

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

Edward G. Shaw, Robin Rosdhal, Ralph B. D'Agostino Jr, James Lovato, Michelle J. Naughton, Michael E. Robbins, and Stephen R. Rapp

ABSTRACT

Purpose

A prospective, open-label phase II study was conducted to determine whether donepezil, a US Food and Drug Administration–approved reversible acetylcholinesterase inhibitor used to treat mild to moderate Alzheimer's type dementia, improved cognitive functioning, mood, and quality of life (QOL) in irradiated brain tumor patients.

Patients and Methods

Thirty-four patients received donepezil 5 mg/d for 6 weeks, then 10 mg/d for 18 weeks, followed by a washout period of 6 weeks off drug. Outcomes were assessed at baseline, 12, 24 (end of treatment), and 30 weeks (end of wash-out). All tests were administered by a trained research nurse.

Results

Of 35 patients who initiated the study, 24 patients (mean age, 45 years) remained on study for 24 weeks and completed all outcome assessments. All 24 patients had a primary brain tumor, mostly low-grade glioma. Scores significantly improved between baseline (pretreatment) and week 24 on measures of attention/concentration, verbal memory, and figural memory and a trend for verbal fluency (all $P < .05$). Confused mood also improved from baseline to 24 weeks ($P = .004$), with a trend for fatigue and anger (all $P < .05$). Health-related QOL improved significantly from baseline to 24 weeks, particularly, for brain specific concerns with a trend for improvement in emotional and social functioning (all $P < .05$).

Conclusion

Cognitive functioning, mood, and health-related QOL were significantly improved following a 24-week course of the acetylcholinesterase inhibitor donepezil. Toxicities were minimal. We are planning a double blinded, placebo-controlled, phase III trial of donepezil to confirm these favorable results.

J Clin Oncol 24:1415-1420. © 2006 by American Society of Clinical Oncology

INTRODUCTION

Cognitive impairment associated with primary or metastatic brain tumors and their treatments, including radiation therapy, 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.¹⁻³ Clinically, patients frequently complain of fatigue, confusion, and cognitive impairment (eg, decreased attention and concentration, poor short term memory, and expressive language difficulty). These symptoms are often associated with distressed mood and reduced quality of life (QOL). The patient's perspective is eloquently described by Mrs Susan T. Sontag, Vice President of the Sontag Foundation, a philanthropic organiza-

tion with the primary focus of improving the lives of individuals with brain tumors. Sontag described her current symptoms 16 years following surgery, radiation therapy, and chemotherapy for a left temporal anaplastic astrocytoma:

"Everything I do is slow. I walk, talk and think slowly. . . I still have no short-term memory. . . Much of the time I can't even remember the names of relatives and close friends. . . I am always confused. . . Because I look normal and often sound normal, people assume I am normal. But I'm not. . . I'm more emotional. I cry a lot. And I get depressed a lot knowing that I will never have my competence back." (Sontag Foundation Distinguished Scientists Awards ceremony speech at the Society for Neuro-Oncology Meeting, Toronto, Canada, November 20, 2004.)

From the Departments of Radiation Oncology, Public Health Sciences, and Psychiatry and Behavioral Medicine, Wake Forest University School of Medicine, Brain Tumor Center of Excellence of WFU, Winston-Salem, NC.

Submitted July 14, 2005; accepted January 3, 2006.

Supported by the Comprehensive Cancer Center of Wake Forest University Community Clinical Oncology Program Research Base Grant No. NCI 1 U10 CA81851.

Presented in part at the Society of Neuro-Oncology Ninth Annual Scientific Meeting, Toronto, Canada, November 18-21, 2004.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Address reprint requests to Edward G. Shaw, MD, Department of Radiation Oncology, Wake Forest University School of Medicine, Medical Center Blvd, Winston-Salem, NC 27157-1030; e-mail: eshaw@wfubmc.edu.

© 2006 by American Society of Clinical Oncology

0732-183X/06/2409-1415/\$20.00

DOI: 10.1200/JCO.2005.03.3001

At the present time, there are no proven treatments for cognitive impairment following brain cancer and subsequent cranial irradiation, nor are there any known effective preventive strategies.

