Cognitive Dysfunction Associated with Cancer and Cancer-Therapy

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Cancer and Cognition

• Background
  – Epidemiology
  – Phenomenology
  – Impact
  – Mechanisms

• Methodology
  – Patient Population
  – Measurement tools
  – Measuring change
  – Outcome selection and trial design

• Clinical trial examples
Epidemiology & Phenomenology

• Cognitive dysfunction is ubiquitous in brain tumor patients
  – 60-100% of primary BT patients, largely dependent on the sensitivity of the test (e.g., 34% MMSE)
  – 90% of brain met patients (correlated with lesion volume not number of mets)

• Profile of Cognitive Impairment
  – Frontal subcortical pattern (location specific cognitive deficits superimposed [e.g., expressive aphasia])
    • Learning and Memory, Attention, Executive Function, Processing Speed
  – Patients with high grade tumors more impaired than patients with low grade tumor

• Disease related symptoms and associated treatments can also adversely affect cognition
  – Seizures and AEDs

Tucha et al., 2000; Gleason et al., 2002; Anderson et al., 1990; Klein et al., 2003
Radiation: Normal Tissue Toxicity

Micro Hemorrhages

Fig 1. Percentage of patients with meaningful declines in cognitive function despite stable disease after radiation and chemotherapy (mean, 8 months; n = 64).

Lupo et al., IJROBP, 2011; Meyers., JCO, 2006
Chemotherapy-Related Changes in Cognition and Brain

Women with breast cancer

Decreased GM density:
- Bifrontal, temp, cblm, R thalamus

Decreased FA:
- Parietal corona radiata, parietal superior longitudinal fasciculus, frontal SLF, and forceps major

Correlation between declines in learning and memory and frontal SLF, and, declines in working memory and parietal SLF

Monozygotic twins, discordant for BC

Decreased GM density:
- Bifrontal, temp, cblm, R thalamus

Graph showing changes in MEM, EF, PS, and ATTN for BC and HC.

Wefel et al., Cancer, 2004 & 2010; Ferguson et al., JCO, 2007; McDonald et al., BCRT, 2010; Deprez et al., JCO, 2012
MECHANISMS
Radiation (RT): Impaired Neurogenesis

[...excitotoxicity, vascular effects...]

Cell fate: 97% reduction in newborn neurons after 2 months (NeuN, Tuj-1), with relative sparing of astrocytes (GFAP) and oligodendrocytes (NG2). Increase in microglial activation (IB-4, ED-1)

RT: apoptosis, cell proliferation, neuronal differentiation in hippocampus

Microglial inflammation→ cytokines→ inhospitable microenvironment to make new neurons

- In vitro: Irradiated NPCs differentiated into neurons
- In vivo: non-irradiated NPCs transplanted into dentate gyrus 1 month after RT showed 81% reduction in differentiation into neurons

BrdU x 6d

1 mo 2 mo

Proliferation: 38 – 52% reduction in newborn cells in the irradiated GCL

Monje et al., *Nature Medicine*, 2002
Chemotherapy: Demyelination

Marked and prolonged increase of cell death in the 5-FU treatment group

Toxicity to nondividing oligodendrocytes and lineage-committed progenitor cells (O-2A)

Suppressed proliferation with delayed effects - not associated with inflammation/vascular damage
Preclinical Interventions: Translational Science Opportunities

- Sprague-Dawley rats
  - SAL: saline
  - AC: adriamycin and cyclophosphamide
  - AC+N: AC with ANTIOXIDANT

- Passive avoidance test to assess short term memory

- ANTIOXIDANT prevented memory loss associated with chemotherapy

Konat et al., 2008
Cognitive Dysfunction: Impact

- Cognitive testing = direct assessment of patient clinical benefit
  - Critical for occupational/scholastic success, familial and social well-being, independence and QOL
  - Brain tumor and treatment directly impact brain/neurocognitive function

- Associated with other outcomes/endpoints of interest:
  - Predictive of survival\(^1,2\)

1: RTOG 0525; 2: Levin et al, 2002;
Cognitive Function Predicts Survival

• N=91 GBM, 54+/−12 years old, median KPS=90, 50% left hemisphere, 21+/−3 days post op

