

Adjuvant Breast Cancer Treatment and Cognitive Function: Current Knowledge and Research Directions

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Evidence is mounting that potentially curative systemic adjuvant therapy for early-stage breast cancer may result in cognitive impairment. Five published studies have investigated cognitive function in this setting, and the consistent results of all five studies suggest an adverse effect of adjuvant chemotherapy. These studies are reviewed with particular attention to their methodologic limitations. For example, all five studies used cross-sectional designs, none controlled for possible confounding hormonal factors, and three examined patients who had not received a uniform chemotherapy regimen. The potential roles of chemotherapy-induced menopause and of adjuvant hormonal therapy in cognitive impairment are also discussed. Priorities for future research include confirmation of an effect of adjuvant chemotherapy in a study with a longitudinal design, closer examination of the potential contribution of hormonal factors, and similar studies on the effect of adjuvant therapy on cognitive function in other cancer types. If an effect of systemic adjuvant therapy on cognitive function is confirmed, such an effect will have implications for informed consent. It may also result in incorporation of objective measures of cognition in clinical trials of adjuvant therapy and in the investigation of preventive interventions that might minimize the impact of cognitive dysfunction after cancer treatment. [J Natl Cancer Inst 2003;95:190-7]

Breast cancer affects up to one in 10 women in Western countries (1). Fortunately, the majority of such women are cured of the disease by a combination of early diagnosis, surgery, and systemic adjuvant therapy, where appropriate (2,3). Indeed, women with a history of breast cancer now constitute the largest group in the cancer survivor community (4). Most of these women will receive systemic chemotherapy and/or hormonal therapy as part of their treatment (5).

Identification, characterization, and minimization of the intermediate- and long-term side effects of potentially curative breast cancer treatments are, therefore, of substantial importance to optimize the quality of life of breast cancer survivors. Most patients adjust well to the transient side effects of cytotoxic treatment. Overall, the adverse effect of standard chemotherapy on quality of life is minor compared with patients' adaptation after diagnosis and surgery (6). A recently recognized possible side effect of a different nature is the impairment of cognitive function. Cognitive function is a prerequisite of functioning in daily life.

In this review, studies on cognitive function of adjuvant chemotherapy and hormonal therapy for breast cancer are reviewed, with particular attention to their methodologic limitations. The potential role of chemotherapy-induced menopause and adjuvant

hormonal therapy on cognitive function and priorities for future research are also discussed.

ADJUVANT CHEMOTHERAPY AND COGNITIVE FUNCTION

Cognitive impairment has been demonstrated in cross-sectional studies of women who have received adjuvant chemotherapy for breast cancer (Table 1) (7-11). However, these studies have had methodologic limitations. Furthermore, the possible mechanisms are poorly understood and may include 1) a direct central effect of some or all of the chemotherapy agents used, 2) an effect from changes in the hormonal milieu (i.e., chemotherapy-induced menopause or use of adjuvant hormonal therapy), and/or 3) an effect from psychologic factors associated with a diagnosis of cancer (although most studies attempted to control for this possibility).

Study of Wieneke and Dienst (7)

Wieneke and Dienst examined cognitive function in 28 patients with early-stage breast cancer on average about 6 months after they completed therapy; 17 were treated with CMF (cyclophosphamide, methotrexate, and 5-fluorouracil), four were treated with CAF (cyclophosphamide, doxorubicin, and 5-fluorouracil), and seven were treated with CMF followed by CAF. Approximately 40% of patients were taking adjuvant tamoxifen at the time of testing. A comprehensive battery of neuropsychologic tests was used to assess cognitive function over nine domains, and the Beck Depression Inventory (12) was used to assess depression. Seventy-five percent of patients showed moderate impairment on one or more test measures when compared with age-, education-, and sex-corrected test norms. The level of cognitive impairment was unrelated to depression, type of chemotherapy, and time since treatment. The average age of patients in the study was 42 years, but the number who experienced chemotherapy-induced menopause was not reported.

