CHEMOBRAIN: CANCER AND CANCER TREATMENT-RELATED COGNITIVE CHANGES

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AGENDA

• Cancer and Cancer Treatment-Related Cognitive Changes
  • 1. What is it and why does it happen?
  • 2. What can you do about it? Common strategies and what the research shows
  • 3. Current and future research
CANCER AND CANCER TREATMENT-RELATED COGNITIVE CHANGES

WHAT IS IT AND WHY DOES IT HAPPEN?
COGNITIVE ISSUES ASSOCIATED WITH CANCER AND CANCER THERAPY

What do we call it?
- Cognitive or Neurocognitive Changes
- Cognitive dysfunction
- Chemobrain
- Chemofog
- Memory lock

What causes it?
- Cancer
- Chemotherapy
- Endocrine therapy
WHAT KIND OF COGNITIVE ISSUES ARE WE TALKING ABOUT?

• General definition: Mild cognitive impairment attributed to non-central nervous system cancers and related treatment.
  
• Forgetfulness, absentmindedness, and inability to focus, trouble with word-finding, misplacing items, problems multi-tasking or driving to familiar places

• Changes in cognitive function, higher-order mental processes including memory, psychomotor/processing speed, and executive functioning

• **Time Frame:** Range: after 1-3 cycles to after completion of chemotherapy

• **Severity:** -1.0 to -1.5 SD below mean scores on two or more objective tests
  - -2.0 SD or more below mean scores on one objective test
  - Many survivors demonstrate normal scores on objective tests but self report significant deficits

• **Recovery:** Within 1-2 years after completion of therapy
  - Long lasting impairment noted 5, 10, 20 years after completion of therapy (Koppelmans et al, 2012).
CONSEQUENCES OF COGNITIVE ISSUES

• Can significantly impair the quality of life among cancer survivors
  • Work life, Home life, Social life
• Prevalence
  • As many as 75-95% of survivors report experiencing cognitive issues
  • Up to 83% of breast cancer survivors report some level of cognitive issues
WHY ARE THESE COGNITIVE ISSUES SO HARD TO STUDY?

• Many confounding and contributing factors make CRCI difficult to investigate
  • No official definition
  • No standard assessment
  • Neuropsychological testing is time-consuming and expensive
  • Self-report of difficulty: Lack of correlation with objective testing (sensitivity to subtle changes)
  • Between 30%-75% of cancer patients report cognitive issues before treatment.
CONFOUNDING AND CONTRIBUTING FACTORS

• Age
• Hormonal status
• Baseline cognitive performance
• Educational level (cognitive reserve)
• Genetic predisposition
• Comorbidities that affect oxygenation
• Depression
• Anemia
• Fatigue
• Anxiety
• Pain (and pain medication)
• Chemotherapy regimen
• Time since treatment
• Dietary factors

(Ahles & Saykin 2001; Ahles & Saykin 2002; Cimprich et al. 2005)
HOW DOES CANCER TREATMENT IMPAIR MEMORY AND CONCENTRATION?

POSSIBLE MECHANISMS

- Changes in cognition, brain structure and function
  - DNA damage and telomere length (premature or accelerated aging)
  - Genetic susceptibility
  - Blood brain barrier integrity & neuroprogenitor cell injury
  - Cytokine dysregulation
  - Estrogen/testosterone reduction

Adapted from diagram in Holland, Psychooncology, 2010
NEUROLOGICAL FINDINGS DOCUMENTING STRUCTURAL AND FUNCTIONAL EFFECTS OF TREATMENT

• Evidence is mounting that chemotherapy results in:
  • cerebral *structural* changes (gray matter reduction)
  • cerebral *functional* changes (hyper-activation vs reduced activation, may be task dependent or due to inability to compensate)
  • The alterations correlate with complaints regarding impaired cognition and performance.
  • The alterations persist over time.

McDonald et al. 2010, 2012; Holohan et al. 2013
Twin Study: 60 y/o identical female twins
A= Breast Cancer & treatment   B= No Cancer

Functional magnetic resonance images of 60-year-old identical twins during a working memory task with incrementally increasing levels of difficulty (left to right)

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WHAT CAN DO ABOUT IT?

COMMON STRATEGIES AND WHAT DOES THE RESEARCH SHOW?
STRATEGIES TO DEAL WITH “CHEMOBRAIN”

• Rule out other causes (fatigue, distress, insomnia)
• Sleep Hygiene
• Nutrition
• “Mindful” approach
  • Accepting “differences,” imperfection
• Use Social Support
  • Enlist friends/family to help, share responsibility for tasks
• Use GPS when needed
• Humor
Healthy sleep & bedtime habits

- Keep a routine sleep-and-wake schedule
- Clear your mind with therapy
- Use the bedroom only for sleep and sex
- Exercise
- Wear a sleep mask
- Keep your bedroom dark and free of electronics
- Get daylight exposure bright and early
- Use relaxation techniques
- Avoid or limit alcohol, caffeine, nicotine, and other mind-altering substances
- Use a red night light if needed

