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PHASE II STUDIES

Atorvastatin in combination with radiotherapy and temozolomide for glioblastoma: a prospective phase II study

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Summary

Glioblastoma is a fast-growing primary brain tumor observed in adults with the worst prognosis. Preclinical studies have demonstrated the encouraging anticancer activity of statins. This study evaluated the efficacy of atorvastatin in combination with standard therapy in patients with glioblastoma. In this prospective, open-label, single-arm, phase II study, patients were treated with atorvastatin in combination with the standard glioblastoma therapy comprising radiotherapy and temozolomide. The primary endpoint was progression-free survival (PFS) at 6 months (PFS-6). Among 36 patients enrolled from January 2014 to January 2017, the median age was 52 (20–69) years; 22% of the patients were aged ≥60 years, and 62% were male. Patients received atorvastatin for a median duration of 6.2 (0.3–28) months. At a median follow-up of 19 months, the PFS-6 rate was 66%, with a median PFS of 7.6 (5.7–9.4) months. In terms of Grade ≥ 3 hematological adverse events, thrombocytopenia and neutropenia occurred in 7% and 12% of patients, respectively. In multivariate analyses, high baseline low-density lipoprotein levels were associated with worse survival ($P = 0.046$). Atorvastatin was not shown to improve PFS-6. However, this study identified that high low-density lipoprotein levels are an independent predictor of poor cancer-related outcomes. Future clinical trials testing statins should aim to enroll patients with slow-growing tumors.

Clinical trial information: NCT0202957 (December 12, 2013)

Keywords Atorvastatin · Statins · Cancer · Glioblastoma · Low-density lipoprotein cholesterol

Introduction

Primary tumors of the central nervous system (CNS) are associated with a high mortality rate and are responsible for 2.9% of all cancer-related deaths [1]. Glioblastoma is an aggressive CNS tumor arising from the glial cells of the brain or spinal cord [2] and is the most common primary brain tumor in adults, accounting for 59% of all malignant gliomas [2].

The standard therapy for newly diagnosed glioblastoma patients is maximal surgical resection, followed by radiotherapy with concomitant and adjuvant temozolomide (TMZ). However, there is an urgent need for more effective first-line treatments as most patients die within 2 years of diagnosis [3].

Statins, commonly administered to lower blood cholesterol levels, inhibit 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase [4]. This leads to the disruption of critical cellular functions such as protein synthesis, cell signaling, membrane integrity, and cell cycle progression [5], which in turn leads to the inhibition of tumorigenesis, tumor growth, and metastasis. Like TMZ, statins cause cell cycle arrest in the

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late G1 phase and may sensitize cells to radiation [6]. We anticipated that the combination of statins and TMZ with radiotherapy would target tumor cells in the G2-M and late G1 phases of the cell cycle, as illustrated in Fig. S1.

Atorvastatin, a synthetic lipophilic statin licensed in 1996, was selected for this study due to its high bioavailability in the CNS [7], favorable safety profile [8], and high efficacy in reducing low-density lipoprotein (LDL) levels [9]. Atorvastatin is the most widely prescribed statin worldwide, and its efficacy and safety have been evaluated in more than 500 randomized clinical trials [10]. Atorvastatin is rapidly absorbed following oral administration, and the maximum plasma concentration is attained within 1–2 h [11]. It also has an absolute bioavailability of 12% and is ≥98% bound to plasma proteins [11]. Atorvastatin metabolites are responsible for 70% of the activity against HMG-CoA reductase [11], resulting in a half-life of inhibitory activity ranging from 20 to 30 h [11]. The positive safety profile of atorvastatin in the 10–80 mg dose range has been supported by a retrospective analysis of pooled data from 49 completed trials (16,495 patients) [12].

Considering the potential anticancer activity of statins, this phase II study was designed to explore the efficacy and safety of atorvastatin in combination with radiotherapy and TMZ in patients with newly diagnosed glioblastoma.

