Keywords: cancer-related fatigue; patient education; randomised control trial; health-related quality of life; non-pharmacologic interventions

Cancer-related fatigue management: evaluation of a patient education program with a large-scale randomised controlled trial, the PEPs fatigue study

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Background: To assess the efficacy of a patient educational program built according to guidelines that aims at reducing cancer-related fatigue (CRF).

Methods: Randomised controlled trial, multicentre, comparing a patient education program, vs the standard of care. Patients were adult cancer outpatients with any tumour site. The primary outcome was fatigue severity assessed with a visual analogical scale (VAS), between the day of randomisation and week 7. Secondary outcomes were fatigue assessed with other scales, health-related quality of life, anxiety and depression. The time to fatigue severity deterioration was assessed. Analyses were performed in a modified intent-to-treat way, that is, including all patients with at least one baseline and 1 week 7 score.

Results: A total of 212 patients were included. Fatigue severity assessment was made on 79 patients in the experimental group and 65 in the control group. Between randomisation and week 7, the fatigue (VAS) improved by 0.96 (2.85) points in the experimental group vs 1.63 (2.63) points in the control group ($P=0.15$). No differences with the secondary outcomes were highlighted between two groups. No other factors were found to be associated with fatigue severity deterioration.

Conclusions: Despite rigorous methodology, this study failed to highlight the program efficacy in fatigue reduction for cancer patients. Other assessment tools should be developed to measure the effect of the program on CRF and behaviour. The implementation of the program should also be explored in order to identify its mechanisms and longer-term impact.

Cancer-related fatigue (CRF) is defined by the National Comprehensive Cancer Centre Network as ‘a distressing, persistent, subjective sense of physical, emotional and/or cognitive tiredness,

or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning’ (Berger *et al*, 2015b). This symptom has been reported to be

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experienced by up to 80% of cancer patients (Hofman *et al*, 2007). Cancer-related fatigue occurs throughout the course of the disease: before diagnosis to beyond treatment completion. It has been reported that one-third of women surviving breast cancer, experience CRF up to 10 years after treatment completion (Bower *et al*, 2006). What's more, the intensity of the CRF is usually and more often than any other cancer-related symptoms, assessed as being severe (Hickok *et al*, 2005). Cancer-related fatigue has a marked impact on the patients, affecting their health-related quality of life and daily activity (Curt *et al*, 2000).

Cancer-related fatigue is considered as a complex symptom, with multidimensional and intricate aspects: the existence of physical, psychological and emotional disturbance has been proved (Curt *et al*, 2000). Numerous evidence-based interventions for the management of CRF have been recommended (Berger *et al*, 2015a,b), most of them being complex non-pharmacological interventions. In order to tackle all the dimensions of CRF, non-pharmacological interventions have been tested and assessed: physical activity and exercise are one of the most effective strategies for improving fatigue (Puetz and Herring, 2012). Yet the safety, the tolerability and the modalities of those mono-thematic strategies have still to be studied. Other non-pharmacological interventions have demonstrated effectiveness: cognitive behavioural therapy (Garland *et al*, 2014), mindfulness-based stress reduction (Berger *et al*, 2015a) and yoga (Bower *et al*, 2014): all recommended to treat CRF. A highly multi-levelled intervention—patient education—may be the most appropriate solution for dealing with all CRF dimensions. Indeed, patient education enables patients to manage their illness and aims at improving both their health and health-related quality of life, outside of the healthcare establishment. It is composed of multi-focused interventions (educational activities, role-playing, case studies, simulations, group sessions and meditation), commonly delivered using educational methods that help the patients to enact coping strategies. Patient education has demonstrated its effectiveness in other chronic diseases such as diabetes, asthma and HIV. In asthma, patient education has demonstrated a reduction in hospitalisations of emergency visits, an improvement of health-related quality of life and also a decrease of health-related expenditures (Gibson *et al*, 2002). To this date in oncology, patient education has been less studied. A dozen randomised controlled trials assessed the efficacy of patient education programs for CRF (Du *et al*, 2015). Only 2 out of 10 trials succeeded in demonstrating the usefulness of education programs in reducing CRF. The contents and the duration of all patient education programs were highly heterogeneous: most of them included patients with different types of tumour sites, but large differences were to be noted regarding the content of the intervention (information, relaxation, nutrition, multi-component or web-based); the duration and frequency of the program (one session to seven sessions) or the follow-up (2 weeks to 1 year). The two effective programs seemed to share long-term educational process, educational strategies such as beliefs expression, training, coping, skills and strategies development, experience exchange, and no web-based interventions. Yet, guidelines for the development of educational interventions exist (CPEN Guidelines draft_Oct7 2013.indd—CPENStandardsofPractice.Nov14.pdf), including standard procedures of construction, shape and content. In this project, we assumed that a patient educational program, developed according to guidelines, with the main objective of reducing CRF among all cancer patients would improve long-term symptoms in a population of all tumour site patients.

The principal objective of this study was to compare the efficacy of an educational program for CRF *vs* the usual care for experienced fatigue severity, among a population of cancer patients, receiving radiotherapy and/or chemotherapy. The secondary objective of this study was to assess the efficacy of the program on other patient-related outcomes: fatigue assessed with Functional

Assessment of Cancer Therapy-Fatigue and Revised-Piper Fatigue Scale; Health-Related Quality of Life; Anxiety and Depression. The last secondary objective was to identify independent predictive factors of fatigue severity.

MATERIALS AND METHODS

Study design. Patients education program fatigue (PEPs fatigue) is a controlled multicentre, randomised, open-labelled trial, with two parallel groups. Patients were randomly chosen and participated either in a patient education program called 'PEPs fatigue' or followed the usual care.

The study was approved by an institutional review board (Ethical Committee of Saint Etienne University Hospital, 14 March 2007). All participants provided informed, written consent on inclusion.

