Bone Marrow Transplantation (2007) 39, 595–603

www.nature.com/bmt

ORIGINAL ARTICLE

Experience of severe fatigue in long-term survivors of stem cell transplantation

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The literature suggests that cancer survivors with more aggressive treatments are more at risk for postcancer fatigue. In this study, we investigated the prevalence of fatigue after completion of stem cell transplantation (SCT). Furthermore, we studied if medical variables are associated with fatigue and if the model of perpetuating factors of postcancer fatigue derived from previous studies in cancer survivors, without SCT, is applicable in SCT survivors. Ninety-eight patients treated with autologous or allogeneic SCT filled out several questionnaires. Medical characteristics were obtained from the medical charts. All patients had to be in persistent complete remission for at least 1 year. Thirty-five per cent of the patients experienced severe fatigue. The percentage of patients with severe fatigue remained stable during the years after transplantation. Several psychosocial factors, but no medical factors, were associated with fatigue. The model of perpetuating factors appeared to be applicable. Contrary to cancer survivors without SCT, we found no decrease in fatigue complaints during the first years after SCT. Cognitive behaviour therapy (CBT) is a general form of psychotherapy directed at changing condition-related cognitions and behaviours. CBT especially designed for postcancer fatigue, aimed at perpetuating factors, can also be used to manage fatigue in cancer survivors treated with SCT.

Bone Marrow Transplantation (2007) **39,** 595–603. doi:10.1038/sj.bmt.1705624; published online 19 March 2007
Keywords: cancer survivors; fatigue; stem cell transplantation

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Received 8 November 2006; revised 23 January 2007; accepted 1 February 2007; published online 19 March 2007

Introduction

Stem cell transplantation (SCT) is a potentially curative treatment for various malignant diseases. Results are improving with the course of time and this has led to reduced morbidity and an increased life expectancy. Therefore, the number of patients surviving an SCT is growing during the last decennia. Because SCT is a highly aggressive and demanding medical intervention, significant concerns related to the long-term well-being of SCT survivors have been voiced. Generally speaking, most patients seemed to have reached an acceptable level of functioning during the first year after transplant.[1–5] However, there seems to be a subgroup of patients who experience ongoing problems following transplantation.[6] One of these problems is persistent fatigue.[3,4,7–9]

More research has been done in the field of postcancer fatigue in cancer survivors who were not treated with a SCT. Fatigue seems to be a problem for about a quarter of these patients long after curative treatment for cancer, with profound effects on quality of life.[10,11] Furthermore, it seems that patients with more aggressive treatments are more at risk for persistent fatigue.[12–14] However, little is known about the aetiology of persistent fatigue and at this moment, persistent fatigue is unexplainable by somatic factors. Fatigue seems to be elicited during the treatment phase, but later on there is no clear relationship between persistent fatigue and initial disease and cancer treatment variables.[10,11,15–17] Therefore, we think it is useful to make a distinction between precipitating factors and perpetuating factors of fatigue after cancer. The assumption is that cancer itself and/or cancer treatment may have triggered fatigue (precipitating factors), but other factors are responsible for the persistence of fatigue complaints (perpetuating factors).[13,18,19]

In a previous study, we found cognitive behaviour therapy (CBT) especially designed for fatigued cancer survivors effective in reducing fatigue and impairment.[18] The rationale of this intervention was based on the model of precipitating and perpetuating factors. The intervention was focused on six perpetuating factors of postcancer fatigue: (1) insufficient coping with the experience of cancer, (2) fear of disease recurrence,[13,16] (3) dysfunctional

cognitions concerning fatigue,[19,20] (4) dysregulation of sleep,[10,11] (5) dysregulation of activity and[10,11,16] (6) low social support and negative social interactions.[19]

However, in this last study, none of the patients included were treated with a SCT. Therefore we conducted this study, to answer the following research questions:

1. What is the prevalence of severe fatigue in patients after successful SCT?
2. Is the model of precipitating and perpetuating factors found in other cancer survivors also applicable in cancer survivors treated with a SCT?

   (a) Is there a relationship between past and/or current medical characteristics and fatigue severity?
   (b) Are the same perpetuating factors, that play a role in persistent fatigue after curation for solid tumours, involved in fatigue after successful SCT?

