The Effect of Cancer Treatment on Cognitive Function

Arash Asher, MD, and Jamie S. Myers, PhD, RN, AOCNS

Abstract: Cognitive dysfunction is an increasingly recognized complication of cancer and its treatment. Most research in this arena has found that a subset of patients appear to be vulnerable to this complication even after treatment has ended, and often have difficulties with multitasking, short-term memory, word-finding, attention, or concentration. The mechanisms underlying these cognitive changes are not fully elucidated but may include direct neurotoxic effects of therapy, oxidative damage, and genetic predisposition. Compelling evidence has accumulated for the role of immune dysregulation and neurotoxicity from inflammatory cytokines. A gold standard for subjective or objective assessment of cancer treatment–related cognitive changes has yet to be established. Current options to assess cognitive function include neuropsychological testing, functional neuroimaging, and subjective assessments. Pharmacologic treatment options for this clinical problem are modest and limited. Nonpharmacologic treatments, including cognitive rehabilitation programs, are an emerging area of research for the management of cancer treatment–related cognitive changes.

Introduction

More than 14 million Americans are alive today with a history of cancer. This number is expected to approach 20 million in the United States alone by 2024. Given the extraordinary number of individuals who are surviving after a cancer diagnosis, increased attention is being given to issues related to function, quality of life, and community integration after treatment. One key concern among cancer survivors is cognitive dysfunction, commonly referred to in the lay community as “chemobrain” or “chemo-fog.” The purpose of this review is to provide clinicians with a scientific overview of the current state of this phenomenon among patients with cancer who do not have central nervous system (CNS) disease, including possible pathophysiology, assessment, and treatment approaches.
Chemobrain is a phenomenon that refers to the general mental fog many patients with cancer experience during or after treatment. This condition encompasses a range of symptoms such as short-term memory loss, difficulty in thinking and concentration, impaired multitasking, and other subtle cognitive changes (Table 1). No single symptom or set of symptoms is pathognomonic for cognitive dysfunction due to cancer and its treatment. Moreover, cognitive complaints often are associated with persistent fatigue and depressive symptoms that historically have complicated evaluation and research. Over the last decade, the literature on cognitive changes after cancer treatment has rapidly expanded and been subjected to much more rigorous study. The research, in general, has demonstrated that cognitive concerns can negatively and sometimes dramatically impact function, quality of life, and community integration.2,3 Fortunately, deficits in long-term memory and syndromes suggestive of cortical dysfunction, such as aphasia, agnosia, and apraxia, generally do not occur4 (Table 1).

Most studies suggest that up to 75% of patients with cancer experience cognitive impairment during treatment, and 15% to 35% of cancer survivors experience cognitive problems months to years following treatment.5,6 However, the prevalence of cognitive dysfunction varies widely in the literature, and multiple challenges impede the accurate assessment of the incidence of cognitive dysfunction, including the lack of prechemotherapy assessment of cognitive function, differences in the populations being studied, and the lack of standardized assessment tools and neuropsychological batteries. Measurement of cancer-related cognitive dysfunction in the literature is hampered further by differences in inclusion criteria, timing of cognitive assessments, and varying comparison groups (ie, published normative data, healthy matched controls, patients with cancer not treated with chemotherapy, etc). Furthermore, patients differ with respect to tumor type, stage of disease, concomitant treatment (nausea regimens, hormonal treatments, and multimodality treatments), and medical comorbidities—all of which could impact cognitive function.7 Some researchers have reported that cognitive changes associated with cancer treatment often resolve within 1 year, whereas others have documented long-term changes that last for more than 20 years.8–10

Multiple studies using prechemotherapy cognitive assessments have demonstrated that some patients have cognitive dysfunction prior to receiving any treatment. For example, several studies have noted that approximately 20% to 35% of patients with breast cancer have lower than expected cognitive performance based on age and education at the pretreatment assessment.5,11–13 Pretreatment cognitive dysfunction also has been found in other populations, including patients with acute myelogenous leukemia and lung cancer.14–15 In addition, it is generally an illness that affects older populations, it is not surprising that age is a confounding factor for cognitive challenges. One-fifth of geriatric patients with cancer screen positively for cognitive disorders.16

