PROs in Phase II Clinical Trials

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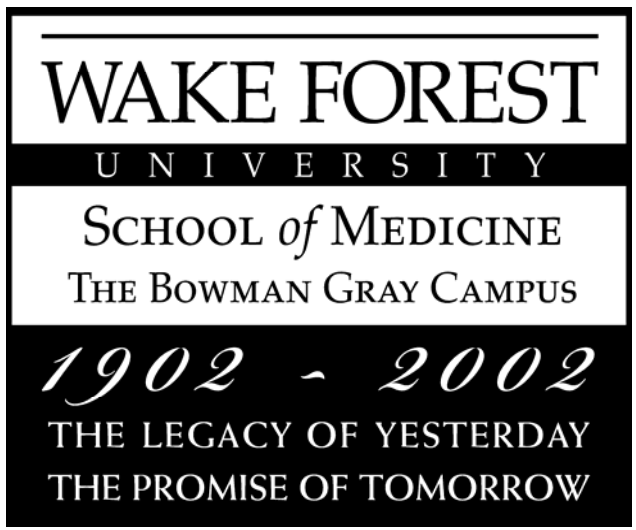

Phase II Study of Donepezil in Irradiated Brain Tumor Patients: Effects on Quality of Life and Cognitive Function

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Comprehensive Cancer Center of WFU CCOP Research Base
Division of Cancer Prevention Community Oncology Branch

Background

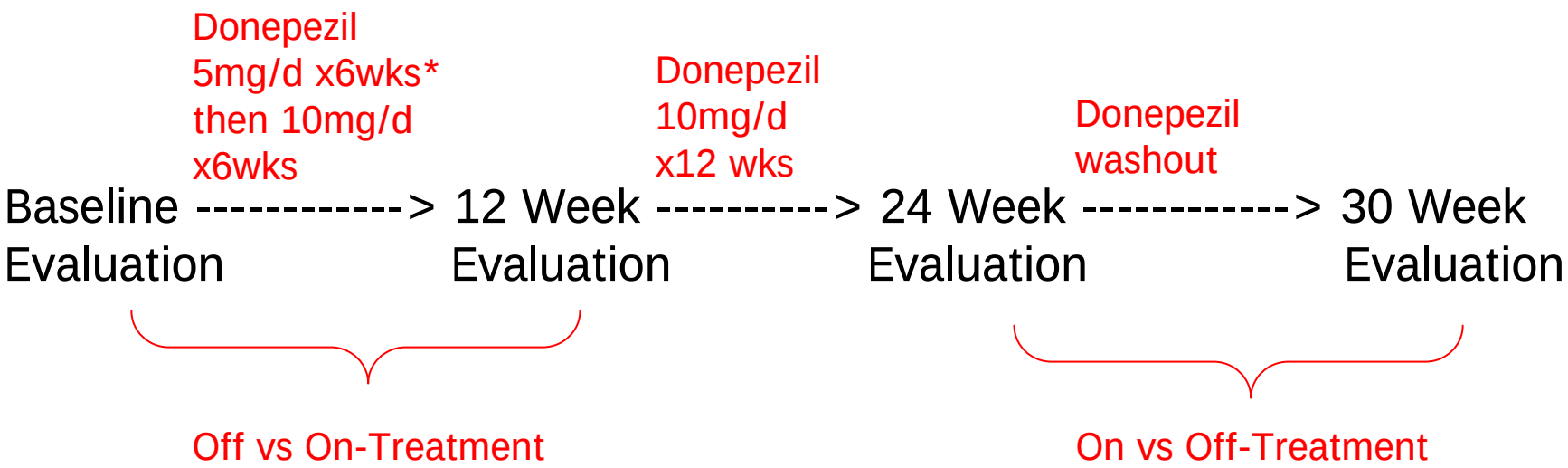
- ~90% long-term survivors of partial- and whole-brain irradiation (RT) have symptoms that include fatigue, mood changes, decreased cognition, short-term memory loss, and word-finding problems, similar to symptoms seen in mild to moderate Alzheimer's dementia (AD)
  - ~50% have abnormal cognitive function tests
  - ~10% develop severe dementia
- White matter changes (demyelination) and small vessel occlusion are also shared features between radiation-induced brain injury and AD
- Donepezil (Aricept), a reversible acetylcholinesterase inhibitor, has been shown in both Phase II and III studies to improve the symptoms of mild-moderate AD using 5-10mg once daily dosing

