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Phase II double-blind placebo-controlled randomized study of armodafinil for brain radiation-induced fatigue

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Background. Common acute-term side effects of brain radiotherapy (RT) include fatigue, drowsiness, decreased physical functioning, and decreased quality of life (QOL). We hypothesized that armodafinil (a wakefulness-promoting drug known to reduce fatigue and increase cognitive function in breast cancer patients receiving chemotherapy) would result in reduced fatigue and sleepiness for patients receiving brain RT.

Methods. A phase II, multi-institutional, placebo-controlled randomized trial assessed feasibility of armodafinil 150 mg/day in participants receiving brain RT, from whom we obtained estimates of variability for fatigue, sleepiness, QOL, cognitive function, and treatment effect.

Results. From September 20, 2010, to October 20, 2012, 54 participants enrolled with 80% retention and 94% self-reported compliance. There were no grade 4–5 toxicities, and the incidence of grade 2–3 toxicities was similar between treatment arms, the most common of which were anxiety and nausea (15%), headaches (19%), and insomnia (20%). There were no statistically significant differences in end-RT or 4 week post-RT outcomes between armodafinil and placebo in any outcomes (Functional Assessment of Chronic Illness Therapy [FACIT]-Fatigue, Brief Fatigue Inventory, Epworth Sleepiness Scale, FACT-Brain, and FACIT-cognitive function). However, in participants with more baseline fatigue, those treated with armodafinil did better than those who received the placebo on the end-RT assessments for several outcomes.

Conclusion. Armodafinil 150 mg/day was well tolerated in primary brain tumor patients undergoing RT with good compliance. While there was no overall significant effect on fatigue, those with greater baseline fatigue experienced improved QOL and reduced fatigue when using armodafinil. These data suggest that a prospective, phase III randomized trial is warranted for patients with greater baseline fatigue.

Keywords: armodafinil, cognitive function, fatigue, primary brain tumors, radiotherapy.

Nearly 180 000 patients each year undergo brain radiotherapy (RT) for either metastatic or primary brain tumors[1] Radiation-induced fatigue, drowsiness, and decreased physical functioning represent some of the most common problems facing patients who receive brain RT and can significantly worsen their quality of life (QOL). A recent European Organisation for Research and Treatment of Cancer (EORTC) randomized trial has demonstrated that patients who receive whole brain radiotherapy (WBRT) experience a worsening of performance status, in part due to fatigue.[2] This worsening of performance status can affect significant clinical decision-making such as when or whether to offer chemotherapy. Pharmaceutical intervention for radiation-induced fatigue has been attempted in

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multiple prospective clinical studies.[3] Psychostimulants have been previously assessed in patients who have been medically ill as well as in brain tumor patients.[4–8] Specifically with regard to patients receiving brain RT, methylphenidate, a substituted phenethylamine psychostimulant commonly used in the treatment of attention deficit/hyperactivity disorder, has been tested for QOL, fatigue, and mental status. A recent phase III study assessing the efficacy of methylphenidate showed no benefit in QOL, fatigue scores, and mental status in participants who received RT to the brain.[9] Other psychostimulants have been considered for the management of patients suffering from psychoneurological sequelae of various medical conditions. Modafinil, a CNS stimulant, is a US FDA-approved drug often utilized for wakefulness in conditions such as narcolepsy or sleep apnea. Modafinil has a unique pharmacologic mechanism in that it is not known to bind to receptors for sleep/wake regulation and does not inhibit MAO-B or phosphodiesterases II–IV. Modafinil does not appear to affect dopaminergic activity. Co-administration of modafinil with other CNS-active drugs such as methylphenidate and dextroamphetamine does not significantly alter the pharmacokinetics of either drug.[10–12] In one randomized study, modafinil was found to reduce fatigue and increase cognitive function in breast cancer participants receiving chemotherapy.[13] In a non–placebo-controlled pilot study, modafinil demonstrated longitudinal improvement in cognitive, mood, and fatigue outcome measures in primary brain tumor participants.[14] However, modafinil 200 mg daily, did not have a significant effect on QOL, cognitive function, depression, or fatigue for 37 primary brain tumor participants in a randomized trial in the Netherlands.[15] An additional randomized study of modafinil versus methylphenidate showed no difference between the modafinil or methylphenidate groups in brain tumor participants.[16]

