Does Adjuvant Chemotherapy for Breast Cancer Cause Cognitive Dysfunction?

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Importance of Understanding Cognitive Deficits Due to Cancer Therapy

- A challenge facing cancer survivors as identified by the National Coalition for Cancer Survivorship
- Negative impact on work/school performance and QOL
- Effect on informed decision-making
- Similar pediatric research resulted in treatment modifications that reduced negative cognitive effects while maintaining treatment efficacy
- Functioning of patients with subtle cognitive deficits improves with cognitive rehabilitation approaches

Predictors of Cognitive Deficits

- Type of chemotherapy?
- Education level and IQ
- Depression
- Co-morbid illness
- History of traumatic brain injury
- History of learning disability
- Genetic variables
- Hormonal factors

Common Cognitive Problems Reported Post-Chemotherapy

- Memory and concentration
- 'Executive' function
  - Short term memory, multi-tasking
- Ability to learn new material /reading comprehension
- Ability to work with numbers

Cognitive Impact of Systemic Chemotherapy

- Wieneke and Deinst (1995)
  - Neuropsychological assessment of 28 breast cancer patients treated with CAF or CMF
  - Assessed cognitive function using formal testing at ~ 6 months following treatment
  - Compared results to population based norms
  - 75% scored below expected levels

Cognitive Function After Adjuvant Chemotherapy

Treatment Arm	N	Cognitive Impairment (%)
Local Therapy	36	9
Standard Dose	36	17
High Dose	34	32

- Patient populations:
  - 4 cycles FEC
  - 4 cycles FEC +STAMP V (cyclophosphamide/thiotepa/carboplatin) with stem cell support
  - Surgery +/- radiation
- Cognitive assessment - 2 years after completion of treatment

van Dam FSAM, et al. *J Natl. Cancer Inst.* 90:210, 1998

Adjuvant Breast Cancer Therapy and Cognition

Treatment Arm	n	Cognitive Impairment (%)	Odds Ratio	*P*-Value
CMF*	39	28	—	—
Controls	34	12	6.4	0.013

- Unaffected by anxiety, depression, fatigue, and time since treatment
- Evaluated a median of 1.9 years after completion of therapy
- No correlation between objective testing and subjective symptoms

* CMF = cyclophosphamide, methotrexate, 5-fluorouracil

Schagen. *Cancer.* 1999;85:640.

Patient assessment of cognitive problems

	CMF		control
Problems with concentration	31%	*p=0.007*	6%
Problems with memory	21%	*p=0.022*	3%
Problems with language	8%	*NS*	3%

Percent of patients who gave score of ≥2 on a 5 point scale

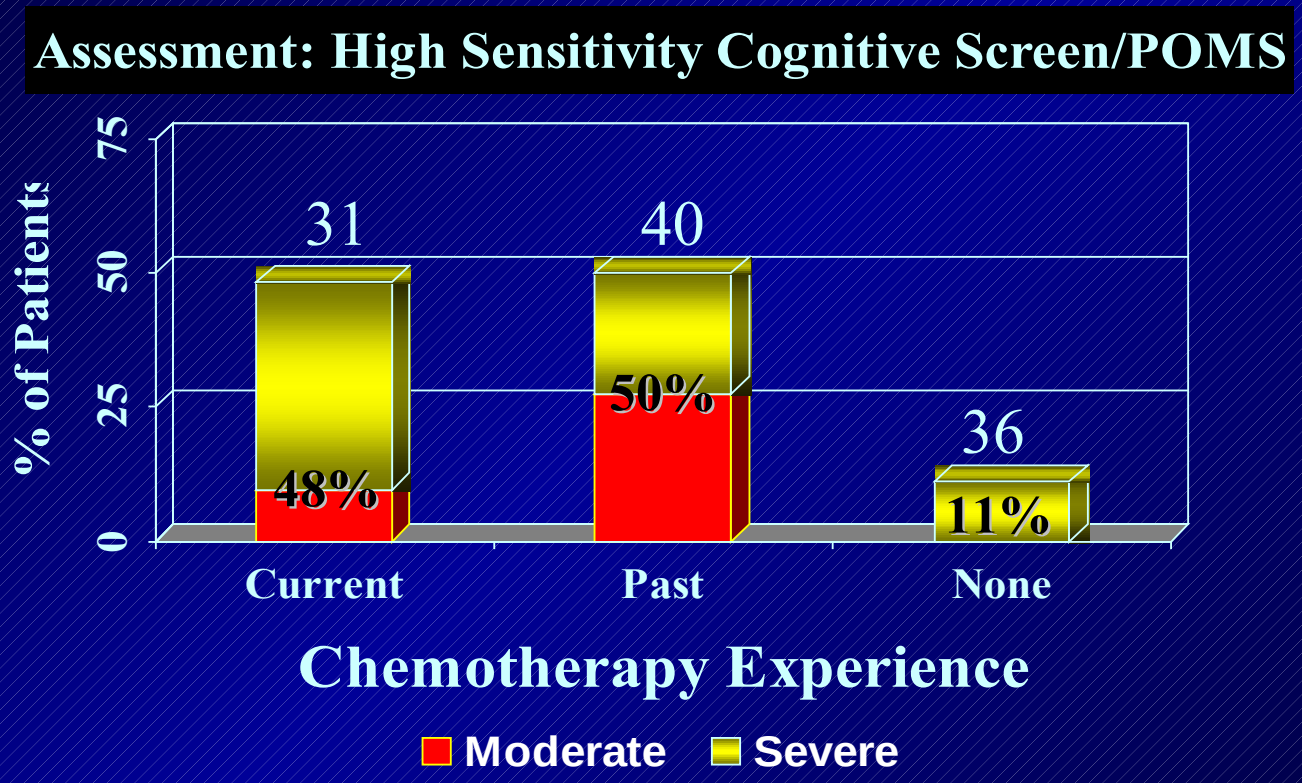
Schagen et al, CANCER 1999

Recovery with Longer Follow-up?

