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

A Bourmaud*,1,2,3, A Anota4,5, C Moncharmont1,6, F Tinquaut1,3, M Oriol1,3, V Trillet-Lenoir7, A Bajard8, S Parnalland4, C Rotonda4,9, F Bonnetain4,5, D Pérol8 and F Chauvin1,2,3

1Public Health Department, Hygiène Centre, Lucien Neuwirth Cancer Institute, Saint Priest en Jarez, France; 2Quality Safety Performance in Health (HESPER) EA7425, Lyon 1 University, Lyon, France; 3Inserm, Clinical Investigation Center 1408, Saint-Etienne 42055, France; 4French National Platform Quality of Life and Cancer, Besançon, France; 5Methodology and Quality of Life Unit in Cancer, INSERM UMR 1098, University Hospital of Besançon, Besançon, France; 6Radiotherapy Department, Lucien Neuwirth Cancer Institute, Saint Priest en Jarez, France; 7Medical Oncology Department, Lyon-Sud Lyon-Sud teaching hospital, Lyon, France; 8Direction of Clinical Research and of Innovation, Léon Bérard Cancer Center, Lyon, France and 9INSERM, CIC-EC CIE6, Nancy, France CHU Nancy, Clinical Epidemiology and Evaluation Department, Nancy, France

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...
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, self-care 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 analogue 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). Anemia (haemoglobin ≤10 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 when receiving 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):
Patients in the control group received the standard intensive training session, in order to standardise the educational content. It was estimated that 75 patients per group had to be included in order to fulfil the following hypothesis: \( z \) level at 0.05, power of 85%, an expected difference of fatigue severity mean 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).

### 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 of 6 (the last day of week 6) and day 0 (fatigue assessed before randomisation).

### 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.
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 (VAS) 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. = 16.41) in control group and 31.33 (s.d. = 15.63) in intervention group. No statistical difference between groups was observed (P = 0.15; 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 = 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.
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 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; Kwakkelboom 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 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.

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,
| 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 (6.5%)                    | 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%)                         |         |
| JIV 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)             |                             |                                  | 0.8     |
| Mean (s.d.)                              | 5.0 (1.8)                   | 5.0 (1.9)                        |         |