Participants. Participants were adult cancer outpatients from six comprehensive French cancer centres. Inclusion criteria were: any tumour site (oncology or lymphoma), a confirmed histological malignancy, having being treated with first-line chemotherapy (third or fourth chemotherapy session) and/or having undergone radiotherapy treatment (eligible until the end of the first week of treatment). Participants could have localised or metastatic disease. Patients had to rate fatigue severity on a visual analogical scale (VAS) equal to or above 2 (VAS graduated between 0: no fatigue and 10: the most imaginable fatigue) during the inclusion consultation and before randomisation. Fatigue severity above 2 represents a fatigue requiring clinical intervention (Jean-Pierre *et al*, 2007). Performance status had to be preserved (≤ 2 , ECOG criterion). Anaemia (haemoglobin $\leq 10 \text{ g dl}^{-1}$) was an exclusion criterion. When an eligible patient was identified by the physician during hospitalisation or an outpatient visit, the study was proposed to him/her. If the patient accepted to participate, he/she was included in the study. The physician then had to log into the internet platform of the study in order to be informed of the arm of randomisation for this patient.

Randomisation. Patients were randomly assigned in a 1:1 ratio via a computer-generated, centralised randomisation sequence, which was done with a block randomisation of four, to the educational program or usual care group. Randomisation was balanced through stratification according to the following hierarchy: the centre (six centres), the treatment (chemo *vs* radiotherapy), the initial fatigue severity score on the VAS (≤ 5 *vs* > 5); Chauvin *et al*, 2006). Randomisation per block of four was conducted in order to avoid imbalanced arms.

Interventions

Educational program PEPs fatigue. Patients in the intervention group received the standard information: a written document wherein CRF, as well as the different management propositions were explained.

Integrating one of the educational groups was proposed to the patients. The maximum time between inclusion and PEPs fatigue first session was set at 1 month. Each group was composed of a maximum of 10 patients, and was managed by two educators, who were trained educational nurses. Each centre had its local educational team. The PEPs fatigue educational program was composed of five 2-h sessions. The first four sessions had 1-week intervals, the last session occurred 2 weeks later. Thus, a complete program lasted 6 weeks. A detailed content of the program is reported in Table 1. The construction of the PEPs fatigue program followed the National Cancer Institute and the Cancer Patient Education Network guidelines (CPEN Guidelines draft_Oct7 2013.indd—CPENStandardsofPractice.Nov14.pdf):

Table 1. Content of the patient education program, PEPs fatigue (for example, see Supplementary Appendix Online)

Sessions	Specific educational objectives	Tools and process
Group session one	Disease and fatigue representations, beliefs and knowledge expression	Photo-expression: individual statement then collective interactions Silhouette: individual statement about the know-how-to-be: positive/ negative attitude
Group session two	Educational diagnosis and therapeutic contract:	Marguerite (daisy) tool: 'express yourself and identify what you do today to fight against fatigue' Individual contract of objectives
Group session three	Knowledge and resources acquisition	Regnier abacus: group certainties construction and validation
Group session four	Fatigue management skills acquisition	Cartography: coping strategies identification and sharing
Group session five	Assessment and skills reinforcement	Learning real-life situations: patients look for possible solutions and scenario sparked discussions New Marguerite (daisy) tool: 'express yourself and identify what you do today to fight against fatigue'

Abbreviation: PEPs fatigue = patients education program fatigue.

- A qualitative study was conducted to identify patients' representations as regards to their cancer and their CRF. Interviews were conducted by a socio-anthropologist and discourse contents were analysed (for more details, see Supplementary Appendix Online).
- Patients' representations were translated into educational needs.
- Educational objectives for each educational need were identified. A tailored program was developed around these objectives by a multidisciplinary team composed of educationalists, healthcare educators, sociologists and methodologists. The program construction was based on the theoretical framework called Health Belief Model (Becker, 1974). Each session was constructed around a theme covering several connected educational objectives (for more details, see Supplementary Appendix Online).
- A specific evaluation tool was chosen according to each specific objective.

All educational teams, from the six centres, received a 2-day intensive training session, in order to standardise the educational sessions, as well as to enhance educators' performance.

Control group. Patients in the control group received the standard information: a written document wherein CRF as well as different management propositions were explained. Patients, and their fatigue, were treated with the usual care of the centre.

At the end of the follow-up (7 weeks), control patients were given all the written material used in the PEPs fatigue program. Once the study was over, control patients were all offered participation in the program routine extension.

An attentional control group was not planned because there was no risk of imbalance in the interest expressed by patients for any of the two arms: patient education was not felt as a mandatory care during that period. The control arm being the usual care, patients felt confident to at least have the care they were used to having. A waiting list control arm enabled us to reach the objective of the study in a pragmatic way: does patient education improve patients' CRF management compared to what is usually done?

Outcomes measures

Primary outcome. All patients evaluated their fatigue severity level daily for 7 weeks on an analogic visual scale (rated from no fatigue to most imaginable fatigue, and transposable into numbers from 0 to 10; Glaus, 1993). The use of this single question allowed a rapid completion of fatigue, and accordingly decreased the risk of missing data, due to patients' lassitude. Visual analogical scale has been recognised to be valid, reliable, sensitive to change and recommended when investigators want to assess the overall value of healthcare interventions (Fitzpatrick *et al*, 1998). The Principal Judgement Criteria was the difference of the mean fatigue severity

between week 7 (the last day of week 7) and day 0 (fatigue assessed before randomisation). Patients' self-assessment allows for the elimination of the evaluation bias of the primary outcome.

Secondary outcome. Among secondary judgment criteria, longitudinal fatigue severity self-assessed by VAS (daily assessment during the 7 weeks) was analysed. A VAS fatigue severity measure was also planned between the 11th and 15th week after baseline, to estimate the treatment effect at medium-term (anytime, once during weeks 11–15). This study also measured fatigue experienced by patients with other specific self-report tools, assessing each of the different aspects of the fatigue: a unidimensional cancer-specific tool, the Functional Assessment of Cancer Therapy-Fatigue (FACT-F; Yellen *et al*, 1997), which focuses on the severity of this symptom. A multidimensional tool, the Revised-Piper Fatigue Scale (R-PFS; Piper *et al*, 1998), which explores four fatigue dimensions: behavioural/severity, affective meaning, sensory and cognitive/mood. The psychometric properties of the R-PFS have been validated in French for several tumour sites including breast, lung digestive and gynaecologic cancer (Gledhill *et al*, 2002). Health-related quality of life was also assessed, with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire cancer-specific questionnaire QLQ-C30 (Aaronson *et al*, 1993). This questionnaire allows to assess 15 dimensions of health-related quality of life: a global health status, five functional scales (physical, role, emotional, cognitive and social), eight symptoms (fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, and diarrhoea) and financial difficulties. Anxiety and depression were assessed with the Hospital Anxiety Depression Scale (Zigmond and Snaith, 1983). All of the secondary outcomes were measured in week 1 and 7 (once during week 1 and once during week 7). The evolution over time (W7–W1) of these outcomes was compared between groups.

