Chemo Brain – Is it Real?
What Myeloma Patients Need to Know

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I Left My Head

I left my head somewhere today.
Put it down for just a minute.
Under the table? On a chair?
Wish I were able to say where.
Everything I need is in it!

--- Lilian Moore

Lilian Moore, “I Left My Head” from See My Lovely Poison Ivy (New York: Atheneum, 1975)
Overview

1. General background
   - What factors affect cognition in cancer survivors?

2. Cognitive Function in Multiple Myeloma
   - What we know and don’t know
   - Lessons from blood cancers

3. Brain 101: What can you do for cognitive health?
   - What works and why?
Factors Affecting Cognition

Approximately 30% of newly diagnosed cancer patients have chemo-brain *BEFORE* starting chemotherapy or other cancer treatment
Factors Affecting Cognition

- Aging
- Distress
- Fatigue
- Illness
- Medication

Thought (Rodin 1886-89)
Factors Affecting Cognition

- **Aging**
  - Normal age-related declines in memory and processing speed
  - Some volume loss/neuronal shrinkage in 40’s
  - Accelerated loss not expected until 50’s and beyond
  - Cognitive slowing, but not a decline in ability

- **What’s typical?**
  - More time to recall names and words
  - Multi-tasking becomes more difficult
  - Less attention and retention of detail
Factors Affecting Cognition

Distress

- Numerous studies demonstrate that distress and depression have adverse effects on cognitive function.
  - Depressed and anxious individuals 40% more likely to develop mild cognitive impairment (MCI)

- Adverse effects of transient and chronic stress on
  - attention
  - memory
  - processing speed
  - spatial learning

- Among myeloma patients, estimates of anxiety and depression range from 27% - 40% (related to treatment)

Factors Affecting Cognition

Distress

- Brief periods of distress impair cognition briefly
- Prolonged periods of chronic life stress
  - reduce brain volume in the hippocampus
  - induce neurochemical changes that impair brain plasticity
Factors Affecting Cognition

A diagnosis of cancer initiates a course of stressful events and life challenges.

- Was anyone listening stressed when you were diagnosed?
- ... when you heard about your treatment plan?
- ... when you finished treatment?
Factors Affecting Cognition

Across cancers, younger survivors are more likely to be depressed and anxious than older survivors.

Factors Affecting Cognition

Fatigue

- Associated with anemia
  - 50% of cancer patients have anemia
  - ~73% - 85% of myeloma patients have anemia *
  - demonstrated associations between declines in hemoglobin and declines in cognitive function
  - even mild anemia is a risk factor for executive-function impairment in older adults

Factors Affecting Cognition

- Fatigue may also result from sleep disruption
  - profound effects on daytime attention and concentration
  - disrupts memory consolidation

- Rats scanned while maze learning and again while sleeping that night
  - During sleep their brains showed the same pattern of activity as during learning
  - They were unconsciously cementing what they had learned in their brains while sleeping

Factors Affecting Cognition

Illness

- Cancer alters neurochemicals and hormones that affect cognitive function
- Strong association between cancer and inflammation
  - TNF Alpha, IL-6, IL-8
- Many of the same inflammatory cytokines
  - affect cognition
  - play a role in development of anemia
Factors Affecting Cognition

- Co-morbid illness
  - hypertension
  - cardiovascular disease
  - multiple sclerosis
  - diabetes
Medication

Treatment may have direct or indirect effects

- **cytotoxic agents**
  - platinum based (cisplatin-DPACE)
  - alkylating agents (melphalan, cyclophosphamide)
  - antimetabolites (fludarabine)

- **corticosteroids** (alone or in combo with other drugs)
  - prednisone
  - dexamethasone

- **immunomodulator**
  - lenalidomide
  - thalidomide

- ***proteasome inhibitors***
  - ***Velcade, in contrast, appears be neuroprotective***
Research
Human Studies: Lenalidomide

- Case study: 2 MM patients (41 and 70 yrs.) with acute negative effects of lenalidomide chemotherapy on cognitive function
  - episodic memory
  - activities of daily living
- Symptoms reversible after withdrawal of lenalidomide
- Mechanism unknown
- Lenalidomide neurotoxicity probably exacerbated by several risk factors
  - prior chemotherapy
  - previous mild cognitive impairment
  - cerebrovascular lesions
  - age

Human Studies: Thalidomide-Prednisone

- Stewart, et al. (2013). 2-arm randomized clinical trial w/4 year follow-up after melphalan w/ autologous stem cell transplant
- N = 332 MM patients receiving either
  - thalidomide-prednisone maintenance therapy or observation
- HRQol was a secondary endpoint and cognitive function was measured by domain questions on the EORTC QLQ-C30
- Self-reported cognitive function was worse in the maintenance arm, but there was improvement and decline in both groups

<table>
<thead>
<tr>
<th>Domain</th>
<th>Maintenance</th>
<th>Observation</th>
<th>P</th>
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<tbody>
<tr>
<td>Cognitive</td>
<td>improved</td>
<td>worsened</td>
<td></td>
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<tr>
<td></td>
<td>40 (25%)</td>
<td>85 (54%)</td>
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<tr>
<td>N (%)</td>
<td></td>
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<tr>
<td></td>
<td>55 (37%)</td>
<td>61 (41%)</td>
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Hematopoietic Stem Cell Transplantation


