Long-term side effects of adjuvant breast cancer treatment

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Chapter 3

Fatigue and relating factors in high-risk breast cancer patients treated with adjuvant standard or high-dose chemotherapy: a longitudinal study

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J Clin Oncol 2005; 23: 8296-8304

ABSTRACT

Purpose

Determine whether standard or high-dose chemotherapy leads to changes in fatigue, hemoglobin (Hb), mental health, muscle and joint pain, and menopausal status from pre to post-treatment and to evaluate whether fatigue is associated with these factors in disease-free breast cancer patients.

Patients and methods

Eight hundred eighty-five patients were randomly assigned between two chemotherapy regimens both followed by radiotherapy and tamoxifen. Fatigue was assessed using vitality scale (score ≤ 46 defined as fatigue), poor mental health using mental health scale (score ≤ 56 defined as poor mental health) both of Short-Form 36, muscle and joint pain with Rotterdam Symptom Checklist, and Hb levels were assessed before and 1, 2 and 3 years after chemotherapy.

Results

Fatigue was reported in 20% of 430 evaluable patients (202 standard-dose, 228 high-dose) with at least a 3-year follow-up, without change over time or difference between treatment arms. Mean Hb levels were lower following high-dose chemotherapy. Only 5% of patients experienced fatigue and anemia. Mental health score was the strongest fatigue predictor at all assessment moments. Menopausal status had no effect on fatigue. Linear mixed effect models showed that the higher the Hb level ($P = .0006$) and mental health score ($P < .0001$), the less fatigue was experienced. Joint ($P < .0001$) and muscle pain ($P = .0283$) were associated with more fatigue.

Conclusion

In 3 years after treatment, no significant differences in fatigue were found between standard and high-dose chemotherapy. Fatigue did not change over time. The strongest fatigue predictor was poor mental health.

INTRODUCTION

Adjuvant chemotherapy is being increasingly administered to women with breast cancer, because it delays disease recurrence and improves long-term survival. High-dose chemotherapy strategies aim at further improving disease-free and overall survival in high-risk breast cancer patients. Studies carried out thus far have yielded varying results.[1-3] In the Dutch randomized study, patients treated with adjuvant standard-dose or high-dose chemotherapy followed by autologous peripheral stem cell transplantation were compared.[2] This study showed an advantage for high-dose chemotherapy, particularly for patients with *HER2/neu*-negative tumors and those with more than nine positive axillary lymph nodes.[2]

Relatively little is known, however, about the long-term effects of both standard and high-dose adjuvant therapy in terms of the patient's well-being. A growing body of evidence indicates that breast cancer survivors experience a variety of problems. A recent review reported that many cancer survivors report fatigue after the completion of cancer treatment.[4] This symptom is reported to be highly distressing to the patients and a limiting factor in the quality of life. Studies in which fatigue has been investigated in treated, disease-free breast cancer patients are rare.[5-11] Moreover, these small, cross-sectional studies mainly consist of heterogeneous samples of cancer survivors with regard to tumor stage or previous treatment. A better understanding of long-term fatigue in cancer survivors is, thus, fundamental to the development of appropriate intervention strategies.[12] A low hemoglobin (Hb) level is generally considered to be a possible reason for fatigue. Several studies in cancer patients investigated the relationship between Hb level and fatigue, but the results, mainly performed during cancer treatment, are not unequivocal.[13-15] Other reasons for the existence of fatigue in cancer patients are depression and pain. Servaes et al,[4] for example, concluded that the influence of these factors on fatigue are highly consistent across several studies. The shifts in menstrual status, caused by the therapy from premenopausal at diagnosis to postmenopausal, may also have an impact on fatigue experienced by breast cancer patients.

The purpose of this prospective, longitudinal study is to analyze whether standard or high-dose chemotherapy leads to changes in fatigue, Hb, mental health, pain (ie, muscle and joint), and menopausal status from pre- to post-treatment and to evaluate whether fatigue is associated with these factors in disease-free breast cancer patients.

PATIENTS AND METHODS

Study population

Eligible patients participated in the Dutch randomized multicenter adjuvant breast cancer clinical trial and the accompanying quality of life study. Recruitment details and study procedures of the Dutch adjuvant breast cancer clinical trial have been published previously.[2] The present analysis included patients with at least 3 years of follow-up and who were without clinical evidence of disease recurrence.