Sociodemographic data were gathered in order to research predictive factors to fatigue severity. Moreover, other symptoms collected in the QLQ-C30 were statistically analysed in order to identify their association with fatigue severity. The fatigue severity, assessed daily, was gathered through the patient study diary. For all the other specific tools assessing fatigue, self-administered forms were given to the patients. All judgment criteria were self-assessed, thus avoiding a possible evaluation bias by an appraiser. Other variables such as sociodemographic data and disease-related data were collected by a researcher, who was blinded to the randomisation arm assignment.

Sample size. It was estimated that 75 patients per group had to be included in order to fulfil the following hypothesis: α level at 0.05, power of 85%, an expected difference of fatigue severity mean evolution assessed by VAS of 2 points between groups, with a s.d.

previously estimated at 3.0 (Chauvin *et al*, 2006). Anticipating a 5% dropout, 80 patients were included in each group.

Statistical analysis. Patient's sociodemographic and clinical characteristics at baseline were described for all patients and for each treatment group. The participation in the therapeutic sessions was described. Baseline characteristics of patients with all the daily measures, of those with at least one missing VAS measure and of those with none VAS measure, were compared to detect non-random missing data profiles. If at least half of the fatigue severity measures per week were filled, missing measures were generated by multiple imputations (Markov Chain Monte Carlo algorithm) taking into account potential confounding variables highlighted by the study of missing data profiles. We performed a modified intention-to-treat (mITT) analysis: only patients with at least a VAS score available at both baseline and week 7 were analysed for the primary outcome (difference of the mean fatigue severity between week 7 and day 0). This analysis on the primary outcome is the first mITT analysis (mITT1).

Courses of fatigue before and after intervention. The fatigue severity level was described at baseline and at the end of the daily assessment (7 weeks later) by mean (s.d.) and mean difference between the two measures. A comparison between groups was done with a paired *t*-test.

The mean difference between baseline and follow-up measure was calculated and compared between groups with a paired *t*-test (mITT1). A second modified intention-to-treat analysis was planned with patients having both the baseline and the medium-term VAS score available, which constituted the second mITT population (mITT2).

Additional questionnaires. QLQ-C30, FACT-F, HAD and Piper scores were described with mean (s.d.) and mean difference between the two assessments. Comparisons between groups were performed by paired *t*-tests.

Longitudinal analysis of fatigue severity level: time to fatigue severity level deterioration. The time to fatigue severity level deterioration (TTD) was defined as the time from baseline to a first deterioration of 1 point at least of the VAS measure of fatigue severity as compared to the baseline measure (Hamidou *et al*, 2011). Patients with the baseline fatigue severity measure and at least one follow-up measure were retained (mITT3). TTD curves were calculated using the Kaplan–Meier estimation and described using median and 95% confidence interval (CI). TTD were compared according to treatment group using the log-rank test and univariate hazard ratio (HR) with 95% CI from the univariate Cox regression model. Multivariate Cox regression was applied to identify independent factors associated with TTD.

All analyses were carried out using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA) and R software (version 3.2.2, R Foundation for Statistical Computing, Vienna, Austria, 2011).

For more details on analysis, see Online Supplementary Appendix.

RESULTS

Two hundred and twelve patients were included between May 2007 and November 2009 (Figure 1). A total of 106 were randomised in the experimental educational group and 106 in the control group. The enrolment exceeded the 160 scheduled patients because of the high level of dropout observed during inclusion period: in order to reach the 75 patients having completed at least one baseline and one week-7 observation, the 160 threshold was raised. The baseline characteristics of the 212 patients are summarised in Table 2. Patients were predominantly women (84.4%), with an average age

of 55.9 (s.d. 11.4). Consequently, 58.5% of the patients had breast cancer. Both groups were comparable for tested variables except for the performance status (PS): 6.6% patients had a PS = 2 in the control arm vs 16.6% in the experimental arm ($P = 0.049$). Eighty-three patients (78.9%) of the intervention group participated in the first therapeutic session, 73 (68.9%) at the second session, 79 (74.5%) at the third session, 73 (68.9%) at the fourth session and 66 (62.3%) at the last session. The program compliance rate was then ~79.5% (66 patients completed the program, while 83 initiated it).

Fatigue severity assessment missing data. Fatigue severity (AVS) was assessed for 212 patients at randomisation and for 144 patients at week-7. Ninety-three patients (43.9%) answered all the daily fatigue severity assessments and 36 patients (17.0%) did not answer any assessment. More missing data were observed for older patients ($P = 0.03$) and patients with metastatic evolution ($P = 0.02$). Missing data imputation was thus performed taking into account these variables. Fifty-six (52.3%) and 65 patients (61.3%) had at least half of the measures available per week in the control group and in the intervention group respectively.

Courses of fatigue severity before and after intervention. Fatigue severity level decreased of 1.63 points (s.d. = 2.6) and 0.96 point (s.d. = 2.85) in mean for the control group and intervention group, respectively, after 7 weeks of daily assessments. No statistical difference between groups was observed ($P = 0.15$; Table 3).

Sixty-two patients (58.5%) in the control group and 67 (63.2%) in the intervention group completed the medium-term fatigue severity measure with a median time between baseline and medium-term measures of 17.1 weeks (range 1.0–28.7) and 17.2 weeks (8.9–39.7), respectively. The mean difference between medium-term fatigue severity level and baseline fatigue severity level was -1.5 points (s.d. = 2.6) for the control group and -0.7 point (s.d. = 3.0) for the intervention group.