Armodafinil is the R-enantiomer of modafinil and, unlike modafinil, is a mixed dopamine receptor antagonist and dopamine reuptake inhibitor, making it more effective as a CNS stimulant than modafinil. It is also FDA approved for treating excessive somnolence caused by narcolepsy, obstructive sleep apnea, and shift work sleep disorders. As the mechanisms for somnolence caused by sleep disorders and brain RT are thought to be similar, there has been significant interest in the use of armodafinil for radiation-induced fatigue. Because of the clinical need, the ineffectiveness of methylphenidate in a randomized trial, and the prior mixed results of modafinil in prospective clinical trials, we elected to perform a double blind, placebo-controlled randomized study of armodafinil verus placebo in patients receiving brain RT.

Methods

Participants/Eligibility and Exclusion Criteria

The study was approved by an appropriate institutional review board and was conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Patients were provided appropriate informed consent prior to participating. Participants included patients with malignant or benign/low-grade primary brain tumors receiving either partial or WBRT. (Only participants with medulloblastoma received RT to the whole brain.) Participants were enrolled consecutively. Inclusion criteria were age ≥18 years, primary brain tumor (benign, low grade or high grade), planned whole or partial brain RT at a dose of at least 45 Gy at ≥1.5 Gy per fraction, KPS ≥60%, and serum hemoglobin ≥10 g/dL. Concurrent chemotherapy was allowed. Patients with pre-existing severe headaches were excluded from enrollment.

Treatment

The 150 mg/day dose of armodafinil was based on 3 randomized control trials of obstructive sleep apnea[17,18] or narcolepsy.[19] All 3 studies showed a significant reduction in moderate-to-severe fatigue and clinically significant sleepiness (compared with participants who received placebo) with both the 150 mg/day and 250 mg/day doses of armodafinil. Based on the clinical data, the armodafinil dose for the proposed study was chosen to be 150 mg/day.

Trial Design and Treatment

This multi-institutional study was a placebo-controlled, randomized trial with a 1:1 allocation of primary brain tumor patients receiving RT. After randomization, each participant received a bottle of pills containing either the study drug (armodafinil 50 mg tablets) or placebo (identical-appearing pills). Both the study drug and placebo were to be taken 3 at a time once daily (totaling 150 mg per day for those on the study drug) for 7 days a week during the duration of RT and then an additional 4 weeks after RT. Participants had to begin the study drug by the fifth fraction of RT. There were no dose modifications or drug holidays allowed for toxicity. If participants did not tolerate the study agent, the agent was discontinued.

Fatigue, QOL, and cognitive function were assessed at baseline, at the end of RT, and 4 weeks after RT by a trained research nurse. A second brief self-report of fatigue was administered weekly during RT. These visits were coordinated by a research nurse and were generally on the same day as the participant's planned visit with the physician. Participants completed self-administered fatigue and QOL questionnaires, and cognitive function tests were performed by the trained research nurse. Toxicities were recorded at baseline, weekly during radiation, during the last week of radiation, and weekly during the 4-week postradiation follow-up. Toxicities were graded using CTCAE version 4.0 criteria and were recorded on a flow sheet as part of the physician assessment.

Study Settings and Study Instruments

Fatigue was measured by the Fatigue subscale of the Functional Assessment of Chronic Illness Therapy-Fatigue subscale (FACIT-F) and the Brief Fatigue Inventory (BFI). Sleepiness was measured with the Epworth Sleep Scale (ESS). QOL, including brain-specific symptoms, was measured by the FACT-Brain (Functional Assessment of Cancer Therapy). Cognitive function was measured by a standardized battery of validated tests of key domains of cognition.[20–23] Tests included Verbal Fluency-Category (VF-C) (Animals), Hopkins Verbal Learning Test-Revised (HVLT- R), Trail Making Tests Parts A and B (TMT-A and TMT-B), and Digit Span Test-Backwards (DST-B). The VF-C test[24] measures speed of mental processing, verbal fluency, and executive functions. The HVLT-R[25] measures verbal learning and episodic memory. The TMT-A and TMT-B[26] measure attention, concentration, and visual

motor speed. The DST-B[27] assesses attention, concentration, and working memory. The FACIT-F subscale[21] has 13 fatigue-specific items. The BFI[28] is a rapid assessment of fatigue that includes several visual analogue scales as well as questions that assess the impact of the patient's fatigue on QOL. The ESS[29] is a measure of daytime sleepiness in which patients record their likelihood of dozing or sleeping during a number of routine daily activities.