The majority of studies in this area have been conducted using women with breast cancer. Cross-sectional data suggest that 16% to 75% of patients with breast cancer experience cognitive impairment during chemotherapy, compared with 4% to 11% of healthy controls.4 Jim and colleagues reported meta-analysis findings on cognitive function obtained from 17 studies of 807 survivors of breast cancer treated with standard-dose chemotherapy at least 6 months previously. Cognitive deficits were limited to verbal and visuospatial ability and were generally small in magnitude.17 However, many experts purport that a subset of cancer survivors may be particularly vulnerable to more significant cognitive changes.18 For example, one recent study used neuropsychological tests to demonstrate that a subgroup of breast cancer survivors continued to experience a decline in cognitive function over time after treatment.19 Another recent report evaluating cognitive function among survivors of allogeneic stem cell transplantation found that, after 5 years, survivors continued to recover within some cognitive domains (eg, verbal fluency and executive function) but deficits remained for more than 40% of patients.20

### Hypotheses for Causal Mechanisms

Many mechanisms have been suggested to explain cognitive dysfunction in patients with cancer (Table 2), including direct neurotoxic effects of therapy (eg, inhibition of hippocampal neurogenesis), genetic predisposition, oxidative...
with breast cancer who had the COMT-Val allele performed worse on tests of attention, verbal fluency, and motor speed than those without the allele.28

The appreciation that some patients with cancer have cognitive problems prior to receiving any chemotherapy has changed our understanding of the mechanisms behind this syndrome. One hypothesis to explain this phenomenon is that risk factors may be shared for cognitive dysfunction and certain cancers. For example, poor DNA repair mechanisms have been linked to both problems.29 Another potential mechanism is known as the “accelerated aging hypothesis,” which proposes that cancer treatment accelerates the aging process through a variety of mechanisms, including increased DNA damage, shortened telomeres, inflammation, and oxidative stress.3 Different patients may be vulnerable to different mechanisms, which can account for the observations that older breast cancer survivors may be at elevated risk for cognitive dysfunction.30

The field of psychoneuroimmunology has shed light on the mechanisms of cognitive change after cancer treatment. Tissue trauma and inflammation from surgery, radiation, chemotherapy, biologic therapy, and targeted therapy can trigger systemic inflammation that can cross the blood-brain barrier and have deleterious effects on the CNS.31,32 Circulating proinflammatory cytokines have been shown to impair learning and memory in animals.33 In these studies, administration of proinflammatory cytokines to the brain increases the metabolism of key neurotransmitters, including noradrenaline, dopamine, and serotonin.34 These neurotransmitters are central to the regulation of memory, learning, sleep, and mood. Moreover, administration of innate immune cytokines to laboratory animals has been shown to disrupt long-term potentiation in the hippocampus and thereby disrupt memory consolidation.35 Once cytokines reach the brain, they stimulate the resident immune cells (ie, microglia) to produce other proinflammatory cytokines and inflammatory mediators.36,37 This may explain why cognitive dysfunction is not limited to patients with brain tumors (primary or metastatic) or to treatment directly targeting the brain.

Psychological and emotional stress can alter the hypothalamic pituitary adrenal axis and sympathetic nervous system, which then can alter the immune system in a similar way.38 In this light, some investigators have argued that chemobrain has a somatic component in some patients, such as may occur in fibromyalgia and chronic fatigue syndrome. This hypothesis purports that the physical and psychological distress of cancer treatment triggers biologic alterations (such as acute shifts in cytokines) that result in epigenetic alterations. These epigenetic modifications may create long-term homeostatic changes that are responsible for the neuroplastic alterations in cancer-related cognitive
damage, and immune dysregulation. Definitive evidence to support a single mechanism is absent, and discovering a final common mechanistic pathway may be unrealistic.

