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Phase II Study of Ginkgo Biloba in Irradiated Brain Tumor Patients: Effect on Cognitive Function, Quality of Life, and Mood

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Abstract

Objective—Ginkgo biloba has been reported to improve cognitive function in older adults and patients with Alzheimer's disease and multi-infarct dementia. We conducted an open-label phase II study of this botanical product in symptomatic irradiated brain tumor survivors.

Methods—Eligibility criteria included: life expectancy ≥ 30 weeks, partial or whole brain radiation ≥ 6 months before enrollment, no imaging evidence of tumor progression in previous 3 months, or stable or decreasing steroid dose, and no brain tumor treatment planned while on study. The ginkgo biloba dose was 120 mg/day (40 mg t.i.d.) for 24 weeks followed by a 6-week washout period. Assessments performed at baseline, 12, 24 (end of treatment), and 30 weeks (end of washout) included KPS, Functional Assessment of Cancer Therapy-Brain (FACT-Br), Profile of Mood States (POMS), Mini-Mental Status Exam (MMSE), Trail Making Test Parts A (TMT-A) and B (TMT-B), Digit Span Test (DST), Modified Rey Osterrieth Complex Figure (ROCF), California Verbal Learning Test Part II (CVLT-II), and the F-A-S Test.

Results—Of the 34 patients enrolled on study, 23 (68%) completed 12 weeks of treatment and 19 (56%) completed 24 weeks of treatment. There were significant improvements at 24 weeks in: executive function (TMT-B) (p=0.007), attention/concentration (TMT-A) (p=0.002), and non-verbal memory (ROCF – immediate/delayed recall) (p=0.001/0.002), mood (p=.002), FACT brain subscale (p=0.001), and the FACT physical subscale (p=.003).

Conclusions—Some improvement in quality of life and cognitive function were noted with ginkgo biloba. However, treatment with ginkgo biloba was associated with a high dropout rate.

Keywords

ginkgo biloba; radiation; cognitive function; quality of life; brain tumors

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Introduction

Each year in the United States, there are an estimated 170,000 cases of brain metastases diagnosed[1,2]. In addition, the annual incidence of primary brain tumors is about 23,000 cases, the majority of which are treated with partial or whole brain radiation following surgery[3]. Unfortunately, cognitive impairment associated with the tumors and their treatments occurs in a substantial proportion of patients, with 10% of patients developing progressive dementia, and 50% to 90% showing deficits when assessed with sensitive tests of cognitive function[4-7]. Symptoms in its most severe form include severe dementia, ataxia, and urinary incontinence[4]. However, in studies specifically assessing neurocognitive function, there is a broader spectrum of findings. Four series have described neurocognitive sequelae and effects on quality of life associated with late-radiation induced brain injury, which include frontal lobe executive functions, short-term memory impairment, mood and personality changes, and inability to resume normal psychosocial functioning[8-11]. A more recent paper found that patients treated with whole brain radiation therapy and stereotactic radiosurgery have a greater risk of a significant decline in learning and memory function[12].

Studies have shown that the end result of late radiation-induced brain injury, demyelination which leads to white matter necrosis, is similar to that observed in Alzheimer's dementia (AD)[13]. Corn et al looked at a series of patients with malignant gliomas who received localized brain radiation to four different doses[14]. They found grade 3 or higher changes in 37% of the patients using a six-grade scoring method of white matter changes occurring in AD described by Fazekas et al[15]. Brain irradiated patients have shown improvement in cognition after treatment with donepezil, an acetylcholinesterase (AchE) inhibitors, which is used to treat symptoms of cognitive problems associated with Alzheimer's dementia[16]. In addition, some reports have described improvement in cognitive function with the use of ginkgo biloba extracts from the leaves of the ginkgo biloba tree[17, 18], though a recent randomized, placebo-controlled clinical trial with older community residents showed that taking ginkgo supplements did not reduce the incidence of dementia nor improve cognitive functioning compared with placebo[19, 20].

