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Impact of particular antiepileptic drugs on the survival of patients with glioblastoma multiforme

Clinical article

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Object. Glioblastoma multiforme (GBM) is the most common astrocytic brain tumor and carries a dire prognosis. Despite current therapeutic options—surgery, radiotherapy, and chemotherapy—survival varies from 11.3 to 14.6 months. A group of drugs known as histone deacetylase inhibitors (HDIs) has demonstrated a potentially beneficial role in cancer treatment, particularly in combination with other therapies. A drug that exhibits potential as an HDI is sodium valproate (VPA), which is frequently used to treat seizures in patients with cerebral neoplasms. The present study was undertaken to investigate the role of VPA as an antitumor agent in the management of patients with GBM.

Methods. A review was conducted in terms of how HDIs work, the use of antiepileptic drugs (AEDs), and the effects of AEDs on survival in a local cohort of patients diagnosed with GBM. The local cohort of patients was determined by reviewing the electronic histopathology and AED informatics systems. A meta-analysis of papers on the use of AEDs in GBM was also performed.

Results. The local cohort consisted of 236 patients with GBM, 210 of whom had complete data available for analysis, a median age of 62 years, and 1-year survival of 26%. Patients treated with AEDs had a significantly longer survival than those who were not (Mantel-Cox log-rank test 19.617, $p < 0.001$). Those treated with VPA had significantly longer survival than those who did not receive an AED (Mantel-Cox log-rank test 17.506, $p < 0.001$), and patients treated with VPA had a significantly longer survival than those who had received other AEDs (Mantel-Cox log-rank test 5.303, $p < 0.02$).

Conclusions. Authors of this study demonstrated evidence supporting the theory that VPA may benefit patients with GBM in terms of survival.
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Key Words • **antiepileptic drug** • **anticonvulsant** • **oncology** • **glioblastoma multiforme** • **sodium valproate**

Glioblastoma multiforme accounts for 53.8% of all gliomas, with an annual incidence of 3.17 cases per 100,000 persons.[2] It has a dismal prognosis even with the best available treatment. One-year survival was estimated at 33.67% in a study evaluating 17,672 GBMs, and recent estimates of median life expectancy have indicated a median survival around 11.3–14.6 months,[2,16,18] with predicted survival varying between 8 and 24 months depending on various risk factors, including treatment with chemotherapy, O^6-methylguanine-DNA methyltransferase promoter methylation status, patient age, extent of surgery, performance status, Mini-Mental State Examination score, and treatment with corticosteroids.[5] Seizures are common in GBM, with 30%–50% of patients experiencing seizures before diagnosis and 6%–45% experiencing seizures postdiagnosis. It has been suggested that patients with GBM presenting with seizures survive longer[11] without knowing the exact reason for the improved survival. This notion raises questions of why GBM accompanied by seizures tends to have a better prognosis, whether AEDs play a role, and whether all AEDs impart the same effect.

Abbreviations used in this paper: AED = antiepileptic drug; EIAED = enzyme-inducing AED; GABA = γ-aminobutyric acid; HDAC = histone deacetylase; KPS = Karnofsky Performance Scale; MCLR = Mantel-Cox log-rank; NEIAED = non–enzyme inducing AED; VPA = sodium valproate.

Sodium valproate, phenytoin, carbamazepine, and Keppra are commonly used in the treatment of seizures in the context of GBM.[12] Sodium valproate is known to have multiple mechanisms of action for the prevention of seizures. As an inhibitor of GABA-transaminase, VPA prevents the transamination and subsequent metabolism of GABA, which leads to increased levels of GABA in the brain. Because GABA is an inhibitory neurotransmitter, increasing its levels in the brain raises the seizure threshold. It is also understood that VPA prevents the action of voltage-gated sodium channels and T-type calcium channels, which prevents repolarization of the cell after an action potential, increasing the duration of the refractory phase and preventing rapid firing of neurons. The modulation of GABA and sodium and calcium flow is thought to be the principal mechanism whereby neuronal modulation is elicited.[14] However, there is some evidence that VPA may also have a number of anticancer effects via a number of novel mechanisms. These mechanisms involve the modulation of epigenetic factors—primarily the inhibition of HDACs. In fact, a number of AEDs have demonstrated potentially inhibitory effects on HDACs. One study has revealed that VPA, topiramate, and a metabolite of levetiracetam inhibit HDACs.[4] Of these agents, VPA was the most potent. Authors of this study found that vigabatrin, gabapentin, carbamazepine, and ethosuximide have no inhibitory effect on HDACs, whereas authors of another paper have suggested that carbamazepine may also act as an HDAC inhibitor.[1] Histone deacetylases have been shown in knockout animal studies to be important in proliferation, migration, and metastasis of cancer cells.[7,17] The present study was undertaken to critically review whether AEDs affect survival in GBM by analyzing the outcomes of a cohort of patients with GBM and reviewing the literature.