Study of van Dam et al. (8)

van Dam et al. reported results of a randomized trial that compared cognitive functioning in three groups of patients:

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Table 1. Studies of cognitive function after adjuvant chemotherapy for breast cancer*

Study	Therapy	No. of patients	Average age, y	No. of patients on tamoxifen when tested (%)	No. of patients with chemotherapy-induced menopause (%)	Timing of measures (average post chemotherapy)	Cognitive impairment in chemotherapy patients	Control
Wieneke and Dienst (7)	CMF/CAF	28	42.0	11 (39)	n/a	6 mo	Yes	Published test norms
Van Dam et al. (8)	CTC (high dose)	34	45.5	29 (85)	34 (100)	2 y	Yes	Stage I breast cancer (no chemotherapy)
Schagen et al. (9)	FEC	36	48.1	28 (78)	34 (94)	2 y	N/S trend	Stage I breast cancer (no chemotherapy)
	CMF	39	47.1	16 (41)	36 (92)	2 y	Yes	
Brezden et al. (10)	CMF/CEF	31	49.0	0 (0)	n/a	During chemotherapy	Yes	Healthy volunteers
	CMF/CEF	40	46.0	16 (40)	n/a	25 months	N/S trend	Healthy volunteers
Ahles et al. (11)	CMF/CAF/other	35	59.1	3 (9)	n/a	9 y	Yes	Breast cancer (no chemotherapy)

*CMF = cyclophosphamide at 100 mg/m² orally days 1–14, methotrexate at 40 mg/m² intravenously days 1 and 8, and 5-fluorouracil at 600 mg/m² intravenously days 1 and 8; cycles repeated every 28 days. CAF = cyclophosphamide, doxorubicin, and 5-fluorouracil (doses not specified). CEF = cyclophosphamide at 0.75 mg/m² orally days 1–14, epirubicin 60 mg/m² intravenously days 1 and 8, and 5-fluorouracil 500 mg/m² intravenously days 1 and 8; cycles repeated every 28 days. FEC = 5-fluorouracil at 500 mg/m² intravenously, epirubicin at 90–120 mg/m² intravenously, and cyclophosphamide at 500 mg/m² intravenously; cycles repeated every 21 days. CTC (high dose) = four cycles FEC followed by cyclophosphamide at 6 g/m² intravenously, thiotepa at 480 mg/m² intravenously, and carboplatin at 1.6 g/m² intravenously with autologous stem cell support. Other = cyclophosphamide and doxorubicin or cyclophosphamide, methotrexate, 5-fluorouracil, vincristine, prednisolone or cyclophosphamide, and carboplatin (doses not specified). N/S trend = statistically nonsignificant trend. n/a = not assessed.

stage II or III (13) breast cancer patients, who had received either high-dose chemotherapy with autologous stem cell support or standard-dose chemotherapy an average of 2 years before testing, and stage I patients who had not received any adjuvant systemic chemotherapy or hormonal therapy (control group). The high-dose regimen consisted of four cycles of FEC (5-fluorouracil, epirubicin, and cyclophosphamide), followed by a single dose of high-dose CTC (cyclophosphamide at 6 g/m², thiotepa at 480 mg/m², and carboplatin at 1.6 g/m²) and stem-cell rescue. The standard-dose group received four cycles of FEC. Cognitive function was assessed with a battery of neuropsychologic tests, and the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) (14) and the Hopkins Symptom Checklist (15) were used to assess health-related quality of life and psychologic distress, respectively. Approximately 80% of the patients who had previously undergone chemotherapy were on tamoxifen at the time of cognitive function testing. The patients who had received high-dose chemotherapy had a risk of cognitive impairment that was 8.2 times higher (95% confidence interval [CI] = 1.8 to 37.7) than that of control subjects ($P = .006$) and was 3.5 times higher (95% CI = 1.0 to 12.8) than that of patients who had undergone standard-dose chemotherapy ($P = .056$, borderline statistical significance). The results were not related to anxiety, depression, fatigue, or time since treatment. Importantly, all patients of the high-dose treatment group and all but two of the standard-dose treatment group were postmenopausal after chemotherapy. This study therefore provides the best evidence currently available for a direct effect of chemotherapy (that is dose-related) on cognitive function rather than an effect mediated purely by hormonal mechanisms. However, it does not exclude the possibility that hormonal mechanisms mediate a partial effect. Evidence for cognitive dysfunction was also provided by a neurophysiologic evaluation of a subpopulation. Asymmetry of the α rhythm of at least 0.5 Hz was more frequent after high-dose chemotherapy than after standard-dose chemotherapy and was not present in the control group (16).

