Subjective cognitive complaints one year after ceasing adjuvant endocrine treatment for early-stage breast cancer

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BACKGROUND: In the BIG 1-98 trial objective cognitive function improved in postmenopausal women 1 year after cessation of adjuvant endocrine therapy for breast cancer. This report evaluates changes in subjective cognitive function (SCF).

METHODS: One hundred postmenopausal women, randomised to receive 5 years of adjuvant tamoxifen, letrozole, or a sequence of endocrine therapy for breast cancer. This report evaluates changes in subjective cognitive function (SCF).

RESULTS: Subjective cognitive function and the other patient-reported outcomes did not change significantly after cessation of endocrine therapy with the exception of improvement for hot flushes (P = 0.0005). No difference in changes was found between women taking tamoxifen or letrozole. Subjective cognitive function was the only psychosocial outcome with a substantial correlation between year 5 and 6 (Spearman’s R = 0.80). Correlations between SCF and the other patient-reported outcomes were generally low.

CONCLUSION: Improved objective cognitive function but not SCF occur following cessation of adjuvant endocrine therapy in the BIG 1-98 trial. The substantial correlation of SCF scores over time may represent a stable attribute.

Keywords: subjective cognitive function; quality of life; breast cancer; aromatase inhibitor; tamoxifen; letrozole

Cognitive deficits following adjuvant breast cancer therapy have been increasingly investigated over the past decade. Earlier studies focused mainly on chemotherapy (Vardy et al, 2007; Vardy, 2009), but more recent research has examined the potential aetiologic role of adjuvant endocrine therapies (Jenkins et al, 2004; Bender et al, 2007; Hermelink et al, 2008; Jenkins et al, 2008; Collins et al, 2009; Debess et al, 2010; Phillips et al, 2010; Schiller et al, 2010; Phillips et al, 2011a, b). In these previous studies, objective cognitive function was usually measured with standardised neuropsychological tests (Vardy, 2009; Phillips et al, 2011a, b). If subjective cognitive complaints were assessed, a range of validated self-report questionnaires, ‘self-developed’ non-validated questionnaires and/or semi-structured interviews were used (Pullens et al, 2010). The prevalence of subjective cognitive dysfunction in women with breast cancer ranged from 21 to 90%, and there was no association between objective cognitive function and SCF (Pullens et al, 2010). Most studies on cognitive function also included measures of psychological distress (mainly depression and anxiety), quality of life (QOL), and fatigue as potential covariates.

Irrespective of therapy received (i.e., chemotherapy or endocrine therapy or both), or of study design (cross-sectional vs longitudinal), studies in women with breast cancer have consistently reported that objective cognitive function is not related to psychological distress (Jenkins et al, 2004; Shilling et al, 2005; Bender et al, 2006; Hermelink et al, 2007), fatigue (Fan et al, 2005; Bender et al, 2006; Jenkins et al, 2006; Mehndert et al, 2007; Collins et al, 2009), or QOL (Fan et al, 2005; Shilling et al, 2005; Jenkins et al, 2006; Mehndert et al, 2007). Only one study found that better scores in cognitive function were weakly related to less fatigue 2 years after chemotherapy completion (Schiller et al, 2008).

In contrast, several studies found SCF to be associated with psychological distress (Castellon et al, 2004; Jenkins et al, 2004;
et al (2007; Jenkins et al, 2008; Weis et al, 2009). There are few longitudinal studies that have investigated subjective cognitive and psychosocial changes in women with breast cancer during adjuvant endocrine therapy (Jenkins et al, 2006; Jenkins et al, 2008; Collins et al, 2009; Legault et al, 2009), and none of them specifically studied changes in these factors after cessation therapy. One study examined the relationship between cognitive limitations and tamoxifen or aromatase inhibitors in employed breast cancer survivors on average 3 years after primary treatment (Breckenridge et al, 2012). Exposure to endocrine therapy was not related to scores on the objective measures, but moderately related to perceived attentional problems at work and perceived cognitive functioning in everyday life.