• After adjusting for age, KPS, time from resection: Kaplan-Meier plot of survival by impairment on (a) COWA p=0.0029, (b) Digit Span p=0.0003, (c) Similarities p<0.0001, and (d) TMTB p<0.0001

<table>
<thead>
<tr>
<th>Test</th>
<th>As a Continuous Variable</th>
<th>Dichotomized by Impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P-value</td>
</tr>
<tr>
<td>FMTA</td>
<td>0.1660</td>
<td>2.13 (1.17, 3.78)</td>
</tr>
<tr>
<td>FMTB</td>
<td>0.0464</td>
<td>2.82 (1.48, 5.50)</td>
</tr>
<tr>
<td>Digit Span</td>
<td>0.4559</td>
<td>3.83 (1.74, 7.75)</td>
</tr>
<tr>
<td>Digit Symbol</td>
<td>0.2009</td>
<td>1.52 (0.77, 2.86)</td>
</tr>
<tr>
<td>Block Design</td>
<td>0.7763</td>
<td>1.13 (0.53, 2.24)</td>
</tr>
<tr>
<td>Similarities</td>
<td>0.0685</td>
<td>5.22 (1.66, 13.90)</td>
</tr>
<tr>
<td>Naming</td>
<td>0.2688</td>
<td>1.49 (0.70, 3.01)</td>
</tr>
<tr>
<td>COWA</td>
<td>0.0040</td>
<td>2.47 (1.34, 4.53)</td>
</tr>
<tr>
<td>foken</td>
<td>0.2246</td>
<td>2.80 (1.23, 5.96)</td>
</tr>
<tr>
<td>HVLT-TR</td>
<td>0.0773</td>
<td>1.30 (0.71, 1.41)</td>
</tr>
<tr>
<td>HVLT-R DR</td>
<td>0.0182</td>
<td>4.80 (1.16, 23.27)</td>
</tr>
<tr>
<td>HVLT-R RECOG</td>
<td>0.0251</td>
<td>1.98 (0.76, 5.53)</td>
</tr>
<tr>
<td>Strip Strength</td>
<td>0.7115</td>
<td>0.99 (0.38, 2.27)</td>
</tr>
<tr>
<td>CTB-COMP</td>
<td>0.0073</td>
<td>4.23 (1.12, 18.67)</td>
</tr>
</tbody>
</table>

• Kaplan-Meier plots of survival by number of impaired tests (COWA, Digit Span, Similarities, TMTB)

Johnson et al., Neuro-Onc, 2012
Cognitive Dysfunction: Impact

- Cognitive testing = direct assessment of patient clinical benefit
  - Critical for occupational/scholastic success, familial and social well-being, independence and QOL
  - Brain tumor and treatment directly impact brain/neurocognitive function

- Associated with other outcomes/endpoints of interest:
  - Predictive of survival\(^1,2\)
  - NCF decline can occur in advance of imaging evidence of progressive disease\(^3\)

Median Time to Decline/Progress

- Cognition: 7.4 weeks
- MRI: 13.4 weeks
- ADL: 43.0 weeks
- QOL: not achieved

Cognitive Dysfunction: Impact

- Cognitive testing = direct assessment of patient clinical benefit
  - Critical for occupational/scholastic success, familial and social well-being, independence and QOL
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- Associated with other outcomes/endpoints of interest:
  - Predictive of survival
  - NCF decline can occur in advance of imaging evidence of progressive disease
  - NCF is a critical determinant of HRQOL
  - NCF decline is associated with and precedes decline in IADLs, HRQOL and functional independence

Cognitive Dysfunction: Impact

- Patients with brain mets treated with WBRT
- Evaluation schedule: Cognitive testing, QOL, ADL, MRI, Neurologic exam
  - Baseline, 1, 2, 3, 4, 5, 6, q3 months until death

- **45 out of 56 correlations** between NCF and QOL, functional independence (Barthel ADL) and Karnofsky Performance Status (KPS) (at baseline) were statistically significant at baseline, 4 months and 6 months

- **NCF predicted subsequent declines** in functional independence and QOL
  
  \[ T_{\text{net}} = \frac{N_{\text{lead}}}{N} \cdot T_{\text{lead}} - \frac{N_{\text{lag}}}{N} \cdot T_{\text{lag}} \]

- On **15 out of 16 comparisons** between NCF tests and ADLs or QOL, more patients had a lead time

