The Phenomenon of Chemo Brain

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As newer and more aggressive cancer therapies improve survival, issues relating to quality of life are becoming more prominent. One adverse effect of cancer treatment often not discussed between patient and provider is chemo brain, a constellation of cognitive deficits experienced by some individuals during and following chemotherapy. The purpose of this article is to define and review what is known about chemo brain and to offer suggestions to patients and professionals for managing this poorly understood phenomenon. The discussion that follows excludes disorders of thinking documented in the pediatric oncology population and the cognitive changes experienced by individuals with central nervous system (CNS) involvement and their treatments.

What Is Chemo Brain?

This cognitive deficit is referred to by a variety of terms (see Figure 1), but the most frequently used is chemo brain. It presents as weakened cognitive abilities, speed of information processing or reaction time, and organizational skills. Specific elements of thinking or cognitive function that can be affected negatively include language ability, memory, concentration, and attention. Executive function (which refers to hindsight, foresight, and judgment) also can be impacted. The clinical features of chemo brain, alone or in combination, can become a serious detriment to multitasking, create stress, and weaken performance when patients are challenged by high-level cognitive demands, including acquiring new skills (Ahles et al., 2002; Coyne & Leslie, 2004; Glaspy, 2002; Olin, 2001; O’Shaughnessy, 2003; Paraska & Bender, 2003; Parker-Pope, 2004; Saykin, Ahles, & McDonald, 2003).

Cognitive dysfunction has been reported in as many as 50% of women undergoing chemotherapy for breast cancer (Paraska & Bender, 2003). Severity has been described as mild to moderate (Foreman, 2003), with most deficits being subtle (Parker-Pope, 2004). High-functioning individuals may possess a heightened awareness of the deficits (Coyne & Leslie, 2004), leading to greater difficulties coping with this side effect. In a small minority of patients, chemo brain still is perceptible 10 years after treatment (Ahles et al., 2002; O’Shaughnessy, 2003; Saykin et al., 2003; Schagen et al., 2002; van Dam et al., 1998). Although the effect is believed to diminish with time, whether a patient returns to pretreatment levels of function is unknown (Breastcancer.org, 2002; Parker-Pope). Consensus exists that chemo brain has a potentially profound psychological impact on those affected by it.

To date, most studies have been conducted with female patients with breast cancer. Likely, this population has been researched because it represents the largest cancer survivorship group (Ganz et al., 2002). The age of patients during treatment laces them at life milestones where deficits are readily observable and potentially debilitating. Chemo brain also has been described in men and women with hematologic malignancies (Saykin et al., 2003) and in the testicular cancer population (Phillips & Pope, 2004). High-functioning individuals may possess a heightened awareness of the deficits (Coyne & Leslie, 2004), leading to greater difficulties coping with this side effect. In a small minority of patients, chemo brain still is perceptible 10 years after treatment (Ahles et al., 2002; O’Shaughnessy, 2003; Saykin et al., 2003; Schagen et al., 2002; van Dam et al., 1998). Although the effect is believed to diminish with time, whether a patient returns to pretreatment levels of function is unknown (Breastcancer.org, 2002; Parker-Pope). Consensus exists that chemo brain has a potentially profound psychological impact on those affected by it.

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Chemo fog  
Chemo brain (chemobrain)  
Central neurotoxicity  
Cognitive dysfunction  
Cognitive impairment  
Chemotherapy-induced cognitive impairment  
Neurocognitive dysfunction

Figure 1. Terminology  
Note. Based on information from Clark & Rummans, 2000; Coyne & Leslie, 2004; Glaspy, 2002.

Bernhard, 2003; Tannock, Ahles, Ganz, & van Dam, 2004). Interestingly, these are the populations in which bone marrow transplant may be part of the treatment regimen or has been extensively clinically trialed as such. Chemo brain may be underreported in other malignancies because of shortened life expectancy or a greater impact of other treatment effects. Similar cognitive deficits also have been described in people with HIV, hepatitis C, chronic fatigue syndrome, and acquired brain injury (National Academy of Neuropsychology, 2002). Clinical advances in treating these groups may provide valuable templates for management of chemo brain in the oncology population.

