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Clinical Study

Preoperative statin use is not associated with improvement in survival after glioblastoma surgery

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ABSTRACT

Cohort studies have suggested that the use of statins is associated with decreased risk of glioma formation and mortality. Here, a cohort of patients with glioblastoma multiforme (GBM) was analyzed to further investigate associations between preoperative use of statins and recurrence, and progression free and overall survival. Patients who had surgery for GBM (N = 284) were followed up for a median of 18.1 months. Seventy-eight patients were taking statins preoperatively while the rest were not. Cox proportional hazards models adjusted for several covariates of interest were applied before and after propensity score matching. Compared with statin users, those not taking the lipid-lowering drugs had similar progression free survival before (hazard ratio [HR] 0.94, 95% confidence interval [CI] 0.70–1.26; p = 0.68) and after propensity score matching (HR 0.95, 95% CI 0.67–1.35; p = 0.68). Mortality was similar between both groups of patients before (HR 0.94, 95% CI 0.70–1.22; p = 0.73) and after propensity score matching (HR 1.13, 95% CI 0.78–1.64; p = 0.49). Age and dexamethasone use were independent prognostic factors of survival. Contrary to previously published evidence, this study could not find an association between preoperative statin use and longer survival in GBM patients. Due to the small number of patients and retrospective nature of the study, further work is needed to understand the role of perioperative statins in GBM patients.

1. Introduction

Glioblastoma multiforme (GBM) is the most common malignant brain tumor. GBM is highly aggressive and is associated with a poor prognosis. With surgical resection followed by chemotherapy and radiation, median overall survival (OS) remains poor at approximately 15 months [1]. Slightly more than a quarter of patients are alive 2 years after diagnosis and treatment with radiation and chemotherapy [2].

Statins, a class of drug used to treat lipid disorders, are one of the most highly prescribed drugs of all time. Multiple cardiovascular safety trials of statins have demonstrated pleiotropic benefits of statin use [3]. There is evidence that statins modulate the inflammatory response, have anti-oxidant properties, inhibit the thrombogenic response, and decrease the oxidative stress response. Statins may also have anti-neoplastic properties. Lovastatin inhibits the proliferation of lung cancer cells in animal models and similarly in breast, prostate and gastric carcinoma [4–6]. Cytotoxic effects via apoptosis have been demonstrated in a variety of cancer cells by lovastatin and other statins [7,8]. Lovastatin has also been shown to inhibit steps in cancer cell metastasis—specifically, attachment, motility, and invasion [9–12]. There is evidence suggesting statins potentiate or have an additive effect upon chemotherapy agents [13]. Laboratory studies have shown that statins sensitize human rhabdomyosarcoma cells in the presence of doxorubicin and cerivastatin has been shown to increase cytotoxicity of 5-fluorouracil in resistant colorectal cancer cells [14,15]. Clinical evidence suggests that patients who were on statins before a diagnosis of certain cancers have decreased mortality compared to non-statin users [16]. Statin drugs may also play a role in chemoprevention of cancer. Ferris et al. demonstrated that duration of simvastatin and lovastatin use was associated with an inverse risk of glioma development [17]. Gaist et al. showed that the use of statins reduced mortality by 21% in GBM patients [18]. The effect was more pronounced with longer duration and higher intensity of statin use [18].

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Our objective was to determine if statins could increase the progression free survival (PFS) and decrease tumor recurrence for GBM patients in the United States. Thus, we conducted a retrospective study evaluating the association between any preoperative statin use and PFS and OS after surgical resection in GBM patients who sought treatment at our tertiary cancer center. Specifically, we hypothesized that any statin use prior to GBM diagnosis would lead to a longer PFS or OS compared to non-statin users.

2. Materials and methods

After obtaining Institutional Review Board approval (IRB# PA12-0447), we conducted a retrospective analysis of our prospectively maintained database that included demographic, perioperative, tumor-related, and survival information from patients (n = 841) who underwent primary brain tumor resection between January 2006 and July 2015 at The University of Texas M.D. Anderson Cancer Center. Patients were included in the study if they were 18 years or older, had surgery for a newly diagnosed supratentorial GBM, had not undergone preoperative chemotherapy or radiation treatment, and received postoperative temozolomide and radiation. Patients who had any other central nervous system tumor, either benign or malignant, or had surgery for recurrent tumor were excluded from the analysis. The data retrieved for statistical analysis included patient age, body mass index (BMI), gender, American Society of Anesthesiology (ASA) physical status, age adjusted Charlson comorbidity index score (aCCI), perioperative corticosteroid use, and type and dose of statin used before surgery.