Study of Schagen et al. (9)

Schagen et al. demonstrated statistically significantly more cognitive impairment in axillary lymph node-positive breast cancer patients who had received adjuvant CMF an average of approximately 2 years before testing. The control group in this study was the same as that used by van Dam et al. (8). An extensive battery of neuropsychologic tests was used to assess cognition. Health-related quality of life was assessed with the EORTC QLQ-C30 questionnaire (14), and anxiety and depression were measured with the Hopkins Symptom Checklist-25 (15). In this study, more than 90% of the patients treated with adjuvant therapy had undergone chemotherapy-induced menopause, and approximately 40% were taking tamoxifen when their cognitive function was tested. No difference was seen in cognitive function between the group treated with chemotherapy plus tamoxifen versus the group treated with chemotherapy alone. The authors did not attempt to examine the impact of chemotherapy-induced menopause presumably because virtually all (92%) of the treated patients underwent menopause.

Study of Brezden et al. (10)

Brezden et al. examined cognitive function in one group of breast cancer patients during adjuvant chemotherapy and in another group of breast cancer patients an average of 2 years after they completed adjuvant chemotherapy; they also compared the results of these two groups with those of healthy volunteer women (10). The High Sensitivity Cognitive Screen was used to assess cognitive function (17). This validated instrument is accurate in predicting the overall results of formal neuropsychologic testing without a comprehensive assessment of the various domains. Psychologic distress was assessed with the Profile of Mood States (18). Cognitive function was statistically significantly worse in the patients currently undergoing chemotherapy than in the healthy control subjects, even when age, educational level, and menopausal status were included in the analysis. The cognitive function results for the group that had undergone pre-

vious chemotherapy (40% of whom were taking tamoxifen at the time of testing) were intermediate between those of the currently treated group and those of the healthy control subjects, although the differences were not statistically significant. There was no statistically significant difference in mood states among the three groups assessed.

Study of Ahles et al. (11)

Ahles et al. studied long-term survivors of breast cancer and lymphoma, comparing the neuropsychologic functioning of those who received standard-dose systemic chemotherapy with those who received local therapy (surgery and/or radiation therapy) only. The patients were evaluated an average of approximately 10 years after their cancer diagnosis. A battery of neuropsychologic tests was used to assess cognitive functioning. Psychologic functioning was assessed with the Center for Epidemiological Study–Depression (19), the Spielberger State–Trait Anxiety Inventory (20), and the Fatigue Symptom Inventory (21). In an analysis that controlled for age and educational level, survivors who had been treated with chemotherapy (predominantly standard-dose CMF or CAF chemotherapy regimens for breast cancer patients) scored statistically significantly lower on the battery of neuropsychologic tests than those treated with local therapy only. Receiving more cycles of chemotherapy was associated with lower neuropsychologic performance. Compared with norms in healthy individuals, performance was generally within the normal range. Only 9% of chemotherapy-treated breast cancer survivors were on tamoxifen at the time of neuropsychologic testing. When those who had ever taken tamoxifen were compared with those who had never taken tamoxifen, no significant differences between any of the neuropsychologic domain scores were observed. The investigators did not assess the role of chemotherapy-induced menopause. This study adds importantly to the literature because it suggests that the effects of chemotherapy on cognitive function may be relatively subtle but prolonged.

Effect on Individual Cognitive Domains

In all five studies, impairment was observed in cognitive function of patients with breast cancer who had received adjuvant chemotherapy when compared with that of control subjects. Because of the small sample sizes, it is difficult to determine whether there was a differential impact on individual cognitive domains. The studies of Wieneke and Dienst, Schagen et al., and van Dam et al. suggest fairly global impairment, although no impairment in verbal memory was observed in the latter study. In the study of Brezden et al. (which used an abbreviated battery of cognitive function measures), the effect appeared to be greatest in the memory and language domains. In the study of Ahles et al., the effect was diffuse but was statistically significant on univariate analysis in the verbal memory and psychomotor functioning domains.

Subjective Cognitive Impairment

Anecdotally, patients with breast cancer often complain of problems with their memory and concentration. Colloquially, this problem is referred to as “chemobrain” or “chemofog” (22,23). In addition to objectively assessing cognitive function, the studies of Schagen et al., van Dam et al., and Ahles et al. assessed subjective cognitive function.

