of 0 (no symptom burden) to 100 (highest possible symptom burden)[24].

The influence of fatigue on daily life was measured with the Brief Fatigue Inventory-Interference subscale (BFI-I), which asked how fatigue has interfered with general activity, mood, walking ability, normal work, relations with other people, and enjoyment of life in the last 24 hours. Each item had to be answered on an NRS with scores ranging from 0 (no interference) to 10 (complete interference)[25].

Anxiety and depressed mood were measured with the Hospital Anxiety and Depression Scale (HADS). Scores for both the anxiety subscale (HADS-A) and the depression subscale (HADS-D) ranged from 0 to 21, with higher scores indicating more distress[26].

Quality of life in the last week was measured on a single seven-point scale, also derived from the EORTC-QLQ-C30 [23]. Higher scores indicated higher quality of life.

Statistical methods

The primary outcome was MFI-General Fatigue. To detect a medium difference in MFI-General Fatigue (Cohen's d of 0.50) with a power of 0.80 and an alpha of 0.05, both groups should consist of 64 patients[27]. We expected 15% of the patients to drop out before the second assessment. Consequently, a total of 76 patients was needed per group.

Differences in patients' characteristics and disease characteristics between the PPT arm and the CAU arm were tested with t-tests for continuous variables and with Chi-squared tests for categorical variables.

Differences between PPT and CAU over time in the outcome measurements were analyzed with linear mixed modeling[28]. Mixed modeling can efficiently handle missing data. It corrects for bias when absence of data is dependent on characteristics that are present in the model[29]. For each outcome variable, we first tested a full random intercept and slope model with the following predictors: group, time since random assignment, hemoglobin level at baseline, treatment at baseline (radiotherapy, chemotherapy, hormonal therapy), an interaction term between group and time since random assignment and an interaction term between group and the quadratic function of time since random assignment. The group*time interaction allowed groups to have different time trends, and the group*time squared interaction permitted

groups to have a different curvature in the course of the outcome variables. Predictors were removed from the model one by one until the model comprised predictors with *P* values less than 0.10 only. In this final model, predictors with *P* values less than 0.05 were considered to be statistically significant. By using the final model, estimates of the scores on the outcome measures were calculated for each group at each time point. These estimates were used to draw the graphs in this study because raw data are likely to be biased by selective dropout. Note that this analysis for repeated measurements is more powerful than the sample size calculation in which no correction for repeated measurements was applied.

Effect sizes were reported as Cohen's d's[27] at each assessment point using the estimated scores of the outcome variables and their estimated standard deviations. The standard deviations were derived from the random effects model by using the formula in the Appendix. An effect size around 0.3 is considered a small effect, around 0.5 a medium effect, and above 0.8 a large effect[27].

Results

Between October 2007 and March 2011, we included 152 patients with advanced cancer, with 76 patients randomly assigned to each study arm (Figure 1). Five patients in the PPT arm and ten patients in the CAU arm dropped out before the second assessment (T1) and were therefore excluded from the analyses. The excluded patients differed from the included patients in the scores on anxiety (9.1 vs. 5.7, p=0.002) and depression (9.4 vs. 6.3, p=0.005) only. Of the patients randomly assigned to the PPT arm, 97% attended at least one intervention session, and 75% attended all sessions.

Baseline characteristics of the patients are reported in Table 1. There were no significant differences between the PPT arm and CAU arm in patient characteristics and disease characteristics. Patients in the PPT arm underwent antitumor therapy categorized as "other treatment", such as tyrosine kinase inhibitors, more frequently (*P*=0.02). There were no significant differences in the baseline values of the outcome measures (Table 2).

An overview of the symptoms scores, medical interventions, and nursing interventions per intervention session is provided in the Appendix. At session 1, patients had a median of two symptoms with a score ≥4, which decreased to a median of one symptom at session 2, 3 and 4. In all intervention sessions, the symptoms most troublesome in the patients' opinion were pain, shortness of breath and lack of appetite.

The changes over time in the fatigue measurements for both groups are shown in Figure 2. There was a significant difference over time in the primary outcome MFI-General Fatigue in favor of the PPT group (group*time *P*=0.01). The PPT group had significantly lower scores than the CAU group on MFI-General Fatigue on T1 (mean difference -0.84 (SE 0.31), p=0.007, effect size 0.26) and T2 (mean difference -1.14 (SE 0.40), p=0.005, effect size 0.35), but not at T3 (mean difference -0.90 (SE 0.50), p=0.07, effect size 0.27).

The scores on the fatigue dimensions MFI-Reduced Activity and MFI-Reduced Motivation also improved significantly over time in the PPT group compared with the CAU group (group*time *P*-values both <0.05). The courses of the intensities of MFI-Physical Fatigue and

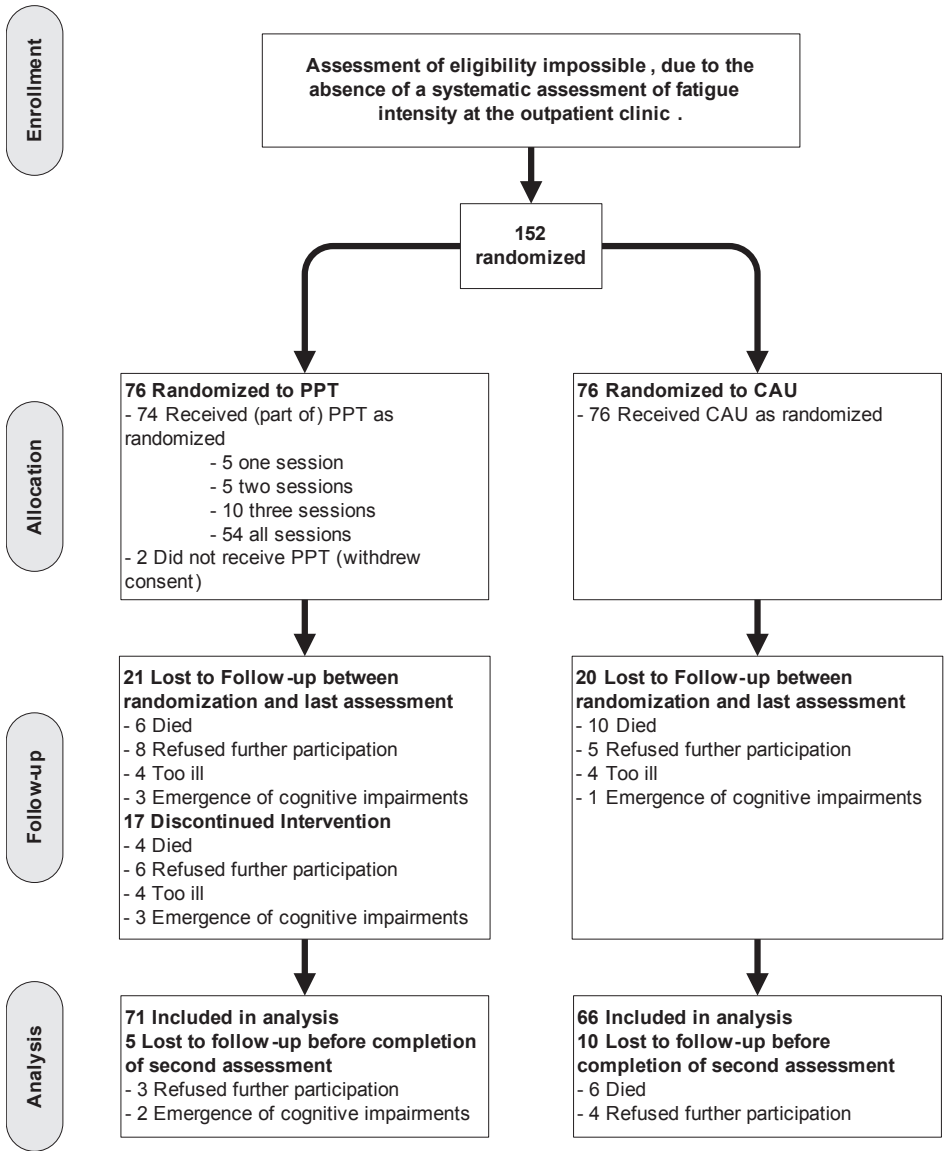

Figure 1: Consort Diagram

MFI-Mental Fatigue were not significantly different between the intervention group and the control group. There was a significant decrease over time in the intensity of fatigue as measured with the 0 to 10 NRS in the PPT group (group*time $P<0.001$; maximal effect size 0.84) compared with the CAU group.

There was a decrease in symptom burden over time in the PPT group whereas the intensity of symptom burden did not change in the CAU group (group*time $P=0.002$, maximal effect

Table 1: Baseline characteristics for patients randomized to protocolized patient-tailored treatment (PPT) and care as usual (CAU)

	PPT (n=76)	**CAU** (n=76)
Age – mean ± SD	57±9.7	59±10.5
Sex – n (%)		
Male	31 (41%)	34 (45%)
Female	45 (59%)	42 (55%)
Marital status – n (%)		
Never married	6 (8%)	8 (11%)
Married or living with partner	65 (86%)	58 (76%)
Divorced	2 (3%)	6 (8%)
Widowed	3 (4%)	4 (5%)
Education – n (%)		
<High school graduate	6 (8%)	13 (17%)
High school graduate	44 (58%)	41 (54%)
College graduate	23 (30%)	20 (26%)
Unknown	3 (4%)	2 (3%)
Ethnicity		
Caucasian	76 (100%)	76 (100%)
ECOG status – n (%)		
1	66 (87%)	67 (88%)
2	10 (13%)	9 (12%)
Tumor – n (%)		
Breast	29 (38%)	27 (36%)
Gastro-intestinal	26 (34%)	21 (28%)
Urogenital	10 (13%)	14 (18%)
Other	11 (14%)	14 (18%)
Disease stage – n (%)		
Locally advanced	3 (4%)	6 (8%)
Metastatic	73 (96%)	70 (92%)
Months since primary tumor diagnosis – mean ± SD	58±67	57±60
Anti-cancer treatment – n (%)		
No anti-cancer therapy	12 (16%)	12 (16%)
Chemotherapy	47 (62%)	51 (67%)
Hormonal therapy	8 (11%)	8 (11%)
Radiotherapy	3 (4%)	2 (3%)
Other*	17 (22%)[1]	6 (8%)[2]
Anemia (Hb ≤10.0 g/dL) – n (%)		
Yes	16 (21%)	17 (22%)
No	60 (79%)	59 (78%)

[1] Bevacizumab (n=6), Trastuzumab (n=4), Bevacizumab+Trastuzumab (n=1), Sunitinib (n=5), Sorafenib (n=1)
[2] Bevacizumab (n=1), Trastuzumab (n=1), Cetuximab (n=1), Sunitinib (n=2), Temsirolimus (n=1)
* PPT vs. CAU P =0.02

