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A Randomized Controlled Open-Label Pilot Study of Simvastatin Addition to Whole-Brain Radiation Therapy in Patients With Brain Metastases

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Statins have been reported to have a potential radiosensitizing effect that has not been evaluated in clinical trials. The aim of this study was to evaluate the efficacy and safety of simvastatin in addition to whole-brain radiation therapy (WBRT) in patients with brain metastases (BM). A prospective randomized, controlled, open-label pilot study was conducted on 50 Egyptian patients with BM who were randomly assigned to receive 30-Gy WBRT (control group: 25 patients) or 30 Gy WBRT+simvastatin 80 mg/day for the WBRT period (simvastatin group: 25 patients). The primary outcome was radiological response at 4 weeks after WBRT. Secondary outcomes were 1-year progression-free survival (PFS), 1-year overall survival (OS), and health-related quality of life (HRQL) that was assessed using the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30) and its brain module (BN-20), at baseline, after WBRT, and 4 weeks after WBRT. The addition of simvastatin was tolerated. Twenty-one patients were not evaluated for radiological response because of death ($n=16$), noncompliance to follow-up ($n=4$), and clinical deterioration ($n=1$). Response rates were 60% and 78.6% ($p=0.427$), 1-year PFS rates were 5.2% and 17.7% ($p=0.392$), and 1-year OS rates were 12% and 8% ($p=0.880$) for the control group and simvastatin group, respectively. Nonsignificant differences were found between the two arms regarding HRQL scales. The addition of simvastatin 80 mg/day did not improve the clinical outcomes of patients with BM receiving WBRT.

Key words: Brain metastases (BM); Quality of life; Simvastatin; Whole-brain radiation therapy (WBRT)

INTRODUCTION

Brain metastases (BM) are the most common intracranial tumors in adults and are considered one of the most feared complications of cancer¹. The incidence of BM is rising because of improved imaging technology and development of effective systemic therapy². Unfortunately, the diagnosis of BM portends a poor prognosis for the vast majority of patients with an expected survival measured in months³.

Whole-brain radiation therapy (WBRT) is the mainstay of BM treatment and has been shown to be effective regardless of the primary tumor histology⁴. In most patients, WBRT is indicated because of the presence of multiple BM or unmanageable extracranial illness making surgery and stereotactic radiosurgery not applicable⁵. Therefore, there have been increasing efforts to enhance the efficacy of radiation therapy while minimizing normal tissue damage⁶.

Multiple drugs have been evaluated for radiation sensitization. With the exceptions of temozolomide and motexafin gadolinium, trials have reported increased toxicity and/or no benefits in tumor control or survival⁷. Several preclinical studies have reported that statins, hydroxymethylglutaryl CoA reductase inhibitors, may have a potential radiosensitizing effect through inhibition of nuclear factor κ B, induction of autophagy, and others^{8–10}. However, these effects have not been evaluated in clinical trials.

The statins as a group are generally very well tolerated. However, muscle toxicity and asymptomatic liver enzyme elevation have been reported^{11,12}.

This is a proof-of-concept study to evaluate the efficacy and safety of simvastatin as a radiosensitizing agent, in addition to WBRT in patients with BM. Simvastatin was selected for this study due to its higher potential to cross the blood–brain barrier and its potential neuroprotective effect compared to other members of statins^{13,14}.

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MATERIALS AND METHODS

Study Design and Setting

A prospective, randomized, controlled, open-label pilot study was conducted on 50 Egyptian patients with BM at the Clinical Oncology Department, Ain-Shams University Hospitals, Cairo, Egypt. The study was carried out according to the principles of the Declaration of Helsinki 1964 and all subsequent revisions. The study protocol was revised and approved by the research ethics committee for experimental and clinical studies at the Faculty of Pharmacy, Ain Shams University. Prior to participation, all patients and/or their guardians were educated about the study protocol and signed the written informed consents. For patients with severe cognitive impairment, guardians were required to sign the informed consents. Since no previous similar studies exist, a prespecified sample size was not determined.