We have previously reported results from the BIG 1-98 study on objective cognitive function (Phillips et al, 2010; Phillips et al, 2011a, b). There was a statistically significant improvement in objective cognitive function after cessation of adjuvant endocrine therapy, with an effect size large enough to be considered clinically meaningful (Phillips et al, 2011a, b). In this report, we present the findings on SCF, psychological distress, fatigue, and QOL. Thus, objectives of the study reported here were (1) to evaluate changes in SCF, psychological distress, fatigue, and QOL 1 year after the cessation of adjuvant endocrine therapy in postmenopausal women with early breast cancer, who were randomised within a double blind controlled trial (BIGI-98) (Thurlimann et al, 2005; Mouridsen et al, 2009) to receive adjuvant tamoxifen or letrozole alone or in sequence; (2) to evaluate whether there are differences in changes in SCF and other psychosocial outcomes 1 year after the cessation of adjuvant endocrine therapy between women taking tamoxifen or letrozole for the last 3 of 5 years of trial treatment; and (3) to evaluate the relationship between cognitive function (objective and subjective), psychological distress, fatigue, and QOL while still on treatment and 1 year after cessation. In addition, subjective complaints of cognitive dysfunction and their correlates were explored.

**MATERIALS AND METHODS**

The BIG 1-98 trial (March 1998–May 2003) randomised 8010 postmenopausal women with hormone receptor-positive tumours to receive one of four adjuvant endocrine therapy options after stratification by institution and chemotherapy (Figure 1). A sub-study assessed cognitive function and psychosocial factors at year 5 (during the fifth year on endocrine therapy (Phillips et al, 2010) and at year 6 (~1 year after cessation therapy (Phillips et al, 2011a, b). The sub-study protocol was approved by the local and International Breast Cancer Study Group (IBCSG) ethics committees and the required health authorities of each participating centre. All women gave informed consent to participate in the sub-study and parent study.

**Cognitive function and patient-reported outcomes**

Objective cognitive function was assessed using a brief computerised test battery (CogState Ltd; http://www.cogstate.com), which is free from practice effects (Collie et al, 2001; Falleti et al, 2003; Snyder et al, 2005; Vardy et al, 2006). Testing consisted of five non-verbal tasks, measuring the speed of psychomotor function, visual attention, attention and working memory, and visual learning and memory. In addition, two verbal learning and memory tasks required subjects to learn a 12-word shopping list, and then to recall this list after 20 min. Details of the test battery have been described elsewhere (Phillips et al, 2010). For the seven tasks, a composite score, representing the age-adjusted average standardised score of each task for each individual, was calculated (Phillips et al, 2010).

After cognitive testing, women completed several questionnaires. Subjective cognitive function was assessed with the Cognitive Failures Questionnaire (CFQ (Broadbent et al, 1982)), a 25-item self-report measure that assesses a person’s failures in memory, perception, attention, and motor function over the past 6 months. The response categories range from 0 (‘never’) to 4 (‘very often’). Studies exploring potential CFQ subscales vary considerably with regard to the number of subscales identified, so in this study only the global summary score was used (Broadbent et al, 1982). To measure psychological distress, a 12-item version of the General Health Questionnaire (GHQ-12 (Goldberg, 1992; Politi et al, 1994; Schmitz et al, 1999; Donath, 2001) was used. In addition, the Brief Fatigue Inventory (BFI (Mendoza et al, 1999), a 9-item instrument to assess severity of fatigue and its incidence with daily living in a 24-h period, was administered. Various global and symptom-specific QOL domains were measured by linear analogue self-assessment indicators (Bernhard et al, 1997). Validated language versions were used where available, otherwise a standard translation procedure was performed (forward-backward).

**Statistical considerations**

Changes in SCF and each of the patient-reported outcome measures from year 5 to year 6 were evaluated by subtracting year 5 from year 6 scores. Higher scores reflect a poorer condition; thus, a negative change in the score indicates an improvement. Owing to the skewness in the distribution of responses for the BFI, GHQ, and QOL measures at the year 5 assessment, analyses were performed using nonparametric methods. The stratified Wilcoxon signed-rank test was used to evaluate changes 1 year after cessation of adjuvant endocrine therapy (regardless of the type of endocrine therapy received). The Van Elteren Wilcoxon rank-sum test, stratified on language, was used to test the difference in the changes from year 5 to year 6 between women taking tamoxifen and women taking letrozole at year 5. Spearman’s correlation coefficients (R) were obtained for pairwise associations among the CogState Battery composite score and the self-reported measures. Where available, cut-offs were applied to identify women with mental disorders or severe fatigue. A widely accepted convention to define a case of mental disorder using the GHQ-12 is a score ≥ 3 (Goldberg et al, 1997). A score ≥31 is considered as cut-off for screening of mental disorder for the QOL mood scale (Singer et al, 2008). A BFI score ≥8 represents severe fatigue (Chang et al, 2007). In the absence of an established cut-off for the CFQ total...
Clinical Studies

1620

Abbreviations: ET = endocrine therapy; Med = median; Min = minimum; Max = maximum; CFQ = Cognitive Failure Questionnaire; BFI = Brief Fatigue Inventory; GHQ = General Health Questionnaire. For all outcomes, higher scores reflect a poorer condition, and a negative change indicates an improvement. *P-value calculated using the Wilcoxon signed-rank test.