Patients and methods

Study design and treatment

This was an open-label, prospective, single-arm, phase II study of atorvastatin in combination with concurrent radiotherapy and TMZ, followed by adjuvant TMZ, in patients with newly diagnosed glioblastoma. The study was conducted at a single cancer center in Saudi Arabia. Patients were administered 40 mg of oral atorvastatin daily for 3 weeks, followed by 80 mg daily. TMZ was administered at an oral dose of 75 mg/m^2 per day with concurrent radiotherapy (2 Gy/5 days per week) for 6 weeks, followed by a resting period of 4 weeks. Subsequently, TMZ was administered at a dose of 150–200 mg/m^2 for 5 days every 4 weeks for 6 months. Atorvastatin treatment was continued until unacceptable toxicity, disease progression, or termination at patient request. Fig. S2 summarizes the trial design.

Patient eligibility

Adult patients with histologically proven, newly diagnosed glioblastoma who had undergone surgery were recruited between January 2014 and January 2017. The inclusion criteria included the following: (1) Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0, 1, or 2; (2) administration of a stable steroid dose for at least 14 days before the study; and (3) an estimated life expectancy of ≥12 weeks. The exclusion criteria included the following: (1) prior exposure to chemotherapy, radiotherapy, or statins; (2) concurrent treatment with other experimental drugs; and (3) severe active co-morbidities. The complete inclusion and exclusion criteria are provided in Supplementary Table S1. Written consent was obtained from all patients before registration according to local institutional requirements. Institutional approval was provided by the local review board (IRB number H-01-R-012).

Objectives and outcome measures

The primary objective of this study was to evaluate the effect of atorvastatin in combination with radiotherapy and TMZ on progression-free survival at 6 months (PFS-6) in patients with newly diagnosed glioblastoma.

The secondary objectives included the evaluation of additional potential measures of efficacy, including overall survival (OS), and determination of the safety and tolerability of the combination of atorvastatin, radiotherapy, and TMZ.

Response determination

Radiographic tumor response (disease progression) was determined according to the Radiology Assessment in Neuro-Oncology response criteria based on the findings of magnetic resonance imaging performed before treatment (baseline), after the 4-week treatment break, and every 3 months thereafter (Fig. S3).

Statistical analyses

The sample size calculation was based on the goal of increasing the 6-month PFS rate by a 20% absolute benefit [13]. Thirty-two patients were required to provide 80% power using a one-sided alpha of 0.05.

A two-stage phase II design was chosen for this study. During the initial stage, 15 eligible patients were enrolled. After fulfillment of the continuation/stoppage criteria, an additional 17 eligible patients were enrolled.

The results were compared to those from a similar cohort of 65 patients who received standard of care radiotherapy and TMZ followed by adjuvant TMZ (control study) [14].

PFS and OS were estimated using the Kaplan–Meier method. OS was assessed using multivariate Cox regression analysis, and the results were adjusted for age, ECOG PS, resection extent, O6-methylguanine-DNA-methyltransferase (MGMT) status, recursive partitioning analysis (RPA) score, LDL level, and adjuvant chemotherapy.

All analyses were performed using IBM SPSS version 22 (IBM SPSS, Armonk, NY, USA). *P*-values <0.05 were considered statistically significant.

Results

Patient characteristics

From January 2014 until January 2017, 76 patients were screened, of which 36 were enrolled in this study. Fig. S4 shows a Consolidated Standards of Reporting Trials (CONSORT) diagram of the screening process.

The median age at the time of enrollment was 52 years (range 20–69 years). Most patients were aged <60 years (78%), were male (62%), and had good PS (62%). Surgical resection was performed in most patients (97%), while a small number of patients underwent biopsy (3%) alone. The patients' characteristics are presented in Table 1.

PS was similar between patients in the current study cohort and the control study cohort; however, the rate of surgical resection was higher in the current study cohort.