Methods

This study was performed with institutional board approval under the Caldicott guardian scheme governing access to medical records.

We reviewed a cohort of 236 consecutive patients in whom GBM had been diagnosed at our institution. Data were obtained from the neurosurgical neurooncology database, the neuropathology database, and the Health Informatics Centre data set. All patients were treated with standard therapy including surgery, radiotherapy, and chemotherapy. Particular attention was given to the type of AED each patient received. The choice of AED was at the discretion of the treating team and department policy. Antiepileptic drugs were given only after the onset of the first seizure. Patients were then divided into 2 main categories: Group A included all patients who had not received an AED (138 patients) and Group B included those who had (98 patients). Group B was then subdivided into smaller subgroups according to the type of AED received.

Data were used to construct Kaplan-Meier survival curves to compare the various groups of patients. Comparisons were drawn between patients who did and did not receive AEDs (that is, seizure-presenting patients and non–seizure presenting patients) as well as between patients receiving VPA and those receiving another AED. The Mantel-Cox log-rank test was applied to compare subgroups by using SPSS statistical software (SPSS, Inc.).

We also identified all previously published clinical papers on GBM and AED by querying ScienceDirect, MEDLINE, PubMed, and Google Scholar using combinations of the following search terms: "valproate" OR "valproic" OR "anticonvulsant" OR "AED" AND "GBM" OR "glioblastoma multiforme" OR "anaplastic astrocytoma" OR "glioma." In addition, references in each paper found were scanned for references to other papers comparing patient groups that did and did not receive AED. For papers to be used in our review, each one had to meet the following selection criteria: study population had GBM, mean age and performance status were given for each subgroup studied, the AED was defined, and outcome for each subgroup was reported. We collated the published literature to build up a cohort of each subgroup and compared the overall results.

Results

Of the 236 patients with a confirmed diagnosis of GBM, 23 had incomplete data sets and 3 were not initially treated at our institution, and thus were eliminated from the study. Of the remaining 210 patients, 6 were still alive at the time of our review. Patients ranged in age from 18 to 78 years (median 62 years) at the time of diagnosis, and the mean KPS score was 70. Prescription data revealed that 138 patients received no AED, 24 had VPA, 19 had carbamazepine, 20 had phenytoin, and 9 had another AED. Because of the varying pharmacological effects of the other AED, these 9 patients were not used in this study. The baseline characteristics of the 201 patients are summarized in Table 1.

Although information on the exact frequency of seizures in our patients before surgery was not available, all who did not receive AEDs experienced no seizures before or after treatment, and those treated with AEDs had good control of their seizures after starting the drugs. None of the patients died as a result of their seizures.

Antiepilepsy Drugs Versus No AEDs

The Kaplan-Meier survival curve comparing patients with GBM who had received any AED and those who did not revealed a statistically significant survival advantage in the former group (MCLR chi-square 19.617, $p < 0.001$; Fig. 1).

Sodium Valproate Versus No AED

The Kaplan-Meier survival curve comparing patients treated with VPA and those who received no AED demonstrated a statistically significant survival advantage in those who received VPA (MCLR chi-square 17.506, $p < 0.001$; Fig. 2).

