Original Article

Anti-epileptic drug use during adjuvant chemo-radiotherapy is associated with poorer survival in patients with glioblastoma: A nationwide population-based cohort study

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ABSTRACT

Introduction: There are emerging but inconsistent evidences about anti-epileptic drugs (AEDs) as radio- or chemo-sensitizers to improve survival in glioblastoma patients. We conducted a nationwide population-based study to evaluate the impact of concurrent AED during post-operative chemo-radiotherapy on outcome.

Material and Methods: A total of 1057 glioblastoma patients were identified by National Health Insurance Research Database and Cancer Registry in 2008–2015. Eligible criteria included those receiving surgery, adjuvant radiotherapy and temozolomide, and without other cancer diagnoses. Survival between patients taking concurrent AED for 14 days or more during chemo-radiotherapy (AED group) and those who did not (non-AED group) were compared, and subgroup analyses for those with valproic acid (VPA), levetiracetam (LEV), or phenytoin were performed. Multivariate analyses were used to adjust for confounding factors.

Results: There were 642 patients in the AED group, whereas 415 in the non-AED group. The demographic data was balanced except trend of more patients in the AED group had previous drug history of AEDs (22.6% vs. 18%, *P* 0.078). Overall, the AED group had significantly increased risk of mortality (HR = 1.18, *P* 0.016) compared to the non-AED group. Besides, an adverse dose–dependent relationship on survival was also demonstrated in the AED group (HR = 1.118, *P* 0.0003). In subgroup analyses, the significant detrimental effect was demonstrated in VPA group (HR = 1.29,*P* 0.0002), but not in LEV (HR = 1.18, *P* 0.079) and phenytoin (HR = 0.98, *P* 0.862).

Conclusions: Improved survival was not observed in patients with concurrent AEDs during chemo-radiotherapy. Our real-world data did not support prophylactic use of AEDs for glioblastoma patients.

KEY WORDS: Anti-epileptic drugs, glioblastoma, population-based study, radio-sensitizers

INTRODUCTION

The glioblastoma multiforme (GBM) is the most common primary malignant brain tumor and almost universally fatal. The peak incidence is between 65 and 75 years of age. The treatment paradigm has been evolving in the past years, but the result is still frustrating. Glioblastoma is not surgically curable due to its nature of extensive infiltration. In the twentieth century, post-operative radiotherapy (RT) was proved to ameliorate patient survival,[1-3] and the treatment field shifted from whole brain to partial brain according to patterns of local failure.[4-6] Many efforts had been made trying to further improve outcome, such as alter-fractionation schedule, dose-escalation trials, concurrent chemotherapy, but had little effect until the Stupp regimen being published in 2005.[7,8]

The research topic getting popular recently is about anti-epileptic drugs (AEDs) as radio-sensitizers or

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chemo-sensitizers.[9-12] Eui Kyu Chie *et al*.[9] founded evident *in vitro* and *in vivo* radio-sensitizing effect of valproic acid (VPA) by the method of tumor growth delay. Dinesh Thotala *et al.*[10] pointed out VPA not only enhanced the efficiency of glioma RT but also mitigated neurocognitive deficits by protecting hippocampal neurons. George C Bobustuc *et al*.[11] proposed that levetiracetam (LEV) enhances p53-mediated MGMT inhibition and sensitizes glioblastoma cells to temozolomide (TMZ). Bianca Maria Scicchitano *et al*.[12] corroborated that LEV enhances TMZ effect by regulating multiple pathways. These results suggested that the choice of AED might have an impact in clinical practice. However, there are other reports against the claim. Marita Eckert *et al*.[13] concluded VPA did not impair clonogenic survival or radioresistance of primary GBM spheroid cultures treated with RT and TMZ. So they did not advocate a general use of VPA as a radio-sensitizer in anti-GBM therapy. Furthermore, the clinical results were also controversial. A single-arm phase II study showed that impressive results with one-year overall survival (OS) and progression-free survival (PFS) were 86% and 43%, respectively, when VPA was added to adjuvant RT and TMZ.[14] However, a pooled analysis of prospective clinical trials presented in 2016 revealed no improvement of outcome.[15] An analysis from single-center data evaluated nine AEDs and showed that only LEV during adjuvant chemo-radiotherapy (CRT) was associated with significant benefit.[16]

Since there is an emerging but inconsistent body of evidence, we conducted a nationwide population-based cohort study to investigate the impact of concurrent AEDs during post-operative CRT on outcome in patients with GBM.