Table 1 Descriptive statistics of patient-reported outcomes by time point and change in score

<table>
<thead>
<tr>
<th>Year 5 (during the fifth year on ET)</th>
<th>Year 6 (~1 year after ceasing ET)</th>
<th>Change (year 6~year 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Med</td>
</tr>
<tr>
<td>CFQ</td>
<td>99</td>
<td>35.00</td>
</tr>
<tr>
<td>BFI</td>
<td>98</td>
<td>1.61</td>
</tr>
<tr>
<td>GHQ</td>
<td>100</td>
<td>0.00</td>
</tr>
<tr>
<td>QOL indicators</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical well-being</td>
<td>100</td>
<td>9.5</td>
</tr>
<tr>
<td>Mood</td>
<td>100</td>
<td>8.0</td>
</tr>
<tr>
<td>Tiredness</td>
<td>100</td>
<td>22.0</td>
</tr>
<tr>
<td>Appetite</td>
<td>100</td>
<td>5.5</td>
</tr>
<tr>
<td>Hot flushes</td>
<td>100</td>
<td>20.0</td>
</tr>
<tr>
<td>Feeling sick</td>
<td>100</td>
<td>2.0</td>
</tr>
<tr>
<td>Effort to cope</td>
<td>100</td>
<td>6.0</td>
</tr>
<tr>
<td>Arm restriction</td>
<td>100</td>
<td>3.0</td>
</tr>
<tr>
<td>Subjective health</td>
<td>100</td>
<td>10.0</td>
</tr>
</tbody>
</table>

RESULTS

Of 135 women recruited to this study, 35 were ineligible for this analysis (see Figure 1 for reasons), leaving 100 women. The year-6 assessment was undertaken a median of 365.5 days (range 191–699 days) after ceasing protocol endocrine therapy.

Most patient and disease characteristics (i.e., age, history of head injury, neurological disorder, anxiety or depression, currently treated for anxiety, depression or mental disorder, alcohol consumption, ECOG status, chemotherapy received, hormone replacement therapy, ER/PG R status, tumour size, and local therapy) were balanced between women who had both assessments vs those who had only year-5 assessment (drop-outs N = 23; see Figure 1), except that women who had four or more positive nodes were more likely to drop out by the year-6 assessment (P = 0.01). No statistically significant differences were found for patient and disease characteristics between the women taking tamoxifen vs letrozole at year 5.

Differences between treatments groups at year 5

At year 5, no differences were found for SCF (P = 0.79), fatigue (P = 0.58), psychological distress (P = 0.16), or the QOL indicators between women taking tamoxifen or letrozole.

Changes from on- to off-treatment

Overall, no significant change was found from on-treatment to 1-year off-treatment for SCF or any of the patient-reported outcomes (Table 1), except for a significant decrease in hot flushes mean change (s.d.) = −10.3 (30.87); median change (range) = −2 (−99, 100), P = 0.0005. Likewise, none of the changes in SCF and other patient-reported outcomes differed significantly between women taking tamoxifen compared with letrozole (data not shown).

Prevalence of severe fatigue and psychiatric or mental disorder

Regarding fatigue, no woman had a BFI score considered as representing severe fatigue at year 5 and only one experienced severe fatigue at year 6. About the same proportion of women had GHQ scores defined as a case of mental disorder at year 5 (14%) and year 6 (18%). Of those, 12 women changed from ‘no case’ at year 5 to ‘case’ at year 6; however, 8 women improved, changing from ‘case’ to ‘no case’. The proportion of women with mood scores indicative for a mental disorder remained stable with 20% of women at year 5 and 18% at year 6. Of those, 9 women worsened, changing from not impaired at year 5 to impaired at year 6; 11 women improved, going from impaired to not impaired.