Table 2: Baseline values of the outcome measures

	PPT (n=76) Mean ± SD	CAU (n=76) Mean ± SD
MFI		
MFI-General Fatigue	15.8 ± 3.0	15.5 ± 3.1
MFI-Physical Fatigue	15.0 ± 3.1	15.6 ± 3.2
MFI-Reduced Activity	14.5 ± 3.9	15.0 ± 3.7
MFI-Reduced Motivation	12.1 ± 4.3	11.8 ± 4.0
MFI-Mental Fatigue	10.5 ± 4.3	11.7 ± 5.0
NRS Fatigue	6.2 ± 1.4	6.1 ± 1.6
BFI-Interference	4.7 ± 1.8	4.6 ± 1.9
Physical symptoms		
Symptom burden	26.9 ± 14.7	23.6 ± 14.6
Scored moderate/severe – n (%)		
Pain	26 (35%)	21 (28%)
Nausea	20 (27%)	10 (13%)
Vomiting	10 (13%)	3 (4%)
Diarrhea	10 (13%)	9 (12%)
Constipation	12 (16%)	4 (5%)
Lack of appetite	31 (41%)	21 (28%)
Shortness of breath	18 (24%)	26 (35%)
Cough	10 (13%)	10 (14%)
Dry mouth	17 (23%)	18 (24%)
Quality of life	4.5 ± 1.3	4.5 ± 1.2
HADS-Anxiety	5.6 ± 3.6	6.4 ± 3.6
HADS-Depression	6.0 ± 4.1	7.1 ± 4.3

MFI = Multidimensional Fatigue Inventory; NRS = Numeric Rating Scale; BFI = Brief Fatigue Inventory; HADS = Hospital Anxiety and Depression Scale.

size 0.41; Figure 3A). Patients in the PPT group reported a decrease of the interference of fatigue with daily life, whereas patients in the CAU group reported an increase (group*time $P<0.001$; maximal effect size 0.64, Figure 3B). During the study, anxiety decreased in the PPT group as compared with the CAU group (group*time $P<0.001$; maximal effect size 0.32, Figure 3C), whereas the course of depression was not different between the groups (Figure 3D). There was no significant difference between the groups over time in the course of quality of life.

Discussion

To our knowledge, this is the first randomized controlled trial that provides evidence for the recommendation to optimize treatment of physical symptoms as part of the treatment of cancer-related fatigue. We found that monitoring and protocolized patient-tailored treatment of physical symptoms is more effective than standard care in improving physical symptoms and in reducing fatigue intensity in fatigued outpatients with advanced cancer. In addition,

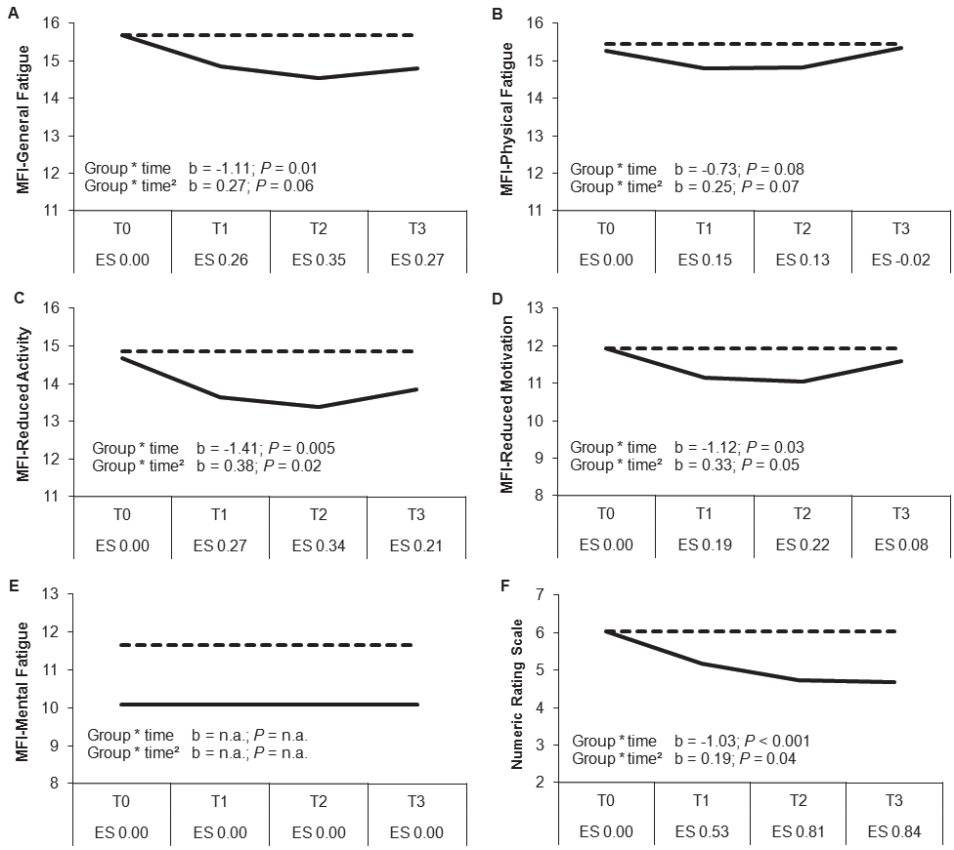

Figure 2: Course of fatigue in patients who received protocolized patient-tailored treatment (PPT, solid lines) and in patients who received care as usual (CAU, dashed lines)

compared with standard care, this intervention also leads to an improvement in the interference of fatigue with daily life and a reduction of anxiety in these patients. It should be kept in mind that these were exploratory analyses on secondary outcomes. We could not find an effect of our intervention on the physical senses of tiredness, difficulties with concentrating, depressed mood, and quality of life.

Although we found a significant difference between the groups over time in the primary outcome MFI-General Fatigue, the maximum effect size of 0.35 did not reach the medium effect we aimed for (effect size 0.5). However, in intervention studies on cancer-related fatigue published in the last few years, the effect sizes of improvements in fatigue were usually small. For example, the effect size of the improvement in fatigue by exercise in curatively treated patients with cancer was 0.23[7] and the effect size of the benefits of methylphenidate was 0.28[30]. Moreover, because treatment options for fatigue in patients with advanced cancer are scarce, we would argue that even small improvements in fatigue should be considered clinically relevant.

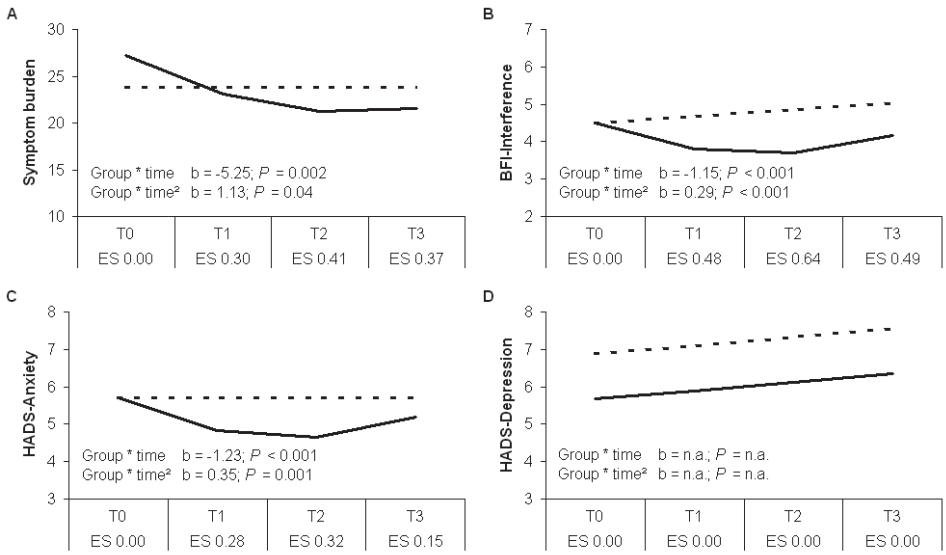

Figure 3: Changes over time in symptom burden (Figure 3A), the interference items of the Brief Fatigue Inventory (Figure 3B), anxiety (Figure 3C) and depressed mood (Figure 3D) for patients which received protocolized patient-tailored treatment (PPT, solid lines) and care-as-usual (CAU, dashed lines)

In contrast to our study, most randomized controlled trials on palliative care interventions in patients with advanced cancer did not find improvements in symptom intensity[31-35]. As in our study, symptoms seemed to be systematically assessed in the studies that found an improvement in symptom intensity[36-37], whereas most other studies did not report a systematic monitoring of symptoms[31,33,35], which might be a prerequisite for an effective treatment[38].

Our intervention resulted in improvements in both fatigue intensity and interference with daily life, which was previously reported by just one study investigating the effectiveness of a nurse-coordinated educational intervention[39]. Other studies that reported results for both intensity and interference found improvements in fatigue intensity, but not in fatigue interference[40-42], or no improvements at all[43].

Performing a randomized controlled trial in patients with advanced cancer has several challenges. First, 18% of the patients dropped out because of disease progression during the study (Figure 1). Second, disease progression will cause an increase in symptom intensity and the emergence of new symptoms. Therefore, alleviation in fatigue and other symptoms will always be transient in these patients unless the intervention is continued. This might explain the observation that the intervention was effective when administered frequently (between T0 and T2) whereas symptom scores started increasing when the intervention was completed (between T2 and T3).

This study has several limitations. First, patients were not routinely screened for fatigue at our outpatient clinic. Therefore, we were not able to determine which patients were eligible for our study. This might have led to a selection bias, i.e. patients who spontaneously complained

about fatigue might be more likely to be referred for inclusion than patients reluctant to report fatigue. However, in patients referred for the assessment of eligibility, we investigated samplewise how many patients could be included and what the main reasons for exclusion were. Forty-three percent of the patients who were assessed for eligibility were included in the trial. The most important reasons for exclusion were: an NRS fatigue score ≤3 (41%), patient refusal (25%), and having a life expectancy less than three months (15%).

Furthermore, this study was conducted in a single center, and the ethnicity of the patients was limited to Caucasians, which might limit the generalizability of the study. In future research, whether the beneficial effects of our intervention could be reproduced should be investigated in other settings and populations.

In this trial, we investigated the efficacy of a complex intervention, consisting of various components: symptom monitoring, protocolized treatment, patient education, adjustment of symptomatic medication, non-pharmacologic interventions, etc. Compared with the standard care group, participants in the intervention group received extra attention from the health care providers, which might have partially contributed to the positive results in our study. To the best of our knowledge, there are no guidelines on strategies for dealing with the issue of extra attention in complex nonpharmacological intervention studies[44]. The design of our study did not allow us to establish which components of the intervention were responsible for the beneficial effect. However, in our opinion, a multidisciplinary intervention is required to treat a multicausal symptom like fatigue.

An important limitation in the assessment of the therapeutic value of multimodal interventions is the difficulty of reproducing these interventions[44-45]. We tried to overcome this barrier by designing an intervention based on the national guidelines for symptom treatment and by giving a summary of the interventions per symptom in the Appendix.

In congruence with the policy of the European Society of Medical Oncology on minimal standards for the provision of palliative care[46], we argue that protocolized monitoring and treatment of physical symptoms should be part of the routine treatment of fatigue in advanced cancer. It is advisable to refer fatigued patients with advanced cancer to a nurse trained in palliative care for monitoring symptom intensity, educating of the patient, and referral to other health care providers if necessary. Further research should focus on elucidating which components are responsible for the effect of improving symptom burden on fatigue and on establishing the cost-effectiveness of this intervention.