MATERIAL AND METHODS

Study subjects

We collected GBM patient data from the Cancer Registry Database in Taiwan between 2008 and 2015. The data was confirmed with a Longitudinal Health Insurance Database for Catastrophic Illness Patients, a part of Taiwan National Health Insurance Research Databases (NHIRDs), by the code of International Classification of Diseases, Ninth and Tenth Revision, Clinical Modification (ICD-9-CM and ICD-10-CM). The NHI system was established by the Taiwanese government in 1995, which covers nearly all Taiwanese citizens. The NHIRDs contain medical claim data which included the registry of beneficiaries, disease registry profile, drug prescriptions, and other medical services. The database underwent de-identification before it was released for research use. The research ethics committee approved this study.

GBM patients with operation (total or subtotal resection) and adjuvant RT and TMZ treatment (RT/TMZ) were the study subjects. Patients with other cancer diagnoses were excluded. The AED history was also identified from the NHIRDs by the drug codes of World Health Organization/Anatomical Therapeutic Chemical Classification (WHO/ATC). Patients who had at least one AED more than 14 days during RT/TMZ were defined as the experimental group (AED group) and those who did not were in the control group (non-AED group). Subgroup analyses were performed for patients with the three most commonly used AEDs, in order of VPA, LEV, and phenytoin.

Statistical analysis

The age (<40, 40–65, >65 years of age), sex, the year of diagnosis, Charlson Comorbidity Index (CCI, calculated by ICD diagnoses, and categorized as 0, 1–2, or ≥3 points), previous drug history of AEDs before brain tumor diagnosis, and status of death till end of follow-up between two cohorts were presented with the number and percentage. Chi-square test was used to test the difference between two categorical variables. Survival analyses were performed by the Kaplan–Meier method, and the log-rank test was used to evaluate the difference. Cox proportional hazards models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for whether AED use were associated with OS. Univariate analyses were followed by multivariate analyses to adjust for potential confounding factors.

Due to the limitation of the database, the information about O6-methylguanine–DNA methyltransferase (MGMT) promoter methylation status and isocitrate dehydrogenase (IDH) mutations was not available. During the period of patients enrolled in our study, namely 2008–2015, these two genetic factors were not routinely checked in most medical centers in Taiwan; thus, we could not retrieve these data. Therefore, we conducted a sensitivity analysis to evaluate the effects of these two important confounding factors. The sensitivity analysis is useful and reliable in measurement of the impact of uncertainties for one or more input variables, which might lead to a biased conclusion in statistics. This analysis improves the prediction of the model, as well as reduces it by studying qualitatively and/or quantitatively the model response to change in input variables.

First, following comprehensive literature review, we assumed that the incidence of IDH1 mutations and MGMT promoter methylation were 15% and 40% in our cohort, and the hazard ratios for death were 0.4 and 0.6, respectively. Second, we randomly selected subjects to be with mutated IDH1 and/or MGMT. The ratio of mutation in the AED/non-AED group was 6:4. Finally, we performed Cox proportional hazards model including mutation of IDH1 and MGMT into adjustment. Furthermore, since information about exact tumor size was not included in the database, we used surgical treatment codes as surrogates. Surgical codes encompassed three categories: 83017B, removal of brain tumor (*intracranial tumors*/cephalocele)≦3 cm; 83018B, removal of brain tumor (*intracranial tumors*/cephalocele) 3-6 cm; and 83019B, removal of brain tumor (*intracranial tumors*/cephalocele) >6 cm). Moreover, another sensitivity analysis was performed for patients with monotherapy of AED.

A two-sided *P* value <0.05 was considered statistically significant. All statistical analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC).

RESULTS

A total of 2296 patients with GBM were identified during 2008–2015. After patients without operation, without adjuvant RT/TMZ, or with other cancer history being excluded, 1057 patients were enrolled in this study. Of them, 642 patients were in the AED group, while the other 415 were in the non-AED group. Regardless of monotherapy or polytherapy of AEDs, 406 patients were treated with VPA, 153 with LEV, and 119 with phenytoin. Other AEDs less commonly used included phenobarbital, carbamazepine, clonazepam, topiramate, gabapentin, oxcarbazepine, lamotrigine, pregabalin, and zonisamide.

