Changes in Cognitive Function Related to Cancer and Cancer Therapy

Catherine M. Bender, PhD, RN, FAAN
University of Pittsburgh
School of Nursing
Overview of presentation:

1. Define cognitive function
2. Delineate the prevalence and severity of changes in cognitive function that may occur with cancer and cancer therapy
3. Discuss the significance of the problem
4. Identify potential mechanisms underlying changes in cognitive function
5. Discuss the methodological challenges in studying cognitive function in cancer
6. Describe potential interventions to manage changes in cognitive function in cancer
Cognitive Function

- Information handling, faculty for the processing of information
- Linked to mood, functional ability
Domains of Cognitive Function

- Attention
- Learning and memory
- Executive function
- Mental flexibility
- Psychomotor speed
- Visuospatial/Constructional ability
- Language
Prevalence of Changes in Cognitive Function

- **Chemotherapy**
  - 18% to 27% with standard-dose (Meyers, 2000)
  - 32% with high-dose (van Dam et al., 1998)
  - No changes (Donovan et al., 2005; Oxman, 1980)

- **Biological Response Modifiers**
  - 50% with Interleukin-2 (Denicoff et al., 1989)
  - 33% to 70% with alpha-interferon (Kirkwood, Bender, Agarwala et al., 2002)
Domains Most Commonly Affected

- Attention
- Learning and memory
- Psychomotor speed
- Executive functioning
Impairments in Children After Leukemia Therapy

- Impaired processing speed & memory
- Inattentive type ADHD
- Lower IQ
Severity and Duration

- Most changes in cognitive function do not meet criteria for “impairment”
- Improvement in cognitive function 4 years post-chemotherapy

(Schagen et al., 2002)
Hi! My name is Steve... and I've forgotten my last name.
FORGET ME NOT

NOW WHERE DID I PARK MY CAR...

PARKING

THE ALZHEIMER

© Original Artist
Reproduction rights obtainable from
www.CartoonStock.com
How would you describe and rate your symptoms?

(Hurricane Voices Breast Cancer Foundation, 2007)
FMRI of 60 y/o identical twins during working memory task with increasing difficulty (L to R). Colored regions denote increased brain activation during working memory relative to simple vigilance task. A) Twin treated with chemotherapy; B) Twin not treated with chemotherapy. Note the expanded spatial extent of cortical activation in the chemotherapy-treated twin.

Ferguson et al, 2007
Significance

- Changes in cognitive function can impact:
  - intellectual and academic development
  - occupational achievement
  - development and maintenance of social relationships
  - appropriate self care

(Walch, Ahles & Saykin, 1998)
Significance

- Changes in cognitive function:
  - increase distress for patients, families and caregivers
  - impact patients’ understanding and decision-making about their illness and informed consent
  - may impact treatment adherence

(Bender et al., 2001)
Patient/Family Perspective

- Attribute cognitive changes to:
  - treatment
  - disease progression
  - senility, psychiatric disease

- Under-reporting due to concerns that therapy may be discontinued
Risk Factors for Developing Changes in Cognitive Function

- Advancing age
- Lower intelligence quotient (IQ)
- History of neurological or psychiatric illness or developmental disorders
- History of substance abuse
- Prior cancer treatment

(Hensley et al., 2000)
Risk Factors for Developing Changes in Cognitive Function

- Forms of therapy or methods of delivery:
  - Therapy delivered directly to the CNS
  - Higher doses of therapy
  - Concurrent chemoradiation or chemotherapy after radiation to the brain
  - Longer duration of therapy (biotherapy)
“CHEMOBRAIN”

“This is my brain on chemo”

www.salon.com/mwt/feature/2007/05/14/chemo_brain
Potential Mechanisms of Changes in Cognitive Function

- Blood-Brain Barrier Integrity
- Reduced Estrogen or Testosterone
- DNA Damage and Telomere Length
- Genetic Susceptibility
- Cytokine Deregulation

(Ahles et al., 2007)
Cognitive Function, Cancer & Cancer Therapy

Demographic
- Age
- Education
- IQ

Physiological
- Menopausal status
- Hormones

Psychological
- Coping with cancer

Pathological
- Symptoms
- Pain, Fatigue
- Anxiety
- Depression

(Minisini et al., 2004)
Poorer Pretreatment Cognitive Function in Women with Early Stage Breast Cancer

- Compared to controls (n=89), women with breast cancer (n=135) have poorer attention (p=.02) and verbal memory (p=.04) (Bender et al., 2010)
- Poorer psychomotor speed than controls (Ahles et al., 2008)
- 35% (n=84) have cognitive impairment
  - Poorer verbal learning (18%)
  - Poorer verbal memory (25%) (Wefel et al., 2004)
Poorer Pretreatment Cognitive Function

