The purpose of this review is to summarize the current literature on the effects of cancer treatment–related cognitive difficulties, with a focus on the effects of chemotherapy. Numerous patients have cognitive difficulties during and after cancer treatments and, for some, these effects last years after treatment. We do not yet fully understand which factors increase susceptibility to cognitive difficulties during treatment and which cause persistent problems. We review possible contributors, including genetic and biological factors. Mostly we focus is on cognitive effects of adjuvant chemotherapy for breast cancer; however, cognitive effects of chemotherapy on the elderly and brain tumor patients are also discussed.

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STATE OF THE FIELD

Up to 75% of cancer patients experience cognitive impairment (eg, problems with memory, executive functioning, and attention) during or after treatment of their cancer. For many (up to 35%), this persists for months or years following treatment.1–6 With more than 11 million cancer survivors in the United States,7 up to 3.9 million individuals may be living with long-lasting cognitive difficulties from cancer and cancer treatments. This is an important area of concern, because these effects could influence adherence to treatments and lead to long-term impairment. Cognitive deficits that occur from cancer or its treatment vary and may be subtle or dramatic, temporary or permanent, and stable or progressive.8 We highlight recent work in cancer- and chemotherapy-related cognitive difficulties and explore possible mechanisms.

SUMMARY OF CLINICAL RESEARCH LITERATURE

Some cognitive problems in those who receive chemotherapy are more severe than in those who only receive locoregional therapy (eg, radiation, surgery).9,10 Cognitive problems with chemotherapy can negatively impact activities of daily living such as (1) work performance,5 (2) access to medical and other health services, and (3) caring for and socially interacting with family members.11

Systematic research to understand cognitive difficulties with chemotherapy was first reported during the mid 1990s to early 2000s2–4,12; early studies often did not include pretreatment assessment data and/or were cross-sectional in design. The lack of pretreatment data was most likely due to difficulty obtaining such information from newly diagnosed patients. Studies over the past decade have incorporated pretreatment assessments of cognitive function. The importance of a pretreatment baseline was evidenced in a study5 of the effects of 5-fluorouracil, doxorubicin, and cyclophosphamide (FAC) chemotherapy on cognitive function in breast cancer. This was one of the first prospective, longitudinal studies to assess cognitive function with pretreatment and post-treatment cognitive measures. There were no overall mean differences in cognitive function between patients and controls (normative data). Within-subject analyses showed that 61% had cognitive declines in learning, attention, and processing speed. If the pretreatment assessment had been
unavailable, 46% would not have had detectable cognitive impairments (because their post-treatment assessment scores were normal). This is extremely important since cognitive dysfunction can be subtle. If a patient scores well on a cognitive test before chemotherapy and less well after treatment (but that score is still within the normal range), the decline may nevertheless represent a clinically significant difference.

Approximately 10 additional longitudinal studies have investigated cancer- and/or treatment-related cognitive difficulties; many treatment studies assessed the effects of chemotherapy and used standard neuropsychological assessments. In all, 12% to 82% of patients had cognitive difficulties in the domains of executive function, memory, psychomotor speed, and attention. Not all studies revealed significant changes in all domains; those in memory, executive function, processing speed, and attention appear most frequent. Additionally, many studies had small numbers and were not powered to test multiple cognitive domains. These studies used a variety of cognitive assessments and control groups, and most investigated patients on various treatment regimens. One recent study compared patients exposed to chemotherapy, those not exposed, and a healthy control group; those exposed to chemotherapy had the greatest deficits.

Several studies have shown cognitive deficits in cancer patients before chemotherapy. For example, in one study 33% of patients had cognitive difficulties in verbal learning and memory prior to chemotherapy. Another recent study revealed that 23% of women being treated for breast cancer had difficulty before chemotherapy. These could be related to psychological variables related to cancer diagnosis (eg, stress, anxiety, depression) or to other factors (eg, cognitive reserve). More research is needed to explicitly understand factors that lead to cognitive difficulties before and during treatment, and to understand those that contribute to long-lasting impairment.

Most studies of chemotherapy-related cognitive difficulties have focused on breast cancer. Longitudinal studies are needed in other disease groups to understand whether cognitive difficulties are more or less severe in these conditions. For example, in a cross-sectional study, breast and lymphoma patients showed long-term problems; however, no large prospective study in lymphoma has been conducted to confirm these results. More work is needed in well-powered long-term observational studies to understand the course and severity of cognitive difficulties, and possible mechanisms of action.

