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ORIGINAL ARTICLE

Cognitive behavioral therapy or graded exercise therapy compared with usual care for severe fatigue in patients with advanced cancer during treatment: a randomized controlled trial

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Background: Cancer-related fatigue remains a prevalent and burdensome symptom experienced by patients with advanced cancer. Our aim was to assess the effects of cognitive behavioral therapy (CBT) or graded exercise therapy (GET) on fatigue in patients with advanced cancer during treatment with palliative intent.

Patients and methods: A randomized controlled trial was conducted from 1 January 2013 to 1 September 2017. Adult patients with locally advanced or metastatic cancer who reported severe fatigue during treatment [Checklist Individual Strength, subscale fatigue severity (CIS-fatigue) $\geq$35] were accrued across nine centers in The Netherlands. Patients were randomly assigned to either 12 weeks of CBT or GET, or usual care (1 : 1: 1, computer-generated sequence). Primary outcome was CIS-fatigue at 14 weeks. Secondary outcomes included fatigue measured with the European Organisation for Research and Treatment of Cancer-Quality of Life Questionnaire (EORTC-QLQ-C30), quality of life, emotional functioning, physical functioning, and functional impairments at baseline, 14, 18, and 26 weeks.

Results: Among 134 participants randomized, the mean age was 63 (standard deviation 9) years and 77 (57%) were women. Common diagnoses included: breast (41%), colorectal (28%), and prostate cancer (17%). A total of 126 participants completed assessment at 14 weeks. Compared with usual care, CBT significantly reduced fatigue [difference −7.2, 97.5% confidence interval (CI) −12.7 to −1.7; $P = 0.003$, $d = 0.7$], whereas GET did not (−4.7, 97.5% CI −10.2 to 0.9; $P = 0.057$, $d = 0.4$). CBT significantly reduced EORTC-QLQ-C30 fatigue (−13.1, 95% CI −22.1 to −4.0; $P = 0.005$) and improved quality of life (10.2, 95% CI 2.4 to 17.9; $P = 0.011$) and physical functioning (7.1, 95% CI 0.5 to 13.7; $P = 0.036$) compared with usual care. Improvement in emotional functioning and decrease in functional impairments failed to reach significance. GET did not improve secondary outcomes compared with usual care.

Conclusions: Among advanced cancer patients with severe fatigue during treatment, a CBT intervention was more effective than usual care for reducing fatigue. Following GET, patients reported lower fatigue, but results were not significant, probably due to a smaller sample size and lower adherence than anticipated.

Trial Registration: Netherlands National Trial Register, identifier: NTR3812.

Key words: cognitive therapy, exercise therapy, fatigue, neoplasms, quality of life

INTRODUCTION

Patients with advanced cancer frequently suffer from cancer-related fatigue (CRF), a symptom experienced in 70%—90% of patients.[1] CRF negatively impacts patients' quality of life (QoL) and functional status.[1,2] Evidence-based interventions for fatigue during and after primary cancer treatment include both exercise and psychological interventions.[3,4] To date, however, few investigators have tested the efficacy of these interventions in patients with advanced cancer during treatment, which might differ because of ongoing treatment and active disease.

One of the promising interventions for CRF is cognitive behavioral therapy (CBT). According to the cognitive-behavioral model for CRF in early-stage cancer, the presence

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of a malignancy and cancer treatments serve as initial triggers, while cognitive and behavioral factors (e.g. disrupted physical activity patterns), contribute to the persistence of CRF.[5] These factors are also associated with CRF in patients with advanced cancer.[6] A CBT intervention, which targets cognitive-behavioral factors, reduced CRF in disease-free survivors and patients receiving adjuvant treatment.[7–9] Nevertheless, trials examining the efficacy of CBT for fatigue among patients with advanced cancer during treatment are lacking.