Abbreviations: NA = not applicable, VAS = visual analogic scale.
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 |
|--------------------------------------------|-------------------------------|--------------------|-------------------------|-----------------------------|--------|
| VAS on fatigue severity                    |                               | Day 0              | 105                     | 104                         | 0.97   |
|                                           |                               | Week 7             | 66                      | 80                          | 0.18   |
|                                           |                               | Week 7–day 0       | 65                      | 79                          | 0.15   |
| FACT-F                                     | Global score                  | Day 0              | 82                      | 2.29 (0.88)                 | 0.86   |
|                                           |                               | Week 7             | 74                      | 20.09 (11.34)               | 0.60   |
|                                           |                               | Week 7–day 0       | 74                      | 2.86 (9.96)                 | 0.49   |
| Piper Fatigue Scale                        | Behavioural/severity          | Day 0              | 67                      | 53.46 (25.65)               | 0.77   |
|                                           |                               | Week 7             | 60                      | 47.83 (26.71)               | 0.36   |
|                                           |                               | Week 7–day 0       | 57                      | 5.67 (21.36)                | 0.26   |
|                                           | Affecting meaning             | Day 0              | 76                      | 56.08 (24.82)               | 0.61   |
|                                           |                               | Week 7             | 66                      | 53.67 (26.75)               | 0.13   |
|                                           | Sensory                       | Day 0              | 79                      | 51.75 (24.05)               | 0.89   |
|                                           |                               | Week 7             | 72                      | 46.44 (22.77)               | 0.11   |
|                                           |                               | Week 7–day 0       | 69                      | 3.28 (22.89)                | 0.28   |
|                                           | Cognitive/mood                | Day 0              | 79                      | 41.65 (20.24)               | 0.81   |
|                                           |                               | Week 7             | 70                      | 39.86 (20.93)               | 0.32   |
|                                           |                               | Week 7–day 0       | 63                      | 0.92 (26.77)                | 0.70   |
|                                           | HAD Anxiety                   | Day 0              | 80                      | 33.27 (20.91)               | 0.98   |
|                                           |                               | Week 7             | 72                      | 33.00 (19.95)               | 0.77   |
|                                           |                               | Week 7–day 0       | 70                      | 0.41 (12.76)                | 0.60   |
|                                           | Depression                    | Day 0              | 78                      | 31.38 (19.71)               | 0.71   |
|                                           |                               | Week 7             | 73                      | 31.38 (19.95)               | 0.87   |
|                                           |                               | Week 7–day 0       | 70                      | 0.75 (11.82)                | 0.38   |
|                                           | Physical functioning          | Day 0              | 82                      | 48.88 (18.65)               | 0.79   |
|                                           |                               | Week 7             | 72                      | 54.86 (20.35)               | 0.13   |
|                                           |                               | Week 7–day 0       | 72                      | 6.37 (19.71)                | 0.11   |
|                                           | Role functioning              | Day 0              | 77                      | 50.87 (29.36)               | 0.62   |
|                                           |                               | Week 7             | 73                      | 57.77 (29.93)               | 0.64   |
|                                           |                               | Week 7–day 0       | 68                      | 7.84 (30.27)                | 0.74   |
|                                           | Emotional functioning         | Day 0              | 82                      | 67.14 (24.74)               | 0.58   |
|                                           |                               | Week 7             | 73                      | 70.81 (22.61)               | 0.94   |
|                                           |                               | Week 7–day 0       | 73                      | 4.07 (23.40)                | 0.40   |
|                                           | Social functioning            | Day 0              | 81                      | 56.64 (28.52)               | 0.93   |
|                                           |                               | Week 7             | 71                      | 64.08 (29.77)               | 0.54   |
|                                           |                               | Week 7–day 0       | 71                      | 5.40 (24.68)                | 0.53   |
|                                           | Cognitive functioning         | Day 0              | 81                      | 70.37 (26.48)               | 0.81   |
|                                           |                               | Week 7             | 73                      | 74.20 (23.74)               | 0.66   |
|                                           |                               | Week 7–day 0       | 72                      | 3.70 (24.90)                | 0.82   |
|                                           | Fatigue                       | Day 0              | 80                      | 54.24 (24.75)               | 0.54   |
|                                           |                               | Week 7             | 74                      | 50.52 (27.99)               | 0.98   |
|                                           |                               | Week 7–day 0       | 72                      | 4.48 (26.92)                | 0.78   |
|                                           | Pain                           | Day 0              | 78                      | 32.05 (29.15)               | 0.82   |
|                                           |                               | Week 7             | 69                      | 32.85 (28.29)               | 0.98   |
|                                           |                               | Week 7–day 0       | 65                      | 0.51 (27.32)                | 0.98   |
|                                           | Nausea and vomiting           | Day 0              | 80                      | 16.88 (18.28)               | 0.51   |
|                                           |                               | Week 7             | 73                      | 11.87 (21.42)               | 0.32   |
Intervention group (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 some confounding factors remain unexplored in this study, factors adjustment of the results on several variables, it is possible that heterogeneity may have decreased the likelihood of demonstrating an effect of the education intervention. Yet there are no guidelines published in patient education for restricting the targeted population to a cancer stage. Among the other programs constructed to improve CRF and reported in a Cochrane review, on 14 were dedicated to a broad cancer population (Bennett et al., 2016). 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 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...
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 implementation of the program and its adaptation should also be a matter of exploration, with the right temporality.

**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.

**ACKNOWLEDGEMENTS**

We thank Susan Guillaumond (Activeenglish) for translation and editing services. A grant obtained from the French Ministry of Health (PHRC 2006 [Hospital Program of Clinical Research]) covered the cost of the study. The sponsor had no role in the study design.

**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, Flechtmann 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, Breithart WS, Carpenter KM, Cella D, Cleeland C, Dotan E, Eisenberger MA, Escalante CF, 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 FI, 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, Bernaards C, Rowland JH, Meyerowitz BE, Gibson PG, Powell H, Wilson A, Abramson MJ, Haywood P, Bauman A, 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 TD (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 JI (2002) Self-management education and regular practitioner review for adults with asthma. *Cochrane Database Syst Rev* 3.

Glauser 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, Dabakyu TS, Mercier M, Fraisse J, Causeret S, Tixier H, Padeano M-M, Loustalot C, Saurez J, Sauzedde J-M, Smail M, Combier J-P, Chevillotte P, Rousburet 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, Rolland 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, Góeres 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, Høfer S, Heuson 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 thentest 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 the impact of cancer-related fatigue on the lives of patients: new findings from the Fatigue Coalition. *Oncologist* 2: 353–360.

Zigmond AS, Snaith RP (1983) The hospital anxiety and depression scale. *Acta Psychiatr Scand* 67: 361–370.

This work is published under the standard license to publish agreement. After 12 months the work will become freely available and the license terms will switch to a Creative Commons Attribution-NonCommercial-Share Alike 4.0 Unported License.

Supplementary Information accompanies this paper on British Journal of Cancer website (http://www.nature.com/bjc)