Does Adjuvant Chemotherapy for Breast Cancer Cause Cognitive Dysfunction?

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Importance of Understanding Cognitive Deficits Due 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
- Effect on informed decision-making
- Similar pediatric research resulted in treatment modifications that reduced negative cognitive effects while maintaining treatment efficacy
- Functioning of patients with subtle cognitive deficits improves with cognitive rehabilitation approaches
Predictors of Cognitive Deficits

- Type of chemotherapy?
- Education level and IQ
- Depression
- Co-morbid illness
- History of traumatic brain injury
- History of learning disability
- Genetic variables
- Hormonal factors
Common Cognitive Problems Reported Post-Chemotherapy

• Memory and concentration
• ‘Executive’ function
  – Short term memory, multi-tasking
• Ability to learn new material /reading comprehension
• Ability to work with numbers
Cognitive Impact of Systemic Chemotherapy

• Wieneke and Deinst (1995)
  – Neuropsychological assessment of 28 breast cancer patients treated with CAF or CMF
  – Assessed cognitive function using formal testing at ~ 6 months following treatment
  – Compared results to population based norms
  – 75% scored below expected levels
## Cognitive Function After Adjuvant Chemotherapy

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>N</th>
<th>Cognitive Impairment (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local Therapy</td>
<td>36</td>
<td>9</td>
</tr>
<tr>
<td>Standard Dose</td>
<td>36</td>
<td>17</td>
</tr>
<tr>
<td>High Dose</td>
<td>34</td>
<td>32</td>
</tr>
</tbody>
</table>

- **Patient populations:**
  - 4 cycles FEC
  - 4 cycles FEC + STAMP V (cyclophosphamide/thiotepa/carboplatin) with stem cell support
  - Surgery +/- radiation
- **Cognitive assessment - 2 years after completion of treatment**

### Adjuvant Breast Cancer Therapy and Cognition

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>n</th>
<th>Cognitive Impairment (%)</th>
<th>Odds Ratio</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMF*</td>
<td>39</td>
<td>28</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Controls</td>
<td>34</td>
<td>12</td>
<td>6.4</td>
<td>0.013</td>
</tr>
</tbody>
</table>

- Unaffected by anxiety, depression, fatigue, and time since treatment
- Evaluated a median of 1.9 years after completion of therapy
- No correlation between objective testing and subjective symptoms

* CMF = cyclophosphamide, methotrexate, 5-fluorouracil

Patient assessment of cognitive problems

<table>
<thead>
<tr>
<th></th>
<th>CMF</th>
<th>control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Problems with concentration</td>
<td>31%</td>
<td>6%</td>
</tr>
<tr>
<td></td>
<td>( p=0.007 )</td>
<td></td>
</tr>
<tr>
<td>Problems with memory</td>
<td>21%</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td>( p=0.022 )</td>
<td></td>
</tr>
<tr>
<td>Problems with language</td>
<td>8%</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td>( NS )</td>
<td></td>
</tr>
</tbody>
</table>

Percent of patients who gave score of \( \geq 2 \) on a 5 point scale

Schagen et al, CANCER 1999
Recovery with Longer Follow-up?

- Additional assessment performed on CMF patients, control patients (and patients who received either FEC or high dose chemotherapy)
- All treatment groups demonstrated improvement in cognitive functioning over time
- Slight deterioration in functioning of control patients

Schagen et al, Annals of Oncology 1387-1397, 2002
Cognitive Impairment in Breast Cancer Patients Receiving Adjuvant Chemotherapy

Assessment: High Sensitivity Cognitive Screen/POMS

Chemotherapy Experience

- Group A: Presently receiving chemotherapy (CMF, CEF; n=31)
- Group B: Completed chemotherapy at least 1 year ago (CMF, CEF; n=40; median time since chemotherapy-2 years)
- Group C: Healthy female controls (n=36)

Brezden et al, J Clin Onc, 2000
Dartmouth Long-Term Survivor Study

- Patients with a history of breast cancer or lymphoma
  - Minimum of 5 years post diagnosis
  - Completed therapy, free of disease
  - No neurobehavioral risk factors or psychiatric disease
- Treatment included
  - Standard dose chemotherapy
    - 35 breast cancer
    - 36 lymphoma
  - Surgery and radiation (not CNS)
    - 35 breast
    - 22 lymphoma