Patients

Inclusion criteria comprised adult patients (age >18) with measurable intracranial BM on MRI scan who were scheduled to receive 30 Gy WBRT. Patients were excluded if they were on statin therapy or if they had any of the following: hematological central nervous system infiltration, renal impairment (serum creatinine more than 2 mg/dl), hepatic dysfunction [serum alanine transaminase (ALT) and aspartate transaminase (AST) more than three times upper normal levels (UNL)], pregnancy, lactation, or known hypersensitivity to simvastatin or if they were noncompliant with simvastatin administration.

Methods

At baseline, all patients were subjected to a physical examination, thorough collection of medical history, and Karnofsky Performance Status (KPS) assessment. Patients were randomized to either the control group (25 patients) who received 30 Gy WBRT utilizing two-dimensional techniques given in 10 fractions (5 fractions/week) or the simvastatin group (25 patients) who received 30 Gy WBRT utilizing two-dimensional techniques given in 10 fractions (5 fractions/week) in addition to simvastatin 80 mg orally once daily for the WBRT period, including days without radiation.

Liver function tests ALT and AST were assessed at baseline and after WBRT. The patients were educated about symptoms of statin-induced myopathy and were required to report any of those symptoms. MRI scans were done at 4 weeks after WBRT for assessing radiological response, then every 10 weeks unless there was evidence of neurologic deterioration that necessitated earlier radiological evaluation. A complete response (CR) was defined as the disappearance of any contrast-enhancing lesion. A partial response (PR) was defined as a reduction

30% in the sum of the areas of the lesions with stable or neurologic improvement. Progressive disease (PD) was defined as the appearance of any new contrast-enhancing lesions or an increase in enhanced area by 20%. Other situations were defined as stable disease (SD). Patients who have CR, PR, or SD were considered responders. In this study, progression-free survival (PFS) measures time from treatment initiation to either progression, death from any cause, or being lost to follow-up (in case of noncompliance to follow-up visits), while overall survival (OS) measures time from treatment initiation to death from any cause. For those who were noncompliant to follow-up visits, death time was obtained from hospital records or by direct phone call to the patients' families.

Health-related quality of life (HRQL), using the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30)¹⁵ and its brain module (BN-20)¹⁶, was evaluated at baseline, after WBRT, and 4 weeks after WBRT. To permit the assessment of HRQL in patients with severe cognitive impairment, evaluation by caregivers was included. The questionnaire was scored according to EORTC instructions¹⁷.

Radiological response was the primary outcome of the study, while 1-year PFS, 1-year OS, and HRQL were secondary outcomes.

Statistical Analysis

Data management and analysis were performed using Statistical Package for Social Sciences, IBM SPSS Statistics for Windows version 21 (IBM Corp., Armonk, NY, USA). Numerical data were summarized using means and standard deviations or medians and ranges, as appropriate. Categorical data were summarized as numbers and percentages. Numerical data were explored for normality using the Kolmogorov–Smirnov and Shapiro–Wilk tests. Exploration of data revealed that the collected values were not normally distributed.

Comparisons between the two groups, with respect to categorical data, were performed by the chi-square or Fisher's exact tests, as appropriate, while comparisons between the two groups, with respect to numerical data, were performed by the Mann–Whitney test. Comparisons within the same group regarding baseline and after WBRT evaluation were done using Wilcoxon's signed rank test. One-year PFS and 1-year OS were estimated using the Kaplan and Meier method, and the differences were evaluated with the log-rank test. All *p* values were two-sided, and values of *p* < 0.05 were considered significant.