Clinical trial

Patients younger than 56 years of age with stage II and III breast cancer were eligible, if they had four or more positive axillary lymph nodes, a normal chest x-ray, normal bone-scan, normal liver sonogram, a WHO performance status of 0 or 1, and no prior treatment other than surgery. The study compared standard-dose chemotherapy consisting of five cycles of 5-fluorouracil 500 mg/m^2, epirubicin 90 mg/m^2 and cyclophosphamide 500 mg/m^2 (FEC) with four cycles of FEC plus one cycle of high-dose chemotherapy consisting of cyclophosphamide 6 g/m^2, thiotepa 480 mg/m^2 and carboplatin 1600 mg/m^2 administered over four days, followed by peripheral stem-cell reinfusion on day seven. After chemotherapy, treatment in both arms consisted of local radiotherapy and 40 mg tamoxifen daily, during 2 years, and from 1998 onwards, during 5 years.[12] Following chemotherapy, patients were seen on an outpatient basis at a 3-month interval during the first 2 years and biannually thereafter. Patients eligible for the clinical trial were also asked to participate in the quality of life study.

The study was approved by the Medical Ethical Committees of all participating centers. All patients gave informed consent.

Health Related Quality of Life assessments

Participating patients were asked to complete a quality of life questionnaire at several follow-up points. This questionnaire included questions about the socio-demographic characteristics of the patients including age, whether they have a partner, level of education, number of children living at home, and paid employment. Furthermore, the Rotterdam Symptom Checklist, the Short-Form 36 (SF-36), the self-report version of the Karnofsky Performance Index, Visual Analogue Scale evaluation of overall health-related quality of life, and a questionnaire about costs made by the patients were included.[16,17] The questionnaire was sent to the participants by mail before random assignment,

directly after chemotherapy, after radiotherapy, and every half-year thereafter. The data obtained at random assignment and after 1, 2, and 3 years were analyzed. All patients had completed chemotherapy and radiotherapy at the 1-year time point. Fatigue and mental health were assessed by the SF-36.

Standard procedures were employed to compute the score for the subscale vitality and mental health of the SF-36. The subscale vitality is composed of four items: felt full of pep, had a lot of energy, felt worn out, and felt tired. The subscale mental health is composed of five items: been a very nervous person, felt so down in the dumps nothing could cheer you up, felt calm and peaceful, felt downhearted and blue, and been a happy person. These items were assessed in a 6-point Likert scale to determine how the patients experienced these symptoms during the last four weeks.[17] The scores range from 0 to 100, with higher scores representing higher functional level (ie, less fatigue/vitality and better mental health status). General Dutch population norms are available for the SF-36.[18] The mean vitality score for Dutch women (reference value) is 66 and the standard deviation (SD) is 20. Fatigue was defined in this study as a vitality score of one or more SD below the mean of the reference value. Consequently, patients who scored ≤ 46 on the vitality scale were defined as having fatigue, and patients with a score above 46 as having no fatigue.

The mean mental health score reference value for Dutch women is 74 (SD = 18).[18] Poor mental health was defined as one or more SD below the mean of the reference value, and therefore, mental health scores of ≤ 56 were defined as poor mental health. The Rotterdam Symptom Checklist measures both physical and psychosocial dimensions and consists of a 35-item symptom checklist to be answered in a 4-point Likert scale (1 = not at all, 2 = a little bit, 3 = quite a bit, 4 = very much).[19] Muscle pain and joint pain are two of the items. Answers to these questions were condensed into two groups. Scores of 1 (= not at all) and 2 (= a little bit) were categorized as having only limited muscle or joint pain. Patients with scores 3 (= quite a bit) and 4 (= very much) were considered to experience muscle or joint pain.

Hematological determinations

Hb level was determined by using automated Counter particle counts. Peripheral blood counts were evaluated annually after peripheral stem-cell transplantation. A normal Hb level for women was defined as Hb more than 12 g/dL.[20] Hb levels ≤ 12 g/dL were defined as anemia.

Determination of menopausal status

To monitor menopausal status, the date of last menstruation was noted and follicle-stimulating hormone and 17 beta-estradiol serum levels were measured at least every year during tamoxifen treatment and also after discontinuation of tamoxifen, if any uncertainty regarding postmenopausal status remained.

