Cancer Investigation, 30:135–148, 2012
ISSN: 0735-7907 print / 1532-4192 online

DOI: 10.3109/07357907.2011.636116

informa
healthcare

CLINICAL TRANSLATIONAL THERAPEUTICS

Neurocognitive Effects of Chemotherapy and Endocrine Therapies in the Treatment of Breast Cancer: Recent Perspectives

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With an estimated 207,090 patients diagnosed with breast cancer in 2010, the role of chemotherapy-induced cognitive impairment is of growing importance. Studies to determine the impact of chemotherapy-induced cognitive impairment have been hindered by difficulties in study-design, in particular, study methodology. Here, we present a review of existing studies and discuss several mechanisms for chemotherapy-induced neurocognitive impairment in breast cancer patients, such as direct neurotoxic injury, telomere shortening, oxidative stress, cytokine dysregulation, estrogen-mediated effects, and the role of certain genetic polymorphisms. Decreased estrogen levels may serve as a link between multiple mechanisms potentiating the effects of the chemotherapy-induced cognitive impairment.

Keywords: Chemobrain; Cognitive impairment; Breast cancer; Pharmacology, Chemotherapy

INTRODUCTION

Improvements in early detection and increased efficacy of treatment mean the number of cancer survivors are burgeoning, with an estimated 20 million cancer survivors in the U.S. by the year 2020 (1). Chemotherapy-induced cognitive impairment has been recognized as a serious challenge facing cancer survivors by both the President's Cancer Panel and the National Coalition for Cancer Survivorship (2,3). Cognitive impairment may affect the patient's ability to re-enter the work force, decrease participation in social activities, negatively affect quality of life and provoke feelings of depression. A better understanding of the late-effects of cancer treatment will allow healthcare practitioners to advise appropriate treatments for their patients (4). Further elucidation of the mechanisms of these cognitive impairments is needed in order to determine whether all patients are at equal risk of cognitive decline. With 207,090 estimated new breast cancer cases diagnosed in 2010, potential implications of chemotherapy-induced cognitive impairment are vast (1,5).

The percentages of patients suffering from chemotherapy-induced cognitive deficits vary widely with estimates ranging from 17% to 75%, based on study design and other factors (6–8). Yet, contrary studies have been noted in patients with early stage breast cancers, likely due to lack of consistency in study design (9, 10). Difficulties with study design make careful analysis of the neurocognitive effects of the breast cancer treatment difficult. Patients are often treated with multiple medications making neurocognitive comparisons extremely difficult. A recent meeting of the International Cognition and Cancer Task Force defined standards that, in the future, will no doubt simplify comparisons (Figures 1 and 2). Currently, most studies demonstrate acute cognitive deficits as a result of breast cancer chemotherapy (11, 12). Longer term, postchemotherapeutic changes only seem to persist in specific subgroups of patients, lasting for years after treatment (13–15). Patients report memory lapses, poor concentration and attention, and periods of confusion that tend to persist after therapy (16). Furthermore, recent studies have shown impairments in working memory, executive function, processing speed, verbal fluency and memory, visuospatial memory, and other cognitive deficits (6, 7, 17–21). Patients may be predisposed to neurocognitive damage as a result of chemotherapy depending upon hormonal therapy, menopause status, anxiety, depression, fatigue, genetic predisposition, paraneoplastic syndrome, and surgical course undertaken (4, 22). Additionally, the role of estrogen in chemotherapy-induced cognitive decline warrants further evaluation. Further research is needed to better understand the specific mechanisms of chemotherapy-induced neurocognitive decline in order to better predict which patients are at risk, as well as to devise treatment regimes that effectively treat these patients while minimizing side effects.

EVALUATION AND CONFOUNDING FACTORS

With unclear criteria, the diagnosis of chemotherapy-induced cognitive decline often involves a wide range of tests. In general, the frontal area of the brain is most affected, displaying subcortical toxicity with cognitive dysfunction in the areas of information and processing speed, memory retrieval, and executive function (23). As such, patients are generally observed for a range of skills including attention, mental

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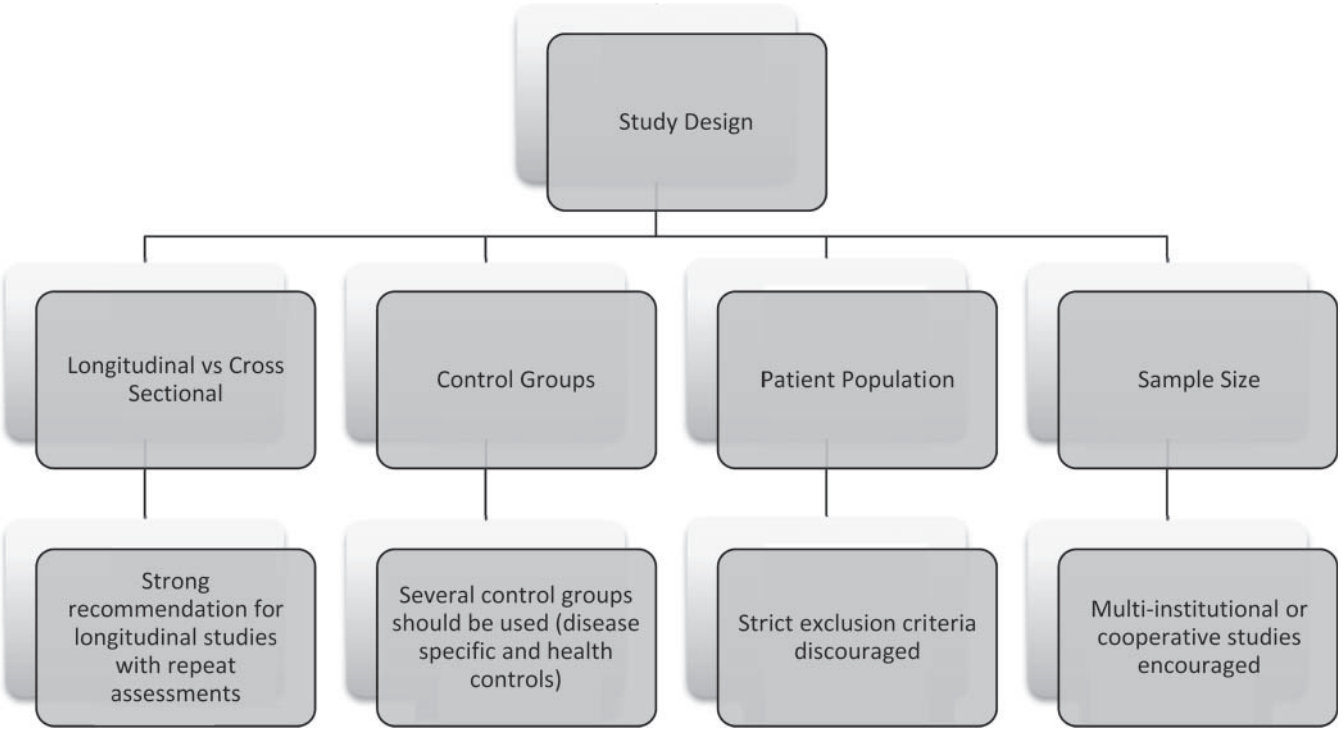

