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SPECIAL ARTICLE

Cognitive Impairment Associated With Chemotherapy for Cancer: Report of a Workshop

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ABSTRACT

Cognitive dysfunction may occur in some patients who receive chemotherapy. We provide a summary of an April 2003 workshop on this topic, that included medical oncologists, radiologists, clinical and experimental psychologists, and patient advocates. Current studies indicate that cognitive deficits are often subtle, although they are observed consistently in a proportion of patients, may be durable, and can be disabling. Deficits have been observed in a range of cognitive functions. Underlying mechanisms are unknown, although preliminary studies suggest there may be genetic predisposition and that cognitive impairment may be accompanied by changes in the brain detectable by neuroimaging. The following priorities were established for future research: (1) large-scale clinical studies that use both a longitudinal design and concurrent evaluation of patients with cancer who do not receive chemotherapy—such studies should address the probability and magnitude of cognitive deficits, factors that predict them, and underlying mechanisms; (2) exploration of discrepancies between subjective reports of cognitive dysfunction and the objective results of cognitive testing; (3) studies of cognitive function in patients receiving treatment for diseases other than breast cancer, and in both men and women, to address the hypothesis that underlying mechanisms relate to changes in serum levels of sex hormones and/or to chemotherapy-induced menopause; (4) development of interventions to alleviate these problems; and (5) development of animal models and the use of imaging techniques to address mechanisms that might cause cognitive impairment associated with chemotherapy.

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INTRODUCTION

Several studies have suggested that cognitive dysfunction may occur in some patients who receive chemotherapy, mostly as adjuvant treatment for breast cancer.[1-8] These studies are summarized in Table 1. There have already been three reviews of this topic.[11-13] Despite methodologic problems in the studies, the consistency of the data provides evidence that cognitive dysfunction is an important and hitherto largely unrecognized effect of treatment. It is of great concern to patients and is a frequent topic of cancer support groups, where it is referred to as "chemo-fog" or "chemo-brain."

The aforementioned studies have stimulated investigators to initiate research seeking to define the extent of cognitive changes associated with chemotherapy, its possible causes, and methods of preventing or treating it. These investigators are medical oncologists, psychologists, radiologists (who are studying possible changes in the brain using imaging techniques), and scientists working with animal models. This diversity of approaches is important, but these individuals rarely interact with each other. An April 2003 workshop therefore brought together such individuals to compare their results and to forge collaborations that might enhance the success of research. The workshop included approximately 30 health professionals and three patient advocates. It was structured to maximize discussion and organized to address four key issues: scope of the problem, evaluation of cognitive problems, possible mechanisms, and prevention, treatment and rehabilitation.

SCOPE OF THE PROBLEM

Participants provided an overview of studies that have evaluated cognitive func-

Table 1. Summary of Studies Examining Cognitive Effects of Chemotherapy in Patients With Cancer