- Additional assessment performed on CMF patients, control patients (and patients who received either FEC or high dose chemotherapy)
- All treatment groups demonstrated improvement in cognitive functioning over time
- Slight deterioration in functioning of control patients

Schagen et al, Annals of Oncology 1387-1397, 2002

Cognitive Impairment in Breast Cancer Patients Receiving Adjuvant Chemotherapy



- Group A: Presently receiving chemotherapy (CMF, CEF; n=31)
- Group B: Completed chemotherapy at least 1 year ago (CMF, CEF; n=40; median time since chemotherapy-2 years)
- Group C: Healthy female controls (n=36)

Brezden et al, *J Clin Onc*, 2000

Dartmouth Long-Term Survivor Study

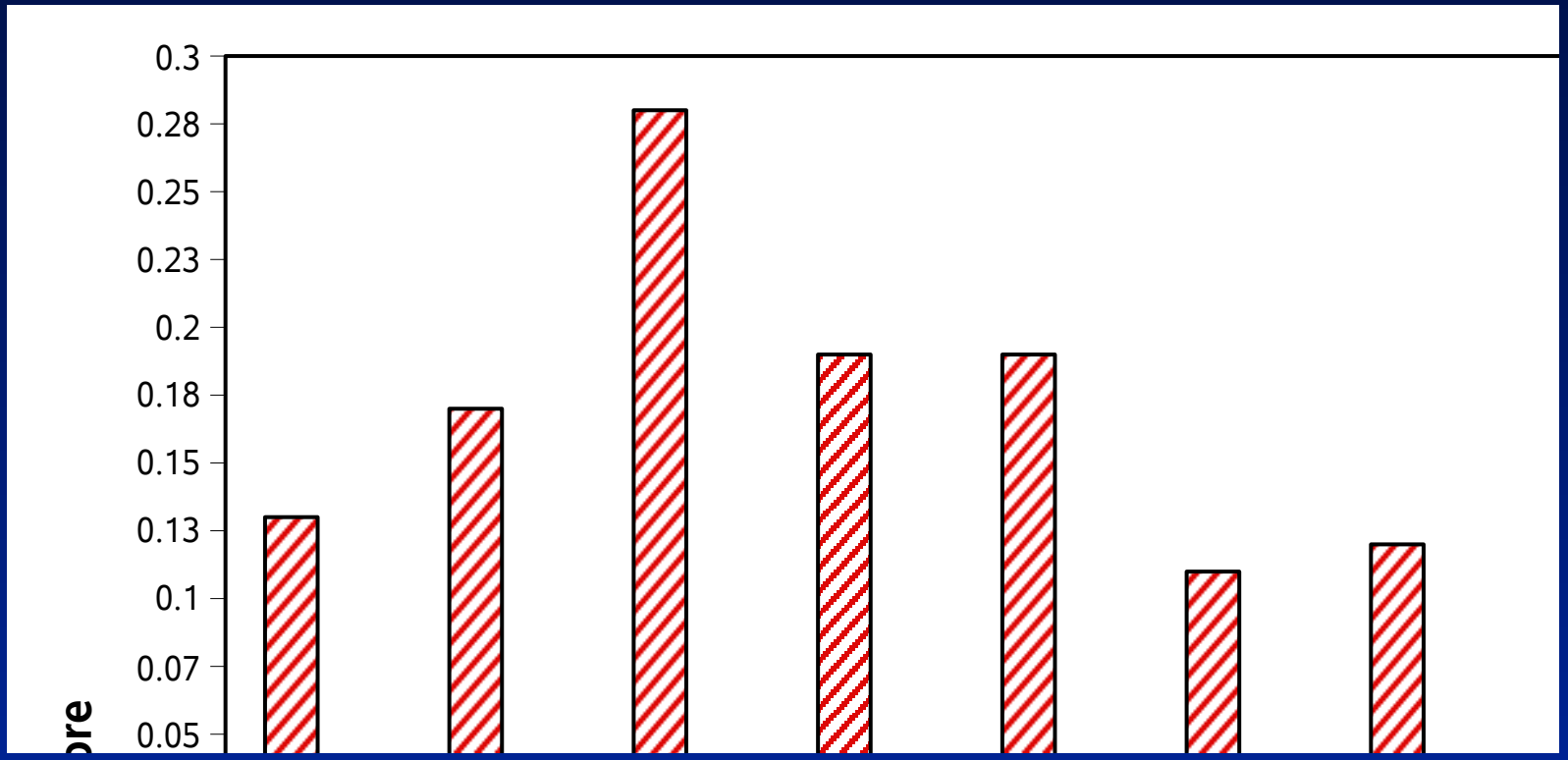
- Patients with a history of breast cancer or lymphoma
  - Minimum of 5 years post diagnosis
  - Completed therapy, free of disease
  - No neurobehavioral risk factors or psychiatric disease
  - Treatment included
    - Standard dose chemotherapy
      - 35 breast cancer
      - 36 lymphoma
    - Surgery and radiation (not CNS)
      - 35 breast
      - 22 lymphoma

Ahles et al, JCO 2002

Percentage of Survivors Treated with Chemotherapy or Local Therapy Scoring in the Low Neuropsychological Performance Range

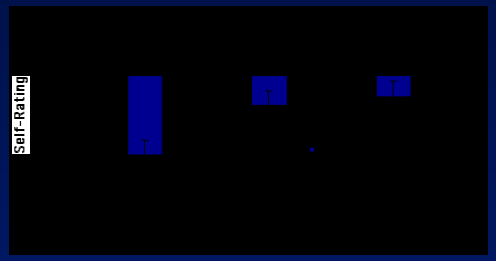
No. Impaired Domains	Chemotherapy	Local Therapy	Chi-square Sig.
3	50%	23%	p = 0.002
4	39%	14%	p = 0.002
5	24%	5%	p = 0.003

Adjusted z-Transformed Domain Scores for the Chemotherapy vs. Local Therapy Groups



*p<.05, adjusted for age and education

Mean Adjusted Squire Memory Subscale Scores



*p≤.05, adjusted for age and education

Summary

- No impact of diagnosis
- Significant differences by multivariate analysis controlled for age and education
  - Battery as a whole
  - Verbal memory
  - Psychomotor function
  - % lower quartile neuropsych performance
  - Self reported problems with working memory

What is the Effect of Diagnosis? Wefel

- 84 women enrolled on therapeutic clinical trials evaluated before adjuvant therapy
  - 35% with cognitive impairment BEFORE start of systemic therapy
    - Verbal learning and memory function
  - Affective distress was related to cognitive impairment