Outcomes and Statistical Analysis

The primary objective of this randomized phase II trial was to assess the feasibility of using armodafinil to reduce fatigue in primary brain tumor patients undergoing brain RT. Secondary objectives were to estimate the rate of toxicity or adverse events associated with armodafinil, to estimate the variability of the fatigue, QOL, and cognitive function outcomes, and to obtain preliminary estimates of the effect of armodafinil on these outcomes. Participants were stratified by KPS (60%–80% vs 90%–100%) and whether or not they had received chemotherapy and were assigned with equal probability to armodafinil or placebo using variably sized permuted block randomization.

The sample size of 54 participants allowed us to detect a 0.80 standard deviation difference in fatigue between the treatment arms with 80% power at the 5% 1-sided level of significance, assuming a 25% loss to follow-up as derived from previous clinical trial retention rates.[9,30] Means, standard deviations, and pre/post correlations, useful for subsequent sample size calculations, were provided for each outcome measure at each time. Chi-square and Fisher exact tests were used to assess treatment differences in toxicities. Mixed effects repeated measures models were used to assess treatment differences in fatigue, ESS, QOL, and cognitive function and to obtain least squares (LS) estimates of the measures over time. An unstructured covariance matrix was used to model the correlation in outcomes over time. The models were constrained to have equal group means at baseline as detailed by Fitzmaurice et al[31] These models use all the data with the assumption that missing data are missing at random. Additional mixed effects repeated measures analysis of covariance models were used, which included baseline levels of fatigue to determine if the effect of the treatment was consistent across initial fatigue levels. Results are presented as LS means and standard errors for each treatment arm as well as 90% 2-sided confidence limits (since we planned to test the primary outcome at the 5% 1-side level of significance). Because this was a small pilot study, we did not adjust *P* values or confidence limits for multiple comparisons.

Results

Patient Accrual and Treatment Compliance

From September 2010 until October 2012, a total of 54 patients in multiple community and academic institutions were enrolled and randomized to either armodafinil ($n = 26$) or placebo ($n = 28$). Baseline patient characteristics are summarized in Table 1 by treatment arm. Ages ranged from 20–79 years with a median of 59 years; 40 (74%) were aged ≥50 years, and 26 (48%) were aged ≥60 years. Most participants were non-Hispanic whites (93%), and most (75%) had a KPS of ≥80%. Slightly more than half (54%) of the participants were women, and 74% percent were within the CDC-defined overweight-to-obese BMI range. The most common brain tumor types were glioblastoma multiforme in 61%. Participant characteristics did not differ significantly between treatment groups. The retention rate was 85% in the armodafinil arm and 89% in the placebo arm by the end of RT and 85% and 75%, respectively, at study completion. The self-reported compliance was 94% while on therapy and did not differ between treatment arms ($P = .55$). Of those participants who dropped out of the study, reasons included progression of disease ($n = 1$ armodafinil), refusal of further therapy ($n = 1$ armodafinil, $n = 2$ placebo), toxicity ($n = 2$ placebo), death (1 participant in each arm), and other (1 participant in each arm). There were no

Table 1. Baseline patient characteristics

Characteristic	Armodafinil *No* (%)	Control *No* (%)
Total	26 (100)	28 (100)
Age (y)		
Median (range)	59 (28–78)	58 (20–79)
Age ≥50	21 (81)	19 (68)
Age ≥60	13 (50)	13 (46)
Body mass index		
Median (range)	27.7 (21.5–47.2)	28.3 (19.4–41.8)
Underweight-normal (<25)	8 (31)	6 (21)
Overweight (25–30)	6 (23)	12 (43)
Obese (≥30)	12 (46)	10 (36)
Performance status strata		
1 – PS 60–80, no chemo	1 (4)	2 (7)
2 – PS 60–80, chemo	14 (54)	15 (54)
3 – PS 90–100, no chemo	3 (12)	4 (14)
4 – PS 90–100, chemo	8 (31)	7 (25)
Karnofsky performance status		
60	3 (12)	1 (4)
70	3 (12)	7 (25)
80	9 (35)	9 (32)
90	10 (38)	6 (21)
100	1 (4)	5 (18)
Sex		
Female	14 (54)	15 (54)
Male	12 (46)	13 (46)
Race/ethnicity		
Hispanic	1 (4)	0 (0)
Asian	0 (0)	1 (4)
Black	0 (0)	2 (7)
White	25 (96)	25 (89)
Histology		
Glioblastoma multiforme	15 (58)	18 (64)
Meningioma	5 (19)	2 (7)
Other*	6 (24)	8 (30)