The age distribution, sex, year of diagnosis, CCI, and status of death till end of follow-up were comparable between two groups. There was a trend toward more patients in the AED group who had previous drug history of AEDs before GBM diagnosis than in the non-AED group (22.6% vs. 18%, *P* 0.078). During the study period, 557 (86.76%) and 347 (83.61%) patients died in AED and non-AED group, respectively (*P* 0.156). [Table 1].

The median survival is 17.5 months in the AED group while 21 months in the non-AED group. The 2-year and 5-year survival rates are 35.2% and 10.7% in the AED group, whereas 43.6% and 13.4% in the non-AED group, respectively. Univariate Cox proportional hazards model showed higher risk of mortality in the AED group compared to the non-AED group (HR 1.216, *P* 0.004). In the AED group, we also investigated the association between the AED dose and the risk of death. When the AED dose was analyzed as a continuous variable, a dose–dependent relationship on survival was demonstrated (HR = 1.118, *P* 0.0003). Among potential confounding factors, male, older age, higher comorbidity score, and previous drug history of AEDs before GBM diagnosis were associated with poorer survival. Taking more TMZ seemed to be protective (HR 0.929, *P* 0.0001). In the subgroup analyses of patients using different types of AED, those with VPA or LEV during RT/TMZ had a significantly worse prognosis (HR 1.317, *P* 0.0001 for VPA) (HR 1.308, *P* 0.004 for LEV). Concurrent phenytoin had no effect on survival (HR 0.935, *P* 0.522). [Table 2] [Figure 1].

Multivariate analyses were performed to adjust for age, sex, previous drug history of AEDs, CCI score, TMZ dosage, and other AEDs in patients with polytherapy. The HR for death was still significantly higher in the AED group than in the non-AED group (HR 1.18, *P* 0.016). When stratified by sex and age, concurrent AEDs during RT/TMZ for more than 14 days were harmful in male (HR 1.3, *P* 0.003); however, there is no significant effect in female (HR 1.057, *P* 0.6). There was also no significance for patients in three different age-groups. In subgroup analyses for patients taking the three most common drugs, the survival deteriorated in patients taking VPA compared to those who did not (HR 1.29, *P* 0.0002). When stratified by sex and age, male patients less than 65 years old had significantly higher risk of death if concurrent VPA was prescribed. Nevertheless, this significant detrimental effect was not observed in patients with LEV or phenytoin. Notably, the impact of LEV was statistically significant in univariate analysis, but there was only an adverse trend after adjustment for other confounding factors (HR 1.18, *P* 0.079) [Table 3].

Sensitivity analyses were conducted to clarify if the detrimental effects persisted in the AED cohort with monotherapy. There were 442 patients receiving monotherapy. Of them, 277 patients were treated with VPA, 82 with LEV, and 70 with phenytoin. The results still supported the conclusions [Table 4].

Since the information about IDH1 mutation, MGMT methylation, and tumor size was not available, we performed additional sensitivity analyses to simulate their impacts on our results. We observed that the HR for death was 1.2 (*P* 0.0086) when IDH1 mutational status as an input variable for adjustment, 1.19 (*P* 0.012) for MGMT methylation, while the HR was 1.18 (*P* 0.016) in the original multivariate analysis. After including these two molecular features, the AED use was still harmful. The results also held true when surgical treatment codes were adjusted in lieu of tumor size (HR 1.18, *P* 0.015) [Table 5].

DISCUSSION

The diagnosis of GBM confers a dismal prognosis, with a median OS of only 14 to 18 months even with standard treatment. Efforts at improving OS have had only modest success. In-field or marginal recurrences after RT are common, leading to the assumption that outcomes will be improved if we could find an agent sensitizing GBM cells to RT or chemotherapy (C/T). Many recent *in vitro* and *in vivo* evidences have emerged indicating that AEDs may act synergistically with RT or C/T; moreover, AEDs may have anti-tumor effects themselves. VPA is the drug being discussed most frequently. It is an anti-epileptic agent with histone deacetylase inhibitor (HDACi) activity shown to sensitize GBM cells in preclinical models, to promote hyperacetylation of DNA-binding histone proteins together with decondensation of chromatin, and to induce a demethylation/activation process of tumor suppressor genes. Besides, LEV has also been reported to sensitize GBM cells to TMZ by enhancing p53-mediated MGMT inhibition, promoting HDAC4 nuclear translocation, and activating apoptotic pathway. However, these results are not universal and have been the subject of much debate. Further studies are needed to determine the exact mechanism and the effect in clinical practice.