Additional questionnaires. Regarding additional questionnaires (FACT-F, Piper, HAD and QLQ-C30), no difference was observed in the two assessments. Insomnia mean score was 43.06 (s.d. = 33.30) in control group and 31.33 (s.d. = 31.81) in intervention group at the second assessments ($P = 0.03$). The mean difference between the two assessments of the two groups was not significant ($P = 0.09$; Table 3).

With the Piper Fatigue scale, fatigue tended to improve in the control group, for the majority of the dimensions, whereas it tended to get worse in the experimental group (all P without statistical significant difference), between the day of randomisation and week 7.

Health-related quality of life evolution did not differ for either group (Table 3, all dimensions $P = \text{NS}$). Yet a tendency of a greater improvement took shape in the control group between the day of randomisation and week 7. Anxiety improved in the experimental group and worsened in the control group (-0.41 (12.76) and 1.03 (13.83), respectively) but the difference was not significant ($P = 0.60$). Depression worsened in the experimental group (0.75 (11.82)) and improved in the control group (-1.65 (14.15)), but the difference was not significant either ($P = 0.38$).

Time to fatigue severity level deterioration. In the control group and in the intervention group, respectively, 59 and 67 patients presented a deterioration of fatigue severity level of 1 point at least, as compared to the baseline fatigue severity level (Figure 2), among the 81 and 92 patients retained. The median TTD was 33 days (31–41) in the control group and 35 days (27–40) in the intervention group ($P = 0.97$). The univariate Cox HR of intervention group vs control group was 0.99 (0.70–1.41). For other univariate analyses results, see Supplementary Online Appendix and Supplementary Table S1.

Figure 1. Study flow chart.

The Cox multivariate analysis (Table 4) underlined no other baseline characteristics associated with a fatigue severity deterioration.

DISCUSSION

This trial, conducted according to guidelines, in order to demonstrate the genuine impact of a patient education program, did not succeed in highlighting its efficacy on fatigue. The construction process of this program followed the National Cancer Institute guidelines for better efficacy (CPEN Guidelines draft_Oct7 2013.indd—CPENStandardsofPractice.Nov14.pdf). Yet no impact on the primary outcome, fatigue severity assessed with VAS, was underlined: the crude mean differences seemed to give a trend of a negative effect of the program, while the longitudinal analysis re-established an equivalent efficacy for both experimental and control arms. No impact of the program was highlighted on the secondary outcomes either. The results are all consistent in concluding that patients experienced no effect of the program on fatigue. This study also found no other significant factors associated with fatigue severity deterioration.

One positive conclusion can still be drawn. The program was associated with no adverse events. Indeed, the program could have developed a more accurate awareness among patients about their CRF symptoms, thus creating a distressing situation for them. But the anxiety and the depression levels assessed by the HAD scale allow us to conclude that no adverse effects of this kind have been highlighted.

The first major strength of this study is linked to its study design construction: with 212 patients included in this study, it is one of the largest studies assessing patient education for CRF improvement (Du *et al*, 2015). With very large selection criteria (all cancer types, all CRF levels experienced and all treatments) and with a multicentre implementation, this study ensures the reliability of these results. Although it also suggests generalisability of these results, it must be underlined that half of the participant population was suffering from breast cancer. The second strength is linked to the patient education program itself: a standardised,

tailored program, constructed according to guidelines, and based on a solid theoretical framework (Health Belief Model, specially adapted to health behaviour changes). Its implementation features are also valuable: the program is spread over a long period, with five sessions allowing a long, profitable and durable learning process. The collective sessions allow the joint creation of new knowledge, highly recommended by the constructivist approach, aiming finally at patient empowerment.

Yet, no efficacy of the patient education program was highlighted, and there are several possible explanations for this. First, the definition of the CRF is complex. It is possible that we failed to identify the element of CRF on which the program was effective. To support that assumption, several patients undergoing the patient education program reported that the CRF they experienced after the program was different from the one they came with at the beginning (in a positive way). New measurement tools should be developed to have a better and more precise understanding of the behavioural changes brought about by the program. A second explanation might be the highly probable presence of a contamination bias in this study: experimental and control patients were followed in the same centres, by the same healthcare providers. They could communicate between themselves and with professionals. The third explanation would be the occurrence of a differential 'response shift' for patients in the patient education program compared to those in the control group. This phenomenon occurs when the measurements used in the study are PRO for people with chronic disability or cancer (Sprangers *et al*, 1999). In this situation, the individual may change. His/her internal standards, values and/or conceptualisation of the health status assessed may also change over time. Response shift can mask the 'real' treatment impact on PRO's (Sprangers and Schwartz, 1999; Ring *et al*, 2005). Finally, this study took place in 2007, and it is possible that at that time, patients were more reluctant to the concept of patient education than is the case today.

The results of this study are not expected, but yet consistent with other previous trials: (Yates *et al*, 2005; Godino *et al*, 2006; Purcell *et al*, 2011; Kwekkeboom *et al*, 2012) who also found no difference in fatigue between patient education and control groups, with similar designs but fewer patients. Only Chan *et al* (2011) and