Statistical analysis

Normal distribution differences between treatment groups were tested using the independent sample *t*-test. If the variables did not fit the normal distribution, the Mann-Whitney test was used. The correlation between fatigue and Hb levels was tested using the Spearman rank correlation *r*. The relationship between anemia-no anemia and fatigue-no fatigue was evaluated using the χ^2 test. Differences in fatigue between the standard-dose and the high-dose chemotherapy were also evaluated using the χ^2 test. Multiple logistic regression analyses with fatigue as dependent variable and Hb, mental health score, joint pain, muscle pain, menopausal status, and treatment group as independent variables were performed. Multiple linear regression analyses with fatigue as continuous variable were also performed on the previously mentioned independent variables. Linear mixed effect models (LME) were used to investigate changes in fatigue over time. Time was defined as the time in years relative to random assignment. Random effects were estimated for the intercept and changes over time. Variables included in the model were Hb, mental health, muscle pain, joint pain, menopausal status, and treatment group. Finally, an interaction term of group with time was entered into the model to determine whether treatment groups showed differences with regard to changes in fatigue over time. The LME analyses were performed on all data collected on the different time points, thus using all information available, and testing whether changes in Hb were associated with changes in fatigue over time.

Data analysis was carried out with the help of Statistical Package for Social Sciences (SPSS version 12.0; SPSS Inc, Chicago, IL) and S-plus 6 (Version 3.3; Statistical Sciences, Seattle, WA). P values $\leq .05$, tested two sided, were considered statistically significant. In case of multiple testing, which was executed to examine the relationship between fatigue with Hb levels, P values were adjusted according to the Bonferroni step-down procedure to reduce the risk of type I errors.[21] The significance level for two tests was adjusted, and therefore, $P \leq .025$ was considered statistically significant.

RESULTS

Patients

Between August 1993 and July 1999, 885 patients entered into the study. After inclusion of the first 47 patients, the next 838 patients were approached to participate in the quality of life study. Of these 838 patients, 27 refused participation and seven did not participate because of logistic reasons. Consequently, 804 patients completed one or more quality of life questionnaires. At the time of analysis, March 2002, 430 patients had a follow-up of at least 3 years and were disease-free. Of these, 202 patients (47%) were randomly assigned into the standard-dose and 228 patients (53%) into the high-dose chemotherapy arm. There was no difference in mean age between the groups (45.8 years (SD 6.4) in the standard-dose, 45.1 years (SD 6.5) in the high-dose chemotherapy group). Fourteen patients randomly assigned to the high-dose chemotherapy treatment did not receive this treatment for various reasons, with most of them receiving a fifth course of FEC chemotherapy instead.[2] None of the patients who were randomly assigned to standard treatment received high-dose chemotherapy outside of the protocol. In accordance with the published clinical data, all analyses were done according to the intention-to-treat principle.[2]

Differences between the two treatment groups and change over time

Vitality scores

The mean vitality scores of the two treatment groups are shown in Table 1. No statistical difference between the treatment groups was found. Figure 1A illustrates the change in scores over time for both treatment groups and did not reveal any changes in time in either group. The percentage of patients with fatigue in both groups is shown in Table 1. The number of patients with fatigue in both groups did not change over time and no statistical differences were found between the treatment groups. Of the 430 patients, 262 patients (61%) did not report fatigue at any of the four time points and only 12 patients (3%) reported fatigue at all four points. Twenty percent of the patients (n = 42) reported fatigue once, 10% (n = 42) twice, and 6% (n = 27) reported fatigue three times.

Hb

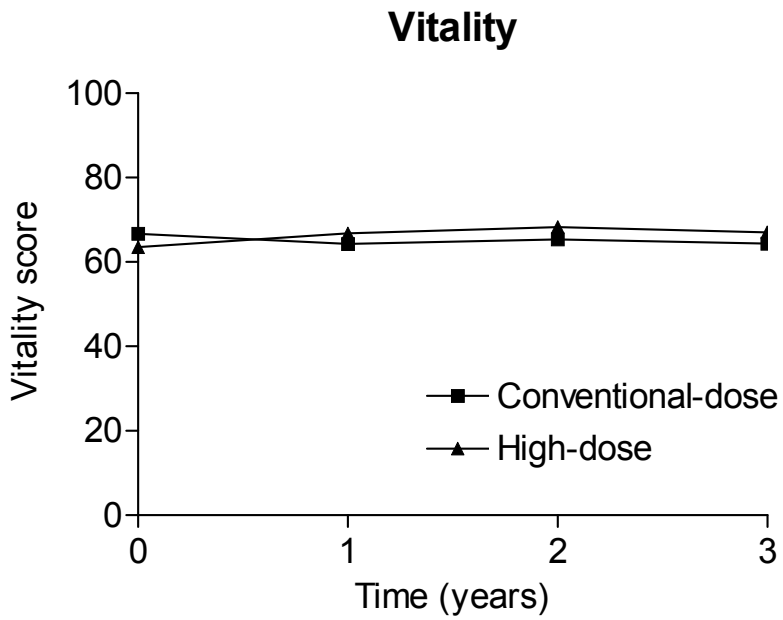
The mean Hb levels at the four time points (random assignment, 1, 2, and 3 years) for the two treatment arms are shown in Table 1. Figure 1B illustrates the