Figure 1. Recommendations of the international cognition and cancer task force (125).

flexibility, reaction time, visuospatial memory, motor function, and verbal function (4).

Magnetic resonance imaging (MRI) studies of postchemotherapeutic patients have shown reduced volume of brain structures essential in executive function (e.g., frontal cortex) as well as changes in the integrity of the white matter (24–26). In addition, functional MRI (fMRI) scans reveal reduced activation of frontal areas during working memory tasks (27). A study with a set of monozygotic twins, one chemotherapy-naive and the other 22 months postchemotherapy, demonstrated only marginal differences in neuropsychological test performance, but marked differences in fMRI images. The postcancer twin had expanded spatial extent of brain activation during working memory tasks, suggesting that additional brain areas had been recruited to compensate for changes in cognition (28). The twins also experienced significant differences in self-reported cognitive changes that were not evident in neuropsychological testing. Positron emission tomography (PET) studies corroborate evidence of

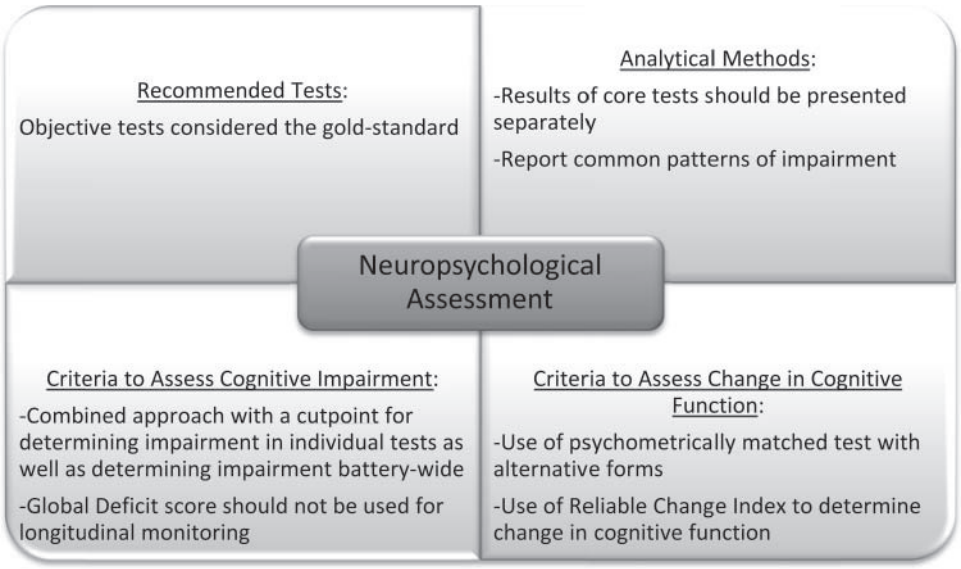

Figure 2. Recommendations of the international cognition and cancer task force (125).

compensatory recruitment of additional areas of the brain. Comparing breast cancer chemotherapy patients 5–10 years post-treatment, blood flow in the frontal cortex and cerebellum in chemotherapy patients was significantly altered, suggesting greater recruitment of these areas (29).

Studies to determine the impact of neurocognitive impairment have been hindered by a number of factors. For example, small sample sizes limit the ability to examine performance across individual tests. Other studies rely on the use of known normal values for control groups rather than performing a longitudinal study. Furthermore, cognitive impairment can exist prior to chemotherapy treatment in up to 35% of patients even when controlling for depression and other mood disturbances. Therefore, longitudinal studies with a baseline prechemotherapy treatment assessment are essential to distinguish cognitive changes due to chemotherapy (8, 17, 30, 31). Interestingly, meta-analyses show that results are highly dependent on study design (23, 32). Studies comparing chemotherapy patients to normative data found significant differences in four domains of cognitive function. On the other hand, when baseline scores were used, effect sizes were not significant in any domain (33). Further difficulties exist in the interpretation of the deficit pattern and their severity, with some studies defining impairment as one standard deviation below the norm on tests, others using two standard deviations. Other authors require patients to score below the norm on multiple tests in order to qualify as impaired. Timing of testing after therapy or diagnosis varies from study to study. The lack of a consistent definition of cognitive impairment further complicates comparisons between studies. For example, when mean effect sizes were differentiated by method of comparison (i.e., controls, normative, or baseline data), effect size in each cognitive area ranged from negligible to moderate (33).

An additional challenge for determining chemotherapy-induced cognitive impairment is the methodology chosen to evaluate patients. Patient self-evaluation has repeatedly been a poor indicator of neurocognitive impairment, strongly linked to anxiety and depression, with complaints more highly linked to mood and fatigue than objective test of cognitive function (7, 18, 21, 22, 34). Commonly utilized tests are also unable to detect subtle changes in highly educated participants. Practice effect, the influence of past experience on repeating a similar test, is of particular concern in longitudinal studies where cognitive improvement can sometimes be seen in the control group (8, 30, 35, 36).