Table 2. Patients' characteristics for both arms

Variables	Control arm (N = 106), N (%)	Intervention arm (N = 106), N (%)	P-value
Gender			
Men	13 (12.3%)	20 (18.9%)	0.18
Women	93 (87.7%)	86 (81.1%)	
Age			
Mean (s.d.)	54.6 (11.7)	57.1 (10.9)	0.15
Marital status			
In couples	73 (68.9%)	80 (75.5%)	0.44
Alone	27 (25.5%)	23 (21.7%)	
NA	6 (5.7%)	3 (2.8%)	
Educational level			
Less than High school diploma	31 (29.2%)	40 (37.7%)	0.51
Over high school diploma	49 (46.2%)	48 (45.3%)	
Apprenticeship	16 (15.1%)	13 (12.3%)	
NA	10 (9.4%)	5 (4.7%)	
Current professional situation			
Still working	57 (53.8%)	53 (50%)	0.53
Retired	30 (28.3%)	39 (36.8%)	
Housewife	6 (5.7%)	7 (6.6%)	
Other	7 (6.5%)	4 (3.8%)	
NA	6 (5.7%)	3 (2.8%)	
Dependent children			
Yes	35 (33%)	40 (37.7%)	0.5
No	68 (64.2%)	64 (60.4%)	
NA	3 (2.8%)	2 (1.9%)	
Cancer site			
Breast	68 (64.2%)	56 (52.8%)	0.07
Lymphoma	6 (5.7%)	18 (17%)	
Colorectal	8 (7.5%)	6 (5.7%)	
Lung	3 (2.8%)	6 (5.7%)	
Ovarian	7 (6.6%)	2 (1.9%)	
Prostate	4 (3.8%)	3 (2.8%)	
Other	9 (8.5%)	14 (13.2%)	
NA	1 (0.9%)	1 (0.9%)	
Advanced cancer			
Yes	19 (17.9%)	22 (20.8%)	0.6
No	86 (81.1%)	83 (78.3%)	
NA	1 (0.9%)	1 (0.9%)	
Time between inclusion and the histological diagnosis (in months)			
Mean (s.d.)	0.92 (2.8)	0.97 (2.5)	0.7
Surgery			
Yes	76 (71.7%)	74 (69.8%)	0.45
No	26 (24.5%)	32 (30.2%)	
NA	4 (3.8%)	0 (0%)	
Endocrine therapy			
Yes	7 (6.6%)	3 (2.8%)	0.33
No	99 (93.4%)	101 (95.3%)	
NA	0 (0%)	2 (1.9%)	
Radiation			
Yes	8 (7.5%)	9 (8.5%)	0.77
No	98 (92.5%)	95 (89.6%)	
NA	0 (0%)	2 (1.9%)	
IV Chemotherapy			
Yes	96 (90.6%)	98 (92.5%)	0.62
no	10 (9.4%)	8 (7.5%)	
Performance status			
0	30 (28.3%)	32 (30.2%)	0.049
1	60 (56.6%)	46 (43.4%)	
2	7 (6.6%)	17 (16%)	
NA	9 (8.5%)	11 (10.4%)	
Haemoglobin (g dl ⁻¹)			
Mean (s.d.)	12.2 (1.1)	12.0 (1.2)	0.13
NA	12	3	
Cancer-related fatigue (VAS)			
Mean (s.d.)	5.0 (1.8)	5.0 (1.9)	0.8

Abbreviations: NA = not applicable; VAS = visual analogic scale.

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Table 3. Cancer-related fatigue assessed by visual analogic scale, FACT-F[®] and Piper fatigue scale, quality of life assessed by QLQ-C30 scale, and anxiety and assessed by the HAD scale at the day of randomisation (day 0), week 7 depression (mean, s.d.)

Questionnaire	Dimension	Time of assessment	Control group (N = 106)		Intervention group (N = 106)		t-test
			N	Mean (s.d.)	N	Mean (s.d.)	
VAS on fatigue severity		Day 0	105	5.02 (1.83)	104	4.99 (1.90)	0.97
		Week 7	66	3.56 (2.42)	80	4.12 (2.69)	0.18
		Week 7–day 0	65	– 1.63 (2.63)	79	– 0.96 (2.85)	0.15
FACT-F	Global score	Day 0	82	22.95 (10.88)	81	22.64 (11.73)	0.86
		Week 7	74	20.09 (11.34)	73	20.98 (10.40)	0.60
		Week 7–day 0	74	– 2.86 (9.96)	67	– 1.75 (9.98)	0.49
Piper Fatigue Scale	Behavioural/severity	Day 0	67	53.46 (25.65)	78	53.18 (25.09)	0.77
		Week 7	60	47.83 (26.71)	72	53.08 (24.70)	0.36
		Week 7–day 0	57	– 5.67 (21.36)	68	0.20 (19.88)	0.26
	Affecting meaning	Day 0	76	56.08 (24.82)	90	58.27 (20.31)	0.61
		Week 7	66	53.67 (26.75)	81	60.10 (22.86)	0.13
		Week 7–day 0	63	– 0.92 (26.77)	79	1.95 (23.09)	0.70
	Sensory	Day 0	79	51.75 (24.05)	92	51.63 (22.43)	0.89
		Week 7	72	46.44 (22.77)	84	52.71 (21.17)	0.11
		Week 7–day 0	69	– 3.28 (22.89)	83	0.39 (23.37)	0.28
	Cognitive/mood	Day 0	79	41.65 (20.24)	90	39.87 (19.64)	0.81
		Week 7	70	39.86 (20.93)	83	42.73 (21.44)	0.32
		Week 7–day 0	67	– 1.19 (19.59)	80	2.00 (16.93)	0.38
HAD	Anxiety	Day 0	80	33.27 (20.91)	92	33.59 (18.25)	0.98
		Week 7	72	33.00 (19.95)	83	33.68 (20.55)	0.77
		Week 7–day 0	70	– 0.41 (12.76)	83	1.03 (13.83)	0.60
	Depression	Day 0	78	31.38 (19.71)	91	33.07 (19.51)	0.71
		Week 7	73	31.38 (19.95)	82	30.60 (17.37)	0.87
		Week 7–day 0	70	0.75 (11.82)	81	– 1.65 (14.15)	0.38
QLQ-C30	Global health status	Day 0	82	48.88 (18.65)	92	48.10 (20.45)	0.79
		Week 7	72	54.86 (20.35)	85	50.20 (18.36)	0.13
		Week 7–day 0	72	6.37 (19.71)	84	1.19 (20.70)	0.11
	Physical functioning	Day 0	80	64.68 (19.33)	92	68.16 (17.97)	0.22
		Week 7	73	69.70 (19.46)	84	68.69 (16.94)	0.73
		Week 7–day 0	72	4.45 (15.65)	83	– 0.05 (15.40)	0.07
	Role functioning	Day 0	77	50.87 (29.36)	90	48.52 (31.86)	0.62
		Week 7	73	57.77 (29.93)	82	55.69 (26.22)	0.64
		Week 7–day 0	68	7.84 (30.27)	80	6.25 (28.48)	0.74
	Emotional functioning	Day 0	82	67.14 (24.74)	91	69.20 (23.75)	0.58
		Week 7	73	70.81 (22.61)	83	71.12 (24.76)	0.94
		Week 7–day 0	73	4.07 (23.40)	81	0.99 (21.47)	0.40
	Social functioning	Day 0	81	58.64 (28.52)	91	58.24 (29.96)	0.93
		Week 7	71	64.08 (29.77)	83	61.04 (31.37)	0.54
		Week 7–day 0	71	5.40 (24.68)	81	2.88 (18.22)	0.53
	Cognitive functioning	Day 0	81	70.37 (26.48)	90	69.44 (24.64)	0.81
		Week 7	73	74.20 (23.74)	83	72.49 (23.92)	0.66
		Week 7–day 0	72	3.70 (24.90)	81	2.88 (18.22)	0.82
	Fatigue	Day 0	80	54.24 (24.75)	93	56.63 (25.85)	0.54
		Week 7	74	50.52 (27.99)	82	50.47 (22.11)	0.98
		Week 7–day 0	72	– 4.48 (26.92)	82	– 5.62 (25.13)	0.78
	Pain	Day 0	78	32.05 (29.15)	85	30.98 (31.09)	0.82
		Week 7	69	32.85 (28.29)	82	32.72 (30.70)	0.98
		Week 7–day 0	65	– 0.51 (27.32)	75	– 0.67 (30.32)	0.98
	Nausea and vomiting	Day 0	80	16.88 (18.28)	93	14.87 (21.20)	0.51
		Week 7	73	11.87 (21.42)	84	8.93 (14.04)	0.32