Hypothesis

- Donepezil 5-10mg/day will improve quality of life (QOL) and cognitive function in long-term (≥6 month) survivors of partial- or whole brain RT

Study Design

- Open label Phase II study in which patient serves as their own control twice



* Subset of QOL tests also performed at 6 weeks

Eligibility Criteria

- Age ≥18 years
- Life expectancy ≥30 weeks
- Prior partial- or whole brain RT ≥6 months from entry for a primary or metastatic brain tumor
- No imaging evidence of progressive disease in 3 prior months
- KPS≥70
- No planned therapy in next 30 weeks

Quality of Life Evaluation

- Karnofsky Performance Status (KPS)
- **Functional Assessment of Cancer Treatment (FACT) with Brain Subscale***
  - FACT has 27 items in four domains including physical, social/family, emotional, and functional well being Additional concerns
  - The brain subscale adds 19 brain-specific items
- **Profile of Mood States (POMS)***
  - 65 items measuring mood-associated symptoms including anger, anxiety, confusion, depression, fatigue, and vigor

*** PROs**

Cognitive Function Evaluation

Cognitive Domain	Test(s)*
Global Cognitive Function	Mini-Mental Status Examination
Executive Function	Trail Making Test Part B
Attention/Concentration	Trail Making Test Part A Digit Span Test
Non-Verbal Memory	Modified Rey Osterrieth Complex Figure
Verbal Memory	California Verbal Learning Test Part II**
Verbal Fluency	F-A-S Test

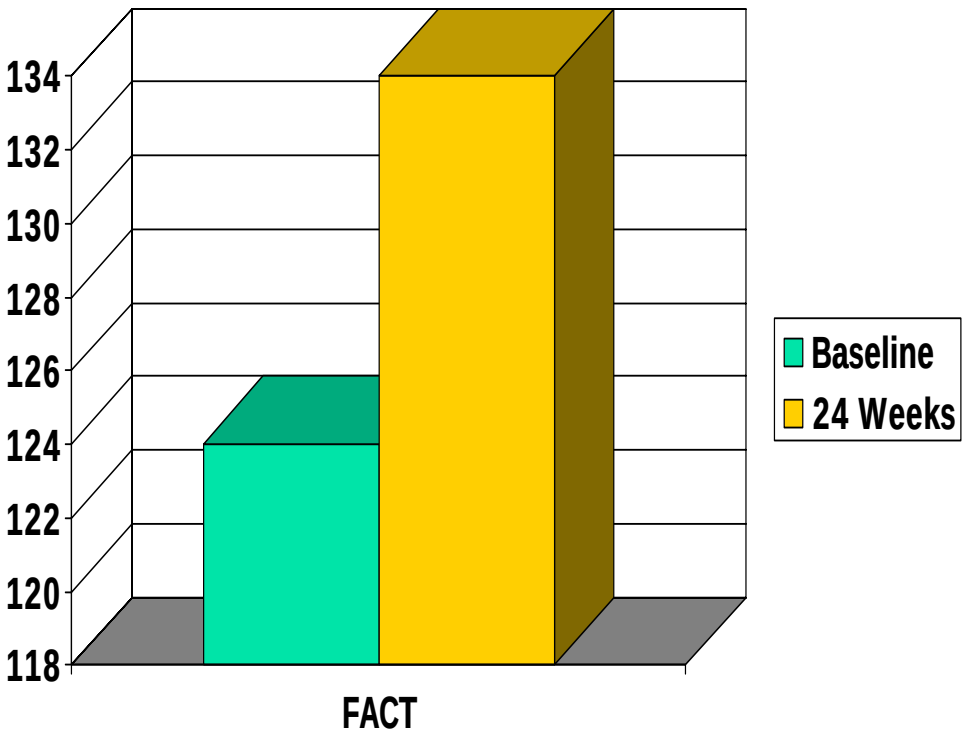
* All tests administered by a trained/certified research nurse