Table 1. Comparisons between the standard-dose and the high-dose chemotherapy groups

	Patients		Standard-dose	High-dose	
	SD	HD	Chemotherapy, %	Chemotherapy, %	*P*
Mean vitality score					
At random assignment	196	220	64	67	.106
1 year	186	206	67	64	.324
2 years	181	207	68	65	.215
3 years	170	195	67	64	.369
Fatigue, vitality score ≤46					
At random assignment			19	16	.291
1 year			19	21	.531
2 years			17	21	.291
3 years			19	22	.536
Mean hemoglobin levels, g/dL					
At random assignment	200	226	12.9	12.9	.848
1 year	198	212	13	12.3	.001
2 years	182	212	13.1	12.8	.001
3 years	133	159	13.3	13	.004
Anemic, ≤12 g/dL					
At random assignment			21	20	.881
1 year			13	41	< .001
2 years			11	24	.001
3 years			9	13	.333
Mean mental health score					
At random assignment	196	220	68	70	.27
1 year	186	206	78	77	.44
2 years	181	207	79	80	.62
3 years	170	195	79	80	.60
Poor mental health (mental health score ≤56)					
At random assignment			25	23	.76
1 year			7	11	.15
2 years			8	8	.99
3 years			15	12	.33
Muscle pain					
At random assignment	196	220	19	15	.29
1 year	185	209	21	20	.91
2 years	180	206	19	28	.06
3 years	168	191	23	29	.19
Joint pain					
At random assignment	196	221	6	2	.04
1 year	183	208	10	11	.83
2 years	179	207	15	16	.61
3 years	169	193	17	23	.18
Menopausal status: pre-/ post-/uncertain					
At random assignment			159/65/7	183/39/6	
3 years			30/141/ 31	4/194/30	

Abbreviations: SD, standard-dose; HD, high-dose.

Figure 1A. Mean vitality scores of the SF-36 subscales in the standard-dose and the high-dose treatment groups at random assignment and the three years thereafter (higher vitality scores represent less fatigue).

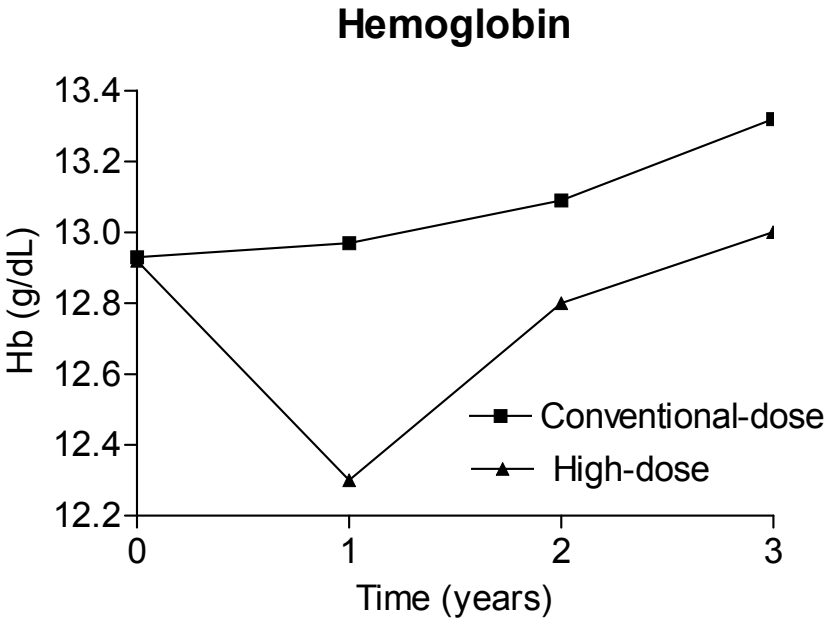


change in Hb levels over time for both treatment groups. The mean Hb level at 1 year was lower than at random assignment in the high-dose chemotherapy group. Thereafter, the mean Hb level recovered to the level measured at random assignment. In the standard-dose chemotherapy group the mean Hb level increased slowly after random assignment to a higher level compared with the level at random assignment ($P < .001$). The standard-dose chemotherapy group had a slightly higher mean Hb level than the high-dose chemotherapy group at all three time points after random assignment. The difference was most pronounced 1 year after random assignment. The percentage of patients with anemia (Hb level ≤ 12 g/dL) in both treatment groups is shown in Table 1. Anemia was seen more often in the high-dose chemotherapy group 1 and 2 years after random assignment (three and two times higher, respectively).