The use of partial or whole brain radiation in the treatment of primary brain tumors and brain metastases is increasing. In 2005, there will be an estimated 18,500 newly diagnosed primary brain tumors.⁴ The number of brain metastases is significantly greater. Approximately 20% to 40% of the > 1,300,000 new cancer patients diagnosed in 2005 will develop brain metastases, making this the second most common site of metastatic cancer and the most common neurologic manifestation of cancer. Currently, approximately 200,000 cancer patients per year receive whole brain radiation for brain metastases, with another 15,000 receiving partial or whole brain radiation for treatment of a primary brain tumor.

Clinically, radiographically, and in some respects pathologically, radiation-induced injury is similar to Alzheimer's dementia (AD).⁵ Imaging findings in AD include cerebral white-matter changes (demyelination), decreased cerebral perfusion, decreased cerebral metabolism, and decreased cerebral *N*-acetyl aspartate, as demonstrated by magnetic resonance imaging, perfusion positron emission tomography, perfusion magnetic resonance imaging, and magnetic resonance spectroscopy. Preliminary data of these modalities in radiation-induced brain injury are consistent with these findings.⁶ Research into treatments for AD has led to the development of several pharmacologic agents to reduce the cognitive impairment and improve behavioral functioning. Among the most widely studied drugs are those enhancing cholinergic neurotransmission. Both choline acetyltransferase and acetylcholine levels are significantly reduced in patients with AD.^{7,8,9,10} The acetylcholinesterase (AChE) inhibitors, including donepezil, rivastigmine, and galantamine, all increase acetylcholine levels in the brain, and their use is rapidly rising.^{9,11,12} Donepezil (Aricept, Pfizer Pharmaceuticals, New London, CT), the most widely used AChE inhibitor, has demonstrated efficacy in mild to severe AD^{10,13} and vascular dementia.¹²

A contemporary view of radiation-induced brain injury¹⁴ suggests that the expression of radiation-induced normal tissue damage involves complex and dynamic interactions between several cell types within a particular organ.¹⁵⁻¹⁸ In the brain, these include not only the classical targets (ie, the oligodendrocytes and endothelial cells), but also the astrocytes, microglia, and neurons. These cells are now viewed not as passive bystanders, merely dying as they attempt to divide, but rather as active participants in an orchestrated, yet limited, response to injury.^{19,20} This new paradigm suggests that radiation-injury can be prevented and/or treated by the application of therapies directed at altering steps in the cascade of events leading to the clinical expression of normal tissue injury. Building on this conceptualization, the existence of animal data suggesting that ionizing radiation decreases both choline acetyltransferase and acetylcholine levels in irradiated mice,⁶ and the clinical similarities between radiation-induced cognitive dysfunction and AD, we hypothesized that partial or whole brain radiation results in neuronal injury that, in turn, causes an acetylcholine deficiency and that an AChE inhibitor, like donepezil, would decrease cognitive symptoms in brain-irradiated patients and improve patients' QOL and mood. Since donepezil had not been tested prospectively in this patient population, we elected to perform an open-label phase II study. Participants were recruited following cranial irradiation, and no attempt was made to partial out cognitive impairment attributable to the brain tumor(s).

PATIENTS AND METHODS

Patient Population and Eligibility Criteria: A Priori Inclusion and Exclusion Criteria Were Established

Eligibility criteria included: age \geq 18 years, life expectancy \geq 30 weeks, partial or whole brain radiation \geq 6 months before enrollment, no imaging evidence of tumor progression in previous 3 months, on stable or decreasing steroid dose, Karnofsky Performance Status (KPS)²¹ \geq 70, and no brain tumor treatment planned during course of study. The study was approved by the institutional review board of Wake Forest University School of Medicine (Winston-Salem, NC). All study participants provided informed consent.

