Addressing Cancer-Related Cognitive Impairment in Cancer Survivorship

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By 2026 an estimated 20.3 million cancer survivors will be living in the United States.[1] Many of these survivors report cognitive symptoms that do not resolve after cancer treatment. These symptoms may include poor executive function, attention and concentration deficits, and impairments to short-term memory. This cluster of symptoms is referred to as *cancer-related cognitive impairment* and can be experienced at multiple times along the cancer diagnosis and treatment trajectory. Approximately 30 percent of patients report cancer-related cognitive impairment symptoms prior to cancer treatment. Up to 75 percent of patients report these symptoms during treatment, and approximately 35 percent of post-treatment survivors report them.[2]

For many oncology providers and cancer care teams, several challenges can impede the treatment of cancer-related cognitive impairment. There is little research on effective interventions, resulting in few standardized evidence-based treatments. Patients and providers may expect symptoms to resolve after treatment, which does not always happen. Providers may perceive their cancer program as lacking adequate resources to effectively address cancer-related cognitive impairment.

This article focuses on cancer-related cognitive impairment in the post-treatment setting. We begin by reviewing the current science on the pathophysiology of these impairments and then explore its clinical presentation and neuropsychological assessment. We then follow with a brief synopsis of existing guidelines for assessment, treatment, and referral. We close with pragmatic suggestions on the use of commonly available resources in the clinical setting to effectively treat cancer-related cognitive impairment.

Cognitive Complaints During Treatment

Though this article focuses primarily on the post-treatment phase, it is important to note that patient cognitive complaints often first emerge during treatment. For providers, supporting cognitive health before and during treatment may help minimize cognitive dysfunction—or begin to strengthen compensatory strategies—prior to survivorship. Though there is a lack of evidence-based interventions, studies have found correlations that suggest several targets for optimizing cognitive health before and during treatment. These targets for interventions may have effects on later cognitive function, although further research is necessary to confirm this. The targets include managing depression, trauma, stress, loneliness, and co-occurring symptoms such as fatigue and sleep disturbances.

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Pathophysiology of Cancer-Related Cognitive Impairment

Many reasons for cognitive dysfunction in patients with non-central nervous system cancers have been suggested, including the direct neurotoxic effects of therapy (such as the inhibition of hippocampal neurogenesis), oxidative damage, immune dysregulation, and genetic predisposition. Definitive evidence to support a single mechanism is absent. Most likely there are multiple mechanisms that contribute to cognitive challenges among patients with cancer.

Direct neurotoxicity from chemotherapy is one obvious hypothesis for the etiology of cognitive dysfunction in the cancer setting (thus the use of the term *chemobrain*). However, determining the

biggest offender of the various classes of chemotherapy agents is problematic, because multiple classes of drugs are often used in combination. Therefore it is difficult to isolate the effects of chemotherapy from other aspects of treatment, including radiation therapy, hormonal therapy, surgery, and psychological factors.

The recognition that some patients with cancer (up to 30 percent) have cognitive problems prior to receiving any chemotherapy has changed the paradigm in understanding the mechanisms behind this syndrome. One potential reason to explain this phenomenon is that shared risk factors may affect both cognitive dysfunction and certain cancers. For example, poor DNA repair mechanisms have been linked to both problems.[3] Another important potential mechanism for cognitive dysfunction among cancer survivors is the "accelerated aging hypothesis."[4] This idea proposes that cancer treatment accelerates the aging process through a variety of mechanisms, including increased DNA damage, shortened telomeres, inflammation, and oxidative stress.

Research suggests that doctors may not be regularly asking their cancer survivor patients about cognitive symptoms despite best practice recommendations, and patients report that they often do not discuss these symptoms with their providers.

The field of psychoneuroimmunology has shed much light on the possible mechanisms of cognitive changes after cancer treatment. Tissue trauma and inflammation from cancer treatment can trigger systemic inflammation, which can cross the blood-brain barrier and have deleterious effects on the central nervous system.[5] In animal studies, the administration of pro-inflammatory cytokines to the brain increases the metabolism of key neurotransmitters, including noradrenaline, dopamine, and serotonin.[6] These neurotransmitters are central to the regulation of memory, learning, sleep, and mood. Cytokines can reach the brain through multiple pathways, stimulating microglial cells to produce other pro-inflammatory cytokines and inflammatory mediators.[7] This may explain why cognitive dysfunction is not limited to patients with brain tumors (primary or metastatic) or treatment directly targeting the brain.