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Supplementary data

Summary of the interventions per symptom

Outline of the intervention

Monitor symptom intensity systematically
Take the symptom history by using protocolized questions
Give causal treatment based on etiology
Reconsider start/stop antitumor therapy
Treat contributing factors, i.e. anxiety, depression
Consider referral to other specialists
Give symptomatic pharmacologic treatment
Give nonpharmacological treatment

Interventions for pain

Start or adjust pain medication according to WHO analgesic ladder
Start or adjust neuropathic pain medication
Administer Pain Education Program (Oldenmenger et al; Pain, 2011)
Enhance knowledge on pain and pain treatment
Stimulate patients' help-seeking behavior

Interventions for nausea

Start or adjust antiemetic
Educate on the importance of medication adherence and how to use antiemetics
Give nonpharmacological interventions
Advise to avoid nausea-inducing stimuli
Give advice on eating habits (in sitting position, frequently small portions, avoid fat and hot spicy meals)
In case of nausea, advise to suck on ice or drink soda
Consider referral to dietician

Interventions for vomiting

See recommendations on nausea

Interventions for constipation

Start or adjust laxatives
In case of fecal impaction, use enemas
Enhance knowledge on the symptoms indicating constipation
Educate on the importance of medication adherence and how to use laxatives
Advise on dietary habits, such as fluid intake, use of fiber-rich meals
Encourage physical activity
Discuss the conditions for an optimal defecation pattern

Interventions for diarrhea

Start or adjust loperamide
Start laxatives in case of overflow diarrhea
Educate on the importance of medication adherence and how to use loperamide
Advise on dietary habits, such as fluid intake, use of fiber-rich meals, avoidance of peristalsis-stimulating food
Discuss possible feelings of embarrassment and practical solutions on fecal incontinence and malodors.

Interventions for lack of appetite

Consider prescribing Megestrol (if life expectancy is >2 months) or Dexamethason (if life expectancy is <2 months)
Give instructions on how to optimize oral hygiene
Consider referral to a dietician
Educate on the role of nutrition in advanced cancer: less eating does not hasten death; anorexia is a frequent symptom in the disease trajectory, etc.
Give practical tips on coping with lack of appetite: use frequent and small portions, consume cold or sour dishes, get some rest before you have to eat, etc.

Interventions for shortness of breath

Treat infections, pulmonary embolisms, and exacerbations of COPD
In case of decreased oxygen saturation, administer oxygen
In case of subjective dyspnea with normal saturation, consider morphine
In case of malignant pleural effusion, consider drainage
Discuss dyspnea-provoking factors, e.g. anxiety, immobilization and posture
Give instructions on inhalation medication
Educate on the optimal breathing technique, the importance of fresh air and what to do when the shortness of breath worsens.

Interventions for cough

Treat infections, pulmonary embolisms and exacerbations of COPD
Consider prescribing codeine or slow-release morphine
Educate on optimal posture in case of productive cough
Educate on action and side-effects of codeine/morphine

Interventions for dry mouth

Consider stimulation of the production of saliva by pilocarpine
Give instructions on how to optimize oral hygiene
Consider referral to a dietician
Advise to stimulate saliva production by using carbonated drinks, chewing gum, or mouth rinses
Advise to drink frequently small amounts of water or suck on ice blocks
Consider the use of Biotene Oral Balance

Formula 1

$$\mathrm{sd} = \sqrt{Var_{\mathrm{int}} + 2 * Cov_{\mathrm{int}-time} * time^2 + Var_{residual}}$$

Supplementary Table 1: Overview of the intervention sessions: frequency of NRS ≥ 4 and interventions delivered in patients with an NRS ≥ 4 for a certain symptom

		Session 1		Session 2		Session 3		Session 4	
		NRS ≥4 n (%)	In case NRS ≥4 n (%)	NRS ≥4 n (%)	In case NRS ≥4 n (%)	NRS ≥4 n (%)	In case NRS ≥4 n (%)	NRS ≥4 n (%)	In case NRS ≥4 n (%)
Pain		**26 (37%)**		**21 (31%)**		**17 (29%)**		**17 (30%)**	
Medical	Medication		11 (42%)		8 (38%)		3 (18%)		6 (35%)
	Diagnostics		3 (12%)		1 (5%)		4 (24%)		3 (18%)
	Other		2 (8%)		1 (5%)		0 (0%)		0 (0%)
Nursing	Medication		17 (65%)		15 (71%)		8 (47%)		4 (24%)
	Lifestyle		4 (15%)		4 (19%)		1 (6%)		0 (0%)
Nausea		**9 (13%)**		**8 (12%)**		**5 (9%)**		**6 (11%)**	
Medical	Medication		3 (33%)		4 (50%)		1 (20%)		5 (83%)
	Diagnostics		1 (11%)		1 (13%)		0 (0%)		0 (0%)
	Other		0 (0%)		0 (0%)		0 (0%)		0 (0%)
Nursing	Medication		5 (56%)		4 (50%)		2 (40%)		4 (67%)
	Lifestyle		1 (11%)		2 (25%)		2 (40%)		2 (33%)
Vomiting		**4 (6%)**		**2 (3%)**		**2 (4%)**		**5 (9%)**	
Medical	Medication		1 (25%)		1 (50%)		0 (0%)		3 (60%)
	Diagnostics		1 (25%)		0 (0%)		0 (0%)		0 (0%)
	Other		0 (0%)		0 (0%)		0 (0%)		0 (0%)
Nursing	Medication		1 (25%)		2 (100%)		1 (50%)		3 (60%)
	Lifestyle		2 (50%)		0 (0%)		0 (0%)		1 (20%)
Constipation		**5 (7%)**		**6 (9%)**		**4 (7%)**		**3 (5%)**	
Medical	Medication		2 (40%)		3 (50%)		2 (50%)		2 (67%)
	Diagnostics		0 (0%)		0 (0%)		0 (0%)		0 (0%)
	Other		0 (0%)		0 (0%)		0 (0%)		0 (0%)
Nursing	Medication		3 (60%)		3 (50%)		2 (50%)		1 (33%)
	Lifestyle		4 (80%)		3 (50%)		1 (25%)		1 (33%)

Diarrhea		**14 (20%)**		**5 (7%)**		**5 (9%)**		**5 (9%)**	
Medical	Medication	3 (21%)		2 (40%)		1 (20%)		0 (0%)	
	Diagnostics	1 (7%)		0 (0%)		0 (0%)		0 (0%)	
	Other	0 (0%)		0 (0%)		0 (0%)		0 (0%)	
Nursing	Medication	3 (21%)		2 (40%)		1 (20%)		1 (20%)	
	Lifestyle	7 (50%)		1 (20%)		1 (20%)		0 (0%)	
Lack of appetite		**28 (40%)**		**19 (28%)**		**16 (28%)**		**13 (23%)**	
Medical	Medication	3 (11%)		3 (16%)		0 (0%)		1 (8%)	
	Diagnostics	1 (4%)		0 (0%)		0 (0%)		0 (0%)	
	Other	3 (11%)		4 (21%)		0 (0%)		0 (0%)	
Nursing	Medication	1 (4%)		2 (11%)		0 (0%)		0 (0%)	
	Lifestyle	11 (39%)		9 (47%)		2 (13%)		4 (31%)	
Shortness of breath		**26 (37%)**		**18 (27%)**		**15 (26%)**		**14 (25%)**	
Medical	Medication	2 (8%)		3 (17%)		0 (0%)		0 (0%)	
	Diagnostics	3 (12%)		1 (6%)		2 (13%)		3 (21%)	
	Other	1 (4%)		1 (6%)		2 (13%)		0 (0%)	
Nursing	Medication	3 (12%)		3 (17%)		0 (0%)		0 (0%)	
	Lifestyle	14 (54%)		8 (44%)		2 (13%)		1 (7%)	
Cough		**10 (14%)**		**4 (6%)**		**3 (5%)**		**5 (9%)**	
Medical	Medication	2 (20%)		0 (0%)		0 (0%)		0 (0%)	
	Diagnostics	1 (10%)		0 (0%)		0 (0%)		0 (0%)	
	Other	0 (0%)		0 (0%)		0 (0%)		0 (0%)	
Nursing	Medication	2 (20%)		1 (25%)		0 (0%)		0 (0%)	
	Lifestyle	2 (20%)		2 (50%)		1 (33%)		0 (0%)	
Dry mouth		**20 (28%)**		**13 (20%)**		**10 (17%)**		**7 (13%)**	
Medical	Medication	1 (5%)		1 (8%)		0 (0%)		0 (0%)	
	Diagnostics	1 (5%)		0 (0%)		0 (0%)		0 (0%)	
	Other	1 (5%)		0 (0%)		0 (0%)		0 (0%)	
Nursing	Medication	0 (0%)		0 (0%)		0 (0%)		0 (0%)	
	Lifestyle	9 (45%)		6 (46%)		4 (40%)		2 (29%)	

7

Summary and Discussion

General

Fatigue is experienced by cancer patients in all stages of the disease trajectory: from before diagnosis to years after completing treatment and also in advanced cancer. Fatigue has a greater negative influence on quality of life and daily activities than any other cancer-related symptom. Although both national and international guidelines have been developed to enhance the management of cancer-related fatigue, cancer-related fatigue is still poorly understood. This thesis describes research that has been performed in order to clarify some aspects of the multidimensional nature, pathogenesis, assessment and treatment of cancer-related fatigue.

Multidimensionality

Summary

Patients describe their feelings of fatigue in terms of physical, cognitive and emotional senses of tiredness, which have been called fatigue dimensions. Although the multidimensional nature of cancer-related fatigue is widely accepted, it could be questioned whether fatigue dimensions are expressions of one symptom (multidimensional concept) or expressions of several phenomena which are all called fatigue but actually are separate symptoms (multiple symptom concept). If fatigue should be considered as a multiple symptom concept, we expect the fatigue dimensions to behave differently. Therefore, we investigated in a systematic review whether physical fatigue and mental fatigue behave differently in cancer patients, by studying their intensity in different stages of cancer; their changes in intensity during anti-tumour therapy; the variables to which they are related; and their changes in intensity by interventions on fatigue **(chapter 2)**.

We found some studies in which physical fatigue and mental fatigue behaved similarly: they were both more intense in cancer patients than in healthy controls and sometimes they had the same course during anti-tumour therapy or improved both during an intervention. In contrast, we found several studies in which physical fatigue and mental fatigue behaved differently: physical fatigue seemed to be more prominent than mental fatigue in some stages of the disease trajectory; several studies reported changes in physical fatigue not accompanied by changes in mental fatigue during anti-tumour therapy or by interventions aimed to relieve fatigue; and physical fatigue and mental fatigue had different correlates. We concluded that these findings of a different behaviour for physical fatigue and mental fatigue might support the multiple symptom concept.