Ahles et al, JCO 2002
Percentage of Survivors Treated with Chemotherapy or Local Therapy Scoring in the Low Neuropsychological Performance Range

<table>
<thead>
<tr>
<th>No. Impaired</th>
<th>Chemotherapy</th>
<th>Local Therapy</th>
<th>Chi-square Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Domains</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>50%</td>
<td>23%</td>
<td>p = 0.002</td>
</tr>
<tr>
<td>4</td>
<td>39%</td>
<td>14%</td>
<td>p = 0.002</td>
</tr>
<tr>
<td>5</td>
<td>24%</td>
<td>5%</td>
<td>p = 0.003</td>
</tr>
</tbody>
</table>
Adjusted z-Transformed Domain Scores for the Chemotherapy vs. Local Therapy Groups

* \( p < .05 \), adjusted for age and education
Mean Adjusted Squire Memory Subscale Scores

* $p < .05$, adjusted for age and education
Summary

• No impact of diagnosis
• Significant differences by multivariate analysis controlled for age and education
  – Battery as a whole
  – Verbal memory
  – Psychomotor function
  – % lower quartile neuropsych performance
  – Self reported problems with working memory
What is the Effect of Diagnosis?

Wefel

- 84 women enrolled on therapeutic clinical trials evaluated before adjuvant therapy
  - 35% with cognitive impairment BEFORE start of systemic therapy
    - Verbal learning and memory function
    - Affective distress was related to cognitive impairment

Wefel et al, Cancer 2004
Longitudinal Studies: Bender

• Three groups evaluated (N=46)
  – Chemotherapy (Group 1, 19)
  – Chemotherapy plus tamoxifen (Group 2, 15)
  – DCIS without tamoxifen (Group 3, 12)

• Three time points
  – After surgery, at end of chemotherapy and one year following end of chemotherapy
  – 24 dropped out before T3

• Results
  – Group 1: Deterioration in verbal working memory
  – Group 2: Deterioration in visual memory, verbal working memory, more memory complaints
  – Group 3: Improvement over time (practice effect)
  – Defects generally subtle

Bender et al, Psycho-oncology 2005
Preliminary Results: Shilling

- **Baseline, 6 and 18 month evaluation**
  - 50 chemotherapy patients (plan 100)
  - 43 healthy controls (family members, friends)

- **Data at baseline and 6 months**
  - Significant group by time interaction on three measures of verbal and working memory

- **OR for chemotherapy patients 2.25**
  - Impairment defined as having cognitive decline in 2 or > measures
  - No correlation with psychological and quality of life variables
  - No correlation between self reported cognitive decline and formal testing

- **Study ongoing**
One and Two Year Follow-up of a Prospective Controlled Study: Tchen

- 100 patients with breast cancer receiving adjuvant or neoadjuvant chemotherapy
  - Completed at least 3 courses of chemotherapy
  - Age ≤ 60
  - Fluent in English
- Matched control by age selected by patient from a neighbor, friend or relative
- Evaluation with High Sensitivity Cognitive Screen (HSCS), mini-mental status exam, others, FACT-B, ES, F, blood tests for endocrine status
- Testing at end of chemotherapy, one and two years later

Tchen, N et al, ASCO 2004
Results

- Median age 48
  - 69% premenopausal at diagnosis
  - 71% anthracycline based chemotherapy
- More fatigue than controls

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Controls</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>FACT-F (range)</td>
<td>N</td>
</tr>
<tr>
<td>Baseline</td>
<td>100</td>
<td>31 (22-39)</td>
<td>100</td>
</tr>
<tr>
<td>Year 1</td>
<td>85</td>
<td>43 (37-48)</td>
<td>79</td>
</tr>
<tr>
<td>Year 2</td>
<td>81</td>
<td>45 (39-49)</td>
<td>80</td>
</tr>
</tbody>
</table>
Results (2)

- More menopausal symptoms at baseline, year 1 and year 2
- Quality of life improved over time
- Cognitive function improved over time as defined by moderate/severe dysfunction by HSCS

