PALLIATIVE CARE NETWORK OF WISCONSIN

FAST FACTS AND CONCEPTS #342
CHEMOTHERAPY RELATED COGNITIVE IMPAIRMENT
Katharine K. Brewster MD, Daniel Shalev MD, Jon A. Levenson MD

Background: Chemotherapy-related cognitive impairment (CRCI) is a frequent, yet poorly recognized complication of cancer therapy. This *Fast Fact* reviews the effects, diagnosis, and management of CRCI.

Clinical Significance: Changes in memory, attention, processing speeds, and problem-solving during or after exposure to chemotherapy have been referred to as "chemobrain" or CRCI. CRCI often begins right away with 50-80% noticing cognitive changes during chemotherapy (1,2); others may not notice the changes for a few weeks after chemotherapy exposure. While most CRCI symptoms resolve after chemotherapy is discontinued, 25-35% experience cognitive changes that persist years after treatment completion (3-4). Patients may describe it to their clinicians as a sense of "forgetfulness" or "cloudiness in thinking." Although the degree of CRCI is usually subtle, even slight changes in cognition can adversely impact decision-making capacity, advanced care planning, treatment adherence, and caregiver burden. One study of breast cancer survivors found only a 10% decrease in standardized cognition scores, but over 45% self-reported these changes as significant to their quality of life (5).

At Risk Patients:
- > 65 years of age, CNS involvement, lower baseline cognitive reserve, social isolation, and depression are the most established risk factors (4,6).
- Genetic factors, including various *APOE and COMT* genotypes, have been implicated in both resiliency or vulnerability to CRCI depending on the allele (7).
- Leukemia, breast, prostate, ovarian, and CNS cancers (8).
- Although methotrexate, cytarabine, and ifosfamide are known for their central neurotoxic effects, other, more general factors about the chemotherapy may have a larger role than the type of chemotherapy administered, such as: a) high-dose exposure; b) multi-agent therapy; c) concurrent chemotherapy with cerebral radiation; d) intrathecal administration (8,9).

Assessment: Cognition can be affected by many other factors common in cancer patients: depression, anxiety, sleep disturbances, metastases, and medications. A full clinical evaluation should be performed to identify modifiable cognitive risk factors prior to diagnosing CRCI. While short cognitive screening tools often lack adequate sensitivity and specificity to detect the subtle changes of CRCI, they may be the most feasible options to incorporate into clinical practice. Examples include the Functional Assessment of Cancer Therapy-Cognitive Function (FACT-Cog) (10), the Montreal Cognitive Assessment (MoCA) (11), the Mini-Mental Status Exam (MMSE) (12), and the Mini-Cog (13). Even these tests can be time-consuming; therefore, many clinicians reserve their use for at-risk and/or symptomatic patients who are not acutely ill or imminently dying, as they are most likely to benefit from the diagnosis and treatment. If the screening tool suggests CRCI, ideally a full neuropsychological evaluation is pursued to confirm the diagnosis, guide rehabilitative efforts, and obtain requisite support such as disability benefits.

Management: Because CRCI often improves weeks to months after chemotherapy exposure, many patients require no intervention. For others with persistent symptoms or for whom discontinuation of the inciting chemotherapy is not a feasible care option, there are several pharmacological agents under investigation for CRCI. However, they are primarily limited to pilot data. As such there are no FDA-approved medications for CRCI.
- Psychostimulants are the most studied medication class for CRCI, yet, most trials look at cognition only as a secondary outcome. Furthermore, the data are mixed: modafinil and methylphenidate have shown mild-moderate cognitive improvement in some studies (14-16) but not others (17-19).
- Donepezil has demonstrated some efficacy in early investigational trials (20,21). Memantine has shown mixed results (22).
- Beyond pharmacologic interventions, the most established efficacy is seen in cognitive rehabilitation approaches like cognitive behavioral therapy (CBT) and a novel therapy called Memory and Attention Adaptation Training which incorporates psychoeducation, stress management, mindfulness, and self-awareness into CBT (23,24). These interventions have been associated with a moderate improvement in FACT-Cog scores that are sustained through a 2-month follow-up (25). A referral to a clinical psychologist is often necessary for this type of cognitive rehabilitation.

Summary: As many patients are not aware of the cognitive side effects of cancer treatment, clinician recognition and psychoeducation about CRCI is likely the most crucial aspect of its management. Some patients may worry that the cognitive changes associated with chemotherapy are a result of an undiagnosed neuro-degenerative disorder like Alzheimer's disease. Clinician counseling about CRCI's signs and symptoms, etiology, and prognosis of likely improvement after cessation of chemotherapy exposure can thereby alleviate excessive concern and validate patient experiences.

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Authors Affiliations: Columbia University College of Physicians and Surgeons, New York Presbyterian Hospital, New York State Psychiatric Institute.
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