Graded exercise therapy (GET) for CRF is based on the deconditioning model, i.e. low physical activity during cancer treatment leads to deconditioning and loss of muscle mass, which can cause and maintain CRF.[10] Reviews provide evidence for reduced fatigue and improved physical capacity and QoL in patients receiving GET during and after adjuvant treatment.[11,12] Due to similar mechanisms of deconditioning during treatment of advanced cancer, GET may also reduce CRF in these patients. A 6-week uncontrolled pilot study of GET, tailored to the physical fitness of participants, showed improvements in CRF and QoL in advanced cancer patients.[13] Based on the limited number of exercise studies during treatment of advanced cancer, with inconsistent findings, we identified the need for a trial examining the efficacy of GET among this population.

Here we report the results of a randomized controlled trial of CBT and GET among severely fatigued patients with advanced cancer. Secondary aims included assessing the effects of both interventions at 14 weeks on overall QoL, physical functioning, emotional functioning, and functional impairments, as well as exploring follow-up effects for all outcomes at 18 and 26 weeks.

METHODS

Study design

In this multicenter, non-blinded, three-arm randomized, controlled trial, we recruited severely fatigued patients with locally advanced or metastatic cancer receiving treatment with palliative intent (further referred to as patients with 'advanced cancer') from nine hospitals in The Netherlands. The trial protocol was approved by the ethical review board of the Radboud University Medical Center (CMO Arnhem-Nijmegen, #2012/240) and has been published.[14] All participants provided written informed consent.

Population

We initially aimed to enroll patients with breast or colorectal cancer before starting their first-line treatment with palliative intent, but expanded the eligibility criteria after trial commencement due to slow recruitment. Eligible patients were receiving systemic treatment with palliative intent for breast, colorectal, prostate, or other cancers (i.e. melanoma, sarcoma, renal cell, bladder, cervix/endometrial, or ovarian cancer). Treatments included chemotherapy, targeted therapy, immunotherapy, and hormone therapy, which could be combined with surgery and/or radiation. Participants were $\geq$18 years old, proficient in Dutch, reported severe fatigue [Checklist Individual Strength, fatigue severity subscale (CIS-fatigue) score $\geq$35] with no known somatic explanation other than cancer and its treatment, and had a life expectancy of $\geq$6 months according to their oncologist. We excluded patients with symptomatic brain metastases, poor performance status (Karnofsky $<$70), a contraindication for exercise, or those currently receiving treatment of a mental disorder.

Setting and recruitment

From 1 January 2013 to 1 September 2017, oncologists and nurses at nine departments of medical oncology screened patients with advanced cancer for severe fatigue by administering a paper version of the CIS-fatigue and provided study information to eligible patients. We only included patients with severe fatigue, to target those patients most in need. A researcher (HP) called patients who agreed to be contacted and provided further information. Patients who consented were scheduled for a study visit at their hospital. At this visit, research assistants obtained informed consent, administered baseline assessments, including a question about patient's a priori randomization preference, and randomized participants. We scheduled the first intervention session 2 weeks after randomization.

Interventions and procedures

CBT. Patients assigned to CBT received a maximum of 10 individual 1-hour sessions over a period of 12 weeks at their hospital. CBT aimed to reduce severe fatigue and fatigue-related disability (i.e. activities or areas of functioning affected by the patient's fatigue) and included several modules addressing different fatigue-perpetuating cognitions and behaviors (see supplementary Figure S1 and supplementary material S2, available at *Annals of Oncology* online). To determine the perpetuating factors that apply to an individual, patients completed additional questionnaires and an intake interview.

GET. GET consisted of a 12-week supervised exercise program at their hospital or local physical therapy clinic. We offered weekly 2-hour sessions of individually graded aerobic and resistance training and a second weekly session to repeat the training (further details in supplementary material S2, available at *Annals of Oncology* online). In the first session, physical therapists assessed patients' physical fitness and discussed physical limitations.

Usual care. All patients were treated for advanced cancer in accordance with national guidelines by the Netherlands Comprehensive Cancer Organisation.[15] While patients assigned to usual care had no access to the study interventions, providers could refer them to a physical therapist or psychologist.