*Other: Anaplastic astrocytoma, anaplastic oligoastrocytoma, low-grade astrocytoma, low-grade oligodendroglioma, atypical meningioma, medulloblastoma, pituitary adenoma, gliosarcoma.

significant differences in patients in either group who were taking concomitant medications that may affect sleepiness, including chemotherapy, steroids, antidepressants, sedatives, or benzodiazepines. These are represented in Supplementary Table S1.

Toxicity

Headache was the most common complaint and was experienced to some degree by 73% of the armodafinil participants and 59% of the control participants ($P = .39$). Insomnia occurred in 46% and 52% of the armodafinil and control groups, respectively ($P = .79$), nausea in 46% and 48% ($P > .99$), anxiety in 58% and 37% ($P = .17$), arthralgia in 12% and 26% ($P = .29$), dizziness in 35% and 30% ($P = .77$), dry mouth 35% and 33% ($P > .99$), sinusitis in 4% and 11% ($P = .61$), sore throat in 23% and 19% ($P = .74$), and upper respiratory infection in 8% and 11% ($P > .99$). The most common grade 2+ toxicities reported included 15% anxiety, 15% nausea, 19% headaches, and 20% insomnia. There were 10 serious adverse events, 4 of which were possibly related to treatment. These included 3 events on the placebo arm; (one grade 2 seizure, one grade 3 increase in liver function tests, one grade 4 agitation/personality change). On the armodafinil arm, a single participant experienced a grade 3 headache with associated chest pain.

Fatigue and Sleepiness

Fatigue and sleepiness outcomes are summarized in Table 2. Note that higher FACIT-fatigue values indicate less patient fatigue, while higher BFI and ESS values indicate worse fatigue and sleepiness, respectively. Fatigue levels worsened during radiation and improved following completion of radiation on both arms. Sleepiness improved slightly for armodafinil participants but worsened slightly for the control participants. Results of the mixed model analyses are summarized in Table 3. There were no statistically significant differences between the placebo and armodafinil groups in either fatigue outcome measure at either time point (one-sided P value of .635 and .449 for FACIT_F and BFI, respectively). Additionally, there was no significant change in ESS over time, and the 2 groups were similar at each time. In the mixed effects covariance model, we noted a significant interaction between baseline fatigue and treatment, indicating that the effect of treatment was not consistent across initial fatigue levels. We subsequently dichotomized baseline fatigue at the median level and repeated analyses for those with greater or lesser baseline fatigue (Table 3). For those participants who presented with worse fatigue at baseline, treatment with armodafinil resulted in significantly improved fatigue compared with those receiving placebo. However, the opposite was true for those participants with lesser fatigue levels at baseline; participants receiving placebo reported significantly less fatigue.

Quality of Life

QOL outcomes are summarized in Table 4. None of the QOL outcomes differed significantly between treatment arms at the end of RT or at 4 weeks post RT. These analyses were repeated, stratified by baseline fatigue level (Table 5). In those participants with greater fatigue at baseline, there was a statistically significant advantage of armodafinil for the total FACT-BR score ($P < .001$) at the end of RT. This was driven by differences in the functional ($P = .003$) and physical ($P = .001$) subscale scores. Among participants with less fatigue at baseline, those receiving armodafinil were significantly worse for the functional subscale ($P = .006$) at the end of RT. None of the other subscale scores differed significantly between treatment arms.

Neurocognitive Function

Neurocognitive outcomes are summarized in Table 6. In general, the scores on most cognitive tests improved slightly over time in both groups. However there were no significant differences between treatment arms at the end of RT or at 4 weeks post RT for any of the neurocognitive tests. Armodafinil also did not improve neurocognitive outcomes at the end of RT or at 4 weeks post RT in the subsets of participants with high or low levels of fatigue at baseline.