Quality of Life  
Minimal and subtle cognitive deficits may be profoundly disturbing and unacceptable to patients (Olin, 2001). The inability to maintain or advance their careers in the face of attention problems can occur. Academic performance also may be affected adversely (O’Shaughnessy, 2005). When deficits are obvious to others, chemo brain can be most difficult for family and friends (Clark & Rummans, 2000). Social role fulfillment may be affected when individuals find themselves unable to multitask as they once did (e.g., manage the challenges of child rearing, marriage, and other significant relationships). In extreme circumstances, it may even put dependants, such as minor children, at risk (Foreman, 2003). To survive the diagnosis and treatment of cancer only to be unable to resume pretreatment functioning can be devastating (Olin). Some patients even may call into question the very rationale for submitting to therapy in the first place. Ignoring or failing to recognize the potential impact can be devastating, demoralizing, and frightening.

Risk Factors for Chemo Brain  
Nonmodifiable and modifiable risk factors for chemo brain are not yet well defined. Genetic makeup may be relevant to understanding some of the observed deficits. A small study (Tannock et al., 2004) suggested that individuals who carry the e4 allele with breast cancer or lymphoma may have an increased susceptibility to chemo brain. Age is another nonmodifiable risk factor for developing chemo brain because hormone levels decrease with age. Supporting this is that adjuvant chemotherapy for breast cancer results in ovarian failure in as many as 77% of premenopausal women (Paraska & Bender, 2003). Deficiencies in estrogen and progesterone secretion have been associated with reduced attention, learning, and memory (Bender, Paraska, Sereika, Ryan, & Berga, 2001). The contribution of variables such as concurrent medications (e.g., antiemetics, sedatives) (Camp-Sorrell, 2000), disease process, and coping abilities are unknown (Breastcancer.org, 2002). The type of chemotherapy may be a risk factor: Cyclophosphamide, methotrexate, and fluorouracil have the strongest known association (Tannock et al.), and high-dose regimens increase the risk of developing chemo brain (van Dam et al., 1998) in vulnerable individuals. Schagen et al. (2002) documented that 32% of patients treated with high-dose chemotherapy experienced cognitive deficits as compared to 17% receiving standard doses. Treatment duration also may confer risk (Ahles & Saykin, 2001; Rugo & Ahles, 2003). Researchers do not understand why only some patients experience chemo brain or why it persists in some and resolves in others. More puzzling is that subjective complaints do not always correlate with objective measures of cognitive function (Schagen et al., 1999) and in at least one report, occurred prior to the first chemotherapy exposure (Paraska & Bender, 2003).

Conditions that can cause similar deficits or amplify those in chemo brain are summarized in Figure 2. Chemo brain can be diagnosed only after these have been ruled out.

Contributing Factors  
Evidence suggests that drugs commonly used alone or in combination to treat cancer have central neurotoxic effects (see Table 1). The existence of a constellation of cognitive deficits seen in association with exposure to chemotherapy suggests a possible link between cytotoxic drug exposure and diminished cognitive function. The mechanism by which these agents produce chemo brain is unclear.

The science of chemo brain is in its infancy. Three reviews of the literature have been published (Phillips & Bernhard, 2003; Rugo & Ahles, 2003; Tannock et al., 2004). These studies have suffered methodologic limitations, including descriptive studies, small samples, confounding variables such as genetic characteristics, and menopausal status. Selection bias existed in that a majority of subjects were women who were receiving or had completed courses of adjuvant chemotherapy for breast cancer. Inconsistent instruments were used to document cognitive dysfunction, and reliability and validity of instruments were not addressed. Statistical analyses often were ambitious given sample sizes (Glaspy, 2002; Olin, 2001; van Dam et al., 1998). Though limited in generalizability, the few small studies serve two powerful functions: They all validate the experience of chemo brain and support the continuing study of this side effect.

To date, no randomized clinical trials have been completed. Small intervention studies currently are under way and focus on pharmacologic (e.g., methylphenidate [Ritalin™, Novartis Pharmaceuticals, East Hanover, NJ], erythropoetin), psychosocial (Tannock et al., 2004), and compensatory cognitive rehabilitation techniques (Parker-Pope, 2004). Activity is under way on multiple research fronts to describe the anatomic and behavioral characteristics of chemo brain, describe correlating aspects of cognitive performance with disorganized cellular or
metabolic function in specific brain regions, and test interventions.