The cognitive subscale of the EORTC QLQ-C30 (14) was used in the studies of Schagen et al. and van Dam et al. This subscale consists of two questions in which the patient is asked to indicate the occurrence and extent of concentration and memory difficulties. The EORTC QLQ-C30 cognitive subscale has been shown to have discriminative validity, although there is a lower degree of support for this subscale than for the other subscales (24). In both studies, patients were also asked to indicate on separate Likert scales the extent to which problems in each of the domains of memory, attention, thinking, and language affected their daily life. In the study of Schagen et al., 31% and 21% of chemotherapy-treated patients reported problems with concentration and memory, respectively, compared with 6% and 3% in the control group ($P = .007$ and $P = .022$, respectively). However, there was no statistically significant difference in reports of disturbances in thinking and language between the two groups. Chemotherapy-treated patients also had statistically significantly lower scores on the cognitive functioning subscale of the EORTC QLQ-C30. Subjective reports of cognitive dysfunction correlated with anxiety and depression but not with objective cognitive function. The findings in the study by van Dam et al. were similar.

The Squire Memory Self-Rating Questionnaire (25) was used to assess subjective cognitive function in the study of Ahles et al. It is an 18-item self-report measure that on cluster analysis yields three groupings of items: working memory, new learning, and remote memory. Working memory was rated statistically significantly lower in the patients who had received chemotherapy. However, correlations between the Squire subscales and neuropsychologic domain scores were low and not statistically significant.

The lack of correlation between objective and subjective cognitive function in these studies suggests that patients' complaints about their cognitive function may be more indicative of emotional distress than true cognitive dysfunction. An alternative hypothesis is that those who report subjective cognitive impairment may indeed be functioning at a level lower than before their adjuvant breast cancer treatment and that this may contribute to their emotional distress.

Methodologic Features

Important methodologic features of these studies are summarized in Table 2. The most important of these features is use of a cross-sectional study design. With this design, it is not possible to determine the amount of change in cognitive function experienced by individuals, and so a strategy of comparing the cognitive function of the treated group with that of a control group is used. Thus, choice of an appropriate control group is critical although difficult. The studies of Schagen et al. and van Dam et al. used the same group of stage I patients as control subjects. The use of the same small control group of patients in two otherwise independent studies is not optimal and amplifies the need for care in their interpretation. A major criticism of the study of Wieneke and Dienst has been the use of published test norms as a control group because there may be pretreatment differences between patients with breast cancer and the subjects used to produce normative data. Similarly, the study of Brezden et al. used a control group of healthy volunteers that may have had an inherent bias (the direction of which is not obvious). In addition, the use of a cross-sectional study design increases the importance of ensuring that there is no recruitment bias in the

Table 2. Methodology features of trials of cognitive function following adjuvant breast cancer chemotherapy

	Wieneke and Dienst (7)	van Dam et al. (8)	Schagen et al. (9)	Brezden et al. (10)	Ahles et al. (11)
Large sample size	No	No	No	No	No
Longitudinal design	No	No	No	No	No
Patient recruitment bias unlikely	No	Yes	Yes	No	No
Adequate control group	Questionable	Yes	Yes	Questionable	Yes
Uniform chemotherapy regimen	No	Yes	Yes	No	No
Uniform timing of measures	No	No	No	No	No
Validated measures of cognitive function	Yes	Yes	Yes	Yes	Yes
Subjective cognitive function assessed	No	Yes	Yes	No	Yes
Analysis controlled for hormonal factors*	No	No	No	No	No
Analysis controlled for psychologic factors	Yes	Yes	Yes	Yes	Yes

*Hormonal factors = chemotherapy-induced menopause or use of tamoxifen.

treated patients who are studied. In the study of van Dam et al. (which was a substudy of a randomized trial) and the study of Schagen et al. (which recruited a consecutive series of patients), the possibility of recruitment bias was minimized.

The cross-sectional design of these studies also means that the timing of cognitive measures in relation to chemotherapy was not uniform. In the study of Wieneke and Dienst, the range was 0.5–12 months after the completion of chemotherapy. In the study of Brezden et al., the range for the group currently undergoing adjuvant therapy was two to eight cycles, and the cognitive testing of the post-treatment group was performed between 12 and more than 36 months after the completion of adjuvant chemotherapy. The ranges are not stated in the studies of Schagen et al. and van Dam et al. In the study of Ahles et al., patients were assessed approximately 10 years after completion of chemotherapy.