In our study, the inferior OS was observed in the AED group and in the subgroup of VPA. This detrimental effect seemed to be

Table 1: Demographic data of study population

	AED group (*n*=642)		Non-AED group (*n*=415)		*P*
	Number (*n*)	%	Number (*n*)	%	
Sex					0.376
Male	366	57	248	59.8	
Female	276	43	167	40.2	
Age (year)					0.617
<40	92	14.3	58	14	
40-65	382	59.5	237	57.1	
>65	168	26.2	120	28.9	
Year of diagnosis					0.464
2008	60	9.35	39	9.4	
2009	73	11.37	30	7.23	
2010	71	11.06	59	14.22	
2011	77	11.99	48	11.57	
2012	86	13.4	57	13.73	
2013	77	11.99	53	12.77	
2014	101	15.73	66	15.9	
2015	97	15.11	63	15.18	
CCI					0.905
0	244	38	154	37.1	
1-2	268	41.7	179	43.1	
≥3	130	20.3	82	19.8	
Drug history of AED before diagnosis	145	22.6	75	18	0.078
Status of death	557	86.76	347	83.61	0.156
Type of AED[a]					
VPA	406				
LEV	153				
Phenytoin	119				
Others	135				
AED monotherapy	442	68.9			
VPA	277				
LEV	82				
Phenytoin	70				
Others	13				

AED=anti-epileptic drugs; CCI=Charlson Comorbidity Index; VPA=valproic acid; LEV=levetiracetam. [a]. The use of AED could be monotherapy or polytherapy; thus, total number exceeded total patient number

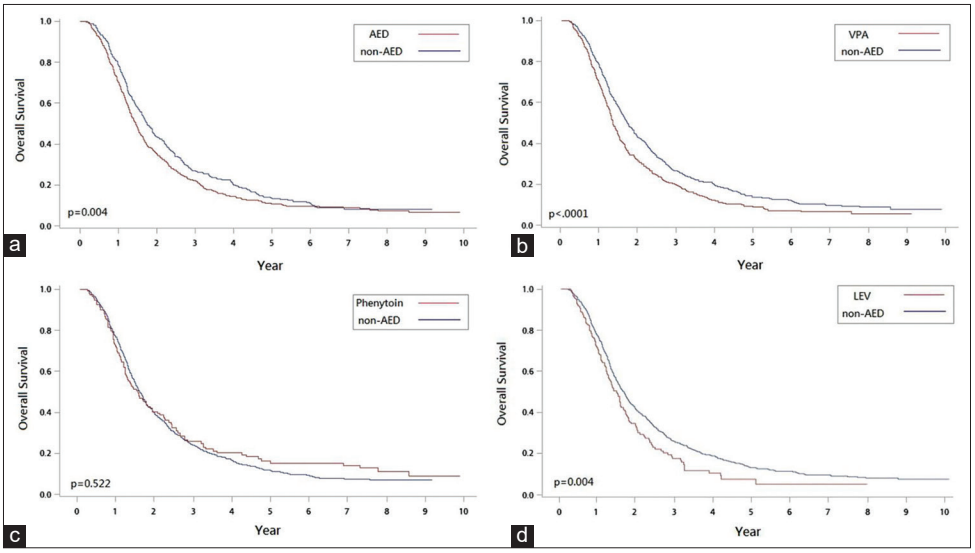

Figure 1: Kaplan–Meier curves of survival in patients with all types of AEDs (a), with VPA (b), with LEV (c), and with phenytoin (d) compared to the non-AED group. Abbreviations: AED = anti-epileptic drugs; VPA = valproic acid; LEV = levetiracetam

more pronounced in male and in younger patients. Importantly, an adverse dose–dependent relationship on survival was also revealed in the AED group. Regarding age, those younger than 40 years old had a trend of higher risk of death in the AED group compared to the non-AED group, while the HR for death was significantly higher for those younger than 65 years old in the subgroup of VPA. [Table 3] The underlying cause of these differences remains unclear. In the literature review, results of

