

Cancer Council Update 2009



“Chemobrain” – cancer, treatment and the brain

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“Chemobrain” Cancer, Treatment and the Brain

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Overview

1. Definitions
2. Incidence - Overview of literature
3. Mechanisms
3. Potential Interventions
4. Clinical Implications

“On the Receiving End”

Two surveys: rank side-effects by patients receiving chemotherapy

1983: (Coates et al, Eur J Oncol 1983;19:203-6)

Most important S/E:

- nausea and vomiting

1993: (Griffin et al, Ann Oncol 1996;7:189-95)

A shift from concerns about physical to psychosocial issues

Cognitive Function in Adult Cancer Survivors

Major concern of survivor support groups:

“chemobrain” or “chemofog”

Studies show :

- 50-70% of breast cancer (BC) patients self report cognitive impairment

Why assess cognitive function?

- 3 broad goals:
 - Diagnose
 - Understand nature of deficit or injury & its impact
 - Measure change in function over time

How is NCF assessed?

- Self-report questionnaires
- OR
- Standardised neuropsychological tests:
 - Link performance on task to specific cognitive domains
 - administered to specific groups of individuals
 - data generated used to develop normative data ("norms")

Self-Report Questionnaire

Below is a list of statements that other people with your condition have said are important. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

<u>PERCEIVED COGNITIVE IMPAIRMENTS</u>	Never	About once a week	Two to three times a week	Nearly every day	Several times a day
I have had trouble forming thoughts	0	1	2	3	4
My thinking has been slow	0	1	2	3	4
I have had trouble concentrating	0	1	2	3	4
I have had trouble finding my way to a familiar place	0	1	2	3	4

Objective Assessment

- Hopkins Verbal Learning Test:
 - Memory – immediate
 - Memory – delayed
 - Learning

Neuropsychological (NP) Performance

15-60% have NP impairment on formal testing after chemotherapy (CTh)

Variability in incidence:

- Treatment received
- Timing of assessments
- Definition - cognitive impairment
- What NP tests are used
- Study design
- How it is analysed

Cognitive Impairment

Affects subgroup of cancer survivors

Subtle

Subcortical impairment

Cognitive domains:

- Working memory
- Executive function – multi-tasking
- Information and processing speed
- Memory retrieval

Duration of Impairment

Ahles et al. (*J Clin Oncol* 20:485-93, 2002)

BC and lymphoma survivors : >5 yrs post dx
71 chemo vs 57 local Rx:
Cognitive impairment: 39% vs 14% (p < 0.04)

Schagen et al: (*Cancer* 85:640-50, 1999)

39 BC survivors – CMF
34 BC survivors - No chemo
Cognitive impairment:
2 yrs post dx: 28% vs 12% (OR 6.4, p=0.013)
Follow up at 4 yrs: no difference *Ann Oncol* 13:1387-97, 2002

Prospective Longitudinal Cognitive Studies

Jenkins et al. *Br J Cancer* 94:828-34, 2006

85 BC Chemo
43 BC No chemo –hormones/RTh
49 Non-cancer
Baseline (pre chemo), 6 mths, 18 mths
After accounting for age, education and IQ – no difference
Greater decline on multiple measures:
trend in cancer vs non-cancer groups - not age related
more likely if CTh-induced menopause

Hermelink et al. *Cancer* 109:1905-13, 2007

101 BC before neoadjuvant chemo (EC/T) and surgery
Pre chemo: 31% cognitive impairment
6 months: Decline 27%, Improved 25%
No assoc with CTh-induced menopause

Pre-CTh Impairment

~30% have cognitive impairment pre chemo

Vardy, Dhillon, Tannock et al: ASCO 2009

CRC - 36% impairment pre chemo:
No difference between pre op and post op patients
No association of NP function with:
fatigue
anxiety/depression
quality of life

Self Reported Cognitive Function

Weak association with NP performance

Vardy, Dhillon, Tannock et al. ASCO 2008:

843 assessments: 420 BC and CRC survivors:

- self reported cognitive impairment (FACT-COG):
33% BC vs 12% CRC (p < 0.001)
- NP impairment:
14% BC vs 22% CRC (p = 0.07)

Self Report: Associations

Weak association of self report with NP test results

- (r = 0.15, p=0.001)

Self reported cognitive function:

moderately strong association with:

- anxiety and depression r = 0.43 (p < 0.0001)
- quality of life r = 0.51 (p < 0.0001)
- fatigue r = 0.48 (p < 0.0001)

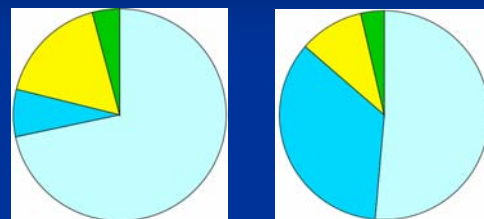
No association between NP performance and:

- anxiety and depression r = -0.02 (p < 0.53)
- quality of life r = 0.11 (p < 0.004)
- fatigue r = 0.04 (p < 0.30)

Self Report and NP Results

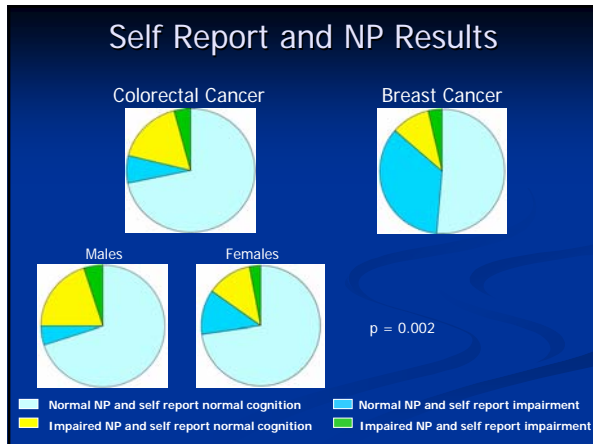
Colorectal Cancer

Breast Cancer



p < 0.0001

■ Normal NP and self report normal cognition
■ Normal NP and self report impairment
■ Impaired NP and self report normal cognition
■ Impaired NP and self report impairment



- ### Potential Causes:
- Direct Neurotoxicity
 - Cytokines
 - Sex Hormones
 - Blood coagulation
 - Genetic predisposition

Neurotoxicity: Rodent Models

Increased chemo across blood brain barrier (BBB):
 Dietrich, Noble et al: *J Biol* 5:22, 2006

- Chemo toxic to some brain cells
 → inc. cell death and less cell division

Winocur, Vardy et al: *Pharmacol Biochem Behav* 85:2006
 Seigers et al: *Behav Brain Res* 186: 2008

- MTX, ± 5-FU vs normal saline – mice/rats
- Chemo mice: impaired memory and ability to learn

Immune Dysregulation: Cytokines

Cytokines cross blood brain barrier & also produced within the brain

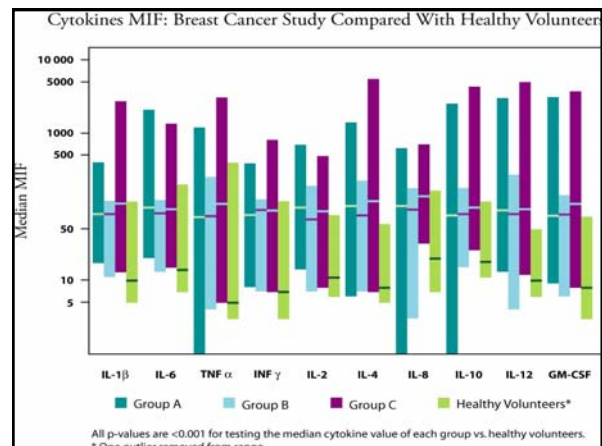
Cytokine therapy (IFN, IL-2):

- cognitive impairment
- fatigue
- ↓ mood

Vardy, Dhillon, Tannock et al, ASCO 2007

Measured 10 cytokines

Elevated in breast and CRC survivors compared to healthy volunteers



Association of Cytokines with NP performance

- Patients with higher cytokine levels had worse cognitive function in BC survivors
- On all 10 cytokines

Causal Relationship? Chemotherapy Studies:

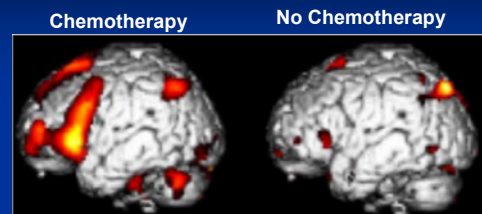
- worse cognitive impairment in cancer survivors who received CTh compared to those who did not
- high dose CTh pts had more impairment than those who received standard dose CTh

Causal Relationship? Brain Imaging Studies:

Structural and functional brain imaging changes in CTh treated survivors:

- changes in grey and white matter
- decreased brain volume

PET scans: Silverman et al



Abnormal activation in inferior frontal cortex in CTh-treated survivors when performing working memory task

Image: Courtesy of Dan Silverman, UCLA

Functional MRI (fMRI)

fMRI: working memory test (e.g. n-back) during scan

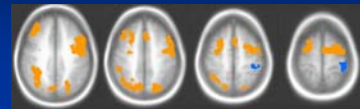
- reflects difference in blood flow at rest and with mental activity