Wefel et al, Cancer 2004

Longitudinal Studies: Bender

- Three groups evaluated (N=46)
  - Chemotherapy (Group 1, 19)
  - Chemotherapy plus tamoxifen (Group 2, 15)
  - DCIS without tamoxifen (Group 3, 12)
- Three time points
  - After surgery, at end of chemotherapy and one year following end of chemotherapy
  - 24 dropped out before T3
- Results
  - Group 1: Deterioration in verbal working memory
  - Group 2: Deterioration in visual memory, verbal working memory, more memory complaints
  - Group 3: Improvement over time (practice effect)
  - Defects generally subtle

Bender et al, Psycho-oncology 2005

Preliminary Results: Shilling

- **Baseline, 6 and 18 month evaluation**
  - 50 chemotherapy patients (plan 100)
  - 43 healthy controls (family members, friends)
- **Data at baseline and 6 months**
  - Significant group by time interaction on three measures of verbal and working memory
- **OR for chemotherapy patients 2.25**
  - Impairment defined as having cognitive decline in 2 or > measures
  - No correlation with psychological and quality of life variables
  - No correlation between self reported cognitive decline and formal testing
- **Study ongoing**

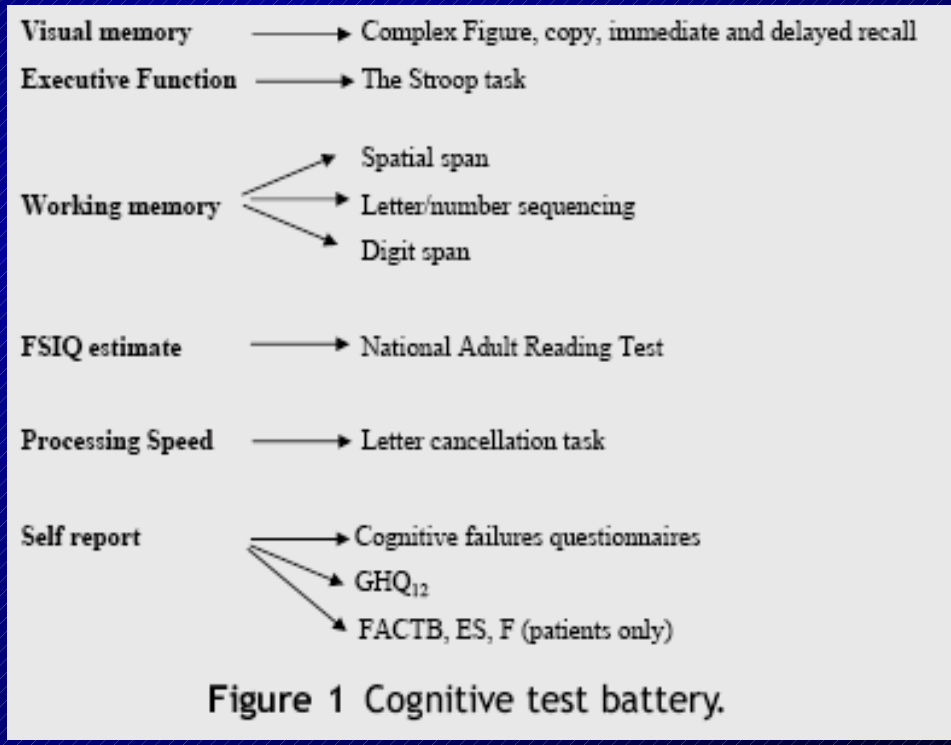


Figure 1 Cognitive test battery.

Shilling et al, Breast 2005

One and Two Year Follow-up of a Prospective Controlled Study: Tchen

- 100 patients with breast cancer receiving adjuvant or neoadjuvant chemotherapy
  - Completed at least 3 courses of chemotherapy
  - Age ≤ 60
  - Fluent in English
- Matched control by age selected by patient from a neighbor, friend or relative
- Evaluation with High Sensitivity Cognitive Screen (HSCS), mini-mental status exam, others, FACT-B, ES, F, blood tests for endocrine status
- Testing at end of chemotherapy, one and two years later

Tchen, N et al, ASCO 2004

Results

- Median age 48
  - 69% premenopausal at diagnosis
  - 71% anthracyline based chemotherapy
- More fatigue than controls

	Patients		Controls		
	N	FACT-F	N	FACT-F	P-value
Baseline	100	31 (22-39)	100	46 (41-49)	<0.0001
Year 1	85	43 (37-48)	79	47 (43-50)	0.0002
Year 2	81	45 (39-49)	80	48 (43-50)	0.012

Results (2)

- More menopausal symptoms at baseline, year 1 and year 2
- Quality of life improved over time
- Cognitive function improved over time as defined by moderate/severe dysfunction by HSCS

	Patients		Controls		
	N	Impaired	N	Impaired	P-value
Baseline	100	16%	100	4%	0.0008
Year 1	85	4%	79	2%	0.06
Year 2	81	3%	80	0%	0.09