Systematic brain imaging studies generally are lacking in patients treated with chemotherapy (Saykin et al., 2003). Table 2 summarizes imaging modalities that can reveal structural and functional responses of the brain in patients susceptible to or suffering from chemo brain. For example, one small study (Silverman et al., 2003) evaluated 12 women with breast cancer. Four had received no chemotherapy, four had adjuvant chemotherapy, and four were treated with adjuvant chemotherapy plus tamoxifen. Positron-emission tomography scans revealed decreased activity in parts of the brain important in executive function and language in those treated with chemotherapy and tamoxifen.

Pathophysiology

A correlation between chemo brain and exposure to chemotherapy exists, particularly in episodic and working memory domains (Saykin et al., 2003). Qualitative and quantitative evidence supports this association. The mechanisms by which exposure to chemotherapy produces the clinical features of chemo brain are still unclear. Saykin et al. identified three major, likely nonexclusive, hypothetical mechanisms: direct neurotoxic, inflammatory or immunologic, and microvascular.

Direct neurotoxicity implies that chemotherapy causes direct toxic injury to brain parenchyma, producing demyelination or altered water content. The blood-brain barrier (BBB) and how it behaves in the presence of cancer and its treatment may explain direct injury. Specifically, how toxic substances enter the CNS is critical, because historically, the CNS (cerebrospinal fluid and brain parenchyma) has been considered a protected space, insulated from harmful substances by the BBB and blood-nerve barriers that restrict passage of potentially harmful substances (Ahles & Saykin, 2001; Ganong, 1997; Gendelman, Rappaport, & Hickey, 1999). Whether cancer, chemotherapy, or host responses

| Table 1. Central Neurotoxicity: Chemotherapy |
|-----------------|-----------------|-----------------|
| **Drug** | **Comments** | **Signs and Symptoms** |
| 5-fluorouracil (5-FU) | 1% incidence; dose related Reversible in one to six weeks Pathology: accumulation of neurotoxic metabolite Readily crosses blood-brain barrier (BBB) into the cerebrospinal fluid and brain | Cerebellar: ataxia, dysmetria, nystagmus, vertigo, limb incoordination, diplopia |
| 5-FU plus leucovorin or le- | – | Multifocal cerebral demyelination, confusion, ataxia, slurred speech |
| vamisole | Cytarabine | Seen in high doses (3 g/m²) May persist more than one month, especially in older adults Pathology: increased transport rate into cells, partial or total resolution after discontinuation | Cerebellar: ataxia, nystagmus, dysmetria, dysarthria, dysdiadochokinesia Cerebral: headache, seizure, personality changes, dyscalculia Leukoencephalopathy Ocular: photophobia, decreased acuity |
| L-asparaginase | Incidence: 25%–50% in adults Not dose related Caused by metabolite changes induced by drug | Altered level of consciousness (LOC)—confusion to stupor |
| Methotrexate | > 1 g/m² Transient and reversible | Cerebral: disturbance in LOC, confusion, depression, hallucinations, personality changes |
| Ifosfamide | Incidence 5%–30%; most spontaneously clear after cessation of drug Pathology: increased metabolite chloroacetaldehyde causes direct central nervous system damage Reversible if drug is discontinued. | Cerebral: altered LOC, ataxia, myoclonus, seizures, encephalopathy, central nervous dysfunction |
| Biologic therapies (e.g., high-dose interleukin-2 [IL-2], interferon) | – | Cognitive problems IL-2 (case report) leukoencephalopathy IL-2 decreased planning skills, reduced spatial memory | |
| Hormonal | Selective estrogen receptor modulator (tamoxifen) Aromatase inhibitors prevent peripheral conversion of androgen to estrogen. Estrogen receptor antagonist (fulvestrant) | Tamoxifen may have antiestrogen effects at the level of the hippocampus. In animal models, raloxifene may have positive effects on cholinergic brain activity in animals and estrogen-antagonist effects on reproductive tissue. |
| Glucocorticosteroids (e.g., methylprednisolone, dexamethasone) | Reduces cerebral blood flow; reduces BBB permeability | Effects may be dose dependent. Gender differences may exist. |

Note. Based on information from Bressler, 1997; Camp-Sorrell, 2000; Chemocare.com, n.d.a; Paganini-Hill & Clark, 2000; Phillips & Bernhard, 2003; Rugo & Ahles, 2003; Saykin et al., 2003.
alter BBB function, allowing an influx of inflammatory cells, chemicals, or their metabolites into the CNS, is unknown. Chemotherapy may damage the physical structure (e.g., integrity of tight microvascular junctions) or the functional properties (e.g., transport processes, kinetics) of the BBB. Structural and chemical alterations may culminate in the cognitive deficits characteristic of chemo brain. Researchers have suggested that some disruption of the BBB triggers a cascade of events that disturbs cellular and biochemical brain processes, culminating in chemo brain (Ganong).