Various studies disagree on the prognosis of those suffering from chemotherapy-induced neurocognitive impairment, with some studies finding the abatement of side effects soon after the cessation of therapy while other studies find evidence of lingering impairment. For example, at 4 years post-therapy, despite earlier results demonstrating impairment, neuropsychological performance was similar in patients who had received high dose, standard dose, or no chemotherapy treatment (34). Conversely, lymphoma and breast cancer survivors exhibited long-term neurocognitive deficits 9.5 years post-therapy (13). In this study, patients treated with systemic chemotherapy had lower scores in domains of verbal memory and psychomotor function. In addition, these patients were more likely to score in the lower quartile on the neuropsychological performance index (13). Verbal memory and psychomotor functioning are highly sensitive to cerebral dysfunction and thus present valuable models for testing long-lasting deficits (13). To assess the longitudinal aspect of these deficits, a series of tests designed to survey seven cognitive domains showed that 61% of patients had a decline relative to baseline in one or more cognitive domains 6 months after treatment initiation. At 18 months, 50% of those who had previously shown impairment had improved while 50% remained stable, indicating that cognitive deficits are long-term in only a subset of cancer survivors (8). Variability in study design contributes to the heterogeneity of data collected from studies. Organizing studies by control method is one way to make order from chaos (Table 1A, B, C). When analyzed by control method (test norms, healthy controls, or diseased controls), evidence for chemotherapy-induced cognitive dysfunction seems strongest when compared to diseased controls. In addition to chemotherapeutic treatment, many patients with breast cancer receive

Table 1A. Chemotherapy and Cognitive Change- Studies Using Test Norms

Study	Participants	Chemotherapy	Evaluation	Results
Hermelink et al. (32)	• 101 patients	• Epirubicin, Cyclophosphamide, paclitaxel • Cyclophosphamide, methotrexate, fluorouracil • subrandomized to receive darbepoetin α	• Evaluated before chemotherapy (T1) and approx. 5 months later before last chemo treatment (T2)	• At T1, group means ranged below test norms in 5 of 12 cognitive tests • At T2, cognitive decline evident in 27% of patients while there was improvement in 28% of patients • No difference noted between treatment regimens
	• Control group = test norms	• N/A		• Therapy-induced menopause and darbepoetin α did not influence cognition
De Jong et al. (126)	• 157 (stages I, II, and III)	• Doxorubicin-containing schedule (n = 111) • CMF (n = 46)	• Interviewed at 1st, 3rd, 5th cycles of adjuvant therapy and 4 and 12 weeks after completion of therapy	• Women who had undergone a mastectomy suffered more mental fatigue than those who had undergone a lumpectomy
	• Control group = test norms	• N/A		• Course of mental fatigue and motivation were not significantly different between the two treatment groups

CMF = cyclophosphamide, methotrexate and fluorouracil.

Table 1B. Chemotherapy and Cognitive Change: Studies Using Healthy Controls

Study	Participants	Chemotherapy	Evaluation	Results
Castellon et al. (18)	• 36 patients	• Chemotherapy	• 2–5 years postdiagnosis and treatment	• Chemo-treated patients fared significantly worse in domains of verbal learning, visuospatial functioning, and visual memory than those who had surgery only • No significant difference between chemotherapy treatment regimens • Patients receiving chemotherapy and tamoxifen showed the most cognitive dysfunction
	• 17 patients	• Surgical therapy but no chemotherapy		
	• 19 healthy patients (age-matched)	• N/A		
Brezden et al. (17)	• 31 patients	• CMF (n = 12) • CEF (n = 19)	• Patients currently receiving chemotherapy treatment	• Overall cognitive function scores were lower for current chemo patients than for control patients • More patients who were receiving or had in the past received chemo had moderate or severe impairment than in the control group • No significant differences between CMF and CEF groups
	• 40 patients	• CMF (n = 21) • CEF(n = 17) • Other chemo regimen (n = 2)	• Patients completed treatment on avg. 2 years previously	
	• 36 healthy controls	• N/A	• N/A	
Tchen et al. (127)	• 100 patients	• CEF (n = 64) • CMF (n = 11) • AC (n = 17) • Other (n = 8)	• Patients currently receiving three or more treatments of chemotherapy • Patients reassessed at 1 to 2 years after initial treatment	• Patients experienced a higher incidence of moderate or severe cognitive impairment (16% patients vs. 4% controls), • Patients experienced more fatigue than controls (31% vs. 46%) • Patients experienced more symptoms of menopause (Median FACT-ES scores was 58 patients vs. 64 controls) • Patients self-reported quality of life was poorer than controls, especially in areas of physical and functional domains • There was a strong correlation between fatigue, menopausal symptoms and quality of life, but none were significantly associated with cognitive function
	• 100 patient- matched healthy controls	• N/A	• Assessment done in conjunction with matched breast cancer patients	

CEF = cyclophosphamide, epirubicin, and fluorouracil, CMF = cyclophosphamide, methotrexate and fluorouracil, AC = Adriamycin and cyclophosphamide.