We found only three studies that compared fatigue experiences of patients in different stages of cancer, but these studies did not match the various groups sufficiently for age, sex and tumour diagnosis. Therefore, we performed a cross-sectional study in which we compared the fatigue experiences of advanced cancer patients, cancer survivors and healthy controls **(chapter 3)**. We recruited 63 advanced cancer patients who had not received systemic anti-tumour therapy in the last 4 weeks and for whom no therapeutic options were available and 63 cancer survivors who had finished treatment 1 to 5 years ago. ACP and CS were matched for age, sex and diagnosis. Fatigue was assessed with a 0-10 Numeric Rating Scale (NRS) and the Multidimensional Fatigue Inventory (MFI). For each advanced cancer patient, 5 age- and sex-

matched controls were randomly drawn from a German dataset with MFI-scores of a sample from the general population. We found that the intensity of all fatigue dimensions of the MFI (general fatigue, physical fatigue, reduced activity, reduced motivation, mental fatigue) was higher in the advanced cancer patients than in the cancer survivors and the controls ($p<0.01$), whereas fatigue levels were not different between cancer survivors and controls. NRS-scores in advanced cancer patients and cancer survivors were significantly predicted by the fatigue dimensions physical fatigue and mental fatigue only. Whereas physical fatigue and mental fatigue were strongly related in the general population ($r = 0.68$, $p<0.01$), the relation was weaker in cancer survivors ($r = 0.35$, $p<0.01$) and not even significant in advanced cancer patients ($r = 0.15$, n.s.). In multivariate analyses, only physical fatigue differentiated advanced cancer patients from cancer survivors and controls ($p<0.01$). We concluded that fatigue is more intense and that especially physical fatigue is more prominent in advanced cancer patients than in cancer survivors.

Discussion

The NCCN guideline and the Dutch guideline for the treatment of cancer-related fatigue both indicate that fatigue is a multidimensional phenomenon. However, it was never investigated whether the dimensions of fatigue are just expressions of the same symptom or whether they might be separate phenomena, which was already suggested in 1943 by W.H. Forbes, a researcher at the Fatigue Laboratory at Harvard University[1]:

"Progress in the study of fatigue has been impeded by the general tendency to speak of fatigue as an entity, without considering the many kinds of fatigue which are observed, each of which may have a different cause and different symptoms."

In this thesis we found that patients in different stages of the disease trajectory have different fatigue experiences. However, we investigated fatigue experiences in two populations in an opposite stage of the disease trajectory: patients with progressive disease in the last months of life and cancer survivors without evidence of disease. Although these extremes were useful in demonstrating differences in fatigue experiences, it has to be investigated what the fatigue experiences are in other oncology populations, such as patients during curative treatment or patients with advanced disease still receiving anti-tumour therapy.

In this thesis we also found some evidence that physical fatigue and mental fatigue are different phenomena. Nevertheless, this conclusion is based on circumstantial evidence only. To prove that physical fatigue and mental fatigue are separate symptoms requiring different treatments, it should be investigated whether they have various pathogeneses.

To improve the understanding of cancer-related fatigue, in future studies, fatigue should not be measured with a questionnaire assessing fatigue as a single entity, but always with a questionnaire which is able to measure the various dimensions of fatigue. Also in future research, investigators should not mix up participants in various stages of the disease trajectory, because the fatigue in various populations might be experienced differently and might be precipitated by different factors.

Pathogenesis

Summary

Since we showed that advanced cancer patients and cancer survivors have different fatigue experiences, we wondered whether there are differences between these groups in the mechanisms underlying fatigue. Inflammation is frequently hypothesized to play a key role in the pathogenesis of cancer-related fatigue. Therefore, we explored in a pilot study whether physical fatigue and mental fatigue are associated with inflammatory markers in a subgroup of 45 advanced cancer patients and 47 cancer survivors derived from the study mentioned previously **(chapter 4)**. The levels of all inflammatory markers were higher in the advanced cancer patients than in the cancer survivors ($p<0.01$). In the advanced cancer patients, C-reactive protein ($r=0.49$, $p=0.001$), interleukin-6 ($r=0.43$, $p=0.003$), interleukin-1 receptor antagonist ($r=0.32$, $p=0.03$), and neopterin ($r=0.25$, $p=0.10$) were correlated with physical but not with mental fatigue. In cancer survivors, only interleukin-1 receptor antagonist was related to both physical fatigue ($r=0.24$, $p=0.10$) and mental fatigue ($r=0.35$, $p=0.02$). We concluded that inflammation is associated with physical fatigue but not with mental fatigue in advanced cancer patients. There was no convincing evidence that inflammation plays a major role in cancer survivors' fatigue.

Discussion

In congruence with the Dutch guideline and the NCCN guideline, we found some evidence that inflammation might be involved in the pathogenesis of fatigue. However, this was only the case for physical fatigue in advanced cancer patients, and not for mental fatigue or fatigue in cancer survivors. This might indicate that physical fatigue has another pathogenesis than mental fatigue, which supports the hypothesis that physical and mental fatigue are separate phenomena (the multiple symptom concept). Our findings might also imply that the pathogenesis of fatigue in advanced cancer patients is different from the pathogenesis of fatigue in cancer survivors.

However, as mentioned previously, the study was performed in two populations in an opposite stage of the disease trajectory, both without concurrent anti-tumour therapy. Consequently, we do not know whether fatigue and inflammation are induced by disease progression only or whether inflammation also is an important fatigue-provoking factor during cancer treatment. Also, in the advanced cancer patients, inflammation and fatigue might also have been caused by prolonged effects of the anti-tumour therapy, as they finished their treatment more recently than the cancer survivors (four weeks vs. twelve months).

Another limitation of this study is the cross-sectional design, which has a high risk of finding false-positive correlations not reflecting causality. To provide more evidence on the causal relation between inflammation and fatigue in cancer, longitudinal studies with frequent measurements are needed. In these studies, it has to be clarified how the relation between inflammation and fatigue is affected by tumor load and anti-tumor therapy; and whether this relation varies between patients in different stages of the disease trajectory. As we only assessed a limited set of inflammatory markers in this pilot study, it should be investigated whether there are other inflammatory markers which play a significant role in the pathogenesis of cancer-related fatigue.

When future studies confirm that inflammation is associated with physical fatigue, we have to study which pathophysiological processes lead from elevated concentrations of inflammatory markers in plasma to subjective complaints of fatigue. Furthermore, because inflammation seems not to be involved in the emergence of mental fatigue, its pathogenesis should be elucidated to promote the development of a rational treatment.

If the inflammatory reaction is proven to significantly contribute to cancer-related fatigue, novel targets of treatment for fatigue may be identified. For example, several agents to block IL6-activity have been developed (e.g. Tocilizumab, a monoclonal anti-IL6 antibody) which subsequently could be investigated in randomized controlled trials for their ability to alleviate fatigue and their safety for use in cancer patients.

Assessment

Summary

Although we showed in this thesis the importance of a multidimensional approach of cancer-related fatigue in research, in daily clinical practice it is important that patients who suffer from fatigue can be identified easily and rapidly. The multidimensional fatigue questionnaires are often considered too extensive for use in daily practice, and are aimed to be used in research. Therefore, clinicians usually screen for fatigue and other symptoms with a 0 to 10 Numeric Rating Scale (NRS). For the interpretation of the NRS-scores, it is important to know which scores reflect clinically relevant burden. The lowest boundary of the scores reflecting clinically relevant burden is called the cut point (CP). Because several guidelines recommend to optimize the management of physical symptoms as part of the treatment of cancer-related fatigue[2, 3], it is also important to investigate the optimal cut points for other symptoms. Therefore, we performed a systematic review to explore the evidence on cut points for the symptoms of the Edmonton Symptom Assessment Scale (ESAS) in cancer patients **(chapter 5)**. The optimal cut point for clinically relevant or moderate fatigue was CP4 and for pain CP5. A lack of evidence exists for the optimal cut point for nausea, depression, anxiety, drowsiness, appetite, wellbeing and shortness of breath. Few studies suggested a cut point below 4. Overall, using a score ≥4 for all symptoms as a trigger for a more comprehensive assessment seems to be justified in daily clinical practice.

Discussion

In this review, we found that an NRS score of 4 or higher best reflected moderate to severe fatigue. Although the studies were very heterogeneous in the patients included and the methods used to determine the cut points, few studies found a cut point below 4 for any symptom. Therefore, when screening for symptoms with a 0-10 NRS, we advise a more detailed assessment when a symptom is scored 4 or higher.

The articles included in our review determined cut points by relating the NRS scores to scores on other questionnaires: questionnaires about the interference of fatigue with daily life, other fatigue questionnaires or a verbal rating scale. However, the cut points on the references questionnaires were determined in the absence of a gold standard. This is reflected by two

studies which both divided their population in a fatigued and a non-fatigued group, but used different cut points on the Functional Assessement of Cancer Therapy-Fatigue scale to make this division[4, 5].To enhance the comparability of research articles and to develop a valuable screening tool with evidence based cut points, consensus has to be reached on a definition for cancer-related fatigue. This was already stated in 1921, by B. Muscio (1887-1926)[6]:

"The condition of experimentation with the purpose of finding a fatigue test is that we know what we mean by fatigue. That this condition is necessary is self-evident: it is obviously absurd to set about finding a test of an undefined entity."

However, the definition for cancer-related fatigue should be formulated after the nature of fatigue is established (i.e. multidimensional concept or multiple symptom concept).

Cut points are frequently used in outcome indicators, which are developed to assess the quality of care of health care institutions. Due to the lack of evidence for cut points for the majority of the symptoms, we should hold back in using a certain cut point in quality indicators.

Treatment

Summary

Over the last two decades, many interventions aimed to relieve fatigue have been studied. Until now, three Cochrane reviews have been published which reported small, but significant benefits of drug therapy[7] (e.g. methylphenidate[8]), exercise[9] and psychosocial interventions[10] (e.g. psycho-education on energy conservation and activity management[11]) on fatigue intensity in cancer patients. However, few randomized controlled trials (RCTs) which were analyzed in these reviews included advanced cancer patients only. Therefore, the conclusions of the Cochrane reviews cannot be extrapolated to advanced cancer patients. Because current treatment options for fatigue in advanced cancer patients are scarce, we urgently need to develop new evidence-based interventions for this population.

Both the NCCN guideline and the Dutch guideline advise to optimize the management of accompanying physical symptoms as part of the treatment of cancer-related fatigue[2, 3]. However, this recommendation is only based on cross-sectional studies in which fatigue was associated with other symptoms, for example with pain[12-17], dyspnoea[12-19] and anorexia/cachexia[12-15, 18-21], whereas evidence from randomized controlled trials is lacking. Therefore, we performed a randomized controlled trial to investigate whether it is possible to alleviate fatigue in advanced cancer patients by optimizing treatment of other physical symptoms **(chapter 6)**. We recruited 152 advanced cancer patients who rated their fatigue intensity ≥4/10. Patients were randomized to protocolized patient-tailored treatment of physical symptoms (PPT) or care as usual (CAU). The patients randomized to PPT had four appointments with a nurse who assessed the severity of nine physical symptoms on an NRS. Patients received a nursing intervention for symptoms scored ≥1/10 and a medical intervention for symptoms scored ≥4/10.

