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COGNITIVE EFFECTS OF DONEPEZIL THERAPY IN PATIENTS WITH BRAIN TUMORS: A PILOT STUDY

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Abstract

Background—Cognitive dysfunction is prevalent among brain tumor patients treated with radiotherapy (RT) and chemotherapy. However, there are no approved pharmacological interventions for cognitive dysfunction in cancer patients. The goal of this pilot study was to examine the efficacy of donepezil, an acetylcholinesterase inhibitor used to treat Alzheimer's disease, in improving cognitive functions in brain tumor patients previously treated with RT + chemotherapy or chemotherapy alone.

Methods—Fifteen patients with a brain tumor received a single daily dose of donepezil for 24 weeks (5mg for 4 weeks, then 10 mg for 20 weeks). Patients completed cognitive evaluations prior to initiating therapy (baseline), and about 12 weeks (mid-study) and 24 weeks (end-of-study) subsequent to initiation of donepezil therapy.

Results—The results of linear mixed models analysis, controlling for each patient's baseline cognitive test score, showed a significant post-baseline improvement in attention (WAIS-III Digit

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Conflict of Interest

Dr. Correa serves on the Editorial Board of *Neuro-Oncology Practice* and on the Neurotoxicity Advisory Board for Juno Therapeutics. Mr. Baser reports no disclosures.

Ms. Kryza-Lacombe reports no disclosures

Dr. Kathryn Beal reports no disclosures.

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Ethical approval: All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Span Forward; $p=0.037$), graphomotor speed (WAIS-III Digit Symbol; $p=0.035$) and visual memory (BVM-T-R-delay; $p=0.025$). There was also an improvement in self-reported quality of life (FACT-Br, Social Well-Being subscale; $p=0.01$).

Conclusions—The findings of this pilot study suggest that treatment with donepezil may improve some aspects of cognitive functions and quality of life in brain tumor patients. Similar findings were reported in two prior trials of donepezil in brain tumor survivors.

Keywords

donepezil; cognitive; brain tumors; radiotherapy; chemotherapy

Introduction

Patients with brain tumors treated with radiotherapy (RT) and chemotherapy are at increased risk for developing delayed neurotoxicity [1]. Central nervous system (CNS) injury from RT and chemotherapy may involve vascular damage, depletion of glial progenitor cells, oxidative stress, inflammation, demyelination, and disruption of hippocampal neurogenesis [2–7]. Primary brain tumor patients in remission of their disease often display cognitive impairment of sufficient severity to interfere with their ability to function at pre-diagnosis professional and social levels, and it is considered the most frequent complication among long-term survivors [1]. The cognitive functions most often disrupted by the delayed effects of RT and chemotherapy include attention and executive functions, graphomotor speed, and memory abilities [8,9].

There are no established preventive or therapeutic interventions for cancer treatment-related cognitive dysfunction. Pharmacological treatments for RT-induced cognitive dysfunction have been based primarily on therapies used for other neurological disorders that cause similar symptoms [10]. Acetylcholinesterase inhibitors such as donepezil have been found to produce benefits in cognitive and functional symptoms in patients with early Alzheimer's disease [11,12] and vascular dementia [13]. Donepezil has been shown to improve cognitive functions in other clinical populations without specific cholinergic deficiency, including patients with traumatic brain injury [14], epilepsy [15], and Parkinson's disease [16]. Two recent studies have documented improvement in specific cognitive domains in patients with brain tumors following 24 weeks of donepezil therapy [17,18]. In this pilot study, we assessed the effects of donepezil on cognitive functions and quality of life in brain tumor survivors treated with RT + chemotherapy or chemotherapy alone.

Materials and Methods

Eligibility

Patients diagnosed with a brain tumor were recruited from a cohort of survivors followed in the Department of Neurology at Memorial Sloan-Kettering Cancer Center (MSKCC). Study eligibility included: age ≥ 18 years, no evidence of active disease on serial MRIs prior to accrual, completion of treatment with radiotherapy (RT) and/or chemotherapy at least 6 months prior to enrollment, Mini-Mental Status Examination (MMSE) score between 18 and 27 at enrollment, no history of psychiatric or other neurological disorders, no changes in

antiepileptic medication or dose for at least 3 months prior to study entry, no use of cognition-enhancing medications, and fluency in English. The MSKCC Institutional Review Board approved the research protocol, and all participants provided written informed consent.