antiestrogenic endocrine treatments, including tamoxifen, raloxifene, and anastrozole. The optimal duration of these treatments is still under investigation but generally ranges 2 to 5 years. Questions have arisen about how these hormonal therapies may affect the brain and cognitive function. The action of estrogen in the brain is not completely understood, but preclinical data indicate that it may have neurotrophic and neuroprotective actions (37). Mounting evidence suggests that estrogen-activated estrogen receptors (ERs) stimulate neuronal differentiation and survival, increase neurotransmitter levels, and prevent ischemic damage (37–39). The idea that estrogen is involved in cognitive function is strongly supported by the fact that estrogen receptors are present throughout the hippocampus, frontal lobe, and cerebral cortex of the brain (39). However, clinical data suggests that role of estrogen in the brain is somewhat more complicated. For instance, the Women's Health Initiative Memory Study (WHIMS) demonstrated that postmenopausal women receiving hormone replacement therapy (estrogen or estrogen plus progesterone therapy) experienced greater cognitive decline than their counterparts receiving no hormone replacement therapy (40, 41). Tamoxifen is a selective estrogen receptor modulator (SERM) with antiestrogenic effects in the breast but estrogenic effects in the bone and endometrium. The effects of tamoxifen in the brain are not well understood. While evidence for impairments due to tamoxifen use has been established in mice, evidence in humans has been more difficult to establish with many studies using subjects exposed to both endocrine and chemotherapeutic treatment (42). Still, some studies have shown a trend to neurocognitive deficits. Though limited by the use of mail-in questionnaires, Pagini-Hill's large study of more than 1,000 women demonstrated that women who were currently using tamoxifen had a lower mean complexity score on a narrative writing task than nonusers. Effects of tamoxifen seemed transient, as cognitive differences between long-term tamoxifen users (> 5 years) and nonusers were not significant (43). Studies on the effects of aromatase inhibitors on cognition point toward increased incidence of cognitive impairment (44). Comparisons of tamoxifen users with users of aromatase inhibitors have been inconsistent, raising interesting questions about the role of estrogen in cognitive decline as aromatase inhibitors lower serum estrogen whereas tamoxifen does not (44–46). One way to account for the heterogeneity of data is the variety of study designs. Table 2 sorts some of the most recent studies, analyzing outcomes of patients receiving endocrine therapies by control method. (Table 2)

MECHANISMS OF NEUROLOGICAL IMPAIRMENT

Direct neurotoxicity

Direct neurotoxic injury to neurons or other brain structures has been suggested as a mechanism for chemotherapy-

Table 1C. Chemotherapy and Cognitive Change: Studies Using Diseased Controls

Study	Participants	Chemotherapy	Evaluation	Results
Bender et al. (30)	• 19 patients (stage I, II) • 15 patients (stage I, II) • 12 ductal carcinoma patients	• Chemotherapy only (cyclophosphamide containing regimen) • Chemotherapy and tamoxifen (cyclophosphamide containing regimen) • Surgical treatment (no chemotherapy or tamoxifen)	• T1: after surgery/ before chemo, T2: within 1 week of conclusion of chemo, T3: 1 year after T2	• Recipients of chemo plus tamoxifen displayed the broadest declines with changes in visual memory and verbal working memory • Women treated solely with chemotherapy exhibited declines in working memory only
Mehnert et al. (22)	• 23 high-risk patients • 24 high risk patients • 29 breast cancer patients	• EC + standard dose CMF (n = 23) • EC + high dose CTM chemotherapy (n = 24) • Surgery and radiation treatment only	• On average 63 months after last treatment	• No significant differences in subjective neurocognitive measures between the three groups • Standard-dose chemotherapy had consistently higher levels of self-perceived cognitive defects and fatigue
Schagen et al. (21)	• 39 breast-cancer patients • 34 control patients (age-matched axillary lymph node negative breast cancer patients)	• CMF (6 courses) ± 3 years of tamoxifen (time since treatment: 1.9 years) • No chemotherapy (time since local therapy 2.4 years)	• Approximately 2 years after treatment	• Likelihood of cognitive impairment was higher in chemotherapy treated group versus control group • Hormonal therapy had no influence of patient's self-reports of symptoms or on objective neurocognitive tests
van Dam et al. (7)	• 34 high risk patients • 36 high risk patients • 34 control patients with stage I breast cancer	• High dose chemotherapy + tamoxifen (FEC + CTC) • FEC • No chemotherapy (time since local therapy mean: 2.4 years)	• Approximate-l- 2 years after treatment	• High dose chemotherapy appeared to impair cognitive functioning more than standard dose (32% vs. 17% with 9% of the control group experiencing cognitive dysfunction)

CMF = cyclophosphamide, methotrexate and fluorouracil, CTC = cyclophosphamide, thiotepa, and carboplatin, CTM = cyclophosphamide, thiotepa, and mitoxantrone, EC = Etoposide and Carboplatin FEC = fluorouracil, epirubicin, and cyclophosphamide.

Table 2A. Recent Studies and Associated Outcomes in Patients Receiving Endocrine Therapies Between Group Comparisons

Study	Participants	Treatment	Evaluation	Results
Bender et al. (44)	• 15 patients • 16 patients	• Anastrozole • Tamoxifen (no group differences in the number of women receiving chemotherapy before hormone therapy)	• After a minimum of three months of therapy	• Treatment with anastrozole resulted in greater verbal/visual learning and memory impairment
Phillips et al. (46)	• 22 patients • 37 patients • 28 patients • 33 patients (all patients postmenopausal women with hormone receptor positive breast cancer)	• Tamoxifen • Letrozole • 2 years tamoxifen followed by 3 years letrozole • 2 years letrozole followed by 3 years tamoxifen • (study controlled for chemotherapy treatment)	• After 5 years of drug treatment • Within 2 days after ceasing letrozole treatment • Within 14 days after ceasing tamoxifen treatment	• Letrozole patients had better overall cognitive function than those taking tamoxifen • In comparison to tamoxifen, aromatase inhibitors are unlikely to impair cognition
Hermelink et al. (128)	• 30 patients • 62 patients	• No antiestrogen therapy • Estrogen therapy (tamoxifen, anastrazole, letrozole) • (Both groups received chemotherapy)	• Before the start of cancer therapy (T1) • Toward the end of neoadjuvant therapy (T2) • 1 year after baseline (T3)	• Antiestrogen treatment with tamoxifen, anastrazole, or letrozole did not impact cognition

Table 2B. Recent Studies and Associated Outcomes in Patients Receiving Endocrine Therapies: Healthy and Diseased Controls