Table 3. (Continued)							
Questionnaire	Dimension	Time of assessment	Control group (N = 106)		Intervention group (N = 106)		t-test
			N	Mean (s.d.)	N	Mean (s.d.)	
		Week 7–day 0	71	– 6.10 (23.10)	84	– 6.15 (21.14)	0.99
	Dyspnoea	Day 0	79	31.65 (31.98)	92	37.32 (30.40)	0.24
		Week 7	73	31.50 (30.88)	80	34.58 (29.26)	0.53
		Week 7–day 0	70	0.48 (30.82)	79	– 1.27 (29.90)	0.73
	Insomnia	Day 0	79	37.55 (31.74)	92	37.32 (30.40)	0.99
		Week 7	72	43.06 (33.30)	83	31.33 (31.81)	0.03
		Week 7–day 0	69	3.38 (37.11)	83	– 6.02 (30.42)	0.09
	Appetite loss	Day 0	80	23.75 (29.62)	93	26.52 (30.91)	0.55
		Week 7	73	21.00 (25.76)	83	19.68 (23.30)	0.74
		Week 7–day 0	71	– 2.82 (32.73)	83	– 6.83 (26.42)	0.40
	Constipation	Day 0	81	28.40 (31.67)	91	25.27 (30.77)	0.52
		Week 7	72	24.07 (27.53)	84	18.25 (24.49)	0.17
		Week 7–day 0	71	– 5.16 (28.53)	82	– 6.91 (26.05)	0.40
	Diarrhoea	Day 0	78	18.80 (31.14)	92	14.49 (24.36)	0.33
		Week 7	71	14.56 (24.39)	83	12.05 (23.03)	0.51
		Week 7–day 0	68	– 3.43 (32.14)	82	– 2.85 (23.54)	0.98
	Financial difficulties	Day 0	81	16.05 (27.44)	91	15.75 (26.45)	0.94
		Week 7	71	12.21 (22.71)	84	14.29 (28.94)	0.62
		Week 7–day 0	71	– 1.88 (17.72)	82	– 0.81 (15.69)	0.69
Abbreviations: FACT-F = Functional Assessment of Cancer Therapy-Fatigue; HAD = Hospital Anxiety Depression scale; VAS = visual analogical scale. Comparison of the difference of mean between week seven and week one according to study group.

Figure 2. Kaplan–Meier survival curve of the time to fatigue severity score deterioration of 1 point at least as compared to the baseline according to treatment arm.

Reif *et al* (2013) found a statistically positive and large effect of the patient education program. In the study by Reif *et al* (2013), the control group was composed of patients from a waiting list: the participants' expectations of the impact of the intervention in this control group might have been the origin of a bias in favour of the educational intervention. What is more surprising is that for the studies that failed to demonstrate the efficacy of the patient education program, the number of educational sessions was low (three sessions for Godino *et al*, one session for Kwekkeboom). On the contrary, the number of sessions was high (six sessions for Reif *et al*, 2013) for programs that did demonstrate efficacy.

We could have assumed that this five-session, 6-week program, with its long-term approach, would have led more easily to efficacy.

This study has some limitations: the first one is due to the patients' attrition bias. Little is known about patients who refused to carry out the study, and especially about those who refused to start the patient education program. Unfortunately, few data were available for those patients. The second limit lies in the contents of the intervention: no physical exercise, relaxation training or telephone follow-up are offered to patients. These components of non-pharmacological interventions are supposed to be beneficial for CRF reduction, as identified in the literature (Du *et al*, 2015). Yet they are not defined as patient education elements *per se*, and it is not mandatory to introduce them into a patient education program (CPEN Guidelines draft_Oct7 2013.indd—CPENStandardsofPractice.Nov14.pdf). Our program followed all the elements that are essential for ensuring a patient education program of quality and that allow good feasibility. Introducing elements other than patient education (physical activity and meditation) could have enhanced the efficacy of the intervention, but could also have required unacceptable supplementary human and financial resources. This larger dissemination possibility is a major issue in terms of politics and is as important as efficacy in an experimental context. The third limit is that all types of cancer or cancer stages have been included in this program. Resulting heterogeneity may have decreased the likelihood of demonstrating an effect of the education intervention. Yet there are no guidelines in patient education for restricting the targeted population to a standardised group: diversity is considered to allow a stronger and wider learning process. Among the other programs constructed to improve CRF and reported in a Cochrane review, 9 on 14 were dedicated to a broad cancer population (Bennett *et al*, 2016).

