Chemotherapy-associated fatigue and cognitive impairment: a proposed SWOG clinical trial

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Patient A

• A 59 y/o woman is diagnosed with a stage II, hormone-receptor positive, HER-2/neu negative breast cancer 1 year ago. She undergoes lumpectomy and axillary dissection.
• She receives adjuvant chemotherapy with doxorubicin and cyclophosphamide followed by paclitaxel.

Patient A

• At completion of chemotherapy, she receives whole breast radiation and starts on anastrozole.
• It has been nearly 6 months since completion of radiation therapy. She complains of continued fatigue and “chemobrain”. She forgets names and numbers or tasks to be completed.
Patient A

• Her exam shows recovering alopecia, no skin toxicities on her breast, and no focal neurological findings.
• Laboratory results are unremarkable.

Patient A

• Is this “chemobrain”?
• What can we tell this patient about the cause of her symptoms and the natural history?
• Is there any intervention which may improve her symptoms?

Objectives

1. Define "chemobrain"
2. Review incidence of "chemobrain" in the literature
3. Discuss promising treatment for "chemobrain"
4. Discuss future direction.
“Chemobrain”

- Fatigue and neurobehavioral impairment during and after cancer diagnosis and treatment
- Disruptions in thinking and memory
  - Short-term vs. long-term memory
  - Verbal, mathematical, spatial ability, motor skills
  - Ability to learn
  - Speed of processing

Patient perspectives

- “I wouldn’t be able to think of a key word in a sentence…”
- So there I was, staring at the cereal and hoping it would remind me of what I had come to buy…”
- “The worst was the day I forgot to pick up my daughter at day care…”

How common is it?

- Internet data:
  - 20-30%
  - >50%
  - Over 99%
  - “We don’t know”
- Meta-analyses: mild-to-moderate effects
  - Jansen, et al., *Cancer*, 2005
How common is fatigue?

- Incidence of fatigue in breast and lung cancer patients ~ 99%
- 61% of chemotherapy and radiotherapy patients continue to experience fatigue after treatment stopped
- No approved treatment

Incidence and Persistence of Cognitive Impairment

- 35% of 85 breast cancer patients exhibited cognitive impairment prior to chemotherapy
- Dysfunction persisted with chemotherapy
  - Baseline – 33% impairment
  - Short-term (>3 weeks after chemotherapy) – 61%
  - Long-term (1 year after chemotherapy) – 45% stable and 45% improved

Why employ neuropsychological testing?

- Cognitive tests measure a critical aspect of brain function and behavior that is important for success in daily life
- Performance status (e.g., KPS) has little relation to cognitive function and QOL
- Self-report of cognitive problems (i.e., questionnaires) correlates poorly with objective test results
- Brief mental status exams only detect delirium or significant dementia
### Characteristics of a Clinical Trial Battery

- Objective and Quantifiable measures
- Brief (on the order of 20-30 minutes)
- Good psychometric properties (test-retest reliability)
- Repeatable (alternate forms, minimal practice effect)
- Sensitive to changes in cognitive function
- Highly standardized, simple administration
- Measure relevant cognitive domains
- Practical: cost, patient burden, compliance
- Oversight by a neuropsychologist

### Analytic Validity of Cognitive Tests

- Published validity and reliability, population norms
- A priori established significant change defined
- Standardized in such a manner that variations among assessors/sites is minimal
  - Requires formal certification and QA procedures
  - Battery can be imported into community settings

### Confounders

- Other treatments (e.g., hormonal treatment)
- Side effects of treatments (e.g., low blood counts, drowsiness)
- Psychological/symptom status (e.g., depression, anxiety, fatigue)
- Menopausal status
- Patient characteristics (e.g., age)
Methylphenidate
A promising treatment?

Methylphenidate Mechanism of Action
• Methylphenidate is a mild CNS stimulant structurally and pharmacologically related to amphetamine
• Non-catecholamine sympathomimetic with direct and indirect adrenergic agonist properties
• Efficacy in ADHD due to ability to release dopamine and block its reuptake at presynaptic terminal

Mechanism of Action
• Precise mechanism for its effectiveness still unclear
• Dose-dependent side-effects include nervousness, insomnia, loss of appetite, weight loss, abdominal pain, tachycardia
Focalin® / Focalin® XR: A Refined Form of Ritalin®

- Methylphenidate products (Ritalin®, Concerta®, Metadate®) contain racemic mixtures of d- and l-isomers.
- Pharmacologic activity resides in the d-isomer.
- Focalin® and Focalin® XR (dexmethylphenidate HCl) contain only the d-isomer.

Focalin® / Focalin® XR Approval History

- Focalin® (Dexmethylphenidate HCl Immediate-Release) approved in US in November 2001 for pediatric ADHD:
  - Administered twice daily, at least four hours apart.
  - Commercially available as 2.5 mg, 5 mg, and 10 mg tablets.