Table 2. Summary of fatigue and sleepiness (raw data) by treatment and time

Outcome	Time	Armodafinil				Control			
		No	Mean	SD	Correlation*	*No*	Mean	SD	Correlation*
FACIT-Fatigue	Baseline	26	34.0	10.9		27	38.3	11.6	
	EndRT	19	31.4	12.2	0.18	23	34.1	13.0	0.68
	4wpRT	20	32.4	12.2	−0.12	20	38.8	11.5	0.72
BFI	Baseline	26	3.45	2.39		27	2.51	2.11	
	EndRT	21	3.90	2.74	0.44	25	3.70	2.87	0.38
	4wpRT	21	3.76	2.74	0.52	21	2.67	2.72	0.32
ESS	Baseline	26	8.62	4.41		27	6.85	3.90	
	EndRT	19	7.32	4.24	0.37	25	7.75	4.53	0.32
	4wpRT	20	7.40	5.60	0.27	20	7.70	3.63	0.37

Abbreviations: 4wpRT, 4 weeks post radiation therapy; BFI, Brief Fatigue Inventory; EndRT, end of radiation therapy assessment; ESS, Epworth Sleepiness Scale; FACIT, Functional Assessment of Chronic Illness Therapy;SD, standard deviation.
Higher scores in the FACIT indicate better symptoms. Higher scores in the BFI and ESS indicate worse symptoms.
*Pearson correlations with baseline.

Table 3. Least squares estimates of fatigue and sleepiness at each time and post-randomization treatment differences

Outcome	Time	Armodafinil LS Mean (SE)	Control LS Mean (SE)	Difference in LS Mean (90% CI)
FACIT-Fatigue	Baseline	36.2 (1.55)	36.2 (1.55)	—
	EndRT	30.9 (2.74)	32.1 (2.56)	−1.25 (−7.28 to 4.78)
	4wpRT	32.0 (2.56)	36.0 (2.52)	−3.99 (−9.86 to 1.88)
BFI	Baseline	2.97 (0.32)	2.97 (0.32)	
	EndRT	3.88 (0.58)	3.97 (0.54)	−0.10 (−1.38 to 1.18)
	4wpRT	3.71 (0.57)	3.29 (0.55)	0.42 (−0.85 to 1.69)
ESS	Baseline	7.72 (0.59)	7.72 (0.59)	
	EndRT	7.70 (1.02)	8.24 (0.92)	−0.54 (−2.77 to 1.70)
	4wpRT	7.26 (1.03)	8.37 (1.00)	−1.11 (−3.47 to 1.26)
Greater fatigue at baseline				
FACIT-Fatigue	Baseline	27.1 (1.89)	27.1 (1.89)	—
	EndRT	31.5 (2.53)	23.2 (3.28)	8.24 (2.16–14.3)
	4wpRT	31.9 (3.45)	28.3 (5.10)	3.62 (−6.56 to 13.8)
Lesser fatigue at baseline				
FACIT-Fatigue	Baseline	44.7 (0.77)	44.7 (0.77)	—
	EndRT	24.9 (4.74)	38.8 (3.15)	−13.9 (−23.6 to −4.11)
	4wpRT	29.2 (3.92)	41.4 (2.77)	−12.2 (−20.4 to −4.02)

Abbreviations: 4wpRT, 4 weeks post radiation therapy; BFI, Brief Fatigue Inventory; CI, confidence interval; EndRT, end of radiation therapy assessment; ESS, FACIT, Functional Assessment of Chronic Illness Therapy; LS, least squares; SE, standard error Epworth Sleepiness Scale.
Lower scores in the FACIT-Fatigue indicate worse symptoms, while higher scores in the BFI and ESS indicate worse symptoms.

