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ORIGINAL ARTICLE

The effects of adjuvant chemotherapy on cognition in women with breast cancer—preliminary results of an observational longitudinal study

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Summary Several studies have reported that chemotherapy-treated patients have impaired cognition function relative to control groups. We are conducting a longitudinal study with cognitive assessments at baseline, 6 and 18 months. A planned preliminary analysis of data from 50 chemotherapy patients and 43 healthy controls at baseline and post-treatment found a significant group by time interaction on three measures of verbal and working memory. Chemotherapy patients were more likely to show cognitive decline than controls (OR 2.25). Patients were significantly more likely to have GHQ_{12} scores indicative of possible psychological morbidity and showed significant increases in endocrine symptoms and fatigue post-treatment however neither GHQ_{12} nor quality-of-life variables were related to cognitive performance.

Introduction

The impact of chemotherapy on cognitive function has recently come under scrutiny due largely to anecdotal reports from patients. Their descriptions of ''fuzzy-headness'' or ''mental-slowness'' have become a recognised phenomenon dubbed chemo-brain/chemofog.[1] Such impairments affect patients' quality of life and may reduce their ability to make a smooth transition from treatment back to activities of normal everyday life such as returning to work. Concerns about the negative implications of chemotherapy have led to the scientific investigation of the chemofog phenomenon. There are a number of potential factors that may affect cognition during and after chemotherapy treatment. First, the treatment itself may have a direct neurotoxic effect. Second, many patients will experience a treatment induced menopause or will have recently stopped taking

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hormone replacement therapy causing great hormonal disruption which may have the capacity to affect cognition. Third, fatigue, anxiety, depression and changes in quality of life can all impact on cognitive function. In addition, patients will often be receiving a good deal of concomitant medication such as steroids and analgesics as well as the chemotherapeutic agents themselves.

All of the published studies on breast cancer and cognition have shown some degree of cognitive impairment in the chemotherapy groups when compared to suitable cancer control groups or population norms. The proportion of patients who demonstrate cognitive impairment varies dramatically from 16%[2] to 75%[3] depending on the study and on what comparison group is used. Most studies are cross sectional,[2–8] with only two employing a longitudinal design.[9,10]

The Wefel study [9] provides the first longitudinal data with a pre-treatment baseline. The study is limited by its extremely small sample size ($N = 18$), however as the first published study with pre-treatment data it is of great interest. Although there were no significant mean group differences in performance between baseline and follow-up, within subject analyses showed that 61% of patients showed decline between pre-treatment and short-term follow-up. One year after completion of chemotherapy, of the 11 patients who had shown decline at the short-term follow-up, 5 remained stable, 5 showed improvement and 1 showed a mixed pattern of results. Interpretation of this study is difficult. In addition to the small sample size, half of the sample went on to have further chemotherapy between the short- and long-term follow-up. However, the study does demonstrate a change in cognitive performance in line with the cross-sectional studies and suggests that for many patients this effect will be relatively short term.

In the Schagen study,[10] participants were recruited from two previous studies [7,8] and had received either high or standard dose chemotherapy or none. At the first time-point, 2 years post-chemotherapy, there was evidence of cognitive impairment in some chemotherapy patients. By the second assessment, 4 years post-chemotherapy, there were no longer significant differences between the groups, implying that the cognitive effects of chemotherapy are transitory.

An additional consideration for the interpretation of cross-sectional studies is that many breast cancer patients will receive endocrine therapy following chemotherapy. Research is currently unclear as to whether hormone therapy may cause or have an additive effect on cognitive impairment. Some studies suggest a negative effect[11–13] while others suggest that tamoxifen may exert a neuroprotective effect on the brain in the same way as HRT.[14] The potentially neuroprotective effects of HRT have themselves been challenged with the publication of the WHIMS study[15] however. Interpretation is further hampered by a lack of consistency regarding which assessment measures are used and not all studies have considered the potentially confounding factors of fatigue and changes in quality of life.