Psychological factors, including symptoms of depression and anxiety, may also play an important role in the development of cancer-related cognitive impairment. Psychological and emotional stress can alter the hypothalamic pituitary adrenal axis and sympathetic nervous system, which then can alter the immune system and inflammatory levels.[8] One hypothesis purports that biologic alterations triggered by the physical and psychological distress of cancer treatment create long-term homeostatic changes (via epigenetic alterations due to acute shifts in cytokines) that are responsible for the neuroplastic changes of cancer-related cognitive dysfunction.[9]

Other factors that may contribute to cancer-related cognitive impairment include a lower pre-treatment cognitive reserve, which may make some patients more vulnerable to the effects of cancer treatment. Other co-morbid conditions—such as menopausal symptoms, cancer-related fatigue, anemia, and insomnia—may also play a role in these impairments.

Clinical Presentation of Cancer-Related Cognitive Impairment

Patients undergoing cancer treatment often describe noticing cognitive changes, sometimes referred to as *chemobrain* or *chemofog*. For many patients, these symptoms may come to the forefront after active treatment has ended and the patient is trying to reintegrate into work and return to familiar societal roles. Some individuals with these symptoms feel they never fully return to their baseline cognitive function. Patients often notice these more lasting difficulties when they return to their pre-cancer daily lives, such as juggling challenging responsibilities at work and home. Some survivors realize that they are not able to manage what they could easily handle before cancer due to cognitive changes. Understandably, this realization can be very distressing.

Symptoms can vary, but commonly reported post-treatment cognitive difficulties include feeling less mentally sharp, having short-term memory problems, and having difficulty maintaining focus. Some patients continue to have difficulty recalling names or words quickly, and others describe mental exhaustion at the end of the day. Importantly, among non-central nervous system cancer survivors, the cognitive symptoms described may not be dramatic; that is, symptoms may be mild and even unnoticeable to others. However, the consequences of these difficulties can be very significant, and patients have reported reducing their work responsibilities or not returning to work at all and reducing responsibilities at home.[10]

Research suggests that physicians may not be regularly asking their cancer survivor patients about cognitive symptoms despite best practice recommendations, and patients report that they often do not discuss these symptoms with their providers.[11] Raising awareness among clinical staff and patients themselves during the informed consent process, treatment, and follow-up visits will help ensure that these symptoms are caught early in survivorship and referred for appropriate assessment.

Neuropsychological Assessment

In some cases, it may be helpful to refer patients to a neuropsychologist for an evaluation. A comprehensive neuropsychological evaluation can be very useful in fully assessing risk factors and characterizing the nature of the cognitive symptoms. This evaluation typically includes conducting a clinical interview with a patient during which the neuropsychologist gathers information regarding the patient's medical, academic or employment, and

psychosocial histories. In addition, the neuropsychologist conducts objective standardized testing evaluating specific cognitive abilities, including memory, attention, executive functioning, and processing speed, among others. The expertise of the neuropsychologist can be particularly helpful in cancer-related cognitive impairment because cognitive symptoms are often subtle (unlike dementia). Further, neuropsychologists are specially trained to describe cognitive strengths and challenges to patients and their families and develop recommendations and strategies to help patients manage their symptoms and improve their quality of life.

Screening Measures

A patient's care team may also identify cancer-related cognitive impairment concerns through cognitive screening measures administered in the clinic setting. Evaluating these impairments through screening has several practical advantages. Cognitive screening may provide a useful alternative to comprehensive neuropsychological evaluations, which can be quite costly and are not always covered by insurance. In addition, full assessments can take a long time (five or more hours), and this is not always practical for patients or within the time constraints of the clinic setting.[12] In contrast, screening measures often take only several minutes, and can be completed within the time frame of an exisisting appointment with a provider, minimizing the need for additional scheduling.

A recent review of cancer-related cognitive impairment screening tools revealed that the Montreal Cognitive Assessment (MoCA), Mini-Mental State Examination, and Clock Draw Test (CDT) were the most frequently studied objective screening tools. The Functional Assessment of Cancer Therapy-Cognitive Function and Cognitive Symptom Checklist-Work 21 were the most commonly studied patient-reported measures in adults. Through their analyses, reviewers have concluded that scientific evidence best supports the use of the MoCA and CDT for objective screening. Findings also suggested that combining objective assessment with a subjective measure of impairment may improve diagnostic validity.[14]

Given the range of screening options available, it may be difficult for a cancer program to determine which is most suitable for individual patients. Psychometric properties, feasibility, and validity are the main factors to consider when choosing any tool to evaluate cancer-related cognitive impairment.[13] Moreover, making a determination of how to assess these impairments often depends on the practical and logistical limitations of a given cancer program.