None of these studies have controlled adequately for possible confounding hormonal factors. The women who were evaluated were mostly premenopausal at the time of breast cancer diagnosis, and in the two studies where it was recorded (and presumably also in the other three), the majority of women were made postmenopausal by the adjuvant chemotherapy. The high prevalence of chemotherapy-induced menopause raises the possibility that this phenomenon may have contributed to the differences seen in cognitive function. However, as mentioned above in the study of van Dam et al., the difference seen in degree of cognitive impairment between the high-dose chemotherapy and standard-dose chemotherapy groups, despite the fact that virtually all women in both groups underwent chemotherapy-induced menopause, strongly suggests a direct, dose-related central effect of chemotherapy. In addition, a possible contributory effect of tamoxifen on cognitive function was not adequately explored in these studies. A substantial proportion of the treated patients were on tamoxifen at the time of cognitive testing, introducing a potentially confounding factor.

It is important that, in three of the studies, patients who had not received a uniform chemotherapy regimen were examined. In the study of Wieneke and Dienst, patients had been treated with CMF, CAF, or a combination of both and with various numbers of cycles. In the study of Ahles et al., most of the patients with breast cancer were treated with CMF or CAF, although doses and number of cycles were not specified. The study of Brezden et al. included patients who had undergone treatment with either CMF or CEF. There were no trends to suggest differences in cognitive function between patients who received CMF and patients who received CEF, but clearly the sample sizes were too small for comparison.

The use of medications before and after chemotherapy is not well documented in any of these studies. Antiemetics such as glucocorticoids, serotonin receptor (5-HT₃) antagonists, metoclopramide, and prochlorperazine can affect the central nervous system, although such effects are generally not thought to be prolonged and thus would be unlikely to affect measurements of cognition several years after completion of chemotherapy.

Appropriately, all of these studies used validated instruments to assess cognitive function and attempted to control for possible psychologic factors that may have had an effect on cognition. It should be noted that these studies are mainly exploratory and investigated the association between multiple clinical factors and cognitive domains in relatively small samples.

ADJUVANT HORMONAL THERAPY AND COGNITION

Despite evidence from both animal model and human studies suggesting a probable role for estrogen in cognitive function, few studies have directly investigated the cognitive impact of hormonal treatments in women with breast cancer (26–28).

Estrogen and Cognitive Functioning

Neurobiology of estrogen. Estrogen receptors are found in many areas of the brain, including the cerebral cortex, hypothalamus, pituitary gland, and the limbic system (the amygdala and the hippocampus, which plays an important role in memory) (29). Possible mechanisms by which estrogen may affect neuropsychologic function include modulation of neurotransmitters, direct effects on neurons, prevention of cerebral ischemia, and alterations in lipoproteins.

Estrogen appears to promote cholinergic activity in the brain. Ovariectomized rats treated with estradiol have increased choline acetyltransferase activity (30,31) and perform better on behavioral memory tasks than estrogen-deprived ovariectomized rats (32). Estradiol also prolongs survival of cholinergic neurons (33). These studies and others (34) support the hypothesis that estrogen may improve cognitive function by promoting cholinergic activity in the brain.

In rats, estradiol administration has also been shown to induce serotonin receptors in forebrain regions that are involved in cognition and behavior (35). Conversely, tamoxifen acts as a pure estradiol antagonist with respect to serotonergic mechanisms in the brain, probably by blocking estradiol receptors involved in mediating estradiol action on central serotonergic mechanisms (36).

Estrogen administration results in sprouting of axons and dendritic spine formation in the rat hypothalamus and CA1 hip-

pocampal pyramidal neurons (a region associated with memory and learning), thus increasing synaptic plasticity (37,38). Conversely, ovariectomy results in a loss of dendritic spine density in CA1 pyramidal cells in rats (39). Thus, estrogen appears to be involved in maintaining and regulating neuronal circuitry in several brain regions that are important in cognition.

Postmenopausal estrogen therapy has a favorable effect on serum lipid profiles by reducing low-density lipoproteins and increasing high-density lipoproteins, which may slow progression of cerebral atherosclerosis and thus prevent cognitive decline (40). Estrogen also modulates the expression of the apolipoprotein E gene (41), one variant of which is associated with an increased risk for Alzheimer's disease and preclinical cognitive decline (42).

Effect of estrogen on cognitive function in women. Several studies have indirectly examined the role of estrogen on cognitive function by studying cognition across or between conditions associated with different hormone levels, such as different phases of the menstrual cycle, surgical menopause, and estrogen replacement therapy, as reviewed by Haskell et al. (43). Studies that have examined cognitive function during different phases of the menstrual cycle (44–46) suggest that high levels of estrogen may be associated with better verbal memory and worse visual-spatial ability. These findings are consistent with what is known about sex differences in specific cognitive abilities, that is, that women tend to excel in verbal abilities, perceptual speed, and accuracy, whereas men excel in spatial and quantitative abilities (47,48).