Neurophysiological studies also suggest that chemotherapy affects brain function reducing both neocortical grey matter and cortical and subcortical white matter evident many years after treatment with chemotherapy.[16,17] There is also reason to believe that different agents will result in differing levels of pathology. Central nervous system complications are usually reported after high-dose treatment however even low-dose systemic methotrexate has been associated with mild cognitive dysfunction.[7] Similarly 5-flourouracil is known to readily cross the blood brain barrier into cerebrospinal fluid and brain [18] and thus may have the potential to cause cognitive damage.

We are conducting a large-scale longitudinal study of cognitive function in women who have had surgery for early breast cancer. The study is ongoing however the preliminary results reported here will hopefully provide a valuable addition to the literature. Despite the current interest in chemotherapy side effects the evidence base remains small and lacks longitudinal studies with pre-chemotherapy baseline measures. We report the neuropsychological test scores of the first 50 patients to complete both a pre- and post-treatment assessment. Scores are compared with those of 43 healthy controls. On the basis of published cross-sectional studies we would expect significant cognitive impairment in the patient group at the post-chemotherapy assessment.

Method

Participants

Women with early breast cancer were recruited into the study prior to the start of adjuvant therapy. There are three participant groups in the main study; women scheduled to receive adjuvant chemotherapy ($N = 100$), others not having chemotherapy, who may have either radiotherapy or

endocrine therapy ($N = 53$), and finally a group of healthy controls ($N = 59$).

Cognitive assessments are made at baseline, 4 weeks after the final chemotherapy session (6 months in the control groups) and eighteen months. Data are presented here on the first 50 chemotherapy patients and 43 healthy controls that have completed baseline and post-chemotherapy/6 month assessment. All participants completed both assessments. Overall dropout rates from the main study are low. 6/100 chemotherapy patients, 2/59 healthy controls and 4/53 cancer controls have dropped out to date. Patients were recruited from four hospitals in the South East of England. The study has full local ethics committee approval and all participants gave full written consent.

Exclusion criteria included advanced disease, having any previous treatment for *any* cancer, receiving neo-adjuvant chemotherapy and patients with a previous history of stroke dementia, degenerative disease and alcohol or drug abuse.

The study was briefly introduced to the patient by the treating clinician and they received a letter of introduction and information sheet. The cognitive assessments were conducted at the woman's home at her convenience at each time-point. The control groups were a sample of convenience made up of friends and family of the patients and experimenters and from a local women's group.

As shown in Table 1, participant groups do not differ significantly on age, estimated IQ or years of education. Menopausal status and HRT use are also shown.

Thirty-nine of the chemotherapy patients received 6 cycles of FEC, 3 received 8 cycles of FEC, 1 received 6 cycles of CMF, 1 received 4 cycles of AC and 6 were part of the TACT trial receiving 4 cycles of FEC followed by four cycles of docetaxel or 8 cycles of FEC.

Assessments

The cognitive test battery assesses several broad areas of cognitive function as outlined in Fig. 1. All measures are standardised, validated and from published test batteries with population norms.

Participants completed the neuropsychological tests and two questionnaires relating to psychological morbidity and everyday cognitive problems. In addition, *patients only* completed questionnaires relating to quality of life. Cognitive tests were always administered in the same order following the requirements of the Wechsler Memory Scale-III[19] with assessments of estimated Full Scale Intelligence Quotient (FSIQ) and processing speed completed during the period prior to delayed recall. All participants were screened for dementia using the information and orientation subtest of the WMS III. The battery of standardised neuropsychological tests is briefly described below.

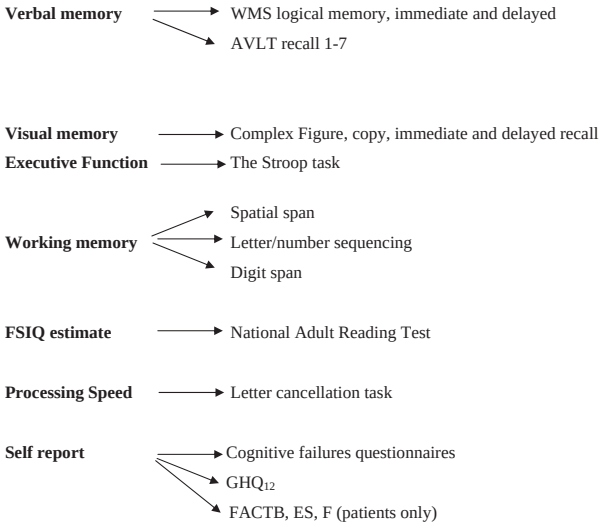

Figure 1 Cognitive test battery.