Direct neurotoxicity from chemotherapy is one obvious hypothesis for the etiology of cognitive dysfunction in this setting (hence the term chemobrain). However, determining the biggest offender in the various classes of chemotherapeutic agents is problematic. Because multiple classes of drugs often are used in combination, it is difficult to isolate the effects of chemotherapy from other aspects of treatment, such as radiation therapy and surgery. Nevertheless, we know that certain agents (eg, methotrexate and 5-fluorouracil) are particularly neurotoxic and cause diffuse white matter changes on neuroimaging.4,21,22 Animal studies have suggested that certain chemotherapeutic agents (eg, Carmustine, cisplatin, and cytarabine) may be more toxic to white matter progenitor cells and hippocampal stem cells than they are to actual cancer cells.23,24 Anemia is also a well-known side effect of myelosuppressive chemotherapies. Anemia may cause cerebral hypoxia due to a decrease in hemoglobin concentration, and has been associated with fatigue and cognitive dysfunction.25

Genetic factors also may predispose some patients with cancer to cognitive dysfunction. Variants of genes encoding apolipoprotein E (APOE) and catechol-O-methyltransferase (COMT) have both been associated with age-related cognitive decline in the general population.26 ApoE plays a role in neuronal repair and plasticity after injury, and one study suggested that long-term cancer survivors with at least 1 ApoE4 allele who were previously treated with chemotherapy had poorer cognitive function.27 COMT plays a role in the breakdown of catecholamines. Small and colleagues found that patients

### Table 2. Factors Potentially Contributing to Cognitive Dysfunction Among Patients With Cancer

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression/anxiety</td>
<td></td>
</tr>
<tr>
<td>Chronic social isolation/stress</td>
<td></td>
</tr>
<tr>
<td>Inactivity/deconditioning</td>
<td></td>
</tr>
<tr>
<td>Other medications (benzodiazepines, corticosteroids, certain antiemetics, opioids, etc)</td>
<td></td>
</tr>
<tr>
<td>Other medical problems (hypothyroidism, anemia, liver disease, etc)</td>
<td></td>
</tr>
<tr>
<td>Hormonal changes (androgen deprivation, estrogen deprivation)</td>
<td></td>
</tr>
<tr>
<td>Genetic factors (APOE4, COMT)</td>
<td></td>
</tr>
<tr>
<td>Inflammatory cytokines</td>
<td></td>
</tr>
<tr>
<td>Nutritional factors and deficiencies</td>
<td></td>
</tr>
<tr>
<td>Direct neurotoxic effects of chemotherapy</td>
<td></td>
</tr>
<tr>
<td>Poor cognitive reserve (due to age, education, etc)</td>
<td></td>
</tr>
</tbody>
</table>

The effect of cancer treatment on cognitive function.
dysfunction. Recent evidence also has pointed to certain single nucleotide polymorphisms (eg, in IL1R1) that may significantly increase the chance for cytokine-induced changes in cognition after treatment. This evidence supports the International Cognition and Cancer Task Force report, highlighting a consistent finding in the literature that subgroups of patients are more vulnerable to cognitive changes.

**Assessment Techniques**

A gold standard for subjective or objective assessment of cancer treatment–related cognitive changes has yet to be established. Many challenges have been noted, including inconsistent correlation between objective and subjective measures, the lack of objective instruments sensitive enough to capture the subtle cognitive changes perceived by some survivors, and the lack of instruments that accurately simulate the real-world environment in which cancer survivors must function. Objective neuropsychological testing requires special training and significant time to administer, thus adding to survivors’ burden. Neuroimaging has been used in the clinical trial setting to document cancer treatment–related changes in brain structure and function. Researchers continue to search for accessible, cost-effective measures of intervention efficacy.

**Self-Report**

Self-reporting of perceived treatment-related changes in cognitive function provides important data to oncology health care professionals. Subjective data frequently are criticized as lacking the robustness of objective neuropsychological testing; however, evidence has shown that perceived cognitive decline precedes the objective evidence demonstrated with neuroimaging. Results from some studies indicate that perceived cognitive function is affected by fatigue and mood, such as anxiety and depression, and self-report instruments actually may measure a different construct than objective testing. Regardless, survivors’ perceptions of cognitive decline, much like other symptoms that are difficult to quantify (eg, pain), are an important indicator of the impact of cancer treatment on daily function and quality of life. These data also are important to assess the efficacy of any interventions.