- Focalin® XR (Dexmethylphenidate HCl Extended-Release) approved in US in May 2005 for pediatric and adult ADHD:
  - Administered once daily in the morning (12-hour duration).
  - Commercially available as 5 mg, 10 mg, and 20 mg capsules.

A Phase II, Randomized Placebo-controlled Trial of the Safety and Efficacy of d-MPH as a New Treatment of Fatigue and “Chemobrain” in Adult Cancer Patients

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2 Beth Israel Cancer Center, New York, NY
3 Celgene Corporation, Warren, NJ
Purpose of Study

• To evaluate the efficacy and safety of dexmethylphenidate for the treatment of fatigue and neurobehavioral (cognitive) impairment associated with chemotherapy

Study Objectives

• Primary objective
  - Evaluate the efficacy of d-MPH in the treatment of chemotherapy-related fatigue in adult cancer subjects using the FACIT-F
• Secondary objectives
  – Evaluate the efficacy of d-MPH in improving cognitive dysfunction
  – Explore the efficacious dose range required to maintain effectiveness
  – Assess the safety of d-MPH doses up to 50 mg/day in this population

Patient Eligibility

• M/F, ages 18-70
• Cancer dx, excl. 1st or metastatic brain tumors
• 4 cycles of cytotoxic chemotherapy (minimum), completed ≥2 months prior to study entry
• Life expectancy >6 months
• No focal neurological deficit
• ECOG ≤2
• ICD-10 criteria for Cancer Related Fatigue
• Mini-Mental Status Exam (MMSE) score ≥20
• Beck Depression Inventory-II (BD-II) score <18
• Clinical Global Impression-Severity (CGI-S) score ≥3
Statistics

• Planned accrual – 160 patients to obtain 60 evaluable subjects in each group
• 2-sided test with Type 1 error rate of 0.05
• 80% power to detect a 15% difference in FACIT-F score between groups with SD=10.5

Study Design

<table>
<thead>
<tr>
<th>Visit #</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week #</td>
<td>(-1)</td>
<td>(0)</td>
<td>(1)</td>
<td>(2)</td>
<td>(3)</td>
<td>(4)</td>
<td>(5)</td>
<td>(6)</td>
<td>(7)</td>
<td>(8)</td>
</tr>
</tbody>
</table>

Pre-Randomization Phase

- Pre-Randomization Visit 1
- Baseline/Randomization Visit 2

Single-Blind Treatment Period

- Screening Period
- Single-Blind Treatment Period
- Dose Maintenance (2-wk minimum)

Double-Blind Treatment

• Subjects eligible if CGI-S maintained or worsened

• d-MPH initial doses 5 mg BID (4-6 hrs apart)

• Dose modifications determined by
  – Weekly Clinical Global Impression-Improvement (CGI-I) score
  – Doses increased by up to 10 mg/day at each weekly visit during first 6 weeks to maximum total daily dose of 50 mg/day
Patient Demographics

• Age 52.8 yrs
• Gender 94% female
• Race 79% white
• Cancer type 76% breast
• FACIT-F score at baseline comparable to published surveys of patients post- chemotherapy
• Treatment groups were well-matched for all baseline characteristics

Results

• d-MPH was significantly superior to placebo in reducing fatigue as measured by the FACIT-F scale compared to baseline values for weeks 2 and 4 through 8
• d-MPH was significantly superior to placebo for the Clinical Global Impression – Improvement at weeks 2 and 4 through 8

Change in FACIT-F (fatigue) Total Score at Each Week

<table>
<thead>
<tr>
<th>Treatment Week</th>
<th>d-MPH</th>
<th>d-MPH LOCF</th>
<th>PLCBO</th>
<th>PLCBO LOCF</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>-2</td>
<td>-2</td>
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<td>-4</td>
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<td>7</td>
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<td>-14</td>
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<td>-14</td>
</tr>
<tr>
<td>8</td>
<td>-14</td>
<td>-14</td>
<td>-14</td>
<td>-14</td>
</tr>
</tbody>
</table>

* p < 0.05
** p < 0.01

LOCF = Last observation carried forward
Clinical Global Impression-Improvement

% of subjects achieving very much or much improved at each week

<table>
<thead>
<tr>
<th>% subjects</th>
<th>wk0</th>
<th>wk1</th>
<th>wk2</th>
<th>wk3</th>
<th>wk4</th>
<th>wk5</th>
<th>wk6</th>
<th>wk7</th>
<th>wk8</th>
<th>LOCF</th>
</tr>
</thead>
<tbody>
<tr>
<td>dMPH</td>
<td>10</td>
<td>20</td>
<td>30</td>
<td>40</td>
<td>50</td>
<td>60</td>
<td>70</td>
<td>80</td>
<td></td>
<td></td>
</tr>
<tr>
<td>placebo</td>
<td>20</td>
<td>30</td>
<td>40</td>
<td>50</td>
<td>60</td>
<td>70</td>
<td>80</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* p<0.05, ** p<0.01

