



# Neurocognitive Effects from Chemotherapy

Medical Psychiatry: A Comprehensive Update

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September 20, 2025



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# Disclosures

I do not have any relevant financial relationships with any commercial interests.

# Learning objectives

Recognize **risk factors** for chemotherapy-related cognitive decline

Characterize neuropsychiatric **symptoms** related to chemotherapy

Predict the **timeline** for onset and resolution of cognitive deficits

# Cancer-Related Cognitive Impairment (CRCI)

## Patient-Related Risk Factors

- Cognitive reserve
- Comorbidities
- Pre-existing CNS lesions or cognitive dysfunction
- Genetic Risk Factors
- Nutritional status

## Disease-Related Contributors

- CNS involvement
- Hormonal effects
- Metabolic Derangements
- Hepatic or renal dysfunction
- Paraneoplastic syndrome

## Treatment-Related Contributors

- Surgical resection
- Radiation treatment
- Chemotherapy
- Immunotherapy

# Chemotherapy-Induced Cognitive Impairment

- Increasingly recognized as frequent outcome of chemotherapy
  - Studies of breast cancer survivors show 17% - 75% of patients experience cognitive deficits following chemotherapy treatment
- Potential for significant impact on patient outcomes
  - Reduction in quality of life **during treatment and in survivorship**
  - May limit patient's ability to tolerate high dose regimens
- Severity of deficits related to multiple factors including: patient risk factors, cancer type, and chemotherapy related factors including agents used, dosing schedule, and route of administration

Schiff, 2018

# Chemotherapy-Induced Cognitive Impairment

- Commonly presents as mild to moderate deficits across multiple cognitive domains including:
  - Attention and concentration
  - Memory
  - Executive Functioning
  - Information Process Speed
  - Reaction time
  - Language
- **Cognitive effects may be mild or subtle, but significant source of distress and frustration.**

Asher, 2011

# Chemotherapy-Induced Cognitive Impairment

- Proposed mechanisms:
  - Vascular injury
  - Direct injury to neurons or disruption in neuronal impulse conduction
  - Inflammation
  - Oxidative stress and DNA damage
    - Oxidative DNA damage has been detected prior to initiation of chemotherapy and may also be independent contributor to Cancer-Related Cognitive Impairment
  - Autoimmune responses
  - Alterations in blood-brain barrier

Országhová, 2021; Vitali, 2017; Ahles 2007

# Chemotherapy-Induced Cognitive Impairment

- Prevalence and individual risk vary widely depending on multiple factors:
  - Cancer-related factors
  - Patient-specific factors
    - Patient age, education, cognitive reserve
    - Pre-existing CNS lesions or cognitive dysfunction
    - Genetic Risk Factors
    - Nutritional status
    - Comorbidities

Cheung, 2015; Ahles, 2007; Ng, 2016

# Chemotherapy-Induced Cognitive Impairment

- Prevalence and individual risk vary widely depending on multiple factors:
  - Chemotherapy regimen
  - Concurrent radiation therapy or other chemotherapy line
    - Current treatment protocols often combine multiple chemotherapeutics with different and/or complementary mechanisms of action

Ahles, 2007; Ng, 2016

# Risk factors associated with specific chemotherapy regimen:

Agent(s)

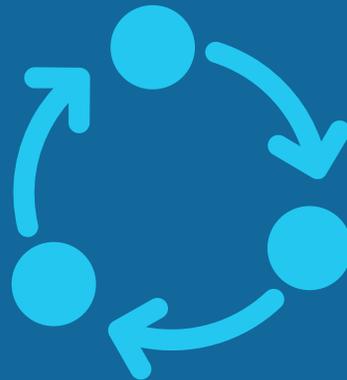
Route

Dosage

Schedule

# Risk factors associated with specific chemotherapy regimen:

- Factors affecting drug metabolism
  - Hepatic and renal dysfunction increase risk of CNS toxicity with certain agents (e.g., high-dose cytosine arabinoside, used as induction agent in AML)