Relationship between cognitive function and patient-reported outcomes

There were no notable correlations between objective cognitive function (composite score) and the various patient-reported outcomes at year 5 or 6 (correlation coefficients ranged from R = −0.15 to R = 0.18). In addition, no notable correlations were found between individual Cogstate tasks and SCF, with correlation coefficients ranging from R = −0.09 to R = 0.14 at year 5 and from R = −0.02 to R = 0.19 at year 6. Subjective cognitive function showed a low correlation with fatigue (BFI, R = 0.33), psychological distress (GHQ, R = 0.31), mood (R = 0.45), tiredness (R = 0.41), and physical well-being (R = 0.37) and no correlations with the other QOL indicators at year 5. Similarly, at year 6 correlations between SCF and fatigue (BFI, R = 0.37), psychological distress (GHQ, R = 0.42), and tiredness (R = 0.41) were low, and no correlations with the other QOL indicators were found.

Subjective cognitive complaints and their correlates

For women with CFQ scores in the highest third, the lowest score was 40 at the year-5 assessment. Thirty-eight women (38%) at year 5 and 36 women (36%) at year 6 had a CFQ score of ≥ 40.

Figure 2A–D shows plots of CFQ scores by GHQ, BFI, mood scores, and age at year 5 for all patients. Whereas there seems to be
some tendency for women who reported the highest 33% of SCF scores (vertical line represents the cut-off) to have worse BFI and mood scores, this is not seen with the GHQ score or age. Women with more cognitive complaints at year 5 (i.e., still on treatment) also reported more complaints at year 6 (i.e., after ceasing endocrine treatment; $R = 0.80$), as shown in Figure 3. In contrast, correlations between on- and off-treatment scores were lower for BFI ($R = 0.53$), GHQ ($R = 0.39$) or the various QOL indicators (ranging from $R = 0.32$ to 0.62).

There were moderate-to-high correlations between responses at year 5 and those at year 6 for individual CFQ items (ranging from $R = 0.24$ to 0.77). When the individual complaints of women with the highest 33% of CFQ total scores at year 5 were explored (Figure 4), four items pertaining to memory lapses (i.e., ‘forgetting reason for going from one part of house to the other’, ‘forget where you put things’, ‘forget people’s names’, ‘cannot remember something (on tip of tongue)’), had high responses for both years 5 and 6, suggesting that these were the most bothersome specific complaints in this particular subgroup of women, and that they remained a problem during treatment (year 5) and 1 year after treatment cessation (year 6).

In summary, although objective cognitive function improved 1 year after treatment completion in the BIG 1-98 Trial (Phillips et al., 2011a, b), hot flushes reduced, and SCF and the other psychosocial measures remained stable with no difference between women taking tamoxifen and letrozole.

**DISCUSSION**

In this sub-study, SCF, fatigue, psychological distress, and QOL did not change between the fifth year on adjuvant endocrine therapy and 1 year after treatment cessation in postmenopausal women with early-stage breast cancer. The only exception was a significant decrease in hot flushes, which is expected on withdrawal of endocrine therapy. Similarly, the proportion of women who were at risk for a mental disorder was stable, with rates <20% at year 5 and 6. Other studies on cognitive function in women with breast cancer using also the GHQ-12 to control for mental disorder have reported similar rates of risks for mental disorder in women receiving radiotherapy and/or endocrine therapy (Jenkins et al., 2006), but higher rates in women receiving chemotherapy (Shilling et al., 2005).

To our knowledge, this is the first study reporting on subjective cognitive changes in women after cessation of endocrine therapy for early-stage breast cancer within a randomised controlled trial.
setting. Most studies reporting on changes in SCF have focused on subjective cognitive changes after chemotherapy (Hurria et al., 2006; Jenkins et al., 2006; Shilling and Jenkins, 2007; Jansen et al., 2008; Quesnel et al., 2009). In the study by Jenkins (Jenkins et al., 2006), one group of patients received radiotherapy and/or endocrine therapy only. In this group no subjective cognitive changes were found over time, but patients were still taking endocrine treatment at the time of their follow-up assessment. In a randomised double-blind chemoprevention trial (IBIS II trial (Jenkins et al., 2008), postmenopausal women at high risk for breast cancer did not report changes in SCF (assessed with the CFQ) during the first two years on the aromatase inhibitor anastrozole.

The fact that in our study SCF remained stable suggests that it may represent a stable attribute. The argument, made by some authors, that subjective cognitive complaints in women treated for breast cancer may solely represent psychological distress or fatigue (Morse et al., 2003; Pullens et al., 2010) is undermined by our finding of only weak-to-moderate associations among SCF and these measures. Similarly, the correlation between on- and off-treatment scores was low for psychosocial distress or fatigue (Morse et al., 2003; Pullens et al., 2010) is undermined by our finding of only weak-to-moderate associations among SCF and these measures. Similarly, the correlation between on- and off-treatment scores was low for psychosocial distress or fatigue (Morse et al., 2003; Pullens et al., 2010). In one study of patients receiving chemotherapy for breast cancer, the personality trait ‘negative affectivity’ was one of the determinants of cognitive self-reports (Hermelink et al., 2010).