clinical studies are inconsistent as well. A single-arm phase II study enrolled 37 patients with GBM, receiving VPA, 25 mg/kg orally, divided into two daily doses concurrent with RT and TMZ. It was inspiring that the median OS reached 29.6 months, and median PFS was 10.5 months.[14] A retrospective analysis of 544 patients from Memorial Sloan-Kettering Cancer center showed that VPA use during RT was associated with improved OS. Patients with AEDs for more than half the duration of RT were enrolled. Of the five most common AEDs during RT, only VPA was associated with significantly improved OS (HR 0.67, *P* 0.047). When the analysis was restricted to those receiving concurrent TMZ, VPA use was marginally associated with better OS (HR 0.54, *P* 0.057). The results implied that HDAC inhibitors, like VPA, may enhance the effect of RT and should be subjected to future clinical trials.[17] An assessment of the impact of the interaction between AED use and CCRT on survival was performed in the European Organization for Research and Treatment of Cancer/National Cancer Institute of Canada (EORTC/NCIC) TMZ trial, and it showed prolonged survival with VPA use.[18] Nevertheless, a combined analysis of four contemporary randomized trials with individual patient information offered a different perspective. They evaluated PFS and OS between two conditions: any VPA or LEV use and no use at baseline or either VPA or LEV use both at start of and still after CCRT. The authors concluded that VPA or LEV use was not beneficial and did not being justified for reasons other than seizure control outside clinical trials.[15]

Table 2: Univariate analysis of demographics, comorbidity, and treatment-related factors for survival

	HR	95%CI	*P*
Concurrent AED during RT ≥14 days			
AED group	1.216	(1.063-1.39)	0.004*
Non-AED group	REF		
Subgroups of AED			
VPA	1.317	(1.153-1.506)	<0.0001*
LEV	1.308	(1.087-1.574)	0.004*
Phenytoin	0.935	(0.761-1.149)	0.522
Non-AED group	REF		
Sex			
Male	1.303	(1.139-1.490)	0.0001*
Female	REF		
Age			
>65	2.027	(1.621-2.535)	<0.0001*
40-65	1.289	(1.049-1.584)	0.016*
<40	REF		
Year of diagnosis			
2008	0.898	(0.673-1.198)	0.465
2009	1.211	(0.920-1.595)	0.171
2010	0.993	(0.761-1.295)	0.959
2011	1.089	(0.836-1.420)	0.528
2012	1.113	(0.861-1.440)	0.414
2013	1.093	(0.838-1.424)	0.513
2014	1.111	(0.862-1.433)	0.416
2015	REF		
Drug history of AED before diagnosis			
Yes	1.211	(1.033-1.421)	0.019*
No	REF		
CCI			
≥3	1.499	(1.252-1.794)	<0.0001*
1-2	1.279	(1.102-1.484)	0.001*
0	REF		
TMZ dose (as continuous variable)			
Dose (mg)	0.929	(0.914-0.945)	<0.0001*
AED dose (as continuous variable)			
Dose (mg)	1.118	(1.052-1.188)	0.0003*

**P* value <0.05 and with statistical significance. AED=anti-epileptic drugs; CCI=Charlson Comorbidity Index; VPA=valproic acid ; LEV=levetiracetam; TMZ=temozolomide

An unresolved issue is that whether the positive effect of VPA occurs only in patients undergoing RT without TMZ. The phase II study mentioned before included a small number of patients, and there was no control arm. Although all of the 37 patients planned to be treated with concomitant RT/TMZ, there were eight patients (21.6%) stopped TMZ mainly due to bone marrow suppression.[14] The study from MSKCC enrolled patients between 1998 and 2008, and only about one-third of this cohort (34.8%) had taken TMZ during RT.[17] So their result must be interpreted carefully. In the pooled analysis of AVAGlio, CENTRIC, CORE, and RTOG 0825, the patient data was obtained from TMZ-containing arms of the four trials. They indicated that the OS was not improved with VPA use both at baseline (HR 0.96, *P* 0.633) and at start of and still after CCRT (HR 1.10, *P* 0.44).[15]

One of the advantages of our study is that all subjects received the standard treatment: post-operative concomitant RT/TMZ and adjuvant TMZ; therefore, we made a greater contribution to current clinical practice compared to previous publications. The interaction between VPA and TMZ has not been fully understood. Although many retrospective series indicated VPA use might be associated with improved survival, publication bias inevitably occurred. To date, there is no randomized data