Seventy-six patients were randomized to each study arm. Mean age was 58±10 years, 57% was female, 65% was on palliative chemotherapy. We found significant improvements over time in

favor of PPT for the primary outcome General Fatigue (*P*=0.01), with significant group differences at month 1 (p=0.007, effect size 0.26) and month 2 (p=0.005, effect size 0.35). Improvements in favor of PPT were also found for the following secondary outcomes: fatigue dimensions Reduced Activity and Reduced Motivation, fatigue NRS, symptom burden, interference of fatigue with daily life and anxiety (all *P*≤0.03). There were no significant differences between the groups in Physical Fatigue, Mental Fatigue, quality of life and depression. We concluded that nurse-led monitoring and protocolized treatment of physical symptoms is effective in alleviating fatigue in advanced cancer patients.

Discussion

In accordance with the guidelines, we found that optimizing treatment of physical symptoms is effective in alleviating fatigue in advanced cancer patients. The improvements in fatigue we found were small (maximal effect size 0.35). However, in research on cancer-related fatigue published in the last few years, the effect sizes of improvements in fatigue by effective interventions were usually small. For example, the effect size of the improvement in fatigue by exercise in curatively treated cancer patients was 0.23[9] and the effect size of the benefits of methylphenidate was 0.28[15]. Moreover, because treatment options for fatigue in advanced cancer patients are scarce, we would argue that even small improvements in fatigue should be considered clinically relevant. Therefore, we recommend to incorporate this intervention in daily clinical practice. However, changing clinical practice of fatigue management is known to be a great challenge[22]. In our opinion, the implementation of our intervention will be supported by the following strategies.

First of all, implementation of our intervention implies a rearrangement of tasks between nurses and physicians. Symptom assessment and monitoring, and delivery of non-pharmacological interventions are tasks that could be transferred from physicians to nurses. It has to be investigated what the preferences of nurses, physicians and patients are on the organisation of symptom management, to determine how this intervention can be implemented best.

Secondly, to enhance the implementation of this intervention, its costs and benefits should be studied in more detail. In our randomized controlled trial, the intervention resulted in modest improvements in fatigue only (maximal effect size 0.35). It is unclear how to value these improvements in fatigue and other symptoms in an health-economic evaluation of our intervention. Furthermore, the nurses needed approximately 2.5 hours per patient to provide the four intervention sessions, which cost about 100 euro. These costs, approximately €40 per hour, are in accordance with reference prices for paramedical care provided by the College of Health Insurances (College voor zorgverzekeringen)[23]. However, we do not know whether our intervention has an effect on health care consumption and drug prescriptions. Therefore, in future research, the costs of this intervention should be studied more comprehensively and should be related to formal and accepted measures of quality of life, such as the SF-36[24].

Finally, our intervention should be implemented combined with other interventions which are known to be effective, such as psycho-education on fatigue[11, 25]. In our study, we focussed on only one possible cause of cancer-related fatigue: symptom burden. This might be an

important explanation for the modest amelioration in fatigue in our study. Combining our intervention with other interventions might lead to greater improvements in fatigue. .

Final conclusions

In this thesis, we showed the importance of investigating the various sensations of fatigue separately. We found that physical fatigue and mental fatigue behaved differently and we found some indications that physical fatigue and mental fatigue might have a different pathogenesis. Therefore, we postulated that physical fatigue and mental fatigue are not two expressions of a single symptom, but should be considered as two different symptoms (a multiple symptom concept). More research on the pathogenesis of physical fatigue and mental fatigue is needed to confirm this hypothesis. If the multiple symptom concept is proven, a paradigm shift in the management of fatigue is needed. Then, the assessment of the severity of fatigue should no longer be performed with a single 0-10 Numeric Rating Scale for fatigue, but the intensity of the various dimensions should be assessed separately. Also, the knowledge on the pathogenesis of the various fatigue dimensions will promote the development of rational, and dimension-specific interventions. Hopefully, in the future, the treatment of cancer-related fatigue will be more effective, by providing patient-tailored evidence-based interventions, depending on the type of fatigue experienced.

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APPENDIX

Samenvatting en discussie

1

Algemeen

Kankerpatiënten hebben in elk stadium van de ziekte last van vermoeidheid: reeds voordat de diagnose gesteld is, tot jaren na het afronden van de behandeling en ook in de palliatieve fase. Vermoeidheid heeft een grotere negatieve invloed op de kwaliteit van leven en de dagelijkse activiteiten dan enig ander kanker-gerelateerd symptoom. Alhoewel nationale en internationale richtlijnen ontwikkeld zijn om de behandeling van vermoeidheid te verbeteren, blijft vermoeidheid bij kanker een slecht begrepen symptoom. Dit proefschrift beschrijft onderzoek dat verricht is om meer inzicht te krijgen in het multidimensionele karakter, de pathogenese, het meten en de behandeling van vermoeidheid bij kanker.

Multidimensionaliteit

Samenvatting

Patiënten beschrijven hun vermoeidheid als lichamelijke, mentale en emotionele gevoelens van uitputting, die ook wel dimensies van vermoeidheid worden genoemd. Alhoewel het multidimensionele karakter van vermoeidheid breed geaccepteerd is, is het onduidelijk of de vermoeidheidsdimensies uitingen zijn van één symptoom (multidimensioneel concept) of van verschillende entiteiten, die allen "vermoeidheid" worden genoemd, maar in feite verschillende symptomen zijn (meerdere symptomen concept). Als vermoeidheid bestaat uit verschillende symptomen, verwachten wij dat de vermoeidheidsdimensies zich verschillend gedragen. Daarom hebben wij in een systematische literatuurstudie onderzocht of lichamelijke en mentale vermoeidheid zich verschillend gedragen bij kankerpatiënten wat betreft: hun intensiteit in verschillende stadia van kanker, hun beloop tijdens antitumor therapie, de variabelen waaraan zij gerelateerd zijn en het effect van interventies gericht op vermindering van de vermoeidheid op deze dimensies **(hoofdstuk 2)**.

We vonden enkele studies waarin lichamelijke en mentale vermoeidheid zich gelijk gedroegen: zij waren beide ernstiger bij kankerpatiënten dan bij gezonde controlepersonen, zij hadden soms hetzelfde beloop tijdens antitumor therapie of verbeterden beiden door een interventie gericht op het verminderen van vermoeidheid. Echter, wij vonden ook verschillende studies waarin lichamelijke en mentale vermoeidheid zich verschillend gedroegen: lichamelijke vermoeidheid was meer prominent aanwezig dan mentale vermoeidheid in sommige stadia van het ziekteverloop, verschillende studies rapporteerden veranderingen in lichamelijke vermoeidheid zonder veranderingen in mentale vermoeidheid tijdens antitumor therapie of tijdens interventies gericht op vermoeidheid; en lichamelijke en mentale vermoeidheid waren aan verschillende variabelen gecorreleerd. Onze conclusie was dat het verschillende gedrag van lichamelijke en mentale vermoeidheid zou kunnen passen bij het "meerdere symptomen concept".

Wij vonden slechts drie studies die de vermoeidheidsbeleving van patiënten in verschillende stadia van kanker hadden onderzocht, maar deze studies hadden geen groepen geïncludeerd die vergelijkbaar waren qua leeftijd, geslacht en diagnose. Daarom hebben wij een cross-sectionele studie uitgevoerd, waarin we de vermoeidheidsbeleving van kankerpatiënten in de palliatieve fase (advanced cancer patients, ACPs), patiënten die in het verleden behandeld zijn voor kanker (cancer survivors, CSs) en gezonde controles met elkaar vergeleken hebben

(hoofdstuk 3). Wij rekruteerden 63 ACPs, die geen systemische antitumor therapie hadden ondergaan in de laatste vier weken voor het onderzoek en voor wie zinvolle antitumor therapie ook niet meer beschikbaar was. Ook includeerden wij 63 CSs die de kankerbehandeling 1 tot 5 jaar geleden hadden afgerond. ACPs en CSs werden gematcht voor leeftijd, geslacht en diagnose. Vermoeidheid werd gemeten met een 0-10 numerieke beoordelingsschaal (NRS) en met de Multidimensionele Vermoeidheids Index (MVI). Voor iedere ACP werden vijf gezonde controles van hetzelfde geslacht en in dezelfde leeftijdscategorie geselecteerd uit een Duits databestand met MVI-scores van gezonde proefpersonen. We vonden dat de intensiteit van alle vermoeidheidsdimensies van de MVI (algemene vermoeidheid, lichamelijke vermoeidheid, verminderde activiteit, verminderde motivatie, mentale vermoeidheid) hoger was bij de ACPs dan bij de CSs en de gezonde controles ($p < 0,01$). Er waren geen verschillen in de intensiteit van vermoeidheid tussen CSs en gezonde controles. Alleen de dimensies lichamelijke vermoeidheid en mentale vermoeidheid waren significante voorspellers van de scores op de 0-10 NRS, zowel bij de ACPs als bij de CSs. Terwijl lichamelijke vermoeidheid en mentale vermoeidheid sterk aan elkaar gecorreleerd waren bij de gezonde controlepersonen ($r = 0,68$; $p<0,01$), was deze associatie zwakker bij de CSs ($r = 0,35$; $p<0,01$) en zelfs niet significant bij de ACPs ($r = 0,15$). In multivariate analyses bleek alleen de lichamelijke dimensie de vermoeidheid bij ACPs te differentiëren van die bij CSs en gezonde controles ($p<0,01$). Wij concludeerden dat vermoeidheid meer intens is en dat met name lichamelijke vermoeidheid meer prominent is bij ACPs dan bij CSs.

Discussie

De nationale en internationale richtlijnen voor de behandeling van kanker-gerelateerde vermoeidheid geven aan dat vermoeidheid een multidimensioneel fenomeen is. Het was echter nooit onderzocht of de dimensies van vermoeidheid uitingen zijn van één symptoom, of dat de dimensies van vermoeidheid verschillende fenomenen zijn. Dit laatste is reeds gesuggereerd in 1943 door W.H. Forbes, onderzoeker bij het vermoeidheidslaboratorium van de universiteit van Harvard[1]:

"De vooruitgang in het onderzoek naar vermoeidheid is belemmerd door de tendens om te spreken over vermoeidheid als één entiteit, zonder de verschillende soorten vermoeidheid die gezien worden in aanmerking te nemen, die elk een verschillende oorzaak en verschillende uitingen zouden kunnen hebben."

In dit proefschrift hebben we gevonden dat patiënten in verschillende fasen van het ziektebeloop een verschillende vermoeidheidsbeleving hebben. Echter, wij hebben de vermoeidheidsbeleving onderzocht bij twee populaties in twee uitersten van het ziektebeloop: patiënten met progressieve ziekte in de laatste maanden van het leven en patiënten zonder tekenen van recidief ziekte na een behandeling in het verleden. Hoewel deze uitersten bruikbaar zijn in het aantonen van verschillen in de vermoeidheidsbeleving, moet nog onderzocht worden wat de vermoeidheidsbeleving is van andere populaties kankerpatiënten, zoals patiënten tijdens curatieve behandeling en patiënten met gemetastaseerde ziekte die nog behandeld worden met palliatieve antitumor therapie.