Mental health scores

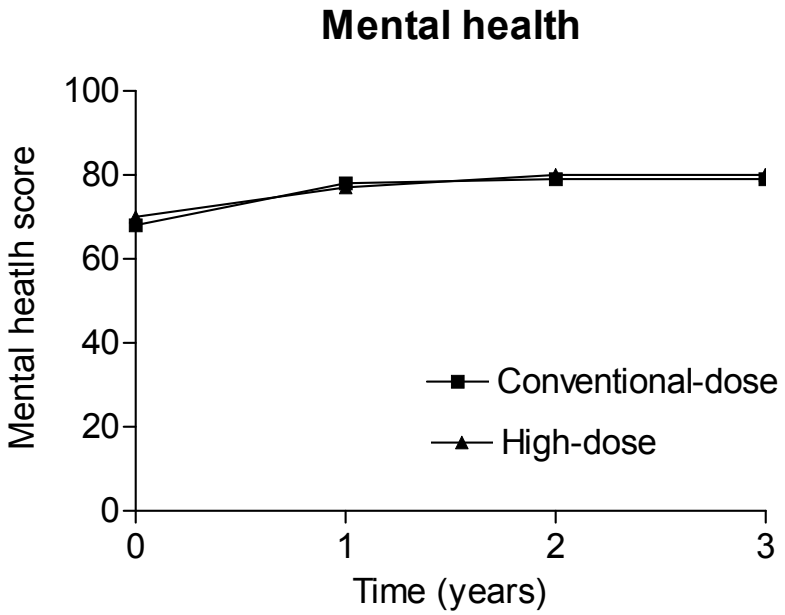
The mean mental health scores and the percentage of patients with poor mental health in both treatment groups are shown in Table 1. The mean mental health scores in both groups increased after random assignment and remained stable thereafter. The percentage of patients with a poor mental health decreases after random assignment. No statistically significant differences in scores were found

Figure 1B. Mean hemoglobin levels of the SF-36 subscales in the standard-dose and the high-dose treatment groups at random assignment and the three years thereafter.



between the treatment groups. Figure 1C illustrates the change in mental health scores over time for the two treatment groups.

Figure 1C. Mean mental health scores of the SF-36 subscales in the standard-dose and the high-dose treatment groups at random assignment and the three years thereafter (higher mental health scores represent better mental health).



Muscle and joint pain

The percentages of patients with muscle pain and joint pain in both treatment groups are presented in Table 1. There were no statistically significant differences between the standard and high-dose groups. The percentage of patients with muscle pain in the standard-dose group remained stable over time while in the high-dose chemotherapy group this percentage increases over time. The percentage of patients suffering from joint pain increases in time in both treatment groups ($P = .001$).

Menopausal status

Sixty percent (103 patients in the standard-dose and 154 in the high-dose groups) of the patients were premenopausal at random assignment and were postmenopausal after 3 years. Sixteen percent (33 patients in the standard-dose and 35 patients in the high-dose groups) were postmenopausal at random assignment and only 34 patients (30 patients in the standard-dose and four patients in the high-dose groups; 8%) were still premenopausal at 3 years after random assignment. The other patients had an uncertain menopausal status (36 patients in the standard-dose and 35 patients in the high-dose groups). Fewer patients in the standard-dose chemotherapy group than in the high-dose chemotherapy group were premenopausal at random assignment and postmenopausal 3 years after random assignment ($P < .001$).

Factors predicting fatigue

Hemoglobin

There was no statistical difference in the mean Hb levels of patients with fatigue or without fatigue at any of the time points (Table 2). Table 2 also shows the number of anemic patients with or without fatigue. More patients with fatigue had anemia compared to patients without fatigue both at randomization ($P = .025$) and 3 years later ($P = .016$). Anemia was frequently encountered in the patients with fatigue (18% to 29% at the four different time points); however, among the patients without fatigue, anemia was also often observed (8% to 27%). Three to 8% of all patients (at the different time points) had both fatigue and anemia. Spearman analysis of the relationship between fatigue and Hb levels did not reveal significant correlations at any of the four time points ($r_{t0} = 0.005$, $r_{t1} = 0.035$, $r_{t2} = 0.039$, $r_{t3} = 0.07$ all $P > .05$).