GoodTherapy.org
NUTRITION
OMEGA 6 TO OMEGA 3 RATIO

Inflammatory:
Transfats
Hydrogenated/processed oils
Fried foods
Sucrose/sugar
Processed foods
Mayonnaise
Chips
Corn/whole grain-fed meat

Anti-Inflammatory
Fish: Salmon, Halibut, Trout
Oils: Flaxseed, Canola
Avocado
Whole grains
Vegetables/legumes
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STRATEGIES TO FOR COGNITIVE ISSUES

• Behavioral
  • Organizational strategies
    • Establish and follow routines
    • Prioritize activities
    • Write it down!
  • “Techno” prompts
  • Mind-challenging activities
    • Sudoku
    • Crossword puzzles
  • Novel Stimuli
WHAT DOES THE RESEARCH SHOW?

• Evidence is building for the benefits of **Exercise and Mindfulness-based Exercise**

• **National Comprehensive Cancer Network (NCCN) Guidelines for exercise (150 minutes per week)**
  - Reduce risk of recurrence
  - Reduce fatigue
  - Improve sleep
  - May also improve memory and concentration (increase blood flow, decrease inflammation)

• **Proposed mechanism for mindfulness benefit:**
  - Downregulation of Hypothalamic-pituitary-adrenal axis and sympathetic nervous system
  - Decreased markers of inflammation

• Evidence is building for the benefits of **cognitive rehabilitation** (which can encompass cognitive training, cognitive behavioral training, and psycho-education)
IDENTIFICATION OF PREDICTORS

Cross-sectional study

N=363 (317 BCS, 46 HC). BCS classified as pre-chemo, current chemo, and post chemo.

FACT-Cog, MDASI, demographics

Group effect for PCI (higher scores = better cognitive function) (p<0.0001)

Neuropathy inversely correlated with PCI (p<0.0001) for BCS

Multiple linear regression model explained 24% variance (adjusted $R^2$) for PCI in BCS: BMI, exercise, fatigue, distress.

Exercise frequency moderated relationship between BMI and PCI ($F_3, 198=2.4, p=0.07$) and reduced negative effects of high BMI. Moderating effect was significant when limited to participants exposed to chemotherapy ($F_3, 133=3.1, p=0.03$)
Randomized, single-blind, 3-arm, feasibility pilot for 50 BCS

- Randomized to Qigong, Gentle Exercise, or Support Group
- 8 weekly sessions and home practice
- Overall attrition 28%, 50% for Gentle exercise group.

- Self-report improvement for Qigong group for cog function ($p=0.01$), and distress ($p=0.02$). Processing speed improved for Gentle Exercise group ($p=0.007$). Verbal fluency improved for support group ($p=0.02$).
- Mindfulness-based exercise may be superior to gentle exercise alone or survivorship support for improving self-report of cognitive function and distress after treatment for breast cancer.
- The mindfulness component may enhance the positive impact of exercise on cognitive function.
Haze Series

- Provides tools to help combat cognitive changes after chemotherapy
- Series Components:
  - Managing negative thoughts
  - Memory, coping, and attention strategies
  - Stress management and the effects of loneliness
  - Exercise, sleep, and nutrition

Trained facilitator in room to ensure questions are answered and participants stay for the duration of session.

Cedars-Sinai

**EMERGING FROM THE HAZE™**

Haze Series - Broadcast live to The University of Kansas groups*

*Trained facilitator in room to ensure questions are answered and participants stay for the duration of session.
• Wait-list controlled pilot study
• 61 BCS (30 intervention, 31 control)
• Pre-/post-testing for self report of cognitive function, physical function, mood, and satisfaction with the intervention
• Cross-sectional fingerstick bloodspot testing for Omega-3 fatty acid indices

**Benefits for intervention group:**
• Improvement in self-report of cognitive function ($p < 0.01$)
• Association between Omega 3 Fatty Acid Index levels and self-report of cognitive issues ($p=0.04$)

**Next steps:**
• Conduct a larger study for survivors of stage I-III breast or gynecologic cancers
• Evaluate a pre-recorded, digital adaptation
• Reviewed by SWOG Clinical Trials Research Network as a limited-institution feasibility pilot.
CANCER AND CANCER TREATMENT-
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CURRENT AND FUTURE RESEARCH
ARE THERE MORE SENSITIVE WAYS TO ASSESS COGNITIVE EFFORT THAN STANDARD NEUROPSYCHOLOGICAL TESTING?

TASK EVOKED PUPILLARY RESPONSE (TEPR)
Cross-sectional pilot to evaluate cognitive effort, indexed by pupillary response, for BCS with c/o cog dysfunction after chemo.