Carbamazepine and Phenytoin Versus No AED

The Kaplan-Meier survival curve comparing patients treated with carbamazepine or phenytoin and those treated without AEDs demonstrated a statistically significant survival advantage in the former group. However, the dif-

TABLE 1: Baseline characteristics of 201 patients in the GBM cohort*

Parameter	No AED	Phenytoin	Carbamazepine	VPA	p Value
no. of patients	138	20	19	24	
mean age in yrs	61.5	62.8	60.9	62.4	>0.05
% female	43	19	34	29	
mean KPS score	70	70	70	70	>0.05
% tumors in frontal/temporal lobe	75	70	68	67	>0.05
% patients who underwent debulking op	95.6	95	94.7	95.8	>0.05

* All patients received chemoradiation as a standard.

ference was much smaller than for the VPA effects, and the survival curves crossed over on the far right side of the curve (MCLR chi-square 6.501, $p < 0.01$; Fig. 3).

Sodium Valproate Versus Other AED

The Kaplan-Meier survival curve comparing patients treated with VPA and those receiving either carbamazepine or phenytoin demonstrated a statistically significant survival advantage in the former group (MCLR chi-square 5.303, $p < 0.02$; Fig. 4).

Carbamazepine Versus No AED

The Kaplan-Meier survival curve comparing patients treated with carbamazepine and those who received no AEDs revealed a statistically significant survival advantage in the former group (MCLR chi-square 7.988, $p < 0.005$; Fig. 5).

Phenytoin Versus No AED

The Kaplan-Meier survival curve comparing patients treated with phenytoin and those who received no AEDs demonstrated no statistically significant survival advantage in the former group, and the survival curves crossed over in favor of no AED (MCLR chi-square 0.768, $p > 0.05$; Fig. 6).

Sodium Valproate Versus Carbamazepine

The Kaplan-Meier survival curve comparing patients treated with VPA and those treated with carbamazepine showed that the former group had better survival, but the difference was not statistically significant (MCLR chi-square 1.358, $p > 0.05$; Fig. 7).

Multivariate Analysis

To find out if the choice of AED was an independent prognostic factor, we performed multivariate regression analysis of all factors considered to be of prognostic value including age (< 65 vs ≥ 65 years); KPS score (< 60 or ≥ 60) at the time of treatment; location of the GBM (eloquent vs noneloquent area); and extent of resection (biopsy, debulking, or maximum safe resection). We found the choice of AED might be an independent prognostic factor. Patients treated with VPA were 2.7 times less likely to die of their disease at any one time than were those who received no AEDs, 2.3 times less likely to die than were those treated with phenytoin, and 1.3 times less likely to die than were those treated with carbamazepine (Fig. 8).

Literature Review

Our literature search returned 7 potential studies;

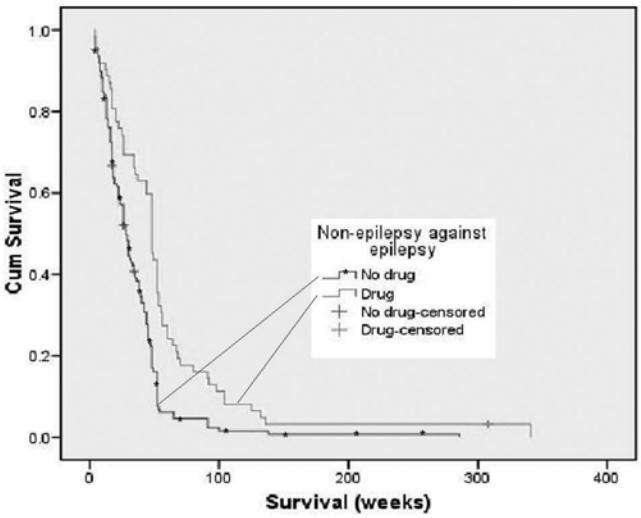

Fig. 1. Kaplan-Meier survival curves of patients with GBM treated using any AED versus no AED, showing an increase in survival in the AED-treated patients. Cum = cumulative.

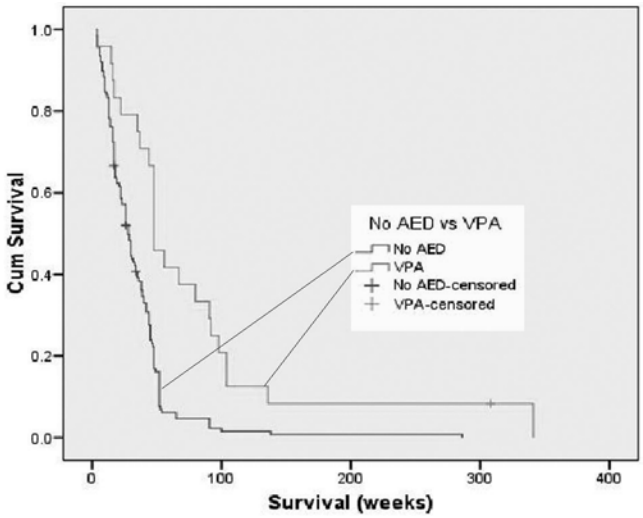

Fig. 2. Kaplan-Meier survival curves of patients with GBM treated using VPA versus no AED, showing an increase in survival in VPA-treated patients.