Methods

Patients

This study involved all patients who were treated at the age of 18 or older with an autologous or an allogeneic SCT between 1981 and 2003 at the Department of Haematology of the Radboud University Nijmegen Medical Centre. Diagnoses included were acute myeloid or lymphatic leukaemia in first complete remission (CR1), chronic myeloid leukaemia in first chronic phase (CP1), non-Hodgkin's lymphoma in CR1. The conditioning regime included total body irradiation. All patients had to be in persistent complete remission for at least 1 year after SCT.

Graft-versus-host disease (GVHD) is a frequent complication of an allogeneic SCT in which the engrafted donor cells attack the patient's organs and tissue. Acute GVHD was classified as grades I–IV according to Glucksberg *et al*.[21] and chronic GVHD as limited or extensive following the Shulman criteria.[22] Patients with severe GVHD after allogeneic SCT (i.e. grades III and IV, acute GVHD or extensive chronic GVHD) may experience many acute and chronic medical problems, are treated with several drugs and other therapies, which may influence an unstable clinical balance and may provoke fatigue. Therefore, these patients were excluded from this study.

Anaemia is a well-known physical factor that can cause fatigue. Therefore, all patients with a haemoglobin (Hb) concentration of 10 g/dl and lower were not eligible for this study.

Recruitment procedure

All patients that underwent SCT since 1981 could be identified by a database that was set up at the research centre of the Department of Haematology. Inclusion and exclusion criteria were checked according to the data of the most recent clinical check-up. All patients were sent a package of questionnaires and an informed consent form, together with a letter of their physician, explaining the purpose of the study. Patients were asked to fill out and send back the questionnaires together with the informed consent to the Expert Centre Chronic Fatigue. The Ethics Committee of the hospital approved the study.

Demographic and medical characteristics

The demographic characteristics like age, gender, marital status, education and employment were gathered by self-report.

Characteristics of the medical history of patients were obtained from the medical chart and consisted of type of diagnosis, type of transplantation, time since transplantation, grade of GVHD, duration of hospitalization during SCT and number of hospitalizations for complications after SCT. Additionally, we acquired information about current medical characteristics from the medical chart, like comorbidity, medication use, Hb concentration and body mass index (BMI) at time of participation in the study.

Questionnaires

Fatigue severity was measured by the 'fatigue severity' subscale (CIS-fatigue) of the Checklist Individual Strength (CIS),[23–26] consisting of eight items designed to measure fatigue severity during the previous 2 weeks. Each item was scored on a 7-point Likert scale. High scores indicated a high level of fatigue. A CIS-fatigue score equal or higher than 35 was used to identify severe fatigue.[19,23] The questionnaire has been used in cancer survivors,[13,18,19,27,28] showed good reliability, discriminative validity and sensitivity to change.[18,22,29,30]

Coping with the experience of fatigue was measured with the Dutch version of the Impact of Event Scale. This 15-item scale consists of two subscales (intrusion: seven items and avoidance: eight items) on a 6-point Likert scale and measures the extent to which a subject is currently occupied with the coping process after a major event (in this study, the diagnose and treatment for cancer). High scores are indicative for intrusively experienced ideas, images, feelings or bad dreams about the event and avoidance of unpleasant feelings or memories of the event.[31–33]

Fear of disease recurrence was measured by two items of the Cancer Acceptance Scale (CAS) scored on a 4-point Likert scale.[13] The items are (1) I am worried about a tumour relapse, (2) I am anxious about my health. High scores are indicative of a high level of fear.

Cognitions related to fatigue. Self-efficacy was measured with the Self-Efficacy Scale (SES), consisting of five questions, which measured sense of control in relation to fatigue complaints.[13,19,30,34] Cancer-related attributions with regard to fatigue complaints were measured with the Causal Attribution List (CAL),[19] consisting of four items (cancer, SCT, radiation therapy, chemotherapy). For each item, patients were asked to indicate their opinion regarding the cause of their fatigue complaints on a 4-point scale (1 = not at all applicable to 4 = very applicable). Internal reliability of this questionnaire was good, with a Cronbach's α coefficient 0.95.

Sleep disturbances was measured with the sleep/rest subscale of the Sickness Impact Profile (SIP-8),[35,36] and the insomnia subscale of the Quality of Life Questionnaire-

C30 (QLQ-C30),[37] with higher values reflecting an increased presence of symptoms.