Numerous self-report instruments have been employed in clinical trials for this patient population. However, only a few were specifically designed to measure cancer and cancer treatment–related cognitive changes as a primary outcome; most studies tested cognitive decline merely as a subscale or component of the trial while measuring multiple symptoms. The Attentional Function Index (AFI) was designed for use in individuals with cancer to assess their perceived effectiveness in daily activities that require attention, working memory, and higher-level executive functions, including setting goals, planning and carrying out tasks, and monitoring behavior to meet intended goals. The AFI assesses patients’ perceived losses in their capacity to direct their attention. The AFI consists of a 13-item visual analogue scale (0-100 mm) that can be converted to a numeric rating scale (0-10). Factor analysis revealed 3 subscales: effective action (7 items), attentional lapses (3 items), and interpersonal effectiveness (3 items). Higher scores indicate better perceived functioning and less attentional fatigue. Attentional fatigue can be categorized as high (<5.0), moderate (5.0-7.5) and low (>7.5).

The Functional Assessment of Cancer Therapy-Cognitive Function (FACT-COG, version 3) is a 33-item instrument designed to measure patients’ self-reports of chemotherapy-related cognitive function. Participants rank items for 4 scales: perceived cognitive impairments (18 items), perceived cognitive abilities (7 items), comments from others (4 items), and impact on quality of life (4 items) as applicable during the past 7 days. Items for perceived cognitive impairments and comments from others are ranked from 0 (never) to 4 (several times a day). Items for perceived cognitive abilities and impact on quality of life are ranked from 0 (not at all) to 4 (very much). Higher scores indicate better-perceived cognitive function and quality of life.

Developers of the FACT-COG recently expanded the items to create item banks for 2 Patient Reported Outcomes Measurement and Information System (PROMIS) scales. These 2 scales, PROMIS v1.0-Applied Cognition-Abilities and PROMIS v1.0-Applied Cognition-Concerns, include 33 positively worded items and 42 negatively worded items, respectively. Both scales utilize 5-point intensity ratings in which higher numbers reflect survivors’ perceptions of better cognitive function. These instruments were validated with data from 509 individuals diagnosed with cancers of the breast, colon, rectum, prostate, and lung. Validated short forms for both instruments (8 items, 6 items, and 4 items) are available as well.

The National Comprehensive Cancer Network (NCCN) Guidelines for Survivorship do not yet recommend any one brief screening tool for assessing cognitive function, but suggest screening survivors with questions regarding their ability to pay attention, find words, remember things, think clearly, and perform functions. They also suggest ascertaining the time of onset for cognitive complaints and assessing the trajectory over time. Additionally, survivors should be assessed for concomitant conditions that may contribute to cognitive issues, such as anxiety, depression, fatigue, sleep disturbance, and pain. These conditions should be appropriately addressed.
Likewise, survivors’ medications should be reviewed, because many medications can contribute to alterations in cognition.

**Neuropsychological Testing**
A lack of consistency among the neuropsychological tests for the various cognitive domains affected by cancer treatment has made comparisons across studies difficult. The International Cognition and Cancer Task Force (ICCTF) published the recommendation that 3 core tests be used in future studies so that meta-analyses would be possible. These recommended tests are the Hopkins Verbal Learning Test-Revised, the Trail Making Test, and the Controlled Oral Word Association Test of the Multilingual Aphasia Examination. The ICCTF made these recommendations based on the adequate sensitivity of the tests in measuring the key cognitive domains affected (learning and memory, processing speed, and executive function), sufficient psychometric properties, suitability for multinational application, and the existence of alternative forms (to decrease practice effects). The task force acknowledged the need to reduce the time and energy necessary to conduct the neuropsychological testing battery so that undue burden is not placed on study participants or investigators.

Specific descriptions of the multitude of available neuropsychological tests are well summarized elsewhere. The NCCN Guidelines recognize the importance of validating survivors’ cognitive complaints and suggest that neuropsychological evaluation in itself can be reassuring to survivors. The guidelines also suggest referring patients to a neuropsychologist when clarity is needed about the nature of the impairment and/or the survivor is pursuing disability status related to limitations in cognitive function.

