Cancer-Related Cognitive Dysfunction

Myron Goldberg, PhD, ABPP-CN
Clinical Neuropsychologist
Department of Rehabilitation Medicine
• No financial disclosure or conflicts
Overview

• Focus today will be on systemic, non-CNS cancer conditions
• Overview of cancer-related cognitive dysfunction
• Etiology considerations
• Management strategies
Cancer Treatment

• Balance between treatment outcome and side effects

• Side effects: historically focused largely on physiological symptoms, like:
  • Nausea
  • Appetite loss
  • Fatigue
  • Vomiting
  • Anemia
  • Hair loss
  • Pain

• More recent focus on quality of life
  • Satisfaction
    • Neurocognitive functioning - “Cancer treatment-related cognitive dysfunction (or impairment)”
Risk Factors for Cognitive Dysfunction in Cancer

• Location of cancer
  • Brain (primary/metastasis tumor)
  • Organs with effects on brain functioning
  • All others (e.g., breast, prostate)

• Treatments
  • Surgery
  • Radiation therapy
  • Medication
    • Chemotherapy
    • Immunotherapies
    • Hormone therapies
“Chemobrain”

• Does it exist?
• If yes, what’s it etiology?
• What kinds of cognitive problems arise?
• How long does it last?
What Does the Research Say?

• Across studies, self-reported cognitive difficulties in persons with various systemic cancers and receiving chemotherapies have varied greatly: typically, 50% - 90%

• However, research using performance-based testing commonly show a lower frequency of patients with cognitive impairment.
  • E.g., Impairment also varies across studies, but often is no more than 50% over the course of treatment.

• Difference in frequency between self-report and formal testing thought to be related to:
  • Difference in “reference points” —
    • Patient self-report often references “noticed declines”
    • Research studies reference operationally defined “impaired ability” (e.g., 2 or more tests ≤ -1.5 standard deviations from normative mean)
  • Question of sensitivity of performance-based tests
  • Transient increased effort on tests / compensatory brain activity helps to achieve a good level of test performance
  • Self-reported cognitive symptoms more correlated with mood and anxiety
Question of Etiology

• Is it all just chemotherapy?

• Yes and no....... 

• It’s typically *multifactorial*!
  • Several factors can influence a person’s cognitive functioning
Predicting Cognitive Functioning Problems: It’s Not that Easy!
The Biopsychosocial Model

- Biological
- Social
- Psychological
  - Cognitive Functioning
The Complexity of It All – Pre-treatment Cancer Effects?

- Women with breast cancer: 11 to 35% had cognitive dysfunction (Cimprich et al 2010)
  - Patients showed reduced efficiency in attention and working memory compared to healthy controls
  - fMRI results – differences in attention/working memory circuitry during more demanding task
- Acute myelogenous leukemia (AML) and myelodysplastic syndrome (MDS) (Meyers et al., 2005)
  - 41-44% deficits in memory functioning
  - 28% diminished cognitive processing speed
- Colon cancer (Cruzado et al 2014)
  - 37% demonstrated some form of “cognitive impairment” prior to chemotherapy
- Prostate cancer (Buskbjerg et al 2020)
  - 57.5% of untreated patients met criteria for clinically significant cognitive impairment

- Possible Reasons:
  - Inflammatory processes
    - Meyers et al (2005) – positive correlations between proinflammatory cytokine activity and cognitive dysfunction, fatigue and ratings of quality of life in pts with AML and MDS
  - Autoimmune mechanisms / paraneoplastic processes - syndromes
  - Hormonal changes – e.g., changing levels of testosterone in prostate cancer
  - Other medications
    - E.g., pain medications
  - Concomitant medical conditions
  - Emotional functioning / fatigue
    - A number of studies (e.g., Jenkins et al 2006):
      - Stronger relationship between self-reported cognitive impairment and disturbance in mood and fatigue than self-report and objective cognitive test results

- Gives rise to the need for well-controlled studies
Addressing the Complexity of Chemotherapy Effects

• International Cognition and Cancer Task Force (ICCTF):
  “Recommendations to Harmonize Studies of Cognitive Function in Cancer Patients,”
Wefel at al. (2011), *The Lancet Oncology*, 12 (7): 703-8

