Cognitive Effects of Cancer Treatments: State of the Science

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Common Cognitive Problems Reported Post-Treatment

- Memory and Concentration
- Executive Function
- Ability to Learn New Material /Reading Comprehension
- Ability to Work with Numbers
Cognitive Effects of Chemotherapy: Findings Based on Neuropsychological Testing

- Survivor studies found cognitive problems 6 months to 10 years post-treatment (17-75%)
- Longitudinal studies find:
  - 20-25% of patients have cognitive impairment prior to starting adjuvant treatment
  - Persistent cognitive problems identified 15-20% of patients (although some studies found no evidence of impairment and others 60%)
  - 16 of 21 longitudinal studies found evidence of post-treatment cognitive decline
Predisposing Factors: Age and Cognitive Reserve

- Innate and developed cognitive capacity
- Influenced by genetics, education, occupational attainment, life-style
- Higher cognitive reserve has been associated with less change in cognitive functioning following a brain insult or with normal aging
Predictors of Cognitive Decline

(a) WRAT below–median

(b) WRAT above–median

Standardized Change in Processing Speed

Chemotherapy  No Chemotherapy  Control

30–49 year olds  50–59  60–70
Structural MRI (atrophy)

Diffusion tensor imaging (white matter connectivity)

Functional MRI (brain activity)

PET (brain metabolism)

Neuroimaging methods relevant to cognitive changes
Results of MRI, DTI, PET and EEG Studies

- MRI and PET studies suggest that there are changes in brain structure (grey and white matter) and function associated with chemotherapy.

- EEG studies suggest changes in measures of information processing (P300) associated with chemotherapy.
Regions Showing Decreased Gray Matter Density from Baseline to 1 Month Post Chemotherapy

McDonald et al, BCRT, 2010

17 healthy control, 12 local, 18 chemotherapy
(A) Brain activation decrease in CTx+ patients from baseline to M1 with return to baseline levels of hyperactivation at Y1, displayed over atlas template. (B) Activation pattern at left frontal peak displayed in (A) shown graphically for all groups at all time-points. These frontal changes in CTx+ patients overlapped with regions of gray matter change following the same pattern of change over time as illustrated in (C), where brain activation change is shown in yellow, gray matter change is shown in blue, and the intersection of activation and gray matter changes is shown in green.
Decreased prefrontal cortex activity in chemotherapy treated breast cancer survivors compared to survivors not treated with chemotherapy 10 years post-treatment

Potential Integration of fMRI Studies

- Four studies have reported pretreatment over activation in frontal areas as well as other cortical areas.
- Two studies have reported decreased activation 1-month post-chemotherapy with recovery to pre-treatment over activation in one.
- Four studies of long-term survivors show decreased activation.
- Pretreatment over activation is compensatory, but the ability to compensate is lost with age-related change in brain structure and function.
Predisposing Factors: Genetics

- Repair of nerves and blood vessels (APOE)
- Neurotransmitter activity (COMT)
- DNA repair
- Inflammatory response
- Blood brain barrier

Understanding genetic risk factors may lead to tailored treatments which avoid toxicities like cognitive problems
Apolipoprotein E

- APOE -ε4 is a risk factor for Alzheimer’s and has been implicated in cognitive decline associated with cardiac surgery, head trauma, and aging.
- Initial study implicated APOE as a risk factor for lower cognitive performance in long-term survivors.
APOE: Potential Mechanisms

- Reduction in microvascular or neuronal repair processes associated with the APOE-ε4 allele
- Cognitive effects of APOE may be modified by smoking history
- Smoking may correct for a deficit in nicotinic receptors density / dopamine levels in APOE-ε4 carriers
Catechol-o-Methyl Transferase (COMT)

- Individual homozygous for the Val allele have lower levels of dopamine in frontal cortex due to higher rates of post synaptic metabolism.
- Small et al. found that COMT-Val allele carriers who were treated with chemotherapy performed more poorly on tests of attention, verbal fluency and motor speed as compared to COMT-Met homozygotes. (Small et al., Cancer 117: 1369-1376, 2011)
Implications

- Points to potential molecular mechanisms of cognitive changes associated with chemotherapy
- Implicates neurotransmitter systems as involved in chemotherapy-induced cognitive change
- May lead to the development of targeted treatments designed to prevent chemotherapy-induced cognitive changes (e.g., nicotine patch?)
- Animal studies demonstrating that Fluoxetine prevents deficits in behavior and hippocampal function associated with 5-FU
Animal Studies

- Deficits on learning and memory tasks following administration of chemotherapy
- Disruption of hippocampal neurogenesis even at doses that are ineffective for killing cancer cells
- Acute and delayed damage to white matter tracks associated with 5-FU
- Many of these effects can be blocked with various anti-oxidants
Effects of neuroprotectants on chemotherapy-induced changes in neurogenesis

BrdU positive cells per DG

- vehicle
- DOX + CP
- DOX + CP EBSELEN
- DOX + CP lox inhibitor MK-886
- DOX + CP Cox inhibitor NIMESULIDE
- DOX + CP B-oh-toluene

Control
Negative control
DCE
DCMK
DCN
DCB
Biology of Aging and the Impact of Cancer Treatments

- Accumulation of DNA damage
- Shortening of telomeres
- Chronic inflammation
- Increased oxidative stress
- Depletion of stem cell reserve
Aging and the Brain

- Volume reduction
- Decrease in white matter integrity
- Decrease in vascularization
- Decrease in neurotransmitter activity
Cognitive Function in Breast Cancer Survivors 20 Years After Chemotherapy

- Case-Cohort Study
- Breast cancer survivors who received adjuvant cyclophosphamide, methotrexate, and fluorouracil (CMF)
- Health controls
- Battery of 7 neuropsychological & psychological tests
- One timepoint

Survivors of breast cancer exposed to chemotherapy performed similar or worse when compared to the healthy control group

Koppelmans et al, J Clin Oncol, 2011
Chemotherapy and Cognitive Function

Decreased:

- Verbal Memory
- Processing Speed
- Executive Function
- Psychomotor Speed

Koppelemans et al, J Clin Oncol, 2011
Potential Trajectories of Cognitive Function

- **No Cancer**: The trajectory of cognitive dysfunction parallels normal aging.
- **Cancer survivor**: The trajectory of cognitive dysfunction is accelerated in comparison to normal aging.

Phase Shift Hypothesis:
The trajectory of cognitive dysfunction parallels normal aging.

Accelerated Aging Hypothesis:
The trajectory of cognitive dysfunction is accelerated in comparison to normal aging.

*Hurria & Ahles 2012*
Figure 1: Impact of Change in Brain Resources on Cognitive Performance by Age

Cognitive Performance vs. Age

- Low Cognitive Reserve
- High Cognitive Reserve

Brain Resources

Lines a, b, c represent different stages or conditions in the impact of brain resources on cognitive performance.

High Cognitive Reserve

Low Cognitive Reserve
Future Directions

- Potentially multiple mechanisms for cancer- and cancer-treatment related cognitive changes
- Risk for cognitive problems is likely the interaction of vulnerability factors (including age, cognitive reserve, genetics, life-style, environmental exposures) and specific treatments
- The biology of cancer and the impact of cancer treatments are linked to the biology of aging
- Critical to study the impact of cancer and cancer treatments on the trajectory of cognitive change in older, long-term cancer survivors
Collaborators

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