Treatment

Donepezil 5 mg/d was given for 6 weeks and then increased to 10 mg/d for 18 weeks (total duration = 24 weeks), if there were no severe adverse events defined as \geq grade 3 toxicities according to the National Cancer Institute Common Toxicity Criteria (version 2.0). Treatment was then discontinued for a 6-week wash-out period. Thus, patients served as their own control twice, ie, baseline versus on-treatment and on-treatment versus the postwashout.

Cognitive functioning was the primary outcome. Mood and QOL were secondary outcomes. The cognitive test battery included standardized measures of global cognitive functioning (Mini-Mental State Exam [MMSE]²²), attention and concentration (Trail Making Test Part-A²³ and Digit Span Test²⁴) visual-constructional skills (Revised Rey-Osterrieth Complex Figure Test²⁵), verbal fluency (Controlled Oral Word Association test²⁶), executive function (Trail Making Test Part B²³), verbal memory (California Verbal Learning Test-II²⁷), and figural memory (Revised Rey-Osterrieth Complex Figure Test²⁵). 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 scale²¹ and the Functional Assessment of Cancer Therapy-Brain (FACT-Br),²⁸ 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),²⁹ 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 donepezil administration, and again at weeks six (dose escalation from 5 mg/d to 10 mg/d), 12, and 24 (cessation of treatment), then at week 30 (following wash-out). Toxicities were evaluated at each assessment point. At week 30, patients were given the choice to resume donepezil 10 mg/d.

Statistical Considerations

On the basis of existing data,³⁰ a normal test score for the Trail Making Test Part B, a test of executive brain function, is 82 seconds with a standard deviation (SD) of 31 seconds. Data from Laukkanen¹ indicate that patients who have had whole brain irradiation have a mean score of about 3 SDs above the normal value (173 seconds). This variable was used to determine the power and sample size needed to accomplish the study goal of having sufficient power to detect a change in the time to complete the Trail Making Test Part B equal to 0.74 SD (23 seconds) to consider the donepezil effective. Using methods described by Dupont and Plummer³¹ and setting the power equal to 80% with $\alpha = .05$ (for a two-sided test), 23 analyzable patient subjects who completed 24 weeks of treatment were needed to detect a significant change. Because the potential for disease recurrence is high in patients with brain tumors, a sample size of 35 patient subjects was chosen, estimating that about one third of patients who enrolled on the study would not complete it. For the present report, descriptive statistics are presented comparing patients at week 0 (baseline) to week 24. The difference in baseline to week 24 scores for cognitive, mood, and QOL variables were assessed with paired *t*-tests. Given the number

of outcomes variables and planned tests, we chose the more conservative alpha level of .01.

RESULTS

Patient Characteristics

Thirty-five patients were enrolled between 2001 and 2003, including 23 patients with glioma (about half low-grade, half high-grade), four patients with meningioma, seven patients with other primary brain tumor histologies, and one patient with metastatic disease. Tumor locations were: whole brain ($n = 3$; 9%), parietal ($n = 6$; 17%), temporal ($n = 8$; 23%), frontal ($n = 7$; 20%), meninges ($n = 3$; 9%), pituitary ($n = 3$; 9%), and other ($n = 7$; 20%). Eleven patients went off-study before 24 weeks—five because of tumor progression, one because of nausea, two because of poor adherence, and three patients withdrew from study without explanation. Twenty-four patients remained on-study for the 24 weeks and completed all assessments. All 24 patients had a primary brain tumor, mostly low-grade glioma, their median age was 45 years, 46% were female, 92% were white, and 8% were black. Patients who remained on-study did not differ significantly at baseline from those who dropped out of the study in terms of sex, race, mood, cancer-related QOL (FACT-Br, KPS), or cognitive performance (all $P > .28$). Those remaining on-

study were younger (38.4 years of age v 44.7 years of age; $P = .04$). As a result of a data collection error, education level was not obtained.

Cognitive Function

At baseline, there was evidence of significant cognitive impairment in the sample. Mean scores on the tests of attention and concentration, memory, and executive function were at least 1.5 SDs below the mean for normative sample. Following 24 weeks of treatment with donepezil, scores had improved significantly on tests in several cognitive domains (Table 1) including attention/concentration (Digit Span Test Total), verbal memory (California Verbal Learning Test-II), figural memory (Modified Rey-Osterrieth Figure Test recall), and a trend toward significance for verbal fluency (Controlled Oral Word Association Test). No significant change was found for global cognitive function (MMSE) or executive function (Trail Making Test).