Physical activity was measured with the physical functioning and role functioning subscale of the QLQ-C30, with higher scores representing a better level of physical/role functioning. Furthermore, physical activity was measured with the subscales: home management, work, and recreation and pastimes from the SIP, with high scores reflecting more functional impairments.

Social functioning was measured with the social functioning subscale of the QLQ-C30 and the social interaction subscale of the SIP.

Statistical analysis

Data analyses were performed using Statistical Package for Social Science (SPSS; version 12.1). Descriptive statistics were used for description of the sample. χ^2, independent samples *t*-tests and analyses of variance general linear model (GLM) have been performed to test differences between groups. Pearson correlations were used to investigate the association between fatigue severity (CIS-fatigue) and medical characteristics. Furthermore, Pearson correlations between fatigue severity and the six perpetuating factors were used as preparatory analyses to examine the contribution of these factors to fatigue severity. Those measures that correlated highest with the fatigue severity score were used as independent variables in a linear regression analyses (enter-method). Correlations between the six perpetuating factors were tested on multicolinearity ($r<0.9$).

Results

Response

Hundred twenty-four patients met the eligibility criteria and were asked to participate in this study. Ultimately, the questionnaires were filled out and returned by 98 patients (79%). Reasons for non-participation ($n=26$) were: too emotional to participate ($n=6$), did not feel like taking part because they had no complaints at the moment ($n=3$), bad concentration and therefore not able to fill out the questionnaires ($n=1$) and unknown ($n=16$). Non-participants did not differ from the participants with regard to demographic characteristics (data not shown), except for age. Nonparticipants were significantly younger compared with the participants (40.5 (s.d. = 8.9) vs 45.3 (s.d. = 10.8); $P=0.038$). Information about demographic, disease and treatment characteristics of the participants are listed in Table 1.

Table 1 Demographic and medical characteristics ($n=98$)

	Cancer survivors treated with a SCT (n = *98*)
Age	45.3 (10.9) range = 19.0–67.3
Gender	
Male	57 (58%)
Female	41 (42%)
Marital status	
Married/cohabiting	77 (79%)
Unmarried	17 (17%)
Divorced	2 (2%)
Widowed	2 (2%)
Higher education ($\geqslant$12 years)	34 (35%)
Employment	
Work outside home	54 (54%)
Study	6 (6%)
Disablement insurance act	26 (26%)
Partial disablement insurance act	7 (7%)
Sick leave	3 (%)
No work	4 (4%)
Primary diagnosis	
Acute leukaemia	70 (72%)
Chronic leukaemia	21 (21%)
Lymphoma	7 (7%)
Transplantation	
Allogeneic	79 (81%)
Autologous	19 (19%)
Time since transplantation (years)	9.3 (5.5) range = 1.0–21.5

Abbreviation: SCT = stem cell transplantation.

Research questions

What is the prevalence of severe fatigue in patients after successful SCT? The mean CIS-fatigue severity score of the total sample was 26.9 (s.d. = 14.0). Thirty-four patients (35%) meet the cutoff criteria for severe fatigue (CIS-fatigue $\geqslant$ 35), whereas an additional 12 patients (12%) had heightened fatigue scores (CIS-fatigue between 27 and 35).

There were no differences in fatigue severity between male (27.6, s.d. = 14.0) and female cancer survivors (25.9, s.d. = 14.2, *P*-value = 0.558), younger (24.7, s.d. = 12.6) and older survivors (29.0, s.d. = 15.1, *P*-value = 0.125) (median = 45.7 years), married/cohabiting (27.0, s.d. = 14.0) and unmarried/divorced/widowed survivors (26.5, s.d. = 14.3, $P=0.880$) and survivors with lower and higher education, respectively 27.7 (s.d. = 14.9) and 26.0 (s.d. = 12.2) ($P=0.552$).

Is there a relationship between past and/or current medical characteristics and fatigue severity?

Medical history. Diagnose and transplantation: No significant difference was seen in mean fatigue score between patients who were diagnosed with acute leukaemia, chronic leukaemia or lymphoma and between patients who were treated with allogeneic transplantation or autologous transplantation (Table 2).