Table 1 Participant group differences in age (at baseline), IQ and years in education.

		Patient mean (S.D.) ($N = 50$)	Control mean (S.D.) ($N = 43$)	F (p)
Age (years)		51.10 (8.55)	52.30 (5.82)	0.608 (0.438)
IQ		109.57 (11.50)	112.77 (8.16)	2.303 (0.133)
Years in education		11.96 (2.47)	12.37 (2.55)	0.627 (0.431)
Menopausal status	Pre-menopausal	26	11	
	Peri/post-menopausal	24	32	
HRT use	Never	10	10	
	Current	—	13	
	Past	14	9	

Intelligence

Intelligence was assessed using the National Adult Reading Test.[20] Wechsler Adult Intelligence Scale FSIQ was predicted from this score.

Verbal memory

WMS III logical memory parts 1 and 2: immediate and delayed recall of a short paragraph.

Rey Auditory-verbal learning test:[21] a word list-learning task consisting of five verbal presentations with recall of a 15-word list. Three scores are reported from this test: supraspan score (number of words recalled from the first presentation of the list), total recall score (total words recalled from the first five presentations) and delayed recall score (total words recalled after half an hour delay).

Visual memory

Complex Figure Task with two alternate forms:[22,23] copy, immediate and delayed recall of a complex geometric figure.

Working memory

WMSIII letter-number sequencing: sequences of letters and numbers must be reordered giving numbers first in ascending order then letters in alphabetical order.

WMSIII digit span: strings of digits must be repeated in the same and then in the reverse order to presentation.

WMSIII spatial span: spatial patterns must be reproduced first in the same and then in the reverse order to presentation.

Executive function

The Stroop task[24] has 3 conditions colour word reading, colour patch naming and the interference condition in which colour words are printed in incompatible ink colour. The participant names the colour of the ink, requiring the inhibition of the more salient word reading.

Processing speed and vigilance

Processing speed and vigilance are assessed using a letter cancellation task. A composite score is calculated based on both speed and accuracy.

Self-report measures of quality of life, cognitive failures and psychological morbidity

Quality of life was measured using the Functional Assessment of Cancer Therapy (Breast)[25] with endocrine symptoms (ES)[26] and fatigue (*F*)[27] subscales. The FACT-B comprises the FACT general, a 27-item questionnaire covering four quality-of-life domains: physical well-being, social/family well-being, emotional well-being and functional well-being along with 9 questions specifically related to breast cancer. The fatigue subscale consists of 13 specific items such as 'I feel weak all over' and the endocrine symptoms subscale comprises 19 questions incorporating symptoms such as hot flushes and night sweats. In all cases the participant responds on a five-point scale from 'not at all' to 'very much' as to the extent to which they have been affected by the item in the past 7 days.

In addition all participants complete the GHQ_{12} questionnaire and the Broadbent cognitive failures questionnaire.[28] The GHQ_{12} is a self-report questionnaire designed to detect non-psychotic psychiatric disorder in community and medical settings.[29] The cognitive failures questionnaire comprises of a series of 25 questions relating to lapses in attention in everyday life, such as forgetting what the person went into a room to do. Questions are rated on a five-point scale ranging from 0-'never' to 5-'very often'.

At time 2 a semi-structured interview was conducted with all patients to determine whether they had noticed any changes in their memory and attention. Detailed analysis of this data will be presented elsewhere however the patients' yes/no rating of whether they had experienced memory problems is included in this paper.