For the HRQL assessment, comparisons between the two groups at different time points were done by the Mann–Whitney test. Regarding assessment within a

Table 1. Baseline Patients' Baseline Characteristics in the Study Groups

Parameter	Control Group	Simvastatin Group	p Value
Age (years) [mean (SD)]	55.2 (11.8)	53.6 (10.6)	0.655*
Gender			0.396†
Male [n (%)]	14 (56)	11 (44)	
Female [n (%)]	11 (44)	14 (56)	
Primary tumor site			0.261‡
Breast [n (%)]	8 (32)	7 (28)	
Lung [n (%)]	16 (64)	13 (32)	
Others [n (%)]	1 (4)	5 (20)	
Presence of extracranial metastatic sites			0.777†
Yes [n (%)]	13 (52)	14 (56)	
No [n (%)]	12 (48)	11 (44)	
Time until progression to BM (years) [median (range)]	1.1 (0–11.3)	1.3 (0–4.8)	0.690*
KPS score			0.762†
Score ≥ 70 [n (%)]	7 (28)	9 (36)	
Score < 70 [n (%)]	18 (72)	16 (64)	
RPA classification			0.630‡
Class 1 [n (%)]	2 (8)	1 (4)	
Class 2 [n (%)]	5 (20)	8 (28)	
Class 3 [n (%)]	18 (72)	16 (64)	

RPA, recursive partitioning analysis.

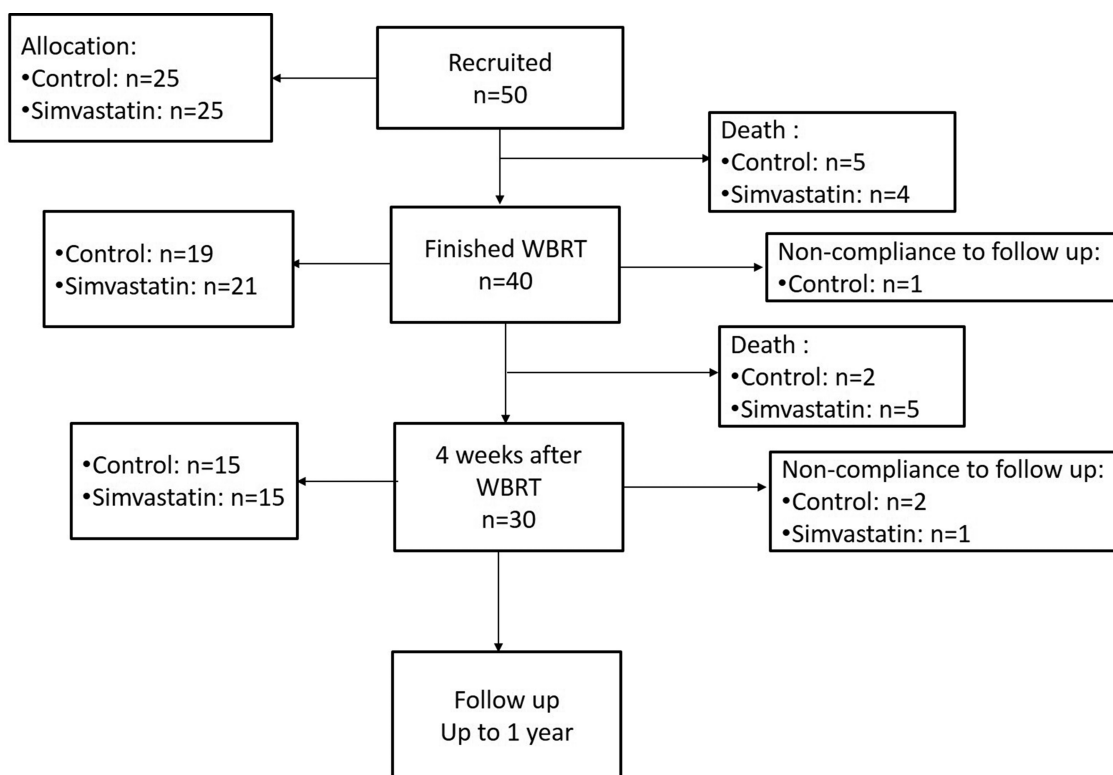
*Mann–Whitney test: $p > 0.05$ nonsignificant.†Chi-square test: $p > 0.05$ nonsignificant.‡Fisher's exact test: $p > 0.05$ nonsignificant.**Figure 1.** Patients' flow diagram.