**Neuroimaging**
Considerable work has been done in the area of neuroimaging, both to objectively demonstrate structural and functional changes due to non-CNS cancer and the related treatments, and to investigate potential causal mechanisms. However, the bulk of this work has been conducted in the breast cancer population. The majority of the neuroimaging work to date has employed magnetic resonance imaging (MRI) to measure white and gray matter volume and functional MRI to measure neural activity. Some studies have employed proton MR spectroscopy to measure brain metabolite levels and neurochemical changes. Brain activity and metabolism also have been measured with positron emission tomography. Most breast cancer studies have demonstrated decreased gray and white matter volumes, changes in brain activation during memory tasks, and a correlation between self-reports and objective deficits on neuropsychological batteries. Both hyperactivation and hypoactivation have been noted, appear to be task dependent, and may be compensatory. These differences have been more pronounced in women who have received chemotherapy, and have been shown to persist for many years after completion of cancer treatment. Neuroimaging studies conducted in mixed cancer populations also have demonstrated decreased metabolism in patients with cancer (both treated and untreated with chemotherapy). Further longitudinal work is needed to compare patients receiving chemotherapy, patients not receiving chemotherapy, and healthy controls. The NCCN Guidelines suggest that neuroimaging outside of the clinical trial setting be restricted to patients who demonstrate focal neurologic deficits or those at high risk for CNS disease.

**Overview of Intervention Research**
The search for efficacious interventions for cancer treatment–related cognitive changes is critically important to cancer survivors and oncology health care providers. Relatively modest results have been demonstrated for pharmacologic interventions and no agents have been granted US Food and Drug Administration (FDA) approval to date for this indication. Likewise, research conducted to investigate nonpharmacologic interventions is in preliminary stages; however results have been interesting in a number of areas. Categorizations of the intervention studies conducted to date are listed in Tables 3 and 4.

**Pharmacologic Interventions**
**Neurostimulants.** Research results thus far have been equivocal regarding the use of neurostimulants (such as methylphenidate and modafinil) as interventions for cancer-related cognitive changes. Both drugs have been of interest owing to their FDA-approved indications for attention deficit disorder (methylphenidate) and narcolepsy (modafinil). Early work with methylphenidate looked promising for patients with advanced disease; both subjective and objective improvements were seen for alertness, attention, memory, executive function, and psychomotor function. These studies were very small (N≤30) and included patients receiving continuous intravenous opioids or those with hypoactive delirium. However, later studies have been negative for efficacy or the results have been mixed. Modafinil studies also have been equivocal because of small sample sizes, non-controlled designs, differences in dose and duration of therapy, and variations in which cognitive domains show improvement. Additionally, many of these studies do not use cognition as the primary endpoint. At this time, neither drug has sufficient evidence of efficacy to move forward with an approved indication.
Antioxidants. One hypothesis is that cognitive decline may be caused by DNA damage from antineoplastic agents and the production of reactive oxygen species. For this reason, antioxidants have been investigated as possible therapeutics. Both vitamin E and ginkgo biloba have been studied in the cancer population. High doses of vitamin E (1000 mg twice a day for 12 months) were shown to positively impact executive function, verbal memory, and visual memory. However, concerns have been expressed that doses greater than the recommended daily allowance (400 international units) may be associated with increases in mortality. No positive impact on cognition has been demonstrated with the use of ginkgo biloba in patients with breast cancer. A recent secondary analysis of a randomized, double-blind, placebo-controlled trial for the effect of melatonin on cognitive function and sleep showed improved sleep efficiency, but no effect on cognitive function.

Erythropoiesis-stimulating agents. Initial interest was shown in the investigation of erythropoietin owing to the associations seen between anemia (lower oxygen carrying capacity to the brain and fatigue) and cognitive complaints. Despite encouraging results, these agents are no longer being studied because of safety concerns, including an increased risk for cardiovascular and thrombotic events and decreased survival.

None of the pharmacologic agents are without side effects and toxicities. As such, the investigation of nonpharmacologic interventions is very appealing from an economic and patient satisfaction perspective.