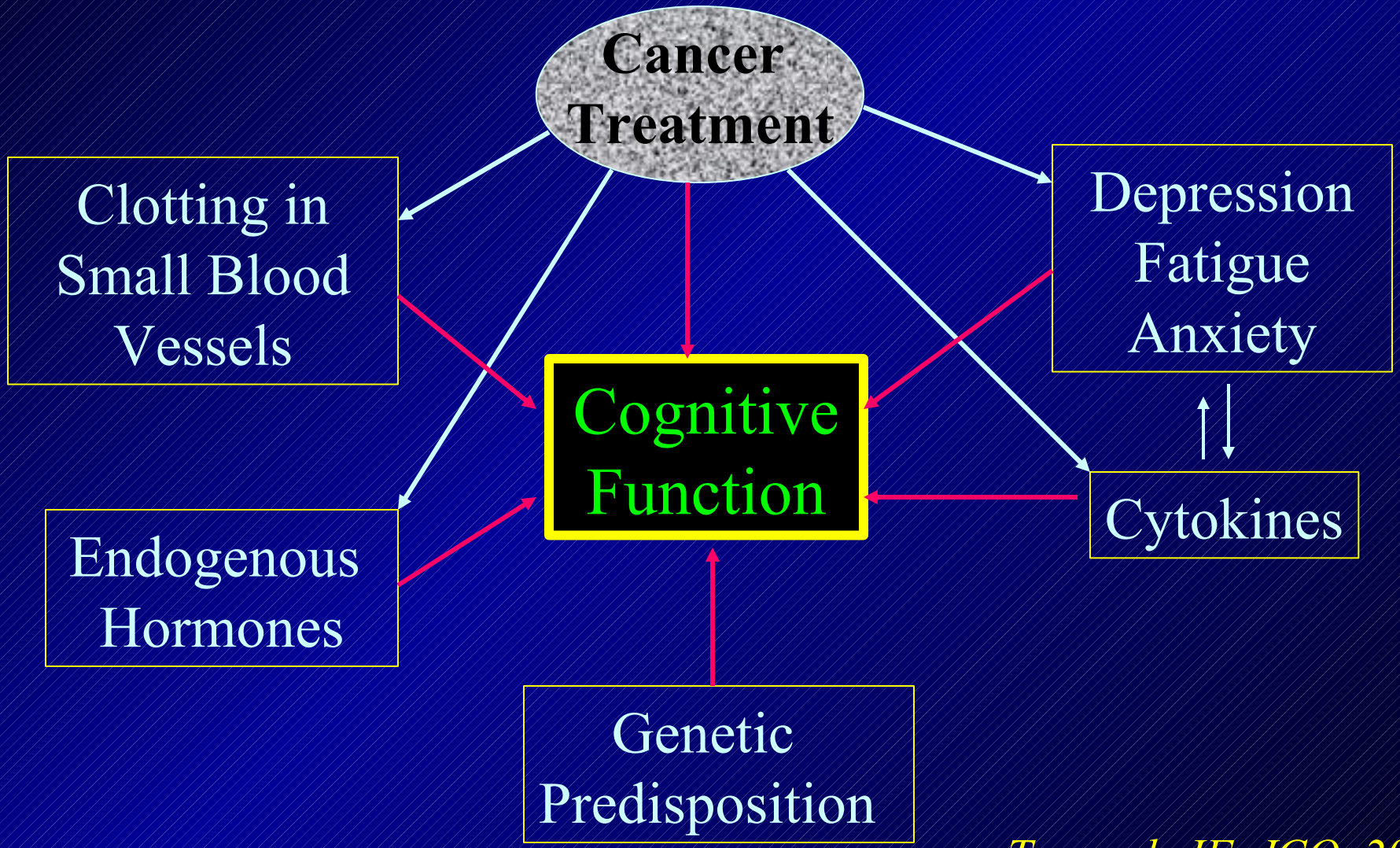
Conclusions

- There was a strong relationship at all time points between:
  - Fatigue and QOL ($p<0.0001$)
  - Menopausal symptoms and QOL ($p<0.0001$)
  - Fatigue and menopausal symptoms ($p<0.0001$)
- Cognitive dysfunction is temporary in most patients
- Fatigue and menopausal symptoms are important side effects of chemotherapy that improve but do not resolve over two years

Summary of Data

- Standard-dose adjuvant breast cancer chemotherapy appears to impair cognitive function in a subset of women
  - There is very little prospective data with flawed controls
  - In the majority of patients, effects appear to resolve over time
- Current testing methods generally do not reflect patient reported symptoms
- Longitudinal assessments will be critical to
  - Determine impact and duration of cognitive function
  - Assess populations at risk
  - Define role of baseline defects in cognition
- Mechanisms?

In Search Of Mechanisms



Tannock, IF, JCO, 2004

Mechanisms

- Possible mechanisms of direct chemotherapy induced cognitive change
  - Direct toxic impact on the brain
  - Byproducts of cytotoxic agents, e.g., free radicals?
  - Injury response: Chemotherapy stimulates central release of neurotoxic cytokines
  - Immune response: Autoimmune mechanisms

Hormones and Cognitive Functioning

- Reduced estrogen and testosterone levels have been associated with cognitive decline
- Chemotherapy and hormonal levels may interact to increase cognitive decline in cancer survivors
- Little data to support an impact of menopause or tamoxifen on cognitive function
- Rapid changes associated with treatment may play a contributory role

Genetic Factors

- APOE -ε4 allele has been implicated in cognitive decline in patients with
  - Cardiac surgery
  - Head trauma
  - Increased age
    - In normals and with associated chronic illnesses
- Is APOE-ε4 a risk factor for cognitive deficits secondary to chemotherapy?

Z-Transformed Domain Means by APOE Status: Long-term Follow-up Study at Dartmouth in 80 Breast and Lymphoma Survivors

Domains	APOE E4 Positive	APOE E4 Negative	p value*
	Mean (SD)	Mean (SD)	
Visual Memory	**-0.30 (1.12)**	**0.04 (0.81)**	**0.03**
Spatial Ability	**-0.38 (1.17)**	**-0.13 (0.97)**	**0.05**
Psychomotor Function	**-0.24 (0.80)**	**0.05 (0.66)**	**0.08**
Verbal Ability	0.10 (0.68)	-0.16 (0.86)	0.83
Verbal Learning	-0.20 (1.16)	-0.03 (0.94)	0.48
Verbal Memory	0.21 (0.90)	-0.15 (0.89)	0.21
Motor Functioning	-0.01 (0.72)	-0.11 (0.73)	0.93
Attention CR	-0.14 (0.97)	-0.01 (0.87)	0.33
Attention RT	-0.19 (0.69)	-0.05 (0.67)	0.30

*Controlling for age, gender, education, diagnosis, and WRAT-R (reading subset)

Ahles et al, Psycho-oncology, 2003

Potential Mechanisms

- Reduction in microvascular or neuronal repair processes associated with the APOE -ε4 allele
- Pre-existing morphologic differences (e.g., smaller hippocampal volume) associated with the APOE -ε4 allele