Table 4. Summary of quality of life outcomes (raw data) by treatment and time

Outcome	Time	Armodafinil				Control			
		No	Mean	SD	Correlation*	*No*	Mean	SD	Correlation*
Social	Baseline	26	24.8	3.29		27	23.3	4.09	
	EndRT	19	23.4	4.39	0.62	25	22.1	5.59	0.72
	4wpRT	20	23.1	3.99	0.58	20	22.6	5.12	0.71
Emotional	Baseline	26	16.3	5.47		27	18.8	3.51	
	EndRT	20	18.3	3.76	0.64	25	18.3	4.27	0.62
	4wpRT	20	17.7	2.89	0.51	20	19.5	3.68	0.41
Functional	Baseline	26	13.7	7.63		27	17.7	5.98	
	EndRT	20	13.8	7.16	0.53	25	16.2	6.96	0.78
	4wpRT	20	15.5	6.44	0.46	20	17.3	6.82	0.73
Physical	Baseline	26	20.7	4.75		27	23.8	3.85	
	EndRT	20	19.4	5.71	0.23	25	19.8	5.67	0.54
	4wpRT	20	20.3	6.53	0.13	20	23.2	4.13	0.63
FACT-G	Baseline	26	75.4	16.1		27	83.6	13.7	
	EndRT	19	75.3	14.2	0.57	25	76.4	16.3	0.82
	4wpRT	20	76.7	15.6	0.50	20	82.4	16.2	0.76
Brain	Baseline	26	57.8	16.5		27	66.5	13.7	
	EndRT	19	62.5	15.2	0.81	25	67.5	15.3	0.83
	4wpRT	20	62.5	12.5	0.66	20	69.8	16.0	0.78
FACT-Br	Baseline	26	133.2	30.6		27	150.2	25.0	
	EndRT	19	137.8	27.5	0.74	25	143.9	29.9	0.89
	4wpRT	20	139.2	26.8	0.61	20	152.2	30.3	0.79

Abbreviations: 4wpRT, 4 weeks post radiation therapy; EndRT, end of radiation therapy assessment; FACT, Functional Assessment of Cancer Therapy; SD, standard deviation.
Social, Emotional, Functional, and Physical are the core components of the FACT quality of life questionnaire. FACT-G is the sum of the 4 components. FACT-Br is the sum of FACT-G and the brain function subscale. Higher scores indicate better function in each of these measures.
*Pearson correlations with baseline.

Table 5. Least squares estimates of selected quality of Life outcomes at each time and post-randomization treatment differences stratified by baseline fatigue

Outcome	Time	Armodafinil LS Mean (SE)	Control LS Mean (SE)	Difference in LS Means (90% CI)
Greater fatigue at baseline				
Functional	Baseline	11.9 (1.20)	11.9 (1.20)	—
	EndRT	15.4 (1.45)	8.8 (1.73)	6.59 (3.25–9.92)
	4wpRT	15.7 (1.66)	11.0 (2.25)	4.75 (0.31–9.19)
Physical	Baseline	19.3 (0.89)	19.3 (0.89)	—
	EndRT	20.4 (1.25)	13.4 (1.52)	7.01 (3.84–10.19)
	4wpRT	20.5 (1.47)	19.6 (2.14)	0.85 (−3.41 to 5.12)
FACT-G	Baseline	70.2 (2.72)	70.2 (2.72)	—
	EndRT	75.0 (2.76)	58.9 (3.25)	16.17 (10.12–22.22)
	4wpRT	75.3 (3.55)	70.0 (4.90)	5.29 (−4.17–14.75)
Lesser fatigue at baseline				
Functional	Baseline	19.0 (1.26)	19.0 (1.26)	—
	EndRT	12.0 (1.93)	18.0 (1.50)	−6.00 (−9.42 to −2.58)
	4wpRT	15.1 (2.13)	17.1 (1.67)	−2.02 (−6.04 to 2.01)
Physical	Baseline	24.7 (0.54)	24.7 (0.54)	—
	EndRT	18.2 (1.85)	22.0 (1.27)	−3.74 (−7.57 to 0.09)
	4wpRT	19.7 (1.98)	23.4 (1.45)	−3.61 (7.78–0.57)
FACT-G	Baseline	87.1 (2.45)	87.1 (2.45)	—
	EndRT	71.7 (4.85)	81.2 (3.65)	−9.51 (−18.14 to −0.88)
	4wpRT	76.6 (5.17)	82.1 (4.14)	−5.47 (−14.90 to 3.97)

Abbreviations: 4wpRT, 4 weeks post-radiation therapy;CI, confidence interval; EndRT, end of radiation therapy assessment;. FACT, Functional Assessment of Cancer Therapy.
Social, Emotional, Functional, and Physical are the core components of the FACT quality of life questionnaire. FACT-G is the sum of the 4 components. FACT-Br is the sum of FACT-G and the brain function subscale. Higher scores indicate better function in each of these measures.