The first randomized controlled trial data using ginkgo biloba for the treatment of dementia in the United States was reported by Le Bars et al[17]. In that study, patients treated with ginkgo biloba showed significant improvements in two of the three primary outcome measures, including objective tests of cognitive performance (Alzheimer's Disease Assessment Scale-Cognitive subscale or ADAS-Cog) and recognition by caregivers (Geriatric Evaluation by Relative's Rating Instrument or GERRI). A more recent randomized trial in elderly individuals with normal cognition and mild cognitive impairment did not find benefit for ginkgo biloba in reducing the incidence rate of dementia or improving cognitive functioning[21]. Despite these mixed results, we hypothesized that ginkgo biloba may be helpful for patients with radiation-induced cognitive dysfunction.

Methods

Patient Population and Eligibility Criteria

Eligibility criteria included: age ≥ 18 years, life expectancy ≥ 30 weeks, partial or whole brain radiation ≥ 6 months before enrollment, no imaging evidence of tumor progression in previous 3 months, on stable or decreasing steroid dose, Karnofsky Performance Status (KPS) (Karnofsky) ≥ 70, MMSE score ≥ 20 and no brain tumor treatment planned during the course of study. Five patients received whole brain radiotherapy and the remaining received partial brain irradiation. Patients who underwent whole brain radiotherapy received a dose of 30 Gy in 10 fractions. Otherwise, patients received partial brain irradiation to 50 –

60 Gy at 1.8 – 2 Gy per fraction. The study was approved by the institutional review board of Wake Forest University School of Medicine. All study participants provided informed consent.

Treatment

Ginkgo biloba, 120 mg/day (40 mg t.i.d.) was given for 24 weeks, and then treatment was discontinued for a 6-week washout period. Thus, patients served as their own control twice, i.e., baseline versus on-treatment and on-treatment versus post washout.

Cognitive function was the primary outcome. Mood and quality of life (QOL) were secondary outcomes. The cognitive test battery included standardized measures of global cognitive functioning (Mini-Mental State Exam [MMSE][21]), attention and concentration (Trail Making Test Part-A[22] and Digit Span Test[23]), visual-constructional skills (Revised Rey-Osterrieth Complex Figure Test[24]), verbal fluency (F-A-S test[25]), executive function (Trail Making Test Part-B[22]), verbal learning and memory (California Verbal Learning Test-II[26]), and figural memory (Revised Rey-Osterrieth Complex Figure Test[24]). All cognitive tests were administered to the patient by a trained and certified research nurse in approximately 60 minutes.

Health-related quality of life (HRQoL) was assessed with the KPS rating scale (Karnofsky) and the Functional Assessment of Cancer Therapy-Brain (FACT-Br)[27], a well-validated instrument for measuring cancer-related HRQoL in brain tumor patients. In addition to an overall score (FACT-Br Total), the FACT-Br includes subscales for physical, social, emotional, and behavioral functioning and a 19-item brain-specific concerns subscale.

Mood was assessed with the Profile of Mood States (POMS)[28], with subscales for depression, anxiety, anger, subjective confusion, fatigue, and vigor in addition to an overall (distressed) mood score.

The FACT-Br and POMS were supervised by a trained research nurse and completed by the patient in about 10 minutes.

Study Design

The study was an open-label, phase II clinical trial. All outcome measures were obtained at baseline before the initiation of ginkgo biloba administration, and again at 12, 24 (cessation of treatment), and 30 weeks (following washout). Toxicities were evaluated at each assessment point using National Cancer Institute Common Toxicity Criteria (version 3.0). At week 30, patients were given the choice to resume ginkgo biloba.

Statistical Considerations

The sample size for this study was calculated to provide 80% power at the 5% two-sided level of significance for detecting a 23 second difference in the time needed to complete Part B of the Trail Making Test from baseline to 24 weeks, assuming a standard deviation of approximately 37 seconds for the pre-post differences. Twenty-three patients were required. Because the potential for disease recurrence is high in patients with brain tumors, we decided to accrue a sample size of 35 patients, estimating that about one third of patients who enrolled on the study would not complete it.