Time since transplantation: To investigate the relationship between fatigue severity and time since transplantation, the total sample has been divided into four groups: patients who were treated with a SCT between 1 and 5 years ago ($n=32$), between 5 and 10 years ago ($n=19$), between 10 and 15 years ago ($n=30$) and more than 15 years ago ($n=17$). Mean fatigue scores and percentages of severe fatigue for these four groups are shown in Table 3. No statistically significant differences were found in mean fatigue scores and in percentages of severe fatigue. In

Table 2 The association of fatigue with medical characteristics (medical charts)

	n	*Mean CIS-fatigue (s.d.)*	P-*value*
Diagnosis			
Acute leukaemia	70	27.3 (13.9)	0.733
Chronic leukaemia	21	27.8 (14.2)	
Lymphoma	7	22.9 (16.0)	
Transplantation			
Allogeneic	79	27.6 (13.9)	0.285
Autologous	19	23.8 (14.4)	
Graft-versus-host disease			
Absent	36	26.8 (13.8)	0.562
Grade I	34	29.4 (14.5)	
Grade II	9	24.4 (12.4)	
Duration of hospitalization SCT			
$\leqslant$5 weeks	51	27.3 (13.4)	0.471
>5 weeks	47	26.5 (14.8)	
Hospitalizations after SCT for complications			
0 hospitalizations	55	24.7 (12.5)	0.181
1 hospitalization	26	28.9 (15.9)	
>1 hospitalization (range = 2–7)	17	31.1 (15.2)	
Comorbidity at the time of participation			
(7 missing)			
Yes	38	31.7 (14.9)	0.018
No	53	24.7 (12.7)	
Medication at the time of participation			
No medication	51	25.8 (13.5)	
Medication but no antibiotics			
And/or beta blocker	17	29.9 (14.8)	0.174
Antibiotics	11	35.8 (14.9)	
Beta blocker	9	26.6 (13.7)	
Hb concentration at the time of participation			
= Normal concentration	78	26.7 (14.1)	0.814
< Normal concentration	20	27.6 (14.0)	
BMI at the time of participation			
Normal BMI	53	25.0 (12.6)	0.156
>Or <normal BMI	45	29.1 (15.4)	

Abbreviations: BMI = body mass index; CIS = Checklist Individual Strength; SCT = stem cell transplantation.

Table 3 Mean CIS-fatigue scores and percentages of fatigue for patients who finished SCT within a different time period

	n	*Mean CIS-fatigue (s.d.)**	*% of severe fatigue***
Time since transplantation			
Between 1 and 5 years ago	32	27.5 (12.3)	41
Between 5 and 10 years ago	19	28.4 (14.2)	32
Between 10 and 15 years ago	30	25.4 (14.5)	30
More than 15 years ago	17	26.7 (16.9)	35
Total	98		

Abbreviations: CIS = Checklist Individual Strength; GLM = general linear model; SCT = stem cell transplantation.
*Analyses of variance (GLM), $P = 0.901$.
**χ^2, $P = 0.832$.

addition, the correlation between the CIS-fatigue score and time since transplantation proved to be very low and nonsignificant (Figure 1).

GVHD: From the medical charts, we obtained for each patient the maximum GVHD grade after transplantation. As described in the Methods section, patients with severe GVHD were excluded. There were no differences in the mean fatigue score between patients who experienced no GVHD after transplantation, or who suffered from grade I or II.

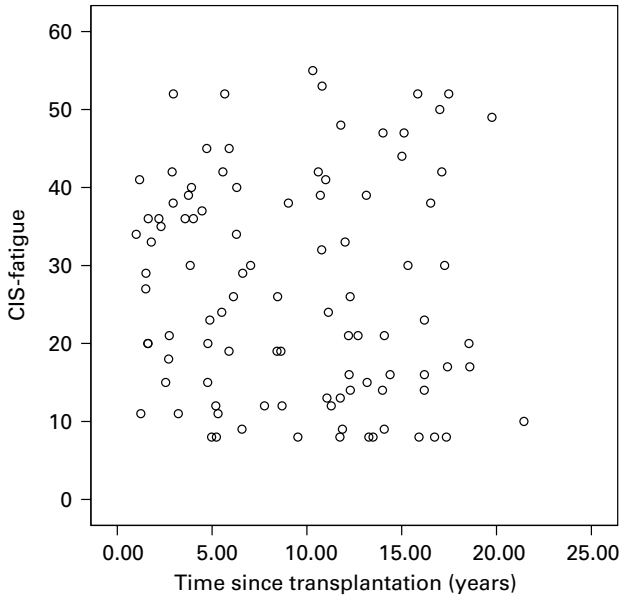

Figure 1 The association of time since treatment with fatigue severity (CIS-fatigue); $r = -0.080$, $P = 0.434$.