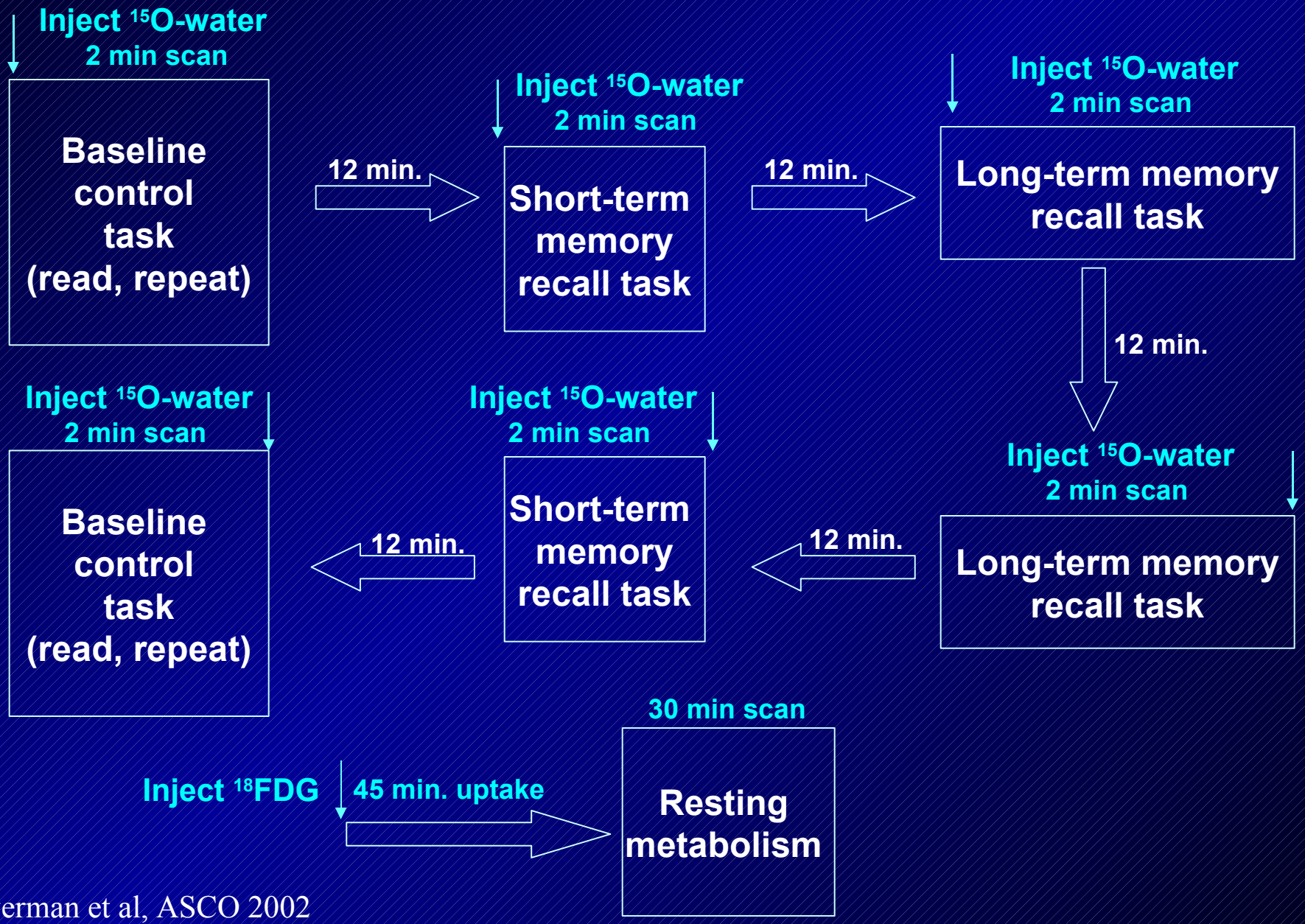
Methods of Testing

- **Formal neuropsychiatric testing evaluates common domains**
  - **Verbal Ability, verbal learning and memory (speed of information processing), visual memory, spatial functioning, psychomotor functioning, attention/concentration, executive (frontal) functioning motor function and coordination**
  - **QOL self-report measures include global quality of life, depression, anxiety, memory and fatigue**
- **Requires expertise to administer test, ~ 2 hours testing time**

Methods of Testing (2)

- **Newer computerized testing methods**
  - **Easy to administer, short testing time**
  - **Provide global rather than detailed results**
- **Imaging**
  - **MRI/PET scans to evaluate changes in baseline blood flow and metabolism**
  - **Measure changes in real time with cognitive tests/mental status exam**
  - **Costly and time consuming**

PET Scan Protocol



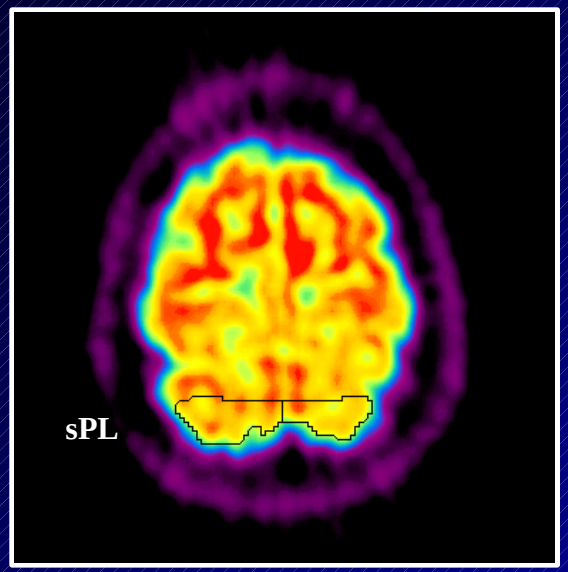
Silverman et al, ASCO 2002

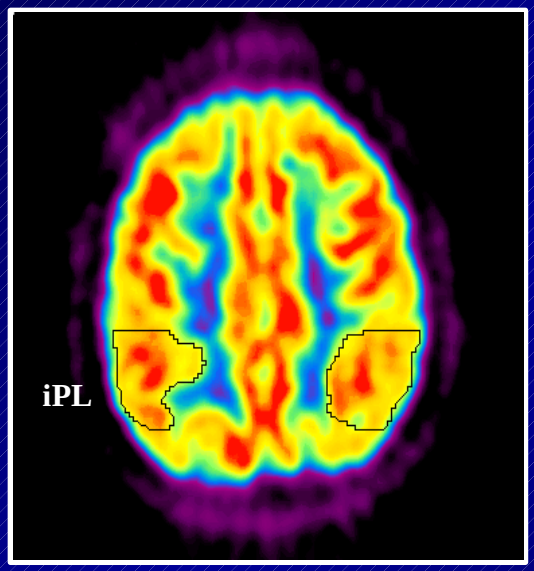
Abnormal regional brain activity was identified in adjuvant chemotherapy-treated breast cancer survivors