Mood

At 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 for normative sample). Following 24 weeks of treatment, scores were significantly improved for confusion with trends toward significance for overall distressed mood, fatigue, and anger; but not for the depression, anxiety, or vigor subscales (Table 1).

Table 1. Pre- and Post-Treatment Scores on Cognitive, Mood, and Quality of Life Measures

Measure	Baseline		Post-Treatment		<i>P</i>
	Mean	SD	Mean	SD	
Cognitive functioning					
Mini-Mental State Exam	28.2	2.2	28.5	1.8	.11
Digit Span Test, total	14.2	3.7	15.5	5.0	.007
Controlled Oral Word Association	29.3	12.9	32.5	13.9	.02
Trail Making Test-A, sec.	52.1	32.8	42.3	19.4	.21
Trail Making Test-B, sec.	137.4	87.7	132.9	93.4	.64
California Verbal Learning Test-II					
Short-delay recall	7.8	4.1	8.4	4.7	.20
Short-delay (cued) recall	8.7	4.1	10.3	4.2	< .0001
Long-delay recall	8.6	4.6	9.8	4.5	.02
Long-delay (cued) recall	9.5	3.9	10.6	4.3	.004
Modified Rey-Osterrieth Figure					
Immediate recall	16.6	4.9	19.5	4.3	< .0001
Delayed recall	16.3	5.0	18.9	4.1	< .0001
Mood					
Profile of mood states, total	47.0	38.4	30.5	30.4	.03
Confusion subscale	12.0	5.4	8.0	3.5	.004
Fatigue subscale	12.5	6.7	9.9	6.0	.03
Depression subscale	12.6	11.8	8.8	8.2	.19
Anxiety subscale	11.6	7.5	9.3	6.8	.26
Anger subscale	11.4	10.7	7.8	9.1	.05
Vigor subscale	12.9	5.5	13.3	4.7	.97
Health-related quality of life					
Total FACT-Br Score	124.4	24.4	134.2	23.6	.07
Brain Specific Concerns subscale	47.6	11.1	53.1	10.9	.003
Physical Functioning subscale	20.7	4.8	21.8	5.0	.35
Emotional Functioning subscale	17.9	4.4	19.8	2.9	.04
Social Functioning subscale	20.2	5.4	21.6	5.1	.02
Functional subscale	18.0	5.7	18.0	5.5	.44

Abbreviations: SD, standard deviation; FACT-Br, Functional Assessment of Cancer Therapy-Brain.

HRQOL

Baseline scores on the FACT-Br total and brain-specific concerns subscale scores were all within 1 SD of the means reported by Weitzner et al²⁸ in their validation of the FACT-Br, indicating that our participants were comparable with Weitzner's sample of brain tumor patients. After treatment with donepezil, significant improvement occurred in brain-specific symptoms with a trend toward significant improvement in overall QOL, emotional functioning, and social functioning (Table 1). No significant improvement was observed for physical well-being and functional well-being measured by the FACT-Br or by the KPS ($P = .13$).

Other Results

Of the 21 patients who completed the 6-week washout (weeks 24 to 30), HRQOL, mood, and cognitive function worsened, but the differences were not statistically significant (data not shown). Toxicity was assessed at six, 12, 24, and 30 weeks. A total of 63 toxicities were reported, 51 grade 1 (81%), seven grade 2 (11%), and five grade 3 (8%). The most common toxicities were fatigue (11; all grade 1), neuro-miscellaneous (four grade 1, three grade 2, and four grade 3), insomnia (nine grade 1, one grade 2), and diarrhea (eight grade 1, one grade 2). One patient discontinued protocol treatment because of toxicity (nausea). Ten of 21 patients (48%) who completed the study through the 30 week assessment chose to go back on donepezil. Patients choosing to remain on drug were not significantly different from patients choosing to go off drug in terms of demographics, baseline mood, QOL, or cognitive performance scores. However, patients choosing to continue donepezil had significantly better scores on several cognitive tests (CVLT long-delayed recall, CVLT short-delayed recall, and DST total; all $P < .05$) than those choosing to come off drug following treatment.