** Alternate forms used every other testing session

Results

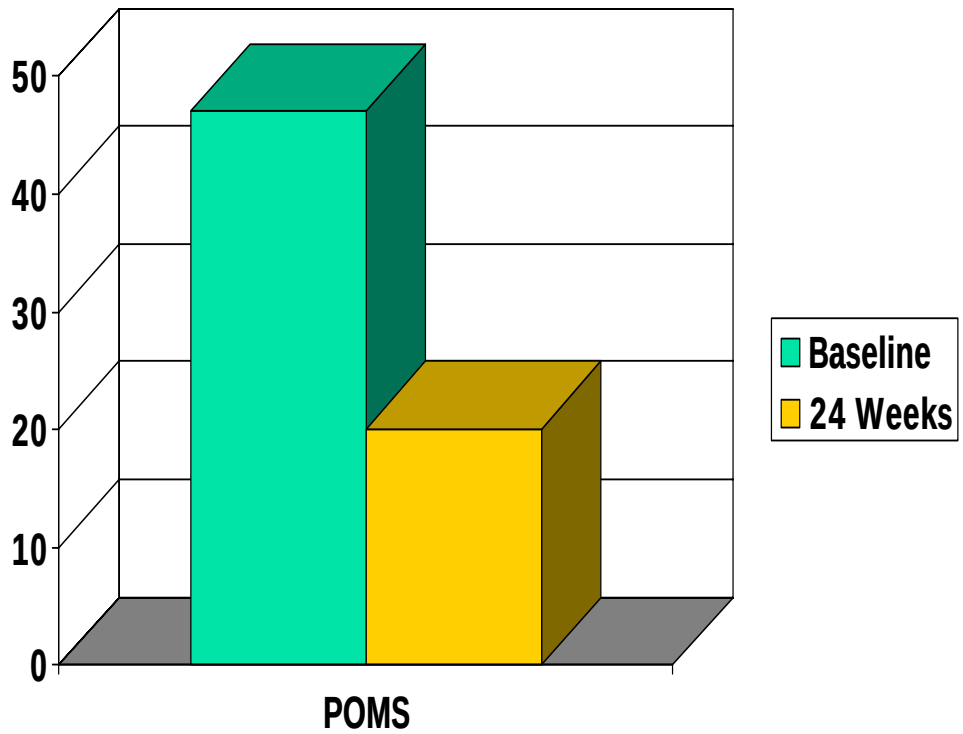
- 34 pts enrolled between 2000 and 2003
  - 22 gliomas (half low-grade, half high-grade), 4 meningiomas, 7 other primary brain tumors, and 1 brain mets
  - Other characteristics: mean age 43, 47% female, 91% white
- 24 pts completed the study from baseline through the 24 week evaluation and form the basis of this report

Results – Quality of Life



- ***FACT score*** increased from 124 (SD 24) to 134 (SD 24)(p=0.0065)
- ***Brain subscale score*** increased from 48 → 54 (p=0.003)

Results – Quality of Life



- ***POMS total score*** decreased from 47 (SD 38) to 30 (SD 30) reflecting improved mood (p=0.0272)
- ***Fatigue symptom score*** decreased from 12 → 10 (p=0.0383)
- ***Confusion* symptom *score*** decreased from 12 → 8 (p=0.0020)

Results – Cognitive Function I

- Significant improvement occurred in the following cognitive function tests:

Cognitive Domain	Tests	p-value
Attention/Concentration	Digit Span Test, backward	0.0039
	Digit Span Test, total	0.0067
	Trail Making Test Part A	0.0316
Non-Verbal Memory	Rey Osterrieth Complex Figure	
	Immediate recall	<0.0001
	Delayed recall	<0.0001

Results – Cognitive Function II

- Significant improvement occurred in the following cognitive function tests:

Cognitive Domain	Test(s)	p-value
Verbal Memory	California Verbal Learning Test Part II	
	Short delay cued recall	<0.0001
	Long delay cued recall	0.0042
	Long delay recall	0.0245
Verbal Fluency	F-A-S Test	0.0237