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Impaired</td>
</tr>
<tr>
<td>Baseline</td>
<td>100</td>
<td>16%</td>
</tr>
<tr>
<td>Year 1</td>
<td>85</td>
<td>4%</td>
</tr>
<tr>
<td>Year 2</td>
<td>81</td>
<td>3%</td>
</tr>
</tbody>
</table>
Conclusions

• There was a strong relationship at all time points between:
  – Fatigue and QOL (p<0.0001)
  – Menopausal symptoms and QOL (p<0.0001)
  – Fatigue and menopausal symptoms (p<0.0001)

• Cognitive dysfunction is temporary in most patients

• Fatigue and menopausal symptoms are important side effects of chemotherapy that improve but do not resolve over two years
Summary of Data

• Standard-dose adjuvant breast cancer chemotherapy appears to impair cognitive function in a subset of women
  – There is very little prospective data with flawed controls
  – In the majority of patients, effects appear to resolve over time
• Current testing methods generally do not reflect patient reported symptoms
• Longitudinal assessments will be critical to
  – Determine impact and duration of cognitive function
  – Assess populations at risk
  – Define role of baseline defects in cognition
• Mechanisms?
In Search Of Mechanisms

Cancer Treatment

Clotting in Small Blood Vessels
Endogenous Hormones
Genetic Predisposition

Cognitive Function

Depression
Fatigue
Anxiety
Cytokines

Tannock, IF, JCO, 2004
Mechanisms

• Possible mechanisms of direct chemotherapy induced cognitive change
  – Direct toxic impact on the brain
  – Byproducts of cytotoxic agents, e.g., free radicals?
  – Injury response: Chemotherapy stimulates central release of neurotoxic cytokines
  – Immune response: Autoimmune mechanisms
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
• Little data to support an impact of menopause or tamoxifen on cognitive function
• Rapid changes associated with treatment may play a contributory role
Genetic Factors

• APOE-ε4 allele has been implicated in cognitive decline in patients with
  – Cardiac surgery
  – Head trauma
  – Increased age
    • In normals and with associated chronic illnesses

• Is APOE-ε4 a risk factor for cognitive deficits secondary to chemotherapy?
Z-Transformed Domain Means by APOE Status: Long-term Follow-up Study at Dartmouth in 80 Breast and Lymphoma Survivors

<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)

Ahles et al, Psycho-oncology, 2003
Potential Mechanisms

• Reduction in microvascular or neuronal repair processes associated with the APOE -\(\varepsilon4\) allele

• Pre-existing morphologic differences (e.g., smaller hippocampal volume) associated with the APOE -\(\varepsilon4\) allele
Methods of Testing

• Formal neuropsychiatric testing evaluates common domains
  – Verbal Ability, verbal learning and memory (speed of information processing), visual memory, spatial functioning, psychomotor functioning, attention/concentration, executive (frontal) functioning motor function and coordination
  – QOL self-report measures include global quality of life, depression, anxiety, memory and fatigue

• Requires expertise to administer test, ~ 2 hours testing time
Methods of Testing (2)

• **Newer computerized testing methods**
  – Easy to administer, short testing time
  – Provide global rather than detailed results

• **Imaging**
  – MRI/PET scans to evaluate changes in baseline blood flow and metabolism
  – Measure changes in real time with cognitive tests/mental status exam
  – Costly and time consuming
PET Scan Protocol

Inject $^{15}$O-water
2 min scan

Baseline control task (read, repeat)

Inject $^{15}$O-water
2 min scan

Baseline control task (read, repeat)

Inject $^{15}$O-water
2 min scan

Short-term memory recall task

Inject $^{15}$O-water
2 min scan

Short-term memory recall task

Inject $^{15}$O-water
2 min scan

Long-term memory recall task

Inject $^{15}$O-water
2 min scan

Long-term memory recall task

Inject $^{18}$FDG
45 min. uptake

Resting metabolism

30 min scan

12 min.

Silverman et al, ASCO 2002
Abnormal regional brain activity was identified in adjuvant chemotherapy-treated breast cancer survivors

- Resting hypometabolism in frontal cortex: superior frontal gyrus of the dorsolateral prefrontal cortex, L/R Broca’s areas (9% below normal, p < 0.001 for each).

- Activation pattern during recall task in L/R Broca’s area was abnormal.