The second hypothesis is that inflammatory or immune mechanisms may involve cytokine activity. This hypothesis suggests that cytokines enter the brain and trigger significant decreases in cognitive function (Saykin et al., 2003). Evidence indicates that proinflammatory cytokines are involved in blood-borne and neural signaling in the brain and can influence normal activity; cytokines even may disrupt memory consolidation by disturbing normal hippocampal activity (Saykin et al.). Characterizing the biology of cytokines in breast cancer and identifying host responses to disease and treatment may shed more light on the genesis of chemo brain.

The third major hypothesis involves a vascular mechanism in which injury obstructs the microvasculature, causing ischemia or infarction of dependent brain tissue (Saykin et al., 2003). Lesser hypotheses, including altered neurotransmitter behavior, indirect chemical toxicity, and oxidative damage, also have been suggested (Ahles et al., 2002; Saykin et al.).

**Practice Implications**

Nurses monitor patients over time and support, advocate for, and educate patients and their families. In so doing, nurses enable patients to achieve the highest quality of life possible. Patients often describe their symptoms to nurses. With an appreciation for the phenomenon, nurses can listen with empathy and intelligence. Chemo brain should not be dismissed as being “all in your head” or minimized as insubstantial. It is all in a patient’s head and is as real—if not as tangible—as mucositis and alopecia. The fact is that despite only small studies completed so far, chemo brain doesn’t necessarily equate to a “small” problem (Breastcancer.org, 2002; Parker-Pope, 2004).

Observational assessment is the most sensitive and appropriate method to screen for cognitive dysfunction (O’Shaughnessy, 2003). Nurses play a significant role in educating patients about their diagnoses, treatments, and potential side effects, and cognitive dysfunction should be discussed. Patients experiencing symptoms may feel isolated and alone. Education allows patients to cope more effectively. For some, the knowledge that chemo brain is not a unique event and the reassurance that the deficits may dissipate with time is sufficient (Parker-Pope, 2004). Patients need reassurance that they are not alone and that chemo brain does not signal or lead to progressive neurologic decline (e.g., Alzheimer disease) or signal a relapse in their disease. Awareness may restore some sense of control and serve as the catalyst for connecting to appropriate sources of support. For others, it may stimulate them to access and explore credible and responsive resources and engage more fully with care providers (see Figure 3).

Nurses also can share with patients and families the resources in Figure 4 and Table 3. The survival tips summarized in Figure 4 include well-recognized techniques used in brain injured and minimal cognitive impairment populations. These techniques represent low-cost, low-risk lifestyle modifications that may ameliorate deficits in memory and attention and improve quality of life. They are simple strategies that can be used to minimize the frustrations and limitations created, however transiently, by this adverse treatment effect.

A myriad of organizational supports also are available to survivors, some of which are listed in Table 3.

Two other issues challenge the treatment team. Should the risk of cognitive dysfunction be disclosed during the consent process? The question has stimulated debate. When a treatment regimen has known central neurotoxicity (Ahles et al., 2002; Saykin et al., 2003), informed consent is mandatory. However, given the limited knowledge regarding chemo brain, should this be included? The incidence of cognitive impairment must be confirmed before it becomes a part of the routine therapy discussion (Phillips & Bernhard, 2003). Those who have experienced chemo brain firsthand have emphasized the desire for full disclosure of risks before they commit to chemotherapy (Tannock et al., 2004).

Although the “survival benefit of chemotherapy far outweighs the potential risks to memory or concentration” (Chemocare.com,
Mentally
Simplify: Clear clutter; break big tasks into manageable bites; renegotiate work hours or academic load; reduce extracurricular stresses. 
Empower yourself: Read and take control. 
Avoid concurrent multiple tasks. 
Decrease workload. 
Don’t sweat small stuff. 
Avoid emergencies. 
Avoid distractibility: Reduce or eliminate background television and radio noise.
Be patient. 
Control your expectations: Do not set yourself up for failure.
Establish and stick to a routine.
Ask people to repeat.
Keep lists and a detailed calendar; use adhesive notes to eliminate reliance on memory.
Exercise your brain: Read, do crosswords.