The fourth limit is that despite a large sample size, and the adjustment of the results on several variables, it is possible that some confounding factors remain unexplored in this study, factors

Table 4. Multivariate Cox analysis of the time to deterioration of the fatigue severity level

Variables	Modality	Hazard ratio (CI 95%)	P-value	N (events)
Treatment group	Standard support group	1		146 (103)
	Intervention group	0.82 (0.54–1.26)	0.37	
Dependent children	No	1		
	Yes	0.58 (0.34–1.01)	0.052	
Educational level	Less than high school diploma	1		
	Over high school diploma	1.50 (0.94–2.37)	0.09	
	Apprenticeship	1.56 (0.69–3.56)	0.3	
Advanced cancer	No	1		
	Yes	0.60 (0.31–1.19)	0.14	
Performance status	0	1		
	1	0.73 (0.45–1.19)	0.20	
	2	0.71 (0.34–1.49)	0.36	
Age*		0.99 (0.96–1.02)	0.53	
Delay between diagnosis and date of inclusion (into quintiles)				
	<76 days	1		
	<103 days	1.94 (0.98–3.82)	0.06	
	<132 days	1.58 (0.82–3.02)	0.17	
	<215 days	1.04 (0.53–2.06)	0.9	
	≥215 days	1.67 (0.80–3.49)	0.18	

Abbreviations: * = for 1 year more; CI = confidence interval.

that may have explained the absence of difference observed. Another limit lies in the outcomes collected to assess the effectiveness of the patient education program: Fatigue severity—a one dimension scale—may not have been as sensitive as a Global Fatigue questionnaire could have been. The R-PFS, being constructed for breast cancer, may have limited generalisability to other cancer types: this would imply potential measurement error for non-breast cancer patients in this study. Fatigue severity and health-related quality of life cannot depict the whole impact of the intervention on behaviour changes: this study probably failed to adequately measure the effect of the program on actions and psychosocial skills. However, some adequate tools to assess those changes were unavailable. This limit illustrates how urgent it is for patient education research to obtain specific outcome measurement tools. Another limit is the impossibility of including and starting the program for all the patients immediately after the diagnosis: patients in the program experienced the different timing of treatments (first treatment for some, end of the treatments for others). This difference of timing may have acted as an unmeasured confounder. However, our study was pragmatically organised so as to be representative of the real-life patient education program process. Finally, the timescale used in this study to assess the efficacy of the program was perhaps not adapted to the time of action of the program. One week following the completion of the program is obviously too short a period to observe behavioural changes. What's more with a 2-year long study the program in itself probably did not benefit from a long enough period to fulfil its implementation. This short period could have jeopardised the adaptation—the way the different local educational teams modified or customised the program to fit their setting of the program to the local context, and by that could have jeopardised its sustainability in all centres: adaptations and adjustments were still being explored and more time seemed to be needed in order to achieve a completely tailored and sustainable program for patients.

CONCLUSION

Cancer-related fatigue is a complex, multi-faceted, subjective syndrome. Although this study followed rigorous methodology in the construction of the program as well as in its assessment, it failed to highlight the program efficacy in CRF reduction for

cancer patients. Other interventions should be assessed, with more multi-focused, yet feasible components. Other assessment tools should be developed to measure the precise effect of the educational intervention on the CRF and on behaviour. The implementation of the program and its adaptation should also be a matter of exploration, with the right temporality.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

FC, DP and VTL conceived the project. AA, CM and CR collected all the data. AA, FT, MO, Aba, SP and FB did the statistical analyses. ABo wrote the first draft and revised drafts of the manuscript. AA, CM, FT, MO, VTL, ABa, SP, CR, FB, DP and FC critically revised the manuscript for important intellectual content. The final version of the manuscript was approved by all the authors. ABou and AA had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. ABou is the guarantor for the study.

REFERENCES

- Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, Filiberti A, Flechtner H, Fleishman SB, de Haes JC (1993) The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* **85**: 365–376.