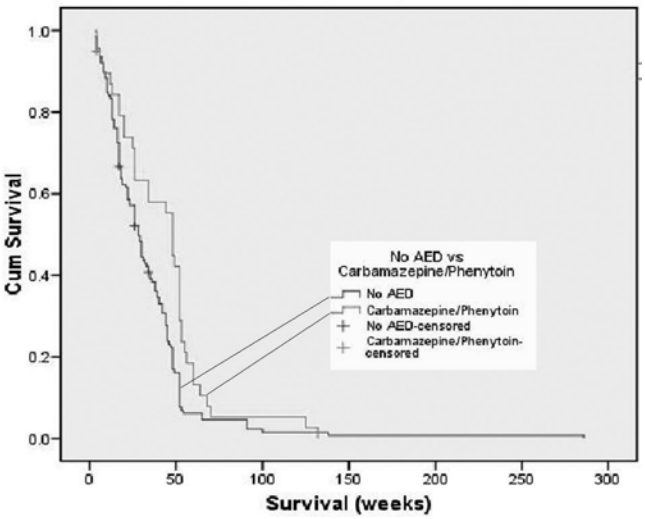

Fig. 3. Kaplan-Meier survival curves of patients with GBM on carbamazepine or phenytoin versus no AED, showing a small difference in survival.

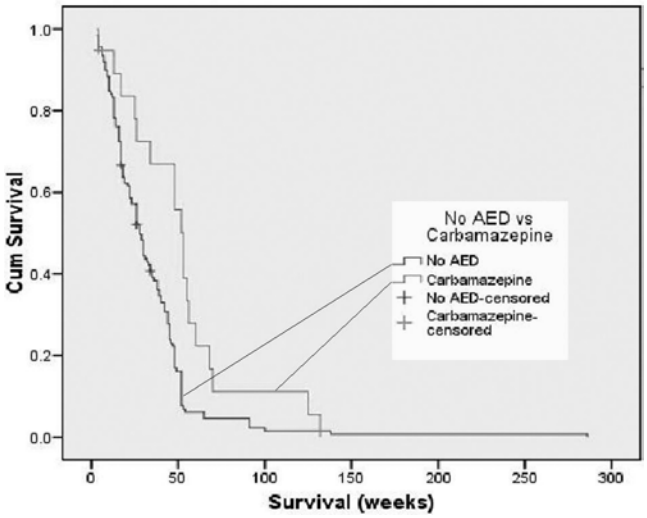

Fig. 5. Kaplan-Meier survival curves of patients with GBM on carbamazepine versus no AED, showing an increase in survival in the carbamazepine-treated patients.

however, only 2 fulfilled our inclusion criteria. Nonetheless, all of them are summarized in Table 2.

Compiling data from the included studies produced 261 patients without AEDs, as compared with 475 patients on EIAEDs, such as phenytoin and carbamazepine, and 37 patients on NEIAEDs, such as VPA, lamotrigine, or levetiracetam. The mean KPS score was 90 in each group, and the mean age was 59, 56, and 56 years, respectively. The median survival was 10.8 months for patients without AEDs, 11.6 months for those on EIAEDs, and 13.7 months for those on NEIAEDs including VPA (Table 3).