Socially
Ask for help: neighbors to shop for groceries or take care of kids.
Let your healthcare provider know, especially if the effects are “severe, consequential, or progressive” (Kaplan & Kaplan, 2000, p. 1).
Celebrate life.
Keep a diary.
Consider support groups.
Take someone with you to your appointments.

Physically
Exercise to optimize strength and oxygenate.
Get enough sleep.
Cut down on nicotine and caffeine to reduce anxiety.
Wear glasses and hearing aids if you need them.
Consider relaxation therapy: yoga, guided meditation.
Let go of the small stuff and take one day at a time.

Note. Patients may need constant presence, supervision with medication administration, and limitation of hazardous activity (e.g., driving, operating dangerous machinery).

Figure 4. Tips for Surviving Chemo Brain
Note. Based on information from Breastcancer.org, 2002; Chemocare.com, n.d.a, n.d.b; Chemo Chicks, 2003; Kaplan & Kaplan, 2000; Meyers et al., 2002; National Coalition for Cancer Survivorship, 2003; Paraska & Bender, 2003; Tannock et al., 2004.

n.d.b, p. 1) for the majority of patients, the decision to proceed with neurotoxic treatment may not be a foregone conclusion. Occasionally, when therapy offers minimal additional benefit, some patients may choose to forego additional treatment rather than subject themselves to the possibility of cognitive dysfunction. Factoring in cognitive issues may be critical when quality of life is paramount for a patient (National Coalition for Cancer Survivorship, 2003). At the opposite end of the disease continuum, those with very aggressive, widespread disease and/or limited life expectancy may opt for treatments that improve their quality of life and spare cognitive abilities if given the choice (Balducci, 2000; Di Maio & Perrone, 2003).

The second challenge facing clinicians is the availability of and access to diagnostic or evaluative resources and rehabilitative treatment should the severity of chemo brain preclude return to work, school, or prior lifestyle. For example, patients and family members may be concerned about the safety of patients resuming care of dependent children, driving, or resuming career activities that normally are associated with some level of risk (e.g., accountant, lawyer, pilot). Access to psychometric testing and cognitive or vocational assessment and rehabilitation may be unavailable in all areas. Traditional oncology networks may not possess the expertise required to address this side effect comprehensively. Private insurance companies often have strict criteria for qualifying for cognitive assessment and rehabilitation. Occupational therapists may be best able to provide the appropriate referral or service privately or in public sector settings. Specific employers may choose to fund specialized assessments or design reintegration plans with “back-to-work preceptors” to facilitate the safe transition of highly skilled employees (e.g., engineers, accountants) back to their preillness levels of function and responsibility.

Pharmacotherapy
Pharmacotherapy may be used for neuroprotection or to decrease the negative effects of chemotherapy in vulnerable individuals. Neuroprotection may result in a reduction of negative cognitive sequelae, provide symptom amelioration, or both. Although drug therapy ideally derives from clear targeting of well-understood pathophysiologic processes, in the case of chemo brain, these currently are hypothetical and often are borrowed from other diseases with similar symptom constellations (Saykin et al., 2003).

Erythropoietin and Epoetin Alfa
Erythropoietin (EPO) has a well-recognized role in supportive oncology for the management of symptomatic anemia. The brain, with its high rate of metabolic activity and high oxygen extraction ratio, is particularly vulnerable to ischemia and hypoxia. Investigators now are asking whether chemo brain is a neurologic adverse effect of anemia and whether the correction of anemia might lead to cognitive improvement (Glaspy, 2002). An EPO response system to injury appears to exist that is likely to have a neuroprotective role. EPO receptors are abundant around the structures of the BBB (Jumbe, 2002), and, during hypoxic stresses, the permeability of the barrier increases, which may facilitate the achievement of therapeutic EPO levels in the CNS.