DISCUSSION

Historically, the sequelae of severe radiation-induced brain injury have received the most attention, including white-matter necrosis and dementia.^{15,32,33} In recent years, cognitive function and QOL have received more attention because of a growing emphasis on the management of symptoms related to cancer and its treatments and survivorship issues.³⁴⁻³⁶ Brown et al³⁷ observed 8%, 5%, and 5% incidence of cognitive decline at 1, 2, and 5 years, respectively, following partial brain irradiation in 203 adults with supratentorial low-grade glioma. The global measure of cognitive functioning used in that study, the MMSE, probably was too insensitive to the breadth and extent of cognitive impairment typically documented.³⁸ The lack of change in the KPS and MMSE in the present study, when more specific measures showed change, supports this hypothesis.

Others studies have reported greater impairment when more sensitive measures are used. Between 50% to 67% of patients receiving low-dose (20 to 40 Gy) prophylactic cranial irradiation for small-cell lung cancer were found to have moderate to severe cognitive deficits.^{1,3} In a study of accelerated radiation therapy followed by procarbazine/lomustine/vincristine chemotherapy for anaplastic glioma, 40% to 60% of patients had worsened cognitive functioning and 10% had severe dementia.^{39,40}

The specific cognitive impairments that have been associated with brain tumors and their treatments are quite varied and have

included information processing speed, frontal lobe executive functions, memory, attention, verbal learning, mental flexibility, problem-solving, complex perceptual tracking, motor coordination, gait disturbance, and manual dexterity,^{39,41-44} indicating the importance of assessing cognitive functioning with a battery of tests. In a recent prospective study of fractionated whole brain radiation with or without the investigational radiosensitizer moxetaxin gadolinium in patients with brain metastases, Meyers et al² reported a 91% incidence of baseline (ie, before treatment) cognitive impairment. Improvements were found in executive function and memory; baseline test scores correlated with tumor volume and predicted survival.

The first therapeutic agent used to reduce cognitive morbidity and improve the QOL in irradiated brain tumor patients was the amphetamine methylphenidate. Weitzner and Meyers^{45,46} reported improved visual-motor speed, verbal memory, expressive speech, executive function, fine-motor coordination, and QOL with methylphenidate. To our knowledge, the present study is the first study of an AChE inhibitor administered to ≥ 6 month survivors of partial or whole brain radiation therapy. Pretreatment assessments of cognition, mood, and QOL clearly revealed clear dysfunction and distress. Following 24 weeks of donepezil treatment, significant improvements on tests of attention and concentration, verbal memory, and figural memory were observed with a trend toward significant improvement in verbal fluency. Improvements in mood (ie, fatigue, confusion, and anger) and HRQOL (ie, emotional, social, brain specific concerns) were also observed. These results suggest that patients who are ≥ 6 -month survivors of brain tumors and partial or whole brain radiation therapy may have neuronal injury with an associated acetylcholine deficiency, and that they can clinically respond to the AChE inhibitor donepezil, with a similar low incidence of primarily mild toxicity. Additional research is needed to further assess this and other AChE inhibitors in this population.

After 24 weeks of treatment with donepezil, 48% of patients chose to continue taking the drug. A review of mean differences for all our outcome variables (data not shown here) revealed a pattern of better cognitive functioning and improved mood among those who elected to continue treatment. This suggests that donepezil may have benefited some patients more than others. This study was underpowered for sub-group analyses, but a planned larger randomized trial will help to explore differential response to treatment.