MECHANISMS

We are far from understanding the underlying molecular mechanisms that contribute to cognitive difficulties. Various biological and psychological mechanisms have been proposed (Figure 1). Assessment of various biological factors (eg, inflammatory markers, genetic markers, and brain imaging) may help identify high-risk groups for cognitive difficulties or those at highest risk for persistent long-term effects. Although we currently have no treatments for cognitive difficulties in cancer patients, identifying biological markers related to cognitive function would enable us to understand possible mechanisms and eventually develop successful interventions.

Brain Volume, Activity, and Metabolism

Subtle cognitive changes pose unique challenges to detection and management. First, the cause may not be apparent, and the impairments not evaluable with standard, objective neuropsychological measures. Second, subtle cognitive changes may be confounded by other problems commonly associated with cancer and its treatment, like depression, anxiety, and fatigue.

To develop prophylactic interventions, we must understand the mechanisms behind the effects of treatment on cognition. We need to use every tool at our disposal, not only to document the extent of the cognitive changes via neuropsychological testing but also to probe changes in brain volume, metabolic status, and CNS activity following treatment. Documenting these changes is possible with neuroimaging techniques. These include computerized tomography (CT), single-photon emission-computed tomography (SPECT), positron emission tomography (PET), and magnetic resonance imaging (MRI). The latter two are particularly powerful because they allow one to assess metabolic activity (PET via radiolabeling and MRI via various spectroscopic techniques). MRI has particular value.
because of the range of techniques available to probe brain anatomy and physiology. These include high-resolution anatomical images, which allow accurate measurement of therapy-induced changes in gray and white matter volumes. Functional MRI measures areas of brain activation during stimuli such as a motor task or neuropsychological assessment. Diffusion MRI allows measurements of the diffusivity of water in the brain. Spectroscopic MRI provides information about the biochemical processes in the brain. Finally, because it does not use ionizing radiation, MRI can be repeated on the same individual to assess short- or long-term longitudinal changes. Although similar studies can be done with PET, they are limited by dose exposure guidelines and may not be possible at frequent intervals.

The application of any of the neuroimaging techniques, but particularly the combination of MRI techniques, will prove useful in elucidating the structural, metabolic, and functional consequences of cancer and cancer therapies. Neuroimaging techniques have matured and are readily available in most clinical settings. Thus, future studies of the effects of cancer therapies on cognition should include neuroimaging, as well as conventional neuropsychological testing, to test hypotheses about the fundamental processes involved in the cognitive dysfunction following therapy. Preliminary work showed reductions in gray matter volume of frontal and temporal brain regions over the course of chemotherapy with partial recovery after treatment; these reductions were not seen in patients not exposed to chemotherapy or in healthy controls. These data temporally coincide with functional changes in neurocognitive assessment.

Neuroimaging studies would also determine whether patients use compensatory mechanisms to enhance performance on neuropsychological testing even though they are aware that their function is worse than before treatment. Evidence for this hypothesis may be the lack of correlation between self-report and performance on neuropsychological testing. Preliminary imaging work has demonstrated by functional MRI that a patient diagnosed with breast cancer receiving chemotherapy had to “work harder” to complete a cognitive task than her twin sister who did not have cancer.

Cytokines and Other Inflammation Markers

Although increased inflammatory markers are associated with cognitive difficulties in numerous neurodegenerative diseases and cognitive disorders, there is little information about the relationship of inflammatory responses to cognitive function in cancer. Elevated peripheral levels of pro-inflammatory cytokines may be related to cognitive problems. Chemotherapy has been associated with increased levels of pro-inflammatory cytokines (eg, interleukin [IL]-1β) in those treated for Hodgkin’s disease. In breast cancer patients receiving paclitaxel, levels of IL-6 increased 3 days after treatment compared to pretreatment but not in those who received a combination of fluorouracil, cyclophosphamide, and methotrexate. Significant changes in markers of endothelial and platelet activation were found in breast cancer on anthracycline-based treatment, further supporting the hypothesis that inflammation occurs as a result of chemotherapy.

Increased levels of IL-6 have been associated with poorer executive function, whereas higher levels of IL-8 were associated with better memory performance in patients with acute myelogenous leukemia and myelodysplastic syndrome prior to treatment. Another study found a trend between cytokine levels and cognitive performance in breast cancer. The investigators are currently assessing cytokine levels in relationship to cognitive function (via neuropsychological and computerized tests) in an ongoing observational study of cognitive function in colorectal cancer. Further clarification of the role of cytokines, chemokines, and other immune factors on cognitive function in cancer is needed. Large-scale observational studies that correlate changes in cytokines and chemokines with those in cognitive function should help clarify the association between inflammation and cognitive function in cancer patients on different chemotherapy regimens.

Genetic Contributors

Only a subgroup of breast cancer survivors may experience long-term changes in cognitive ability. Several genome-wide association studies have identified single-nucleotide polymorphisms (SNPs) in genes in multiple signaling pathways (ie, inflammation, dopamine, DNA repair, oxidative stress) perhaps related to cognitive decline in normal aging, Alzheimer’s disease and other syndromes with cognitive decline.