Although anecdotal reports of positive neurocognitive effects exist, clinical trial evidence of efficacy in chemo brain is not available (Jumbe, 2002). A small study (N = 94) in breast cancer survivors subjected to chemotherapy did not demonstrate any difference compared with a placebo at six months (Tannock et al., 2004). Although widely used in oncology and renal populations, EPO is not risk free. Adverse effects include drug resistance and hypertension, especially during treatment initiation. More importantly, EPO is not a panacea for cognitive deficits. In nonanemic patients, studies to evaluate EPO as a protectant against cognitive impairment were halted by the U.S. Food and Drug Administration because of safety concerns. Once hemoglobin targets are reached, EPO is not recommended (Rizzo et al., 2002); therefore, this neuroprotectant could be used only in patients with documented anemia.

Methylphenidate
An interesting option for those with significant chemo brain may be methylphenidate (Ritalin), a psychostimulant best known for its efficacy in children with attention-deficit/hyperactivity disorder (National Institutes of Mental Health, 2000). The drug is thought to increase extracellular dopamine levels and possibly noradrenergic and serotonergic neurotransmitter systems (Challman & Lipsky, 2000; Royal College of Psychiatrists, 2004), exerting a preferential effect on mental over motor. The clinical features of attention-deficit/hyperactivity disorder share many similarities with chemo brain. Specifically, indicators of inattention include frequent failure to pay close attention to details; repeated careless mistakes; difficulty sustaining attention and listening; failure to follow through on instructions; failure to complete school work, chores, or duties; problems organizing tasks; distractibility; and forgetfulness (BehaveNet.com, 2002). Moreover, performance typically worsens in situations that are unstructured, minimally supervised, boring, or require sustained attention or mental effort (Dulcan, 1997). Documented effects in Ritalin
responders (with attention-deficit/hyperactivity disorder) include “improved sustained attention, especially to boring tasks, reduced distractibility, improved short term memory, reduced impulsivity, enhanced use of cognitive strategies already in repertoire, [and] increased accuracy of academic work” (Duclan, p. 113).

Some researchers have suggested that Ritalin improves concentration, psychomotor slowing, fatigue, and attention, allowing a return to normal life pleasures and work (Kibiger, Kirsh, Wall, & Passik, 2003; Meyers, Seabrooke, Albitar, & Estey, 2002). Tannock et al. (2004) reported on a workshop of a study that is enrolling patients with breast cancer who are receiving adjuvant chemotherapy to receive Ritalin or placebo at cycle 2 of chemotherapy and is studying its effect on fatigue, memory, and concentration. Advantages of Ritalin include side effects that are mild to moderate and easily reversed (Challman & Lipsky, 2000; Duclan, 1997; Royal College of Psychiatrists, 2004). Absolute contraindications include prior sensitivity to stimulants, glaucoma, symptomatic cardiovascular disease (e.g., hypertension, arrhythmias, angina), and hyperthyroidism. Because it is a U.S. Drug Enforcement Administration schedule II controlled substance, its abuse potential is lower than the amphetamines and cocaine, but addiction has been reported (Challman & Lipsky; Royal College of Psychiatrists).

### Hormone Replacement Therapy

Literature supporting the critical role of sex hormones in nervous system development and cognition exist (Paraska & Bender, 2003; Phillips & Bernhard, 2003). The role of estrogen became apparent because reductions in reproductive hormone levels have been associated with deficits in memory, attention, and psychomotor efficiency in healthy women who have experienced natural or surgical menopause (Bender et al., 2001; Paraska & Bender). Although estrogen replacement—given its trophic effects in brain development—has been assumed to play a role in chemo brain, great prudence is called for. The strongest argument for caution are findings emerging from the Women’s Health Initiative, a 15-year research agenda of observational studies and randomized clinical trials (N = 161,000) studying the effects of a variety of interventions (treatments) in healthy menopausal women (National Heart, Lung, and Blood Institute, 2004a, 2004b; Rapp et al., 2003). The Women’s Health Initiative Memory Study reported a heightened risk of developing dementia with exposure to combination (estrogen and progesterone) therapy. Moreover, this treatment did not protect against the development of mild cognitive impairment, and the study concluded that combination hormone therapy should not be prescribed for older, post-menopausal women to maintain or improve cognitive function (National Institutes of Health, 2003). Results from the estrogen-only arm of the trial regarding memory and cognitive function are not yet available (National Heart, Lung, and Blood Institute, 2004a, 2004b). A Cochrane review reached a similar conclusion (Hogervorst, Yaffe, Richards, & Huppert, 2002). Estrogen is contraindicated in patients with estrogen receptor-positive lesions and is relatively contraindicated in men. At this time, any role for estrogen remains controversial at best.