Statistical methods

Statistical Package for the Social Sciences (SPSS) version 11.5 was used for all statistical analyses. Group comparisons on cognitive performance were made at Time 1 (T1) and Time 2 (T2) using one-way and repeated measures ANOVA, Chi-squared or Mann–Whitney *U* tests as appropriate. Pearson's correlations were used to examine the relationship between self-reported measures and cognitive test scores.

Group comparisons of cognitive test scores can mask significant impairment in a sub-group of the population and are ill-equipped to cope with changes in performance that are mere artefacts

of practice effects due to prior exposure to the task or due to the potential low test–retest reliability of the task. Ignoring either of these factors can lead to the under or overestimation of cognitive impairment. Therefore, we used the reliable change index (RCI) with a correction for observed practice effects on each measure.[30] Using the method put forward by Jacobson and Truax[31] an RCI was calculated for each cognitive measure using the baseline and follow-up data of the control subjects.

The RCI was calculated as follows:

The test–retest reliability coefficient (r_{xx}) was computed for each measure. The standard error of measurement (SE_m) was calculated by

$$SE_m = SD_1(\sqrt{[1 - r_{xx}]}),$$

where SD_1 is the SD of the baseline score. The standard error of the difference (SE_{diff}) was calculated by

$$SE_{diff} = \sqrt{[2(SE_m)^2]}.$$

The standard error of the difference describes the spread of distribution of change scores that would be expected if no change occurred.

To establish a 90% RC confidence interval the SE_{diff} was multiplied by ± 1.64 SD.[32] These cut-off points were corrected for practice effects.[30] The practice effect for each variable is the mean difference between the follow-up and baseline scores. Thus, for each variable an RC 90% confidence interval was calculated by

$$\text{RC interval} = (SE_{diff})(\pm 1.64) + \text{practice effect}.$$

For each participant, a difference score was calculated representing the performance difference on each measure (T2–T1). If this score fell outside the RC interval, a statistically significant change in performance was considered to have occurred. Participants with a reliable decline on two or more tests are considered to have shown cognitive changes that are reliable.

Results

Cognitive test performance at baseline

The control group scored significantly higher than the patient group on 2/14 measures, letter cancellation efficiency ($F = 5.52$, $p = 0.02$) and logical memory (delayed) ($F = 5.09$, $p = 0.03$). These effects were independent of GHQ_{12} scores.

Cognitive test performance at time two

Repeated measures ANOVAs showed significant main effects or interactions for 9/14 measures; these are shown along with mean scores in Table 2.

Scores on 5 tasks (letter cancellation, complex figure immediate and delayed recall, digit span backwards and Stroop) showed a significant overall improvement in performance from T1 to T2 for all participants. Three tasks (letter cancellation, WMS logical memory delayed recall and digit span backwards) showed a significant main effect of group with the patient group scoring significantly lower overall than the control group. Three tasks, AVLT supraspan, AVLT total score and letter number sequencing showed a significant group $\times$ time-point interaction. In each case, group scores were comparable at T1, however, while the control group showed a practice effect on all tasks, scores in the patient group remained static (letter number sequencing) or declined significantly (AVLT supraspan, $p = 0.024$; AVLT total $p = 0.020$, T1–T2 within patient analysis).

Reliable change analyses

Table 3 shows the calculations for reliable change. Meaningful cognitive decline (reliable decline on at least 2/14 measures) was found in 17 (34%) patients compared to 8 (18.6%) controls (odds ratio 2.25, $\chi^2 = 2.788$, $p = 0.0475$, one sided). Of these, 9/17 (53%) patients and 6/8 (75%) controls also showed reliable improvement on at least one measure.

Exploratory analysis was conducted for the 8 patients who showed reliable decline with no corresponding improvement on any measure. They did not differ significantly from the remaining patient group in terms of age or estimated FSIQ neither were they more likely to report higher GHQ_{12}, lower quality-of-life scores or more everyday lapses on the cognitive failures questionnaire.