Investigators	Disease Site(s)	Status	No. of Patients and CT Treatment	Time After CT	% of Patients With Cognitive Problems	Tests Used (comments)
Wieneke and Dienst [1]	Breast	Complete	28	6 months	75	Test battery (normative data/no controls)
Netherlands Cancer Institute Group [2-4]	Breast	Complete	34 high-dose CT	2 years	32	Test battery ± neurophysiologic exam
			36 standard CT		17	
			34 local CT		9	
	Breast	Complete	39 CT (CMF for N+)	2 years	28	
			34 no CT (N−)		12	
	Various	Ongoing	178	Variable	0-24	
	Breast	Ongoing	320 CT	Longitudinal	Data not available	
			65 no CT			
			66 healthy			
Toronto group [5,6]	Breast	Complete	31 CT	—	48	HSCS[9] (CT was mainly CMF)
			40 post-CT	2 years	50	
			36 controls		11	
	Breast	On CT; complete	100 patients	On CT, 1 and 2 years later	16	(CT was mainly AC or CEF)
			100 controls		4	
Ahles et al [7]	Breast/lymphoma	Complete	71 CT	5-10 years	39	Test battery
			57 local		14	
	Breast/lymphoma	Ongoing	65 CT	Longitudinal	Data not available	Test battery + imaging studies
			75 no CT			
			40 healthy			
O'Shaughnessy et al [8]	Breast	Complete	47 CT	Longitudinal	36 (decline)	EXIT25 [10]
			47 CT + epoetin		22 (decline)	
Meyers*	Breast	Complete	60	Longitudinal	33 (pre-CT)	Test battery
					50 (decline after CT)	
Wieneke and Rugo*	Breast	Complete	41 CT	Longitudinal	22	Test battery
			29 local	0, 6, 18 months	13	
Jenkins*	Breast	Ongoing	100 CT	Longitudinal	Not available	Test battery
			50 endocrine			
			50 control			
Correa*	CNS tumors	Complete	60 (CT ± RT)	Variable	~75% (RT + CT more than CT alone)	Test battery
Ganz and Castellon*	Breast	Ongoing	36 CT	2-5 years	Z score = −0.32	Test battery
			17 no CT		Z score = 0.14	
			19 healthy		(compared with controls)	
International Breast Cancer Study Group*	Breast	Planned	~130	Longitudinal	—	Computerized assessment

Abbreviations: CT, chemotherapy; N, node; RT, radiotherapy; C, cyclophosphamide; M, methotrexate; F, fluorouracil; A, adriamycin (doxorubicin); E, epirubicin; HSCS, High Sensitivity Cognitive Screen.
*Unpublished data, presented at this workshop (Banff, Alberta, Canada, April 23, 2003).

tioning in adult cancer patients treated with cytotoxic agents and of other studies that are planned or in progress. The diversity in methodology in therapeutic regimens and in patient groups was reflected in the presentations, and an outline of the studies is provided in Table 1.

The majority of the studies were of patients with breast cancer, and for this disease site the rate of cognitive impairment in controlled studies (evaluated using a variety of tests) ranged from 16% to 50%. Cognitive dysfunction was durable in some patients (up to 10 years), and even when tests revealed cognitive function to be within the normal range, low-normal function was associated with receipt of prior chemotherapy. There was a suggestion of greater cognitive dysfunction in patients who had received cyclophosphamide, methotrexate, and fluorouracil in combination, compared with those who had received anthracycline-based chemotherapy; there is no information about patients who received taxanes. Investigators from the Netherlands Cancer Institute are studying a large number of patients who have received chemotherapy for other types of

Table 2. Types of Cognitive Deficits That Have Been Associated With Chemotherapy

Study	Attention/Concentration	Verbal Memory	Visual Memory	Visual/Spatial	Speed of Information Processing
Wieneke and Dienst [1]	++	++	++	++	++
van Dam et al [2]	++		++		++
Schagen et al [3]	++	++	++		++
Brezden et al [4]		++	++		
Ahles et al [5]		++			++
Castellon*			++	++	

NOTE. ++ indicates deficits noted in a particular study.
*Unpublished data presented at this workshop (Banff, Alberta, Canada, April 23, 2003).

cancer (eg, lymphoma, testicular cancer). Their data show that the problem is not restricted to patients with breast cancer and that cognitive dysfunction is observed in various groups receiving different regimens of treatment.

Major points raised in discussion were as follows: (1) There was support for studies that include pretreatment cognitive assessment with longitudinal follow-up during and after chemotherapy. However, pretreatment assessment takes place at a time of stress for the patient (soon after receiving the diagnosis and usually after undergoing primary surgery), and this must be taken into account when interpreting the results of subsequent tests (ie, postchemotherapy) in relation to baseline evaluation. (2) The definition of clinically relevant change for determining sample sizes and the standardization of criteria for determining cognitive impairment are important. Methods of assessment are required that are valid in cross-cultural clinical trials, which include patients who speak different languages. (3) Several participants reported that patients who describe cognitive deterioration may perform within the normal range on neurocognitive tests. Some of these patients may have functioned at a high level before chemotherapy and have a substantial decline in performance, but still score in the normal range. However, there might be a true dissociation between cognitive performance and the patient's impressions, such that this is in part a disorder of insight. Certainly, information regarding premorbid functioning (eg, intellectual abilities, education, occupation) should be considered in evaluating the extent (if any) of cognitive decline. (4) Patient advocates stressed that problems with memory and concentration are most evident when they resume their daily work and have to perform multiple tasks at the same time. Measures are required that give insight into the problems that cognitive impairment causes in daily life.