Data collection and outcome measures

Primary outcome. Our primary outcome was 14-week fatigue severity using the eight-item CIS-fatigue severity subscale (CIS-fatigue). CIS-fatigue items are rated on a 7-point scale with scores ranging from 8 to 56, and a diagnostic cut-off $\geq$35

indicating severe fatigue.[16] We assessed fatigue severity with the CIS-fatigue at screening, baseline, 14, 18, and 26 weeks.

Secondary outcomes. Secondary outcomes were assessed at all time points and included: emotional functioning, physical functioning, and fatigue, measured with the European Organisation for Research and Treatment of Cancer-Quality of Life Questionnaire-Core 30 (EORTC-QLQ-C30).[17] We assessed the level of fatigue-related disability with the Sickness Impact Profile (SIP8).[18] Further details on the measures are included in supplementary material S3, available at *Annals of Oncology* online. We assessed adverse events during the trial by patients' self-report at 14 weeks. Investigators recorded serious adverse events during the study.

Randomization and blinding

We randomized participants to CBT, GET, or usual care (1 : 1 : 1) using a central web-based randomization program (block size of nine, stratified by study site, and minimized for sex), which was concealed until after group assignment.[19] Although it was infeasible to mask patients, interventionists, or the research assistants administering the study assessments, the independent researcher who analyzed the data (PN) was blinded to treatment allocation.

Sample size

We needed 51 patients per group to detect a clinically meaningful difference of six points on the CIS-fatigue between one of both interventions and usual care,[20] with 80% power and a two-sided alpha of 0.025 to correct for two comparisons. Assuming an attrition rate of 30%, we aimed to enroll 219 patients.

Statistical analysis

Statistical analyses were carried out using SPSS Statistics, version 22.0 (SPSS, Armonk, NY; IBM Corp.). Analyses were done by intention-to-treat. No interim analyses were carried out. Main analyses were conducted on available participants using one-way between-group analysis of covariance (ANCOVA) with group allocation as a fixed factor and scores at screening (CIS-fatigue) or baseline (EORTC-QLQ-C30 or SIP8) as covariates. Cohen's *d* effect sizes were calculated for all outcomes.[21] We used evidence-based guidelines to interpret the clinical relevance of improvements on EORTC-QLQ-C30 subscales (i.e. trivial, small, or medium).[22]

Post hoc analysis was carried out to assess whether participants in the intervention groups reported a clinically significant improvement in CIS-fatigue more frequently compared with usual care. We defined clinically significant improvement as a CIS-fatigue score <35[16] and a statistically reliable change.[23] Differences in the proportion of participants with clinically significant improvements were analyzed with chi-square tests and graphically displayed using the Leeds Reliable Change Index calculator.[24]

We conducted three sensitivity analyses to test the robustness of our results. First, we replaced missing values with multiple imputation. The imputation model included all baseline sociodemographic and clinical characteristics, and primary and secondary outcomes assessed at baseline and 14 weeks. We imputed a total of five datasets and pooled according to Rubin's rules.[25] Second, we used linear mixed models to investigate the follow-up effects of CBT and GET on all outcomes with treatment group and time included as fixed effects and the screening (CIS-fatigue) or baseline (EORTC-QLQ-C30 or SIP8) scores included as covariates. This was a deviation from the trial protocol in which we proposed ANCOVAs for follow-up effects.[14] Third, because screening data might bear the risk of overestimation of effects,[26] we reanalyzed our data using baseline CIS-fatigue scores.

We considered a two-sided P value <0.025 statistically significant in the main analysis of the primary outcome. In all other analyses, two-sided P values <0.05 were considered statistically significant.

RESULTS

Study participants

Of 232 severely fatigued patients contacted, 134 (58%) enrolled and were randomized (Figure 1). Table 1 shows patient characteristics at baseline; mean age was 63 years, 57% were female. Most patients preferred being randomized to GET at baseline (70%). Among the 134 patients, eight (6%) had missing data for the primary outcome at 14 weeks. Patients with missing data had lower CIS-fatigue screening scores compared with those with complete data (-4.7, $P = 0.045$) but did not differ significantly on other characteristics. The study reached 82% of its anticipated sample size (126/153) when the funding period ended. Two patients were erroneously included (CIS-fatigue <35). We did not exclude them from further study participation or main analysis, but excluded them in sensitivity analyses.