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Cholinesterase Inhibitors

A signature deficit in Alzheimer disease is deterioration in memory function. Evidence is compelling that cholinesterase inhibitors can stabilize memory capacity and improve cognitive function in patients with Alzheimer disease and vascular dementia (Birks, Evans, Lakovidou, & Tsolaki, 2000; Malouf & Birks, 2003); they also may increase alertness and improve mood. This drug class represents a third possibility for study in severe chemo brain (Saykin et al., 2003).

Ginkgo Biloba

Ginkgo biloba is a leaf extract of the Ginkgoaceae family that has been widely studied and used in Western Europe and North America to treat symptoms of early Alzheimer disease, among other disorders (National Center For Complementary and Alternative Medicine, 2004). Ginkgo biloba may have neuroprotective, antioxidant, and membrane-stabilizing effects. It also may inhibit loss of cholinergic receptors, known to be important in memory and cognition (Sierpina, Wollschlaeger, & Blumenthal, 2003). A recent meta-analysis found the beneficial effects of ginkgo biloba on cognitive function to be equivalent to donepezil (Sierpina et al.). A Cochrane review found it to be safe and promising in improving cognition and function (Birks & Evans, 2002) but urged more rigorous randomized, controlled trials to confirm treatment effects. Although readily available without a prescription, it must be used with caution because it may stimulate blood vessel growth (Tannock & Weiss, 2002), which could disqualify its use in patients with cancer. Further, it prolongs bleeding times in patients taking anticoagulants and antiplatelet agents (Sierpina et al.).

Indications for Future Research

Additional research is needed to more fully describe the phenomenon, understand the mechanisms of central neurotoxicity, and prevent and treat chemo brain. More rigorous research is needed with control of extraneous variables such as anemia and fatigue (Rugo & Ahles, 2003). Despite historic underrepresentation of the older population in randomized clinical trials, sampling should not exclude the geriatric population because toxicities and quality of life need to be better understood in this age group (Balducci, 2000; Di Maio & Perrone, 2003).

The ability to define and quantify the impact of systemic chemotherapy on different domains of cognitive function requires attention to instrument development. At this time, no brief screening tool exists for detection of cognitive impairment in patients with cancer (Clark & Rummans, 2000; Kibiger et al., 2003). Use of test batteries borrowed from other groups can be problematic; patients have reported suboptimal function and cognitive difficulties despite achieving “normal” test scores (Tannock et al., 2004). To measure chemo brain, tests need to reflect performance in real-life multitasking (Tannock et al.). Instruments must have pragmatic validity and possess the sensitivity to detect functionally important cognitive elements (Ahles & Saykin, 2001). Ideally, they ought to be short, easy to administer, resistant to practice effects, and modifiable to non-English speaking groups (Tannock et al.). The Repeatable Battery for the Assessment of Neuropsychological Status may prove to be the most sensitive tool when combined with self-report to evaluate chemo brain (Coyne & Leslie, 2004).

Conclusion

Clinically, many questions challenge clinicians and patients. Should cognitive function be formally screened when symptoms appear to identify patients who might respond to simple interventions to improve function? What interventions have efficacy and at what cost? As understanding evolves, healthcare providers may be able to pinpoint predictors that can identify those likely to develop chemo brain (Ahles et al., 2002) before treatment commences. In the meantime, survivors who complain of cognitive impairment can be assured that their concerns are being actively addressed (Phillips & Bernhard, 2003).

The plausibility of an “optimal” therapy offering drug and nonpharmacologic interventions acting synergistically at different physiologic points is most likely. Once chemo brain is more fully understood, issues of consent and patient assessment of the risks and benefits of therapy (Clark & Rummans, 2000) must be reevaluated. Improving the quality of life of patients with cancer and their caregivers requires attention to the recognition and diagnosis of neurocognitive dysfunction and the interventions available for maintaining or improving neurocognitive status (Clark & Rummans).

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Rapid Recap

The Phenomenon of Chemo Brain

- Chemo brain refers to a constellation of cognitive deficits that is described following chemotherapy.
- Potential causes include ischemic, inflammatory, and direct neurotoxic brain injury.
- A variety of low-risk lifestyle modifications can be used to reduce its negative impact on quality of life.
- For the minority of people who experience severe deficits, a variety of pharmacologic, psychological, and vocational interventions may reduce chemo brain's functional impact.