In dit proefschrift hebben we ook aanwijzingen gevonden dat lichamelijke vermoeidheid en mentale vermoeidheid verschillende fenomenen zijn. Deze conclusie is echter slechts gebaseerd op indirect bewijs. Om definitief vast te kunnen stellen dat lichamelijke vermoeidheid en mentale vermoeidheid verschillende symptomen zijn, die verschillend behandeld moeten worden, moet onderzocht worden of zij een verschillende pathogenese hebben.

Om het inzicht in kankergerelateerde vermoeidheid te verbeteren, moet in toekomstig onderzoek vermoeidheid niet gemeten worden met een vragenlijst die vermoeidheid als één entiteit beoordeelt, maar altijd met een vragenlijst die in staat is om de verschillende dimensies van vermoeidheid te meten. Tevens dienen onderzoekers in toekomstig onderzoek geen patiënten te includeren uit verschillende stadia van het ziektebeloop, omdat vermoeidheid in de verschillende stadia van kanker zich verschillend kan uiten en uitgelokt zou kunnen worden door verschillende factoren.

Pathogenese

Samenvatting

Omdat we aangetoond hebben dat kankerpatiënten in de palliatieve fase en kankerpatiënten die in het verleden behandeld zijn voor kanker een verschillende vermoeidheidsbeleving hebben, vroegen wij ons af of er verschillen zijn tussen deze twee groepen in de mechanismen die ten grondslag liggen aan vermoeidheid. Een hypothese die vaak genoemd wordt, is dat inflammatie een sleutelrol speelt in de pathogenese van kanker-gerelateerde vermoeidheid. Wij hebben daarom in een pilot studie onderzocht of lichamelijke vermoeidheid en mentale vermoeidheid geassocieerd zijn met ontstekingsmediatoren in een subgroep van 45 ACPs en 47 CSs uit de studie die hierboven beschreven is **(hoofdstuk 4)**.

De concentratie van alle onstekingsmediatoren was hoger bij ACPs dan bij CSs ($p<0,01$). Bij de ACPs waren C-reactive protein ($r=0,49$; $p=0,001$), interleukine-6 ($r=0,43$; $p=0,003$), interleukine-1 receptor antagonist ($r=0,32$; $p=0,03$), and neopterine ($r=0,25$; $p=0,10$) gecorreleerd met lichamelijke vermoeidheid, maar niet met mentale vermoeidheid. Bij de CSs was alleen de interleukine-1 receptor antagonist gecorreleerd met zowel lichamelijke vermoeidheid ($r=0,24$; $p=0,10$) als mentale vermoeidheid ($r=0,35$; $p=0,02$). Wij concludeerden dat inflammatie geassocieerd is met lichamelijke vermoeidheid, maar niet met mentale vermoeidheid bij kankerpatiënten in de palliatieve fase. Er was geen overtuigend bewijs dat inflammatie een belangrijke rol speelt in de pathogenese van vermoeidheid bij patiënten zonder ziekte-activiteit na een behandeldeling voor kanker in het verleden.

Discussie

In overeenstemming met de richtlijnen voor de behandeling van kankergerelateerde vermoeidheid, vonden wij aanwijzingen dat inflammatie onderdeel uitmaakt van de pathogenese van vermoeidheid. Echter, dit was alleen het geval voor lichamelijke vermoeidheid bij kankerpatiënten in de palliatieve fase en niet voor mentale vermoeidheid of vermoeidheid bij patiënten zonder aanwijzingen voor recidief ziekte na een behandeling voor kanker in het verleden. Dit zou kunnen betekenen dat lichamelijke vermoeidheid een andere pathogenese

heeft dan mentale vermoeidheid; en dat ondersteunt onze hypothese dat lichamelijke vermoeidheid en mentale vermoeidheid twee verschillende fenomenen zijn (het meerdere symptomen concept). Onze bevindingen wijzen ook op verschillen in de pathogenese van vermoeidheid tussen kankerpatiënten in de palliatieve fase patiënten zonder ziekte na een eerdere behandeling voor kanker.

Echter, zoals eerder ook al genoemd, deze studie is uitgevoerd in twee geheel verschillende patiëntenpopulaties, nl. patiënten uit twee uiterste stadia van het ziektebeloop; beide groepen werd niet behandeld met antitumor therapie. Daarom weten we niet of vermoeidheid en inflammatie een gevolg zijn van ziekteactiviteit alleen, of dat inflammatie ook tijdens de behandeling van kanker een belangrijke uitlokkende factor is voor vermoeidheid. Verder kunnen vermoeidheid en inflammatie bij patiënten in de palliatieve fase ook veroorzaakt zijn door de verlate effecten van antitumor therapie, omdat zij de behandeling recenter hadden afgerond dan de patiënten die in het verleden waren behandeld (vier weken vs. twaalf maanden voor inclusie).

Een andere beperking van deze studie is de cross-sectionele studieopzet, die een hoog risico geeft op het vinden van vals-positieve associaties, die niet het gevolg zijn van causaliteit. Om meer bewijs te leveren dat er een causaal verband is tussen inflammatie en vermoeidheid bij kankerpatiënten, dienen longitudinale studies met frequente metingen te worden uitgevoerd. In deze studies moet verhelderd worden hoe de relatie tussen inflammatie en vermoeidheid beïnvloed wordt door enerzijds de tumor load en anderzijds de toegepaste antitumor therapie, en of deze relatie wisselt tussen patiënten in verschillende stadia van het ziektebeloop. Omdat we slechts een beperkt aantal ontstekingsstoffen gemeten hebben in deze pilot studie, moet ook nog onderzocht worden of er andere ontstekingsstoffen zijn die een belangrijke rol kunnen spelen in de pathogenese van vermoeidheid bij kanker.

Als toekomstige studies bevestigen dat inflammatie geassocieerd is met lichamelijke vermoeidheid, moet nog onderzocht worden hoe verhoogde concentraties van ontstekingsmediatoren leiden tot de subjectieve klachten van vermoeidheid. Omdat inflammatie niet betrokken lijkt te zijn bij het ontstaan van mentale vermoeidheid, zal ook die pathogenese bestudeerd moeten worden om de ontwikkeling van rationele behandelingen mogelijk te maken.

Als bewezen is dat de inflammatoire reactie significant bijdraagt aan het ontstaan van fysieke vermoeidheid bij kanker, hebben we mogelijk nieuwe aangrijpingspunten voor behandeling ontdekt. Er zijn bijvoorbeeld reeds verschillende medicamenten ontwikkeld die interleukine-6 activiteit kunnen blokkeren (bijvoorbeeld Tocilizumab, een monoklonaal anti-interleukine-6 antistof). Voor deze middelen zou in gerandomiseerde studies onderzocht kunnen worden of zij in staat zijn vermoeidheid te verlichten en of zij veilig zijn om te gebruiken bij kankerpatiënten.

Meting van vermoeidheid

Samenvatting

Hoewel we in dit proefschrift het belang van een multidimensionele benadering van kankergerelateerde vermoeidheid hebben aangetoond, is het in de dagelijkse klinische praktijk van belang dat snel en makkelijk beoordeeld kan worden of een patiënt last heeft van

vermoeidheid. De multidimensionele vermoeidheidsvragenlijsten zijn vaak te lang voor gebruik in de klinische praktijk en zijn ontwikkeld voor gebruik bij onderzoek. Daarom screenen clinici vaak op vermoeidheid en andere symptomen met een 0 tot 10 Numerieke Beoordelingsschaal (NRS). Om de NRS-scores te kunnen interpreteren is het belangrijk om te weten bij welke scores de intensiteit van een symptoom klinisch relevant is. De ondergrens van de klinische relevante scores, wordt ook wel het afkappunt genoemd. Omdat diverse richtlijnen aanbevelen om de behandeling van lichamelijke symptomen te optimaliseren als onderdeel van de behandeling van kankergerelateerde vermoeidheid[2, 3], is het van belang om te weten wat de optimale afkappunten zijn voor andere symptomen. Wij hebben in een systematische literatuurstudie onderzocht welke bewijs er is voor afkappunten voor de symptomen die gemeten worden met de Edmonton Symptom Assessment Scale (ESAS) bij kankerpatiënten **(hoofdstuk 5)**. Het optimale afkappunt voor klinisch relevante, c.q. matige vermoeidheid was 4 en voor klinisch relevante pijn 5. Het optimale afkappunt voor misselijkheid, depressie, angst, slaperigheid, eetlust, welzijn en kortademigheid kon op grond van de literatuur niet gedefinieerd worden. Wel werden er nauwelijks studies gevonden die een afkappunt lager dan 4 voor deze symptomen adviseerden. Daarom adviseren wij voor het gebruik in de dagelijkse praktijk een intensiteitscore ≥4 als een trigger voor een uitgebreidere beoordeling van alle symptomen.

Discussie

In deze literatuurstudie hebben we gevonden dat een NRS score van 4 of hoger het beste matig tot ernstige vermoeidheid representeert. Hoewel de studies erg heterogeen waren qua geïncludeerde patiënten en methode waarmee het optimale afkappunt bepaald is, hebben weinig studies een afkappunt onder de 4 gevonden. Als er gescreend wordt op de aanwezigheid van symptomen met een 0-10 NRS, adviseren wij daarom een uitgebreidere symptoombeoordeling te verrichten als een patiënt een score van 4 of hoger heeft gegeven voor een bepaald symptoom.

De artikelen opgenomen in onze literatuurstudie hebben de afkappunten bepaald door de NRS scores te relateren aan scores op andere vragenlijsten: vragenlijsten naar de beperkingen in het dagelijks leven, andere symptoomvragenlijsten of een verbale beoordelingsschaal. Echter, de afkappunten op de referentievragenlijsten zijn vastgesteld terwijl er geen gouden standaard is. Dit wordt met name duidelijk bij twee studies die beiden hun onderzoekspopulatie in een vermoeide en niet-vermoeide groep hebben ingedeeld, maar een verschillend afkappunt op de Functional Assessment of Cancer Therapy-Fatigue scale hebben gebruikt om deze indeling te maken[4, 5].

Om de vergelijkbaarheid van studies te verbeteren en om een waardevol screeningsinstrument te ontwikkelen, dient er consensus te worden bereikt over een definitie voor kankergerelateerde vermoeidheid. Dit werd reeds in 1921 gesteld door B. Muscio (1887-1926)[6]:

"De voorwaarde voor onderzoek met het doel een vermoeidheidstest te ontwikkelen is dat we weten wat we bedoelen met "vermoeidheid". Dat dit een noodzakelijke voorwaarde is, spreekt voor zich: het is absurd om te proberen een test te vinden voor een ongedefinieerde entiteit."

De definitie voor kanker-gerelateerde vermoeidheid zou echter pas geformuleerd moeten worden, nadat het karakter van vermoeidheid is vastgesteld (m.a.w. multidimensioneel concept of meerdere symptomen concept).

