Chemo Fog

Ottawa Lymphoma Support Group
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Chemo Fog

- Devlen et al., *1987* *(Br Med J 295:953-957)*
  - Surveyed patients with Hodgkin's disease or non-Hodgkin's lymphoma treated with radiotherapy and/or chemotherapy 2.7 years post-dx; mostly disease free and off treatment
  - ~1/3 of sample (30/90) complained of impairment in thinking or short-term memory
  - Second in frequency only to lack of energy

"We were also concerned about the substantial proportion who had persistent symptoms and complained of memory impairment"

Our Survey

- Questionnaires sent to lymphoma patients seen at TOH in past 5 years
- 262 responses analyzed
- 26% reported experiencing cognitive changes and 30% reported significant fatigue and these were highly correlated
- Frequency of depression, anxiety, pain and insomnia low

Our Survey

- 99 patients did computerized cognitive testing
- 25% showed impairment in 1 of 7 cognitive domains
- But no difference in perceived or objective cognitive function between those who received chemotherapy and those who had not (only 22) and no relationship between cognitive dysfunction* and number of chemotherapy cycles

Chemo Fog

- Most studies in hematological cancers done in patients undergoing HSCT
- Several studies report increased frequency of subtle cognitive dysfunction in hematological Ca pts post-HSCT
- But longitudinal studies with pre-HSCT baseline indicate similar rates of mild impairment prior to transplant (20-40%) suggesting that it may be associated with chemotherapy prior to transplant (previous treatment or conditioning), to other treatments, or to disease itself (e.g.Syrjala et al., *Blood* 2004;104:3386-92)

Chemo Fog

FAQs

What Exactly is *Chemo Fog*?

- Increase in the frequency of “everyday slips and lapses”
  - Recalling words and names (books, people, places)
  - Misplacing things
  - Forgetting intentions (what to get at store, why went into a room, what had agreed to do)
  - Forgetting things others have said
  - Can’t concentrate for prolonged period--hard to read a book
  - Distractible—go from task to task without completing
  - Perhaps foremost complaint—difficulty with MULTI-TASKING!
- NOT dementia, delirium
- More noticeable to the sufferer than to others

Is there an association between chemotherapy exposure and cognitive disturbance?

- According to a recent review article (Wefel & Schagen, 2012)
  - 78% of cross-sectional studies and 69% of prospective longitudinal studies found evidence in support of chemotherapy-related cognitive impairment

Is the cognitive disturbance actually *caused* by chemotherapy?

- Patients blame chemotherapy but other factors, treatments may also be contributory
  - Stress, depression
  - Hormonal therapies in breast and testicular cancer
  - Symptomatic treatments such as steroids, pain medications, hypnotics
  - Hematopoietic stem cell transplantation (HSCT)
  - Radiation
  - Biologic therapies

Is the cognitive disturbance actually *caused* by chemotherapy?

- Prospective studies show elevated frequency of cognitive impairment, as well as changes in brain structure and function, prior to starting adjuvant treatment, so may be partly related to disease itself
- Suggested that terms like “chemo fog” and “chemobrain” be replaced with “cancer- or cancer-therapy related cognitive change”

Is the cognitive disturbance actually *caused* by chemotherapy?

- But multiple lines of evidence of chemotherapy neurotoxicity
  1. Animal studies have shown deficits in animal models of learning and memory, decreased neurogenesis and increased cellular death in areas of the brain involved in cognition following chemotherapy exposure
  2. Brain imaging studies in humans show differences and, more importantly, *changes* in brain structure (volume of white and gray matter, white matter integrity) and function (blood flow patterns during cognitive activity, electrical activity) in BC patients exposed to chemotherapy