- On **13 out of 16 comparisons** between NCF tests and ADLs or QOL, net lead time was greater for NCF tests (56-153 days)

- **Memory tests showed the greatest lead time** – indicating that memory decline is the earliest sign of functional deterioration (153 days before ADLs, 82 days before QOL)

Li et al, IJROBP 2008
Methods: Cognition in Cancer Trials

• Assessing cognitive function in oncology clinical trials
  – Patient Population
  – Measurement tools
  – Measuring change
  – Outcome selection and trial design
General Issues to Consider in Oncology

- Course of AE (acute vs delayed vs acute and delayed vs delayed) – e.g., surgery vs radiation

- In some cancers the symptom trial will necessarily occur during the active treatment phase (SOC and/or experimental)
  - Ensure symptom intervention does not adversely impact oncologic outcome

- Assessment of cognition not as familiar as it is in other neurologic diseases
  - Investigator buy in and test administrator training (“rater” training)

- Frequent re-evaluation may be required given disease course in glioblastoma and mets with median survival times of 16 and 4 months, respectively
  - Practice effects, alternate/equivalent forms

- Heterogeneous lesion location – impact on sensitivity of outcome measure

- Confounders: edema/steroids, seizure/AED, treatment induced menopause, changing meds (chemotherapy) with new and often unknown cognitive side effects....

- Mechanistic pathways for the neurotoxicity often unknown
  - AEs tend to increase as dose increases. Dose finding studies to establish MTD/SOC do not assess cognition. Thus, often unknown how dose modifications (reductions) will impact cognition.
Considerations in the selection of target population when cognitive deficit may be present before treatment?

- Select those with cognitive complaint?
  - Agreement between objective and PRO?
- Select those with cognitive impairment?
  - Norm based?
- Select those with cognitive change?
  - Longitudinal assessment?
- SWOG: PSYCHOSTIMULANT to treat women with breast cancer that experienced cognitive decline and fatigue associated with chemotherapy
  - Pretreatment cognitive dysfunction ≈ 30% requiring longitudinal “screening” (pre and post chemo testing)
  - Multiple outcomes (cognition, fatigue/co-primary versus 1° and 2°) required patients to meet multiple eligibility criteria (presence of both AEs versus one, severity of the AEs, etc)
  - Different response times to PSYCHOSTIMULANT (cognition may be more rapid than fatigue)? Different dose? Different duration of treatment?
  - Different response criteria (RCI versus MID) – equivalence?
  - Limited preliminary data with both outcomes = power and SAP issues

Challenges in the absence of a pretreatment test
- Case 1: False Negative
- Case 2: True Positive
- Case 3: False Positive
Methods: Measurement Tools

• Measurement Tool(s)
  – Objective vs Subjective
  – Cognitive Test vs Screening Measure
  – Traditional vs Technology-based

• Choice of cognitive domains
  – e.g., Radiation – Memory
  – Global cognitive function
    • Composite variable (CTB COMP)
    • Time To Event with individual tests

• Characteristics of a clinical trial battery
  – Objective, Standardized
  – Reliable and Valid
  – Brief, Repeatable
  – Simple to administer by trained staff
  – Few/no ceiling and floor effects
  – Amenable to international applications
  – Normative data / Contextual info

• Clinical Trial Battery in Neuro-Oncology
  – HVLT-R (MATRICS)
  – TMT (MATRICS)
  – COWA
  • Response Assessment in Neuro-Oncology (RANO)
  • International Cognition and Cancer Task Force (ICCTF)
  • Cooperative group, Consortia & Industry trials

• Computerized Tests
  – CogState, CDR, CNS Vital Signs...
  – ? > Internationally friendly
  – ? > amenable to high freq re-eval
Methods: Measuring Change

• Stability vs Improvement
  – Maintain cognition in the face of a progressive neurodegenerative condition (e.g., brain tumor / radiation model)
    • Fixed deficits in patients with “focal” lesions
  – Improve treatment induced cognition decline (e.g., chemotherapy-related cognitive decline)

• Reliable Change Index
  – Frequently used to categorize changes in performance
  – “Clinically” significant criterion standard

• Statistical significance versus clinical significance? (See RCI....)
  – Given the early sensitivity of cognitive tests relative to functional measures (ADLs) and the generally poor relationship between objective cognitive tests and subjective measures of patient function (e.g., HRQOL - - “response shift”), is a functional correlate necessary?
“Net clinical benefit” includes beneficial effects on disease related symptoms and/or quality of life