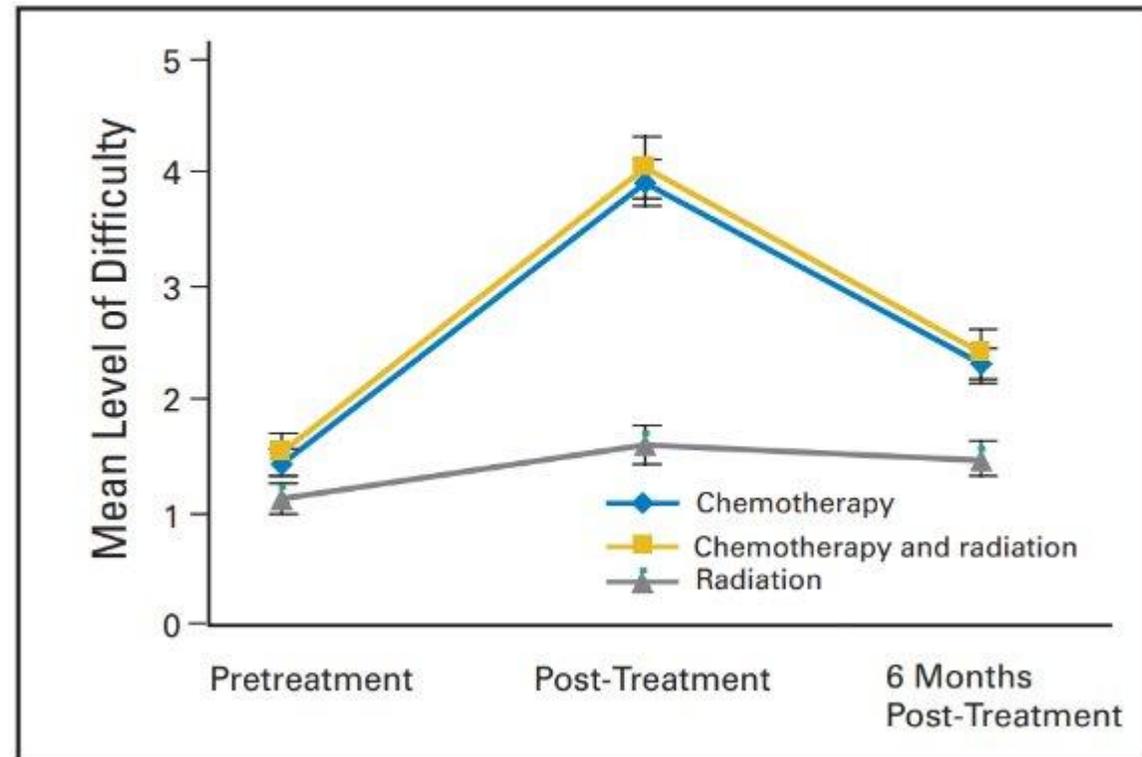
# CICI Symptom Timeline: Onset and Duration

- Deficits may begin during treatment and persist for months or years
  - Studies investigating duration of symptoms after completing chemotherapy have been mixed.
  - Similar to the risk of developing deficits, the duration of deficits likely varies based on personal risk factors, disease/cancer specific risk factors, and details of chemotherapy regimen.



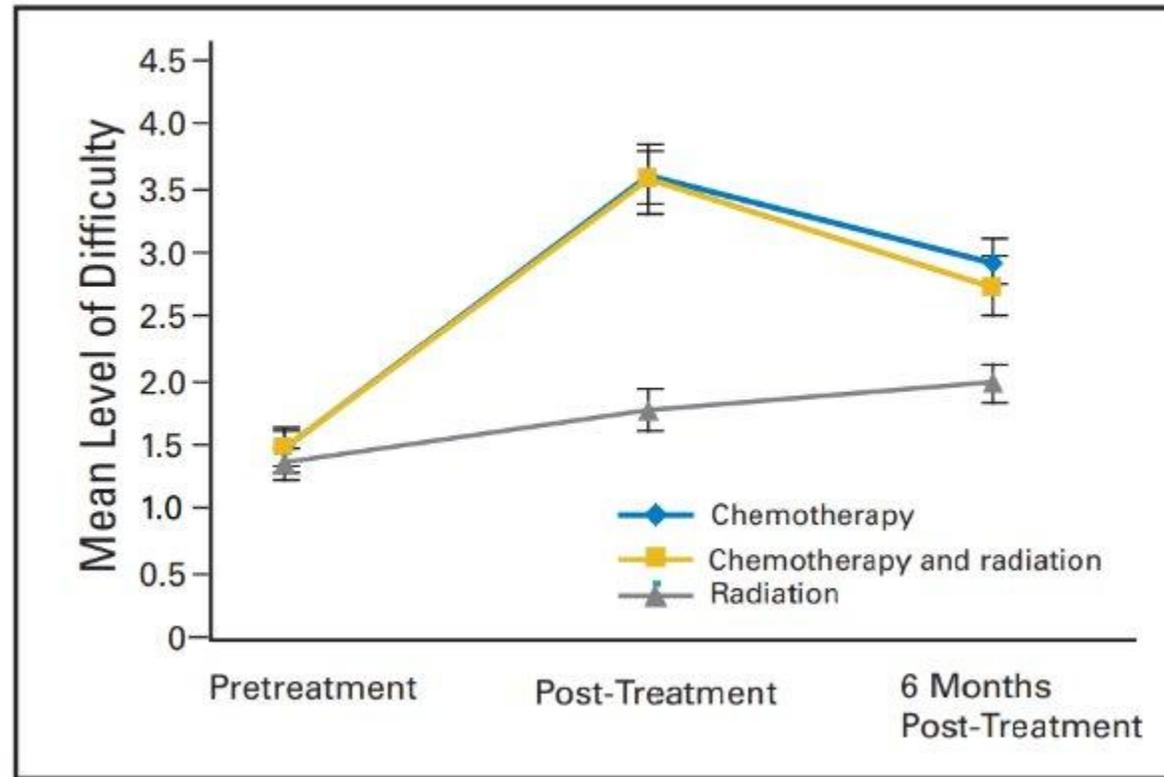
# Kohli, et al: Longitudinal multicenter study, 2007

Figure 1. Difficulties with concentration over time, by treatment type.