A limitation of this study was the lack of a control group. Were the improvements in cognitive test scores a result of a practice effect?⁴⁷ Within a 7½ month period of our study, participants took the test battery four times. Alternate forms for most of the tests are not available. While practice effect may account for some of the change in test scores, it is unlikely that it accounts for all the observed improvement in scores. In addition to improved cognitive test scores, we also observed robust changes on the POMS and FACT-Br, instruments that are not influenced by practice effects. Other possible explanations for the observed improvements are concurrent tumor shrinkage, resolution of radiation-induced fatigue, and/or repair/recovery from radiation-induced brain damage. Armstrong et al^{48,49} observed a biphasic pattern of long-term memory deficits in 12 patients with various primary brain tumors treated with partial brain irradiation. Impairment present at baseline began improving by 4½ months following radiation and continued to improve to 1 year postbaseline but worsened again by 2 years. They postulated that at least during

the first year postirradiation, demyelination followed by remyelination was occurring. However, the trend towards worsening of scores following termination of treatment (week 24 to week 30) suggests that brain recovery cannot fully explain the improvement in scores. The cognitively damaging effects of brain tumor(s) and cancer treatments, including cranial radiation therapy, were confounded in the present study, thus, we cannot isolate impairments attributable to irradiation. Our primary interest, however, was to test donepezil's efficacy at relieving neurocognitive symptoms and to improve mood and QOL. A common concern in studies such as this one is whether

study drop-out influenced the outcome. This is doubtful since we found no significant baseline differences (except age) between completers and noncompleters.

The results of this initial phase II trial encourage continued investigation of donepezil and other AChE inhibitors in this population. A phase III, double-blind, placebo-controlled study of donepezil in this patient population is planned as a joint effort between the Comprehensive Cancer Center of Wake Forest University (Winston-Salem, NC), the MD Anderson Cancer Center (Houston, TX), and their respective Community Clinical Oncology Program Research Bases.