Hospitalization and complications: To analyse the association between postcancer fatigue and the duration of hospitalization during the transplantation, the group was divided into two groups based on the median time of hospitalization (5 weeks). No difference in mean fatigue scores of the two groups was found. Furthermore, the correlation between the fatigue score and total days of hospitalization was nonsignificant ($r = 0.046$, $P = 0.652$).

Owing to complications, 44% of the patients ($n = 43$) had been re-admitted after the SCT ($n = 5$, abdominal pain; $n = 9$, nausea/vomiting/diarrhoea; $n = 21$, fever; $n = 9$, respiratory insufficiency/failure; $n = 7$, Herpes Zoster; $n = 11$, other complications). No difference was found between the mean fatigue score of patients who had no complications after transplantation, patient who had been hospitalized once, and patients who had been hospitalized more than one time. Additionally, post-treatment fatigue was not related to the number of hospitalizations and to the number of days of hospitalization due to complications (respectively, $r = 0.128$, $P = 0.208$; $r = 0.043$ $P = 0.676$).

Current medical characteristics. Comorbidity: Patients with comorbidity at the time of participation ($n = 38$) were significantly more fatigued than patients without comorbidity ($n = 53$; $P = 0.018$) (Table 2). The group of patients with comorbidity was divided into three subgroups;

(a) comorbidity that possibly can cause fatigue ($n = 10$; four hepatitis C, four hypertension with use of a beta blocker, two recurrent respiratory infections);
(b) co-morbidity possibly caused by the SCT ($n = 13$, six iron overload, five good controlled hypothyroidism (normal levels of thyroid stimulating hormone (TSH) and Free T4 at the time of participation in the study), two postherpetic neuralgia);
(c) remaining comorbidities ($n = 15$, five diabetes mellitus, six hypercholesterolaemia, two epilepsy, one haematuria, one gout).

Within these three groups, mean fatigue scores were, respectively, 33.9 (s.d. = 14.7), 33.2 (s.d. = 15.0) and 28.9 (s.d. = 15.5) and were not significantly different ($P = 0.662$).

Medication use: We investigated medication use by patients at the moment of participation in the study. There was no significant difference between postcancer fatigue in patients

(a) without medication ($n = 51$),
(b) with antibiotics ($n = 11$),
(c) with beta blocker ($n = 9$),
(d) with other medication ($n = 17$).

Hb concentration: To test the association between postcancer fatigue and the Hb concentration at the moment of participation, two subgroups were identified based on the normal distribution of Hb concentration of the WHO.[38,39] No difference was seen in the mean fatigue score between patients with a normal Hb concentration ($n = 78$: men = 13.6–17.2 g/dl; women = 12–15 g/dl) and patients with a low Hb concentration ($n = 20$: men = 13.6 g/dl; women = <12 g/dl). Additionally, the correlation between fatigue severity and Hb concentration was nonsignificant ($r = -0.024$, $P = 0.813$).

BMI: Based on WHO standards, BMI was categorized as underweight (BMI <18.5), normal weight (BMI = 18.5–24.9), overweight (BMI = 25–29.9) and obese (BMI $\geqslant 30$).[40] To analyse the association between postcancer fatigue and the weight of patients at the time of participation, the total group was divided into two groups. Patients with a normal weight ($n = 53$) and patients with underweight, overweight and obese patients ($n = 43$). There was no difference in fatigue severity between these two groups. Additionally, the correlation between fatigue severity and BMI was low and nonsignificant ($r = 0.098$, $P = 0.338$).

Are the same perpetuating factors, that play a role in persistent fatigue after curation for solid tumours, involved in fatigue after successful SCT? In Table 4, comparisons have been made between fatigued cancer survivors (CIS $\geqslant 35$) and non-fatigued cancer survivors (CIS <35) with regard to the six perpetuating factors. Results were consistent; patients experiencing severe fatigue had more difficulties in coping with the experience of cancer, more fear of disease recurrence, more dysfunctional cognitions, sleep disturbances, less physical activity and low social functioning. Furthermore, all measurements correlated significantly with the fatigue severity score.