Other Results

- There were no significant differences from baseline to the 12, 24 and 30 week evaluations in the following:
  - KPS (88-90)
  - MMSE (28-29)
  - Executive function (TMT-B, secs: 133-149)
- 21/24 pts completed the 30 week evaluation (i.e., the week 24-30 washout period)
  - QOL trended towards being worse at 30 weeks
  - Ten of 21 patients (48%) who completed the study through the 30 week evaluation chose to go back on donepezil

Results - Toxicity

- Toxicity was assessed at 6, 12, 24, and 30 weeks, i.e., 4 evaluation points per patient
- 63 toxicities were reported
  - 51 grade 1 (mild)
  - 7 grade 2 (moderate)
  - 5 grade 3 (severe)
- The most common toxicities were fatigue, insomnia, diarrhea, and neuro-miscellaneous
- No patient discontinued protocol treatment due to toxicity

Conclusions I

In ≥6 month survivors of brain irradiation completing 24 weeks of donepezil at doses of 5-10 mg/day:

- QOL – donepezil resulted in a significant improvement in overall and brain-specific QOL as well as mood (based on PROs from the FACT-Br and POMS)
- Cognition – donepezil resulted in a significant improvement in attention/concentration, non-verbal and verbal memory, and verbal fluency (based on cognitive function testing)
- Toxicity was minimal/acceptable

Conclusions II

- Donepezil did not affect global QOL (KPS), global cognitive function (MMSE), and executive function (TMT-B)
  - Insensitivity of measures?
  - Selective effects of donepezil?
  - Sample size too small?
  - Of interest, neither KPS, MMSE, or the TMT are PROs

Symptom Clusters in Irradiated Brain Tumor Survivors Based on Patient-Reported Outcomes

Secondary Analysis of the Phase II Donepezil Study

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Methods

- PROs
  - FACT-Br and POMS
  - Assessment points – baseline (pre-donepezil), then at 6, 12, and 24 weeks while on donepezil, then at 30 weeks (6 weeks after donepezil discontinued)
- Statistical methods used to characterize symptom clusters
  - Factor analysis
  - Cluster analysis
  - Multidimensional scaling

Factor Analysis – Mood

Symptoms	Factor1 Mood	Factor2 *Cognition*	Factor3 ENERGY
Depression	**0.92**	0.18	0.16
Anger	**0.91**	0.12	0.12
Anxiety	**0.75**	0.36	0.13
Confusion	**0.70**	0.40	0.34
Inability to concentrate	0.28	**0.75**	0.14
Inability to read like used to	0.14	**0.54**	0.002
Inability to remember new things	0.09	**0.54**	0.03
Inability to find the right words to say	0.19	**0.48**	0.20
LACK OF ENERGY	0.06	0.07	**0.74**
FATIGUE	0.43	0.20	**0.67**
FRUSTRATED	0.19	0.07	**0.62**

Factor Analysis – Cognition

Symptoms	Factor1 Mood	Factor2 *Cognition*	Factor3 ENERGY
Depression	**0.92**	0.18	0.16
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Factor Analysis – Energy