EVALUATION OF COGNITIVE PROBLEMS

Batteries of neuropsychological tests can provide comprehensive evaluation of cognitive functioning, but their administration requires specialized training and can be time-intensive (1 to 6 hours), especially for patients dealing with cancer and its treatment. Several investigators have used shorter screening assessments of cognitive function, some of which include an overall score that can be used conveniently as an end point in clinical trials. Relatively brief measures include the High Sensitivity Cognitive Screen,[5,6,9] the EXIT25,[10] a 25-item bedside measure of frontal function, and the CLOX, a clock-drawing task.[14] There are potential advantages to computerized tests, particularly those that are (1) sensitive to subtle cognitive change; (2) absent of practice effects; (3) valid for assessment of subjects with variable proficiency in English; and (4) rapidly administered with the data rapidly analyzed. Dr Maruff (see Acknowledgment for affiliations of contributors) described a computer-based assessment battery (CogState) based on presentation of playing cards, which appears to fulfill the above criteria.[15] Such an assessment may be more feasible for evaluating changes in cognitive functioning associated with chemotherapy within large multicenter clinical trials. Another computerized test is the Cognitive Drug Research computerized battery, which allows for reliable assessment of relevant cognitive domains, such as attention, reaction time, memory, and cognitive efficiency.[16]

Published studies have shown rather broad cognitive deficits associated with chemotherapy that differ from one study to another[17] (Table 2). Dr Castellon focused on the frequent lack of association between self-report of cognitive problems and the results of neuropsychological testing; this has been attributed to the influence of mood. Additionally, neuropsychological tests evaluate performance at a point in time, whereas self-report encompasses assessment of performance over prolonged times and in different settings. Also, many neuropsychological tests do not have "ecological validity"—that is, we have not determined how well they translate into "real-world" skills and performance. To address this problem, Dr Wagner described the initial development of the Functional Assessment of Cancer Therapy-Cognitive (FACT-Cog) scale, a self-report measure of cognitive function that aims to evaluate the

"real-world" impact of chemotherapy-induced cognitive impairment. It evaluates mental acuity, attention and concentration, memory, verbal fluency, functional interference, deficits observed by others, change from previous functioning, and impact on quality of life. Items developed for the FACT-Cog were based on interviews and focus groups with oncology patients and providers[18]: they include behavioral examples of cognitive dysfunction, and responses are based on frequency of occurrence. Ongoing studies are focusing on validation of the FACT-Cog and item reduction, using neuropsychological evaluation and functional magnetic resonance imaging (MRI). Ultimately, the FACT-Cog aims to be a brief instrument that can be used to evaluate cognitive impairment and its treatment in the context of large clinical trials.

The discussion emphasized that the optimal method for assessing cognitive function depends on the question being asked and on the context of the study. If the goal is to carefully evaluate the cognitive domains affected by chemotherapy, then conventional neuropsychological assessment remains the gold standard. However, if the goal is to evaluate whether cognitive change occurs in a large sample of patients included in a clinical trial, then brief validated assessments may be appropriate. The two approaches can be combined. For example, patients who demonstrate change in cognitive functioning with the CogState or other brief type of assessment could be targeted for more thorough assessment with conventional neuropsychological testing. However, a two-stage approach requires that the screening tests have high sensitivity: unfortunately, most of them do not include sensitive tests of executive function, and they may lead to underreporting of deficits. All agreed that examining the "real-world" impact of chemotherapy-induced cognitive decline is important.