Table 3: Multivariate analyses[a] for survival stratified by sex and age and subgroup analyses

	AED group (*n*=642)		*P*	Valproic acid (*n*=406)		*P*	Levetiracetam (*n*=153)		*P*	Phenytoin (*n*=119)		*P*
	HR	95%CI		HR	95%CI		HR	95%CI		HR	95%CI	
Overall	1.18	(1.032-1.354)	0.016*	1.29	(1.128-1.484)	0.0002*	1.18	(0.981-1.425)	0.079	0.98	(0.792-1.214)	0.86
Sex												
Male	1.3	(1.096-1.552)	0.003*	1.47	(1.233-1.760)	<0.0001*	1.11	(0.874-1.405)	0.37	1.12	(0.850-1.476)	0.42
Female	1.06	(0.848-1.316)	0.6	1.1	(0.883-1.375)	0.39	1.34	(0.982-1.826)	0.06	0.83	(0.590-1.175)	0.30
Age												
<40	1.42	(0.946-2.132)	0.09	2.26	(1.492-3.427)	0.0001*	1.45	(0.834-2.506)	0.19	1.52	(0.856-2.712)	0.15
40-65	1.13	(0.943-1.347)	0.19	1.27	(1.055-1.520)	0.01*	1.22	(0.944-1.568)	0.13	0.83	(0.623-1.092)	0.18
>65	1.22	(0.948-1.576)	0.12	1.04	(0.810-1.347)	0.74	1.08	(0.768-1.514)	0.66	1.34	(0.868-2.069)	0.19

**P* value <0.05 and with statistical significance. AED=anti-epileptic drugs. [a]. adjusting for age, sex, previous drug history of anti-epileptic drugs, CCI score, temozolomide dosage, and other AEDs in patients with polytherapy

Table 4: Multivariate analyses[a] for survival in patients with AED monotherapy stratified by sex and age

	AED group (*n*=442)		*P*	Valproic acid (*n*=277)		*P*	Levetiracetam (*n*=82)		*P*	Phenytoin (*n*=70)		*P*
	HR	95%CI		HR	95%CI		HR	95%CI		HR	95%CI	
Overall	1.14	(0.982-1.318)	0.09	1.19	(1.009-1.410)	0.039*	1.11	(0.849-1.443)	0.45	0.95	(0.714-1.257)	0.71
Sex												
Male	1.28	(1.059-1.541)	0.002*	1.42	(1.415-1.142)	0.002*	1.09	(0.769-1.538)	0.64	1.42	(1.142-1.752)	0.002*
Female	1	(0.787-1.271)	0.1	0.94	(0.718-1.239)	0.68	1.26	(0.825-1.916)	0.29	0.94	(0.718-1.239)	0.68
Age												
<40	1.46	(0.928-2.308)	0.1	1.84	(1.103-3.066)	0.02*	0.58	(0.200-1.700)	0.32	1.06	(0.509-2.188)	0.89
40-65	1.09	(0.898-1.321)	0.39	1.14	(0.913-1.418)	0.25	1.4	(0.983-2.003)	0.06	0.77	(0.535-1.109)	0.16
>65	1.16	(0.880-1.530)	0.012*	1.05	(0.763-1.441)	0.77	1.32	(0.855-2.048)	0.21	1.79	(0.995-3.235)	0.05

**P* value <0.05 and with statistical significance. AED=anti-epileptic drugs. [a]. adjusting for age, sex, previous drug history of anti-epileptic drugs, CCI score, and temozolomide dosage

Table 5: Sensitivity analyses[a] of simulated IDH1 mutation, simulated methylation status of MGMT, and tumor size by surgical treatment codes[b]

	AED group (*n*=642)		*P*	Valproic acid (*n*=406)		*P*	Levetiracetam (*n*=153)		*P*	Phenytoin (*n*=119)		*P*
	HR	95%CI		HR	95%CI		HR	95%CI		HR	95%CI	
Overall	1.18	(1.032-1.354)	0.016*	1.29	(1.128-1.484)	0.0002*	1.18	(0.981-1.425)	0.079	0.98	(0.792-1.214)	0.86
Adjustment for IDH1	1.2	(1.048-1.376)	0.0086*	1.29	(1.120-1.475)	0.0003*	1.23	(1.022-1.487)	0.029	0.98	(0.790-1.210)	0.84
Adjustment for MGMT	1.19	(1.039-1.363)	0.012*	1.3	(1.133-1.490)	0.0002*	1.19	(0.984-1.432)	0.07	1.005	(0.812-1.243)	0.97
Adjustment for tumor size by surgical treatment codes‡	1.18	(1.033-1.356)	0.015*	1.29	(1.123-1.478)	0.0003*	1.18	(0.979-1.423)	0.082	0.98	(0.789-1.212)	0.84