Mental health

The mean mental health scores of patients with fatigue were always lower compared to the patients without fatigue at all time points (Table 2). Spearman analysis showed significant correlations between fatigue and mental health

Table 2. Mean Hb levels, percentage anemia, mental health scores, muscle and joint pain in patients with and without fatigue

	No. of Patients	Mean Hb g/dL		Patients with anemia			Mean mental health score		Patients with muscle pain			Patients with joint pain		
			P	No.	%	P		P	No.	%	P	No.	%	P
Random assignment			.163			0.25		<.001			.002			<.001
Fatigue	72	12.8		21	29		47		21	29		9	13	
No fatigue	340	13.0		60	18		74		49	14		6	2	
1 year			.09			.515		<.001			<.001			.003
Fatigue	79	12.4		24	30		58		41	52		16	20	
No fatigue	307	12.7		82	27		82		39	13		26	8	
2 years			.696			.984		<.001			<.001			<.001
Fatigue	67	13.0		12	18		63		39	54		26	36	
No fatigue	292	12.9		52	18		84		53	17		34	11	
3 years			.137			.016		<.001			<.001			<.001
Fatigue	56	13.0		11	20		61		38	51		30	40	
No fatigue	204	13.2		17	8		83		57	20		43	15	

Abbreviation: Hb, hemoglobin.

scores at all four measurement times (r_{t0} = 0.69, r_{t1} = 0.66, r_{t2} = 0.693, r_{t3} = 0.686 all $P = < .001$).

Muscle and joint pain

Table 2 shows that patients with fatigue had significantly more muscle pain compared with the patients without fatigue at all four time points.

Menopausal status

Patients with fatigue did not differ from patients without fatigue on menopausal status (data not shown).

Multivariate analyses

Table 3 presents the results of the multiple logistic regression of treatment and factors on higher vitality score (no fatigue). No effect of treatment arm was seen on fatigue at any of the four time points. A significant relation between Hb levels and fatigue was only seen at random assignment. At all four time points the strongest predictor of fatigue was the mental health score. The relation between muscle pain and fatigue was significant at 1 and 2 years after random assignment. No effect of menopausal status on fatigue was observed (Table 3). The results of the linear regression were consistent with the results of the logistic regression as presented in Table 3. On this analysis, about 30% to 35% of the variance in high vitality score (no fatigue) could be explained by the combination of Hb, mental health score, muscle pain, joint pain, treatment group, and menopausal status.

LME analyses

The LME analyses showed that the higher the level of Hb ($P = .0006$) and mental health scores ($P < .0001$), the less fatigue. The presence of joint pain ($P < .0001$) and muscle pain ($P = .0283$) was associated with more fatigue. Treatment group and menopausal status were not associated with fatigue. There were no differences between treatment groups over the years.

Because only two of the patients did not receive tamoxifen, the effect of tamoxifen on fatigue could not be studied.

Fifty-three patients did not receive radiotherapy. There was no difference in fatigue between the patients who did and did not receive radiotherapy.

All analyses were also performed without the 14 patients randomly assigned to the high-dose arm, who did not receive this treatment. Excluding these patients, however, did not affect any outcome of this study (data not shown).

Table 3. Multiple logistical regression of effect of hemoglobin, mental health score, muscle pain, joint pain, treatment group, and menopausal status on high vitality score (no fatigue)

Variable	Odds Ratio	95% CI	P	Variance explained (%)
Random assignment				33
Hemoglobin	3.5	1.7 to 7.1	.001	
Mental health	12.4	6.5 to 23.4	<.001	
Muscle pain	0.9	0.4 to 1.8	.669	
Joint pain	0.3	0.08 to 1.0	.059	
Treatment group	1.2	0.6 to 2.2	.509	
Menopausal status	1.0	0.7 to 1.4	.923	
1 year				35
Hemoglobin	1.1	0.5 to 2.2	.789	
Mental health	15.7	6.3 to 38.6	<.001	
Muscle pain	0.1	0.07 to 0.2	<.001	
Joint pain	1.4	0.5 to 3.6	.478	
Treatment group	1.0	0.5 to 1.9	.942	
Menopausal status	1.0	0.7 to 1.4	.973	
2 years				31
Hemoglobin	0.9	0.7 to 2	.724	
Mental health	13.7	5.3 to 35.4	<.001	
Muscle pain	0.3	0.1 to 0.6	<.001	
Joint pain	0.5	0.2 to 1.2	.135	
Treatment group	0.8	0.4 to 1.4	.404	
Menopausal status	1.23	0.8 to 1.8	.278	
3 years				30
Hemoglobin	2.0	0.7 to 5.5	.176	
Mental health	1.0	4.8 to 24.7	<.001	
Muscle pain	0.4	0.2 to 1.0	.062	
Joint pain	0.5	0.2 to 1.3	.172	
Treatment group	1.0	0.5 to- 2	.927	
Menopausal status	1.0	0.7 to 1.5	.871	