Discussion

Curing or even prolonging the survival of patients with GBM beyond 2 years remains an elusive goal. Multimodal therapy tailored to each patient seems the right way to proceed since we are certain that a single treatment protocol does not fit everyone and because GBM may not be a single disease. Further studies on all aspects of management are required if we hope to one day solve the mystery of GBM. Our aim in the present study was to look at whether the use of AEDs had any bearing on survival in the context of GBM. The strengths of our study were a homogeneous cohort with newly diagnosed GBM, uniform standard therapy, KPS scores over 60, and detailed AED use that was prospectively recorded. Our cohort, with its detailed AED history, would seem to indicate that there are some grounds for using HDAC-inhibiting AEDs such as VPA in patients with newly diagnosed GBM. Our review of the literature also suggested that the use of NEIAEDs, such as VPA, may impart at least 3 months of survival as compared with EIAEDs or no AEDs.[6,10] Some authors have asserted that there are no statistical differences in the survival of patients with GBM on or off AEDs, although they have

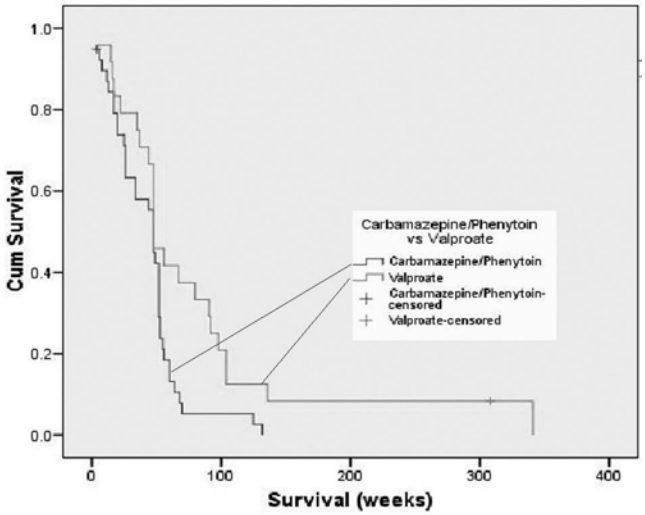

Fig. 4. Kaplan-Meier survival curves of patients with GBM on VPA versus carbamazepine or phenytoin, showing an increase in survival in VPA-treated patients.

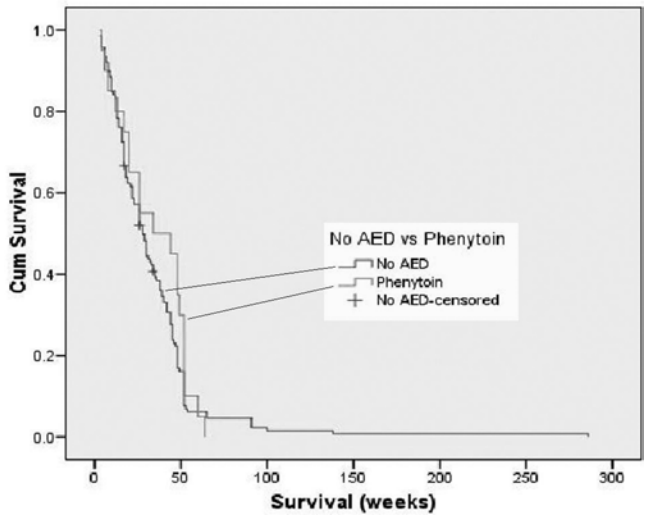

Fig. 6. Kaplan-Meier survival curves of patients with GBM on phenytoin versus no AED, showing no difference in survival.

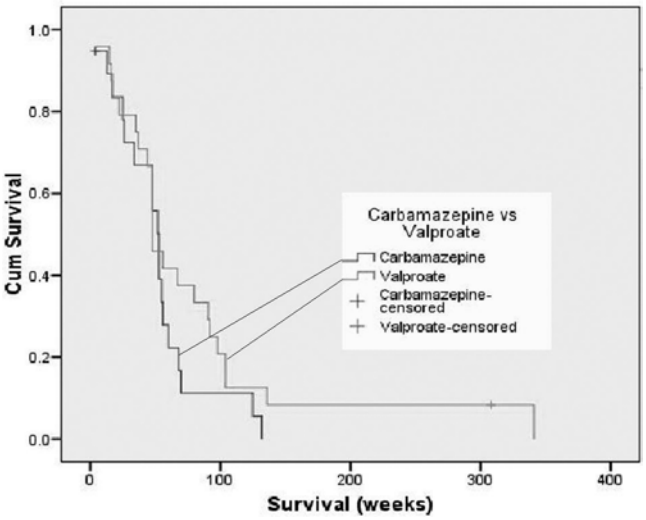

Fig. 7. Kaplan-Meier survival curves of patients with GBM on VPA versus carbamazepine, showing an increase in survival in the VPA-treated patients, although the difference was not statistically significant.