Study	Participants	Treatment	Evaluation	Results
Jenkins et al. (129)	• 94 female breast cancer patients	• Anastrozole, tamoxifen alone or combined (mean treatment time = 36 months) • None received chemotherapy	• At routine clinic visits	• Endocrine therapy patients were impaired on processing speed tasks and verbal memory
	• 35 healthy postmenopausal women (control group)	• N/A		
Jenkins et al. (10)	• 85 women with early stage breast cancer who received chemo	• Chemotherapeutic treatment	• Tested at baseline (T1), post chemotherapy or 6 months (T2), and at 18 months (T3)	• After 18 months, lasting cognitive decline noted in 18% of chemotherapy patients, 14% of endocrine/radiotherapy patients, and 11% of control group. • Patients who sustained treatment -induced menopause were more likely to show reliable declines in multiple measure of cognitive function. • Few experienced objective changes in cognitive function and the majority either were unaffected or improved over time.
	• 43 breast cancer patients scheduled for endocrine therapy or radiation therapy, but not chemo	• Treated with endocrine or radiation therapy only		
	• 49 healthy subjects (control group)	• N/A		
Schilder et al. (130)	• 30 postmenopausal patients	• AC chemotherapy + tamoxifen	• 2 years after completion of chemotherapy	• Both treatment groups fared worse than the control group on tests of verbal fluency and information processing speed • No significant difference between tamoxifen users and exemestane users
	• 50 postmenopausal patients	• AC chemotherapy + exemestane		
	• 48 healthy postmenopausal women (control group)	• N/A		
Collins et al. (131)	• 31 postmenopausal patients	• Tamoxifen	After surgery, closely coinciding with treatment initiation (T1) 5–6 months after T1 (T2)	• 39% and 64% of patients using tamoxifen and anastrazole, respectively, experienced cognitive decline from T1 to T2 compared with 7% of control group
	• 14 postmenopausal patients	• Anastrazole		
	• 28 healthy postmenopausal women	• N/A		
Schilder et al. (45)	• 80 patients	• Tamoxifen	After breast surgery but before endocrine treatment (T1) After 1 year of endocrine treatment (T2)	• Tamoxifen users experienced verbal memory and executive function deficits • Exemestane use was not associated with cognitive dysfunction
	• 99 patients	• Exemestane		
	• 120 healthy patients (control group)	• Surgery and radiation treatment only		
Bender et al. (30)	• 19 patients (stage I, II)	• Chemotherapy only (cyclophosphamide containing regimen)	T1: after surgery/ before chemo, T2: within 1 week of conclusion of chemo, T3: 1 year after T2	• Recipients of chemo plus tamoxifen displayed the broadest declines with changes in visual memory and verbal working memory • Women treated solely with chemotherapy exhibited declines in working memory only
	• 15 patients (stage I, II)	• Chemotherapy and tamoxifen (cyclophosphamide containing regimen)		
	• 12 ductal carcinoma patients (control group)	• Surgical treatment (no chemotherapy or tamoxifen)		

AC = doxorubicin and cyclophosphamide.

induced cognitive deficits. While chemotherapeutic agents do not typically cross the blood-brain barrier in significant doses, PET studies indicate that after intravenous (IV) administration, low levels of radiolabeled cisplatin and paclitaxel can be found in the brain (47). It is unknown whether these levels may cause the cognitive dysfunction noted in chemotherapy patients. Evidence for direct neurotoxic injury exists in mice when cisplatin and cytarabine are administered in doses lower than those normally required to induce cell death. Increased cell death and decreased cell division are noted in the subventricular zone, the dentate gyrus of the hippocampus and corpus callosum (48). Particularly susceptible to the effects of these chemotherapeutic agents were neural progenitor cells and oligodendrocytes (48). Rats treated with cisplatin show degenerative changes in the central nervous system with focal areas of necrosis, neurophagia, gliosis, neurofibrallar accumulations, axonal shrinkage, and parenchyma, nonspecific vacuolar changes in white matter (49–52)

Telomere shortening

Chemotherapeutics may also affect telomeres. Located at the ends of chromosomes, telomeres protect against DNA degradation and recombination and play an important role in

supporting chromosomal stability (53). In the presence of telomerase, telomeres will shorten by 20–30 base pairs during replication (15). In situations of decreased telomerase, the shortening can be increased to 100 base pairs, leading to replicative senescence and apoptosis (54). The rate of telomere shortening is influenced by several factors including genetic variation and oxidative stress (55, 56). While telomerase activity naturally decreases with age, several chemotherapeutic agents, including anthracyclines, camptothecins, taxanes, alkylating agents, and epipodophyllotoxin-derived agents, have also been shown to decrease its activity (54, 57). Telomere shortening has also been observed in the leukocytes of breast cancer patients undergoing standard-dose chemotherapy, with telomerase activity below detection limit during chemotherapeutic treatment (56). While most neuronal cells are postmitotic, glial cells are mitotic and thus susceptible to telomere shortening (58, 59).

Although telomere shortening has been associated with Alzheimer's disease, more recent research suggests an associated with nondemented patients. One study of 2,734 elderly, nondemented patients (mean age 74) found that telomere length predicted change in modified mini-mental state exam scores; those with longer telomere lengths experienced fewer declines in global cognition over a 7 year period. In addition, at baseline, longer telomere length was associated with increased baseline attention and psychomotor speed (60). A UK study of 382 nondemented women twins (mean age 50) found significant correlations between telomere length and episodic memory, recognition memory, and, in particular, working memory ($p<0.013$). In twins with discordant telomere length, the twin with longer telomere length had significantly better recognition memory and working memory capacity (61). Thus, telomere length may serve as a biomarker for aging and a record of the burden of oxidative stress (60, 61). In addition, the cognitive outcome of stroke survivors has been linked to telomere length. Stroke survivors with longer telomere lengths exhibited less reduction in mini mental state exam scores and less dementia when evaluated at 2 years poststroke. These findings suggest that longer telomere length may serve as a protection against chemotherapy-induced neurocognitive deficits (62).