Discussion

Fatigue has been shown to be a prominent symptom that leads to worsening QOL in brain tumor patients.[32,33] Multiple randomized trials have now demonstrated that fatigue is worsened by WBRT. The EORTC 22952 study comparing surgical or radiosurgical management with WBRT in participants with brain metastases revealed a clinically significant mean difference of 11.9 points in FACIT-F in the WBRT arm by 8 weeks post WBRT.[2] A prior EORTC phase III study of prophylactic cranial irradiation in extensive stage small cell lung cancer also demonstrated that the participants who received WBRT experienced worsened fatigue scores.[26] Prospective data demonstrating the degree of fatigue in patients with partial brain irradiation are scarce. In a recent prospective study of mixed primary and metastatic brain tumors, a mean 3-point decrease in FACIT-F scores was detected between baseline and completion of partial or WBRT.[9] Several prospective studies have evaluated the efficacy of CNS stimulants for the treatment of radiation-induced fatigue. In the same study by Butler et al, a randomized trial of methylphenidate was performed in participants with primary brain tumors who received brain RT.[9] While this study was negative, there have been anecdotal reports of patients responding to methylphenidate.[5,6] Modafinil is another CNS stimulant that has gathered interest. While the exact mechanism of modafinil for relief of fatigue is unknown, there has been significant interest in wakefulness-promoting drugs for radiation-induced fatigue. Kaleita et al performed a pilot study of 30 participants with primary brain tumors that assessed the efficacy of modafinil using cognitive function, mood, and fatigue measures.[14] In this pilot study, 87% of participants received RT.

The current trial represents the first randomized trial evaluating armodafinil for radiation-induced fatigue. While there was no overall difference detected in fatigue between the 2 arms, participants who had worsened baseline fatigue scores and were assigned to armodafinil treatment experienced statistically significant improvements in fatigue at the end of radiation. There was a corresponding improvement in QOL scores as measured by the FACT-Br in this subpopulation, possibly due to the improvement in fatigue. Interestingly, the participants who had significantly less fatigue at baseline were found to have worse fatigue measures in the armodafinil group versus the placebo group. It is unclear how to attribute this difference, but it does not appear to be related to any worsened side effects of armodafinil because the participants with less fatigue were found to have the same rate of adverse side effects as those with more fatigue at baseline. Preliminary results of another recent trial of armodafinil for radiation-induced fatigue in participants with malignant gliomas were recently presented at the American Society of Clinical Oncology national meeting in 2014. The investigators found a nonsignificant trend ($P = .07$) for improved FACIT-F scores among 80 participants.[34] Neither study assessing armodafinil showed any difference between armodafinil and placebo with regard to toxicity. The

Table 6. Summary of neurocognitive outcomes (raw data) by treatment and time

Outcome	Time	Armodafinil				Control			
		No	Mean	SD	Correlation*	*No*	Mean	SD	Correlation*
HVLT immediate recall	Baseline	26	17.6	8.04		27	21.7	6.40	
	EndRT	19	19.3	8.33	0.91	24	20.3	6.42	0.88
	4wpRT	19	20.5	9.29	0.91	20	22.7	7.16	0.66
HVLT delayed recall	Baseline	24	5.42	4.19		26	6.73	3.72	
	EndRT	19	6.26	4.27	0.88	23	6.78	2.95	0.84
	4wpRT	19	6.05	4.03	0.96	19	7.21	3.44	0.86
HVLT true positive	Baseline	26	10.1	1.97		27	10.5	1.81	
	EndRT	20	10.3	2.87	0.64	24	10.8	1.42	0.64
	4wpRT	19	10.3	2.62	0.67	20	10.9	1.33	0.23
HVLT discrimination	Baseline	26	8.81	2.68		27	9.56	2.44	
	EndRT	20	8.55	3.15	0.83	24	8.96	2.07	0.70
	4wpRT	19	8.68	3.40	0.78	20	9.85	1.87	0.54
HVLT % savings	Baseline	23	64.2	41.5		26	74.1	35.3	
	EndRT	19	72.3	37.4	0.71	23	78.3	19.5	0.64
	4wpRT	19	67.2	36.9	0.68	19	81.5	29.8	0.40
COWA	Baseline	26	12.6	5.89		27	16.5	6.62	
	EndRT	19	14.9	6.25	0.82	25	15.4	6.27	0.79
	4wpRT	19	14.6	7.05	0.77	20	17.4	5.76	0.79
TMT_A	Baseline	25	68.0	66.5		27	54.7	46.0	
	EndRT	20	49.2	34.1	0.62	23	59.2	61.6	0.96
	4wpRT	19	50.0	43.8	0.66	19	39.8	30.6	0.82
TMT_B	Baseline	24	167.6	101.6		27	142.3	100.5	
	EndRT	19	141.8	98.4	0.82	22	106.7	74.9	0.81
	4wpRT	19	152.9	103.3	0.93	18	114.0	81.6	0.78
DST_B	Baseline	26	4.77	2.60		27	5.89	2.62	
	EndRT	19	5.21	1.93	0.80	23	6.48	2.43	0.51
	4wpRT	19	5.63	2.73	0.84	20	6.75	2.31	0.71