Adverse Events

• No deaths

2 Serious Adverse Events - both in the placebo group (1 pneumonia, 1 incisional hernia)

• 78% of placebo and 90% of dMPH subjects reported at least one adverse event

• Dose reduction to an optimal dose was allowed-often following an adverse event

• Mean final dose was 25.5 mg/day (d-MPH) and 38.5 mg/day (Placebo)

Adverse Events

• Adverse events reported by 10% or greater in either group

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>dMPH %</th>
<th>Placebo %</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>40.8</td>
<td>33.3</td>
<td>NS</td>
</tr>
<tr>
<td>Nausea</td>
<td>27.6</td>
<td>7.7</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>26.3</td>
<td>9.0</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Dizziness</td>
<td>19.7</td>
<td>7.7</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Insomnia</td>
<td>18.4</td>
<td>10.3</td>
<td>NS</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>14.5</td>
<td>12.8</td>
<td>NS</td>
</tr>
<tr>
<td>Anxiety</td>
<td>13.2</td>
<td>6.4</td>
<td>NS</td>
</tr>
<tr>
<td>Nervousness</td>
<td>13.2</td>
<td>5.1</td>
<td>NS</td>
</tr>
<tr>
<td>Feeling Jittery</td>
<td>13.2</td>
<td>1.3</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>10.5</td>
<td>6.4</td>
<td>NS</td>
</tr>
</tbody>
</table>

p values – 2-sided Fisher’s Exact Test
Adverse Events

AE severity distribution for all subjects

<table>
<thead>
<tr>
<th>Highest level of AE severity</th>
<th>d-MPH</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>mild</td>
<td>34.2%</td>
<td>30.8%</td>
</tr>
<tr>
<td>moderate</td>
<td>47.4%</td>
<td>37.2%</td>
</tr>
<tr>
<td>severe</td>
<td>9.2%</td>
<td>10.3%</td>
</tr>
</tbody>
</table>

Conclusions

• Dexmethylphenidate (d-MPH) significantly reduced chemotherapy–related fatigue in adult cancer subjects compared to placebo.
• d-MPH at doses up to 50 mg per day is safe, well-tolerated in adult cancer subjects.
• d-MPH therapy should be considered for randomized trial of patients with fatigue and memory impairment after chemotherapy.

Limitations

• Randomized phase II study
• Underpowered to detect difference in cognitive function
• Heterogeneous group of patients
Proposed SWOG trial

A phase III randomized placebo-controlled study of dexamethasphenidate hydrochloride (d-MPH) in patients with early stage breast cancer and chemotherapy-related fatigue

Behavioral and Health Outcomes Committee
Committee on Special Populations
Breast Cancer Committee

Endpoints

1. Primary objective: efficacy of d-MPH in chemotherapy-related fatigue
2. Secondary objectives:
   --efficacy of d-MPH in chemotherapy-related cognitive dysfunction
   --toxicities of d-MPH

Eligibility

2-step registration process:
STEP 1 (initial registration)
• Patients with stage I, II, or III breast cancer who are scheduled to receive at least 4 cycles of adjuvant chemotherapy
• Pre-existing fatigue allowed
• ≥18 years
• Ability to read and complete forms in English
Eligibility

STEP 2 (randomization)
• Patients with worsened chemotherapy-related fatigue (increase of ≥ 3 points on FACIT-F subscale)
• Resolved chemotherapy-related anemia
• Patients may receive adjuvant endocrine therapy

Design

Baseline evaluation of fatigue and cognitive dysfunction
Post-chemo evaluation of fatigue and cognitive dysfunction:
If fatigue worsening,
Randomization

placebo
dimethylphenidate

Daily x 6 months
Measures at 6 weeks and 6 months

Stratification

• Menopausal status
• Current endocrine therapy
• Radiation therapy
• Duration of adjuvant chemotherapy (≤ or > 12 weeks)
• Baseline fatigue at initial registration
Measures

- Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F)
- Hopkins Verbal Learning Test-Revised
- Controlled Oral Word Association Test
- Trail Making Test
- Web-based and on-site (?) certification proposed

Sample Size

- Anticipate approximately 680 initial registrations and randomization of 510 patients with early stage breast cancer
- Expect accrual to be brisk based on the prevalence of chemotherapy-related fatigue

Summary

- Proposed phase III trial powered to see a benefit in chemotherapy-related fatigue
- Homogeneous population, which allows chemotherapy at the discretion of the MD
- Stratify for other variables
- Validated tests that will take <30 minutes to administer; certification will be facilitated