REFERENCES

- Laukkanen E, Klonoff H, Allan B, et al: The role of prophylactic brain irradiation in limited stage small cell lung cancer: Clinical, neuropsychologic, and CT sequelae. *Int J Radiat Oncol Biol Phys* 14:1109-1117, 1988
- Meyers CA, Smith JA, Bezjak A, et al: Neurocognitive function and progression in patients with brain metastases treated with whole-brain radiation and motexafin gadolinium: Results of a randomized phase III trial. *J Clin Oncol* 22:157-165, 2004
- Johnson BE, Becker B, Goff WB, et al: Neurologic, neuropsychologic, and computed cranial tomography scan abnormalities in 2- to 10-year survivors of small-cell lung cancer. *J Clin Oncol* 3:1659-1667, 1985
- Jemal A, Murray T, Ward E, et al: Cancer statistics, 2005. *CA Cancer J Clin* 55:10-30, 2005
- Frytak S, Shaw JN, O'Neill BP, et al: Leukoencephalopathy in small cell lung cancer patients receiving prophylactic cranial irradiation. *Am J Clin Oncol* 12:27-33, 1989
- Dimberg Y, Vazquez M, Soderstrom S, et al: Effects of X-irradiation on nerve growth factor in the developing mouse brain. *Toxicol Lett* 90:35-43, 1997
- Bryson HM, Benfield P: Donepezil. *Drugs Aging* 10:234-239, 1997
- Roberson MR, Harrell LE: Cholinergic activity and amyloid precursor protein metabolism. *Brain Res Brain Res Rev* 25:50-69, 1997
- Birks J, Grimley EJ, Iakovidou V, et al: Rivastigmine for Alzheimer's disease [Cochrane Database System Review]. Oxford, United Kingdom, Cochrane Library, CD001191, 2002
- Birks JS, Melzer D, Beppu H: Donepezil for mild and moderate Alzheimer's disease [Cochrane Database System Review]. Oxford, United Kingdom, Cochrane Library, CD001191, 2000
- Olin J, Schneider L: Galantamine for Alzheimer's disease [Cochrane Database System Review]. Oxford, United Kingdom, Cochrane Library, CD001747, 2002
- Scarpini E, Scheltens P, Feldman H: Treatment of Alzheimer's disease: Current status and new perspectives. *Lancet Neurol* 2:539-547, 2003
- Birks J, Melzer D, Beppu H: Donepezil for mild and moderate Alzheimer's disease [Cochrane Database System Review]. Oxford, United Kingdom, Cochrane Library. Review Update: Cochrane Database System Review, 2002
- Shaw EG, Robbins ME: The management of radiation-induced brain injury, in: *Radiation Toxicity: A Practical Guide*. New York, NY, Kluwer Academic Publishers, 2004
- Schultheiss TE, Kun LE, Ang KK, et al: Radiation response of the central nervous system. *Int J Radiat Oncol Biol Phys* 31:1093-1112, 1995
- Hornsey S, Myers R, Jenkinson T: The reduction of radiation damage to the spinal cord by post-irradiation administration of vasoactive drugs. *Int J Radiat Oncol Biol Phys* 18:1437-1442, 1990
- Jaenke RS, Robbins ME, Bywaters T, et al: Capillary endothelium: Target site of renal radiation injury. *Lab Invest* 68:396-405, 1993
- Moulder JE, Robbins ME, Cohen EP, et al: Pharmacologic modification of radiation-induced late normal tissue injury. *Cancer Treat Res* 93:129-151, 1998
- Belka C, Budach W, Kortmann RD, et al: Radiation induced CNS toxicity—molecular and cellular mechanisms. *Br J Cancer* 85:1233-1239, 2001
- Tofilon PJ, Fike JR: The radioresponse of the central nervous system: A dynamic process. *Radiat Res* 153:357-370, 2000
- Karnofsky DA, Burchenal JH: The clinical evaluation of chemotherapeutic agents in cancer, in Macleod CM (ed): *Evaluation of Chemotherapeutic Agents*. New York, NY, Columbia University Press, 1949, pp. 199-205
- Folstein MF, Folstein SE, McHugh PR: "Mini Mental State": A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 12:189-198, 1975
- Reitan R: Validity of the Trail Making Test as an indicator of organic brain damage. *Percept Mot Skills* 8:271-276, 1958
- Wechsler D: *Wechsler Adult Intelligence Scale-Revised*. New York, NY, Psychological Corporation, 1981
- Fastenau PS, Denburg NL, Hufford BJ: Adult norms for the Rey-Osterrieth Complex Figure Test and for supplemental recognition and matching trials from the Extended Complex Figure Test. *Clin Neuropsychol* 13:30-47, 1999
- Benton AL, Hamsher K: *Multilingual Aphasia Examination*. Iowa City, IA, AJA Associates, 1983
- Delis DC, Kramer JH, Kaplan E, et al: *California Verbal Learning Test-II*. New York, NY, Psychological Corporation, 2000
- Weitzner MA, Meyers CA, Gelke CK, et al: The Functional Assessment of Cancer Therapy (FACT) scale: Development of a brain subscale and revalidation of the general version (FACT-G) in patients with primary brain tumors. *Cancer* 75:1151-1161, 1995
- McNair DM, Lorr M, Droppleman LF: *Profile of Mood States Manual*. San Diego, CA, Educational and Industrial Testing Service, 1992
- Bak JS, Greene RL: Changes in neuropsychological functioning in an aging population. *J Consult Clin Psychol* 48:395-399, 1980
- Dupont WD, Plummer WD: Power and sample size calculations: A review and computer program. *Control Clin Trials* 11:116-128, 1990
- Sheline GE, Wara WM, Smith V: Therapeutic irradiation and brain injury. *Int J Radiat Oncol Biol Phys* 6:1215-1228, 1980
- Crossen JR, Garwood D, Glatstein E, et al: Neurobehavioral sequelae of cranial irradiation in adults: A review of radiation-induced encephalopathy. *J Clin Oncol* 12:627-642, 1994
- Regine WF, Schmitt FA, Scott CB, et al: Feasibility of neurocognitive outcome evaluations in patients with brain metastases in a multi-institutional cooperative group setting: Results of Radiation Therapy Oncology Group trial BR-0018. *Int J Radiat Oncol Biol Phys* 58:1346-1352, 2004
- Kondziolka D, Niranjan A, Flickinger JC, et al: Radiosurgery with or without whole-brain radiotherapy for brain metastases: The patients' perspective regarding complications. *Am J Clin Oncol* 28:173-179, 2005
- Duffner PK: Long-term effects of radiation therapy on cognitive and endocrine function in children with leukemia and brain tumors. *Neurologist* 10:293-310, 2004
- Brown PD, Buckner JC, O'Fallon JR, et al: Effects of radiotherapy on cognitive function in patients with low-grade glioma measured by the folstein mini-mental state examination. *J Clin Oncol* 21:2519-2524, 2003
- Meyers CA, Hess KR: Multifaceted end points in brain tumor clinical trials: Cognitive deterioration precedes MRI progression. *Neuro-oncol* 5:89-95, 2003
- Levin VA, Yung WK, Bruner J, et al: Phase II study of accelerated fractionation radiation therapy with carboplatin followed by PCV chemotherapy for the treatment of anaplastic gliomas. *Int J Radiat Oncol Biol Phys* 53:58-66, 2002
- Scheibel RS, Meyers CA, Levin VA: Cognitive dysfunction following surgery for intracerebral glioma: Influence of histopathology, lesion location, and treatment. *J Neurooncol* 30:61-69, 1996
- Archibald YM, Lunn D, Rutnan LA, et al: Cognitive functioning in long-term survivors of high-grade glioma. *J Neurosurg* 80:247-253, 1994
- Grant R, Slattery J, Gregor A, et al: Recording neurological impairment in clinical trials of glioma. *J Neurooncol* 19:37-49, 1994
- Hochberg FH, Slotnick B: Neuropsychologic impairment in astrocytoma survivors. *Neurology* 30:172-177, 1980
- Imperato JP, Paleologos NA, Vick NA: Effects of treatment on long-term survivors with malignant astrocytomas. *Ann Neurol* 28:818-822, 1990