Efficacy analysis

The PFS-6 rate was 66% in this trial compared to 55% in the control study ($P = 0.32$) (Fig. 1). The median PFS was 7.6 months (range, 5.7–9.4 months) with a median follow-up of 19.3 months; in the control study, the median PFS was 7.8 months (range, 4.6–11.1 months) with a median follow-up 12.5 months. The difference in median PFS between these studies did not reach statistical significance (log-rank $P = 0.348$).

Overall survival

The median OS in this study (19.9 months [range, 14.8–25.1 months]) was similar to that (19.6 months [range = 11.9–27.3 months]) in the control study (Fig. 2). The difference in median OS did not reach statistical significance (log-rank $P = 0.984$). The proportion of patients who were alive 1 year after the initiation of the study treatment was higher in this study (75%) than in the control study (64%) ($P = 0.29$).

The multivariate analysis revealed that worse OS was associated with high baseline LDL levels ($P = 0.046$) (Fig. S5) and that better OS was associated with methylated tumors ($P = 0.013$) (Table 2).

Table 1 Comparison of baseline characteristics with those of two historical control cohorts

Characteristics		ART Study ($N = 36$)	Historical control	
			EORTC-NCIC RT/TMZ ($N = 287$)	Control trial ($N = 65$)
Age, years	Median (range)	52 (20–69)	56 (19–70)	47 (18–81)
	<60	78%	–	80%
	≥60	22%	–	20%
Sex	Male	62%	64%	75%
	Female	38%	36%	25%
PS (ECOG/KPS)	0–1 (≥70)	62%	87%	61%
	2 (50–60)	38%	13%	39%
Surgical status	Biopsy only	3%	17%	11%
	Any resection	97%	83%	89%
MMSE score	<27	43%	28%	–
	≥27	57%	68%	–
RPA score	III	16%	15%	–
	IV	41%	53%	–
	V	43%	32%	–
Steroids (baseline)	Yes	32%	67%	–
MGMT status	Methylated	36%	16%	2%
	Non-methylated	42%	20%	5%
	Unknown	22%	64%	93%
LDL (baseline)	High	53%	–	–

EORTC, European Organisation for Research and Treatment of Cancer; *ECOG*, Eastern Cooperative Oncology Group; *LDL*, low-density lipoprotein; *KPS*, Karnofsky performance status; *RPA*, recursive partitioning analysis; *RT*, radiotherapy; *MGMT*, O6-methylguanine-DNA-methyltransferase; *MMSE*, Mini-Mental State Exam; *NCIC*, National Cancer Institute of Canada; *PS*, performance status; *TMZ*, temozolomide

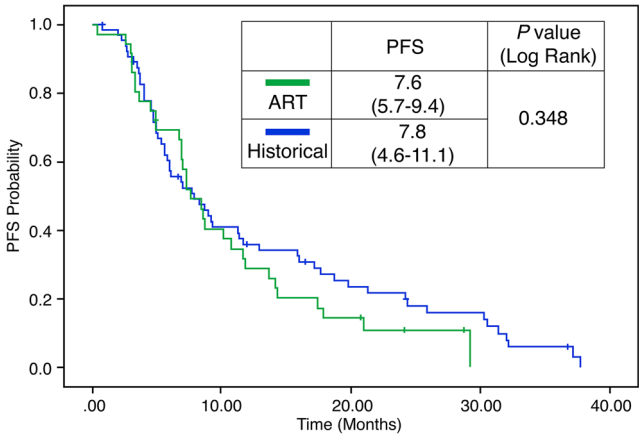

Fig. 1 Kaplan–Meier estimates of progression-free survival (vs. the control study cohort) PFS, progression-free survival

Safety analysis

Overall, treatment was discontinued in 29/36 (80%) patients. Of these, 25 (69%) patients discontinued treatment due to disease progression. During the concurrent therapy period, three (11%) patients discontinued TMZ: one due to disease progression and two due to toxicity. During the adjuvant therapy period, a median of four cycles of TMZ was completed, with 13/36 (44%) patients completing all six cycles. Table 3 shows the discontinuation data for each treatment period.

