Chemo Brain and Fatigue

Chemotherapy Related Cognitive Impairment

Chemotherapy Related Fatigue

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Chemotherapy Related Cognitive Changes

- Attention
- Concentration
- Learning
- Memory
- Information processing
- Language
- Visuospatial skill

Scope of the Issue

- CRCI has been described since the 1970s
- Poorly understood
- Most of the data comes from breast cancer literature
  - 94% of BCS reported significant PCI 1 year following completion of chemotherapy
- 69% of OC survivors reported cognitive decline
- Even minimal impairment can profoundly impact QOL
  - As OS improves, attention to all aspects of QOL become more important

Description of the Experience

- “Walking into a room and forgetting what I was doing”
- Repeating themselves
- Misplacing keys and cell phones
- Names and phone numbers
- Trouble with word finding
- Repeating themselves
- Inability to multitask
- Reading comprehension and staying absorbed in a book
- Tasks taking longer
- Repeating themselves
- Feeling “foggy” and “spacy”

Impact of the Experience

- Depression, anxiety, frustration and embarrassment
- Family tension
- Withdrawing from social activities
- Job security
  - Difficulty returning to work when treatment is done
- Cognitive decline exacerbated by fatigue and stress

Timing of Cognitive Issues

- Wide range
- Sometimes no symptoms until chemotherapy completed
- Many symptoms after 1-2 cycles of chemotherapy
- Some noted improvement between cycles
- Some noted improvement 6-12 months following treatment
    - Some noted no improvement more than a year after chemotherapy

Direct effect of chemotherapy on CNS

- MTX and 5-FU cause progressive damage to myelin
- Minimal data on carboplatin and paclitaxel
  - One study of 28 Ov CA patients showed no EEG changes after 6 cycles of treatment
  - Reduced EEG processing speed 4 years following platinum in breast cancer patients
- Difficult to pinpoint specific chemotherapy agents

Indirect effects of chemotherapy on CNS

- Certain chemotherapeutics cause increased inflammation
  - Cytokine activation linked to:
    - Fatigue, sleep issues, poor concentration
  - Paclitaxel and docetaxel linked to increased levels of IL-6, 8, 10
- Increased free radical formation leads to neuron death
  - Especially in Adriamycin (Doxil)
    - Co-administration with anti-oxidants reversed these effects in mice

Non-treatment Causes

- Studies have shown cognitive decline before initiation of therapy
- Pain, fatigue and anemia
  - All have been shown to result in cognitive decline
- Hormone regulation
  - Increased glucocorticoid levels associated with cognitive decline
    - Dexamethasone for Taxol
  - Estrogen deficiency
    - Breast cancer patients who underwent both chemo and hormonal therapy showed the most deterioration and persistent decline

Official Diagnosis

- Difference in self-reported versus objectively measured
  - Some studies show up to 90% of patients exhibit cognitive decline
  - Some studies show no decline by objective measures
- 17 neuropsychological tests used to assess cognitive function
  - Heterogeneous group makes data interpretation difficult
- Imaging
  - Reduction in brain volume on MRI following chemotherapy in breast cancer
  - Lower resting metabolism on PET imaging of the brain following chemo

GOG Prospective Study

- 231 Ov Ca patients
- Web-based questionnaire/surveys to assess:
  - QOL, depression/anxiety, cognitive function, self-reported cognition
- Assessed before chemo, before C4, after C6, 6 months after chemo
  - Processing speed, motor reaction time and attention
- 25% of patients noted significant impairment in at least one area during chemotherapy
- 17% noted persistent impairment 6 months after finishing
  - No relation noted between QOL scores and cognition
- Does the testing confound the results?