Intervention

Patients received a single daily 5mg dose of donepezil for 4 weeks, and the dose was escalated to 10mg per day for 20 weeks, if tolerated. The dose escalation and schedule used were consistent with prior studies of donepezil in patients with dementia [12,13] and traumatic brain injury [14]. Patients underwent a neuropsychological evaluation and completed a quality of life (QoL) questionnaire prior to (baseline/Time 1), about 12 weeks (mid-study/Time 2) and about 24 weeks (end-of-study/Time 3) subsequent to starting donepezil.

Neuropsychological and Self-Reported QoL Measures

- Attention: Digit Span subtest of the WMS-III (Longest Digit Span Forward-LDSF; Longest Digit Span Backward-LDSB) [19]; Brief Test of Attention (BTA) [20].
- Graphomotor Speed & Executive function: Digit Symbol subtest of the WMS-III (DSYM) [19]; Trail Making Test Parts A & B (TMT-A, TMT-B) [21].
- Verbal Memory: Hopkins Verbal Learning Test-Revised [22] (Learning [HVLTL], Delayed Recall [HVLTD], Discrimination Index [HVLTDI]). Alternate forms were used at the 12- and 24-week evaluations to minimize practice effects.
- Visual Memory: Brief Visuospatial Memory Test-Revised [23] (Learning [BVMTL], Delayed Recall [BVMTD], Discrimination Index [BVMTDI]). Alternate forms were used at the 12- and 24-week evaluations to minimize practice effects.
- The Functional Assessment of Cancer Therapy-Brain (FACT-Br Version 4) [24].

The test battery was administered by a neuropsychologist (DDC) or a trained research assistant. Raw neuropsychological test scores were compared with published normative values according to age, and when available, to education, and converted into z-scores. Z-scores of 1.5 or more standard deviations below the mean of the normative sample (i.e., Z-score -1.5) indicate impairment.

Statistical Analysis

Neuropsychological test z-scores were summarized using descriptive statistics. Independent t-tests were used for comparisons on demographic and cognitive test scores at baseline. Paired t-tests were used to compare 12-week and 24-week scores to baseline scores. Overall

change from baseline on each test was evaluated using linear mixed models (LMMs) controlling for each patient's baseline score.

Results

Patient Characteristics

The target sample size for this pilot study was 30 patients, and 24 were enrolled between 2005 and 2009, and the study was subsequently closed due to the relatively slow accrual rates. Of the 24 patients enrolled, 10 (42%) had a glioma, 9 (38%) had primary CNS lymphoma (PCNSL), and 5 (21%) had other brain tumors (i.e., germ cell tumor, medulloblastoma). Twenty patients (84%) received treatment with conventional fractionated RT + chemotherapy, and 4 (16%) had chemotherapy-only regimens.

Fifteen of twenty-four patients completed 24 weeks of donepezil therapy. As shown in Table 1, among patients who completed the study, most were male (67%) and the median age was 53 years. Disease and treatment history for the 15 patients are also described in Table 1 & 2. Seven patients went off study before 24 weeks due to reported side effects including gastrointestinal symptoms (n=3), fatigue and sleep disturbance (n=2), and seizures (n=2); in addition, one patient discontinued the medication at the request of his physician and one for unknown reasons. Patients who remained on study did not differ significantly at baseline from those who went off study in age, education, MMSE score, QoL (FACT-Br), and cognitive test performance with the exception of the BVMT-DI with patients who went off study performing worse than patients who completed it (mean z-score = -1.67, SD=1.14; mean z-score = -0.33, SD=0.72, respectively; $t(22)=13.6$, $p=0.024$).

Neuropsychological Functions

At baseline, mean cognitive test z-scores were impaired on tests of attention (BTA), executive functions (TMT-B) and verbal memory (HVLT-L). Baseline test z-scores ranged between 0.33 and 1.44 standard deviations *below* the normative mean on all other cognitive measures (Table 2). The results of linear mixed models analysis, controlling for each patient's baseline cognitive test score, showed a significant post-baseline improvement in attention (WAIS-III LDSF; $p=0.037$), graphomotor speed (WAIS-III DSYM; $p=0.035$), and visual delayed recall (BVMT-D; $p=0.025$). Improvements occurred mostly from baseline to 12 weeks on the DSYM and BVMT-D. There was a significant decline in verbal delayed recall (HVLT-D; $p=0.013$), and this was primarily due to a decline from baseline to 12 weeks, as scores improved to near baseline levels at 24 weeks. There were no significant changes in other aspects of attention (LDSB; BTA), graphomotor speed and executive functions (TMT-A; TMT-B), or memory (HVLT-D; HVLT-DI; BVMT-L; BVMT-DI).