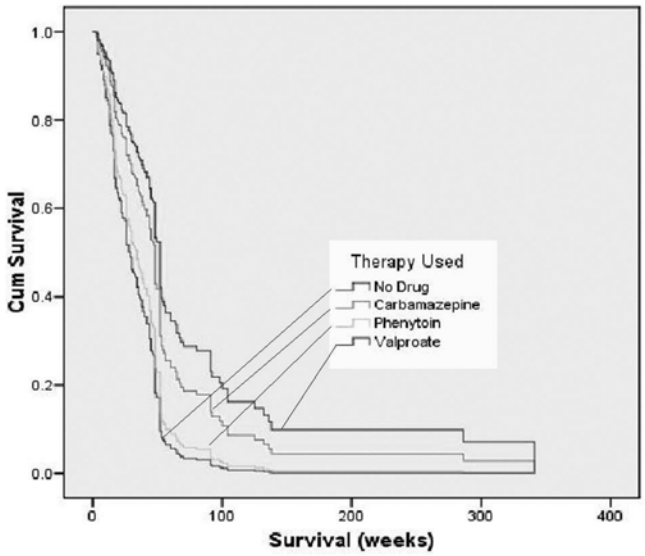

Fig. 8. Kaplan-Meier survival curves of patients with GBM treated using different AEDs (phenytoin or carbamazepine) or no AED compared with VPA.

provided no data to support these claims.[15] Our findings demonstrated a statistically significant improvement in survival when using AEDs ($p < 0.001$), which is in line with previous reports.[10] Oberndorfer et al.[10] compared a control group not taking AEDs, a group on non–cytochrome P450 EIAEDs (35 on carbamazepine, 8 on phenytoin, and 5 on polytherapy), and a group on NEIAEDs (32 on VPA, 7 on lamotrigine, 2 on levetiracetam, and 4 on polytherapy). A statistically significant increase of 3 months' survival was found in the NEIAED group over the EIAED group. There was little difference in median survival between patients suffering and those not suffering from seizures (12.4 vs 11.8 months, respectively).[10] Hence, the notion that patients on AEDs survive longer because they demonstrate seizures earlier does not hold. There must be a more plausible scientific mechanism for this clear survival difference.

Jaeckle et al.[6] compared patients on EIAEDs (432 patients, breakdown of drugs not given, at least 82 patients had no history of seizures) with those not receiving EIAEDs, whether on NEIAEDs or no AEDs whatsoever (173 patients, only 5 given NEIAEDs). The median survival was 16.4 months for the patients with a history of seizures on EIAEDs, 12.4 months for those on EIAEDs with no history of seizures, and 9.9 months for those not on EIAEDs with no history of seizures. Note, however, that the increased life expectancy in the group experiencing seizures was not statistically significant (16.4 vs 9.9 months, $p = 0.20$), and the trend for patients on EIAEDs with no seizures to survive longer than patients receiving no therapy was also not significant ($p = 0.079$). Our data also showed that there was no survival difference between

TABLE 2: Literature review of studies on VPA and AED treatment in GBM

Authors & Year	Title	Included in Present Study	Reason for Exclusion
Oberndorfer et al., 2005	P450 enzyme inducing and non-enzyme inducing antiepileptics in glioblastoma patients treated with standard chemotherapy	yes	
Jaeckle et al., 2009	Correlation of enzyme-inducing anticonvulsant use with outcome of patients with glioblastoma	yes	
Cloughesy et al., 2006	Phase II trial of tipifarnib in patients with recurrent malignant glioma either receiving or not receiving enzyme-inducing anti-epileptic drugs: a North American Brain Tumor Consortium Study	no	recurrent gliomas; measured outcome was progression-free survival only rather than survival
Masoudi et al., 2008	Influence of valproic acid on outcome of high-grade gliomas in children	no	pediatric patients; no survival data given for VPA use
Riva et al., 2006	Tumour-associated epilepsy: clinical impact and the role of referring centres in a cohort of glioblastoma patients. A multicentre study from the Lombardia Neurooncology Group	no	patients grouped according to AED use, but not subgroups based on specific AED or AED class
Salmaggi et al., 2008	Multicentre prospective collection of newly diagnosed glioblastoma patients: update on the Lombardia experience	no	no survival data based on AED therapy given
Marx et al., 2001	Phase II study of thalidomide in the treatment of recurrent glioblastoma multiforme	no	no survival data based on AED therapy given