Repeated measures analysis of covariance (RMANCOVA) was used to assess changes over time in cognitive functioning, mood, and health related quality of life. All available data was used in the analyses, not just data from those who completed all questionnaires. Several covariance structures were considered (such as unstructured, compound symmetry,

autoregressive, etc.) and the final structure for each outcome was chosen to minimize the Bayesian Information Criteria (BIC). Age, sex, and performance status were included as covariates in the models. The primary interest was in the change from baseline to 24 weeks, and a linear contrast was used in the RMANCOVA to assess the significance of that change. Linear contrasts were also used to assess other pair-wise differences (e.g. 24 weeks vs. 30 weeks). Some variables were highly skewed so log or rank transformations were used in the analysis; least squares estimates are based on models done one the original scales; p-values are based on the transformed data.

Results

Patient Characteristics / Baseline Summary

Thirty-four patients were enrolled between January 2003 and February 2005. Patient characteristics are summarized in Table 1. Ages ranged from 22 to 82 with a median of 47, 68% were females, 18% black, and 56% had an ECOG performance status of 0 initially. At baseline, there was evidence of cognitive impairment and depressed mood in the sample. Mean scores on the tests of attention and concentration, memory, and executive function were all ≥ 1.5 SDs below or above the mean for the age-matched normative sample[22, 23, 26] indicating clinically significant impairment. Additionally, baseline scores on the POMS subscales measuring angry mood, anxious mood, confusion, depressed mood, and fatigue were all significantly worse (≥1.5 SD above the mean) than the normative sample[28]. Baseline scores on the FACT-Br total and brain-specific concerns subscale scores were all within 1 SD of the means for brain tumor patients reported by Weitzner et al[27] in their validation of the FACT-Br, indicating that our participants were comparable with Weitzner's sample of brain tumor patients. None of the patient characteristics or the cognitive, mood, or quality of life measures differed significantly between those who did and did not complete the study.

Cognitive Function

Least squares means for the cognitive function tests are shown for each time in Table 2. Following 24 weeks of treatment with ginkgo biloba, times to complete the Trail Making Test had significantly decreased. The Trail Making Test, Part B, also improved significantly from 24 to 30 weeks, so it is not clear if the change from baseline to 24 weeks was due to treatment or a learning effect. The Trail Making test, Part A, did not change significantly from 24 to 30 weeks. Scores for the immediate and delayed recall on the Modified Rey-Osterrieth Figure were significantly higher (better) with a trend toward significance for the California Verbal Learning Test-II Short-Delay Free recall). No significant change was found for global cognitive function (MMSE), attention/concentration and working memory (Digit Span Test Total), verbal fluency (F-A-S Test), or in Long-Delay Free Recall of the California Verbal Learning Test-II.

Mood

Following 24 weeks of treatment, scores were significantly improved for overall distressed mood (Table 2). The POMS score actually got worse from 24 to 30 weeks, although the change was not significant, which might indicate that the initial improvement could be due to an immediate treatment effect that disappeared once treatment was stopped.

HRQOL

After treatment with ginkgo biloba, a significant improvement occurred in patient-reported brain-specific symptoms and physical well-being, with a trend towards improved emotional functioning (Table 2). Changes from 24 to 30 weeks were not significant for these outcomes

and actually decreased slightly for most measures, again indicating a possible effect of treatment at disappeared once treatment was stopped.

Toxicity

Toxicity was assessed at six, 12, 24, and 30 weeks. A total of 70 toxicites were reported, 53 grade 1 (76%), 14 grade 2 (20%), and 3 grade 3 (4%). The most common toxicities were neuro-miscellaneous (e.g., difficulty finding the right words, cognitive issues, and memory problems). Eight patients had grade 1, three grade 2, and one grade 3 (difficulty speaking) toxicity. Ten patients complained of grade 1 fatigue and one patient had grade 2 fatigue. Five patients had grade 1 nausea and one patient had grade 3 nausea. Five patients discontinued protocol because of toxicity (four with GI symptoms, one with intracranial bleed). Five patients discontinued ginkgo biloba because of no perceived benefit. Lastly, five patients discontinued treatment because of intercurrent illness (three medical and two tumor progression).