NOTE: Hb ≤ 12 g/dL versus > 12 g/dL, mental health score ≤ 56 versus > 56, muscle pain yes or no, joint pain yes or no, treatment group high-dose versus standard-dose, menopausal status. Mental health-a high score is associated with less fatigue; muscle pain-a low score is associated with less fatigue.

DISCUSSION

This prospective longitudinal study evaluates fatigue, using the vitality scores of the SF-36, in patients treated for high-risk breast cancer and who were disease-free till at least 3 years after random assignment. The patients received either standard-dose or high-dose chemotherapy followed by stem cell reinfusion. The relationships between fatigue and Hb levels, mental health scores, muscle/joint pain, and menopausal status are described.

Fatigue occurred in 20% of the patients. Fatigue did not change over time in either group, and no differences between the treatment groups were found. Only 5% of all patients experienced both fatigue and anemia. The strongest predictor for fatigue was poor mental health. The presence of joint pain and muscle pain were associated with fatigue. Menopausal status was not associated with experiencing fatigue.

Compared to other studies, this 3-year follow-up period for fatigue is long and the use of a prospective design is unique. Moreover, these studies usually consisted of heterogeneous samples of cancer survivors with regard to tumor stage or previous treatment.[22] Most other studies in disease-free breast cancer patients after adjuvant therapy observe a somewhat higher percentage of patients with fatigue: 30% as compared with the 20% found here. Different from our study, these studies, however, are cross-sectional. Lindley et al[23] reported fatigue in 31% of 86 breast cancer patients who survived for 2 to 5 years following adjuvant chemotherapy and/or tamoxifen. Broekel et al[7] compared fatigue in 61 breast cancer patients more than 1 year after adjuvant chemotherapy, with women without a history of cancer. Patients reported more severe fatigue and worse quality of life due to fatigue. Bower et al[6] studied fatigue measured with the RAND 36-item health survey, which is almost identical to the SF-36, in a large sample of disease-free breast cancer patients (n = 1,957). Most patients did not experience prominent or disabling fatigue. However, approximately one-third indicated that they felt tired and lacked energy. Energy levels were relatively low at 1 year after diagnosis, increased at 2 years after diagnosis, and remained relatively stable for 3, 4, and 5 years after diagnosis. These findings could not be confirmed here. There are, however, some differences between the study presented here and Bower's study, which may explain these differences, namely, a longitudinal versus Bower's cross-sectional design and two randomized versus diverse types of treatments. Furthermore, the mean age of the patients in this study is 45 years compared with 55 years in Bower's study. All patients in this study had a disease-free

follow up of 3 years compared to 1 to 5 years post-therapy (mean, 3 years; SD, 1 year) in Bower's study. Bower et al[6] used a slightly higher cutoff level of 50 for fatigue. If this cutoff point is used in the present study, the percentage of patients reporting fatigue will rise accordingly. However, this does not alter the results of the comparisons and correlations. Interestingly, in our study, only 3% of the patients reported fatigue (vitality score ≤ 46) at all four time points.

Interpreting the results of the above studies remains difficult because fatigue is commonly reported by both patients and healthy individuals.[24] Prevalence rates of fatigue in healthy individuals range from 7 to 46%.[23] Almost any disease, physical or mental, can be accompanied by fatigue.[25] In the context of breast cancer, investigators have proposed that fatigue may be caused by the disease itself, the treatment of the disease, physical symptoms or conditions resulting from the disease or its treatment, and/or psychological responses to the disease.[6]

In this study, no difference in fatigue was observed between the standard-dose and high-dose chemotherapy groups. This is in contradiction with the expectations. In a recent study of breast cancer patients Brandberg et al[26] reported no differences in fatigue between the tailored chemotherapy and the high-dose adjuvant chemotherapy group 1 year after treatment. However, the tailored arm in the Brandberg study actually received more chemotherapy than the high-dose arm. Other data directly comparing fatigue in high-dose and real standard-dose chemotherapy for breast cancer are not yet available.