It is important to note that a screening assessment does not provide comprehensive information about a patient's cognitive status. Instead, these measures are meant to inform decisions about how to triage a patient and help create a roadmap to appropriate next steps (e.g., recommend a comprehensive neuropsychological evaluation or refer for other services). In this way, both assessment techniques work in tandem to assist the patient, family, and treatment team in further clarifying cognitive difficulties. Identifying these challenges is essential to inform intervention and treatment planning, given the effect that cancer-related cognitive impairment can have across multiple areas of life.

Timing of Assessment

Optimal timing for the evaluation of cancer-related cognitive impairment in adults remains unclear. Patient- or family-reported concerns are often the impetus for further evaluation. In other cases, members of the care team may be the first to bring concerns regarding these impairments to a patient's attention. The development of screening guidelines and assessment of cancer-related cognitive impairment remain areas rich with opportunity for further exploration. These are increasingly important issues, given the rising rates of cancer survivorship.

Guidelines for Cancer-Related Cognitive Impairment Care

Though some questions remain about the causes and optimal timing of cognitive assessment, growing evidence supports assessment and management of cognitive complaints and cancer-related cognitive impairment across the treatment trajectory. The National Comprehensive Cancer Network (NCCN) recommends regular assessment of cognitive symptoms as part of three evidence-based guidelines: Distress Management, Survivorship, and Older Adult Oncology. These recommendations cover multiple levels of cognitive function and severity, including dementia, delirium, mild cognitive impairment, and cancer-related cognitive impairment.

The NCCN Distress Management Guidelines address cognitive functioning as a possible cause of psychosocial distress and specify that patients with impaired cognitive functioning should be referred to a mental health team for assessment and treatment. In addition to the well-recognized disorders mentioned above (e.g., dementia), the guidelines state that there is no standard treatment for cancer-related cognitive impairment at present and conclude with a brief summary of the current literature. The Distress Thermometer, a tool included with the guidelines, allows patients to report cognitive complaints as a cause of distress.

The NCCN Older Adult Oncology Guidelines include evaluating cognition as part of a comprehensive geriatric assessment. The recommended cognitive assessment includes screening for dementia or delirium, determining capacity for decision making, and advanced care planning. Definitions, differential diagnoses, medications that can impair cognitive function, and specific measures are also provided. If there is cognitive impairment, the guidelines include specific interventions to address the deficits. Two elements of these guidelines stand out in comparison to the other NCCN guidelines. First, the role of function in the cognitive assessment is emphasized by recommending assessment of activities of daily living/instrumental activities of daily living. Second, the recognition of the role that depression can play in cognitive impairment is recognized and incorporated into the assessment.

The NCCN Survivorship Guidelines also address cognitive functioning, specifically post-treatment cancer-related cognitive impairment. The suggested survivorship assessment includes three

questions within the domain of cognitive functioning (i.e., attention/multi-tasking, memory, slowed thinking). A "yes" response to any of the questions results in a more detailed assessment, as well as an examination of confounding factors, such as medication or other symptoms that can influence cognitive functioning (e.g., depression, fatigue). Taken together, these three guidelines provide brief summaries of the current state of the science and guidance for treating professionals to design processes of care for this group of patients.

Implementing Cancer-Related Cognitive Impairment Screening, Assessment, and Intervention

As the body of evidence about cancer-related cognitive impairment continues to grow, what can cancer programs do for patients when cognitive symptoms impede their ability to return to work or engage in daily activities? Cancer-related cognitive impairment treatment can benefit from the different expertise and abilities that members of a multidisciplinary treatment team can bring to patient care. Team members can use their respective expertise to design processes for screening, assessing, and intervening in a manner that best suits the needs of a given cancer program's patient population. Though we may consider the full-time availability of a neuropsychologist as essential to performing neuropsychological assessment and cognitive rehabilitation for patients, most cancer programs cannot afford this resource. A more practical approach to cancer-related cognitive impairment assessment and treatment is to ask, "What clinical and patient-reported outcomes do we need?" and "What available resources do we have to address those needs?" Many cancer programs can design a cancer-related cognitive impairment program using their current staffing and resources.

Screening for Patient-Reported Cognitive Symptoms

Addressing cancer-related cognitive impairment in the clinical setting can be conceptualized as a three-step process: screening for symptoms, assessing the patient, and conducting interventions.