Discussion

Extracts from the leaves of Ginkgo biloba tree have been used for centuries to treat various ailments. In Germany and France, the extract is commonly used for peripheral vascular disease and “cerebral insufficiency.” In the herbalist literature, cerebral insufficiency is characterized by difficulties of concentration and memory, absent-mindedness, confusion, lack of energy, tiredness, decreased physical performance, depressed mood, anxiety, dizziness, tinnitus, and headache[31].

The exact mechanism of action of ginkgo biloba is still unknown; however, its effects at the tissue level include membrane stabilization, anti-oxidation, platelet activating factor inhibition, lipid peroxidase inhibition, enhanced microcirculation and tissue perfusion, and stimulation of endothelium-derived relaxing factor and prostacyclin release[32]. There is *in vitro* evidence that apoptosis induced by oxidative stress in rat cerebellar neurons can be inhibited by pretreatment of cells with ginkgo biloba[33, 34]. Post-hypoxic brain damage is associated with an activation of phospholipases and a subsequent increase in choline release. In *ex vivo* studies of rat hippocampal slices, the increase in choline, which is indicative of hypoxia-induced membrane breakdown, can be inhibited by oral ingestion of ginkgo biloba extracts given one hour prior to slice preparation[35].

There is evidence that ginkgo extract can facilitate recovery from radiation injury. Chromosomal damage induced by clastogenic factors in the plasma of Chernobyl accident recovery workers showed a significant decrease after treatment with ginkgo biloba (40 mg t.i.d.)[36]. Furthermore, rat liver microsomes treated with ginkgo biloba were protected against free radical damage induced by UV radiation[37].

The sequelae of severe radiation-induced brain injury have received much attention recently, including cognitive function and QOL due to the growing emphasis on the management of symptoms related to cancer and its treatments[38-40]. In patients receiving low-dose (20 to 40 Gy) prophylactic cranial irradiation for small-cell lung cancer, between 50% to 67% were found to have moderate to severe cognitive deficits[6,7]. In another study evaluating accelerated radiotherapy followed by procarbazine/lomustine/vincristine chemotherapy for anaplastic glioma, 40% to 60% of patients had worsened cognitive functioning and 10% had severe dementia[35, 42].

Methylphenidate was the first therapeutic agent used to reduce cognitive morbidity and improve QOL in irradiated brain tumor patients. Weitzner and Meyers reported improved visual-motor speed, verbal memory, expressive speech, executive function, fine-motor

coordination, and QOL with the amphetamine methylphenidate[43,44]. To our knowledge, the present study is the first study using ginkgo biloba to reduce cognitive morbidity and improve QOL in irradiated brain tumor patients. Pretreatment assessments of cognition, mood, and QOL clearly revealed that our sample was experiencing significant cognitive impairment and symptoms compared to normative groups. Following 24 weeks of ginkgo biloba treatment, we observed significant improvement in figural and verbal memory, QOL, patient-reported brain-related symptoms, and mood suggesting that ginkgo biloba may provide a benefit for brain tumor patients who have received cranial radiation.

Despite these encouraging results, the study has several limitations that must be considered. As a phase II, open-label study there was no control group. The observed improvements might be due to a practice effect[46] or other uncontrolled factors. However, we noted improvement in the POMS and some FACT subscales, which are not influenced by practice effects and no change in some of the cognitive measures. In addition, no outcome measures, other than the TMT PartB, improved significantly after discontinuation of the ginkgo biloba. The small sample size limited the power to detect changes, thus making smaller improvements in QOL or cognitive function difficult to detect. In addition, 44% of patients dropped out of the study. This dropout was slightly higher than expected and resulted in lower than planned power. However, we did see a significant change over time in our primary outcome measures. Additionally, there were no significant differences in patient characteristics or baseline measures of cognitive function, mood, or quality of life between those who did and did not drop out. The high drop-out rate was attributable in part to lack of perceived benefit and toxicity. Reasons for drop-out included GI toxicity and intracranial bleeding. These potentially serious side effects of ginkgo biloba must be weighed when considering it for treatment of cognitive impairment.