Studies on the effect of estrogen replacement therapy in postmenopausal women are difficult to evaluate because of extreme heterogeneity in the subjects, type and duration of hormone replacement, and tests used to assess cognition. In postmenopausal women, modest improvements in some aspects of cognitive function, particularly verbal memory, have been demonstrated with estrogen in some small randomized placebo-controlled studies (49–51) but not in others (52–55). In addition, some epidemiologic studies have indicated that estrogen replacement therapy may delay the onset of Alzheimer's disease (56,57), although this effect was not observed in other studies (58–60). At least three recent comprehensive reviews (43,61,62) of the studies in this area concluded that, although there are plausible biologic mechanisms by which estrogen may lead to improved cognition and there is encouraging evidence for a beneficial effect of estrogen from observational studies, there is currently inadequate evidence from randomized controlled trials to support or refute the hypothesis that estrogen replacement therapy improves cognitive function.

Effect of antiestrogens on cognitive function in women. There are few studies evaluating the impact of tamoxifen on cognitive function. In a cross-sectional, observational study of nursing home residents, Breuer and Anderson (63) found that those receiving tamoxifen had better cognitive skills for decision making, as assessed by nursing home staff. Clearly, there are serious methodologic limitations with this study design that make these data difficult to interpret. Paganini-Hill and Clark (64) described the opposite effect in a population-based case-control study. In this study, women were mailed a questionnaire in which cognitive function was assessed in a limited way with the use of three tests: clock drawing, copying a box drawing, and narrative writing to describe a pictured scene. Although no difference was seen in performance on the three cognitive tests,

more women who used tamoxifen for 4 or 5 years, and especially the current users, reported seeing their physician for memory problems than nonusers.

Raloxifene is a selective estrogen receptor modulator with estrogen agonist effects on bone and lipid metabolism and estrogen antagonist effects on reproductive tissues. Its effects on the human brain remain to be established, although animal model studies suggest that it may exert estrogen-like effects on cholinergic neurotransmission (65). A study on the effect of raloxifene on osteoporosis in postmenopausal women examined the effect of raloxifene on cognitive function as a secondary end point (66). Women were randomly assigned to receive raloxifene or placebo, and no difference in performance was observed between the two groups on tests of cognitive function after treatment for 1 year. Similarly, treatment for 3 years did not affect overall cognitive scores (67). However, a trend toward less of a decline on verbal memory and attention was noted in women receiving raloxifene.

Aromatase and Cognitive Function

Conversion of adrenally secreted androstenedione to estrone by aromatase predominantly in adipose tissue (and then to estradiol by 17 β -hydroxysteroid dehydrogenase) is the major source of estradiol in postmenopausal women. Aromatase is also expressed in many regions of the brain (68–70), although little is known about its function and its implications for cognitive functioning (71).

Aromatase inhibitors have recently been shown to be superior to tamoxifen as first-line therapy for metastatic breast cancer in postmenopausal women, and randomized trials examining their use in the adjuvant setting are ongoing (72,73).

In a quality-of-life study in a randomized trial of the aromatase inhibitor letrozole versus megestrol acetate in women with advanced breast cancer, patients taking letrozole experienced an improvement in subjective cognitive function, as measured by the cognitive subscale of the EORTC QLQ-C30 (28). Given the inherent difficulties with subjective measures of cognitive function, the interpretation remains unclear.

IMPLICATIONS OF AVAILABLE DATA FOR INFORMED CONSENT

For many women, particularly those with small, axillary lymph node-negative breast cancer, the absolute benefits of adjuvant systemic therapy will be quite small (5,74). Nevertheless, surveys in women who have undergone adjuvant chemotherapy for breast cancer consistently showed that many perceive the treatment as worthwhile, even for a very modest benefit in survival (75–77). The few data available on patients' preferences regarding hormonal treatment suggest that toxicity may be of more concern (78).