Symptoms	Factor1 Mood	Factor2 *Cognition*	Factor3 ENERGY
Depression	**0.92**	0.18	0.16
Anger	**0.91**	0.12	0.12
Anxiety	**0.75**	0.36	0.13
Confusion	**0.70**	0.40	0.34
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LACK OF ENERGY	0.06	0.07	**0.74**
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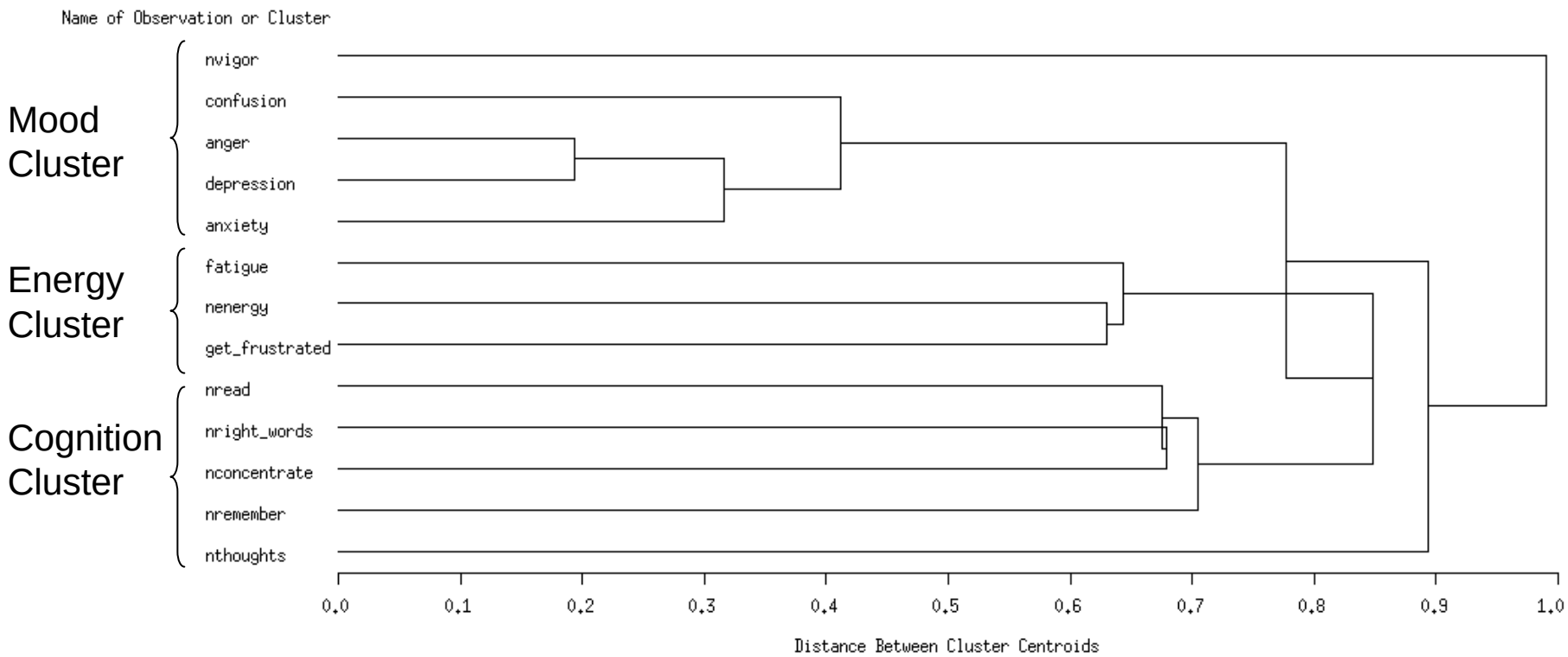
Cluster Analysis



Multidimensional Scaling

Conclusion

- Three symptom clusters were identified in irradiated brain tumor survivors based on analyses of PROs from the Brain subscale of the FACT-Br and several items from the POMS (energy, mood, and cognitive function clusters) suggesting that the following symptoms characterize this patient population:
  - Fatigue / lack of energy
  - Depression / anger / anxiety / confusion
  - Difficulty concentrating / reading / remembering / finding right words

Observation

Time to complete assessments

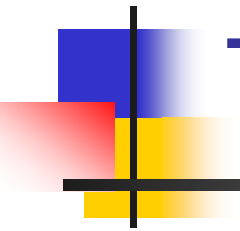
- Original study design: KPS, MMSE, cognitive function testing (75+ minutes by trained research nurse) + FACT-Br, POMS (PRO, 30+ minutes)
- Future study design?: Brain subscale of FACT-Br, POMS (PRO, 20+ minutes)
  - Result → study is easier on patient, much more feasible in CCOP research base

Future Directions I

- Similarly designed Phase II study using Ginkgo Biloba has been completed at Wake Forest in adults
- Phase II study of donepezil in children who are long term survivors of brain irradiation opened in 8/06
- Phase III placebo controlled double blind study of donepezil in adult long-term survivors of brain irradiation has been NCI-approved and will open in the CCCWFU and MDACC CCOP Research Bases in 11/06

Future Directions II

- Symptom cluster analysis is being performed on the Phase II Ginkgo Biloba data set, and the combined Donepezil and Ginkgo Biloba data sets
- The CCCWFU CCOP Research Base has developed its first study using multiple pharmacologic interventions to address symptom clusters in irradiated brain tumor patients (donepezil + modafinil)



Thank you