Therefore, genetic variation related to cognitive function may be associated with increased risk for long-term cognitive changes. Two studies examined the association between apolipoprotein E (APOE) and catechol-o-methyltransferase (COMT) genotypes and cognitive function in cancer survivors. Apolipoprotein E (ApoE) is a complex glycoprotein that facilitates uptake, transport, and distribution of lipids. It appears to play an important role in neuronal repair and plasticity after injury. The human E4 allele has been associated with a variety of disorders with prominent cognitive dysfunction. These include otherwise normal patients with memory complaints, Alzheimer’s disease, and poor outcomes in stroke and traumatic brain injury. Cancer survivors with at least one E4 allele scored significantly lower in the visual memory and spatial ability domains, with a trend to score lower in executive function compared to survivors who did not carry an E4 allele.
The COMT Val158Met SNP has been associated with dopamine levels in the prefrontal cortex. COMT-Val carriers metabolize dopamine more rapidly, with less availability of a neurotransmitter critical for cognitive function. COMT-Val carriers perform more poorly on tests of attention and executive function compared to COMT-Met carriers.45 Breast cancer survivors who were COMT-Val carriers and exposed to chemotherapy performed more poorly on tests of attention than healthy controls who were also carriers.43

These studies support the hypothesis that genetic factors increase vulnerability to cognitive changes with cancer treatments. Examination of other neural repair/plasticity genes and neurotransmitter activity genes, and those associated chemotherapy-induced cognitive change such as DNA damage/repair (eg, recombination 11 homolog A46) or blood-brain barrier damage may reveal important associations with post-treatment cognitive function.32 Finally, increasing interest in epigenetics (changes in gene activity without any in DNA structure) and cognitive function may lead to examination of chemotherapy-induced epigenetic changes associated with cancer-treatment related cognitive impairment.47

Menopausal Status and Hormonal Therapies

Most evidence for cognitive difficulties in cancer patients and survivors is attributed to chemotherapy. The literature on hormonal balance and cognition suggests that menopausal status and endocrine therapy can also influence cognitive function in cancer. For example, the transition from pre- to post-menopausal status is associated with alterations in cytokines such as IL-648 and cognitive difficulties in learning and memory.49 Case studies in cancer reveal that cognitive difficulties can vary among patients who received the same course of chemotherapy; this could be related to menopausal status.50

Breast cancer patients who received chemotherapy and tamoxifen have greater difficulty than those who received chemotherapy alone.25 Another cross-sectional study assessing tamoxifen in premenopausal breast cancer patients compared to healthy controls found greater difficulty in visual and verbal memory and processing speed.51 One prospective study found deterioration in verbal memory and executive function in post-menopausal patients taking tamoxifen for 1 year (but not in those taking the aromatase inhibitor, exemestane, compared to healthy controls).52 Larger studies are needed to confirm these results and to address the combined effects of chemotherapy and endocrine therapy on cognitive function in cancer.

TREATMENT-RELATED COGNITIVE IMPAIRMENT IN ELDERLY CANCER PATIENTS

Impaired cognitive function is a common complaint among older patients presenting for medical treatment. The differential diagnosis of the type and extent of impairment is important in treatment planning and prognosis.53 Cognitive disorders such as dementia limit life expectancy and can affect whether patients should receive adjuvant therapy. Cognitive disorders interfere with medication compliance and consent to treatment and increase caregiver burden. Cognitively impaired persons receive less definitive cancer care than others.54-56

Cognitive disorders in older patients present prior to cancer treatment are often underdiagnosed without screening. Six percent to 10% of people age ≥65 years suffer from dementia. Prevalence approaches 50% in community-living populations older than 80 years.57 Cognitive impairment is associated with an increased risk for progression to dementia, with progression rates of 10% to 15% per year compared with 1% to 2.5% in the cognitively intact.58-60 One fifth of geriatric cancer patients screen positively for cognitive disorders in an academic setting.61,62

Chemotherapy

Investigators have prospectively studied the impact of cancer treatment on cognitive function in older patients with breast cancer, following complaints of memory changes and impaired concentration. The data are still limited regarding the impact of cancer treatment on an older person’s cognition. In one longitudinal prospective study of older patients with breast cancer, 51% of 45 evaluable patients perceived a decline in cognitive function after 6 months of chemotherapy.55 Other studies demonstrated no significant change in Mini-Mental Status Exam (MMSE) scores after chemotherapy or hormonal therapy over a short time period.64,65 In one longitudinal study, 28 older women with breast cancer scheduled for adjuvant chemotherapy underwent neuropsychological testing and a comprehensive geriatric assessment (CGA) before therapy and 6 months after completion.14 Thirty-nine percent scored 2 standard deviations below normative data at 6 months compared to their baseline neuropsychological test scores.14 Exploratory analyses of longitudinal CGA results demonstrated no changes in functional status, comorbidity, or depression scores.56 At the same time, one population-based study suggests that women with breast cancer who receive chemotherapy have a higher likelihood of dementia after long-term follow-up.57 More large, prospective, long-term studies are necessary to definitively assess the impact of breast cancer treatment on the cognitive function of older patients.