• Best studies are those that:
  • Longitudinal – compare pre-treatment and post-treatment measurement of cognitive functioning
  • Use of good comparison groups
    • Not just healthy controls, but where possible patients with similar conditions, except the same treatment (e.g., no chemotherapy)
  • Use of well-validated performance-based measures of cognitive functioning
    • Self-report is useful, but less reliable
    • ICCTF prescribes a set of tests (core battery), that can be repeated over time and can be supplemented with other tests
      • Verbal memory – word list test
      • Verbal fluency – letter
      • Psychomotor speed & executive functioning
      • Additional tests – working memory
Longitudinal Studies: Breast Cancer

- **Wefel et al (2004) – one of the first prospective studies on chemotherapy**
  - Early-stage breast cancer survivors
  - Measurement: pre; 3-weeks post; 1-year post neuropsychological testing
  - Findings:
    - Pre-chemo (baseline):
      - 33% showed impairment
    - 3-weeks post treatment:
      - 61% showed evidence of decline in one or more cognitive areas
    - 1-year post:
      - 50% with initial decline improved
      - Rest remained stable – i.e., ~ 30% showed persistent declines

- **Breast cancer – hormonal treatment**
  - Tamoxifen Exemestane Adjuvant Multinational (TEAM) Study (Schilder et al, 2010)
    - Prospective study of postmenopausal patients who did not receive chemotherapy
    - Compared tamoxifen, exemestane, healthy control groups
    - Measurement times: Immediate after breast surgery – before start of endocrine tx (T1); after 1-year of endocrine tx (T2)
    - Eight cognitive domains assessed with neuropsychological tests
    - Findings:
      - At T2 (after adjusting for T1 performance):
        - Tamoxifen group:
          - < exemestane group on processing speed
          - < healthy controls on verbal memory and executive functioning
        - Exemenstane group = healthy controls

- **Updated study by Wefel et al (2010)**
  - Essentially replicated findings from 2004 study
  - Also – nearly a third showed new decline at the 1-year measurement point
  - Vast majority showed only one cognitive area affected
Longitudinal Studies: Other Groups

• **Bone marrow transplant: Harrison et al (2021): Review paper**
  - Pre-transplant: up to 50% of patients exhibit impairment in one or more cognitive domains
  - 1-month post transplant: nearly 50% of patients experience decline from their pre-transplant baseline
  - Long-term: mixed trends

• Allogenic transplant patients appear to be a greater risk than autologous patient for chronic cognitive impairment
  - 3-5 years post transplant:
    - Allogenic group: 35%-40% showed evidence of persistent impairment
    - Autologous group: 19%
  - Trends maybe in part related to type of cancer
    - E.g., gains evidenced on tests of verbal fluency at 12 and 18 months in patients with chronic myeloid leukemia but not in those with myelodysplastic syndrome

• **Across other forms of non-brain cancer results for relationship between chemotherapy and cognitive functioning have varied**
  - For example:
    - Small cell lung cancer study (Whitney et al; 2008)
      - 62% showed some form of cognitive decline 1 month after chemotherapy
      - At 7 months post chemotherapy nearly total resolution for most
    - Review of advance prostate cancer studies – hormone therapy (Nelson et al; 2008)
      - 9 studies from 2002 to 2006: nearly all with small sample sizes
      - Compared pre-treatment to 6 to 12 months post-treatment
      - Conclusions:
        - 47% to 69% of men showed “subtle but significant declines” in one or two domains (e.g., memory), but not across all cognitive domains.
Typical Reported / Demonstrated Cognitive Problems

• Often the degree of decline is mild
  • But may not be proportional to effect on quality of life and daily functioning – e.g., home or work setting demands
  • E.g., survey of 1600 of mostly breast cancer survivors
    • 75% of respondents reported post-treatment cognitive symptoms
    • 75% of respondents with subjective cognitive symptoms – impacted ability to return to work
• Memory functioning - learning efficiency and memory retrieval
  • Preserved retention
  • Improvement with recognition cues
• Working memory capacity / sustained attention
• Speed of mental processing
• Executive functioning
  • Cognitive flexibility (mental multitasking)
  • Problem solving
  • Verbal fluency (response initiation and organization)
  • Organization and planning

• Frontal-subcortical circuitry disruption
Structural Brain Imaging Studies & Chemotherapy

- Performed mainly in patients with breast cancer – adjuvant therapies

- Brain MRI findings
  - Consistently shown lower grey and white matter volume – frontal and temporal lobes
  - Structural changes correlated with self-reported cognitive difficulties and impairments on testing

- Diffuse Tensor Imaging (DTI)
  - e.g., Deprez et al (2010)
    - Groups:
      - BC – post anthracycline–based chemotherapy (80-160 days post)
      - BC – non-chemotherapy
      - Healthy controls
    - Findings
      - Decreased fractional anisotropy (FA) in frontal and temporal lobes in BC chemo pts compared to other 2 groups
      - Correlated with np findings for attention and processing speed
Functional Brain Imaging & Chemotherapy