The highest correlations were used as independent variables in a linear regression analyses. There was no multicolinearity between the six perpetuating factors entered in the regression analyses. Results of the regression analyses (Table 5) indicated that insufficient coping with the experience of fatigue, fear of disease recurrence, low self-efficacy, sleep disturbances and low role functioning contributed significantly to fatigue severity. In total, 68% of the variance of fatigue severity was explained by the six perpetuating factors.

Table 4 Comparisons between severely fatigued cancer survivors (CIS ⩾35) and nonfatigued cancer survivors (CIS <35) long after SCT

	Nonfatigued (n = 64)	*Severe fatigued (n = 34)*	P-*value*	*Correlation: CIS-fatigue*
Coping with the experience of fatigue				
Impact of event scale	7.6 (10.6)	16.5 (16.1)	0.004	0.380**
Fear of disease recurrence				
Cancer acceptance scale	12.7 (3.3)	16.8 (4.9)	0	0.454**
Dysfunctional cognitions				
Self-efficacy (SES)	22.3 (3.6)	17.4 (3.3)	0	−0.639**
Cancer-related attributions (CAL)	11.1 (4.0)	14.7 (1.9)	0	0.599**
Sleep disturbances				
Sleep/rest (SIP)	20.5 (36.9)	85.1 (76.4)	0	0.550**
Insomnia (QLQ-C30)	13.0 (21.1)	29.4 (35.5)	0.021	0.407**
Dysregulation of physical activity				
Home management (SIP)	32.0 (66.9)	93.3 (70.6)	0	0.514**
Recreation and pastimes (SIP)	30.1 (53.6)	91.7 (71.7)	0	0.518**
Work (SIP)	61.7 (125.0)	149.5 (157.0)	0.001	0.358**
Physical functioning (QLQ-C30)	91.8 (13.7)	71.8 (13.7)	0	−0.614**
Role functioning (QLQ-C30)	94.5 (11.2)	57.8 (30.5)	0	−0.675**
Social functioning				
Social functioning (QLQ-C30)	90.4 (18.3)	71.1 (25.4)	0	−0.472**
Social interactions (SIP)	52.1 (92.7)	150.3 (136.1)	0	0.544**

Abbreviations: CAL = Causal Attribution List; CIS = Checklist Individual Strength; QLQ-C30 = Quality of Life Questionnaire-C30; SES = Self-Efficacy Scale; SIP = Sickness Impact Profile.
**$P < 0.01$.

Table 5 Linear regression (enter) to predict fatigue severity

Independent variables	*Dependent variable: CIS-fatigue severity*	
	Beta	P-*value*
Coping with the experience of cancer (IES)	0.172	0.016
Fear of disease recurrence (CAS)	0.175	0.034
Dysfunctional cognitions (SES)	−0.243	0.002
Sleep disturbances (SIP-sleep/rest)	0.215	0.007
Dysregulation of physical activity (QLQ-C30 – role functioning)	−0.376	0.000
Social functioning (SIP – social interactions)	0.005	0.958
Total R^2 (adjusted)	0.679	

Abbreviations: CIS = Causal Attribution List; CAS = Cancer Acceptance Scale; IES = Impact of Event Scale; QLQ-C30 = Quality of Life Questionnaire-C30; SES = Self-Efficacy Scale; SIP = Sickness Impact Profile.

Discussion

In this study, 35% of a group of patients experienced severe fatigue long after finishing SCT (mean = 9.3 years). The percentage cancer survivors with severe fatigue remained stable during the years after transplantation, even after more than 15 years.

Cross-sectional studies investigating the prevalence of fatigue (all not including patients who were treated with a SCT) showed that the percentage of cancer survivors with severe fatigue decreases during the years after treatment: this was 38% after 2.5 years,[19] 30% after 3 year,[41] 37% after 4 years,[42] 26% after 12 years[43] and 16% after 12 years.[44] The course of fatigue was also investigated in four longitudinal studies, measuring the prevalence of fatigue in cancer survivors two times at different time points. Bower *et al*.[12] found a decrease of 35% (3.5 years after treatment) to 21% (6.3 years after treatment) and Servaes *et al*.[27] found a decrease of 38% (2.5 years after treatment) to 23% (4.5 years after treatment). In the two other longitudinal studies, the percentage of patients with severe fatigue remained equal, 28% (6 after treatment) to 26% (8 years after treatment)[12] and Hjermstad *et al*.[15] investigated disease-free cancer patients 16 and 24 years after treatment for cancer. In this longitudinal study, the percentage of fatigued cancer survivors was respectively, 25% and 28%. These results seem to suggest that fatigue complaints continue to decrease during the first 3–4 years after curative treatment and remains a persistent problem for about a quarter of the cancer survivors. However, in the current study we investigated the course of fatigue, and we found no decrease of fatigue even up to 15 years after completing SCT. So it seems that in patients after a SCT the percentage of fatigue remains high. This finding is in agreement with

the assumption that patients with more aggressive treatments are more at risk for persistent fatigue.[12–14,45]