IN SEARCH OF MECHANISMS

Because the e4 allele of apoliprotein has been associated with an increased probability of dementia and reduced neuropsychological performance,[19,20] Dr Ahles and his colleagues have determined whether expression of this allele might be predictive for cognitive changes caused by chemotherapy. Carriers of the e4 allele with breast cancer or lymphoma who were treated with chemotherapy tended to score lower on tests of visual memory, spatial ability, and psychomotor functioning than survivors with other alleles of apoliprotein.[21] These studies are being extended to a larger series of patients who are participating in a longitudinal study examining the cognitive effects of chemotherapy.

Participants presented early results from studies that used neuroimaging to examine cerebral anatomy and function in patients treated with chemotherapy. Dr Saykin and his colleagues have used structural and functional brain imaging with MRI to examine chemotherapy-induced alterations in long-term survivors of breast cancer and lymphoma drawn from a prior study,[7,22] and have initiated a prospective longitudinal study. They have observed reduction in gray matter using voxel-based morphometry in chemotherapy-treated cancer survivors, compared with healthy controls.[22,23] These reductions in gray matter were widely distributed throughout the brain, and there were also regions of locally-decreased white matter. Studies using functional MRI during which participants performed a working-memory task appear to show increased activation in the cingulate area in patients who received chemotherapy. Magnetic resonance spectroscopy might be used to investigate metabolic changes in targeted regions that exhibit structural change on voxel-based morphometry or physiologic changes on functional MRI.

Positron emission tomography (PET) scanning has been used to examine regional brain metabolism and blood flow in a cross-sectional sample of noncancer controls and breast cancer survivors (approximately 5 to 7 years after diagnosis) who received no therapy, or adjuvant chemotherapy with or without tamoxifen. Silverman et al[24] have identified decreased metabolic activity in the prefrontal gyrus and Broca's area and its contralateral counterpart in a study of 12 patients who received adjuvant chemotherapy.[24] This appears in the resting metabolism scans (fluorodeoxyglucose-PET) and correlates strongly ($r = 0.79$; $P < .02$) with reduced ability to perform a task evaluating short-term memory. During the PET scanning, subjects were also asked to do a short-term and long-term memory task while changes in cerebral blood flow were measured using radiolabeled water. This procedure revealed an abnormal pattern of activity in the chemotherapy-treated patients in comparison with the controls, particularly in Broca's area.

Dr Kreukels and her colleagues from the Netherlands Cancer Institute described neurophysiologic studies in breast cancer patients treated with adjuvant therapy.[25] The assessment included a standard electroencephalogram (EEG) and monitoring of the EEG during an auditory task in which the subject had to make a "mental count" of deviant tones. In a visual task, processing of information was divided into input, central and output processes and event-related potentials in the EEG were examined. No particular stage of information processing seems to be affected by chemotherapy. However, patients who received chemotherapy appeared to be slower than controls, and there were amplitude differences in the P3 component of the EEG between treatment groups.

Other presentations focused on animal models that might be used to evaluate cognitive impairment associated with chemotherapy. Dr Koolhaas described an animal model of cognitive dysfunction associated with a single high-dose of chemotherapy. Using an inbred-mouse strain, behavioral tests were performed 6 weeks

after treatment and abnormalities in anxiety and spatial learning were noted. The mice learned to negotiate a maze well, but had trouble retaining the information. Dr Koolhaas described a model using wild rodents that may allow an experimental approach to individual vulnerability. Two populations of animals are found in the wild: one uses "proactive" coping strategies, analogous to the fight-or-flight response, and the other uses "reactive" coping strategies, consistent with conservation/withdrawal behavior. These animals differ in neurochemical as well as neuroendocrine characteristics: neuronal plasticity in the hippocampus has been shown to vary in the "reactive" coping animals and may be a source of vulnerability.