- Mixed finding across a limited number of studies – stability of findings

- Ferguson RJ et al., (2007)
  - Brain fMRI study of monozygotic twin sisters (60 y.o.)
  - One with hx of breast cancer and chemotherapy (doxorubicin, cyclophosphamide, docetaxel, ongoing tamoxifen)
  - Other sister no history of cancer

- Little to no differences on cognitive testing. However, sister with cancer reported more cognitive functioning complaints

- Working memory task used: n-back

- fMRI - more spatial activation in typical working memory circuitry (bifrontal and biparietal regions) in sister with cancer

**Top scans: patient

- Deprez et al (2014) – fMRI with breast cancer patients – pre-post design
  - Baseline no differences
  - Decreases in anterior frontal cortex
  - Increases in posterior frontal lobe on multitasking
  - Correlated with subjective and objective executive dysfunction – may reflect impaired working memory and associated compensatory mechanisms.
Chemotherapy Effects: Hypothesized Mechanisms

• **Neural mechanisms underlying cognitive changes – poorly understood**
  • Chemotherapy agents vary by neurotoxicity risk
  • E.g., high risk - 5-fluorouracil, Cisplatin, Cyclophosphamide, Doxorubicin, Etoposide, Methotrexate, Vincristine, Vinblastine

• **Blood-brain barrier damage**

• **Oxidative stress**
  • Reaction to oxygen creates free radicals – lead to cell damage
  • Normal metabolism creates oxidative stress
  • Chemotherapy can induce further oxidative stress

• **Metabolic changes causing inflammatory reactions that injure nerve cells**
  • Increased circulating cytokines

• **Microvascular injury in the brain**
  • White matter may be especially vulnerable

• **Reduced synaptic plasticity - effects on nerve cell generation and repair – e.g., suppression of neurogenesis in hippocampus**

• **Change in hormones**

• **Genetic vulneraries**
  • Certain alleles in the APOE and COMT genes have been associated with increased risk for CRCI

• **Age and Cognitive Reserve**
Conceptual Model of Chemotherapy Effects

Figure 1. Conceptual Model of Chemotherapy-Related Changes in Cognitive Function

Management Approaches
Initial Step – Validation & Assessment

• Query about quality of life – changes in functional status

• Ask if any changes in cognitive functioning are noticed and degree of effect on daily functional status

• Consider using a self-report cognitive symptom measure
  • E.g., Functional Assessment of Cancer Therapy – Cognitive (FACT – Cog)
    • Rate various cognitive abilities on a 0-4 scale
    • Can be used to track perception of cognitive abilities over time in the office

• Consider use of a performance-based cognitive screening test
  • Montreal Cognitive Assessment (MoCA)
  • Mini-Mental Status Examination (MMSE)
  • St. Louis University Mental Status (SLUMS) Exam

• Neuropsychological Evaluation
Neuropsychological Evaluation

- Refer for evaluation – if cognitive problems persist and especially if:
  - Day-to-day functional status is being significantly affected (e.g., work performance)
  - Difficulties seem to be worsening over time
  - Diagnostic issues are present

- Provides objective measurement of cognitive capacities using sensitive measures
  - Attention / Mental Processing Speed / Memory / Communication / Visuospatial Functioning / Executive Functions (Problem Solving, Reasoning, Thinking Flexibility)

- Evaluates emotional / personality / behavioral factors contributions

- Length of evaluation can vary depending on patient and questions to be answered

- Neuropsychological evaluations help to
  - Determine the type and degree of problems
  - Disentangle factors affecting cognitive functioning
  - Helps to determine readiness to return to or engage in certain activities, like work, school, drive
  - Devise a road map for treatment
Treatment Approach

Biopsychosocial Model

Biological

Cognitive Functioning

Social

Psychological

Reversible Causes

Symptom Alleviation
Key Reversible Biopsychosocial Cognitive Dysfunction Risk Factors

**Biological**
- Concomitant Medical Conditions
- Medications
- Sleep
- Fatigue
- Pain
- Use of alcohol or recreational drugs

**Psychological**
- Depression
- Anxiety
- Other psychiatric conditions
  - E.g., bipolar disorder

**Social**
- Perceived social support
- Family stressors
- Work stressors
- Financial stressors
- Housing / basic needs stressors
Addressing Fatigue