Over the entire study period, the Grade ≥ 3 adverse events (AEs) of thrombocytopenia and neutropenia occurred in 13% and 6% of patients, respectively, with both AEs occurring more commonly in the adjuvant therapy period than in the concurrent therapy period (Table S2).

Statin-related toxicities were mostly Grade 1 and 2 toxicities, including muscle pain (10 patients [22%], Grade 1), creatine phosphokinase elevation (one patient [3%], Grade 2), and hepatic dysfunction (two patients, [5%] Grade 1).

Serious AEs occurred in 2/36 (5%) patients. One patient died within 30 days of the last treatment secondary to rapid disease progression, and another patient required hospitalization secondary to severe thrombocytopenia.

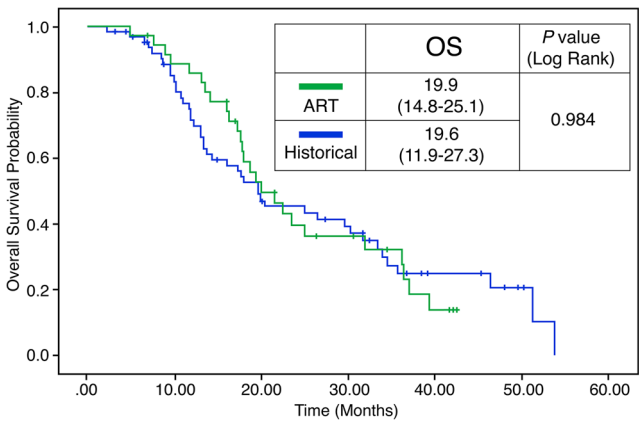

Fig. 2 Kaplan–Meier estimates of overall survival (vs. the control study cohort) OS, overall survival

Discussion

Despite numerous clinical trials on various types of cancer, the real clinical role of statins as anticancer agents is yet to be determined [15]. Thus, this phase II clinical trial was conducted to address and investigate the efficacy and safety of atorvastatin in combination with radiotherapy and TMZ in patients with newly diagnosed glioblastoma.

We anticipated that atorvastatin would further enhance the synergism between TMZ and irradiation. Although previous experimental evidence suggests that statins may augment the efficacy of radiotherapy [16], the combination used in this study was unique in terms of the choice of statin, the statin dose, and the duration of use.

Although the PFS-6 rate observed in this study was numerically superior to those in the control study and the EORTC-NCIC trial [13], the difference did not reach statistical significance. The median PFS and OS were also comparable to those in the control and EORTC-NCIC studies, with only marginal numerical improvements in 1-year OS [13]. Overall, this study failed to achieve the expected improvements in PFS and OS, a finding replicated in a recent retrospective analysis of statin use in patients with high-grade glioma [17]. One possible explanation for these results is the aggressive nature of both glioblastoma and high-grade glioma; in our study, atorvastatin was administered for a median duration of 6 months, during which time glioblastoma is likely to have progressed rapidly. Interestingly, the long-term use of statins pre-diagnosis may improve survival in glioblastoma patients [18], suggesting that future studies on statin treatment might be better suited to more indolent or slow-growing tumors.

Multivariate analysis revealed that the OS of the study participants was significantly inversely associated with baseline LDL levels, suggesting that high LDL levels may have prognostic implications for poor cancer-related outcomes. This finding is in line with the growing evidence on the impact of hyperlipidemia on cancer-related mortality [19]; to our knowledge, this is the first clinical trial to report this association in a prospective study.