- Becker MH (1974) The health belief model and sick role behavior. *Health Educ Behav* **2**: 409–419.
- Bennett S, Pigott A, Beller EM, Haines T, Meredith P, Delaney C (2016) Educational interventions for the management of cancer related fatigue in adults. *Cochrane Database Syst Rev* **11**: CD008144.
- Berger AM, Mitchell SA, Jacobsen PB, Pirl WF (2015a) Screening, evaluation, and management of cancer-related fatigue: Ready for implementation to practice? *CA Cancer J Clin* **65**: 190–211.
- Berger AM, Mooney K, Alvarez-Perez A, Breitbart WS, Carpenter KM, Cella D, Cleeland C, Dotan E, Eisenberger MA, Escalante CP, Jacobsen PB, Jankowski C, LeBlanc T, Ligibel JA, Loggers ET, Mandrell B, Murphy BA, Palesh O, Pirl WF, Plaxe SC, Riba MB, Rugo HS, Salvador C, Wagner LI, Wagner-Johnston ND, Zachariah FJ, Bergman MA, Smith C (2015b) Cancer-related fatigue, version 2.2015. *J Natl Compr Canc Netw* **13**: 1012–1039.
- Bower JE, Ganz PA, Desmond KA, Bernards C, Rowland JH, Meyerowitz BE, Belin TR (2006) Fatigue in long-term breast carcinoma survivors: a longitudinal investigation. *Cancer* **106**: 751–758.
- Bower JE, Greendale G, Crosswell AD, Garett D, Sternlieb B, Ganz PA, Irwin MR, Olmstead R, Arevalo J, Cole SW (2014) Yoga reduces inflammatory signaling in fatigued breast cancer survivors: a randomized controlled trial. *Psychoneuroendocrinology* **43**: 20–29.
- Chan CWH, Richardson A, Richardson J (2011) Managing symptoms in patients with advanced lung cancer during radiotherapy: results of a psychoeducational randomized controlled trial. *J Pain Symptom Manage* **41**: 347–357.
- Chauvin F, Péro D, Régnier V, Toutenu P, Lefranc A, Dudzinski G, Merrouche Y, Chvetzoff G (2006) Développement et implémentation de programmes d'éducation thérapeutique en oncologie. L'exemple de la douleur et la fatigue. Premières Journées Scientifiques du Cancéropôle Lyon-Auvergne-Rhône-Alpes, Clermont-Ferrand 16–17 mars 2006—poster.
- CPEN Guidelines draft_Oct7 2013.indd—CPENStandardsofPractice.Nov14.pdf. Available at <http://www.cancerpatienteducation.org/docs/CPEN/Educator%20Resources/CPENStandardsofPractice.Nov14.pdf> (accessed on 02 May 2016).
- Curt GA, Breitbart W, Cella D, Groopman JE, Horning SJ, Itri LM, Johnson DH, Miaskowski C, Scherr SL, Portenoy RK, Vogelzang NJ (2000) Impact of cancer-related fatigue on the lives of patients: new findings from the Fatigue Coalition. *Oncologist* **5**: 353–360.
- Du S, Hu L, Dong J, Xu G, Jin S, Zhang H, Yin H (2015) Patient education programs for cancer-related fatigue: a systematic review. *Patient Educ Couns* **98**: 1308–1319.
- Fitzpatrick R, Davey C, Buxton MJ, Jones DR (1998) Evaluating patient-based outcome measures for use in clinical trials. *Health Technol Assess* **2**(14): i-iv, 1–74.
- Garland SN, Johnson JA, Savard J, Gehrman P, Perlis M, Carlson L, Campbell T (2014) Sleeping well with cancer: a systematic review of cognitive behavioral therapy for insomnia in cancer patients. *Neuropsychiatr Dis Treat* **10**: 1113–1124.
- Gibson PG, Powell H, Wilson A, Abramson MJ, Haywood P, Bauman A, Hensley MJ, Walters EH, Roberts JLL (2002) Self-management education and regular practitioner review for adults with asthma. *Cochrane Database Syst Rev* **3**.
- Glaus A (1993) Assessment of fatigue in cancer and non-cancer patients and in healthy individuals. *Support Care Cancer* **1**: 305–315.
- Gledhill JA, Rodary C, Mahé C, Laizet C (2002) [French validation of the revised Piper Fatigue Scale]. *Rech Soins Infirm* **68**: 50–65.
- Godino C, Jodar L, Durán A, Martínez I, Schiaffino A (2006) Nursing education as an intervention to decrease fatigue perception in oncology patients. *Eur J Oncol Nurs* **10**: 150–155.
- Hamidou Z, Dabakuyo TS, Mercier M, Fraisse J, Causeret S, Tixier H, Padeano M-M, Loustalot C, Cuisenier J, Sauzedde J-M, Smail M, Combiér J-P, Chevillote P, Rosbarger C, Arveux P, Bonnetain F (2011) Time to deterioration in quality of life score as a modality of longitudinal analysis in patients with breast cancer. *Oncologist* **16**: 1458–1468.
- Hickok JT, Morrow GR, Roscoe JA, Mustian K, Okunieff P (2005) Occurrence, severity, and longitudinal course of twelve common symptoms in 1129 consecutive patients during radiotherapy for cancer. *J Pain Symptom Manage* **30**: 433–442.
- Hofman M, Ryan JL, Figueroa-Moseley CD, Jean-Pierre P, Morrow GR (2007) Cancer-related fatigue: the scale of the problem. *Oncologist* **12**(Suppl 1): 4–10.
- Jean-Pierre P, Figueroa-Moseley CD, Kohli S, Fiscella K, Palesh OG, Morrow GR (2007) Assessment of cancer-related fatigue: implications for clinical diagnosis and treatment. *Oncologist* **12**(Suppl 1): 11–21.
- Kwekkeboom KL, Abbott-Anderson K, Cherwin C, Roiland R, Serlin RC, Ward SE (2012) Pilot randomized controlled trial of a patient-controlled cognitive-behavioral intervention for the pain, fatigue, and sleep disturbance symptom cluster in cancer. *J Pain Symptom Manage* **44**: 810–822.
- Piper BF, Dibble SL, Dodd MJ, Weiss MC, Slaughter RE, Paul SM (1998) The revised Piper Fatigue Scale: psychometric evaluation in women with breast cancer. *Oncol Nurs Forum* **25**: 677–684.
- Puetz TW, Herring MP (2012) Differential effects of exercise on cancer-related fatigue during and following treatment: a meta-analysis. *Am J Prev Med* **43**: e1–e24.
- Purcell A, Fleming J, Burmeister B, Bennett S, Haines T (2011) Is education an effective management strategy for reducing cancer-related fatigue? *Support Care Cancer* **19**: 1429–1439.
- Reif K, de Vries U, Petermann F, Görres S (2013) A patient education program is effective in reducing cancer-related fatigue: a multi-centre randomised two-group waiting-list controlled intervention trial. *Eur J Oncol Nurs* **17**: 204–213.
- Ring L, Höfer S, Heuston F, Harris D, O'Boyle CA (2005) Response shift masks the treatment impact on patient reported outcomes (PROs): the example of individual quality of life in edentulous patients. *Health Qual Life Outcomes* **3**: 55.
- Sprangers MA, Schwartz CE (1999) Integrating response shift into health-related quality of life research: a theoretical model. *Soc Sci Med* **48**: 1507–1515.
- Sprangers MA, Van Dam FS, Broersen J, Lodder L, Wever L, Visser MR, Oosterveld P, Smets EM (1999) Revealing response shift in longitudinal research on fatigue—the use of the thetest approach. *Acta Oncol* **38**: 709–718.
- Yates P, Aranda S, Hargraves M, Mirolo B, Clavarino A, McLachlan S, Skerman H (2005) Randomized controlled trial of an educational intervention for managing fatigue in women receiving adjuvant chemotherapy for early-stage breast cancer. *J Clin Oncol* **23**: 6027–6036.
- Yellen SB, Cella DF, Webster K, Blendowski C, Kaplan E (1997) Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) measurement system. *J Pain Symptom Manage* **13**: 63–74.
- Zigmond AS, Snaith RP (1983) The hospital anxiety and depression scale. *Acta Psychiatr Scand* **67**: 361–370.

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