Nonpharmacologic Interventions
Cognitive rehabilitation. Cognitive rehabilitation encompasses a number of interventions with different (or different combinations of) foci. In very general terms, cognitive training typically involves a series of exercises to enhance attention, concentration, and memory skills. These exercises may be computerized, and repetition and practice are important to the success of the intervention. Cognitive behavioral training is focused more on adaptive strategies to compensate for deficits in the various cognitive domains, and may also focus on confounding factors such as anxiety, depression, and fatigue. Many study designs include a combination of cognitive training and cognitive behavioral training. Additional terminology that is used includes psychoeducation, which involves providing didactic information about the challenges of cancer and cancer-related cognitive changes in addition to content about adaptive strategies and exercises to

<table>
<thead>
<tr>
<th>Table 3. Pharmacologic Intervention Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Agent</strong></td>
</tr>
<tr>
<td>Neurostimulants</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Antioxidants</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

DBPC, double-blind, placebo-controlled; RDBPC, randomized, double-blind, placebo-controlled.
improve various domains. Likewise, some programs are referred to as psychosocial or residential rehabilitation and provide psychoeducational content within the context of a retreat setting. This overlap in terminology makes review of studies somewhat difficult when attempting to synthesize the evidence in support of cognitive rehabilitation interventions. An attempt at differentiating the various studies conducted to date can be seen in Table 4. Promising preliminary results have been demonstrated in a number of studies. The Oncology Nursing Society’s Putting Evidence Into Practice (PEP) panel for cognitive impairment recently published an update stating that cognitive training research has reached a level of evidence to imply this intervention is “likely to be effective.” By contrast, the evidence from studies evaluating cognitive behavioral training requires additional research to achieve the same level of recommendation because of the need for additional larger randomized, controlled trials.57

<table>
<thead>
<tr>
<th>Intervention Type</th>
<th>Design (N)</th>
<th>Reference No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive rehabilitation</td>
<td>Cognitive training, Randomized, controlled (41)</td>
<td>94</td>
</tr>
<tr>
<td></td>
<td>Cognitive training, randomized, single-blind (82)</td>
<td>95</td>
</tr>
<tr>
<td>Cognitive behavioral training</td>
<td>Prospective, nonrandomized (29)</td>
<td>96</td>
</tr>
<tr>
<td></td>
<td>Prospective, randomized (40)</td>
<td>97</td>
</tr>
<tr>
<td></td>
<td>Randomized, controlled (98)</td>
<td>98</td>
</tr>
<tr>
<td></td>
<td>Prospective, nonrandomized (22)</td>
<td>99</td>
</tr>
<tr>
<td></td>
<td>Prospective, nonrandomized (53)</td>
<td>100</td>
</tr>
<tr>
<td>Combination</td>
<td>Prospective, randomized (28)</td>
<td>101</td>
</tr>
<tr>
<td></td>
<td>Prospective, nonrandomized (27)</td>
<td>102</td>
</tr>
<tr>
<td></td>
<td>Randomized, controlled (90)</td>
<td>103</td>
</tr>
<tr>
<td>Residential rehabilitation programs</td>
<td>Randomized, controlled (394)</td>
<td>104</td>
</tr>
<tr>
<td>Biofeedback</td>
<td>Electroencephalography or neurofeedback, Prospective, nonrandomized (23)</td>
<td>81</td>
</tr>
<tr>
<td>Exercise: aerobic</td>
<td>Cross-sectional, nonrandomized (37)</td>
<td>71</td>
</tr>
<tr>
<td></td>
<td>Prospective, nonrandomized (26)</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td>Prospective, nonrandomized (408)</td>
<td>74</td>
</tr>
<tr>
<td>Exercise: resistance</td>
<td>Prospective, nonrandomized (17)</td>
<td>70</td>
</tr>
<tr>
<td>Exercise: mindfulness-based</td>
<td>Yoga, Randomized, controlled (200)</td>
<td>72</td>
</tr>
<tr>
<td></td>
<td>Case series (4)</td>
<td>105</td>
</tr>
<tr>
<td></td>
<td>Tai chi, Prospective, nonrandomized (23)</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td>Qigong, Prospective, randomized, controlled (81)</td>
<td>73</td>
</tr>
<tr>
<td>Physical activity intensity</td>
<td>Prospective, nonrandomized (15)</td>
<td>106</td>
</tr>
<tr>
<td>Biofeedback/exercise combination</td>
<td>Speed feedback with bicycle ergometer, Randomized, controlled, single-blind (78)</td>
<td>107</td>
</tr>
<tr>
<td>Meditation/mindfulness-based stress reduction</td>
<td>Prospective, randomized (42)</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>Prospective, randomized, controlled (229)</td>
<td>79</td>
</tr>
<tr>
<td>Natural restorative environment</td>
<td>Prospective, nonrandomized (32)</td>
<td>76</td>
</tr>
<tr>
<td></td>
<td>Prospective, randomized, controlled (157)</td>
<td>77</td>
</tr>
<tr>
<td>Guided imagery</td>
<td>Telemedicine delivery of imagery intervention, Randomized, controlled (118)</td>
<td>78</td>
</tr>
<tr>
<td>Combination therapy</td>
<td>Exercise and psychoeducation, Prospective, nonrandomized (658)</td>
<td>108</td>
</tr>
</tbody>
</table>