The addition of atorvastatin to standard chemoradiotherapy was well-tolerated, with only 11% of patients discontinuing treatment during the adjuvant therapy period and 11% discontinuing treatment during the concomitant therapy period. These results are comparable to those from the EORTC-NCIC trial [13], which reported discontinuation rates of 8% and 5% due to toxicity in the adjuvant and concomitant therapy periods, respectively. The incidence of Grade ≥ 3 AEs was also similar between this study and the EORTC-NCIC trial (thrombocytopenia, 13% vs. 12%; and neutropenia, 6%

Table 2 Multivariate Cox regression analysis adjusted for age, performance status, extent of resection, MGMT status, RPA score, and LDL levels (baseline and percent reduction at 3 months)

Characteristics		Multivariate analysis		
		HR	95% CI	*P* value
Age, years	≥65	1.1	0.6–1.8	0.72
	<65			
ECOG performance status	>2	1.7	0.9–2.5	0.56
	≤2			
Surgery	Biopsy	1.8	0.8–2.8	0.64
	Any resection			
Residual	Yes	2.0	0.9–2.9	0.12
	No			
MGMT status	Non-Methylated/Unknown	2.74	1.24–6.10	0.013
	Methylated			
RPA score	V	1.8	0.8–2.1	0.32
	IV	1.6	0.5–1.8	0.56
	III			
Baseline LDL level	High	2.23	1.02–4.90	0.046
	Normal			
Percent reduction at 3 months	<50%	1.2	0.6–1.8	0.81
	≥50%			

CI, confidence interval; *ECOG*, Eastern Cooperative Oncology Group; *HR*, hazard ratio; *LDL*, low-density lipoprotein; *RPA*, recursive partitioning analysis; *MGMT*, O6-methylguanine-DNA-methyltransferase

vs. 7%), with no observed statin-related musculoskeletal or hepatic Grade 3 toxicities. These results indicate that the addition of statins to standard therapy did not substantially increase safety concerns.

The main limitation of this study was that prospectively collected data were compared to retrospective control data. Although most baseline patient characteristics were similar between this study and the control study, comparisons with historical data are always associated with reduced confidence. Furthermore, glioblastoma is an aggressive cancer with an inherently poor prognosis, providing little time for the evaluation of treatment efficacy due to high treatment discontinuation and/or disease progression rates. This was a single-arm trial; thus, we could not reach conclusions regarding comparative disease improvement. Thus, large, prospective, randomized clinical trials for less aggressive forms of cancer are warranted to better assess the anticancer effect of statins in combination with standard therapy.

Conclusion

To our knowledge, this is the first clinical trial to investigate the role of statins in combination with standard

Table 3 Patient disposition and treatment tolerability

Treatment period			(*N* = 36)
Overall	Duration, months		6.2 (0.3–28.8)
	Early discontinuation		29 (80%)
	Reason	Disease progression	25 (69%)
		Toxicity	0
		Patient decision	4 (11%)
Radiotherapy + temozolomide	Duration, weeks		6 (1.3–8.5)
Radiotherapy	Early discontinuation		1 (3%)
Concomitant temozolomide	Early discontinuation		3 (8%)
	Reasons	Disease progression	1 (3%)
		Toxicity	2 (5%)
Adjuvant temozolomide	Cycles of temozolomide		4 (1–6)
	Patients who completed 6 cycles		13 (44%)

chemoradiation therapy in newly diagnosed glioblastoma patients. Though the addition of atorvastatin to standard chemoradiation therapy was well-tolerated, it did not result in a significant improvement in PFS or OS. High LDL levels were identified as an important independent prognostic factor of poor cancer-related outcomes in this study cohort. Further prospective randomized studies are warranted to confirm the anticancer potential of statins.

Authorship All authors were involved in study conceptualization, reviewing and editing, formal analysis, and writing.

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Compliance with ethical standards

Conflict of interest All authors declare no conflicts of interest related to this study.

Ethical approval All procedures 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.

Informed consent Informed consent was obtained from all participants included in the study

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