45. Weitzner MA, Meyers CA, Valentine AD: Methylphenidate in the treatment of neurobehavioral slowing associated with cancer and cancer treatment. *J Neuropsychiatry Clin Neurosci* 7:347-350, 1995

46. Meyers CA, Weitzner MA, Valentine AD, et al: Methylphenidate therapy improves cognition,

mood, and function of brain tumor patients. *J Clin Oncol* 16:2522-2527, 1998

47. McCaffrey RJ, Westervelt HJ: Issues associated with repeated neuropsychological assessments. *Neuropsychol Rev* 5:203-221, 1995

48. Armstrong C, Mollman J, Corn BW, et al: Effects of radiation therapy on adult brain behavior:

Evidence for a rebound phenomenon in a phase 1 trial. *Neurology* 43:1961-1965, 1993

49. Armstrong C, Ruffer J, Corn B, et al: Biphasic patterns of memory deficits following moderate-dose partial-brain irradiation: Neuropsychologic outcome and proposed mechanisms. *J Clin Oncol* 13:2263-2271, 1995

Authors' Disclosures of Potential Conflicts of Interest and Author Contributions

The authors indicated no potential conflicts of interest.

Author Contributions

Conception and design: Edward G. Shaw, Ralph B. D'Agostino Jr, Michelle J. Naughton, Stephen R. Rapp

Administrative support: Edward G. Shaw

Provision of study materials or patients: Edward G. Shaw, Robin Rosdhal

Collection and assembly of data: Edward G. Shaw, Robin Rosdhal

Data analysis and interpretation: Edward G. Shaw, Robin Rosdhal, Ralph B. D'Agostino Jr, James F. Lovato, Michelle J. Naughton, Michael E. Robbins, Stephen R. Rapp

Manuscript writing: Edward G. Shaw, Robin Rosdhal, Ralph B. D'Agostino Jr, James F. Lovato, Michelle J. Naughton, Michael E. Robbins, Stephen R. Rapp

Final approval of manuscript: Edward G. Shaw, Robin Rosdhal, Ralph B. D'Agostino Jr, James F. Lovato, Michelle J. Naughton, Michael E. Robbins, Stephen R. Rapp

Other: Stephen R. Rapp