Quality of life

Table 4 shows the mean scores on the overall FACT-B and the fatigue and endocrine subscales for the patient group along with T1 vs. T2 comparisons. There is no significant change from T1 to T2 on the overall FACT-B but a significant increase in endocrine symptoms and fatigue.

No significant correlations were found between scores on any of the cognitive measures and reported totalled scores on the FACT-B, ES or F subscales at either time-point. Women who showed significant decline in quality of life (identified as a

Table 2 Mean scores (S.D.), significant main effects and interactions from repeated measures ANOVA.[†]

Task	Patient baseline	Control baseline	Patient time 2	Control time 2	Factor	*F*	Sig.
Letter cancellation	37.97	41.84	40.58	43.37	Time point	9.714	0.002 *
efficiency	8.10	7.72	7.58	7.51	Group	5.159	0.025*
					Time × group	0.666	0.417
Complex figure	22.38	24.81	25.09	25.13	Time point	4.418	0.038*
immediate recall	6.58	6.05	6.48	4.82	Group	1.395	0.241
					Time × group	2.743	0.101
Complex figure	22.38	24.13	24.42	24.83	Time point	4.598	0.035*
delayed recall	5.90	5.72	6.41	4.92	Group	1.109	0.295
					Time × group	1.105	0.295
Digit span backwards	6.48	7.23	6.80	7.63	Time point	4.617	0.034*
	1.87	2.22	2.02	1.98	Group	4.200	0.043*
					Time × group	0.051	0.821
Stroop	47.59	48.35	48.69	51.25	Time point	7.834	0.006*
	6.52	7.18	7.91	7.30	Group	1.514	0.222
					Time × group	1.585	0.211
Logical memory	12.46	13.98	12.60	13.58	Time point	0.125	0.725
delayed recall	3.40	3.03	3.74	3.62	Group	4.013	0.048*
					Time × group	0.548	0.461
AVLT supraspan	7.00	6.98	6.32	7.21	Time point	1.149	0.287
	1.83	1.58	1.54	2.07	Group	2.067	0.154
					Time × group	4.779	0.031*
AVLT total recall	53.46	52.42	51.18	54.26	Time point	0.097	0.757
trials 1–5	8.86	7.74	8.22	7.90	Group	0.429	0.514
					Time × group	8.352	0.005*
Letter-number	10.78	10.79	10.74	11.67	Time point	3.741	0.056
sequencing	2.20	2.14	2.45	2.60	Group	1.165	0.283
					Time × group	4.484	0.037*

*Sig. 0.05.
[†]$N = 50$ in all cases except for Stroop, $N = 49$.

Table 3 Reliable change index calculations.[†]

Measure	*r*	RC cut off (90%)	Practice correction	Reliable change interval
Letter cancellation efficiency	0.731	±9.29	1.530	−7.762 ⩾ RC ⩾ +10.822
AVLT supraspan	0.461	±2.69	0.233	−2.460 ⩾ RC ⩾ +2.925
AVLT total recall trials 1–5	0.595	±11.42	1.837	−9.582 ⩾ RC ⩾ +13.256
AVLT delayed recall	0.654	±3.73	0.000	−3.725 ⩾ RC ⩾ +3.725
Complex figure immediate recall	0.349	±11.32	0.321	−11.00 ⩾ RC ⩾ +11.643
Complex figure delayed recall	0.400	±10.27	0.698	−9.572 ⩾ RC ⩾ +10.968
Logical memory immediate recall	0.502	±4.88	−0.093	−4.969 ⩾ RC ⩾ +4.783
Logical memory delayed recall	0.570	±4.60	−0.395	−4.998 ⩾ RC ⩾ +4.207
Letter-number sequencing	0.517	±3.45	0.884	−2.571 ⩾ RC ⩾ +4.338
Digit span forwards	0.701	±3.14	−0.023	−3.165 ⩾ RC ⩾ +3.118
Digit span backwards	0.594	±3.28	0.395	−2.889 ⩾ RC ⩾ +3.680
Spatial span forwards	0.174	±3.38	−0.372	−3.749 ⩾ RC ⩾ +3.005
Spatial span backwards	0.606	±2.29	0.140	−2.153 ⩾ RC ⩾ +2.432
Stroop	0.574	±10.93	2.881	−8.052 ⩾ RC ⩾ +13.814

[†]$N = 43$ with the exception of complex figure immediate recall and Stroop where $N = 42$.