Dr Lee described a rat model to study the effects of monthly treatment with high-doses of either single agent fluorouracil or cyclophosphamide compared with saline-treated controls. Female F344 rats were given five monthly cycles of chemotherapy. The rats receiving chemotherapy exhibited symptoms of toxicity including reduction in body weight and impaired grooming and growth of teeth. After recovery from chemotherapy for 2 months or 8 months, rats were tested for their performance in two maze tasks that have proven sensitive to neurotoxicity, the Stone 14-unit T-maze and the Morris water maze. Suprisingly, the rats undergoing chemotherapy performed better than the control animals after 2 months recovery, but after 8 months' recovery there was no difference in performance as compared with controls. Results of this study did not support a direct detrimental effect of high-dose single-agent chemotherapy on spatial cognitive function in rats.

Discussion focused on the possible role of cytokines in causing cognitive dysfunction. Dr Dunn described the relationship between stress and sickness behavior in animals, in which the animal conserves energy and shows changes in behavior in response to an inflammatory insult. The behaviors in this setting include lethargy, hyperthermia, anorexia, decreased interest in exploring the environment, decreased libido and increased sleep time. This syndrome can be reproduced by administration of interleukin-1 (IL-1). In animals, IL-2 enhances exploration, and interest in novel stimuli, whereas response to IL-6 is variable. Tumor necrosis factor-alpha is a mediator of anorexia but does not cause sickness behavior. The interferons cause reduction in activity of mice, symptoms suggestive of depression, modest impairments in learning, and sometimes opiate-like effects. Research is required to determine whether cytokine levels might change following administration of chemotherapy to patients, and whether measurement of cytokine levels in the peripheral circulation reflects their activity in the brain.

Other potential mechanisms leading to cognitive dysfunction after chemotherapy include induced changes in sex hormones[6,26] and vascular effects. Chemotherapy is known to cause damage to the endothelium of blood vessels leading to increased blood clotting,[27] which might cause micro-infarcts in the CNS. Damage to blood vessels could also lead to increased levels of IL-1 and induction of cyclooxygenases, thus providing a secondary mechanism for changes in cerebral functioning and/or increased uptake of chemotherapy in the brain. A model is presented in Fig 1, which links factors involved in cerebral functioning to cancer treatment; the model includes cancer treatment as well as genetic predisposition, affective factors, endogenous hormones, induced blood coagulation and cytokines.

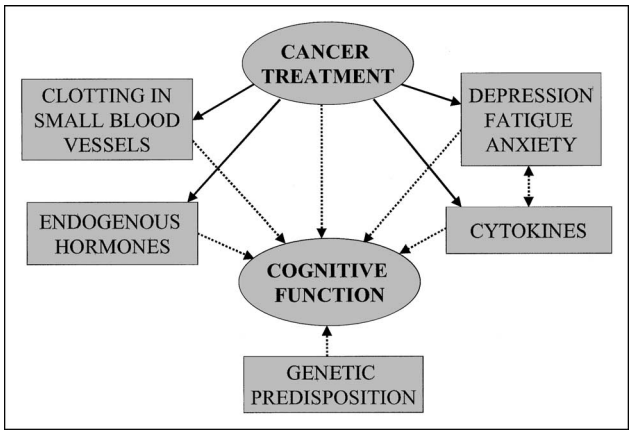

Fig 1. A conceptual framework including factors that might influence cognitive function in women with breast cancer (adapted from a model proposed by Ganz et al at this workshop).

PREVENTION, TREATMENT, AND REHABILITATION

Although there is uncertainty about the mechanisms that can lead to cognitive impairment, some studies have been initiated to try to prevent or treat this side effect. Dr O'Shaughnessy described a study in which 94 patients who were receiving adjuvant anthracycline-based chemotherapy for breast cancer were randomized to epoietin-α or placebo[8] (Table 1). This study was stimulated by the demonstration of functional erythropoietin receptors in the brain[28,29] and evidence that erythropoietin can enhance performance of rats on cognitive tests following various insults[30] and decrease infarct size in patients suffering from stroke.[31] The major measure of cognitive function was the EXIT25.[10] Patients randomly assigned to receive epoietin-α had improved cognitive performance as compared with baseline on this test when evaluated at cycle 4, compared with controls, who had slight deterioration. There were no differences in cognitive function at 6 months after chemotherapy, and both groups of patients then had improved performance compared with baseline. Hemoglobin levels were higher in

patients receiving epoietin-α, and they had less fatigue and better quality of life.