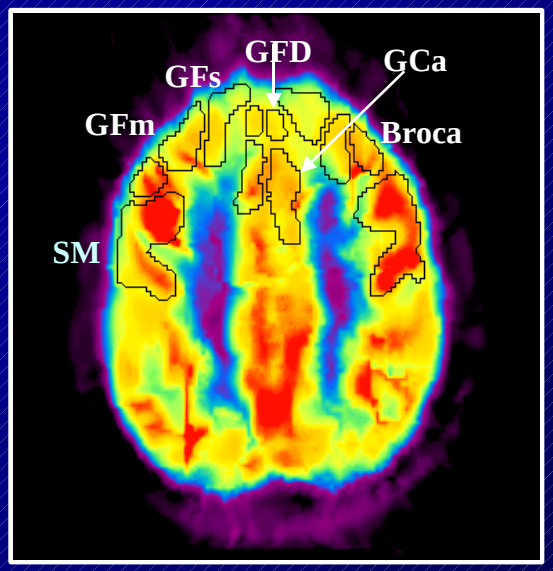
- Resting hypometabolism in frontal cortex: superior frontal gyrus of the dorsolateral prefrontal cortex, L/R Broca's areas (9% below normal, $p < 0.001$ for each).
- Activation pattern during recall task in L/R Broca's area was abnormal.
- Resting hypometabolism in lentiform nucleus for tamoxifen + chemo, but not chemo-only, patients (-10%, $p<0.001$).
- Severity of regional brain abnormalities correlated significantly with severity of neurocognitive impairment.

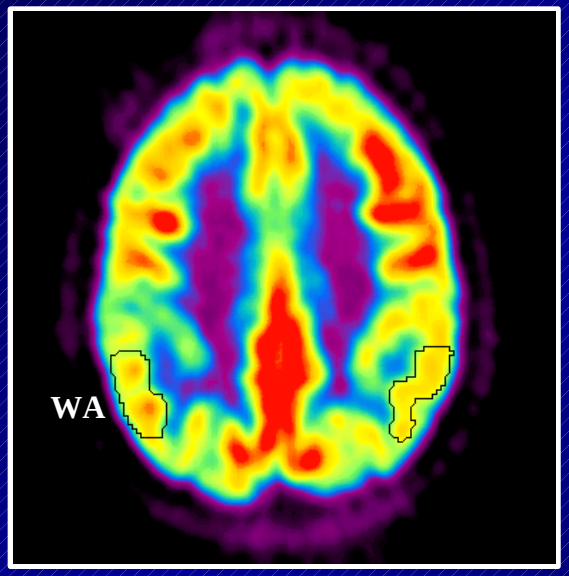
Silverman et al, ASCO 2002

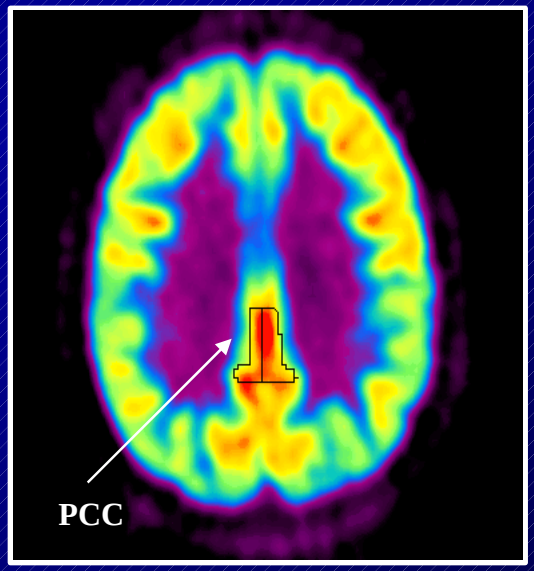
Regions of Interest on Superior Brain Normal Template

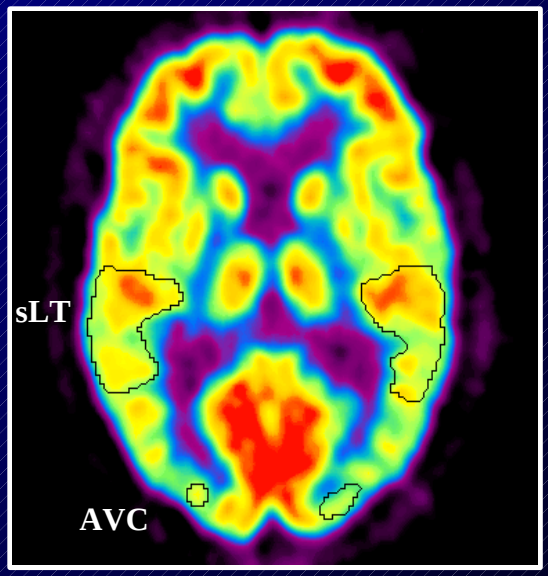












Interventions

- Possible pharmacologic interventions
  - Erythropoietin
  - Methylphenidate (Ritalin)
  - Statins – HMG-CoA reductase inhibitors to preserve blod flow, decrease inflammatory cytokines, reduce oxidative stress
  - Modafinil – wakefulness and cognitive enhancer
  - Antidepresssants
  - Treat insomnia
  - Herbal remedies
    - Gingko Biloba and Ginseng – no standardized formulation
- Cognitive rehabilitation (R. Ferguson, Darmouth)
  - Structured programs
    - Exercise, memory tasks, puzzles, avoid fatigue