- Mood
- Symptoms
- Effects of general anesthesia
- Disease-related effects
- Co-morbidities/Concomitant medications
Methodological Challenges

- Designs
- Control/Comparison Groups
- Measurement
- Statistical Analysis
Design: Cross-sectional vs. Longitudinal

- Design considerations:
  - Pre-treatment evaluations permit examination of treatment-related effects
  - Determination of potential physiologic mechanisms
Control/Comparison Groups

- Control/Comparison methods
  - Normative data
  - Control groups
  - Comparison to baseline
Issues in the Measurement of Cognitive Function

- Practice effects
  - Alternate equivalent versions
  - Interval between testing
  - Healthy controls

- Sensitivity of measures
  - Screening measures
Issues in the Measurement of Cognitive Function

- Battery length
  - Multidimensional
  - Subject burden
- Clinically significant deterioration
- Ecological validity
- Objective vs. subjective measurement
  - Not related
Grooved Pegboard

Klove, 1963
Rey-Osterrieth Complex Figure Test (RCF)

Osterrieth, 1944
CANTAB: Paired Associate Learning

(Cambridge Neuropsychological Test Automated Battery)
CANTAB: Rapid Visual Information Processing

(Cambridge Neuropsychological Test Automated Battery)
Statistical Analysis Issues

- Multiple measures and timepoints
  - Mixed effects modeling
    - Between group differences
    - Within group differences at different time points
  - Data-reduction techniques
    - Composites versus individual measures
Statistical Analysis Issues

- Accounting for practice effects
  - Reliable change index
  - Standard regression based approach

- Handling covariates
  - Fixed (i.e., age, estimated IQ) and time dependent (depression, anxiety)
  - ANCOVA
Cognitive Function in Breast Cancer and Breast Cancer Therapy
Meta-Analysis: Magnitude of Cognitive Impairment Averaged for Each domain in Cross Sectional Studies

<table>
<thead>
<tr>
<th>Cognitive Domain</th>
<th>N Effect Sizes</th>
<th>N Chemotherapy Patients</th>
<th>N Controls</th>
<th>Average Effect Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attention</td>
<td>36</td>
<td>208</td>
<td>122</td>
<td>-0.03</td>
</tr>
<tr>
<td>Motor function</td>
<td>12</td>
<td>172</td>
<td>103</td>
<td>-0.51</td>
</tr>
<tr>
<td>Memory</td>
<td>35</td>
<td>208</td>
<td>122</td>
<td>-0.26</td>
</tr>
<tr>
<td>Executive function</td>
<td>31</td>
<td>208</td>
<td>122</td>
<td>-0.18</td>
</tr>
<tr>
<td>Language</td>
<td>3</td>
<td>35</td>
<td>35</td>
<td>-0.41</td>
</tr>
<tr>
<td>Spatial ability</td>
<td>5</td>
<td>99</td>
<td>54</td>
<td>-0.48</td>
</tr>
</tbody>
</table>

(Falleti et al., 2005)
Meta-Analysis: Magnitude of General Cognitive Impairment Detected for Each Cross Sectional Study

<table>
<thead>
<tr>
<th>Study</th>
<th>General Effect Size</th>
<th>Mean Time Since Last Chemo. (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ahles et al, 2002</td>
<td>-0.071</td>
<td>9.4</td>
</tr>
<tr>
<td>Castelon et al., 2004</td>
<td>-0.220</td>
<td>3.5</td>
</tr>
<tr>
<td>Schagen et al., 1999</td>
<td>-0.223</td>
<td>1.9</td>
</tr>
<tr>
<td>Van Dam et al., 1998</td>
<td>-0.500</td>
<td>1.6</td>
</tr>
<tr>
<td></td>
<td>-0.222</td>
<td>1.9</td>
</tr>
<tr>
<td>Wieneke &amp; Dienst 1995</td>
<td>-0.430</td>
<td>0.5</td>
</tr>
</tbody>
</table>

(Falleti et al., 2005)
Cognitive Function Prior to Adjuvant Hormonal Therapy for Breast Cancer

- Compared to controls (n=120), women with breast cancer receiving tamoxifen or exemestane (n=179) had poorer overall cognitive function (p=.03)

(Schilder et al., 2010)
Follow-up – One Year Post Hormonal Therapy Initiation

- Compared to controls (n=120), tamoxifen users (n=80) had poorer:
  - Verbal memory ($p<.01$, $d=.43$)
  - Executive functioning ($p=.01$, $d=.40$)
- Compared to exemestane users (n=99), tamoxifen users had poorer:
  - Information processing speed ($p=.02$, $d=.36$)
- No differences between exemestane users and controls

