Cognitive Changes Associated with Cancer and Its Treatments: Current Knowledge and Challenges

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Importance of Studying Cognitive Decline Secondary to Cancer Therapy

- A challenge facing cancer survivors as identified by the National Coalition for Cancer Survivorship
- Negative impact on work/school performance and QOL
- Informed decision-making
- Similar pediatric research resulted in treatment modifications that reduced negative cognitive effects while maintaining treatment efficacy
- Development of interventions to prevent or treat cognitive decline
Previous research by our Cancer Psychiatry Division (1, 2) has suggested the need for an investigation of mild cognitive impairment in patients with cancer. Mild cognitive impairment may go undetected, yet it may influence a patient’s ability to perform routine daily functions and to comply with treatment protocols.
Cognitive Impact of Cancer

- Brain tumors
- Brain metastases
Common Cognitive Problems Reported Post-Treatment-Brain Tumors

Depends on:
Size and location of the tumor
Extent of surgery
Cognitive Impact of Cancer Therapies

- Cranial radiation +/- intrathecal chemo
- Cranial surgery
- Biological response modifiers
- High-dose chemotherapy
- Standard-dose chemotherapy
- Hormonal Therapies
Common Cognitive Problems Reported Post-Treatment

- Memory and Concentration
- Executive Function
- Ability to Learn New Material /Reading Comprehension
- Ability to Work with Numbers
Pattern of Cognitive Problems

- Acute vs. persistent cognitive problems
- Problems may come and go (Good and bad days)
- Often worse when: Multitasking or under stress or deadline pressure
- Recent study suggests that a subgroup of patients experience delayed cognitive change (Wefel et al, 2010)
Factors Affecting Cognitive Functioning

- Sleep disorders (insomnia, sleep apnea)
- Depression, anxiety, stress
- Pain and pain medications
- Other physical illnesses
Sources of Data

- Self-report of cognitive functioning
- Neuropsychological testing
- Imaging
- Animal models
Findings Based on Self-Report of Cognitive Functioning

- Nearly 100% of patients report acute changes during or shortly after treatment.
- 50% or greater report long term (> 1 year post-treatment) cognitive changes.
- Self-report of cognitive problems do not correlate well with performance on neuropsychological tests, but correlate with measures of depression, anxiety, and fatigue.
Cognitive Effects of Chemotherapy: Findings Based on Neuropsychological Testing

- Survivor studies found cognitive problems 6 months to 10 years post-treatment (17-75%)
- Longitudinal studies find:
  - 20-25% of patients have cognitive impairment prior to starting adjuvant treatment
  - Persistent cognitive problems identified 15-20% of patients (although some studies found no evidence of impairment and others 60%)
  - 16 of 21 longitudinal studies found evidence of post-treatment cognitive decline
Is it All Chemotherapy? The Cognitive Impact of Endocrine Therapy

- Evidence for a significant cognitive effect for breast cancer patients randomized to tamoxifen but not exemestane (Schilder, et al. JCO, 2010)

- Accumulating evidence suggesting a negative cognitive effect for hormone ablation for prostate cancer
Neuroimaging methods relevant to cognitive changes

- **Structural MRI (atrophy)**
- **Diffusion tensor imaging (white matter connectivity)**
- **Functional MRI (brain activity)**
- **PET (brain metabolism)**
Results of MRI, DTI, PET and EEG Studies

- MRI and PET studies suggest that there are changes in brain structure (grey and white matter) and function associated with chemotherapy.

- EEG studies suggest changes in measures of information processing (P300) associated with chemotherapy.
fMRI Activation Pattern for Identical Twins Discordant for Breast Cancer

1-back > 0-back

2-back > 0-back

3-back > 0-back

Chemotherapy-treated Twin-Twin A

Non-cancer Twin-Twin B

Ferguson et al, JCO, 2007
Regions Showing Decreased Gray Matter Density from Baseline to 1 Month Post Chemotherapy

17 healthy control, 12 local, 18 chemotherapy  McDonald et al, BCRT, 2010
(A) Brain activation decrease in CTx+ patients from baseline to M1 with return to baseline levels of hyperactivation at Y1, displayed over atlas template. (B) Activation pattern at left frontal peak displayed in (A) shown graphically for all groups at all time-points. These frontal changes in CTx+ patients overlapped with regions of gray matter change following the same pattern of change over time\textsuperscript{13} as illustrated in (C), where brain activation change is shown in yellow, gray matter change is shown in blue, and the intersection of activation and gray matter changes is shown in green.