Intervention compliance and adherence

Eight of 42 patients (19%) assigned to GET completed ≤ 1 GET session and five (12%) withdrew from GET. One of 46 patients (2%) assigned to CBT completed ≤ 1 CBT session and seven (15%) withdrew from CBT. CBT patients received an average of 7.14 sessions [standard deviation (SD) 2.6], compared with 8.0 supervised sessions (SD 3.5) for GET patients. Only 10 patients (24%) repeated at least one GET session in the same week. Treatment integrity, the degree to which an intervention was implemented as intended, was high for both CBT (90%) and GET (86%). Supplementary material S4, available at *Annals of Oncology* online, provides details on treatment integrity check and safety outcomes. Among patients with usual care, 36% received care from either a physical therapist ($n = 7$) or psychologist ($n = 8$) and 12% consulted another health care provider ($n = 5$) between baseline and 14 weeks. However, none of the usual care patients received care from a study interventionist.

Primary outcome

One-way ANCOVA for CIS-fatigue showed a statistically significant difference between groups ($P = 0.012$, Table 2).

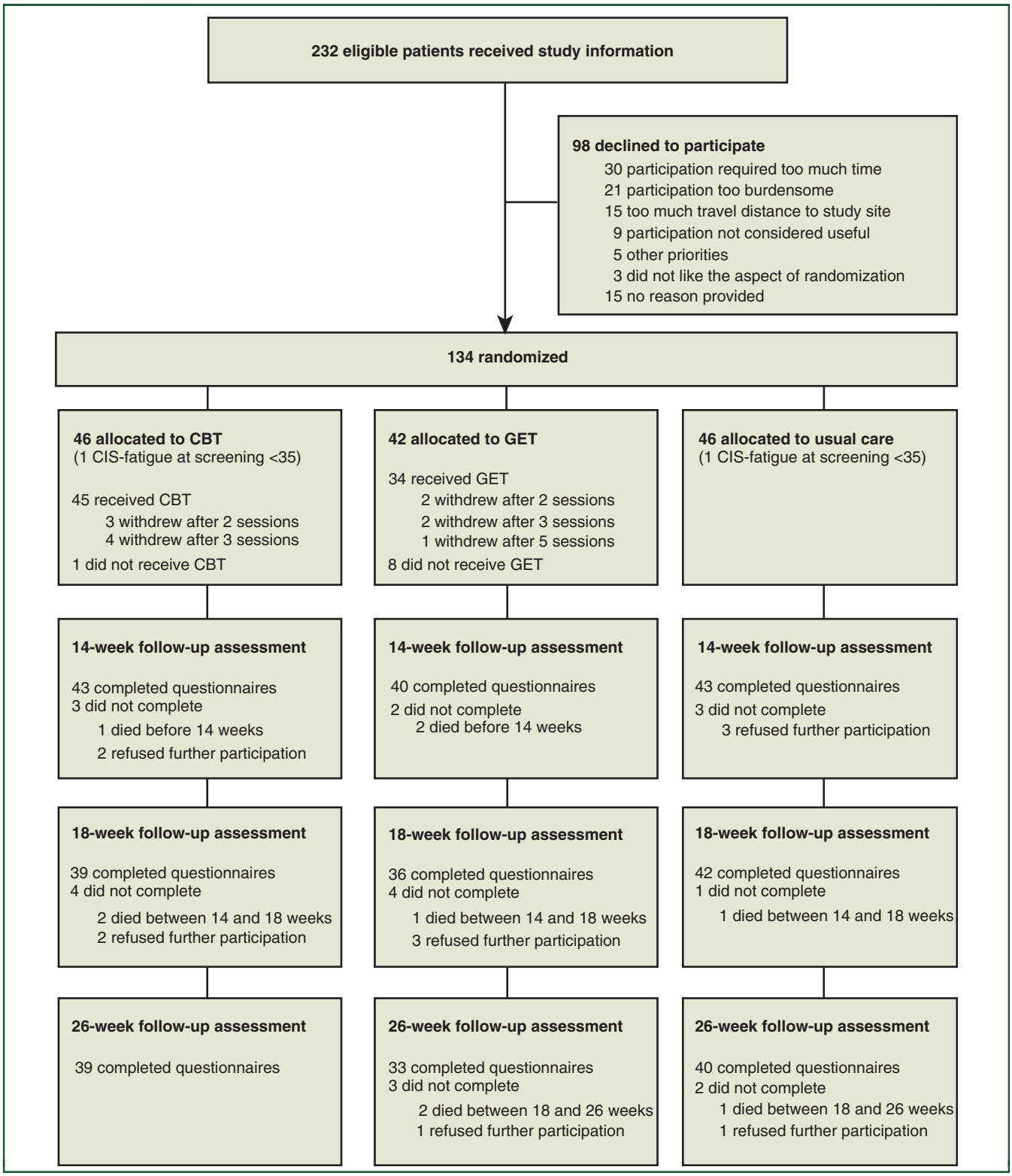

Figure 1. Trial profile.
CBT, cognitive behavioral therapy; CIS, checklist individual strength; GET, graded exercise therapy.

CBT significantly reduced fatigue at 14 weeks compared with usual care [−7.2, 97.5% confidence interval (CI) −12.7 to −1.7; $P = 0.003$, $d = 0.7$]. The difference between GET and usual care was not statistically significant (−4.7, 97.5% CI −10.2 to 0.9; $P = 0.057$, $d = 0.4$).

Secondary outcomes

We found significant exploratory differences for EORTC-QLQ-C30 fatigue, QoL, and physical functioning, but not for emotional functioning or SIP8 functional impairments. Patients in the CBT group reported significantly lower