(Schilder et al., 2010)
The AIM Study: Anastrozole Use In Menopausal Women

National Institutes of Health/ National Cancer Institute
RO1 CA107408
Purpose

- To examine and compare the effect of anastrozole on cognitive function in 4 cohorts
  - women with stage I, II or IIIa breast cancer who receive chemotherapy plus anastrozole
  - women with stage I, II or IIIa breast cancer who receive anastrozole alone
  - healthy control group of women matched on age, race and level of education to the treatment groups
Design

- Observational, repeated measures design
- Study timepoints:
  - Baseline: prior to the initiation of adjuvant therapy
  - Follow-up: at 6 month intervals post-initiation of adjuvant therapy up to 2 years
Exploration of individual test results via mixed effects modeling
Anastrozole Alone Poorer Than Controls

- Measures of attention and visual and verbal learning and memory at pre-anastrozole and at 6 mo., 12 mo., and 18 mo. post-anastrozole initiation
- Magnitude of these effects was small to moderate (d= -.13 to -.48)
# Anastrozole Alone Deterioration Over Time

<table>
<thead>
<tr>
<th>Domain/Measure</th>
<th>Pre-Anast. (n=132)</th>
<th>6 mo. Post Anast. (n=89)</th>
<th>p</th>
<th>d*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Attention</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digit Vigilance (Time)</td>
<td>354.31 (6.29)</td>
<td>367.99 (6.64)</td>
<td>.004</td>
<td>-.49</td>
</tr>
<tr>
<td><strong>Verbal Learning &amp; Memory</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rivermead Story (Immed.)</td>
<td>7.38 (.21)</td>
<td>6.43 (.23)</td>
<td>.0002</td>
<td>-.68</td>
</tr>
<tr>
<td>Rivermead Story (Delay)</td>
<td>5.88 (.19)</td>
<td>5.39 (.21)</td>
<td>.03</td>
<td>-.39</td>
</tr>
<tr>
<td><strong>Visual Learning &amp; Memory</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rey Complex Figure (Immed.)</td>
<td>21.80 (.53)</td>
<td>19.31 (.58)</td>
<td>&lt;.0001</td>
<td>-.71</td>
</tr>
<tr>
<td>Rey Complex Figure (Delay)</td>
<td>21.04 (.51)</td>
<td>18.24 (.56)</td>
<td>&lt;.0001</td>
<td>-.71</td>
</tr>
</tbody>
</table>

*Cohen’s d*
Anastrozole Alone Deterioration Over Time

<table>
<thead>
<tr>
<th>Domain/Measure</th>
<th>Mean (SE) 6 mo. Post Anst. (n=89)</th>
<th>Mean (SE) 12 mo. Post Anst. (n=45)</th>
<th>p</th>
<th>d*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Verbal Learning &amp; Memory</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rivermead Story (Immed.)</td>
<td>6.43 (.23)</td>
<td>5.78 (.30)</td>
<td>&lt;.0001</td>
<td>-.71</td>
</tr>
<tr>
<td>Rivermead Story (Delay)</td>
<td>5.39 (.21)</td>
<td>4.21 (.27)</td>
<td>&lt;.0001</td>
<td>-.71</td>
</tr>
</tbody>
</table>

*Cohen’s d*
### Anastrozole Alone Deterioration Over Time

<table>
<thead>
<tr>
<th>Domain/Measure</th>
<th>12 mo. Post Anast. (n=45)</th>
<th>18 mo. Post Anast. (n=25)</th>
<th>p</th>
<th>d*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Attention</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digit Vigilance (Time)</td>
<td>350.98 (7.54)</td>
<td>372.37 (8.69)</td>
<td>.006</td>
<td>-.47</td>
</tr>
<tr>
<td><strong>Verbal Learning &amp; Memory</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Auditory Verbal Learning Test (Total)</td>
<td>59.48 (.91)</td>
<td>56.20 (1.08)</td>
<td>.002</td>
<td>-.54</td>
</tr>
<tr>
<td><strong>Visual Learning &amp; Memory</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rey Complex Figure (Immed)</td>
<td>24.63 (.70)</td>
<td>21.74 (.85)</td>
<td>.0002</td>
<td>-.60</td>
</tr>
<tr>
<td>Rey Complex Figure (Delay)</td>
<td>23.67 (.67)</td>
<td>21.10 (.81)</td>
<td>.001</td>
<td>-.59</td>
</tr>
</tbody>
</table>