- N = 388 mixed HSCT patients (79% autologous, 63% MM)
- Objective neurocognitive testing before HSCT, at 6 months and 12 months post HSCT.
- some deficits prior to HSCT
- significant improvements between baseline and 6 months
- BUT…there was 70% attrition over time and results may reflect a best case scenario for healthier patients

Scherwath, et al. (2012)

- N = 102 blood cancer patients (~15% MM) assessed pre-HSCT ($T_0$), and at 3 months ($T_1$), and 1 year post-HSCT ($T_2$).
- Before and after HSCT, patients performed below test norms.
- Impairment on $\geq 1/5$ cognitive domains occurred in:
  - 47% of patients before HSCT ($T_0$)
  - 41% of patients 12 months after HSCT ($T_2$)
- From $T_0$ to $T_2$, 16% of the patients showed reliable decline on $\geq 3/14$ test scores for the majority of neurocognitive subtests.
- Substantial differences in perceived cognitive function corresponded to structural and functional differences in brain images.


- N = 53 MM autologous HSCT patients
- Objective neurocognitive testing before HSCT, at 1 month and 3 months post-HSCT.
- 47% with cognitive impairment prior to HSCT (25/53)
- 49% with clinically significant decline 1 month post-HSCT (20/41)
- 48% with further decline at 6 months post-HSCT (14/29)
- Overall, 45% attrition

Autologous Hematopoietic Stem Cell Transplantation

- Risk factors for continued decline are:
  - older age
  - advanced stage disease
  - minority status
  - previous impairment
  - more induction cycles

- Note the difference in assessment times between these 3 studies
What Does it Mean?

- HSCT patients have cognitive deficits prior to transplant.
- Unclear if these are a direct result of induction treatment.
- For most patients, impairments present at 1-3 months following HSCT seem to resolve after 6-12 months.
- A small subset of patients may experience continued mild impairment.
Is Chemo-Brain A Misnomer?

a) Yes

b) No

c) It depends…

✔️ d) All of the above
Chemo Brain?

- It’s a complex issue
  - a subset of patients and survivors probably do have chemo-related cognitive loss.
  - some chemotherapeutic agents may be directly associated with cognitive difficulties

- We can’t rule out
  - pretreatment disease factors
  - inflammatory cytokines
  - anemia
Brain 101
3 Pounds, 100 Billion Neurons → Magic

Lifelong Neuroplasticity
This Is Your Brain

An orchestra performing a symphony

- Conductor: executive function
- Musicians: neurotransmitters → perform cognitive processes
- Instruments: cells and structures
- Sheet music: sensory input
This Is Your Brain’s Prefrontal Cortex

Executive function

- Thought, planning, goal directed behavior, decision
- Observes, directs, coordinates
- Always center stage and performing
instruments need to be structurally sound
undamaged
in tune

musician needs to know
how to play the instrument
read the music
when to play, when to rest
Great musicians and great brains have something in common

What makes a musician great?
- practice & versatility
  - knows lots of music & different genres
  - plays several instruments
  - always striving to improve and grow

What are the fundamentals of neuroplasticity?
- practice & versatility

You can train and grow the instruments and musicians in your brain to help it perform better
Improving Brain Health—
What Can You Do?
What Can You Do?

- Exercise your brain (use it or lose it)
- Your brain is an intellectual!
- It likes complexity & requires challenge
  - solve problems
  - learn new things
  - learn complex tasks
  - practice, practice, practice
What Can You Do?

Personalized practice in critical cognitive tasks to improve fluency and speed

- **Cognitive Remediation Training (CRT)**
  - Supervised remediation by a neuropsychologist

- **Online Cognitive Training Programs**
  - CogniFit Personal Coach
  - Posit Science BrainHQ
  - Lumosity
What Can You Do?

Exercise your body

- reduces fatigue
- increases oxygen to the brain
- increases neurochemicals that support cognitive health
- improves mood
- reduces stress
- reduces risk of dementia
What Can You Do?

- Walk, walk, walk
  - 30 minutes a day
  - 3x a week
  - more is better

Walkers are 25-30% less likely to develop vascular dementia
Socialize: Your brain likes company

- Social support is associated with better cognitive function in the elderly
- Social support protects against cognitive impairment following stroke
- Social support reduces risk of dementia
What Can You Do?

Eat Healthy

- Neurotransmitters need nutritional support
- B6 is essential for memory
- Choline is essential for learning & plasticity
- Omega 3 fatty acids
- Antioxidants
- Calcium
What Can You Do?

- Meditate
  - reduces stress
  - improves sleep
  - some evidence for greater cortical thickness
  - some evidence that it improves immune function
What Can You Do?

Medicate?

- Modafinil
  - improves memory
  - improves verbal working memory
  - does not improve attention

- Medication for depression.
  - increases BDNF
  - improves cognition
  - contraindicated in some patients with some treatments
Ask Your Health Care Providers

- to screen for distress, depression and fatigue
- to either provide OR refer for
  - psychosocial support
  - education on symptom management
  - stress reduction programs
  - cognitive testing

Early intervention targeting symptoms may improve cognitive function.
Take Home Message

Whether or not patients’ reported cognitive difficulties are clinically relevant, they are personally meaningful.

Poster by Irving Sarnoff, PhD, Emeritus Professor of Psychology, NYU
Questions?
Thank you!