Cognitive Impairment in Cancer Patients

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Outline

- Overview of cognitive impairment
  - Background
  - Incidence
  - Current literature on chemotherapy related cognitive dysfunction
- Pharmacologic management of cognitive impairment in cancer patients
  - Peer Review recommendations
  - Medications under study
- Study Proposals within SWOG

What is Cognitive Impairment (CI)?

- aka “chemo-fog” or “chemo-brain”
- Fatigue and neurobehavioral impairment during and after cancer diagnosis and treatment

Signs and Symptoms of CI

- Fatigue
- Disruptions in thinking and memory
  - Short-term vs. long-term memory (Verbal and Visual)
  - Verbal, mathematical, spatial ability, motor skills
  - Ability to learn
  - Speed of processing information
  - Concentration
  - Attention

Etiology of Cognitive Impairment in Cancer Patients

- Cancer
- Cancer Treatments
  - Anti-cancer chemotherapy
  - Hormonal therapy
  - Biologic therapy such as interferon
  - Cranial surgery
  - Cranial radiation therapy
- Inactivity after cancer therapy
- Anemia
- Metabolic/endocrine (menopause, thyroid)
- Pain
- Emotional Distress (depression, anxiety)
- Sleep Disturbance
- Poor Nutrition
- Adverse effects of supportive medications
- Comorbid diseases

Mechanisms of Chemotherapy-associated CI

- Direct neurotoxic effects of chemotherapy causing injury to neurons or surrounding cells, altered neurotransmitter levels
  - *Frontal cortex and integrity of white matter*
- Oxidative stress and DNA damage
  - *Cell death and slowing of cell division in subventricular zone*
- Induced hormonal changes
- Immune dysregulation and/or release of cytokines
  - *IL-6*
- Blood clotting in small central nervous system
- Genetic predispostion e.g impaired DNA repair capability
  - *E4 allele of apolipoprotein E*

Incidence of Cognitive Impairment

- Earlier studies (2002-2004)reported 15-50% of adults solid tumor survivors who had received chemotherapy
  - *Validity of these studies being questioned*
- Incidence of fatigue in breast and lung cancer patients ~ 99%
- 61% of chemotherapy and radiotherapy patients continue to experience fatigue after treatment stopped
- Reported to last up to 10 years

Incidence and Persistence of Cognitive Impairment

- 35% of 84 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

Wefel, et al, Cancer, 2004

Impact of CI

- Both patient and families
  - QOL
  - Physical
  - Psychosocial
  - Economic/occupational
- Cancer survivors need continual monitoring and support

Clinical Significance of CI in Cancer Survivors

- An important survivorship issue as fear of these long-term side effects may influence a patient's decision to take adjuvant chemotherapy.
- As we refine who gets adjuvant chemotherapy, we need information on how to treat symptoms in survivorship.
- Yet, there are no approved treatments for CI at this time.

Collaborative Efforts

- 2004 – First International workshop in Baniff, Canada focused on chemotherapy-induced cognitive changes secondary to adjuvant chemotherapy for breast cancer

J Clin Oncol 22:2233-2239,2004

- 2006 – Second International workshop in Venice, Italy with an expanded focus on breast, testicular, and prostate cancers and treatments with chemotherapy and hormonal therapy

Annals of Oncology 19:623-629,2008

- Formation of the International Cognition and Cancer Task Force (ICCTF)

Treatment Approaches

- Specific treatment for potentially reversible causes
  - Anemia, metabolic or endocrine abnormalities, pain, insomnia, depression, and anxiety
- Symptomatic measures when no obvious etiology or reversible cause can be identified
- Non-specific symptomatic treatment measures
  - Education
  - Counseling
  - Pharmacologic (psychostimulants)
  - Non-pharmacologic (exercise, yoga, acupunture)

What are some promising agents?

Pharmacologic Agents

Preventive agent: micro-coagulation – **Aspirin**

Treatment for Reversible Causes

- Anemia – **Erythropoietin stimulating agent (ESA)**
- Metabolic or endocrine abnormalities
- Pain – Pain medications, non-pharm therapy
- Insomnia – Sleep Therapy, Sleeping aid medications
- Depression – Psychotherapy, antidepressants
- Anxiety – psychotherapy, anxiolytics

Treatment of Non-Specific Symptoms

- Fatigue –**Methylphenidate, Modafinil, Armodafinil**

Aspirin

- Rational:

1) chemotherapy and free radicals can damage blood vessels and cause decrease in blood perfusion and flow
2) Inflammatory process associated with CI in Alzheimer disease

- NSAIDs have anticoagulation properties to prevent mico-coagulation and anti-inflammatory properties
- Literature data are in non-cancer population are limited due to sample size
- No published peer-reviewed data in cancer patient

ESA

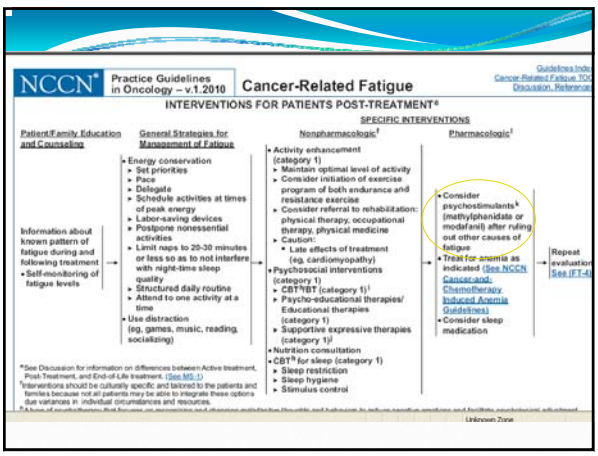
- Benefits of ESA (epoetin alfa and darbepoetin) are primarily related to improvement of fatigue
- Mata-analysis results:
  - 10 studies and N = 5712, epoetin alfa was significantly superior to placebo for improvement of fatigue
  - 4 studies of darbepoetin showed borderline statistically significant improvement in fatigue
- The recent reported risks for disease outcome and adverse events compromised the use of ESA