- 23 BCS and 23 controls
- Neurocognitive testing while measuring TEPR
- Self-report of cognitive function
- Both groups performed well on the neurocognitive tests
- Breast cancer survivors reported worse cognitive function (p<0.0001).
- Breast cancer survivors demonstrated greater cognitive effort to get same results (p<0.05).
- Pupillary response was correlated with self-report measures of cognitive function (r = 0.33-0.45).

**Future Plans:** modular R01 submission to prospectively evaluate measurement of pupillary response/cognitive effort for 50 BCS receiving chemo (and 50 HC) and confirm sensitivity w/ EEG evoked relaters of potential (ERPs) for cognitive load.
COMBINED EXERCISE AND GAME-BASED COGNITIVE TRAINING (SPEED FEEDBACK THERAPY) INTERVENTION FOR BREAST CANCER SURVIVORS: PROSPECTIVE MIXED METHODS STUDY IN THE US AND JAPAN

- Previous Japanese studies with positive results for cognitive function in older survivors of breast and prostate cancer (Miki 2014) and older adults with dementia (Ootani 2005; Okamura 2018). Proposed mechanisms: increased brain blood flow, frontal lobe activation during sustained motor/attention tasks.

  - Participating sites
    - Hiroshima Univ (PI: Myashita, funded)
    - KUCC
    - Centura Health (Denver)
    - Indiana University (qualitative analyses)

  - Study purpose: Evaluate the effects the intervention on cancer therapy-related cognitive impairment in pts with BC and compare the differences of the intervention effects between the two countries.

  - Started Oct. 3, 2019: Funded through March 2021
RANDOMIZED (1:1), WAIT-LIST CONTROLLED, MIXED METHODS DESIGN.

- Sample size = 120 (60 intervention, 60 wait-list controls)
  - Japan- 60
  - US- 60
    - KUCC- 30
    - CH- 30
- Eligibility
  - Stage I-III BC with cog complaints
  - 6 mo to 5 yrs after chemo
  - No cardiac, respiratory, CNS, or orthopedic comorbidities
  - Concurrent endocrine or anti-HER-2 therapy allowed
- Exercise/game-based brain training at least 3 times a week for 4 weeks (BP/P parameters to start/stop exercise)
- Questionnaires
  - FACT-Cog
  - FACT-G (HRQOL)
  - TMT A&B (Exec function/processing speed)
  - POMS
  - IPAQ
- Assessment timepoints
  - Questionnaires: Baseline, Wk 4, Wk 16
  - Semi-structured Interviews: Baseline, Wk 4

KUCC Enrollment: 18 of 30 as of June 2020
CORRELATIVE STUDY OF NEUROTROPHIC AND INFLAMMATORY BIOMARKERS

• **Companion Study**
  
  Compare the between-group differences in terms of changes in neurotrophic and inflammatory biomarker levels from prospectively collected dried blood spots.

  Explore the relationship between change in neurotrophic and inflammatory biomarker levels and change in cognitive function for the intervention group.

• **Collection**: baseline, 4-weeks, 16 weeks
  
  Magnetic fluorescent bead-based immunoassays (Luminex assays)

  BDNF, IGF1, VEGF, TNFα, CRP, IL-1β, IL-6, IL-8

  Sample collection and storage on-going

  Seeking funding for assays and analyses
STAYING STRONG AND HEALTHY DURING ANDROGEN DEPRIVATION THERAPY FOR PROSTATE CANCER

- Randomized, controlled study for men within 3-months of initiating ADT
- Goal: minimize the risk of metabolic syndrome/cardiovascular risks and related symptoms
- Diet and nutrition education, individualized aerobic and resistance band exercise prescription, 12-weekly followed by 3-monthly telephone coaching and goal setting sessions
- Physical measures: serum lipids, HgA1c, BMI and anthropomorphics, VO2 max, strength/flexibility
- Self-report measures: activity level, mood, SE’s of ADT, cognitive function
- Neurocognitive testing
- Assessments: baseline, six, and twelve months.
- Enrollment complete. Now analyzing the data.
Lied Pre-Clinical Pilot Grant

- Very little research done to date to assess changes in cognitive function from immune therapy
- MOA for immune therapy involves cytokine release and chronic inflammation.
- Many of these agents now are approved as 1st-line therapy for a number of different types of cancer.
- Feasibility pilot funded to build towards a prospective, observational registry.

For patients receiving 1st-line therapy with checkpoint inhibitors (CPIs):

1. Recruit adults ≥60 yrs old diagnosed with any stage of cancer (without brain mets) to be treated with 1st-line therapy with CPIs.
2. Complete study questionnaires (15-20’) and neurocognitive tests (40’) at baseline (before or shortly after starting CPIs) and 6-mo later.
3. Extra tubes of blood drawn in conjunction with standard of care to be analyzed for biomarkers.
4. Comparisons will be made between the two timepoints, and with an existing cohort of cognitively intact older adults.

To enroll 20 participants.
12-month funding period.
Expect to start up in mid July.
FOR INQUIRIES OR REFERRALS TO OUR STUDIES:

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