An informed patient decision about adjuvant chemotherapy has to be based on a clear understanding of the relative risks and benefits of such treatment. Should the possibility of cognitive impairment be part of such a discussion? Currently, this possibility must be considered controversial given the methodologic limitations of the studies published to date. In the authors' view, the effect should be confirmed in large, well-designed longitudinal studies before it becomes part of the routine adjuvant therapy discussion. However, in the meantime, it can be reassuring to women who complain of cognitive impairment during or after their systemic breast cancer therapy to learn that this

issue is being actively investigated. In any case, patients' complaints of cognitive dysfunction should prompt a professional evaluation, given that they may be intertwined with anxiety and depression.

FUTURE RESEARCH DIRECTIONS

Confirmation of an Effect of Adjuvant Chemotherapy for Breast Cancer on Cognitive Function

The consistent findings of the studies reviewed above strongly suggest a measurable (7–11) and sustained (11) effect of adjuvant chemotherapy for breast cancer on cognitive function, although all studies had multiple confounding factors as noted. Thus, the immediate priority for research in this area is to confirm this effect in the setting of large, well-designed longitudinal studies. Such studies are currently underway (79,80). Using patients as their own controls by measuring cognitive function before and at various times during and after adjuvant chemotherapy is an important advantage of such studies. However, methodologic difficulties still exist. The baseline time point is problematic because it is not possible to identify patients before their cancer diagnosis. Nevertheless, the psychologic effects of a recent cancer diagnosis would most likely result in a lower (rather than higher) true baseline measurement of cognitive function, so that the observation of a subsequent worsening after chemotherapy could still be considered valid. Measures and their timing will need to be carefully chosen, and alternative test versions should be developed to avoid the impact of possible practice effects. Such longitudinal studies afford the opportunity to collect demographic, treatment, psychologic, biologic, and functional imaging data that could be analyzed to identify factors that might be associated with cognitive impairment after chemotherapy. Their results should help further to define the incidence, nature, severity, functional significance, and time course of cognitive dysfunction in this setting.

Examination of Possible Contribution of Adjuvant Hormonal Therapies

In future longitudinal studies of chemotherapy-treated patients, it will be important to carefully collect data on chemotherapy-induced menopause and on the use of adjuvant hormonal therapy. These potential confounders thus will be able to be appropriately controlled for in the analyses.

The cognitive effects of adjuvant hormonal therapies such as tamoxifen (and perhaps in the future selective estrogen receptor modulators and aromatase inhibitors) are largely unexplored. Well-designed studies to look at the impact of adjuvant hormonal therapies should be a research priority, particularly given the mounting evidence of the importance of estrogen in cognition.

Studies of Possible Effects of Chemotherapy in Adjuvant Treatment of Other Cancers

A confirmed effect of adjuvant chemotherapy on cognition in breast cancer patients will, of course, mean that it is likely that chemotherapy has similar effects in other types of cancer. Studies of the effects of adjuvant chemotherapy in other cancer types is likely to help sort out questions about the cognitive toxicity of specific chemotherapy agents and the possible interactions of age and sex. A study of testicular cancer patients treated with platinum-based therapy has shown deficits in attentional pro-

cesses when compared with those processes in similar patients not treated with chemotherapy, although the possible impact of anxiety was unclear (81). Studies of colorectal cancer patients treated with adjuvant 5-fluorouracil will also be of interest, particularly given the known neurotoxicity of high doses of this agent and the observation that 5-fluorouracil was a component of the chemotherapy used in all of the five published breast cancer and cognition studies reviewed above.

Incorporation of Objective Measures of Cognition in Clinical Trials of Adjuvant Therapy

If effects of chemotherapy and/or hormonal therapies on cognition are confirmed in longitudinal studies, arguments should be made for the routine incorporation of objective cognitive function assessment as part of the toxicity evaluation in phase II studies. In randomized comparisons (phase III trials) of adjuvant systemic treatments, assessment of cognitive function will be expensive because it requires one-on-one administration of tests by trained personnel. Two strategies may be followed. First, cognitive function may be studied in subgroups of large-scale clinical trials. Second, abbreviated and tailored yet validated and sensitive versions of formal neuropsychologic tests or computer-based tests should be developed (82,83).

Investigation of Interventions to Prevent or Minimize Cognitive Dysfunction After Cancer Treatment

Ultimately, if an effect is confirmed, intervention trials to minimize cancer therapy-induced cognitive impairment will be important. Possible interventions that might be investigated in clinical trials could include cognitive rehabilitation strategies or, perhaps, even the use of pharmacologic agents such as cholinesterase inhibitors or γ -aminobutyric acid derivatives (84).

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NOTES

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