- Improvement in length of survival may come at significant costs for the patient
- Treatments that have equivalent OS, PFS, OR may have differential net clinical benefit (e.g., more or less neurocognitive dysfunction)
- “Clinical Benefit” (for the patient) is **not** determined by imaging or survival alone.
  “Radiological response alone is not acceptable for approval. However, improvement in neurocognitive function or delay in neurocognitive progression are acceptable endpoints” (FDA, Minutes of end-of-phase II meeting, 10/21/98)

Potential Composite Endpoint in Brain Tumor trials – how to do the math?:

- Neurologic Stability
- Neurocognitive Stability
- Radiographic Stability
What if the oncologic and cognitive outcomes are discrepant—e.g., better tumor control but worse cognition?

RTOG 0214: Phase III Comparison of Prophylactic Cranial Irradiation Versus Observation in Patients With Locally Advanced Non–Small-Cell Lung Cancer

- PCI had no impact on OS or PFS, but was associated with improved CNS control
- Despite PCI conferring better CNS control, PCI was associated with significantly more frequent deterioration in memory at 3, 6 and 12 months
- NCF testing with the HVLT was more sensitive than the MMSE or QOL
- No between arm differences on MMSE or QOL (with the exception of the MMSE at 3 months)

<table>
<thead>
<tr>
<th>Component by Time Point</th>
<th>PCI Deterioration</th>
<th>PCI No Deterioration</th>
<th>Observation Deterioration</th>
<th>Observation No Deterioration</th>
<th>P*</th>
<th>Adjusted P†</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
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<tr>
<td><strong>3 months</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recall</td>
<td>28</td>
<td>45</td>
<td>34</td>
<td>55</td>
<td>10</td>
<td>13</td>
</tr>
<tr>
<td>Delayed recall</td>
<td>25</td>
<td>44</td>
<td>32</td>
<td>56</td>
<td>7</td>
<td>10</td>
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<tr>
<td><strong>6 months</strong></td>
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<tr>
<td>Recall</td>
<td>11</td>
<td>19</td>
<td>46</td>
<td>81</td>
<td>3</td>
<td>5</td>
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<tr>
<td>Delayed recall</td>
<td>8</td>
<td>15</td>
<td>44</td>
<td>85</td>
<td>8</td>
<td>14</td>
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<td><strong>12 months</strong></td>
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<tr>
<td>Recall</td>
<td>10</td>
<td>26</td>
<td>28</td>
<td>74</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Delayed recall</td>
<td>10</td>
<td>32</td>
<td>21</td>
<td>68</td>
<td>2</td>
<td>5</td>
</tr>
</tbody>
</table>

*From two-sample proportional test statistic comparing the percentage of people who deteriorated since baseline.
†Adjusted using the Hommel’s method; adjustment is made within time point.

Sun et al., JCO, 2011
NMDA Receptor Antagonist for the Prevention of Cognitive Dysfunction in Patients with Brain Metastases Receiving Whole-Brain Radiotherapy (WBRT): Report of RTOG 0614, a Placebo-Controlled, Double-Blind, Randomized Trial

Jeffrey Wefel; Stephanie Shook; Paul Brown; Nadia Laack; Ali Choucair; John Suh; David Roberge; Vivek Kavadi; Minesh Mehta; Deborah Watkins-Bruner
At 2 months, patients with radiographic progressive disease (PD) demonstrated greater decline on all tests compared to patients with partial response (PR). Memory decline in patients with PR suggest WBRT still has an adverse effect on memory.

At 4 months after RT, 60% of patients experience declines in >=1 cognitive domain.
RTOG 0614: Schema and Assessment Schedule

WBRT: 37.5 Gy (15 Fx of 2.5 Gy)

20mg MEDICINE Daily x 24 weeks
(<3 days RT, thru PD)

Placebo Daily x 24 weeks

Stratify:
- RPA Class*
- Prior Surgery**

* RPA Class I vs. II: stable systemic disease for last 3 months
** None vs. radiosurgery or surgical resection within 14-56 days of randomization