Table 2. Radiological Response of the Study Groups at 4 Weeks After Whole-Brain Radiation Therapy

Radiological Response	Control Group (n=15)	Simvastatin Group (n=14)	p Value*
Nonresponders [n (%)]	6 (40)	3 (21.4)	0.427
Responders [n (%)]	9 (60)	11 (78.6)	

Nonresponders: patients who have progressive disease. Responders: patients who have stable disease + progressive disease.

*Fisher's exact test: $p > 0.05$ nonsignificant.

group, comparisons among baseline, after WBRT, and 4 weeks after WBRT were done using the Freidman test. Values of $p < 0.01$ were considered significant in order to take into account the multiplicity of tests (several HRQL scales and different time points).

RESULTS

Baseline Characteristics

From April 2014 until October 2015, 50 patients were included with mean (SD) age of 54.4 (11.1) years. The primary tumor origins were lung (58%), breast (30%), and others (12%). The baseline characteristics of the patients in the study groups were summarized in Table 1. Patients' flow diagram is represented in Figure 1.

Efficacy Evaluation

Radiological Response at 4 Weeks After WBRT. Radiological responses at 4 weeks after WBRT were available for 15 patients in the control group and 14 patients in the simvastatin group (1 patient was unable to do an MRI scan

because of clinical deterioration). None of the patients had CR. There was 5 patients with PR in both groups, and there was 4 patients in the control group and 6 patients in the simvastatin group with SD.

One-Year PFS and 1-Year OS. One-year PFS rates were 5.2% (median PFS time=1.47 months, 95% confidence interval: 0.91–2.02) versus 17.7% (median PFS time=1.6 months, 95% confidence interval: 0.68–2.52), while 1-year OS rates were 12% (median OS time=3 months, 95% confidence interval: 2.46–3.54) versus 8% (median OS time=3.4 months, 95% confidence interval: 0.69–6.01) in the control group and the simvastatin group, respectively. A statistically nonsignificant difference was found between the two groups regarding 1-year PFS ($p=0.392$) and 1-year OS ($p=0.880$). Five (10%) patients completed the study; the cause of death was presumed to be due to systemic progression in 18 (36%) patients, neurologic progression in 22 (44%) patients, and unreported in 5 (10%) patients.

Safety Evaluation

The addition of simvastatin was tolerated. No signs and symptoms of statin-induced myopathy were reported. Hence, serum creatinine kinase was not assessed for any patient. Comparisons of serum ALT and AST between baseline and after WBRT in the two groups are represented in Table 3. Although there was a significant difference within the simvastatin group between baseline and after WBRT regarding serum ALT, comparisons between the groups were not significant. Nonsignificant differences were found between groups and within the group regarding serum AST.

Table 3. Comparisons of Serum ALT and AST in the Study Groups at Baseline and After Whole-Brain Radiation Therapy

Parameter	Control Group	Simvastatin Group	p Value*
Baseline ALT (IU/L)			0.950
Median (range)	22 (7–28)	24 (11–67)	
95% CI of the median	17–29	16–29	
After WBRT ALT (IU/L)			0.330
Median (range)	21 (6–77)	36 (9–83)	
95% CI of the median	20–35	17–59	
p Value†	0.850	0.035	
Baseline AST (IU/L)			0.950
Median (range)	28 (18–73)	26 (13–69)	
95% CI of the median	21–34	21–45	
After WBRT AST (IU/L)			0.925
Median (range)	28 (19–69)	29 (13–70)	
95% CI of the median	27–36	25–46	
p Value†	0.586	0.679	

*Mann-Whitney test: $p > 0.05$ nonsignificant.

†Wilcoxon signed rank: $p > 0.05$ nonsignificant.