Anemia is a possible explanation for fatigue. This is of special interest because erythropoietin has become available as a supportive treatment option. Turner et al[27-30] reviewed several studies examining the effect of erythropoietin on Hb and quality of life in patients with various tumor types during, and several weeks after, chemotherapy. Erythropoietin administration unequivocally increased the Hb values, decreased the necessity for blood transfusions, and improved quality of life.[15] In these studies, no statements were made about the long-term effect of erythropoietin on Hb levels and fatigue. We used multiple regression analysis to study the association of Hb values on four different time points and found Hb to be significantly associated with fatigue only at random assignment, and not at any of the other time points. The fact that Hb is only a predictor at random assignment is most likely because the breast operation before random assignment is often accompanied by significant blood loss. The present study also evaluated the association of Hb and fatigue, taking all time points into account, using LME analysis. In this analysis, the Hb level was found to be a significant predictor of fatigue. This is probably because the LME analysis was performed on all measurements combined over all different time points, which may lead to smaller confidence intervals associated with the effect estimates.

Additionally, in the LME analysis, fatigue was analyzed as a continuous variable, and thus, as a dichotomous variable fatigue versus no fatigue as in the logistic regression analysis. Both these factors might explain the supposedly contradictory results of both types of analysis. In the present study, only 5% of all patients experienced both fatigue and anemia during the 3 years follow-up.

Sixteen percent of the patients in the present study experienced poor mental health at 3 years after therapy. Although we are aware of the fact that depression is not identical to poor mental health, a comparison was made between evidence of depression after breast cancer found in the literature and the data from the current study. In a recent review studying the relation between breast cancer (treatment) and depression, prevalence rates for depression between 10% and 32% are mentioned.[31] However, in a cross-sectional study by Ganz et al[32] in 864 disease-free breast cancer patients, 3.1 years after diagnosis, the frequency of depression was similar to general population samples. The differences in these percentages may be partly because of the lack of uniform criteria and diagnostic tools. In the present study, the strongest predictor for fatigue was poor mental health. Servaes et al[4] reviewed several studies in which strong correlations between fatigue and depression were observed. Possible explanations for the positive association between fatigue and depression are because the cancer, as well as its treatment, can induce fatigue leading to depression, or that fatigue develops as a consequence of depression.[7,33] Joint pain was observed in 20% of the patients and muscle pain in 27% of the patients at 3 years. Ganz et al[34] observed percentages of joint pain between 33% and 55% of the patients and muscle stiffness between 38% and 55% of the patients in different age groups in 577 breast cancer survivors, aged 50 years or younger at diagnosis, at a mean follow-up of 6 years. In their study, the majority of the women were premenopausal at diagnosis. There were substantial shifts in menstrual status at an average of 6 years later: the majority of the patients who were ≥ 40 years old at diagnosis were postmenopausal at the time of the survey. In the study presented here, 19% of the patients with a known menopausal status were postmenopausal at diagnosis and 92% were postmenopausal at 3 years. This might be an explanation for the high percentage of pain in both studies. These differences in percentage between the study of Ganz and the study here might be explained by the prospective design here versus the Ganz's cross-sectional design. In addition, their population was slightly younger and included any rate of bother (the study here included quite a bit and very much).

This study found, like others did previously, that fatigue was associated with pain.[22,24] In a number of studies, patients consistently identify pain as provoking

increased feelings of fatigue and, conversely, that relief of pain alleviates fatigue.

After the start of this quality of life study, more refined instruments have been developed to assess fatigue in cancer patients. As is the case in many other studies, this study design did not have an age-matched control group of healthy women without a cancer history.[22] Fortunately, normal values of the SF-36 in Dutch women are available to put the results in perspective.[18] The mean vitality scores in both groups at all four time points were at most 2 points lower than the normal value, which is 66 for Dutch women (Table 1). This small difference has no clinical relevance.

In conclusion, the present study shows that long-term fatigue occurs in 20% of the women adjuvantly treated for breast cancer. Fatigue scores did not differ between the two treatment groups nor from norm population scores and did not change over time. Anemia plays a small causative role in fatigue, but less than expected. The strongest relationship was found between fatigue and poor mental health.

Many of the processes underlying long-term fatigue in this group of cancer patients are still unknown. Development of effective clinical strategies to manage fatigue continues to be a challenge for future research.

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