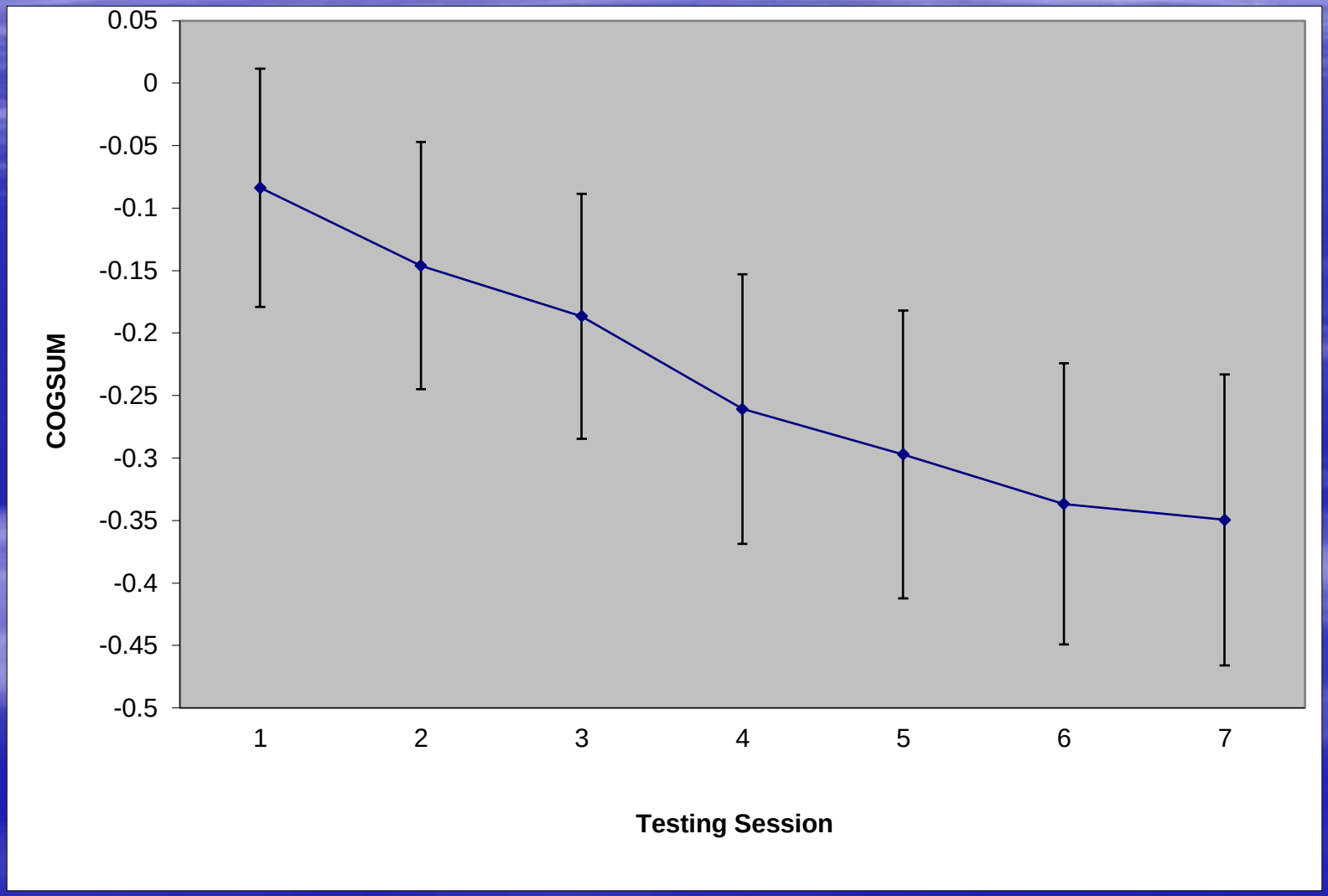
Is the cognitive disturbance actually *caused* by chemotherapy?

3. Dose-response relationship
   - Van Dam et al. found that 32% of high-dose chemotherapy group showed cognitive impairment 2 years after tx compared to 17% of standard-dose group and 9% of control group (Similar findings in a subsequent prospective study)
   - High-dose group also more likely to show late electrophysiological abnormalities
   - Other cross-sectional studies also find duration of treatment and number of chemotherapy cycles to be risk factors for cognitive disturbance

Is the cognitive disturbance actually *caused* by chemotherapy?

- Our dose-response study
  - BC patients tested before chemotherapy and following each chemo cycle
  - Healthy matched controls tested on same schedule
  - Linear decline in cognitive function after controlling for baseline performance, practice effects, and changes in mood and fatigue
  - Compelling evidence of a causative relationship between chemo and cognitive changes

Is the cognitive disturbance actually *caused* by chemotherapy?



How Common is CRCI?

- Estimates from different studies vary from 17% to 78%
- Probably due in large part to differences in study design and methodology
- In two recent prospective longitudinal studies with BC patients, we found approximately 1/3 of participants were affected which
  - in keeping with the results of others

What Mental Functions are Most Impaired?

- All cognitive domains implicated in one study or another
- Our studies suggest working memory and processing speed to be more vulnerable than more specific, focal cognitive abilities
- Fits with patient descriptions of diminished cognitive efficiency and inability to multi-task

What is the Severity of the Mental Changes?

- Effects are subtle (ES in meta-analytic studies generally in -0.2 to -0.5 range) but may still affect QOL for some people
- In 2010 survey of BC survivors conducted by Canadian Breast Cancer Network
  - 8% reported “chemobrain” as a significant barrier to returning to work
  - Women who had received chemo had greatest reduction in household income, had taken more time off work, were more likely to have quit their jobs
- Chemotherapy exposure has also emerged as a significant predictor of work changes after cancer in other studies of BC patients and more heterogeneous groups of cancer patients
- A couple of studies have shown an association between neuropsychological performance and work-related outcomes

How Long do the Changes Last?

- Some post-hoc studies find evidence of cognitive disturbances and irregularities in brain structure and function as long as 20 years post-tx
- Prospective longitudinal studies (including our own) generally find that problems remit after termination or chemotherapy, although there may be a small subgroup with more persistent, even permanent, effects
- No clear evidence at this point that CRCI a risk for developing dementia later in life

What are the Risk Factors for CRCI?

- Few, if any, definitive risk factors identified
- Candidates include:
  - Age
  - "Cognitive reserve"
  - Dose (intensity, cumulative dose)
  - Combined chemo and hormonal therapy in BC patients
  - Treatment-induced menopause
  - Genotype (e.g., ε4 allele of apolipoprotein E gene)

Why the fuss?

- Allow informed choices--should know of risk if one exists but not be unnecessarily frightened
- Reduce distress, catastrophizing if understand what is happening
- Provide appropriate support and treatment
- Guide insurance companies
- Consider in new drug development

What Can You Do?

- Cut yourself some slack
- Consider other factors that might be contributing
- Use external aids and reminders
- Eliminate distractions
- Avoid multi-tasking situations
- Practise “present-mindedness”
- Educational session offered at Maplesoft
- Seek medical attention or formal testing if problems are more severe, persistent
- Studies assessing benefits of cognitive-behavioural interventions, physical exercise, and medications (e.g., stimulants, Aricept)

What Next?

- Why the disconnect between complaints and performance?
- Mechanism—how do these cancer treatments exert their effects?
- Risk factors—why are some patients affected more than others?
- Extend studies to other types of cancer, including hematological cancers

Thank You!

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