Table 4. Comparisons of EORTC QLQ-C30/BM-20 Scales Between Groups and Within Group at Baseline, After WBRT, and 4 Weeks After WBRT Evaluation

Scale	Control Group [Median (Range)]	Simvastatin Group [Median (Range)]	<i>p</i> Value*
Baseline QL2	33 (0–67)	50 (33–67)	0.033
After WBRT QL2	50 (0–100)	50 (0–67)	0.813
4 weeks after WBRT QL2	50 (0–100)	50 (0–100)	0.847
<i>p</i> Value†	0.282	0.502	
Baseline PF2	13 (0–87)	33 (0–80)	0.561
After WBRT PF2	33 (0–87)	33 (0–67)	0.914
4 weeks after WBRT PF2	10 (0–100)	40 (0–67)	0.780
<i>p</i> Value†	0.807	0.233	
Baseline RF2	0 (0–100)	0 (0–100)	0.505
After WBRT RF2	0 (0–100)	0 (0–67)	0.715
4 weeks after WBRT RF2	0 (0–100)	33 (0–100)	0.880
<i>p</i> Value†	0.839	0.839	
Baseline EF	67 (0–100)	75 (0–100)	0.377
After WBRT EF	92 (0–100)	100 (0–100)	0.354
4 weeks after WBRT EF	79 (0–100)	92 (0–100)	0.914
<i>p</i> Value†	0.723	0.337	
Baseline CF	67 (0–100)	67 (0–100)	0.561
After WBRT CF	58 (0–100)	67 (0–100)	0.621
4 weeks after WBRT CF	67 (0–100)	83 (0–100)	0.880
<i>p</i> Value†	0.575	0.836	
Baseline SF	100 (0–100)	100 (0–100)	0.652
After WBRT SF	100 (0–100)	100 (0–100)	0.591
4 weeks after WBRT SF	92 (0–100)	100 (0–100)	0.683
<i>p</i> Value†	0.761 ^b	0.840 ^b	
Baseline FA	94 (0–100)	89 (22–100)	0.847
After WBRT FA	100 (0–100)	100 (33–100)	0.847
4 weeks after WBRT FA	83 (0–100)	89 (0–100)	0.591
<i>p</i> Value	0.892	0.539	
Baseline NV	25 (0–100)	17 (0–100)	0.880
After WBRT NV	25 (0–100)	17 (0–67)	0.354
4 weeks after WBRT NV	25 (0–100)	33 (0–100)	0.652
<i>p</i> Value†	0.856	0.138	
Baseline PA	42 (0–100)	50 (0–100)	0.477
After WBRT PA	33 (0–100)	50 (0–100)	0.201
4 weeks after WBRT PA	67 (0–100)	83 (0–100)	0.914
<i>p</i> Value†	0.570	0.744	
Baseline DY	33 (0–100)	33 (0–100)	0.591
After WBRT DY	67 (0–100)	0 (0–100)	0.018
4 weeks after WBRT DY	17 (0–100)	0 (0–100)	0.983
<i>p</i> Value†	0.358	0.338	
Baseline SL	100 (0–100)	33 (0–100)	0.041
After WBRT SL	83 (0–100)	67 (0–100)	0.451
4 weeks after WBRT SL	83 (0–100)	33 (0–100)	0.683
<i>p</i> Value†	0.549	0.976	
Baseline AP	67 (0–100)	67 (0–100)	0.914
After WBRT AP	33 (0–100)	33 (0–100)	0.847
4 weeks after WBRT AP	100 (0–100)	100 (0–100)	0.683
<i>p</i> Value†	0.231	0.416	
Baseline CO	0 (0–67)	0 (0–100)	0.252
After WBRT CO	0 (0–100)	33 (0–100)	0.400
4 weeks after WBRT CO	33 (0–100)	67 (0–100)	0.310
<i>p</i> Value†	0.048	0.139	
Baseline DI	0 (0–100)	0 (0–67)	0.914
After WBRT DI	0 (0–100)	0 (0–100)	0.477
4 weeks after WBRT DI	0 (0–100)	0 (0–100)	0.477
<i>p</i> Value†	0.852	0.687	
Baseline FI	0 (0–100)	0 (0–100)	0.949
After WBRT FI	0 (0–100)	0 (0–100)	0.747
4 weeks after WBRT FI	0 (0–100)	0 (0–100)	0.880
<i>p</i> Value†	0.725	0.857	

(continued)

Table 4. (continued)