Table 1. Baseline characteristics ($N = 134$)

Characteristic	CBT *n* (%)	GET *n* (%)	Usual care *n* (%)	Total *n* (%)
Patients	46	42	46	134
Sex				
Male	19 (41)	17 (40)	21 (46)	57 (43)
Female	27 (59)	25 (60)	25 (54)	77 (57)
Age, years				
Mean (SD)	63.50 (8.15)	60.67 (10.75)	63.93 (8.98)	62.76 (9.35)
Range	48–81	34–80	48–85	34–85
Partner status				
Partner	41 (89)	34 (81)	36 (78)	111 (83)
No partner	4 (9)	7 (17)	7 (15)	18 (13)
Missing	1 (2)	1 (2)	3 (7)	5 (4)
Education				
Low (ISCED 0–1)	13 (28)	10 (24)	12 (26)	35 (26)
Medium (ISCED 2–5)	21 (46)	16 (38)	21 (46)	58 (43)
High (ISCED 6–8)	12 (26)	16 (38)	13 (28)	41 (31)
Employment				
Paid job	14 (30)	15 (36)	12 (26)	41 (31)
Unable to work because of health reasons	11 (24)	9 (21)	11 (24)	31 (23)
Retired	18 (39)	15 (36)	21 (46)	54 (40)
Other[a]	3 (7)	3 (7)	2 (4)	8 (6)
Diagnosis				
Breast cancer	19 (41)	18 (43)	17 (37)	54 (40)
Colorectal cancer	13 (28)	10 (24)	11 (24)	34 (25)
Prostate cancer	8 (17)	9 (21)	10 (22)	27 (20)
Renal cell cancer	2 (4)	1 (2)	3 (7)	6 (5)
Ovarian cancer	2 (4)	1 (2)	3 (7)	6 (5)
Bladder cancer	2 (4)	0 (0)	1 (2)	3 (2)
Melanoma	0 (0)	3 (7)	1 (2)	4 (3)
Current treatment type				
Chemotherapy	14 (30)	9 (21)	16 (35)	39 (29)
Hormone therapy	11 (24)	13 (31)	13 (28)	37 (28)
Targeted therapy	5 (11)	5 (12)	4 (9)	14 (10)
Chemo + targeted	12 (26)	7 (17)	8 (17)	27 (20)
Hormone + targeted	2 (4)	4 (10)	1 (2)	7 (5)
Immunotherapy	0 (0)	3 (7)	2 (4)	5 (4)
Drug holiday	1 (2)	0 (0)	0 (0)	1 (1)
Missing	1 (2)	1 (2)	2 (4)	4 (3)
Time since first cancer diagnosis, years				
Mean (SD)	5.31 (4.95)	6.17 (5.29)	5.83 (5.46)	5.76 (5.20)
Range	0–27	0–20	0–21	0–27
No. of comorbid conditions[b]				
0	33 (72)	29 (69)	29 (63)	91 (68)
1	9 (19.5)	11 (26)	12 (26)	32 (24)
2+	4 (8.5)	2 (5)	5 (11)	11 (8)
CIS-fatigue at screening				
Mean (SD)	43.96 (7.83)	45.74 (6.24)	47.07 (6.60)	45.58 (7.01)