Cancer programs that screen for psychosocial distress may already have a process or patient screener in place through which they report and monitor cognitive symptoms. For example, instruments such as the distress thermometer have an item for memory and concentration problems that patients can endorse. Additionally, the NCCN Survivorship guidelines discussed above provide three brief questions that cancer programs can incorporate into their current psychosocial distress screening processes. Based on each cancer program's screening process, endorsing cognitive concerns or reporting them to an oncology provider may initiate a referral to the appropriate department that can provide further assessment and treatment.

Assessment of Patients with Positive Cognitive Screen

Based on staffing, expertise, and supportive services, cancer programs can administer a follow-up assessment measure to determine the extent to which cognitive symptoms are interfering with a patient's quality of life. Self-report—or subjective—tools that focus on cognitive symptoms such as the Functional Assessment of Cancer Therapy-Cognitive Function or Cognitive Symptom Checklist-Work 21 can be completed by patients in waiting rooms. Oncology staff can combine these subjective measures with an objective measure, such as the MoCA or CDT.

Further assessment beyond self-report could be conducted by many rehabilitation, psychological, and neuropsychological professionals. In the absence of neuropsychology, oncology staff could repurpose the brief objective measures of memory and language used by occupational therapists and speech and language pathologists in their patient evaluations. Clinical or rehabilitation psychologists may also use brief measures of cognitive function in their practice. Each of these clinical services could provide a further objective assessment, beyond self-report, of clinically significant cognitive symptoms. Though these adaptations may not provide the full neuropsychological workup needed for a definitive diagnosis of cancer-related cognitive impairment, they do facilitate identifying the nature of a patient's complaint and provide an opportunity for intervention.

Interventions

The goal in addressing cognitive complaints and cancer-related cognitive impairment is to help patients cope with their current levels of cognitive function and re-engage and increase their participation in valued roles and activities at work, at school, and in the community. Interventions to achieve this can include restorative—or rehabilitation—strategies, compensatory strategies, and coping skills. Multiple reviews have called for further research into cancer-related cognitive impairment interventions, given the nascent state of the research.[14,56] At present, there are several promising treatment options, including cognitive and behavioral strategies, physical activity, sleep, and computer-based rehabilitation strategies.

The multi-dimensional nature of cancer-related cognitive impairment suggests that multiple disciplines can be involved in treatment. Many clinical providers, such as nurses, occupational and physical therapists, psychologists, speech and language-pathologists, and social workers can provide patient education about these impairments. Treatment such as cognitive rehabilitation can be provided by neuropsychologists or rehabilitation psychologists. However, if these disciplines are not available, cognitive behavioral strategies such as memory and attention adaptation training can be taught by trained psychologists. Clinical social workers may also have the requisite skills to offer cognitive-behavioral strategies for coping with cancer-related cognitive impairment symptoms.

If a cancer program does not have therapeutically trained professionals, rehabilitation providers can provide several of the services that have shown promise in treating cancer-related cognitive impairment. For example, occupational therapists can provide strategies to help patients compensate for memory or attention challenges and improve their performance of daily activities. Physical therapists can provide education/training on

the role of exercise and physical activity to mitigate the impact of cognitive impairments on daily activities. Speech and language pathologists can provide strategies related to language, such as improving verbal recall or word identification. Specialty physicians may also have a role to play in addressing cancer-related cognitive impairment. Physiatrists—physicians specialty trained in rehabilitation—may serve as facilitators for the other rehabilitation professions discussed above, and they can assess patients for medication options or interactions that may be exacerbating cancer-related cognitive impairment. Psychiatrists may also be able to help with medication management if cancer-related cognitive impairment is complicated by a psychiatric diagnosis such as depression or post-traumatic stress disorder.

Conclusion

In closing, it is evident that cancer-related cognitive impairment is a distressing problem that affects many cancer patients, both during treatment and well into survivorship. Though the gold standard of treatment and timing has yet to be determined, research has produced initial evidence of methods that can be implemented in the community cancer setting by collaborating with other disciplines such as psychology, social work, and rehabilitation. By designing thoughtful screening and assessment processes, oncology staff can identify cognitive complaints and address them within the oncology setting. Oncology programs may not have dedicated cancer-related cognitive impairment clinicians, but they can explore the relationships they have with members of the multidisciplinary care team to identify alternative methods of identifying and treating cognitive issues. The importance of developing service networks for this oft-overlooked problem is critical to maximizing the daily activities of cancer survivors throughout their lives. OI

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