CNS Effects of r-HuEPO

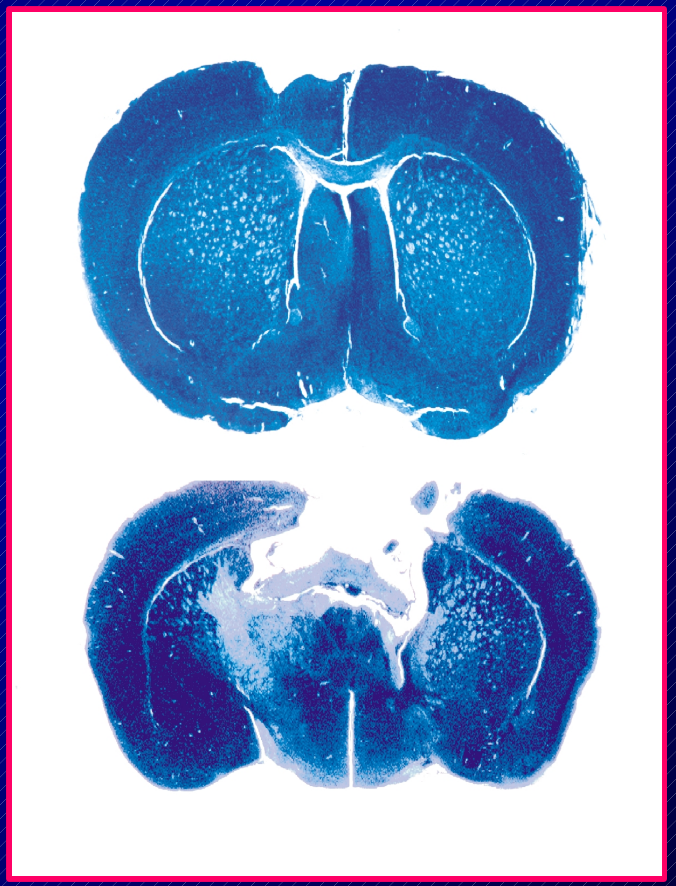
Proposed Mechanism of Neuroprotection

- Peripherally administered r-HuEPO crosses the blood-brain barrier (BBB)
- Exogenous r-HuEPO then interacts with brain EPO receptors
- Receptor binding induces a gene expression program, which inhibits apoptosis and also modulates neuronal excitability

CNS Effects of r-HuEPO

- r-HuEPO administered systemically protects brain from a variety of insults
  - Focal ischemia (stroke)
  - Blunt trauma
  - Excitotoxins
  - EAE
- Improved cognitive function is observed in animals treated with r-HuEPO

Cortical Trauma Model

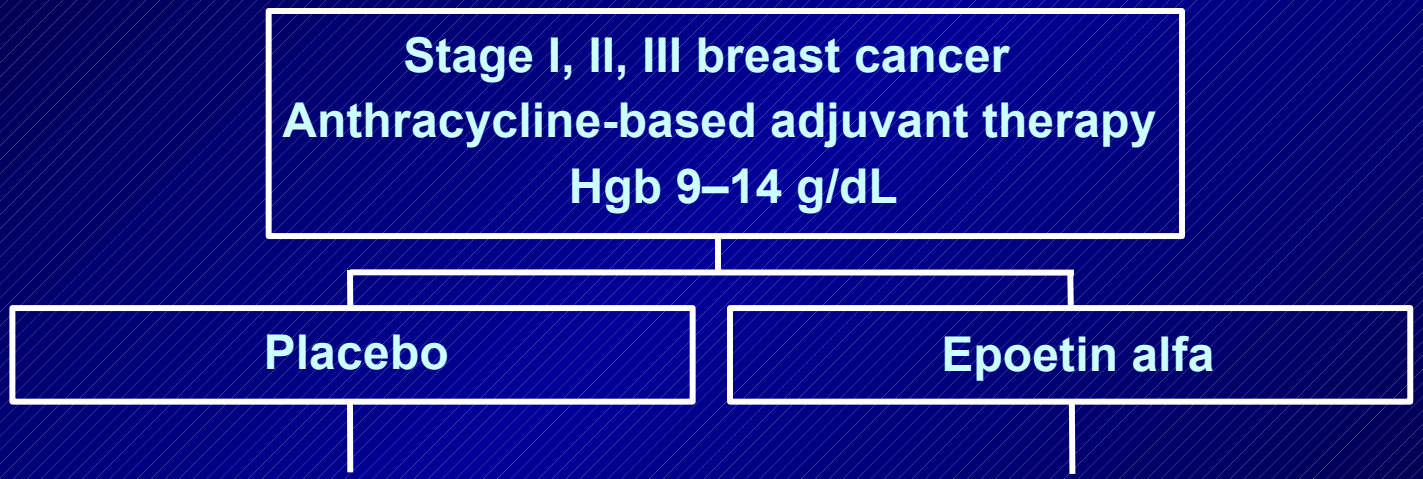


r-HuEPO 24 hours before trauma

saline

Brines et al. *Proc Natl Acad Sci USA*. 2000;97:10526-10531.

Treatment Schema: Adjuvant Breast/Cognition Protocol

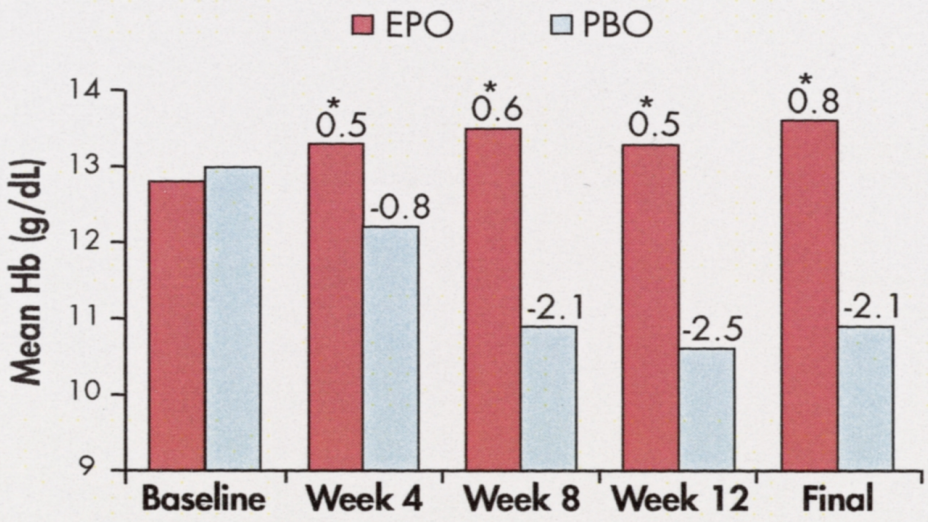


QOL, quality of life.

O'Shaughnessy, et al. *Breast Cancer Res Treat.* 2002.

Epoetin alfa and CT Breast Cancer: Hb Results

FIGURE 1. Mean hemoglobin levels.