Self-Reported QoL

At baseline, the FACT-Br Total mean score was comparable to those of a large group of primary brain tumor patients.[24] The results of linear mixed models analysis, controlling for each patient's baseline scores on the FACT-Br, showed a significant post-baseline improvement in the Social Well-Being subscale ($p=0.010$), and this was primarily due to improvement from baseline to 12 weeks, as scores at 24 weeks remained at similar levels

(Table 2). There were no significant changes on the FACT-Br Total score or on any other subscale scores. Changes in self-reported QoL and cognitive scores were generally negatively correlated, suggesting that improvement in self-reported QoL did not correspond to improvement in cognition.

Other Results

Four patients required dose reduction to 5 mg during the study due to adverse effects including sleep disturbance and fatigue. Among the patients who completed the 24-week donepezil therapy, the most common side effects reported were fatigue (n=9), gastrointestinal symptoms (n=7), headaches (n=6), sleep disturbance and vivid dreams (n=5) and miscellaneous neurological complaints (n=6).

Discussion

The results of this pilot study indicated a significant improvement in attention, graphomotor speed and visual delayed recall, as well as in perceived social well-being in a small cohort of patients with brain tumors treated with donepezil. The findings suggest that treatment with an acetylcholinesterase inhibitor can provide some benefit to brain tumor survivors previously treated with RT and/or chemotherapy, and may translate to more efficient performance of daily activities involving attention and processing speed. There is some evidence from animal studies that RT is associated with reduced acetylcholine signaling [25,26], and that donepezil may reduce chemotherapy-induced impairments in spatial working memory tasks (i.e., delayed non-matching to sample) [27]. It has been suggested that attention may be enhanced by activation of the forebrain cholinergic system, which may have positive effects on executive function and memory [28,29]. In patients with mild-to-moderate Alzheimer's disease, attenuation in the decline of attention and executive function was reported following twelve months of donepezil [30].

Our results of improved attention, graphomotor speed and visual memory are overall consistent with those of two recent clinical trials. Shaw et al. [17] conducted a prospective phase II study to assess the efficacy of donepezil in the treatment of cognitive dysfunction in 24 patients with primary brain tumors treated with RT at least six months prior to enrollment. They reported an improvement in attention, verbal and visual memory, and in mood and QoL (FACT-Br, emotional and social well-being subscales) after 24 weeks of treatment. A recent phase III randomized placebo-controlled trial assessed the effects of 24 weeks of donepezil therapy on cognitive function in 195 brain tumor survivors treated with RT at least six months prior to enrollment [18]. The results showed that the groups did not differ significantly on a cognitive composite score (primary outcome measure), but there was a significant benefit of donepezil on verbal recognition memory and motor speed, particularly for patients with greater pre-therapy cognitive impairment. In our cohort, there was also evidence of baseline impairments in attention, executive functions and verbal memory, likely related to the combined effects of the tumor and the delayed adverse effects of RT. However, our results showed an initial decline in verbal delayed recall at 12 weeks with subsequent return to near baseline levels at 24 weeks of donepezil therapy. This was an unexpected finding of unclear significance and requires further study on a larger sample,

considering that improvement in verbal memory was reported in the two studies of donepezil therapy in patients with brain tumors [17, 18]. The results also suggested that improvement in self-reported QoL did not correspond to improvement in cognition. Several studies in cancer patients and other clinical populations have described that self-reported QoL is often correlated with mood and fatigue, and less consistently with cognitive test performance [31–34]. However, the relatively small sample size may have limited our ability to assess the association between cognitive function and QoL.

Other studies have used pharmacological agents in the attempt to improve cognitive function in patients with brain tumors. In a randomized placebo-controlled study, the potential protective effects of memantine, a N-Methyl-D-aspartate receptor antagonist, versus placebo on cognitive function were evaluated in 508 patients with brain metastases receiving whole-brain RT [35]. The results showed that patients treated with memantine had significantly longer time to cognitive decline, and a reduced rate of decline in memory, executive function and processing speed compared to placebo; however, attrition may have limited statistical power as only 29% of patients completed the 24-week assessment. An open-label randomized pilot study examined the efficacy of four weeks of methylphenidate and modafinil in 24 brain tumor patients either during or following treatment with RT or chemotherapy [36]. The results showed a beneficial effect of stimulant treatment in speed of processing and executive functions requiring divided attention, and on patient-reported fatigue and QoL, regardless of the medication used. Patients with greater deficits in executive functions at baseline benefitted the most from stimulant therapy. However, the results were interpreted with caution given the small sample size and large proportion of drop-outs. A multi-center double-blind placebo-controlled study including 37 patients with primary brain tumors treated with modafinil for 6 weeks showed no beneficial effects on cognitive function, fatigue or mood in comparison to placebo [37].