Patient Desires

- Information about possible cognitive decline BEFORE treatment starts
- Information to be shared with family, co-workers and friends
- Acknowledgement of the existence of cognitive decline

Coping Strategies

- Minimal quality research
- Needing to write things down
- Keep items in consistent locations
- Appropriate amounts of rest/sleep
- Structure and organize daily routine
- Relaxation techniques
- Meditation
- Exercise
- Crossword puzzles

Pharmacologic Interventions

- Erythropoietin (EPO)
  - 7 studies done – 3 with significant improvement
  - EPO no longer widely used due to significant risks
- Psychostimulants (Dexmethylphenidate and methylphenidate)
  - 8 published studies – mixed results
  - Minimal improvement in attention, memory
- Donepezil (cholinesterase inhibitor)
  - Two published trials – mixed results

Non-pharmacological Interventions

- Traditional Chinese Medicine
  - RCT of 81 Ov CA patients undergoing chemotherapy (carbo/taxol)
    - TCM consisted of herbs (?)
    - No difference in QOL noted and no difference in cognitive function
  - RCT of Medical Qigong showed improvement in cognition (all cancers)
    - 90 minutes/week for 10 months
    - Increased perceived cognition
  - RCT of Ginko biloba showed no improvement in cognition (all cancers)

Alternative Approaches

- Nature walks (breast cancer data)
  - 120 minutes/week of exposure to nature → improved attention/focus
- Exercise
  - Extensive research showing improvement in cognition
  - Tai Chi
    - 1 hour/week for 10 weeks
    - Improved perceived cognition but minimal objective response
- Cognitive Behavioral Therapy
  - Programs to improve/restore mental function
  - 4 large studies – 3 showed significant improvement in cognitive function
- Fruits and vegetables
  - CRC patients showed improved cognitive function

Cancer Related Fatigue

- Distressing, persistent, subjective sense of physical, emotional or cognitive tiredness/exhaustion related to cancer or therapy
  - Not proportional to recent activity
  - Significantly interferes with normal functioning
  - Not relieved by rest

Causes of Cancer Related Fatigue

- Progressive tumor growth
  - Metastatic disease
- Cancer therapy
  - Chemotherapy, surgery, RT
- Anemia
- Pain
- Emotional distress/depression
- Sleep disturbances
- Poor nutrition
- Medical co-morbidities

Prevalence of CRF

- Majority of patients undergoing treatment experience CRF
  - 75-90% of all patients
- 30% note persistent fatigue years following therapy
- Thought to be underreported
  - ASCO and NCCN recommend regular screening during treatment and surveillance/survivorship
- Most cases are mild-moderate
  - Recommend energy conserving activities

Fatigue Specific to OC

- PARPi
  - Meta-analysis of 9 trials with >2000 patients on olaparib
  - 70% increased risk of severe fatigue
- Study of 318 patients with PFS > 3 years – matched to 318 control
  - 26% vs 13% SLTF
  - Depression, PN, obesity, lack of exercise, sleep disturbances all associated with SLTF – causation or association?

Severe CRF

- Focused history and evaluation
  - Anemia, metabolic disorders, endocrine issues, cardiac/pulmonary
  - Substance abuse, depression, sleep disturbance
- Non-pharmacologic interventions
  - CBT
  - Moderate aerobic exercise 150 min/week and strength training
    - Less fatigue/emotional distress, better sleep and QOL
  - Relaxation/stress reduction techniques, yoga

Pharmacologic Interventions

- Psychostimulants
  - Methylphenidate/dexmethylphenidate
    - Only 2 of 8 RCTs showed an improvement in fatigue scores
  - SSRI – only seem to benefit when fatigue accompanied by depression
- Vitamins – not effective
- Ginseng – beneficial while on treatment
  - Potential interaction with certain chemotherapies

Conclusions

- Cognitive Changes on Chemotherapy
  - It’s real!
  - Hard to officially diagnose but it is common
  - Multifactorial
  - Medication has mixed results
  - Exercise, mind-body techniques, CBT all seem effective
- Chemotherapy-Related Fatigue
  - Very common with a wide range of severity
  - Rule out underlying medical causes
  - Multifactorial
  - Medication has mixed results
  - Exercise, mind-body techniques, CBT all seem effective