CANCER-RELATED COGNITIVE IMPAIRMENT: MORE THAN A SIDE EFFECT OF CHEMOTHERAPY

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OUTLINE

• Background
• Causes and underlying mechanisms
• Study regarding association with physical function
• Screening and diagnosis
• Treatment

LEARNING OBJECTIVES

1. Identify causes for cancer-related cognitive impairment (CRCI)
2. Discuss morbidity associated with CRCI
3. Describe evidence-based interventions for CRCI
HISTORICAL PERSPECTIVE

- “Chemobrain” defined in late 1990s in cross-sectional studies in breast CA
- 2002 – Ahles et al. showed long-term effects of chemo
- 2004 – Wefel et al. first prospective longitudinal study
- Growing appreciation for cognitive difficulties resulting from cancer and its treatments over the last 15-20 years (i.e. CRCI, CRCD)

QUALITY OF COGNITIVE PROBLEMS REPORTED POST-TREATMENT

- Memory
- Concentration
- Executive function
- Ability to learn new material
- Subtle or dramatic
- Variable course

PREVALENCE OF CRCI

- Up to 30% with cognitive impairment before chemotherapy
- 75% report cognitive deficits during treatment
- 15-50% exhibit objective impairment after chemotherapy
- Lasts years after treatment

Janelsins 2011, Wefel 2006
SIGNIFICANCE OF CRCI

- Associations
  - adverse mental health
  - inability to return to work
  - double the risk of dementia
  - worse HRQOL
  - increased mortality
  - Greater influence on chemotherapy prescribing than age or functional status
  - One of the most feared problems among cancer survivors


NEUROPLASTICITY

- Brain’s ability to reorganize itself to repair, compensate, adapt and learn new things
- Most natural brain recovery occurs in the first 1-2 yr after diagnosis and treatment
- Some return to “normal” function, others with persistent deficits, and some develop new problems not seen earlier in treatment

Correa 2008 and Wefel 2010

MECHANISMS

- Direct toxicity
- Cytokine-mediated neuroinflammation
- Oxidative stress
- Genetic
  - Survivors w/ APOE4 with worse cognitive problems
  - Breast CA survivors treated w/ chemotherapy with COMT Val158Met had greater decline
  - BDNF Met/Met genotype protective against chemo-induced cognitive changes
  - Neuronal plasticity genes, DNA damage and repair genes, mediate inflammation

IMAGING FINDINGS

- ↓ gray matter volume
- ↓ white matter connectivity
- Altered functional brain activation and connectivity
- Decreased volume and connectivity correlate with worse function


INFLAMMATION

- Associated with ↑ risk for cancer and neurocognitive disorders
- ↑ cytokine levels in CA pts at baseline relative to controls
- ↑ during chemo and ↓ (but stay elevated) with time
- Correlate with self-reported and objective cognitive function
- Correlated with hippocampal volume and metabolism
- Strongest data for TNFα, IL-6, and IL-1β

INFLAMMATORY HYPOTHESIS

- Chronic inflammation
- Increased oxidative stress
- Accumulation of DNA damage
- Shortening of telomeres
- Increased cell senescence
- Increased expression of p16INK4a and ARF in breast cancer patients (estimated 10 yrs of aging)
- Increased activation of ERK and AKT signaling pathways in rats

Sanoff 2014, Salas-Ramirez 2015

CANCER TREATMENT AND AGING

- Chronic inflammation
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Ahles 2012
CANCER

- Non-CNS Cancers
  - Immune system dysfunction → disrupt brain structure and function
  - Feeling physically ill, fatigued, depressed, etc.
- Primary brain tumors and brain metastases
  - ↑ Intracranial pressure
  - Edema
  - Displacement of brain tissue
  - ↓ blood supply

CHEMOTHERAPY

- Toxic to neural progenitor cells
- Most chemo cannot cross the BBB
- CA increases BBB permeability
- Even small amounts can cause significant damage
- Chemo elevates levels of pro-inflammatory cytokines
- Elevated cytokines can lead to damage through oxidative stress and DNA damage
- Once a neuron dies, it is gone forever
- Accelerates brain aging

SURGERY

- In pts w/ brain tumors, can improve or worsen cognitive function
- Mastectomy implicated in cognitive effects
- May be 2× increased inflammation and pain
- Impact of anesthesia
  - May be dose-dependent
  - Should last < 6 mo