TABLE 3: Summary of data compiled from studies examining AEDs and survival in patients with GBM

Factor	No AEDs	EIAEDs	NEIAEDs
no. of patients	261	475	37
KPS score	90	90	90
mean age in yrs	58.9	56	56
survival in mos	10.75	11.55	13.7

patients who received no AEDs and those who received the EIAED phenytoin. However, multivariate Cox regression analysis of our data confirmed that at any one time patients with newly diagnosed GBM were 2.7 times more likely to die if they were not on VPA. Although the exact reason why VPA seems to impart a survival advantage is not entirely clear, it is less likely to be explained by mere nonenzyme induction, as suggested by previous reports,[6,7] because carbamazepine (an EIAED) seems to impart similar survival benefits, although less pronounced than with VPA (patients on VPA were 1.3 times less likely to die from GBM than were those on carbamazepine). Phenytoin (EIAED) imparted no survival benefit and may have made survival worse than with no AED. The survival difference between patients on VPA and those on phenytoin or on carbamazepine and phenytoin together was as strong as the difference between VPA and no AED ($p < 0.001$). Therefore, it seems more likely that VPA and carbamazepine impart a survival advantage in patients with GBM by a mechanism other than a simply earlier presentation because of seizures. We hypothesize that VPA imparts a survival benefit via HDAC inhibition. While most researchers agree that VPA is the most potent inhibitor of HDACs, they disagree when it comes to carbamazepine.[1,4] Our data seemed to suggest that carbamazepine has potent HDAC inhibition, imparting survival benefits, although its benefits were dampened by its enzyme-inducing properties, which is a disadvantage.

A number of confounding factors may have affected the results of our study: patients were not randomized among treatment groups and bias may have been introduced by patient selection. Other confounding factors, such as reintervention, complications of surgery or AEDs, and extent of resection, may have played an important part as well. However, the baseline features of the 4 different groups in our cohort seem to be similar, although there were significantly more females among the no-AED group and the choice of AED was based purely on whether a patient did or did not experience seizures rather than on seizure prophylaxis, as our unit's policy does not advocate the use of AEDs prophylactically. The choice of AED was not based on a predetermined protocol but was left to surgeon preference: while some surgeons prefer to use phenytoin because patients can be loaded quickly, others prefer VPA or carbamazepine to avoid frequent blood level measurements of phenytoin. Patients who did not respond to phenytoin, VPA, or carbamazepine and moved to polytherapy or an AED other than the 3 listed were not included in our analysis, as the numbers were very small. Another confounding factor could have been side effects related to the use of AEDs. While none of our patients died as a result of their seizures, AED side effects must be recorded in any planned randomized controlled trial to evaluate the use of AEDs. While we hypothesized that VPA may have an anticancer effect in GBM, our data only demonstrated that patients with GBM treated using VPA survive longer. More basic science studies are required to establish the exact mechanism of VPA effects.

Conclusions

Sodium valproate imparts a statistically significant survival advantage in patients with newly diagnosed GBM as compared with no AEDs, phenytoin, or carbamazepine. Note, however, that carbamazepine may also be beneficial to patients with GBM, but its effects may be dampened by its enzyme-inducing properties. On the balance of probabilities, VPA and carbamazepine are more likely to impart their benefits via HDAC inhibition. Regardless, more basic studies are needed to find out how VPA and other AEDs help survival in GBM. While anti-GBM VPA is still in the hypothesis stage, it is worth considering VPA as an AED in patients with GBM until multicenter, randomized, double-blind crossover trials demonstrate otherwise.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Eljamel. Acquisition of data: Eljamel. Analysis and interpretation of data: both authors. Drafting the article: both authors. Critically revising the article: both authors. Reviewed submitted version of manuscript: both authors. Approved the final version of the manuscript on behalf of both authors: Eljamel. Study supervision: Eljamel.

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