Does Chemotherapy Influence Cognitive Functioning?

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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
Common Cognitive Problems Reported Post-Chemotherapy

- Memory and Concentration
- Executive Function
- Ability to Learn New Material /Reading
- Comprehension
- Ability to Work with Numbers
# Studies Examining Cognitive Effects of Chemotherapy in Breast Cancer Patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Diagnosis</th>
<th>Sample Size</th>
<th>Assessment Timing Post-Tx</th>
<th>Chemo-Therapy</th>
<th>Local Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wienke &amp; Dienst (‘95)</td>
<td>Breast Ca</td>
<td>28</td>
<td>Ave. 6.6 mo.</td>
<td>75%</td>
<td>N/A</td>
</tr>
<tr>
<td>van Dam et al. (‘98)</td>
<td>Breast Ca</td>
<td>36 chemo</td>
<td>Ave. 2 yrs</td>
<td>17%</td>
<td>9%</td>
</tr>
<tr>
<td>Schagen et al. (‘99)</td>
<td>Breast Ca</td>
<td>39 chemo</td>
<td>Median 1.9 yrs</td>
<td>28%</td>
<td>12%</td>
</tr>
<tr>
<td>Brezden et al. (‘00)</td>
<td>Breast Ca</td>
<td>Grp A: 31</td>
<td>Grp A: After min. of 2 cycles</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Grp B: 40</td>
<td>Grp B: Median 2 yrs</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Grp C: 36 (healthy controls)</td>
<td>Grp C: 11%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ahles et al. (‘02)</td>
<td>Breast Ca &amp; Lymphoma</td>
<td>71 chemo</td>
<td>Ave. 10 yrs</td>
<td>39%</td>
<td>14%</td>
</tr>
<tr>
<td>Tchen et al (03)</td>
<td>Breast CA</td>
<td>100 chemo</td>
<td>During chemo</td>
<td>Chemo 16%</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100 controls</td>
<td></td>
<td>Controls 4%</td>
<td></td>
</tr>
</tbody>
</table>
Adjusted z-Transformed Domain Scores for the Chemotherapy vs. Local Therapy Groups

*p < .05, adjusted for age and education
Longitudinal Assessment of Cognitive Functioning

Importance of pretreatment assessments

Importance of appropriate controls given the same test battery over similar time frames
Longitudinal Assessment

18 breast cancer patients treated with FAC were tested at pretreatment and 1 and 12 months post-treatment. 33% exhibited cognitive impairment at pretreatment compared to 61% at 1 month post-treatment. At 1 year, 45% of patients impaired at 1 month demonstrated stable performance, 45% improved, and 10% had mixed results.

– Wefel et al. (2004)
Dartmouth Longitudinal Cognitive Assessment Study

Prospective neuropsychological assessment of breast cancer and lymphoma patients treated with systemic chemotherapy or local therapy (and matched healthy controls) Assessed prior to treatment, and 1, 6 and 18 months post-treatment
Predictors of Cognitive Deficits

- Type of chemotherapy
- Education level and IQ
- History of traumatic brain injury
- History of learning disability
- Genetic variables
- Hormonal factors
Genetic Factors

APOE -ε4 has been implicated in cognitive decline associated with cardiac surgery, head trauma, and aging, both normal and with associated chronic illnesses. APOE-ε4 and cognitive deficits secondary to chemotherapy.
# Z-Transformed Domain Means by APOE Status

<table>
<thead>
<tr>
<th>Domains</th>
<th>APOE E4 Positive</th>
<th>APOE E4 Negative</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td></td>
</tr>
<tr>
<td>Visual Memory</td>
<td>-0.30 (1.12)</td>
<td>0.04 (0.81)</td>
<td>0.03</td>
</tr>
<tr>
<td>Spatial Ability</td>
<td>-0.38 (1.17)</td>
<td>-0.13 (0.97)</td>
<td>0.05</td>
</tr>
<tr>
<td>Psychomotor Function</td>
<td>-0.24 (0.80)</td>
<td>0.05 (0.66)</td>
<td>0.08</td>
</tr>
<tr>
<td>Verbal Ability</td>
<td>0.10 (0.68)</td>
<td>-0.16 (0.86)</td>
<td>0.83</td>
</tr>
<tr>
<td>Verbal Learning</td>
<td>-0.20 (1.16)</td>
<td>-0.03 (0.94)</td>
<td>0.48</td>
</tr>
<tr>
<td>Verbal Memory</td>
<td>0.21 (0.90)</td>
<td>-0.15 (0.89)</td>
<td>0.21</td>
</tr>
<tr>
<td>Motor Functioning</td>
<td>-0.01 (0.72)</td>
<td>-0.11 (0.73)</td>
<td>0.93</td>
</tr>
<tr>
<td>Attention CR</td>
<td>-0.14 (0.97)</td>
<td>-0.01 (0.87)</td>
<td>0.33</td>
</tr>
<tr>
<td>Attention RT</td>
<td>-0.19 (0.69)</td>
<td>-0.05 (0.67)</td>
<td>0.30</td>
</tr>
</tbody>
</table>

*Controlling for age, gender, education, diagnosis, and WRAT-R (reading subset)
Potential Mechanisms

Reduction in microvascular or neuronal repair processes associated with the APOE -ε4 allele

Pre-existing morphologic differences (e.g., smaller hippocampal volume) associated with the APOE -ε4 allele
Potential Candidate Gene

Repair / Plasticity

Neurotransmitters

Blood Brain Transporters
Hormones and Cognitive Functioning

Reduced estrogen and testosterone levels have been associated with cognitive decline. Chemotherapy and hormonal levels may interact to increase cognitive decline in cancer survivors.
Mechanisms

Vascular injury
Direct injury to cerebral parenchyma / demyelination
Immunologic / autoimmune mechanism
Imaging Techniques

- Structural MRI
- Functional MRI
- MR Spectroscopy
- Diffusion Tensor Imaging
- PET
Pilot Study of Structural and Functional MRI in the Assessment of Chemotherapy-Induced Cognitive Problems

Compared 10 survivors who received chemotherapy to 10 matched healthy controls

Evidence for structural differences in both gray and white matter
Regions of Local Gray Matter Volume Reduction in Chemotherapy Treated Cancer Survivors Compared to Healthy Controls on Voxel Based Morphometry

Controls > Chemotherapy

Chemotherapy > Controls

Patients (n=12)
Controls (n=12)

p < .01, k=24
Regions of Local White Matter Volume Reduction in Chemotherapy Treated Cancer Survivors Compared to Healthy Controls on Voxel Based Morphometry

Controls > Chemotherapy

Chemotherapy > Controls

Patients (n=12)
Controls (n=12)

p < .01, k=24
Interventions

Changes in chemotherapy regimens

Pharmacologic Interventions
(erythropoietin, methylphenidate)

Cognitive Rehabilitation
Summary

Evidence suggests that cognitive decline can be long-term post-chemotherapy in a subgroup of survivors.

Imaging research suggests that structural and metabolic changes occur in the brain.

Genetic and hormonal factors may be important determinants of vulnerability.
Future Directions

Large scale prospective studies
Study of factors that increase vulnerability to cognitive decline
Impact of cognitive changes on QOL
Use of imaging techniques and development of animal models
Evaluation of interventions