Minton et al. A Systematic Review and Meta-Analysis of the Pharmacological Treatment of Cancer-Related Fatigue. JNCI 2008; 100:1156-1166

Methylphenidate

- Central nervous system stimulant structurally related to amphetamines
- Methylphenidate - both D- and L- isomer
- Active form : D-isomer, dexmethylphenidate (Focalin®)
- Short half-life and rapid onset of action
- Both drugs have been evaluated in placebo-controlled, randomized trials.
- Meta-analysis concluded that both drugs were significantly superior to placebo for fatigue, but lack strong evidence to support its role in CI improvement

Minton et al. A Systematic Review and Meta-Analysis of the Pharmacological Treatment of Cancer-Related Fatigue. JNCI 2008; 100:1156-1166



Modafinil (Provigil®) & Armodafinil (Nuvigil®)

- Modafinil and armodafanil are central nervous system stimulants, but non-amphetamine molecule
- Modafinil (mixture of R- and S –enantiomer) Armodafinil (R-enantiomer)
- Armadafinil - longer t½ and 1:2 equipotent dose in mg
- Activities: wake-promoting effects, increase locomotor activity in animals
- Exact MOA is unknown, but distinct from other stimulants' sites of action
- Produce psychoactive and euphoric effects and alterations in mood, perception, thinking, and feelings typical of other CNS stimulants in humans.

Modafinil, Armodafinil

- Both drugs are FDA-approved for
  --Narcolepsy/obstructive sleep apnea
  --Shift-work sleep disorder
- Most common toxicities: headache, nausea, anxiety/nervousness, diarrhea, rhinitis, insomnia, dizziness
- Sever e rash (0.8%) has been reported in children only
- Take with empty stomach to avoid delayed in absorption (time to reach peak plasma level delayed by 2-4 hrs with meals)
- Dose reduction in pts with hepatic impairment
- Interest in exploring these agents in cancer-related fatigue and cognitive dysfunction

Modafinil Studies

Malignancy	Post Cancer Treatment?	N	Modafinil	Fatigue improvement	P value
Breast[1]	Y	51	200 QD x 4 weeks	Y	<0.1
Breast[2]	Y	82	200 QD x 4 weeks	Y	<0.001
Brain[3]	Y	30	200 QD up to 12 weeks	Y	Sig
unknown[4]	N	888	200 QD v placebo	Numerical data not published	0.03

[1]Morrow, et al 2005; [2]Morrow, et al 2006; [3]Kaleita, et al 2006; [4]Morrow, et al 2008

Cooper MR, et al, Ann Pharmacother. 2009 ; 43(4):721-5.

Modafinil Study

- In addition, 82 breast cancer patients in 2nd study also evaluated for improvement in cognitive dysfunction.
- Modafinil improved measures of memory in those with baseline severe cognitive dysfunction, but not in mild/moderate

Kohli, et al, Cancer 2009

Limitations of Modafinil Study Data

- Many studies were small, open-label, non-randomized, therefore subject to bias
- Information on staging and specific treatment unavailable
- Randomized trial with a heterogenous group of cancer patients, unknown stages and treatments
- Variable definitions and measures for fatigue and cognitive function
- Variable timing and duration of intervention
- No toxicities reported

Barriers in Conducting CI Studies

- Pre-treatment or baseline assessment has been difficult due to interference of stress cause by news of cancer diagnosis with or without surgery
- Difficult to interpret subsequent results for comparative purpose
- Standardization of evaluation/assessment criteria and tools (sensitivity, reliability, and specificity)
- Provider (single time point) vs Self-report (measurement over prolonged period time points)
- Cultural, premorbid conditions, and ADL influence

Modafinil and Armodafinil

- Reports are encouraging.
- The scope of the problems and these results justify a randomized trial of clearly defined, early stage breast cancer patients with fatigue and memory impairment after adjuvant chemotherapy.
- Propose using armodafinil as it has a longer half-life

Proposed SWOG trial

A phase III randomized placebo-controlled study of armodafinil in patients with early stage breast cancer and chemotherapy-related fatigue and cognitive dysfunction

PIs: Helen Chew, Kathy Albain, Carol Fabian

Cancer Survivorship Committee
Breast Cancer Committee

Endpoints

1. Primary objective: efficacy of armodafinil in chemotherapy-related fatigue and cognitive dysfunction
2. Secondary objectives: toxicities of armodafinil in this population

Eligibility

2-step registration process:

STEP 1 (Initial Registration)

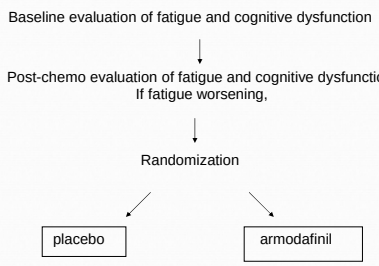
- Patients with stage I, II, or III breast cancer who are scheduled to receive at least 4 cycles of adjuvant chemotherapy
- Pre-existing fatigue allowed
- ≥18 years
- Ability to read and complete forms in English

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



Daily x 6 months
Measures at 6 weeks, 3 months, 6 months,1 and 2 years

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

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

Summary

- Proposed phase III trial powered to see a benefit in chemotherapy-related fatigue in early stage breast cancer
- More 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