*Cohen’s d"
Cognitive Function in Therapy for Lung Cancer
Cognitive Function and Prophylactic Cranial Irradiation in SCLC

- 93 patients with SCLC
  - Previously treated with concurrent chemotherapy and radiation therapy
  - Complete or partial response

(Grosshans et al., 2008)
Cognitive Function Pre-Prophylactic Cranial Irradiation in SCLC

- Compared to norms, 47% (n=93) patients with SCLC had deficits in ≥ 2 cognitive measures
  - 40% - deficits in executive function and learning and memory
  - 30% - deficits in processing speed and motor function

(Grosshans et al., 2008)
Cognitive Function Post-Prophylactic Cranial Irradiation in SCLC

- Up to 449 days post-PCI
  - Declines in executive function \( (p=.008) \) and language \( (p=.049) \)
  - Decline in executive function no longer significant \( (p=.08) \) when disease progression controlled for

- \( \geq 450 \) days post-PCI
  - No significant declines in cognitive function
  - Improvements in language and motor function

(Grosshans et al., 2008)
Changes in Cognitive Function with Chemoradiotherapy for NSCLC

- Sample: 14 patients with stage IIIA & IIIB NSCLC
- Measurements:
  - Before cisplatin/etoposide/radiotherapy
  - 1 month after 2 cycles of chemotherapy
  - 7 months after chemotherapy

(Komaki et al., 2008)
Changes in Cognitive Function with Chemoradiotherapy for NSCLC

- 10 of 14 patients (71%) were cognitively impaired at pretreatment
  - Most commonly impaired domains: verbal memory and executive function
- Patients with impairments at pretreatment were more than twice as likely to have cognitive decline at 1 month post-therapy

(Komaki et al., 2008)
Changes in Cognitive Function with Chemoradiotherapy for NSCLC

- 8 of 13 (62%) had a decline in cognitive function 1 month post-therapy
  - Most commonly impaired domain: executive function

- Significant improvement in cognitive function at 7 months post-therapy

(Komaki et al., 2008)
Interventions
Behavioral Interventions

- CBT-based intervention (n = 29)
  - Education on memory and attention
  - Self awareness
  - Self regulation
  - Compensatory strategies

- Improvements in:
  - Self reported cognitive function (d = .47 to .66)
  - Quality of life (d = .51)
  - Neuropsychological measures
    - Verbal memory (d = .90 to 1.12)
    - Attention (d = .59)
    - Executive function (d = .90)
    - Mental flexibility (d = .55)

(Ferguson et al., 2007)
Pharmacologic Interventions

- Non-specific due to lack of understanding of mechanisms underlying cognitive impairments
- Psychostimulants (Mar Fan et al., 2008)
- Modafinil (Provigil) (Kaleita et al., 2006)
- Erythropoietin (O’Shaughnessy et al., 2005)
Clinically

- Assessment
  - Mood
  - Sleep
  - Other symptoms
  - Concomitant medications
  - Self monitor
  - Impact on daily living
Clinically

- Acknowledge problem
- Manage depression/anxiety
- Compensatory strategies
- Neuropsychological referral
Clinically: Interventions

- Work/school accommodations
- Sleep hygiene
- Exercise
- Psychosocial
  - Psychotherapy
  - Support groups
What we know

- Poorer pretreatment performance on cognitive function measures
- Deterioration in cognitive function with treatment
- Most patients do not experience “impairments”
- Meaning of subjective complaints
- Impact on patients and families
Future Directions

- Factors related to pretreatment differences in cognitive function
- Long term effects of disease and therapy on cognitive function
- Characteristic profile of patients at risk for cognitive changes
- Mechanisms underlying cognitive changes
- Assessment for clinical and research settings
- Interventions to prevent or manage changes in cognitive function
Acknowledgements

- Sarah Berga, MD
- Adam Brufsky, MD, PhD
- Frances Casillo, RN, BSN
- Susan Cohen, PhD, RN FAAN
- Yvette Conley, PhD
- Jacqueline Dunbar-Jacob, PhD, FAAN
- John Kirkwood, MD
- Marie Kratofil, RN
- Susan Richey, BS
- Christopher Ryan, PhD
- Susan Sereika, PhD
- Carol Stilley, PhD, RN
- Nurses of the Comprehensive Breast Program at the University of Pittsburgh Cancer Institute
Acknowledgements

- National Cancer Institute
- National Institute of Nursing Research
- Department of Defense
- American Cancer Society
- Oncology Nursing Society Foundation
- Center for Research in Chronic Disorders, University of Pittsburgh School of Nursing
- University of Pittsburgh Cancer Institute