Data presented as *N* (%).

CBT, cognitive behavioral therapy; CIS, checklist individual strength; GET, graded exercise therapy; ISCED, International Standard Classification of Education; SD, standard deviation.

[a] Including: self-employed ($n = 3$), homemaker ($n = 2$), decided not to work ($n = 2$), unpaid job ($n = 1$).

[b] Most frequent comorbidities: diabetes ($n = 17$), cardiovascular disease ($n = 11$), and chronic obstructive pulmonary disease ($n = 7$).

EORTC-QLQ-C30 fatigue (−13.1, 95% CI −22.1 to −4.0; $P = 0.005$, $d = 0.6$), better QoL (10.15, 95% CI 2.37 to 17.93; $P = 0.011$, $d = 0.4$), and better physical functioning (7.1, 95% CI 0.59 to 13.7; $P = 0.036$, $d = 0.2$) compared with usual care. These differences reflect medium-sized improvements.[22] GET did not significantly improve secondary outcomes. The proportion of patients demonstrating a clinically significant and reliable change in fatigue differed significantly between CBT and usual care (62% versus 31%; $\chi^2 = 8.089$; $P = 0.004$), but not between GET and usual care (43% versus 31%; $\chi^2 = 1.178$; $P = 0.278$; supplementary Figure S5, available at *Annals of Oncology* online).

Sensitivity analyses

First, using multiple imputations, we found similar results for CIS-fatigue, EORTC-QLQ-C30 fatigue, and QoL at 14 weeks. The analyses yielded different results for physical functioning, which was no longer significant ($P = 0.09$), and for emotional functioning, which was significantly better for CBT compared with usual care ($P = 0.043$). Second, using linear mixed models, positive effects of CBT on CIS-fatigue, EORTC-QLQ-C30 fatigue, QoL, and physical functioning at 14 weeks were sustained at follow-up assessments (supplementary Figure S6 and supplementary Table S7, available at *Annals of Oncology* online). In addition, these analyses showed that emotional functioning was significantly better for CBT

Table 2. Mean scores and differences (baseline adjusted) in fatigue severity, fatigue, quality of life, physical functioning, emotional functioning, and functional impairments at 14 weeks