Baseline
CTB***
MMSE
FACT-BR
MOS-CF
MRI/CT

Week 8
CTB
MMSE
FACT-BR
MOS-CF
MRI/CT

Week 16
CTB
MMSE
FACT-BR
MOS-CF
MRI/CT

Week 24
CTB
MMSE
FACT-BR
MOS-CF
MRI/CT

Week 52
CTB
MMSE
FACT-BR
MOS-CF
MRI/CT

*** Clinical Trial Battery (CTB) = Hopkins Verbal Learning Test-Revised, Trail Making Test, Controlled Oral Word Association

Placebo Daily x 24 weeks

<table>
<thead>
<tr>
<th></th>
<th>Daily AM</th>
<th>Daily PM</th>
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</thead>
<tbody>
<tr>
<td>Wk 1</td>
<td>5 mg</td>
<td>None</td>
</tr>
<tr>
<td>Wk 2</td>
<td>5 mg</td>
<td>5 mg</td>
</tr>
<tr>
<td>Wk 3</td>
<td>10 mg</td>
<td>5 mg</td>
</tr>
<tr>
<td>Wk 4-24</td>
<td>10 mg</td>
<td>10 mg</td>
</tr>
</tbody>
</table>

Wefel et al., SNO, 2010
RTOG 0614: Objectives

• **Primary Objective**  
  – Determine whether MEDICINE preserves memory as measured by the HVLT-R Delayed Recall over that of placebo at 24 weeks

• **Secondary Objectives**  
  – Time to cognitive decline  
  – Change in cognition at all other time points  
  – PFS  
  – OS  
  – Toxicity by CTCAE 3.0  
  – QOL  
  – Translational studies
RTOG 0614: Overall and Progression Free Survival

- Median follow up (for those still alive at time of analysis) = 12.4 mos

OS

PFS

Wefel et al., SNO, 2010
Primary Outcome

- $\alpha=0.025$, one-sided Wilcoxon rank sum test
- 80% statistical power to detect a mean difference of 0.87 at week 24 in the HVLT-R DR
- Requires 221 analyzable patients per arm
- Assume 20% attrition (death or missing), N=536 patients

“Given the small sample of analyzable (n=149) and evaluable (n=280) patients at week 24, statistical tests are underpowered, 35% and 59%, respectively to detect treatment differences.”

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>8 weeks</th>
<th>16 weeks</th>
<th>24 weeks</th>
<th>52 weeks</th>
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</thead>
<tbody>
<tr>
<td><strong>Evaluable patients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Analyzable</strong></td>
<td>497</td>
<td>451</td>
<td>346</td>
<td>280</td>
<td>182</td>
</tr>
<tr>
<td>470 (95%)</td>
<td>266 (59%)</td>
<td>179 (52%)</td>
<td>149 (53%)</td>
<td>79 (43%)</td>
<td></td>
</tr>
<tr>
<td>27 (5%)</td>
<td>185 (41%)</td>
<td>167 (48%)</td>
<td>131 (47%)</td>
<td>103 (57%)</td>
<td></td>
</tr>
<tr>
<td><strong>Not Analyzable</strong></td>
<td>10 (2%)</td>
<td>1 (0.2%)</td>
<td>1 (0.3%)</td>
<td>1 (0.4%)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>MEDICINE</th>
<th>Placebo</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>HVLT-R DR (SD), median</td>
<td>0.0</td>
<td>-0.9</td>
<td>0.059</td>
</tr>
</tbody>
</table>

Weigel et al., SNO, 2010
RTOG 0614: Time To NCF Decline

- Defined as the first cognitive failure (RCI or 2 SD change) on any cognitive test.
- MEDICINE reduced time to cognitive decline
  - HR=0.78, p=0.001
  - 17% Relative Risk Reduction
- Cognitive decline at 24 weeks was 65% vs 54% (ARR=11%)
  - Number needed to treat= 9
  - $151 for 6 months, generic

http://www.uws.edu/Research/Number_Needed_to_Treat.pdf
There were no statistically significant differences in patient reported quality of life (FACT-Brain) or subjective cognitive function (MOS-Cognitive Function scale).

**FACT-Brain**
- Total Score: $p = 0.8696$

**MOS**
- Score: $p = 0.4419$
In Progress:

- Growth mixture modeling
  - Subgroup identification?

- Genotyping (e.g., APOE, inflammation pathways)
  - Response and risk prediction in multivariate models?
  - Personalized medicine….