Table 4 Mean scores (S.D.) on quality of life scales at baseline and Time 2.[†]

	Baseline	Time 2	*T*	*p*
FACT-B	109.204 (15.275)	108.209 (18.949)	0.521	0.605
FACT-F	40.270 (9.115)	36.43 (11.993)	2.948	0.005
FACT-ES	66.051 (6.995)	59.758 (8.612)	6.141	<0.001

[†] $N = 50$ with the exception of baseline fatigue where $N = 49$.

change of $\geqslant$0.5 S.D. on the FACTB, ES or F) were not more likely to be classified as showing cognitive decline using the reliable change index.

GHQ_{12}

A GHQ_{12} score equal to or greater than 4 denotes probable non-psychotic psychiatric morbidity.[29] At baseline 26(52%) patients and 6(14%) controls had above threshold scores. At T2, 23(46%) patients and 9(20.9%) controls had above threshold scores. Patients were significantly more likely than controls to have above threshold scores at both time-points ($\chi^2 = 14.828$, $p < 0.0001$ and $\chi^2 = 6.438$, $p = 0.010$, respectively) but there were no significant group $\times$ GHQ interactions on any cognitive measure. Participants who had above threshold scores at T2 were not more likely to be classified as having meaningful cognitive decline using RCI ($\chi^2 = 0.035$, $p = 0.515$).

Patients with above threshold scores reported significantly lower levels of quality of life than those with below threshold scores, at baseline ($p < 0.0001$, $p = 0.015$ for FACT-B and ES subscales, respectively, F subscale was not significant) and at T2 ($p < 0.0001$, $p < 0.0001$, $p < 0.0001$ for FACT-B, ES and F subscales, respectively).

Self-reported cognitive impairment

Both patients and controls reported similar numbers of cognitive failures in everyday life (mean scores 38.16 [S.D.12.19] and 39.65 [S.D. 9.88], respectively, at T1 and 41.92 [S.D.14.33] and 39.12 [S.D.11.03] at T2). There was a significant group by time interaction ($F = 7.43$, $p = 0.008$) with patients reporting significantly higher levels of everyday lapses at T2 ($t = 3.015$, $p = 0.004$). Interestingly participants who had cognitive decline according to objective neuropsychological testing did not have significantly higher cognitive failure scores at T2 ($p = 0.698$).

At T1 scores on the cognitive failures questionnaire did not correlate significantly with FACT-B but did correlate with FACT-ES ($r = -0.329$, $p = 0.020$) and FACT-F ($r = -0.355$, $p = 0.012$) (patient group only). At T2 cognitive failures scores correlated significantly with FACT-B ($r = -0.461$, $p = 0.001$) FACT-ES ($r = -0.491$, $p < 0.001$) and FACT-F ($r = -0.459$, $p = 0.001$).

Participants with above threshold GHQ_{12} scores report significantly more cognitive failures than those with below threshold scores (mean scores 42.28 [S.D. 11.45] and 37.05 [S.D.10.65], respectively) $t = -2.194$, $p = 0.031$ (patient and control groups). At T2 participants with above threshold GHQ_{12} scores report significantly more cognitive failures than those with below threshold scores (mean scores 45.56 [S.D. 14.26] and 38.03 [S.D. 11.44] respectively) $t = -2.765$, $p = 0.007$.

Memory problems reported in interview

In total, 39/50 (78%) patients reported in interview that they had experienced memory problems during chemotherapy. Group comparisons between these patients and those that did not report memory problems (Mann–-Whitney *U*) showed no significant group differences in objective cognitive testing at T2. Those women who reported that they experienced memory problems were not significantly more likely to be classified as showing reliable cognitive decline than those women who did not report memory problems ($p = 0.728$). Nor did they have significantly higher scores on the cognitive failures questionnaire ($p = 0.497$), show a greater incidence of above threshold GHQ_{12} scores ($p = 0.189$) or report a significant drop in quality of life as measured by FACT-B ($p = 0.205$), ES subscale ($p = 0.265$) or Fatigue subscale ($p = 0.299$).