Conclusions

The results of this initial phase II trial reveal that treatment with 120 mg/day of ginkgo biloba may improve memory, reduce patient-reported brain-related symptoms, and improve mood and quality of life in patients who had undergone brain irradiation at least 6 months earlier. Due to the high dropout rate, small sample size and lack of a control groups these results should be viewed as preliminary.

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Table 1

Patient Characteristics and Baseline Performance on Cognitive, Mood, and Quality of Life Measures

Characteristic	Baseline (N=34)
Median Age (yrs) (Range)	47 (22 – 82)
Gender	
Females	23 (68%)
Males	11 (32%)
Race	
Black	6 (18%)
White	28 (82%)
ECOG Performance Status	
0	19 (56%)
1	14 (41%)
2	1 (3%)
Cognitive Functioning	Mean (SD)
Mini-Mental State Exam	28.1 (2.35)
Digit Span Test, total	12.5 (3.24)
FAS test	27.2 (10.7)
Trail Making Test-A, sec.	61.5 (44.2)
Trail Making Test-B, sec.	155.4 (88.0)
California Verbal Learning Test - II	
Short-delay free recall	8.26 (3.97)
Long-delay free recall	9.03 (3.90)
Modified Rey-Osterrieth Figure	
Immediate recall	14.5 (6.45)
Delayed recall	13.9 (6.37)
Mood	
Profile of mood states, total negative scales	52.1 (34.7)
Profile of mood states, total negative - vigor	39.0 (38.9)
Health-related Quality of Life	
Brain Specific Concerns	48.2 (11.2)
Physical Functioning	21.4 (4.93)
Emotional Functioning	17.6 (5.29)
Social Functioning	22.7 (5.21)
Functional	18.8 (6.70)

Table 2

Least Squares Means (SE) for Cognitive, Mood, and Quality of Life Measures

Outcome	Baseline N=34	12 Weeks N=23	24 Weeks N=19	30 Weeks N=19	p-value*
Cognitive Functioning					
Mini-Mental State Exam	28.0 (0.50)	27.7 (0.56)	27.9 (0.59)	27.9 (0.59)	0.791
Digit Span Test, total	12.5 (0.60)	12.3 (0.66)	12.7 (0.69)	---	0.758
FAS test	27.1 (1.83)	27.0 (1.90)	28.7 (1.93)	---	0.131
Trail Making Test-A, sec.	62.3 (6.47)	59.9 (8.08)	52.5 (5.34)	47.1 (4.32)	0.002
Trail Making Test-B, sec.	157.8 (11.3)	142.4 (12.0)	147.9 (12.2)	129.2 (12.9)	0.007
California Verbal Learning Test - II					
Short-delay free recall	7.99 (0.61)	8.55 (0.68)	9.40 (0.71)	9.35 (0.71)	0.023
Long-delay free recall	8.76 (0.63)	9.18 (0.69)	9.50 (0.73)	9.35 (0.73)	0.237
Modified Rey-Osterrieth Figure					
Immediate recall	14.2 (0.90)	16.4 (0.99)	17.5 (1.04)	---	<0.001
Delayed recall	13.7 (0.89)	16.2 (1.00)	17.0 (1.06)	---	0.002
Mood					
Profile of mood states, total negative scales	53.3 (5.18)	43.3 (5.66)	39.0 (5.88)	41.7 (5.88)	0.005
Profile of mood states, total negative - vigor	40.5 (5.76)	29.8 (6.25)	24.1 (6.47)	26.8 (6.47)	0.002
Health-related Quality of Life					
Brain Specific Concerns	48.4 (1.60)	52.2 (1.76)	55.0 (1.93)	54.6 (2.01)	0.001
Physical Functioning	21.5 (0.63)	22.3 (0.73)	24.1 (0.79)	22.7 (0.79)	0.003
Emotional Functioning	17.6 (0.79)	18.6 (0.85)	19.8 (0.91)	19.3 (0.96)	0.011
Social Functioning	22.6 (0.97)	21.6 (1.07)	21.4 (1.17)	22.2 (1.22)	0.306
Functional	18.9 (0.94)	18.3 (1.00)	19.1 (1.08)	18.9 (1.13)	0.842

* contrast between baseline and 24 weeks