Oxidative damage

Oxidative stress can cause single and double DNA strand breaks and is the most frequent cause of DNA damage in neuronal cells (58, 63, 64). Oxidative damage can occur through exposure to foreign agents or result from an endogenous mechanism (15). Previously, oxidative damage has been associated with numerous neurodegenerative diseases such as Alzheimer's disease and Parkinson's (65). Patients displaying mild cognitive impairment exhibit higher levels of oxidative DNA damage in both peripheral leukocytes and the brain (65, 66). Many chemotherapeutic agents take advantage of the DNA damaging effects of oxidative stress; however, the effects of oxidative stress are not confined to abnormal cells. Evidence of oxidative damage has been seen in peripheral blood lymphocytes in breast cancer patients treated with chemotherapy. In addition, chemotherapy patients displayed decreased DNA repair abilities (67, 68). Chemotherapy treatment is associated with increased levels of nonprotein bound iron, increased levels of free radicals, and decreased antioxidant capacity, all factors suggested to increase oxidative stress (69, 70). It is proposed that methotrexate (MTX) treatment inhibits protective factors that may prevent radical damage. As a result, poly-unsaturated fatty acid chains within the cell membranes are more susceptible to attack by reactive oxygen species. These initial attacks signal other lipid peroxy radicals to form, triggering a cascade of cell membrane damage (71–76).

Further evidence for the oxidative damage mechanism is provided by analysis of brain protein and lipid oxidation due to i.p. (intraperitoneal) injection of adriamycin (ADR) in mice. Adriamycin administration increased levels of several oxidative markers, including 4-hydroxynonenal, protein carbonyls, and 3-nitrotyrosine (77). 4-hydroxynonenal is a reactive alkenal resulting from the reaction of amino acids and free radicals. Similarly, levels of 3-nitrtyrosine serve as a marker of attacks by reactive nitrogen species (RNS). Data also showed that the expression of multidrug resistant protein-1 (MRP-1) was upregulated in ADR-treated mice. The authors propose that this is due to the increase in glutathione disulfide (GSSG) or the increased GS-conjugate of ADR, which is transported out of the brain via MRP-1. In further studies, it was discovered that ADR-induced tumor necrosis factor (TNF-α) can lead to the production of RNS or reactive oxygen species (ROS) (78). Circulating TNF-α can lead to mitochondrial dysfunction, triggering apoptotic pathways. Researchers discovered that elevated levels of glutathione (GSH) in ADR-treated mice led to significantly less protein oxidation and lipid peroxidation (78).

Estrogen-mediated effects

Apart from the obvious changes in estrogen-mediated effects due to endocrine therapies, adjuvant chemotherapy can result in chemotherapy-induced amenorrhea in 77% of premenopausal women with breast cancer, a reflection of rapidly declining estrogen levels (39). Factors influencing the onset of chemotherapy-induced amenorrhea include the age of the patient and tend to be dose and chemotherapy-agent specific (79). Sixty-eight percent (68%) of patients treated with cyclophosphamide, methotrexate, and 5-fluoruracil therapy (CMF) develop chemotherapy-induced amenorrhea, while 34% of patients on an anthracycline-based therapy develop amenorrhea (79). In addition, the use of aromatase inhibitors after chemotherapy has been shown to decrease the synthesis of estrogen in peripheral tissues. Ovarian suppression associated with chemotherapy results in a rapid decline in estrogen levels. Deficiencies in estrogen have been reliably linked to deteriorations in verbal memory and cognitive function (80–84). In addition, some studies show a link between patients who have experienced treatment-induced menopause and those suffering neurocognitive impairment (10). The benefits of estrogen have been demonstrated in rhesus monkeys, where estradiol-treated subjects displayed increases in apical and basal dendritic spine density (85). Studies conflict, however, when examining the neuroprotective role that

estrogen may play in humans (80, 86). With estrogen receptors found in the cerebral cortex, hypothalamus, pituitary, and limbic system, several mechanisms for the role of estrogen in chemotherapy-induced neurocognitive impairment exist. Estrogen is known to increase levels of choline acetyltransferase (CHAT), an enzyme critical for the synthesis of acetylcholine (Ach), an important neurotransmitter in memory (87, 88). Administered to rats, estradiol increases levels of CHAT as well as the potassium-stimulated release of acetylcholine (39). Thus, lack of estrogen could have potential negative neurocognitive effects.

Estrogen plays an important role in relieving oxidative stress (89). Estrogen is known to scavenge hydroxyl radicals and inhibit the production of ROS. Overproduction of ROS or inability to enzymatically destroy these species may increase oxidative stress and cause cell damage (89). *In vivo* and *in vitro*, estrogen can increase the expression of superoxide dismutase (SOD) due to estrogen receptor activation (90). In a study examining the influence of hormone replacement therapy (HRT) on antioxidant activity and lipid peroxidation, SOD activity was significantly lower in postmenopausal women not treated with HRT, demonstrating the protective effects of estrogen (89). Another potential mechanism for the role of estrogen in chemotherapy-induced cognitive impairment involves its role in maintaining telomere length (91). At birth, telomere lengths are the same in men and women, but by adulthood women have longer telomeres, possibly due to the protective effects of estrogen (92). Estrogen has the ability to attenuate telomere shortening by protecting against ROS and stimulating telomerase (91, 93, 94). The loss of ovarian function and subsequent decrease in estrogen levels in chemotherapy-treated women can have devastating effects on cellular function, leading to sudden increases in oxidative stress and associated telomere shortening.