Scale	Control Group [Median (Range)]	Simvastatin Group [Median (Range)]	<i>p</i> Value*
Baseline BNFU	25 (0–100)	25 (0–75)	0.621
After WBRT BNFU	0 (0–100)	17 (0–92)	0.561
4 weeks after WBRT BNFU	4 (0–100)	8 (0–100)	0.621
<i>p</i> Value†	0.247	0.924	
Baseline BNVD	56 (0–100)	11 (0–67)	0.016
After WBRT BNVD	17 (0–100)	0 (0–67)	0.146
4 weeks after WBRT BNVD	17 (0–100)	0 (0–100)	0.270
<i>p</i> Value†	0.153	0.261	
Baseline BNMD	94 (0–100)	56 (0–100)	0.652
After WBRT BNMD	33 (0–100)	44 (0–100)	0.747
4 weeks after WBRT BNMD	56 (0–100)	33 (0–100)	0.451
<i>p</i> Value†	0.401	0.281	
Baseline BNCD	17 (0–100)	11 (0–100)	0.533
After WBRT BNCD	0 (0–100)	0 (0–89)	0.880
4 weeks after WBRT BNCD	28 (0–100)	11 (0–100)	0.477
<i>p</i> Value†	0.704	0.697	
Baseline BNHA	83 (0–100)	33 (0–100)	0.561
After WBRT BNHA	33 (0–100)	33 (0–100)	0.652
4 weeks after WBRT BNHA	33 (0–100)	33 (0–100)	0.880
<i>p</i> Value†	0.089	0.266	
Baseline BNSE	0 (0–100)	0 (0–100)	0.451
After WBRT BNSE	0 (0–100)	0 (0–33)	0.621
4 weeks after WBRT BNSE	0 (0–100)	0 (0–100)	0.505
<i>p</i> Value†	0.446	0.867	
Baseline BNDR	0 (0–100)	33 (0–100)	0.377
After WBRT BNDR	0 (0–100)	33 (0–100)	0.201
4 weeks after WBRT BNDR	33 (0–100)	67 (0–100)	0.331
<i>p</i> Value†	0.539	0.378	
Baseline BNIS	0 (0–67)	0 (0–67)	0.400
After WBRT BNIS	50 (0–100)	0 (0–67)	0.112
4 weeks after WBRT BNIS	33 (0–100)	0 (0–100)	0.533
<i>p</i> Value†	0.007	0.629	
Baseline BNHL	0 (0–100)	0 (0–100)	0.621
After WBRT BNHL	67 (0–100)	0 (0–100)	0.085
4 weeks after WBRT BNHL	100 (0–100)	100 (0–100)	0.715
<i>p</i> Value†	0.004	0.008	
Baseline BNWL	100 (0–100)	67 (0–100)	0.591
After WBRT BNWL	67 (0–100)	100 (0–100)	0.234
4 weeks after WBRT BNWL	100 (0–100)	67 (0–100)	0.310
<i>p</i> Value†	0.358	0.328	
Baseline BNBC	0 (0–100)	0 (0–100)	0.290
After WBRT BNBC	50 (0–100)	0 (0–100)	0.020
4 weeks after WBRT BNBC	0 (0–100)	0 (0–100)	0.747
<i>p</i> Value†	0.095 ^b	0.549 ^b	

EORTC QLQ-C30/BN-20, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire C30 and its brain module; WBRT, whole-brain radiation therapy; QL2, global health status; PF2, physical functioning; RF2, role functioning; EF, emotional functioning; CF, cognitive functioning; SF, social functioning; FA, fatigue; NV, nausea and vomiting; PA, pain; DY, dyspnea; SL, insomnia; AP, appetite loss; CO, constipation; DI, diarrhea; FI, financial difficulties; BNFU, future uncertainty; BNVD, visual disorder; BNMD, motor dysfunction; BNCD, communication deficit; BNHA, headaches; BNSE, seizures; BNDR, drowsiness; BNIS, itchy skin; BNHL, hair loss; BNWL, weakness of leg; BNBC, bladder control.

*Comparison between groups was done using Mann–Whitney test: $p > 0.01$ nonsignificant.