Shaw et al. [17] reported better cognitive functions and improved mood among the patients who elected to continue to take donepezil after 24 weeks, suggesting a differential response to treatment. Therefore, it is possible that individual factors may impact response to donepezil in patients with brain tumors. In patients with mild Alzheimer's disease, it has been reported that the presence of the *APOE*ε-4 allele may modulate the response to acetylcholinesterase inhibitors [38,39]. We described recently that among 211 brain tumor survivors, carriers of at least one *APOE*ε-4 allele had significantly lower scores in verbal learning and delayed recall, and a trend toward worse performance in executive functions, relative to non-carriers of the ε-4 allele [40], suggesting that the *APOE* gene may increase the vulnerability of brain tumor patients to cognitive dysfunction. However, it is unknown whether the *APOE*ε-4 allele or other genetic variants may influence the response to donepezil in patients with brain tumors. In future placebo-controlled clinical trials assessing the effects of donepezil and other pharmacological agents on cognitive function, it would be informative to include genotyping of relevant genes with known associations with cognitive outcome, and involvement in the modulation of cholinergic, dopaminergic, GABAergic, or glutamatergic neurotransmitter systems, with the goal of identifying patients who may benefit most from targeted interventions.

The limitations of this pilot study include the small sample size and absence of a placebo control group, which may have impeded our ability to detect small to moderate effect sizes and to exclude possible practice effects. In this study, the duration and schedule of treatment were based on studies of patients with dementia and other neurological disorders [12–14], and the possibility that greater benefit may have occurred with a longer trial or higher dose of donepezil cannot be excluded. We also acknowledge that the heterogeneity of the patient population regarding tumor and treatment type, the variable post-RT and chemotherapy intervals of the baseline neuropsychological assessments, and possible ongoing recovery from treatment delayed effects in some patients, are potential confounding factors. Similar to the studies by Shaw et al. [17] and Rapp et al. [18], the most common side effects reported by our patients included fatigue and gastrointestinal symptoms, and it is possible that adverse effects may limit the utility of the drug in brain tumor patients. Study drop-out was unlikely to influence the results as there were mostly no baseline differences between patients who completed and discontinued the study; however, we cannot exclude the possibility that changes in sleep and fatigue influenced study retention and that patients with better performance remained in the study. The timing of the drug delivery may also impact its benefit, and further research investigating whether concurrent treatment with donepezil and RT and/or chemotherapy may prevent neurocognitive decline is warranted.

In sum, our findings of improvements in some aspects of cognitive functions and QoL are mostly consistent with previous studies in patients with brain tumors, and support the possible use of donepezil in this population. As cancer treatment interventions have improved survival for many patients with brain tumors, investigating the efficacy of pharmacological and behavioral interventions to improve cognitive function has become increasingly relevant. The prevention of cognitive deficits with agents that may protect neurons from treatment-induced damage is also an area of growing interest [10].

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Table 1

Demographics, disease and treatment history (n=15)

Characteristics	
Male	10 (67%)
Right handed	13 (87%)
Age at study entry, years	
Mean (SD)	58.9 (14.1)
Median (range)	53 (43–85)
Mean education, years (SD)	15.3 (3.1)
Mean estimated VIQ (SD)	113 (6.8)
Mean MMSE score ^a (SD)	26.7 (2.3)
Working at study entry	6 (40%)
Tumor type	
Low Grade Glioma	2 (13%)
High Grade Glioma	5 (34%)
Primary CNS Lymphoma	6 (40%)
Other	2 (13%)
Tumor location	
Frontal/temporal	7 (47%)
Parietal/occipital	2 (13%)
Cortical/subcortical	6 (40%)
Predominant tumor side	
Left	7 (47%)
Right	6 (40%)
Bilateral	2 (13%)
Treatment type ^b	
RT + Chemotherapy	12 (80%)
Chemotherapy	3 (20%)
Time since treatment completion, months	
Mean (SD)	70 (55)
Median (range)	47 (7–161)
Anticonvulsants ^c	
Monotherapy	7 (47%)
Polytherapy	2 (13%)
None	6 (40%)

SD standard deviation; *VIQ* verbal IQ (North American adult reading test or barona index)

^aMMSE=Mini-Mental Status Examination at baseline;

^bTreatment history reflects all therapy received including treatment at relapse, if applicable; RT=Radiotherapy;