Outcome measure	Usual care		CBT		GET		*P*	CBT versus usual care			GET versus usual care		
	n	Mean (97.5% CI)	*n*	Mean (97.5% CI)	*n*	Mean (97.5% CI)	Overall	Est. (97.5% CI)	*P*	ES	Est. (97.5% CI)	*P*	ES
Primary outcome CIS-fatigue	43	38.95 (35.58 to 42.32)	43	31.72 (28.36 to 35.09)	40	34.25 (30.79 to 37.71)	0.012	−7.23 (−12.73 to −1.72)	0.003	0.72	−4.70 (−10.24 to 0.85)	0.057	0.44
	n	**Mean (95% CI)**	***n***	**Mean (95% CI)**	***n***	**Mean (95% CI)**	**Overall**	**Est. (95% CI)**	***P***	**ES[a]**	**Est. (95% CI)**	***P***	**ES[a]**
Secondary outcomes													
EORTC-QLQ-C30 Fatigue	42	48.15 (41.69 to 54.60)	43	35.10 (28.72 to 41.48)	38	48.59 (41.79 to 55.39)	0.005	−13.05 (−22.12 to −3.97)	0.005	0.64	0.45 (−8.94 to 9.83)	0.925	0.02
EORTC-QLQ-C30 Quality of life	42	56.56 (51.05 to 62.07)	43	66.71 (61.25 to 72.18)	38	59.59 (53.79 to 65.38)	0.033	10.15 (2.37 to 17.93)	0.011	0.39	3.03 (−4.96 to 11.01)	0.455	0.15
EORTC-QLQ-C30 Physical functioning	42	67.05 (62.39 to 71.71)	43	74.14 (69.50 to 78.79)	38	64.98 (60.08 to 69.88)	0.021	7.09 (0.48 to 13.72)	0.036	0.15	−2.07 (−8.81 to 4.67)	0.544	0.11
EORTC-QLQ-C30 Emotional functioning	42	72.49 (67.69 to 77.28)	43	80.44 (75.68 to 85.21)	38	75.13 (70.07 to 80.19)	0.065	7.96 (1.19 to 14.73)	0.022	0.31	2.64 (−4.32 to 9.60)	0.454	0.18
SIP8 Functional impairments	42	840.23 (721.86 to 958.60)	43	680.48 (563.15 to 797.80)	37	740.94 (613.52 to 868.36)	0.163	−159.76 (−326.03 to 6.52)	0.060	0.27	−99.29 (−273.87 to 75.29)	0.262	0.46

Lower mean scores represent less fatigue and functional impairments. Higher mean scores represent a better quality of life or functioning.
$P < 0.025$ indicates significance for the primary outcome (CIS-fatigue) and $P < 0.05$ indicates significance for secondary outcomes.
CBT, cognitive behavioral therapy; CI, confidence interval; CIS, checklist individual strength; EORTC-QLQ-C30, European Organisation for Research and Treatment of Cancer-Quality of Life Questionnaire-Core 30; ES, effect size; Est., estimated mean difference; GET, graded exercise therapy; SIP8, sickness impact profile.
[a] Cohen's *d*: the difference between the group means divided by the pooled standard deviation; small = 0.2, medium = 0.5, large = 0.8.[26]

compared with usual care ($P = 0.041$). Third, we found similar results for our main analysis when using baseline CIS-fatigue scores. However, the proportion of patients demonstrating a clinically significant improvement in fatigue no longer differed significantly between CBT and usual care (43% versus 26%; $\chi^2 = 2.58$; $P = 0.11$).

DISCUSSION

CBT significantly reduced fatigue and improved QoL and physical functioning at 14 weeks among severely fatigued patients with advanced cancers receiving treatment with palliative intent. Moreover, positive effects of CBT were sustained for 3 months after the intervention. Despite a lower fatigue score at 14 weeks in participants assigned to GET, this difference did not reach statistical significance. GET also did not significantly affect secondary outcomes. Clinical practice guidelines recommend CBT and exercise interventions to reduce fatigue in adult survivors of cancer.[3] Our study is the first study, to our knowledge, to show that CBT has a positive effect on fatigue and QoL in patients with advanced cancers, and our findings extend evidence for CBT from previous trials in patients with early-stage cancers.[7–9]