PFS and OS were the primary clinical endpoints. PFS was calculated as the time between the surgery date and the date of first evidence of progression (usually radiological) or the date of death, whichever happened first. Patients were censored at the last known date if neither recurrence nor death occurred. OS was defined as the time from the date of surgery to the date of death or last follow-up. Patients were censored at the last follow-up if death did not occur.

2.1. Statistical analysis

Summary statistics including mean, standard deviation, median, and range for continuous variables (such as age and BMI), frequency counts and percentages for categorical variables (such as sex and ASA physical status), are provided. We used Fisher's exact test or chi-squared test to evaluate the association between two categorical variables. The Wilcoxon Rank-Sum test was used to evaluate the difference in continuous variables between patient groups.

To adjust for selection bias, we conducted a propensity score matching analysis. The propensity score is the conditional probability of receiving a specific treatment (statin) conditional on a set of observed covariates. In this study, we included the following prognostic covariates in the multivariate logistic model to estimate the propensity scores: age at surgery, BMI, gender, ASA, aCCI, and perioperative use of dexamethasone. The Greedy 5→1 digit match algorithm was used to match the baseline covariates, so that the two groups (with statin or without statin) would have similar propensity scores. Eliminating all patients with incomplete or missing covariate data within our database, a total of 67 patients using a statin drug were matched 1:1 with non-statin using patients with complete data values.

The Kaplan–Meier method was used for time-to-event analysis including PFS and OS duration. The median time to event in months with a 95% confidence interval (CI) was calculated. The log-rank test was used to evaluate the difference in time-to-event endpoints between patient unmatched and matched groups. Univariate Cox proportional hazards models were fitted to evaluate the effects of continuous variables on time-to-event outcomes. Multivariable Cox proportional hazards models were used for multivariate analysis to include important and significant covariates. Statistical software SAS 9.1.3 (SAS, Cary, NC, USA) and S-Plus 8.0 (TIBCO Software, Palo Alto, CA, USA) were used for all the analyses.

3. Results

Out of 841 patients in our database, we analyzed data on a total of 284 GBM patients with complete perioperative and survival information. The mean (SD) age of the entire population of patients was 56.07 (12.63) years. There were more females (n = 170, 59.9%) than males (n = 114, 40.1%) and more than two-thirds of the patients (n = 230, 80.99%) were ASA 3–4 (vs. n = 54, 19.01% ASA

Table 1
Demographic variables of patients with glioblastoma multiforme

Variable		Unmatched cohorts			Matched cohorts	
		Statin = no N = 206	Statin = yes N = 78	p value	Statin = no N = 67	Statin = yes N = 67
Age mean (SD)		53.78(12.77)	62.11(10.06)	<0.0001	61.26(10.27)	60.78(9.82)
(years)	<55	111(53.9%)	13(16.7%)	0.0001	21(31.3%)	13(19.4%)
	⩾55	95(46.1%)	65(83.3%)	.	46(68.7%)	54(80.6%)
Gender	Male	93(45.1%)	21(26.9%)	0.005	19(28.4%)	20(29.9%)
	Female	113(54.9%)	57(73.1%)	.	48(71.6%)	47(70.1%)
BMI mean (SD)		27.23 (5.3)	29.11 (4.92)	0.0037	28.67 (5.93)	28.89(4.95)
	⩽25	74(35.9%)	14(17.9%)	0.003	18(26.9%)	12(17.9%)
	>25	132(64.1%)	64(82.1%)	.	49(73.1%)	55(82.1%)
ASA physical	1–2	48(23.3%)	6(7.7%)	0.002	9(13.4%)	6(9%)
status	3–4	158(76.7%)	72(92.3%)	.	58(86.6%)	61(91%)
aCCI	⩽2	77(37.4%)	13(16.7%)	0.0001	11(16.4%)	13(19.4%)
score	3–4	97(47.1%)	37(47.4%)	.	35(52.2%)	35(52.2%)
	⩾5	32(15.5%)	28(35.9%)	.	21(31.3%)	19(28.4%)
Preoperative	No	56(27.2%)	19(24.4%)	0.629	18(26.9%)	17(25.4%)
dexamethasone	Yes	150(72.8%)	59(75.6%)	.	49(73.1%)	50(74.6%)
Adjuvant	No	8(3.9%)	0.0(.%)	0.111	NA	NA
radiation	Yes	197(96.1%)	78(100%)	.		

Prognostic covariates by statin before and after propensity score matching.
aCCI = age adjusted Charlson comorbidity index, ASA = American Society of Anesthesiologists, BMI = body mass index, NA = not included in the matching analysis, SD = standard deviation.