Hormonal Therapy

The cognitive effects of hormonal therapy with androgen deprivation therapy (ADT) in men with prostate cancer have conflicting results due to small sample size, short observation time, or perhaps a heteroge-
neous effect of ADT. Several studies have evaluated ADT on the cognition of men with prostate cancer but few have described the baseline prevalence of cognitive impairment. One study examined the cognitive function of 25 men, ages 49 to 75, following 12 months of androgen deprivation. They found improvements in visual and semantic memory. While not significantly different, the range on the MMSE of the treatment group at baseline was 21–29. This suggested that some had significant cognitive impairment prior to treatment. A study of outcomes at 1 year found cognitive losses in those undergoing hormonal treatment compared to controls. They also noted that the community control group performed significantly better than the prostate cancer group at baseline. This suggests that some may have cognitive impairment prior to treatment, which may impact overall results. In another study of 32 patients (median age, 71 years), 45% scored >1.5 standard deviations below the mean on >2 neuropsychological measures at baseline. Within exploratory analyses, those who scored below expectation at baseline displayed no change in cognition, while people with average or better scores at baseline displayed improvements in visuospatial planning and timed tests of phonemic fluency. This again suggests that a subset have cognitive impairment before treatment that may impact overall results.

Clinical suspicion of dementia is not as sensitive as available screening tools. A cognitive assessment tool (e.g., Blessed Dementia Rating Scale, MMSE, Mini-Cog, and Short Portable Mental Status Questionnaire) for older cancer patients should screen for baseline impairment and follow effects of therapy on cognitive function. The purpose of screening is to assess cognitive capacity and stratify risk; abnormal scores should trigger a comprehensive work-up with cognitive specialists. Unfortunately, these tools have not yet demonstrated the ability to detect treatment-induced changes in cognition. A more detailed neuropsychological evaluation is needed to accomplish this goal.

TREATMENT-RELATED COGNITIVE IMPAIRMENT IN BRAIN TUMOR PATIENTS

In addition to the neurological complications brain tumors themselves impose, the treatments are often associated with harmful effects on the CNS that can lead to cognitive impairments. These patients may experience a broad array of both acute and late toxicities, resulting both from direct toxic effects on the nervous system and indirect dysfunction (e.g., metabolic dysregulation, cerebrovascular disorders). Toxicity from brain tumor therapy may range from focal neurological deficits to generalized neurological syndromes. These frequently include fatigue and cognitive impairment, including decreased executive function. Since patients with brain tumors live longer, it is important to further understand the effects that chemotherapy and other treatments have on intact brain structures and cognitive function.

ANIMAL STUDIES

Animal models are especially important to the cancer and cognition field. It is not easy to assess molecular changes in the human brain. While parallel findings between animal and human experiments do not establish equivalence, animal models may inform hypotheses relating to the clinical condition. Experiments in animal models can usually be done much more quickly than parallel clinical studies and allow for many more aspects of a research question to be addressed. Furthermore, addressing a research question in an animal model is usually much less expensive than the same research question in a human study, assuming that study in a human is even technologically possible.

Animal studies have found that chemotherapy agents can negatively affect memory behavior in mice, likely due to reductions in adult neurogenesis. Mice exposed to doxorubicin had increased cortical and hippocampal levels of tumor necrosis factor-alpha (TNF-α), hyperactivation of microglia, induction of oxidative stress and mitochondrial dysfunction, and increased neural cell death. This was despite the fact that doxorubicin was not detected in the brains of these mice. These studies suggest that chemotherapy causes neurotoxicity within the brain and that inflammation may be a mediator of cognitive difficulties by reducing neural transmission. Future work in animal models will provide more mechanistic insight and allow testing of interventions for cognitive impairment.

SUMMARY

Cancer and chemotherapy-related cognitive impairment is an important clinical problem that negatively impacts quality of life for many individuals during treatment and post-treatment. We have reviewed various topics relevant to the cognition and cancer field and highlighted important areas for future research. Understanding the factors that lead to cognitive impairments from chemotherapy and other cancer treatments will allow us to better understand how to educate patients about these difficulties and ultimately how to treat them.

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