Our study showed a non-significant reduction in fatigue for GET, although the effect size (0.44) was comparable to a pooled effect size (0.28) found during adjuvant treatment of breast cancer.[27] The findings from our study add to evidence from a systematic review that described inconsistent findings for exercise interventions in the advanced cancer setting.[28] We propose three possible explanations for why GET did not affect any outcomes in our trial. First, the smaller sample size reduced the power to detect a statistically significant difference. However, two recent randomized controlled trials, with larger samples of patients with advanced lung cancer, also found no evidence to support that exercise improves fatigue.[29,30] Second, it is possible that CBT targets more factors that are relevant for CRF compared with GET. Third, participants may not have received the minimum required therapeutic dose of GET and the intervention could have been too intense and demanding for our study population despite pilot testing.[13] In both study arms, patients either did not start or withdrew from the intervention. This proportion was almost twice as high in the GET group compared with CBT, despite an a priori preference for being randomized to GET in the entire sample.

This trial has limitations. We had a smaller sample size because fewer patients were eligible to be contacted than anticipated. Due to slow recruitment in the first year, we revised the inclusion criteria, which resulted in a more heterogeneous sample. In addition, the interventions were not masked. Furthermore, we do not have data on active treatment or response to cancer treatment at 14 weeks, which may also affect fatigue scores. Lastly, while in-person delivery of the intervention may limit the clinical relevance of this study, Internet-assisted delivery of a similar CBT intervention for fatigue yielded comparable results among disease-free cancer patients.[8]

Our trial also has several strengths. First, the interventions we tested are grounded in theory and align with recommendations to develop interventions that reduce suffering and maintain QoL during treatment of advanced cancer. Second, we included fatigue severity as a screening criterion and used a validated questionnaire for our primary outcome. Third, the percentage of missing values was low. Fourth, we included longer-term follow-up assessments.

Conclusion

Our study is the first to show that among advanced cancer patients receiving treatment with palliative intent, CBT reduced fatigue and improved QoL and physical functioning, with effects sustained for 3 months after the intervention. While the current study did not find significant effects of GET on fatigue, replication in a larger trial is warranted to further our understanding of the efficacy of GET among patients with advanced cancer. Our findings indicate that additional adaptations are needed to improve feasibility of a GET intervention for this seriously ill population. We recommend CBT as a supportive care approach for advanced cancer patients with severe CRF. This study also provides a solid foundation to design new trials using Internet-assisted delivery to increase access to a highly effective CBT intervention that addresses a major need in this understudied population.

ACKNOWLEDGEMENTS

We are grateful to the patients for their participation in this trial and to the nurses and oncologists of the Radboud University Medical Center, Nijmegen; VieCuri Medical Center, Venlo/Venray; Canisius-Wilhelmina Hospital, Nijmegen; Gelderse Vallei Hospital, Ede; Isala, Zwolle; Máxima Medical Center, Eindhoven/Veldhoven; Jeroen Bosch Hospital, Den Bosch; Maas Hospital Pantein, Boxmeer; and Academic Medical Center, Amsterdam (The Netherlands) for their efforts in recruiting patients for the trial. We acknowledge the contribution to this study made by the local coordinators at each site (HGG van Balen, PhD; HJA Samwel, PhD; DJ van Spronsen, MD, PhD; DM Somford, MD, PhD; H Vergunst, MD, PhD; M de Lugt, MSc; E Balk, MD; H Withaar, MSc; AH Honkoop, MD, PhD; F Hoogwegt, MSc; G Vreugdenhil, MD, PhD; L van Heertum, MSc; H Schut, MD; Y Kamm, MD, PhD; F van den Bekerom, MSc; and H van Laarhoven, MD, PhD). We thank the psychologists and physical therapists at each study site for providing the interventions, the psychological assistants at each study site for administering the measurements, research assistants L Vermeeren, MSc, J de Natris, MSc, L Waterman, and J Smeets, MSc, for their contribution to the overall data collection, and A Braamse, PhD, for independently carrying out the analyses. The authors thank AA Wright, MD, MPH for providing helpful feedback and comments on an earlier draft of this manuscript.

FUNDING

This work supported by a grant from the Dutch Cancer Society (KUN 2011-5259).

DISCLOSURE

The authors have declared no conflicts of interest.

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