Dr Tannock described three potential agents that might reduce cognitive dysfunction associated with cancer treatment; erythropoietin (for reasons cited earlier), aspirin (to prevent micro-coagulation) and methylphenidate. Methylphenidate has been reported to improve cognitive function in children undergoing chemotherapy, patients with brain tumors, and patients infected with HIV;[32-34] it might also treat fatigue. He described an ongoing study in which 170 patients receiving adjuvant chemotherapy for breast cancer are randomly assigned to *d*-methylphenidate or placebo at cycle 2 of chemotherapy. Subjects are assessed for cognitive dysfunction at baseline at the end of chemotherapy and 6 months later using the High Sensitivity Cognitive Screen[9] and are assessed for fatigue using the Functional Assessment of Cancer Treatment-Fatigue self-report questionnaire[35] after each cycle of chemotherapy. One participant asked whether intervention trials were premature in view of lack of knowledge about mechanisms. Although this might be the case, both the above interventions also have possible beneficial effects to reduce fatigue, another major side effect associated with chemotherapy.

Dr Sprehn described a study of rehabilitation for patients with cognitive dysfunction. The major components of the brief program (four visits and three telephone contacts) are (1) education about possible problems in cognitive functioning following chemotherapy, (2) stress management and arousal reduction, and (3) developing compensatory strategies for memory and attention problems. A controlled trial is underway.

The final presentation by Dr O'Brien, a physician and a breast cancer survivor, described the cognitive problems that followed her treatment with high-dose chemotherapy and stem cell transplantation. She described coping strategies, which include avoidance of concurrent multiple tasks, avoidance of emergency situations, decreasing workload and increasing sleep. In order to function, she is very dependent on making lists for herself. These strategies were emphasized consistently by the other breast cancer survivors.

DISCUSSION AND CONCLUSION

All participants valued the workshop in bringing together health professionals with a variety of disciplines so that they could interact and learn about an important and under-researched area. The breast cancer survivors stressed the role of cognitive dysfunction in limiting their quality of life and ability to function and the need for tests that reproduce the real-life situation of busy women who are used to performing multiple tasks simultaneously. They appealed for more research and emphasized the need for full disclosure of the possibility of changes in cognitive function to patients before they agree to receive chemotherapy. There was commitment from all participants to collaborate and exchange information. Some of the more important needs are the following: (1) Large-scale clinical studies that use appropriate controls, preferably with both a longitudinal design and concurrent evaluation of control patients with cancer who do not receive chemotherapy. Such studies should address the probability and magnitude of cognitive deficits, factors that predict for them, and mechanisms underlying cognitive dysfunction. They should recognize that many women with breast cancer have above average cognitive abilities before onset of their disease, so that tests that are in the normal range might reflect mild cognitive decline. (2) Research to identify neuropsychological tests that are sensitive to chemotherapy-induced cognitive changes, and exploration of discrepancies between subjective reports of cognitive dysfunction and the objective results of cognitive testing. This should include the use of cognitive tests that reflect real life situations (multitasking) and the development and validation of self-report forms. There is also a need for comprehensive evaluation of disturbances of mood, since in other studies subjective complaints have been related to anxiety and depression. (3) Studies of cognitive function in patients receiving treatment for diseases other than breast cancer, and especially in both men and women, to address the possibility that underlying mechanisms might relate to large changes in serum levels of female sex hormones and/or to chemotherapy-induced menopause. (4) Priority funding of research that addresses mechanisms that might cause cognitive impairment associated with chemotherapy, including the development of animal models and the use of imaging techniques.

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Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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