Afkappunten worden regelmatig gebruikt in uitkomstindicatoren, die ontwikkeld zijn om de kwaliteit van zorg van instellingen voor gezondheidszorg te vergelijken. Omdat er onvoldoende bewijs voorhanden is voor de bepaling van de optimale afkappunten voor de meerderheid van de symptomen, zouden we terughoudend moeten zijn een bepaald afkappunt in kwaliteitsindicatoren op te nemen.

Behandeling

Samenvatting

In de laatste twintig jaar zijn veel interventies gericht op het verminderen van vermoeidheid onderzocht. Tot op heden zijn drie Cochrane reviews gepubliceerd die kleine, maar significante verbeteringen in vermoeidheid rapporteerden bij kankerpatiënten door medicamenteuze behandeling[7] (bijv. methylfenidaat[8]), beweging[9], and psychosociale interventies[10] (bijv. psycho-educatie over energie verdeling en indeling van dagelijkse activiteiten[11]). Er waren in deze reviews echter maar weinig gerandomiseerde studies opgenomen die alleen kankerpatiënten in de palliatieve fase van het ziektebeloop hadden geïncludeerd. De conclusies van de Cochrane reviews kunnen daarom niet geëxtrapoleerd worden naar deze groep patiënten. Omdat er momenteel maar weinig behandelingsopties zijn voor vermoeidheid bij kankerpatiënten in de palliatieve fase, moeten er dringend nieuwe interventies voor deze groep ontwikkeld worden.

Zowel de richtlijn van de National Comprehensive Cancer Network (NCCN) en de Nederlandse richtlijn adviseren om de behandeling van begeleidende symptomen te optimaliseren, als onderdeel van de behandeling van kanker-gerelateerde vermoeidheid[2, 3]. Deze aanbeveling is echter slechts gebaseerd op cross-sectioneel onderzoek waarin vermoeidheid geassocieerd was met andere symptomen, bijvoorbeeld met pijn[12-17], benauwdheid[12-19] en anorexie/cachexie[12-15, 18-21]. Er is geen bewijs voor deze aanbeveling vanuit gerandomiseerde studies. Wij hebben daarom een gerandomiseerde gecontroleerde studie verricht, om te onderzoeken of het mogelijk is vermoeidheid bij kankerpatiënten in de palliatieve fase te verminderen door de behandeling van andere lichamelijke symptomen te verbeteren **(hoofdstuk 6)**. Wij includeerden 152 kankerpatiënten in de palliatieve fase die een score van 4 of hoger gaven voor de ernst van hun vermoeidheid. Patiënten werden gerandomiseerd voor protocollaire behandeling van lichamelijke symptomen (protocolized patient-tailored treatment, PPT) of standaard zorg (care as usual, CAU). De patiënten die geloot hadden voor de PPT-groep kregen vier afspraken met een verpleegkundig consulent die hen vroeg de ernst van negen lichamelijke symptomen aan te geven op een numerieke beoordelingsschaal (NRS). Vervolgens pasten de verpleegkundig consulenten verpleegkundige interventies toe voor symptomen met een score ≥1/10; voor symptomen met een score ≥4/10 werd in overleg met de behandelend arts een protocollaire medische interventie toegepast.

Zesenzeventig patiënten werden gerandomiseerd voor iedere studiearm. De gemiddelde leeftijd was 58±10 jaar, 57% was vrouw en 65% werd behandeld met palliatieve chemotherapie.

Wij vonden een significante verbetering over de tijd in de primaire uitkomstmaat, algemene vermoeidheid gemeten met de MVI, ten gunste van de PPT groep (p=0,01), met significante verschillen tussen de groepen na 1 maand (p=0,007, effect grootte 0,26) en na twee maanden (p=0,005, effect grootte 0,35). Verbeteringen over de tijd ten gunste van de PPT groep werden ook gevonden voor de volgende secundaire uitkomstmaten: de vermoeidheidsdimensies verminderde activiteit en verminderde motivatie, vermoeidheid gemeten met de NRS, symptoomlast, beperkingen door vermoeidheid in het dagelijks leven en angst (alle p-waarden ≤0,03). Er waren geen significante verschillen tussen de groepen in lichamelijke vermoeidheid, mentale vermoeidheid, kwaliteit van leven en depressie. Wij concludeerden dat een interventie die bestaat uit monitoring en geprotocolleerde behandeling van lichamelijke symptomen, en die gecoördineerd wordt door een verpleegkundig consulent, effectief is in het verminderen van vermoeidheid bij kankerpatiënten in de palliatieve fase van het ziektebeloop.

Discussie

In overeenstemming met de richtlijnen hebben wij gevonden dat het optimaliseren van de behandeling van lichamelijke symptomen effectief is in het verminderen van vermoeidheid bij kankerpatiënten in de palliatieve fase van het ziektebeloop. De verbeteringen in vermoeidheid die wij vonden waren bescheiden (maximale effect grootte 0,35). In onderzoek bij kankergerelateerde vermoeidheid dat de laatste jaren gepubliceerd is, zijn de verbeteringen in vermoeidheid door effectieve interventies echter gewoonlijk ook klein. De effectgrootte van de verbetering in vermoeidheid door beweging bij kankerpatiënten die met curatieve intentie behandeld waren, was bijvoorbeeld 0,23[9] en de effectgrootte van het gebruik van methylfenidaat was 0,28[15]. Omdat de behandelingsmogelijkheden voor vermoeidheid bij kankerpatiënten in de palliatieve fase beperkt zijn, zouden wij willen stellen dat ook kleine verbeteringen in vermoeidheid als klinisch relevant beschouwd kunnen worden. Wij bevelen daarom aan dat deze interventie wordt geïntegreerd in de dagelijkse klinische praktijk. Echter, een verandering in de aanpak van vermoeidheid in de dagelijkse klinische praktijk betekent een grote uitdaging[22]. Naar onze mening zal de implementatie van onze interventie worden ondersteund door de volgende strategieën.

Ten eerste betekent de implementatie van onze interventie, dat er taken verschoven worden tussen verpleegkundigen en artsen. Symptoombeoordeling en -monitoring en het uitvoeren van niet-farmacologische interventies zijn taken die overgedragen zouden kunnen worden van artsen naar verpleegkundigen. Voorkeuren van verpleegkundigen, artsen en patiënten ten aanzien van de organisatie van symptoombehandeling moeten onderzocht worden, om te kunnen bepalen in welke vorm onze interventie het beste geïmplementeerd zou kunnen worden.

Om de implementatie van onze interventie te bevorderen, zouden de kosten en baten van deze interventie in meer detail onderzocht moeten worden. In onze gerandomiseerde studie resulteerde de interventie slechts in bescheiden verbeteringen in vermoeidheid (maximale effect grootte 0,35). Het is onduidelijk hoe de verbeteringen in vermoeidheid en andere symptomen gewaardeerd moeten worden in de economische evaluatie van de interventie. Verder hadden de verpleegkundig consulenten ongeveer 2,5 uur nodig voor de vier interventiesessies;

de kosten hiervan bedragen ongeveer €100. Deze kosten, ongeveer €40 per uur, zijn in overeenstemming met de richtprijzen voor paramedische zorg die opgesteld zijn door het College voor Zorgverzekeringen[23]. We weten echter niet of onze interventie een effect heeft op de zorgconsumptie en medicatievoorschriften. Daarom moeten de kosten van de interventie in toekomstig onderzoek uitgebreider onderzocht worden en zouden de kosten gerelateerd moeten worden aan algemeen geaccepteerde maten voor kwaliteit van leven, zoals de SF-36[24].

Tenslotte zou onze interventie geïmplementeerd moeten worden in combinatie met andere interventies die bewezen effectief zijn, zoals psycho-educatie over vermoeidheid[11, 25]. In onze studie hebben we ons slechts gericht op één mogelijke oorzaak van kanker-gerelateerde vermoeidheid: bijkomende lichamelijke symptomen. Dit zou een belangrijke verklaring kunnen zijn voor het bescheiden effect van onze interventie in onze studie. Het combineren van onze interventie met andere interventies zou kunnen leiden tot grotere verbeteringen in vermoeidheid.

Slotconclusies

In dit proefschrift hebben we het belang aangetoond van het apart onderzoeken van de verschillende dimensies van vermoeidheid. Wij hebben gevonden dat lichamelijke vermoeidheid en mentale vermoeidheid zich verschillend gedragen en hebben enkele aanwijzingen gewonden dat lichamelijke vermoeidheid en mentale vermoeidheid een verschillende pathogenese zouden kunnen hebben. Wij hebben daarom gepostuleerd dat lichamelijke vermoeidheid en mentale vermoeidheid niet twee uitingen zijn van één symptoom, maar beschouwd zouden moeten worden als twee verschillende symptomen (het meerdere symptomen concept). Meer onderzoek naar de pathogenese van lichamelijke vermoeidheid en mentale vermoeidheid is nodig om deze hypothese te kunnen bevestigen. Als het "meerdere symptomen concept" bevestigd wordt door toekomstig onderzoek, moet de behandeling van vermoeidheid bij kanker anders worden aangepakt. De ernst van de vermoeidheid zou niet langer gemeten moeten worden met een enkele 0 tot 10 numerieke beoordelingsschaal, maar de ernst van de verschillende dimensies zou apart gemeten moeten worden. Verder zal de kennis van de pathogenese van de verschillende dimensies van vermoeidheid de ontwikkeling van rationele en dimensie-specifieke interventies stimuleren. Hopelijk zal de behandeling van kanker-gerelateerde vermoeidheid in de toekomst hiermee effectiever worden, door het aanbieden van interventies op maat, afhankelijk van het type vermoeidheid.

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APPENDIX

Dankwoord

2

Dankwoord

Waarschijnlijk zijn dit de eerste woorden die u leest in dit proefschrift. Ik begrijp dat u nieuwsgierig bent of u ook nog bedankt wordt, maar ik moet u waarschuwen: het dankwoord is niet peer-reviewed, maar het enige gedeelte van het proefschrift dat ik helemaal alleen bedacht en geschreven heb. Prof. dr. Karin van der Rijt heeft er geen correcties in aangebracht, dr. Cora de Klerk heeft het niet bijgeschaafd, de leescommissie heeft niet beoordeeld of het dankwoord wel van voldoende wetenschappelijke kwaliteit was en ook collega's mochten geen commentaar leveren. Eventuele blunders komen dus volledig voor mijn rekening.

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"Hebt gij niet gehoord, dat de eeuwige God, de HEERE, de Schepper van de einden der aarde, noch moede noch mat wordt? Er is geen doorgronding van Zijn verstand. Hij geeft den moeden kracht, en Hij vermenigvuldigt de sterkte dien, die geen krachten heeft." De Bijbel, Jesaja 40 vers 28 en 29

APPENDIX 3

Curriculum Vitae

Curriculum Vitae

Pleun Johannes de Raaf werd geboren op 28 mei 1985 in Rotterdam. In 2003 behaalde hij zijn VWO diploma op het Wartburg College te Rotterdam. Aansluitend ging hij geneeskunde studeren aan de Erasmus Universiteit Rotterdam. In 2007 begon Johan aan de coschappen. Deze periode werd afgesloten met een oudste-coschap op de afdeling Interne Geneeskunde (Algemene Interne Geneeskunde, Interne Oncologie en Spoedeisende Hulp) van het Maasstad ziekenhuis te Rotterdam.