# Kohli, et al: Longitudinal multicenter study, 2007

**Figure 2. Difficulties with memory over time, by treatment type.**



# Cognitive Dysfunction Based on Cancer Type

- **Breast Cancer**
  - More extensively studied than other cancer types
  - Patients may also receive hormonal therapies which have their own cognitive effects
  - Impacts 15-50% of patients, potentially more

Wagner, 2020; Rodriguez Martin, 2020; Raysi Dehcordi, 2013

# Cognitive Dysfunction Based on Cancer Type

- **Brain Cancer**

- Difficult to isolate effects of chemotherapy vs direct tumor effects, radiation effects, post-surgical effects and other treatments
- Cognitive deficits progress with progression of disease
- Analysis of pre-operative and post-operative patients with high-grade gliomas and low-grade gliomas detected improvement in processing speed and memory after resection (Raysi Dehcordi, 2013)

Wagner, 2020; Rodriguez Martin, 2020; Raysi Dehcordi, 2013

# Cognitive Dysfunction Based on Cancer Type

- **Hematologic Malignancy**
  - Complication of Hematopoietic Cell Transplantation
    - Conditioning Type: Myeloablative Conditioning Versus Reduced-Intensity Conditioning
    - Allogeneic transplant vs autologous transplant
  - Symptoms may persist for prolonged periods
- **Prostate Cancer**
  - Patients may also be affected by androgen deprivation therapies

Sharafeldin, 2018

# Evaluation of Cognitive Deficits

- **Track symptoms and objective measures over time**
  - Formal screenings of memory, language, attention, executive function, and processing speed
  - Montreal Cognitive Assessment (MoCA)
  - Hopkins Verbal Learning Test-Revised (HVLT-R)
  - Trail Making Test (TMT)
  - Controlled Oral Word Association (COWA) of Multilingual
  - Aphasia Examination
- **Monitor throughout treatment cycle**
- **Referral for neuropsychological testing may be indicated to better define symptoms**

Wefel, 2011

# Management of CICI

- Behavioral Interventions: First-line treatment for cognitive changes during or after cancer treatment
  - Mindfulness based relaxation techniques
  - Physical exercise
  - Cognitive rehabilitation
  - Brain-training programs (“Neurobics”)
  - Compensatory strategies
  - Psychoeducation
  - Both for patients in survivorship and at start of treatment
  - Avoiding alcohol, marijuana, other substances

Bail, 2016; Lv 2020

# Management of CICI

- Investigations of pharmacotherapy options have demonstrated mixed results overall
  - **Psychostimulants:**
    - Methylphenidate
    - Modafinil, Armodafinil
    - Miladi, et al. 2019: Systematic review and meta-analysis including three RCTs investigating Methylphenidate and three RCTs investigating Modafinil found insufficient evidence to determine benefit of psychostimulants in study population. Similarly, did not demonstrate significant rate of adverse events

Miladi, 2019; Brown, 2013 , Davis, 2013; Das, 2020

# Management of CICI

- Investigations of pharmacotherapy options have demonstrated mixed results overall
  - **Donepezil:**
    - No clear evidence of benefit as of yet
  - **Memantine:**
    - Brown, et al. (2012): Randomized placebo-controlled double-blind trial in patients undergoing whole-brain radiation found that patients receiving Memantine did experience cognitive dysfunction, however the deficits were delayed compared to placebo

Davis, 2013; Brown, 2012

# Management of CICI

- Investigations of pharmacotherapy options have demonstrated mixed results overall
  - **Antidepressants:**
    - Potential benefit in reducing cognitive deficits, more research is needed.
    - May be mediated via anti-inflammatory effects



Davis, 2013; Das, 2020

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# Additional Patient Resources:

## Patient Educational Material from Reliable Resources

American Society of Clinical Oncology (ASCO): [Cancer.Net](https://www.cancer.net)

American Cancer Society (ACS): [Cancer.org](https://www.cancer.org)

National Cancer Institute (NCI): [Cancer.gov](https://www.cancer.gov)

Dana-Farber Cancer Institute Resources:

[Tips for Managing Chemobrain](#)



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# Thank you!

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