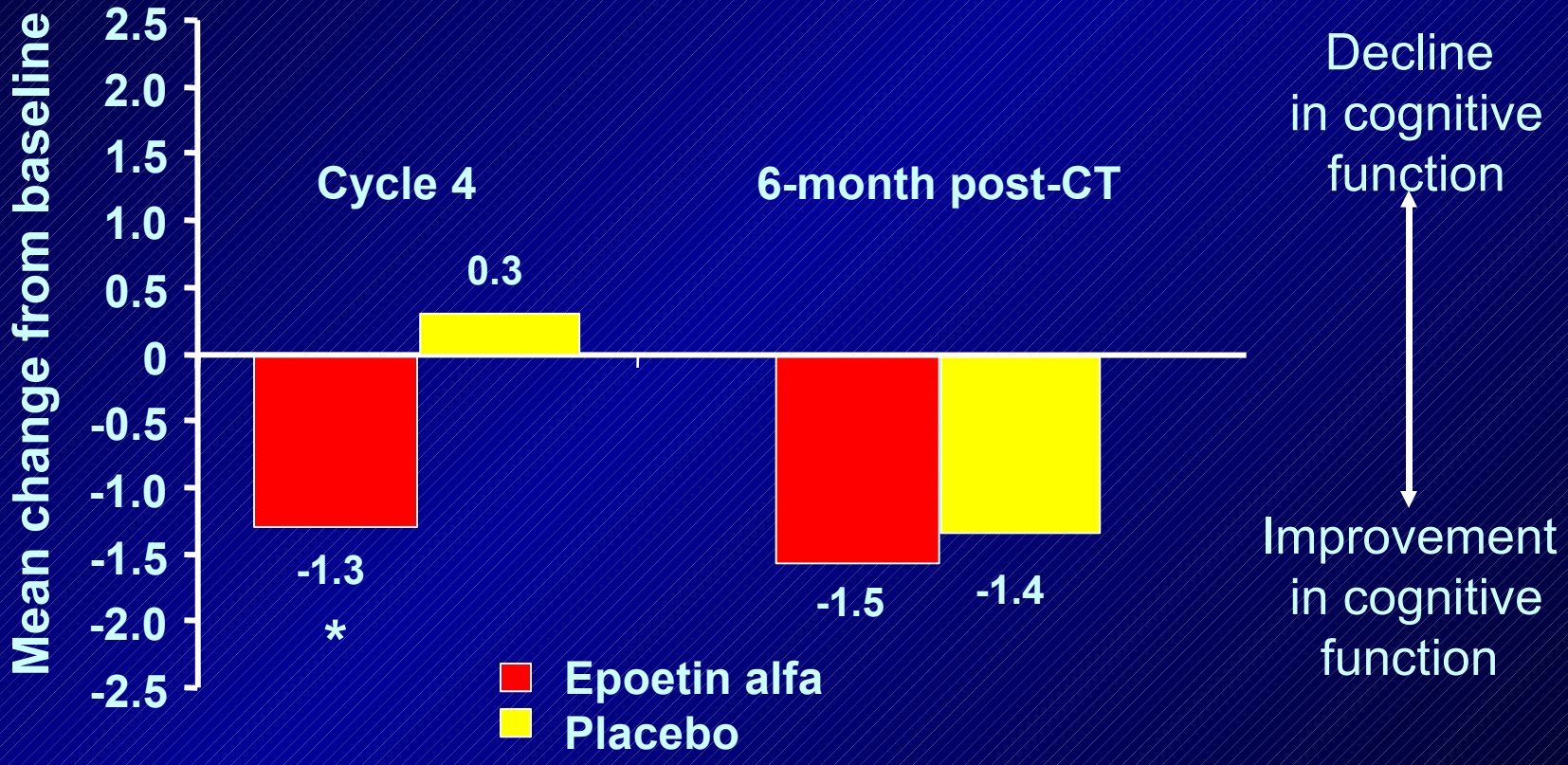
Final, Week 16 Hb value for patients who completed 4 cycles of CT or last available value (Week 12 to 15) for patients who discontinued early.

*$P<.001$ for difference between groups at each postbaseline week. Numbers above each bar represent mean changes from baseline.

- *Hb levels significantly improved with EPO treatment compared to placebo*

O'Shaughnessy et al. Proc Am Soc Clin Oncol. 2002;21. Abstract 1449

Mean Change From Baseline to Cycle 4 in EXIT25



* *P* = .011.

O'Shaughnessy, et al. *Breast Cancer Res Treat.* 2002.

Effects of r-HuEPO

- Potential toxicities
  - Thrombosis risk at higher than normal hemoglobin levels
  - Hemoglobin levels must be monitored and controlled
- Effects on outcome?
  - Two randomized trials suggested a negative effect of erythropoietin on recurrence and survival
  - Subsequent studies showed no impact

Leyland-Jones, Lancet 2003; Hencke et al, Lancet 2003

Patient Controlled Methylphenidate

- 31 patients with advanced cancer
  - Fatigue as measured by 0-10 scale
  - Treated with Methylphenidate 5 mg every 2 hrs as needed for 7 days.
  - Symptoms assessed daily by scale and FACT-F
- Significant improvements in
  - Fatigue ($p<.001$)
  - Overall well-being ($p<.001$), Functional well-being ($p<.001$), Physical well-being ($p<.001$)
- Most patients took 3 or more doses per day
- All chose to continue methylphenidate > 7d
- No serious side effects

Bruera et al, JCO 2003

Future Directions

- Large scale prospective studies are needed
  - ?Role of tamoxifen vs aromatase inhibitors
- Study of factors that increase vulnerability to cognitive decline
- Use of imaging techniques and development of animal models
- Examination of the temporal patterns of cognitive decline and recovery
- Important issue to discuss with patients when considering adjuvant chemotherapy, particularly when the benefit of treatment is borderline

Ongoing Longitudinal Studies

- Dartmouth
  - Breast cancer and lymphoma
  - Assessing APOE - ε4 as a possible risk factor
  - Longitudinal functional MRI scanning
- Shilling
- Component of adjuvant hormonal trials
- Interventions ongoing or planned
  - Methylphenidate (randomized)
  - Behavioral modification and cognitive rehabilitation
  - Erythropoietin