Cytokine dysregulation

Cytokines are polypeptides produced principally by lymphocytes and macrophages that mediate inflammation and immune responses. They have also been shown to modulate glial cell function, play a role in neural repair, and modulate neurotransmission (68, 95). Studies in both animals and humans demonstrate that dysregulation and stimulation of cytokines can be associated with cognitive deficits, including associations with Alzheimer's disease, multiple sclerosis, and Parkinson's (96–99). Paclitaxel, docetaxel, and carboplatin treatment have been correlated with schedule-dependent increases in interleukin-6 (IL-6), interleukin-1 (IL-1), interleukin-8 (IL-8), and interleukin-10 (100–102). IL-1 has the ability to cross the blood-brain barrier, particularly in the hypothalamus, and is known to decrease the influx of calcium into hippocampal neurons (103). TNF-α has been associated with demyelination in the brain (104). Elevated TNF-α levels are commonly associated with breast cancer. Cytokines can activate stress hormone cascades that can affect brain neurotransmitter system and affect mood and cognition (105, 106). Proinflammatory cytokine release in the brain induces "sickness behavior," decreased activity level, fatigue, diminished motivation, and cognitive disturbances (107, 108). The administration of endotoxin, increase levels IL-6, IL-1, TNF-α, soluble TNF receptors, which is correlated with decreased verbal and nonverbal memory functions, executive functions, and mood (35, 97). Lower levels of IL-6 have been correlated with higher memory functioning (98). High IL-6 levels are associated with poorer executive functioning; it should be noted that chemotherapeutic treatments with paclitaxel, docetaxel, and carboplatin have been specifically correlated with higher IL-6 levels (35, 109). The frequency of cognitive impairment is higher in subjects who have received interferon-α, TNF-α, or IL-2 in addition to chemotherapy (53% vs. 34%) (110). In addition, decreases in cognitive performance were noted in patients who received solely IL-2 or interferon-α without adjuvant chemotherapy (111, 112). Dysregulation of cytokines may be responsible for both direct and indirect mechanisms of cognitive changes in chemotherapy-induced cognitive impairment. Cytokine exposure, as occurs in chemotherapy treatment, may cause neuronal damage due to excitotoxic glutamate receptor-mediated damage and oxidative stress (99). The release of cytokines in response to DNA damage may begin a cycle of increasing DNA damage and cytokine activity (15). Once in the brain, TNF-α activates glial cell-induced local TNF-α production (TNF-α is detected in the hippocampus and cerebral cortex). In turn, this activates NO synthase production creating an overproduction of ROS species (e.g., peroxy-nitrite).

Possible roles of genetic polymorphisms

Polymorphisms in several candidate genes have been suggested as a mechanism for varying levels of susceptibility to chemotherapy-induced cognitive deficits. Genetic differences in Apolipoprotein E (APOE) expression are a likely model for this mechanism. APOE is a glycoprotein responsible for the uptake, transport, and distribution of lipids; it has also been shown to play a role in neuronal repair and plasticity (15, 113). In a study comparing the neuropsychological performance of long-term breast cancer and lymphoma survivors treated with standard-dose chemotherapy, survivors with at least one E4 allele scored significantly lower in visual memory and spatial ability (113). Though the mechanism of action of the APOE E4 allele is not fully understood, the E4 allele may be less effective than the E3 allele in promoting neuronal repair and neuritic growth and branching (15).

Genetic variability in cellular transporters can alter the amount of chemotherapeutic agent that can cross the blood-brain barrier. P-glycoprotein (P-gp) in the brain has the ability to influence cellular drug levels by transporting a wide variety of substrates out of the cell (15). Importantly, substrates of P-gp included many chemotherapeutic agents. High levels of P-gp may limit uptake, while reduced levels or activity may lead to an abnormal accumulation of drug and undesired side effects. Overall activity of P-gp is dependent upon the levels of expression of multidrug resistant-1 (MDR-1) gene and the functionality of the protein (114). Several polymorphisms of the gene that encodes for P-gp, MDR-1, have been identified (115). A significant correlation between

the C3435T polymorphism and expression and function of P-gp has been demonstrated (15, 114, 115). Those homozygous for this allele demonstrate significantly lower MDR-1 expression and decreased P-gp functionality (114). Thus, homozygous individuals may develop higher blood levels of drugs transported by P-gp such as doxorubicin, docetaxel, and vincristine. Animal studies reveal that mice deficient in P-gp have increased brain concentrations of vincristine (116). The suggestion that P-gp polymorphism may be involved in increasing neurotoxic effects of chemotherapeutic agents is supported by the finding the single nucleotide polymorphisms (SNPs) of MDR-1 have been associated with several hematological tumors, presumably because of the increased exposure to toxins due to decreased P-gp activity.

Brain-derived neurotropic factor (BDNF), a protein expressed in the prefrontal cortex and hippocampus, is associated with the repair and survival of neurons, the growth of axon and dendrite cells, and the long-term increases in synaptic function. Though limited data exist, these activities are thought to be related to the cellular basis for memory and learning (117, 118). A functional polymorphism of this protein, an aminoacid substitution of valine to methionine at codon 66, has been associated with reduction in memory, executive function and lower hippocampal volumes in noncancer patients (119–121). Currently, no studies have examined the relationship of this BDNF polymorphism with chemotherapy-induced cognitive changes, but it may be another important area for inquiry (15).

Altered levels of neurotransmitters present another possible mechanism for the changes seen in chemotherapy patients. Catechol-o-methyltransferase (COMT) is responsible for 60% of the dopamine metabolism in the frontal cortex (122). Dopamine is released while performing executive and memory functioning tasks. Decreased dopamine levels have been associated with poor performance on various cognitive tests (15). Thus, genetic factors affecting COMT may greatly influence cognition (122). One polymorphism (Val158Met) in the COMT gene, results in a significant change in enzymatic activity. Individuals with the valine allele have a COMT enzyme with four-fold higher dopamine metabolism. In line with this, breast cancer patients treated with chemotherapy who carry the methionine allele have been shown to perform better than those with the valine allele on neurocognitive tests (15). Table 3 presents a synopsis of proposed mechanisms for chemotherapeutic-induced neurocognitive injury along with relevant findings and references.