• Fatigue:
  • Cancer-related fatigue: physical / cognitive domains
  • Mechanisms not fully understood
  • Across studies, majority of patients report fatigue
  • Prevalence range: 60% - >90% depending on type and course of cancer and treatment
  • Duration varies, but can still be prevalent for many decades after treatment completion
  • Possible inverse relationship with age

• Pharmacological intervention –
  Thong et al (2020): Review of literature in the last 5 years
  • Stimulants
    • Methylphenidate: better than placebo, but modest effects; side effects
    • Modafinil: no better than placebo
    • Erythropoietin – effect in ameliorating CRF if associated with anemia; but safety concerns (tumor regrowth; cardiovascular risks)

• Nonpharmacological interventions - possibly more empirical support:
  • Examined nonpharmacological interventions
    • Exercise: either resistance, aerobic, yoga
    • Psychotherapy
    • Acupressure
  • 471 studies examined; 11 studies included involving 1067 patients
  • Results:
    • Exercise: moderate benefit for both physical and cognitive fatigue
      • Best - resistance combined with aerobic
      • Yoga showed benefits for cognitive fatigue
    • Some evidence for acupressure
    • Psychotherapy; no significant findings; although study selection was thought to be contributory, as other meta-analytic studies found a significant effect
Improving Non-CNS Cancer-Related Cognitive Functioning: Pharmacological Interventions


• Stimulants (methylphenidate):
  • Methylphenidate / modafinil:
    • Mixed results for adults with systemic forms of cancer
    • Improvement in fatigue; but inconsistent changes on tests of cognitive functioning
    • Ongoing RCT with methylphenidate
  • Methylphenidate - better findings with children

• Erythropoietin (tx for anemia)
  • Studied in non-CNS cancer: positive effects on fatigue not conclusively shown so far; side effect risks

• Donepezil (acetylcholinesterase inhibitor)
  • Cites on RCT study on patients with breast cancer Lawrence et al (2016)
    • 24 weeks of donepezil versus placebo
    • Neuropsych evaluation: baseline – 24 weeks
    • Donepezil > placebo on measures of memory functioning
    • No difference on other cognitive functions

• Memantine (NMDA antagonist)
  • No data on non-CNS cancer
Improving Non-CNS Cancer-Related Cognitive Functioning: Non-Pharmacological Interventions

  • Reviewed literature from 2010-2019
  • 29 RCTs identified
  • 10 types of interventions

• National Cancer Institute

• Significant, but typically modest effects compared to control groups
  • Cognitive rehabilitation – modest, but appreciable effects in RCTs on both subjective and objective measures
    • Compensatory training (e.g., external memory aids; pacing; minimizing distractions)
    • Cognitive training (restoration of ability through repetitive training)

• Physical activity / exercise

• Mindfulness-based stress reduction / meditation
Management of Cancer-Related Cognitive Dysfunction

- First steps:
  - Validate
  - Assess type and impact of cognitive symptoms
    - Clinical interview – self-report measure
    - Cognitive screen
    - Neuropsychological evaluation
  - Assess for contributory factors using biopsychosocial model
  - Focus on possible reversible factors
Reversible Factors

Management of Cancer-Related Cognitive Dysfunction

• Consider the need for further evaluation of possible reversible factors
  • Fatigue
  • Sleep
  • Anemia
  • Pain
  • Depression/anxiety

• Judicially, treat reversible factors
  • Pharmacological management of fatigue/sleep/pain/emotional symptoms?
    • Benefit/side effects profile
  • Non-pharmacological management, e.g.,
    • Physical therapy for pain
    • Psychotherapy for depression/CBT for pain/sleep management
Addressing Cancer-Related Cognitive Impairment:

Prescribing Activities to Promote Cognitive Functioning

- Regular exercise
- Dietary changes
- Sleep hygiene strategies
- Participation in stimulating activities
  - Start a new hobby
  - Take a college course
- Continue / increase social interactions
- Stress management, e.g., psychotherapy/yoga classes
Management of Cancer-Related Cognitive Dysfunction

Treating Cognitive Symptoms

- Pharmacological management has yet to be shown to be particularly effective – ongoing research

- Cognitive Rehabilitation
  - Speech Therapy at a rehabilitation center for individual treatment
    - Focus on compensatory strategies
  - Computer-based restorative treatment?

- Consider referral to a Neuro-rehabilitation treatment program
  - Integrative treatment: Rehab Medicine, Speech, PT, OT, Psychology, Rehabilitation Counseling (Vocational Counseling)
Thanks!