Our exploratory analysis showed that among women in the highest third of SCF scores at the end of treatment, there were few specific cognitive problems persisting over time, in particular four specific lapses concerning memory. Shilling and Jenkins (2007) interviewed women with breast cancer receiving adjuvant therapy, who reported memory problems regarding the kind of problems they encountered. Few were able to mention more than one to two specific cognitive problems. A notable problem was remembering what they are doing, or were supposed to have done that is similar to the problem of ‘forgetting reason for going from one part of house to the other’ in our study. Other frequently reported problems (e.g., forgetting the names of people, forgetting appointments, forgetting where things are, and remembering a word they wished to use) were also consistent with the kind of problems reported as most bothersome by the women who reported the highest 33% of SCF scores. There was no indication that these women differed substantially from the rest of the sample with respect to age, psychological distress or fatigue. This is in contrast to studies reporting evidence for a moderate-to-strong relationship between SCF and psychological distress, fatigue or QOL during and after adjuvant treatment for breast cancer (Jenkins et al., 2006; Shilling and Jenkins, 2007; Weis et al., 2009; Breckenridge et al., 2012).

In line with the existing evidence, we found no association between objective cognitive function and SCF. It has been argued that the reason for this dissociation may be that standardised neuropsychological tests are insufficiently sensitive to detect mild impairments in cancer patients (Schagen et al., 2009). Furthermore, objective cognitive tests are usually conducted at specific time points in a clearly defined test situation, and therefore may fail to assess cognitive function in relevant everyday settings (Sbordone, 2001) or to cover a broader time period (Tannock et al., 2004).

There are some limitations to consider. In the absence of an established cut-off or normative data for the CFQ, we had to rely on an arbitrary, distribution-based criterion. This frame of reference allowed an exploration of the clinical observation, that there is a subgroup of patients with complaints of cognitive impairment persisting after completing adjuvant therapy. The lack of a definition for subjective cognitive impairment is a general

Figure 4  Plots of four selected CFQ items (A–D) at year 5 vs score at year 6 for women who reported the highest 33% of SCF (CFQ) scores.
problem; only 7 out of 27 studies conducted in women with breast cancer (Pullens et al, 2010) described the definition of subjective cognitive dysfunction, using either theoretical definitions or cutoffs. At the time the study was designed, subjective data from women with breast cancer indicated that they were concerned most about their ability to concentrate and remember, and none of the available studies had highlighted executive function as an area of specific concern. In a recent review, subjective cognitive deficits consisted of problems with memory, concentration, language, and self-reported retardation in mental processes or lower effectiveness (Pullens et al, 2010). Yet, it is possible that our study missed patients with executive function deficits, which may be correlated with changes in SCF. We had no assessment of cognitive function before the start of endocrine therapy and were not able to control for the potential preexistence of cognitive impairment.

In conclusion, it is reassuring that objective cognitive function improves significantly after ceasing endocrine therapy (Phillips et al, 2011a, b). However, given the results reported here, there is a subgroup of women who may not feel that their everyday cognitive abilities, in particular those related to memory, are better after ceasing therapy. The quite clear disconnect between objective cognitive function and SCF, whatever the underlying reason, is a crucial issue that must be addressed in subsequent research, in order for the research community to respond effectively to the concerns of women about their cognition during and after breast cancer treatment.

REFERENCES


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Conflict of interest

Novartis contracted with the International Breast Cancer Study Group (IBCSG) for provision of services related to the conduct and management of the trial. Dr Thürlimann owns stock in Novartis; Dr Cardoso has received consulting and/or lecture fees from Novartis, Dr Thompson and Dr Goldhirsch have received honoraria from Novartis. The remaining authors have no conflicts to report.
APPENDIX

BIG 1-98 Collaborative Group Participants in cognitive function substudy


Breast International Group (BIG)

International Breast Cancer Study Group

Australian New Zealand Breast Cancer Trials Group (ANZ BCTG):
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New Zealand: Auckland Hospital: V J Harvey, J Proctor, J Millet, B Joppa, B Evans, W Jones, M McCrystal, D Porter, P Thompson, and M Vaughan.


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