†Comparison within group was done using Friedman test: $p > 0.01$ nonsignificant.

The toxicity profile of radiotherapy had no unexpected or added substantial toxicity reported in either arm. The reported side effects were alopecia, dermatitis, tinnitus, fatigue, drowsiness, and others.

Evaluation of HRQL

Evaluation of HRQL by caregivers for nine patients with severe cognitive impairments was included. The

EORTC QLQ-C30 comprises nine multi-item scales; five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea and vomiting), and a global health scale. It comprised six single-item scales (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial impact). The EORTC BN-20 comprises four multi-items scales (visual disorder, motor dysfunction, communication deficit, and

future uncertainty) and seven single-item scales (headaches, seizures, drowsiness, hair loss, itchy skin, weakness of legs, and bladder control).

Evaluation at baseline was available for all patients. The main prominent problems were limited physical functioning, role functioning, and social functioning, fatigue, pain, insomnia, appetite loss, motor dysfunction, headache, drowsiness, and leg weakness. Comparison between the two groups at baseline was not significant for all scales ($p < 0.01$).

Results of the HRQL scales at 4 weeks after WBRT were available for 14 patients in the control group (1 patient refused to fill out the questionnaire) and 15 patients in the simvastatin group. Comparisons of HRQL scales for "4 weeks after WBRT" survivors between the two groups regarding baseline, after WBRT, and 4 weeks after WBRT, showed that there were statistically significant differences within the control group with respect to itchy skin scale and within the control group and the simvastatin group regarding hair loss scale. However, comparisons between groups with respect to these two scales at different time points were statistically nonsignificant. Comparisons between groups and within the group regarding other scales were statistically nonsignificant. These data are summarized in Table 4.

DISCUSSION

The radiosensitizing effect of statins has not been evaluated in randomized, controlled trials before. Only one retrospective cohort study on inflammatory breast cancer (IBC) has shown an improvement in local control of the tumor after postmastectomy radiotherapy in statin users with IBC compared to nonstatin users¹⁸.

The current study has shown that the addition of simvastatin did not improve the radiological response evaluated at 4 weeks after radiation. Despite radiological response being the primary study outcome, only 58% of the patients could be evaluated. The current study was limited by the patients' short survival with 32% of the patients dying before the radiological response evaluation. Sixty-eight percent of the patients recruited were RPA class 3, which has a poor prognosis.

In agreement with the radiological response results, the addition of simvastatin did not affect the 1-year PFS and 1-year OS rates.

This study evaluated the safety of simvastatin use for a very short duration. No myopathy has been reported, and none of the increases in serum ALT were clinically significant. The radiotherapy toxicity profile in both groups was expected with no added substantial toxicity.

Quality of life assessment is very important in clinical practice. However, it is difficult to obtain information about HRQL in patients with cognitive impairment¹⁹. Using EORTC QLQ-C30 and BN-20 in primary brain

tumor patients, Giesinger and his colleagues found that the assessment of HRQL using caregivers in patients unable to provide information themselves was a feasible strategy²⁰.

In the current study, WBRT did not improve the HRQL of the patients, even with the addition of simvastatin.

The current study was limited by the small sample size and the heterogeneity with respect to primary tumor origin and RPA classification. Most of the recruited patients had a poor prognosis and short survival. Severe cognitive impairment limited self-rating HRQL assessment. Noncompliance and short survival limited the patients available for evaluation at longer endpoints.

Neither the precise mechanism for radiation sensitization nor the optimum schedule for simvastatin use as a radiosensitizer is known. The mechanism of postulated radiosensitizing effect depends on inhibition of post-translational processing via the inhibition of mevalonate pathway, the same mechanism involved in cholesterol synthesis, and hence simvastatin was administered at the same dosage regimen used in hypercholesterolemia. It is questionable whether shorter dosing intervals, higher doses, or use for longer periods is needed for simvastatin to significantly show its radiosensitizing effect. Further clinical trials using different members and different dosing regimens are needed to assess the radiosensitizing effect of statins.

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