RDBC, randomized, double-blind, controlled.

Table 4. Nonpharmacologic Intervention Studies
Exercise. Exercise is currently an exciting area of research for this patient population. Evidence continues to build in support of aerobic, resistance, and mindfulness-based exercise as potential interventions for cancer and cancer treatment–related cognitive changes. The primary rationales proposed for the success of physical activity and exercise are: (1) a reduction in markers of inflammation that accompany cancer and cancer treatments and (2) an increase in brain-derived neurotrophic factor levels and hippocampal volume.62-64 Exercise is known to combat fatigue and sleep disturbances65,66 and has been shown to improve cognitive performance in a variety of patient populations, such as the elderly,67 those with Alzheimer disease,68 those with Parkinson disease,69 and preliminarily those with various types of cancer.55,70-74

Mindfulness-based exercises (such as yoga, tai chi, and qigong) are postulated to have additional benefits, possibly because they tap into different pathways than aerobic or resistance exercise alone.72,73,75 Likewise, other mindfulness-based interventions such as meditation, natural restorative environments, and guided imagery have shown efficacy in the reduction of cognitive complaints.76-80

Exercise intervention studies thus far have been preliminary in nature and many questions remain regarding the most effective type(s) of exercise regimens, timing, duration, frequency, and intensity (ie, dosage).

Electroencephalography biofeedback. Pilot study results regarding the feasibility of electroencephalography biofeedback to reduce subjective cognitive complaints for breast cancer survivors demonstrated significant improvements in perceived cognitive function (N=23).81 This intervention involves the use of a “real-time display of the brain’s electrical activity, fed back as visual or auditory information” enabling the participant to “modify that brainwave activity.” This intervention is based on the premise that the brain’s neuroplasticity can be used to restore brain function.

Nonpharmacologic interventions show promise, but a great deal of research still is needed to provide appropriate levels of evidence to recommend specific interventions to cancer survivors with cognitive complaints, or to justify preventative measures to be employed prior to and during treatment for cancer.

Future Research Needs

Over the last decade, mounting evidence for the biologic effects of cancer treatment on behavioral symptoms has validated patient complaints of persistent cognitive difficulties after cancer treatment ends. In general, the magnitude of impairment appears to be modest, although the symptoms may have a major impact on quality of life.

A subset of cancer survivors may be most profoundly affected, with negative implications for community reintegration, social pursuits, and viability of returning to the workplace. Future research is needed to further refine our understanding of underlying mechanisms and identify those patients who might be most vulnerable to cognitive changes. Many potential confounders, including fatigue, insomnia, medication side effects, and hormonal changes, need to be accounted for before arriving at a definitive conclusion on the pathophysiology of this important clinical problem. Most studies of cognitive change after cancer treatment have excluded those who would presumably be the most vulnerable to cognitive decline—ie, geriatric patients and those with a history of head injury, neurological disorders, or depression. More research is needed to determine the effects of cancer treatment on these susceptible patients to allow for better decision making in the real-world clinical setting. Finally, larger studies are needed to find effective rehabilitation and treatment strategies for this important clinical problem.

Disclosures

The authors have declared no relevant conflicts of interest.

References

14. Meyers CA, Albitar M, Este E. Cognitive impairment, fatigue, and cytokine...