References:
RADIATION

- Cranial, Head & Neck
  - Radiation necrosis
  - Disrupts creation of new neurons in the hippocampus
  - Accelerate brain aging, increase risk of dementia
- Local
  - Some evidence for adverse cognitive effects
  - May act through DNA damage, inflammation


HORMONAL THERAPY

- Estrogen and testosterone support brain function
- Tamoxifen
  - Smaller hippocampal size
  - Combination with chemo may lead to greater cognitive difficulties
  - Other studies show no association
  - Aromatase inhibitors independently associated with cognitive decline
- ADT


COMORBIDITIES AFFECTING COGNITIVE FUNCTION

- Sleep disorders (insomnia, sleep apnea)
- Depression, anxiety, distress
- Pain and pain medications
- Other physical illnesses
- Fatigue
SELF-REPORT VS. OBJECTIVE MEASUREMENT

- Self-reported problems more common
- Self-report limitations
  - Is it really measuring cognitive impairment?
- Objective measurement limitations
  - Is it sensitive enough?
  - Logistically feasible?

MEASUREMENT OF CRCI

- No standard for screening, monitoring
- ICCTF recommends
  - Hopkins Verbal Learning Test
  - Trail Making Test
  - Controlled Oral Word Association Test
- Objective screening instruments: MMSE, MOCA, RBANS
EVALUATION

- Self-report screeners
- Screening Instruments
  - Psychiatry, Psychology
  - Occupational Therapy
  - Speech Therapy
- Neuropsychological Assessment
  - Neuropsychologists in PM&R, Neurology, Psychiatry

FUNCTIONAL, PSYCHOSOCIAL, AND DEMOGRAPHIC VARIABLES ASSOCIATED WITH COGNITIVE SCREENING IN CHEMOTHERAPY NAÏVE BREAST CANCER PATIENTS


STUDY DESIGN

- 331 stage I-III breast cancer
- University of North Carolina Hospitals
- 2009-2018
- Completed the Cancer-Specific Geriatric Assessment prior to chemotherapy
MEASURES

- Cognition (BOMC)
- Functional status
  - Patient reported Karnofsky
  - MOS Physical Function
  - OARS IADL
  - Falls
  - Time Up and Go
- Depression & Anxiety (Mental Health Inventory)
- Social Function & Support (MOS)
- Nutrition (BMI, % weight loss in last 6 mo)

OBJECTIVES

1. Evaluate the use of the BOMC to establish baseline of cognitive function in breast CA pts prior to chemotherapy
2. Describe association between baseline BOMC with wide array of functional, psychosocial, medical, and socio-demographic variables

BLESSED ORIENTATION MEMORY CONCENTRATION TEST (BOMC)

- 6-items
- < 5 min
- Range 0-28; higher is worse cognition
- Developed for dementia (cut point ≥ 11)
- Unclear if sufficiently sensitive to be used to screen for or to monitor CRCI
- Potentially compatible with a busy oncology practice

Katzman et al. 1983
**DEMOGRAPHICS**

- Age: 65.2
- Caucasian: 80%
- Married: 56%
- Employed full time: 21%
- HS education or less: 43%
- Lived alone: 25%

**MENTAL HEALTH**

- Depression (26%)
- Anxiety (42%)
**PHYSICAL FUNCTION**

- KPS $\geq 80$
  - 87%
- Physical Function=20
  - 76%
- TUG < 14 s
  - 81%
- Vigorous Activity
  - 70%
- No Falls
  - 82%

**COGNITIVE FUNCTION**

![Bar chart showing distribution of BOMC scores](chart)

**ASSOCIATIONS WITH BOMC**

- Demographics
  - Age ($p=0.001$)
  - Education ($p<0.001$)
  - Employment ($p<0.001$)
- Psychosocial
  - Depressive symptoms ($p=0.04$)
  - Social activity limitations ($p=0.01$)
- Medical
  - HTN, cardiac dz, stomach or intestinal dz and problems with circulation associated in bivariate analyses
  - None sig in adjusted model
BOMC AND PHYSICAL FUNCTION