Discussion

The results of this study support the findings in the existing literature that chemotherapy treatment for breast cancer affects cognition in a significant proportion of women. The inclusion of a pre-treatment baseline strengthens the argument that chemotherapy may induce cognitive decline and that the finding is not related to heightened anxiety or depression or impact of disease and treatment on quality of life.

Three measures in particular showed a significant group by time interaction; the AVLT supraspan and

total recall and the WMS letter number sequencing task. All three tasks require a high degree of concentration and attention, precisely the function that patients complain most about. It may be the case that these measures are particularly sensitive to the type of impairment associated with chemotherapy treatment. In more general terms when we identified participants as impaired or not impaired on the basis of showing reliable cognitive decline on two or more measures, we found that patients were 2.25 times as likely as the control group to be classified as showing cognitive impairment. It is clear from interview data, such as the examples shown here, that many patients experienced cognitive problems:

*CP*1: My brain felt like cotton wool as if it couldn't think clearly and since I've been off the chemotherapy I've been thinking more clearly.

*CP*23: I suppose I feel now as if I am coming out of a mist, that I've been in a sort of mental fog for a while. Going through it coming out and clearing for a bit and then going into another patch.

However, the percentage of women experiencing change was not as severe compared with other studies.

Dose and type of chemotherapy may influence cognitive impairment. Where relatively low doses of chemotherapy are given it is possible that little or no cognitive impairment will be seen, conversely higher dose treatment may cause severe and lasting impairment.[8] Even slight variations in dose or duration within a 'standard' regimen may have different effects on cognitive function, for example it will be important to investigate possible differences between six and eight cycles of the same combination. The majority of studies of standard dose treatment reporting significant cognitive impairment have looked at CMF regimens. By contrast van Dam and colleagues[8] found no significant impairment in a group of patients who had received FEC some years previously and we found relatively low levels of impairment in our group made up largely of patients who had received FEC just a few weeks earlier. There is clearly the need for a full investigation of different treatment types and doses within the same trial.

It is not the case that chemotherapy will cause cognitive impairment in all patients. When studying cognitive function in cancer patients many factors must be considered that may impact on performance and may increase the likelihood of an individual experiencing cognitive impairment. Age and IQ for example are factors known to be related to test performance. Normal age-related changes may result not only in reduced performance from the outset but may leave the older patient with less capacity to overcome the detrimental effects of chemotherapy. Once all patients have completed the post-treatment assessment we will be better positioned to conduct a full analysis of individual differences that may increase the risk of cognitive impairment.

The quality-of-life assessments showed a significant increase in levels of fatigue and endocrine symptoms but, as in some other studies,[6–8] totalled scores on the quality-of-life measures did not relate to cognitive performance. Self-reported cognitive failures were related to quality of life and GHQ_{12} scores and may reflect emotional distress rather than true cognitive impairment.

The results reported so far should be viewed as preliminary and results from the final assessment 12 months after the completion of chemotherapy will provide us with further data on the extent of cognitive impairment and whether it is long lasting. Until we have more information about the nature of cognitive impairment after chemotherapy, they possible underlying mechanisms and causal relationships between them, the recent drive to provide neuroprotective agents may be premature.[33]

Conclusions

Cognitive impairment after chemotherapy occurs in some patients and must be considered along with other potential side effects when treatment options are discussed, particularly for women with very favourable prognosis in whom absolute survival gain from chemotherapy may be less than 5%.[34] There is a crucial need for future research to focus on the comparison of different chemotherapy agents, doses and number of cycles within the same trials. The use of cross-sectional methodology and a variety of assessment measures has made further generalisation difficult at this stage. The preliminary results from our study and from the self-report of patients show that even low-dose chemotherapy can impair performance on cognitive tests.

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