In 2008 startte Johan met zijn wetenschappelijke stage op de afdeling Interne Oncologie van het Erasmus MC te Rotterdam onder supervisie van dr. C.C.D. van der Rijt en dr. C. de Klerk. In deze tijd verrichte hij onderzoek naar verschillen in vermoeidheidsbeleving tussen kankerpatiënten in de palliatieve fase en patiënten die in het verleden zijn behandeld voor kanker. Behalve in een publicatie, die tevens is opgenomen in dit proefschrift, resulteerde dit ook in het behalen van het doctoraaldiploma op 4 juni 2009.

Na het cum laude behalen van het artsendiploma op 11 september 2009 werd Johan aangenomen als arts-onderzoeker op de afdeling Interne Oncologie van het Erasmus MC (afdelingshoofd prof. dr. J. Verweij). Onder supervisor van prof. dr. C.C.D. van der Rijt en dr. C. de Klerk (Afdeling Medische Psychologie en Psychotherapie) werd gestart met het onderzoek naar vermoeidheid bij kanker zoals beschreven in dit proefschrift.

Tijdens het afronden van zijn proefschrift werkte Johan als ANIOS op de afdeling Interne Geneeskunde van het IJssellandziekenhuis te Capelle aan den IJssel. Per 1 januari 2013 is hij begonnen aan de opleiding tot internist in dit ziekenhuis (opleiders prof. dr. J.L.C.M. van Saase en dr. H.E. van der Wiel).

Johan is sinds 2008 getrouwd met Marieke van den Brink. Samen kregen zij twee dochters: Anneloes en Anne-Mirthe.

APPENDIX

4

Publications

Publications

Articles

Oldenmenger WH, Sillevis Smitt PAE, van Montfoort CAGM, de Raaf PJ, van der Rijt CCD. *A combined pain consult and pain education program decreases average and current pain and decreases interference in daily life by pain in oncology outpatients: a randomized controlled trial*. Pain 2011; 152(11): 2632-2639

de Raaf PJ, van der Biessen AJ, Oldenmenger WH, de Jonge MJA, van der Rijt CCD. *Stoppen of doorgaan? Over autonomie van de patiënt en opvattingen van zorgverleners.* Nederlands-Vlaams Tijdschrift voor Palliatieve Zorg 2011; 11(4): 61-64

de Raaf PJ, de Klerk C, Timman R, Hinz A, van der Rijt CCD. *Differences in fatigue experiences among patients with advanced cancer, cancer survivors, and the general population.* Journal of Pain and Symptom Management 2012; 44(6): 823-830

de Raaf PJ, Sleijfer S, Jager A, Lamers C, Gratama JW, van der Rijt CCD. *Inflammation and fatigue dimensions in advanced cancer patients and cancer survivors: an explorative study.* Cancer 2012; 118(23): 6005-6011

Oldenmenger WH*, de Raaf PJ*, de Klerk C, van der Rijt CCD. *Cut points on 0-10 Numeric Rating Scales for symptoms included in the Edmonton Symptom Assessment Scale in cancer patients: a systematic review.* Journal of Pain and Symptom Management 2012, Epub ahead of print
* Authors had an equal contribution to the final paper

de Raaf PJ, de Klerk C, van der Rijt CCD. *Elucidating the behavior of physical fatigue and mental fatigue in cancer patients: a review of the literature*. Psycho-oncology 2012, Epub ahead of print

de Raaf PJ, de Klerk C, Timman R, Busschbach JJV, Oldenmenger WH, van der Rijt CCD. *Systematic monitoring and treatment of physical symptoms to alleviate fatigue in patients with advanced cancer: a randomized controlled trial.* Journal of Clinical Oncology 2013, Epub ahead of print

Abstracts

de Raaf PJ, de Klerk C, Passchier J, van Busschbach JJ, van der Rijt CCD. Differences in fatigue experiences between advanced cancer patients and cancer survivors. Palliative Medicine 2010; 24(4 Suppl):S131.

Oldenmenger WH, Sillevis Smitt PAE, van Montfoort CAGM, de Raaf PJ, van der Rijt CCD. Less pain and better functioning due to a combination of a pain consult and pain education. 12th Congress of the European Association for Palliative Care, May 2011

de Raaf PJ, de Klerk C, van der Rijt CCD. Cut-off points for cancer-related fatigue: where do we stand? 12th Congress of the European Association for Palliative Care, May 2011

Oldenmenger WH, Sillevis Smitt PAE, van Montfoort CAGM, de Raaf PJ, van der Rijt CCD. Less pain and better functioning due to a combination of a pain consult and pain education. Multidisciplinary Cancer Congress of the ECCO/ESMO, September 2011

de Raaf PJ, de Klerk C, Timman R, van Busschbach JJ, Oldenmenger WH, van der Rijt CCD. The effectiveness of protocolized treatment of physical symptoms in improving cancer-related fatigue: a randomized controlled trial. Palliative Medicine 2012; 26(4): 405

de Raaf PJ, Sleijfer S, Lamers CHJ, Jager A, Gratama JW, van der Rijt CCD. The association between inflammation and fatigue dimensions in advanced cancer patients and cancer survivors. Palliative Medicine 2012; 26(4): 449

Oldenmenger WH, de Raaf PJ, Sillevis Smitt PA, van der Rijt CCD. The effectiveness of patient pain education combined with a pain consult in improving medication adherence: a randomized controlled trial. Palliative Medicine 2012; 26(4): 455

de Raaf PJ, de Klerk C, Timman R, van Busschbach JJ, Oldenmenger WH, van der Rijt CCD. Het effect van protocollaire behandeling van lichamelijke symptomen op de intensiteit van kanker-gerelateerde vermoeidheid. Nederlands-Vlaams Tijdschrift voor Palliatieve Zorg 2012; 12(1): 43-44

de Graan AJM, Elens L, Sparreboom A, Friberg LE, van der Holt B, de Raaf PJ, Wiemer EAC, Verweij J, van Schaik RH, Mathijssen RHJ. Influence of drug exposure and genetic variation on paclitaxel-induced neurotoxicity. 2012 Congress of the ESMO, Vienna, September 2012

Oral presentations

de Raaf PJ
Differences in fatigue experiences between advanced cancer patients and cancer survivors.
6th Research Congress of the European Association for Palliative Care, Glasgow, June 2010

de Raaf PJ
Verschillen in vermoeidheidsbeleving tussen kankerpatiënten in de palliatieve fase en patiënten die in het verleden behandeld zijn voor kanker.
Nederlands-Vlaams onderzoeksforum, Antwerpen, November 2010

de Raaf PJ
Behandeling van kankergerelateerde vermoeidheid.
IKNL regiodagen netwerk Hemato-Oncologie, Vlissingen, November 2011

de Raaf PJ, de Klerk C, Timman R, van Busschbach JJ, Oldenmenger WH, van der Rijt CCD. The effectiveness of protocolized treatment of physical symptoms in improving cancer-related fatigue: a randomized controlled trial. 7th Research Congress of the European Association for Palliative Care, Trondheim, June 2012

de Raaf PJ, Sleijfer S, Lamers CHJ, Gratama JW, van der Rijt CCD. The association between inflammation and fatigue dimensions in advanced cancer patients and cancer survivors. 7th Research Congress of the European Association for Palliative Care, Trondheim, June 2012

de Raaf PJ
Kankergerelateerde vermoeidheid.
Onderwijs arts-assistenten Interne Geneeskunde Erasmus MC, Juni 2012

APPENDIX

PhD portfolio

5

PhD Portfolio

Summary of PhD training and teaching

Name PhD student: P.J. de Raaf	**PhD period: September 2009 – August 2012**
Erasmus MC Department: Medical Oncology	**Promotor(s): Prof. dr. C.C.D. van der Rijt**
Research School: MolMed	**Supervisor: dr. C. de Klerk**

1. PhD training

	Year	Workload (Hours/ECTS)
General courses		
Biomedical English Writing and Communication	2010	4.0
Classical Methods for Data-analysis	2010	5.7
BROK ('Basiscursus Regelgeving Klinisch Onderzoek')	2010	1.0
Minicursus Methodologie van Patiëntgebonden Onderzoek en Voorbereiding Subsidieaanvragen	2010	0.3
NWO talentendag	2010	0.2
Seminars and workshops		
Seminar "Implementatie" (CPO)	2011	0.1
Research Meetings Expertise Center Palliative Care Rotterdam	2008-2012	0.5
Seminar Nijmeegs Kenniscentrum Vermoeidheid	2012	0.2
Seminar "Study design" (CPO)	2012	0.1
Presentations		
Oral presentation - ZonMW meeting "Palliative Care"	2010	0.3
Oral presentation - 6th EAPC Research Congress	2010	1.0
Poster presentation - 6th EAPC Research Congress	2010	1.0
Oral presentation - Nederlands-Vlaams onderzoeksforum	2010	0.5
Oral presentation - Research meeting Erasmus MC Medical psychology and psychotherapy	2011	1.0
Oral presentation - Expertise Center for Palliative Care	2011	0.5
Poster presentation - 12th EAPC Congress	2011	1.0
Oral presentation - Research Meeting Erasmus MC Medical Oncology	2011	1.0
Oral presentation - 19th NVPO Congress	2012	1.0
Oral presentation - 8th Nederlands-Vlaams onderzoeksforum	2012	0.5
2 Oral presentations - 7th EAPC Research Congress	2012	2.0

(Inter)national conferences		
6th Nederlands-Vlaams onderzoeksforum	2009	0.2
Research Meetings Erasmus MC Medical Oncology	2009-2011	0.5
6th EAPC Research Congress	2010	0.5
7th Nederlands-Vlaams onderzoeksforum	2010	0.2
12th EAPC Congress	2011	0.5
Netwerkdagen IKNL	2011	0.6
8th Nederlands-Vlaams onderzoeksforum	2012	0.2
19th NVPO Congress	2012	0.2
7th EAPC Research Congress	2012	0.5

2. Teaching

	Year	Workload (Hours/ECTS)
Lecturing		
Training oncology nurses Daniel den Hoed	2009-2012	0.5
Lecture "Fatigue" (IKR-training palliative care)	2010	1.0
Lecture "Research in palliative care" (palliative care nurses)	2010-2011	1.5
Lecture "Fatigue" (palliative care nurses)	2011	1.0
Lecture "Treatment of cancer-related fatigue" (oncologists)	2011	1.0
Lecture "Cancer-related fatigue" (residents Internal Medicine)	2012	1.0
Supervising practicals and excursions, Tutoring		
Communication skills and professional attitude (medical students)	2011-2012	5.0
Supervising Master's theses		
Supervising student: determining a cut-off point for clinically relevant fatigue on the Numeric Rating Scale	2010	4.0
Other		
Review IKR-richtlijn "Vermoeidheid bij kanker in de palliatieve fase"	2010	0.2