- KPS<80 (p=0.01)
- Physical function score<20 (p=0.0006)
- IADL<14 (p=0.02)
- TUG>14 s (p=0.001)
- Unable to engage in vigorous activity (p=0.009)

IMPLICATIONS

- Concern for cognitive impairment should raise concern for deficits in physical function and vice versa
- Explore interventions that simultaneously target both cognitive and physical function

INTERVENTIONS FOR CRCI

- Behavioral: Cognitive rehabilitation, Cognitive Training, Cognitive Behavioral Therapy
- Physical activity: Yoga, Exercise programs
- Mind-Body: Meditation, Mindfulness, Acupuncture
- Pharmacotherapies: Donepezil, Memantine, Modafinil, Methylphenidate, Epo-stimulating agents, Vitamin E, Ginkgo biloba
INTERVENTIONS FOR CRCI

- Mostly limited to breast CA
- Generally years after completion cancer treatment
- Small sample sizes
- Prevention trials are rare
- Challenges with access, cost, patient participation

COGNITIVE TRAINING

- Repetitive, increasing challenging tasks (often via computer) to improve, maintain, or restore cognitive function
- Has been tested in 5 studies
  - Primarily in early stage breast CA survivors
  - Completed adjuvant therapy and were reporting cognitive concerns
  - Start out with 4-5, 30-60 min sessions per week for at least 6 weeks


COGNITIVE REHABILITATION

- ↑ self-awareness to support problem-solving and compensatory strategies
- Mostly used in TBI and stroke populations
- Research
  - Individual and group delivery (in person or online)
  - 4-7 sessions
  - Improved cognitive symptoms but not neuropsychological performance
  - Usually weekly therapy for 30-60 min with neuropsychologist, occupational therapist, speech/language pathologist
- Not widely available or covered by health insurance
- CPT codes: 97532, 97535, 97537

PHYSICAL ACTIVITY

- ↑ new neurons in the hippocampus, BDNF levels, reduces inflammation
- ↓ risk of Alzheimer’s and slows age-related cognitive decline
- Moderate intensity exercise (60% max HR - walking, yoga, dancing, stair climber, weight lifting) at least 150 min/week or vigorous exercise (70% max HR - jogging, running, boxing) at least 120 min/week
- Local Resources
  - Get REAL & HEEL - Individualized exercise combined with psychosocial therapy (e.g. pain and stress management, relaxation techniques, mindfulness training, etc.), 3x/week x 16 wk, Free LIFESTRONG at the YMCA - 12-week program, 10 locations, Raleigh, Durham, Sanford, Chapel Hill
  - Live Fit Cancer Exercise Program
  - Yoga - Prevents Health Institute, $150 for 12 classes; CCSP Yoga ($5/class); Breast Cancer Survivor Yoga Series at Carolina Yoga Company

MIND-BODY

- Bring an awareness of individual potential for healing or restoration
- Guided imagery, meditation, mindfulness-based stress reduction, neuro/biofeedback, and acupuncture
- Mindfulness
  - UCLA MAPS classes - 6-wk online courses - wwww.mwm.ucla.edu
  - Apps: Mindfulness App (145), Seating Tall, Headspace, Insight Timer, Mindfulness Bell
  - Local courses through UNC-Chapel Hill Program on Integrative Medicine and Duke Integrative Medicine
  - Acupuncture
    - UNC Family Medicine Acupuncture Clinic
    - NC Society of Acupuncture and Asian Medicine (www.ncsac.com/Find-a-Local-Acupuncturist)

PHARMACOTHERAPIES

- Stimulants (methylphenidate and modafinil)
- Alzheimer’s drugs (donepezil and memantine)
- SSRIs (sertraline and paroxetine)
- Ginkgo biloba
- Vitamin E
- Erythropoietin-Stimulating agents
- Weight risk/benefit

FOR ALL PATIENTS

- Active journaling
  - Describe an experience, why it was important, what it meant for you, what you learned from it
  - Goal to increase "idea-density"

- External aids
  - Day planner
  - Alerts/reminders on smartphone or tablet
  - Sticky notes, whiteboards

- Routine

- Workplace accommodations
  - Examples and procedural information available at www.eeoc.gov/policy/docs/accommodation.html

UNC COMPREHENSIVE CANCER SUPPORT PROGRAM (CCSP)

https://unclineberger.org/ccsp/