^cMedication throughout study participation

Table 2

Tumor and treatment history per patient

Pt #	Tumor type	Treatment type	RT extent	RT dose (cGy)	Months since treatment ^a
1	Primary CNS lymphoma	RT + chemotherapy	Whole brain	4500	118
2	Primary CNS lymphoma	RT + chemotherapy	Whole brain	4500	125
3	Primary CNS lymphoma	RT + chemotherapy	Whole brain	4500	16
4	Primary CNS lymphoma	RT + chemotherapy	Whole brain	Unknown	47
5	Primary CNS lymphoma	chemotherapy only	N/A	N/A	24
6	Primary CNS lymphoma	chemotherapy only	N/A	N/A	7
7	Anaplastic oligodendroglioma	chemotherapy only	N/A	N/A	59
8	Anaplastic oligodendroglioma	RT + chemotherapy	focal	Unknown	161
9	Anaplastic astrocytoma	RT + chemotherapy	focal	5400	25
10	Anaplastic astrocytoma	RT + chemotherapy	focal	5940	45
11	Anaplastic astrocytoma	RT + chemotherapy	focal	6000	27
12	Oligodendroglioma	RT + chemotherapy	focal	Unknown	115
13	Oligodendroglioma	RT + chemotherapy	focal	5940	8
14	Medulloblastoma	RT + chemotherapy	focal	5400	139
15	Non-germinomatous germ cell tumor	RT + chemotherapy	focal	5400	128

RT Radiotherapy;

^aTime since treatment completion at study entry

Table 3

Neuropsychological & quality of life scores at baseline and weeks 12 & 24 of donepezil therapy

Measure	Baseline		Week 12		Week 24		<i>p</i> ¹
	Mean	SD	Mean	SD	Mean	SD	
Neuropsychological functioning (z-scores)							
LDSF	-0.68	0.75	-0.48	0.82	-0.04*	1.01	
LDSB	-0.62	0.52	-0.64	0.79	-0.43	0.78	
DSYM	-1.07	1.05	-0.89	1.01	-0.89	0.91	
TMT-A	-1.44	1.23	-1.24	1.48	-1.18	1.05	
TMT-B	-1.55	1.03	-1.54	1.05	-1.74	0.97	
BTA	-1.76	1.08	-1.67	1.10	-1.68	1.38	
HVLT-R							
HVLT-L	-1.87	0.93	-2.25	1.30	-1.87	1.00	
HVLT-D	-1.43	1.23	-2.15*	0.81	-1.83	1.08	
HVLT-DI	-1.37	1.22	-1.48	1.02	-1.44	1.30	
BVMT-R							
BVMT-L	-1.09	1.11	-0.45*	1.14	-1.08	1.20	
BVMT-R	-1.14	1.17	-0.42*	1.37	-0.81	1.39	
BVMT-DI	-0.33	0.72	-0.46	0.71	-0.41	0.61	
Quality of life (raw scores)							
FACT-Br, total	129	24.2	129	28.6	129	29.3	
SWB	21	5.2	23	4.4	23*	4.3	
FWB	20	4.2	19	5.5	18	5.8	
PWB	22	4.4	21	5.8	22	4.8	
EWB	18	2.7	19	3.1	18	4.0	
BrCS	49	16.7	54	18.0	49	14.2	

SD = Standard Deviation; LDSF = Longest Digit Span Forward; LDSB = Longest Digit Span Backward; DSYM = Digit Symbol; TMT-A = Trail Making Test, Part A; TMT-B = Trail Making Test, Part B; BTA = Brief Test of Attention; HVLT-R = Hopkins Verbal Learning Test - Revised; HVLT-L = Hopkins Verbal Learning Test - Learning; HVLT-D = Hopkins Verbal Learning Test - Delayed Recall; HVLT-DI = Hopkins Verbal Learning Test - Discrimination Index; BVMT-R = Brief Visuospatial Memory Test - Revised; BVMT-L = Brief Visuospatial Memory Test - Learning; BVMT-D = Brief Visuospatial Memory Test - Delayed Recall; BVMT-DI = Brief Visuospatial Memory Test - Discrimination Index. FACT-Br = Functional Assessment of Cancer Therapy-Brain; SWB = Social/Family Well-Being; FWB = Functional Well-Being; PWB = Physical Well-Being; EWB = Emotional Well-Being; BrCS = FACT-Br Brain Cancer Subscale.

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value from linear mixed model indicating whether overall change from baseline (i.e., taking into account both Week 12 and Week 24 scores) was significantly different from 0, controlling for baseline scores

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$p < 0.05$, significantly different from baseline mean using a two-sided paired t-test.

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