- Resting hypometabolism in lentiform nucleus for tamoxifen + chemo, but not chemo-only, patients (-10%, p<0.001).

- Severity of regional brain abnormalities correlated significantly with severity of neurocognitive impairment.
Regions of Interest on Superior Brain Normal Template

- sPL
- iPL
- SM
- GFm
- GFS
- GFD
- GCa
- Broca
- WA
- PCC
- sLT
- AVC
Interventions

• Possible pharmacologic interventions
  – Erythropoietin
  – Methylphenidate (Ritalin)
  – Statins – HMG-CoA reductase inhibitors to preserve flow, decrease inflammatory cytokines, reduce oxidative stress
  – Modafinil – wakefulness and cognitive enhancer
  – Antidepressants
  – Treat insomnia
  – Herbal remedies
    • Gingko Biloba and Ginseng – no standardized formulation

• Cognitive rehabilitation (R. Ferguson, Dartmouth)
  – Structured programs
    • Exercise, memory tasks, puzzles, avoid fatigue
CNS Effects of r-HuEPO
Proposed Mechanism of Neuroprotection

• Peripherally administered r-HuEPO crosses the blood-brain barrier (BBB)

• Exogenous r-HuEPO then interacts with brain EPO receptors

• Receptor binding induces a gene expression program, which inhibits apoptosis and also modulates neuronal excitability
CNS Effects of r-HuEPO

- r-HuEPO administered systemically protects brain from a variety of insults
  - Focal ischemia (stroke)
  - Blunt trauma
  - Excitotoxins
  - EAE
- Improved cognitive function is observed in animals treated with r-HuEPO

Treatment Schema: Adjuvant Breast/Cognition Protocol

- Stage I, II, III breast cancer
- Anthracycline-based adjuvant therapy
- Hgb 9–14 g/dL

QOL and cognitive assessments by EXIT25 at baseline, Cycle 4, and 6 mo post-chemotherapy

QOL, quality of life.

Epoetin alfa and CT Breast Cancer: Hb Results

- Hb levels significantly improved with EPO treatment compared to placebo

Mean Change From Baseline to Cycle 4 in EXIT25

Mean change from baseline

-2.5 -2.0 -1.5 -1.0 -0.5 0 0.5 1.0 1.5 2.0 2.5

Cycle 4

6-month post-CT

-2.5 -2.0 -1.5 -1.0 -0.5 0 0.5 1.0 1.5 2.0 2.5

* P = .011.

Epoetin alfa

Placebo

Decline in cognitive function

Improvement in cognitive function

Effects of r-HuEPO

• Potential toxicities
  – Thrombosis risk at higher than normal hemoglobin levels
  – Hemoglobin levels must be monitored and controlled

• Effects on outcome?
  – Two randomized trials suggested a negative effect of erythropoietin on recurrence and survival
  – Subsequent studies showed no impact

Patient Controlled Methylphenidate

- 31 patients with advanced cancer
  - Fatigue as measured by 0-10 scale
  - Treated with Methylphenidate 5 mg every 2 hrs as needed for 7 days.
  - Symptoms assessed daily by scale and FACT-F
- Significant improvements in
  - Fatigue (p<.001)
  - Overall well-being (p<.001), Functional well-being (p<.001), Physical well-being (p<.001)
- Most patients took 3 or more doses per day
- All chose to continue methylphenidate > 7d
- No serious side effects

Bruera et al, JCO 2003
Future Directions

• Large scale prospective studies are needed
  – Role of tamoxifen vs aromatase inhibitors
• Study of factors that increase vulnerability to cognitive decline
• Use of imaging techniques and development of animal models
• Examination of the temporal patterns of cognitive decline and recovery
• Important issue to discuss with patients when considering adjuvant chemotherapy, particularly when the benefit of treatment is borderline
Ongoing Longitudinal Studies

• Dartmouth
  – Breast cancer and lymphoma
  – Assessing APOE - ε4 as a possible risk factor
  – Longitudinal functional MRI scanning

• Shilling

• Component of adjuvant hormonal trials

• Interventions ongoing or planned
  – Methylphenidate (randomized)
  – Behavioral modification and cognitive rehabilitation
  – Erythropoietin