Abbreviations: 4wpRT, 4 weeks post radiation therapy assessment; COWA, Controlled Oral Word Association Test;EndRT, end of radiation therapy assessment; HVLT, Hopkins Verbal Learning Test; TMT-A, Trailmaking Test A; TMT-B, Trailmaking Test B; DST-B, Digit Span Test Backwards.
Higher scores on the HVLT, COWA, and DST-B indicate better performance, while lower scores on the TMT-A and TMT-B indicate worse performance.
HVLT % savings is the percentage of the immediately recalled words that were remembered correctly after a delay of some time.
*Pearson correlations with baseline.

results of these 2 small randomized studies support a phase III study of armodafinil, especially among more fatigued patients.

It has been hypothesized that fatigue may contribute to the worsening of cognitive function in the brain-irradiated population. In the study by Kaleita et al, participants receiving modafinil also experienced statistically significant improvement in executive functioning on the Verbal Fluency and Trail Making tests.[14] In the current study, however, there was no significant improvement in cognitive function in either the sample as a whole or in the more fatigued subset whose fatigue and QOL scores benefited from armodafinil. It is unclear if the differences in outcomes in these 2 studies may be due to a difference in participant selection between the 2 studies.

Cella et al have previously reported that a 3-point change in the FACIT-F scale constitutes a clinically important difference in patients with cancer-related anemia. In the current study, participants with fatigue scores on the FACIT-F that were less than the median score were considered to have more severe fatigue. Of those 18 participants with more severe fatigue, 8 of them (44%) improved by more than 3 points. Of the 24 participants who had better than median scores for fatigue at baseline, only 4 (17%) improved with armodafinil. The comparison of participants with more versus less fatigue had a *P* value of .0486. Thus, these data show an encouraging trend and will be useful to help power future prospective studies.

There are several limitations of the current study. The accrued participant sample was heterogeneous and included patients with high- and low-grade tumors as well as those receiving brain irradiation at a wide range in volumes. The study was not adequately powered to detect treatment differences within subpopulations. Furthermore, there has been previous evidence to suggesting that for cognitive endpoints, the volume of brain irradiated and the location of the targeted treatment may predict symptoms after treatment.[35] The study also did not have central imaging review, and thus tumor volume and location data were not obtained. With heterogeneity of tumor locations and treatment volumes, the effects of armodafinil may have been diluted by the inclusion of participants with

smaller tumors or with tumors in locations that would lead to less fatigue.

The heterogeneity of the sample is a major limitation of the study. Unfortunately, the study was not powered to detect differences in the subgroups; thus, this is a shortcoming of the trial design as opposed to analysis. As a phase II study, however, our major goals were to show feasibility and inform us on the power needed for a phase III study. A phase III study is currently being performed through the Alliance for Clinical Trials in Oncology, and hopefully this larger study will be able to evaluate subgroups.

There was also a possible self-selection bias of patients motivated to enroll into a study as well as physician selection preference for healthier patients to enroll; thus, these participants may not be representative of all primary brain tumor patients or of more fatigued patients who might have benefited from the addition of armodafinil. However, nearly all brain tumor patients, regardless of benign or malignant histology, are known to be affected by radiation-induced fatigue. Several studies have shown that patients with benign or low-grade tumors also experience fatigue with RT to the brain.[36] Follow-up studies may be best designed to enroll only patients with significant baseline fatigue scores.

Conclusion

Armodafinil was well tolerated, and the majority of participants completed the study and adhered to the treatment schedule. While there was no overall difference between participants with irradiated primary brain tumors who received armodafinil versus placebo, those with worse baseline fatigue scores appeared to have a benefit from armodafinil. A phase III study in patients with greater baseline fatigue is needed to adequately test this treatment.

Supplementary Material

Supplementary material is available online at *Neuro-Oncology* (http://neuro-oncology.oxfordjournals.org/).

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