The respondent sample consist of almost 80% of the patients who were treated for acute leukaemia in CR1, non-Hodgkin lymphoma in CR1 and chronic leukaemia's in CP1. The population of (A)SCT patients from the Department of Hematology of the Radboud University Nijmegen Medical Centre does not differ from other Dutch and European centres for (A)SCT.[46] Our study involved patients who were 18 years or older at the time of (A)SCT and who had to be in persistent CR for at least 1 year after (A)SCT. Patients with acute GVHD grade III or IV and/or extensive GVHD were excluded and this was also true for patients with a Hb concentration of 10 g/dl at the time of inclusion. This is given in the Methods section. The exclusion of patients with severe acute or severe chronic GVHD and the exclusion of patients with a Hb level of less than 6.0 g/dl may result in a respondent sample with relatively more patients who are less prone to fatigue than the general population after (A)SCT. This means that the impressive number of patients that experienced severe fatigue will be even higher in a general (A)SCT population.

We found no associations with fatigue severity and characteristics of the medical history. Owing to shorter time in protective isolation, fewer treatment-related side effects and no risk of GVHD, the assumption has been uttered that patients with allogeneic SCT have more late effects than patients with a autologous SCT. However, the literature is ambiguous on this point.[1,47–50] Concerning fatigue, Hjermstad *et al*.[1] also found no differences between the two types of transplantation. However, similar to their studies, the small number of patients in our autologous group implies that chance findings cannot be ruled out.

Because in this study the focus was on fatigue with no somatic cause, we excluded beforehand patients with medical problems that could possibly cause fatigue, like GVHD grade of III and IV and Hb concentration of 10 g/dl and lower. This could be the reason why no relation between fatigue severity and somatic characteristics were found.

Thirty-eight of the 98 patients (39%) had a medical comorbidity besides persistent fatigue. Patients with a medical comorbidity scored higher on fatigue severity compared with patients without a medical comorbidity. However, no differences were found in fatigue severity between the different kinds of medical comorbidity (comorbidity that possibly can cause fatigue, comorbidity possibly caused by the SCT and the remaining comorbidities). Because of the relatively small numbers of patients in the different groups, an actual difference cannot be ruled out fully.

The model of perpetuating factors derived from previous studies in cancer survivors, not undergoing transplantation, appears to be applicable in SCT cancer survivors as well. Persistent fatigue was well predicted by the supposed perpetuating factors: insufficient coping with the experience of cancer, fear of disease recurrence, dysfunctional cognitions concerning fatigue, dysregulation of sleep and dysregulation of activity. In total, 68% of the variance of fatigue severity was explained by the six factors. Only impairment in social functioning did not contribute significantly to fatigue severity. Servaes *et al*.[19] demonstrated that severely fatigued cancer survivors experienced more negative interactions and insufficiency of supporting interactions than those who were not fatigued. No significant difference was found in the frequency of supporting interactions. So, it seems that the experienced insufficiency and negative interactions have more influence on fatigue severity than impairment in social functioning as measured in this study. Additionally, these results suggest that in the absence of clear medical causes, the CBT especially designed for fatigued cancer survivors after conservative treatment, can also be used in the management of fatigue after SCT.

The strength of this paper is characterized by an underlying theoretical perspective of postcancer fatigue, the model of precipitating and perpetuating factors. However, it could be argued that the factors do not perpetuate fatigue, but represent, for example, psychosocial consequences of stress. Furthermore, the study is cross-sectional and limits our ability to draw conclusions about the course of postcancer fatigue in patients following a SCT. For definitive conclusions, a longitudinal design would be more appropriate.

Acknowledgements

We thank all the patients who gave their time to participate in the study. Carmen Ariens and Tiny Fasotti for assisting in data collection. Funding for this study was provided by the Interzol, Comprehensive Cancer Centre South.

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