Functional MRI Activation Map

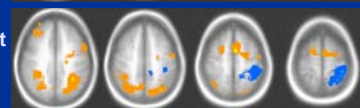
Booth, Vardy, Tannock et al
ASCO 2006

$t > 2.73$, $cl > 226$; mapwise $p < 0.05$

No CTh n=19



CTh - Self report normal n=17



CTh Self report problems n=15



Hormonal Treatment for BC

Ahles, Schagen & Tchen studies:

no difference in cognitive function in BC pts on CTh vs CTh + Tamoxifen

Castellon:

worse cognitive function in those who received tamoxifen after CTh

Shilling:

women on hormonal treatment had specific impairments on verbal memory & info processing tasks vs healthy post menopausal controls

Shilling:

Anastrozole vs placebo as prevention: No difference in NP performance

Interventions for Treating Cognitive Impairment Associated with Cancer?

No high level evidence to recommend any intervention to prevent or treat cognitive impairment in cancer survivors

Medicines that do not work!

- Methylphenidate – 2 studies – both negative
- Erythropoietin – 2 studies –both negative

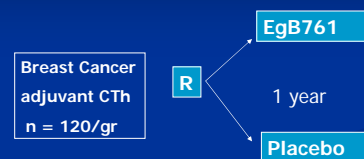
Unproven as yet

- Modafinil
- Ginkgo Biloba
- Other potential agents:
Alzheimer drugs: *Side Effects
Aspirin or Anti-inflammatories

Efficacy and safety of *Ginkgo biloba* for cognitive function and fatigue in breast cancer patients undergoing adjuvant chemotherapy

Janette Vardy
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Andrew Mc Lachlan
Martin Tattersall

Ginkgo Biloba



Assessments: 0 (preCTh), 3, 6, 12, 24 months: NP tests,
Self-report: cognitive, QOL, Fatigue, anxiety/depression
Blood tests: cytokines, sex hormones, clotting factors
fMRI substudy, interactions of Ginkgo - CTh/hormones

Cognitive Behaviour Therapy

Ferguson, Ahles et al *Psychooncology* 16:772-7, 2007

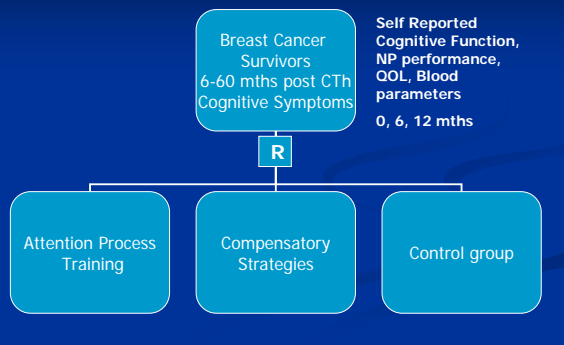
- Single arm pilot study
- Memory & Attention Adaptation Training
- Included education, self-awareness training, self regulation/relaxation, and compensatory strategies
- Improved: self report, NP performance, QOL post intervention, 2 and 6 months

Cognitive Rehabilitation

Focus either on:

1. Restore underlying cognitive function
eg. Attention Process Training
2. Compensatory strategies to cope with underlying impairment

Cognitive Rehabilitation



Evaluation of a Web-based Cognitive Rehabilitation Programme in Cancer Survivors with Self Reported Cognitive Impairment

Victoria Bray
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"Brain Train"

Early stage Cancer Survivors
6-60 mths post Chemo
Cognitive symptoms

30 minute phone consultation - strategies

R

Computer rehabilitation program
- 4x 40 min/week at home
- for 15 weeks

Control Group

Home based intervention and assessments:
NP and self report

Phone: 1800 778 167

Conclusions

Cancer and cancer treatment
→ cognitive impairment – subset of survivors
→ Impact on QOL

Self reported cognitive function:
Weak association with formal NP performance
Moderately strong association with:
fatigue
anxiety and depression
decreased QOL
NP performance is not associated with above

Conclusions

Further research is needed to delineate:

Incidence and duration

Underlying mechanisms: to facilitate intervention trials

Optimal Prevention and Treatment

INTERNATIONAL COGNITION AND



CANCER TASK FORCE



COGNITIVE SYMPOSIA



March 8th - 9th 2010

Memorial Sloan-Kettering
Cancer Center
New York, NY

FOR FURTHER INFORMATION: www.icctf.com

Remember the words?

- Lion
- Emerald
- Horse
- Tent
- Sapphire
- Hotel
- Cave
- Opal
- Tiger
- Pearl
- Cow
- Hut

Next week's lecture

Cancer - another reason to rethink drink

Assoc Prof Tanya Chikritzhs

National Drug Research Institute,
Curtin University of Technology