Table 3. Suggested Mechanisms for Neurocognitive Decline

Mechanism	Hypothesis	Relevant Findings	References
Direct Neurotoxic Injury	• Increased cell death and decreased cell division due to presence of chemotherapeutic agents	• PET studies have indicated the presence of chemotherapeutic agents in the brain after IV administration	(47, 49–52)
Telomere shortening	• Increased telomere shortening due to oxidative stress may lead to replicative senesce and apoptosis • Replicative senesce and apoptosis can be associated with neurotoxic injury	• Telomere shortening observed in leukocytes of breast cancer patients	(54, 56, 57)
Oxidative damage	• Chemotherapy treatment signals a cascade of oxidative stress that triggers cell membrane damage	• Patients displaying mild cognitive impairment exhibit higher levels of oxidative DNA damage	(65, 66, 69, 77)
Estrogen-mediated effects	• Estrogen plays a protective role in the brain by relieving oxidative stress • Decreased estrogen leads to decreased SOD, an important antioxidant responsible for protecting cells • Chemotherapy treatment often induces menopause, triggering lower levels of estrogen	• Estrogen has been shown to maintain telomere length, protect against ROS, and stimulate telomerase	(87–91, 93, 94, 98)
Cytokine dysregulation	• Increased levels cytokines may activate a stress hormone cascade that can affect cognition • Cytokine exposure may also lead to oxidative stress and neuronal damage due to excitotoxic glutamate receptor-mediated damage	• Chemotherapy treatment has been correlated with increases in IL-6, IL-8, and IL-10 • Increases in IL-6 and TNF-α have been correlated with cognitive dysfunction	(35, 97, 98, 100–102, 105, 106, 111, 112)
Role of genetic polymorphisms	• Patients with the APOE4 allele are less able to repair neuronal damage from chemotherapy • Differing levels of exposure to chemotherapy agents due to polymorphisms in P-gp • Polymorphisms in dopamine metabolism	• Patients with one E4 allele tested after several years chemotherapy score lower on visual memory and spatial memory tests • Mice deficient in P-gp have increased brain levels of vincristine • Breast-cancer patients with higher dopamine metabolism have better performance on neurocognitive tests	(113) (116) (15)

Conclusions and perspectives

Overall, mounting evidence supports the existence of neurocognitive side effects due to breast cancer therapeutic agents. While studies differ in design and in the number of participants affected, meta-analyses indicate strong evidence for neurocognitive deficits in executive function, information processing speed, verbal memory, and visual memory (33). Generally, frontal areas of the brain are affected and display subcortical toxicity. Neurocognitive damage in chemotherapy patients has been assessed with neuropsychological tests, and the results of these tests are bolstered by imaging results and electrophysiological tests, which show damage to brain areas involved in these responses.

As outlined here, suggested mechanisms for chemotherapy-induced neurocognitive deficits include: direct neurotoxic effects, telomere shortening, oxidative stress, estrogen-mediated effects, and cytokine dysregulation. The fact that only certain subsets of chemotherapy patients are affected may be a result of genetic polymorphisms that increase the effects of certain mechanisms. In addition, the action of several mechanisms may be necessary in order to produce a phenotype detectable by neurocognitive tests. Lowered estrogen levels may be the link for several of these mechanisms. Up to 77% of women experience chemotherapy-induced amenorrhea, the resulting lowered estrogen levels would deplete their ability to "fight off" oxidative species at the very time when their bodies are receiving large doses of chemotherapeutic drugs that cause oxidative stress to the body. Researchers in Korea demonstrated the importance of estrogen in maintaining telomere length, finding that long-term hormone therapy in postmenopausal women alleviated telomere attrition (91). A postmenopausal woman with C3435T polymorphism might demonstrate the perfect storm for chemotherapy-induced neurocognitive changes. The polymorphism might induce increased uptake of chemotherapy drugs. With decreased estrogen levels, she would be less able to handle the oxidative stress. Left unprotected by decreased estrogen levels, the telomeres would be even more marred by this oxidative stress.

Research is currently underway to find ways to prevent the detrimental effects of these chemotherapeutic agents. 5-FU and oxaliplatin have previously been shown to impair hippocampal recall tasks in rats, but one group demonstrated that cognitive impairments can be prevented by exercise after administration. Rats that were exposed to wheel running overnight after 5-FU and doxorubicin administration showed increased cognition relative to nonexercising rats (123). A pharmacologic method to prevent the neurocognitive decline induced by chemotherapeutic decline is being investigated by Aluise et al. (124). They found that 2-mercaptoethane sulfonate (MESNA) administration prevented DOX-induced plasma protein oxidation and TNF-α release. The study demonstrated the DOX oxidized plasma APOA1, which enhances macrophage TNF-α release, a contributor to potential cytokine toxicity. MESNA interacts with DOX to block this pathway. In conventional chemotherapeutic treatments, MESNA is administered with cyclophosphamide to prevent bladder damage, but it would be interesting to know if it could prevent other types of cellular damage as it may help to prevent the cytokine cascade that is part of the proposed mechanism of chemotherapy-induced neurocognitive decline.

In 2006 and again in 2011, in an effort to provide guidelines for future research as well as recommendations for symptom management, the International Cognition and Cancer Task Force brought together scientists to discuss evidence for and studies relating to chemotherapy-induced neurocognitive deficits. In order to simplify the comparison of results between studies and establish a consistent baseline, this panel made a series of recommendations, including the proposal that studies should assess a wide variety of domains and use a summary or global deficit score as impairments may occur in a variety of patterns. Future studies are needed with a focus on a longitudinal design, with careful selection of a control group. Control groups that are disease specific or undergoing a major-life event are preferred. Healthy control groups may also be included, but strict exclusion criteria (e.g., mild psychiatric illness) are discouraged. In order to address the concern for practice effect in longitudinal studies, the administration of tests with multiple versions and that is sensitive to change is recommended (23, 125). An accurate definition of chemotherapy-induced cognitive decline must be established so that new pharmaceutical agents can be evaluated for this potential side effect. Most importantly, in order to address potential treatments for chemotherapy-induced neurocognitive decline, further research into the mechanisms should be undertaken so that the underlying causes can be understood.

DECLARATION OF INTEREST

The authors report no conflict of interest. The authors alone are responsible for the content and writing of this paper.

Abbreviations

Ach	acetylcholine
ADR	adriamycin
APOE	apolipoprotein
CHAT	choline acetyltransferase
COMT	catechol-o-methyltransferase
DNA	deoxynucleic acid
EPSPs	excitatory post-synaptic potentials
fMRI	functional magnetic resonance imaging
GSSG	glutathione disulfide
HRT	hormone replacement therapy
IL	interleukin
IV	intravenous
MRI	magnetic resonance imaging
MRP-1	multi-drug resistant protein-1
MTX	methotrexate
PET	positron emission tomography
P-gp	p-glycoprotein
RNS	reactive nitrogen species
ROS	reactive oxygen species
SNPs	single nucleotide polymorphisms

SERM selective estrogen receptor modulator
SOD superoxide dismutase
TNF tumor necrosis factor

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