McDonald, et al, JCO, 2012
Challenges

- Compensatory activation implies that data from neuropsychological testing may underestimate the degree of post-treatment cognitive change.
- Change within the normal range may have a negative effect on return to work/school and quality of life.
Potential Mechanisms: Role of DNA Damage

- DNA damage and deficits in DNA repair mechanisms are associated with risk for cancer and neurocognitive disorders
- Breast cancer patients and patients with mild cognitive impairment have higher levels of DNA damage compared to controls
- Cancer treatments (chemotherapy, radiation therapy, endocrine therapy) increase DNA damage
- Working Hypothesis: DNA damage may be related to cognitive functioning both pre- and post-chemotherapy
DNA Damage

- Decreased Cognitive Function
- DNA Repair Genes
- Endogenous Oxidative Stress
- Genotoxic Exposures

Pre-Cancer Diagnosis

Cancer Treatments
- Chemotherapy
- Radiation Therapy
- Endocrine Therapy
Memorial Studies Examining the Relationship between Cognition and DNA Damage-
Longitudinal Study

- Breast cancer patients treated with chemotherapy or no chemotherapy and healthy controls
- Assessed pre- and post-treatment
- Neuropsychological Assessment
- Structural and Functional MRI
- DNA damage-Comet Assay
Potential Mechanisms: Role of Inflammation and Cytokines

- Inflammation has been associated with increased risk for cancer and neurocognitive disorders.
- TNF-alpha associated with greater report of memory problems and reduced brain metabolism in inferior frontal cortex (PET) post-chemotherapy (Ganz et al, 2013).
- Chemotherapy induced increases in TNF-alpha, IL-1 beta, IL-4 and IL-6 were associated with impairment in attention and memory (Cheung, et al, ASCO abstract, 2013).
Role of Inflammation and Cytokines

- Working Hypothesis: Inflammation may be related to cognitive functioning both pre- and post-chemotherapy
- Cytokine neurotoxicity may be related to increase in oxidative stress and excitotoxic glutamate receptor-mediated damage
- Inflammation and DNA damage are likely interactive
Animal Studies

- Deficits on learning and memory tasks following administration of chemotherapy
- Disruption of hippocampal neurogenesis even at doses that are ineffective for killing cancer cells
- Acute and delayed damage to white matter tracks associated with 5-FU
- Many of these effects can be blocked with various anti-oxidants
Tamoxifen Toxicity on CNS Glial Progenitor Cells

- Tamoxifen toxic for various cell populations and reduced cell division in mouse subventricular zone, hippocampal dentate gyrus, and the corpus callosum

- In vivo, MEK 1/2 inhibition prevented tamoxifen-induced cell death in systemically treated mice

Chen, Yang, Han, Noble, 2013
Pharmacologic Interventions

- Methylphenidate
- Focalin
- Modafinil
- Donepezil
- Ginkgo Biloba
Cognitive Rehabilitation Interventions

- Cognitive Rehabilitation delivered by rehabilitation psychologists or occupational therapists
- Preliminary evidence of effectiveness of computer-based interventions like Lumosity and CogMed
Memory and Attention Training:

A Brief Behavioral Skills Program for Cancer Survivors
with Attention and Memory Problems Associated with Chemotherapy

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RUNNING HEAD: Memory and Attention Training

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Memory and Attention Training

- Education
  - Common cognitive errors
  - Different types of memory and attention
Memory and Attention Training

- Compensatory Strategies
  -- Lists, calendars, palm pilots
  -- Self-instructional training
  -- Scheduling / Time management
  -- Sleep hygiene / Fatigue management
Memory and Attention Training

- Relaxation Training
  --Progressive Muscle Relaxation
  --Breathing exercises
Memory and Attention Training

- Problem-Solving
  -- A structured approach to applying the skills in everyday life
Intervention Challenges

- Current interventions are not mechanistically-based
- Need to develop treatments that protect the brain but to not interfere the efficacy of cancer treatments
Conclusions

- Cognition can be affected by various aspects of cancer and cancer treatments.
- Models of post-treatment cognitive change need to account for pretreatment cognitive deficits.
- Integration of data from self-report, neuropsychological testing, and imaging is required.
- Animal models are providing data on potential mechanisms which will hopefully lead to more targeted treatments.
Collaborators

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Save the Date:

2014 ICCTF COGNITION & CANCER CONFERENCE

When: February 10-11th, 2014
Where: Virginia Mason Medical Center, Seattle, USA
(Prior to the International Neuropsychological Society Meeting)

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