**P* value <0.05 and with statistical significance. AED=anti-epileptic drugs; IDH=isocitrate dehydrogenase; MGMT=O6-methylguanine-DNA methyltransferase. [a]. adjusting for age, sex, previous drug history of anti-epileptic drugs, CCI score, temozolomide dosage, and other AEDs in patients with polytherapy. [b]. surgical treatment codes: 83017B, removal of brain tumor (*intracranial tumors*/cephalocele)≦3 cm; 83018B, removal of brain tumor (*intracranial tumors*/cephalocele) 3-6 cm; 83019B, removal of brain tumor (*intracranial tumors*/cephalocele) >6 cm)

to illustrate this issue. Our result discouraged the prophylactic use of VPA during RT/TMZ.

With regard to LEV, our data showed there was a trend to be worse when LEV being prescribed during RT/TMZ (HR 1.18, *P* 0.079); furthermore, it seemed to be more harmful in female (HR 1.34, *P* 0.06). Notably, male had significantly higher risk of death in the subgroup of VPA (HR 1.47, *P* 0.0001) [Table 3]. Another retrospective, single-center study reported different conclusion about LEV. A total of 418 patients were treated as per the current protocol, and all used at least one AED. A total of nine AEDs were evaluated, and the three most common drugs are LEV, VPA, and gabapentin. The significant benefit existed only in patients with LEV compared to those without it (median OS: 21 versus 16 months, *P* 0.001). To go a step further, the positive impact of LEV on OS was seen in the group with a methylated MGMT promoter (HR 0.174, *P* 0.006), but not in the unmethylated group (*P* 0.623). In addition, the median OS in patients with VPA was shorter than those without VPA (18 vs. 20 months, *P* 0.38).[16] Although the difference was not statistically significant, the adverse effect of VPA on OS was consistent with our work. Our result still did not show the benefit of LEV during RT/TMZ.

Likewise, the results of preclinical studies were also controversial. Eui Kyu Chie *et al.*[9] demonstrated evident radio-sensitizing effect for fractionated RT of VPA in tumor-bearing mice with two different cell lines. Dinesh Thotala *et al.*[10] revealed that VPA led to significant tumor growth delay and radio-sensitization with survival benefit, inhibition of cancer cell proliferation, cell cycle arrest, and accumulation at G_2/M. Zhiying Li *et al.*[19] reported survival rate in human glioma cell populations exposed to VPA + TMZ or ACNU was significantly decreased compared with that of the TMZ or ACNU alone groups. VPA not only enhanced the inhibitory effects of TMZ and ACNU but also induced tumor apoptosis. The interaction of LEV and TMZ has been discussed in some *in vitro* studies. They proposed that LEV itself is the most potent MGMT inhibitor among several AEDs, and it could inhibit malignant glioma cell proliferation and increase glioma cell sensitivity to the monofunctional alkylating agent TMZ.[11,12] However, there are researchers holding the converse opinion. A study from Germany used three GBM cell lines and primary spheroid cultures to evaluate the effect of VPA and did not suggest a radio-sensitizing effect of VPA in general at concentrations achieved in the clinical situation. They also observed VPA-mediated acceleration of GBM cell migration which might boost tumor spreading and brain infiltration.[13]

Another issue worthy of discussion is the prognostic value of epilepsy in patients with GBM. An incidence of epilepsy was in the range of 25–60% in the literature. Some authors believed that epileptogenic GBM conveys a favorable outcome, which might be due to early diagnosis.[20-22] But there are still other studies referring that epilepsy at presentation is not an independent prognostic factor for longer survival.[23] Additionally, Sharon Berendsen *et al.*[20] reported that for those who presented with epilepsy, the use of VPA did not associate with survival. The aim of AED use is therapeutic or prophylactic which may play a role in outcomes. Anti-convulsant prophylaxis

is not recommended in patients with newly diagnosed primary or secondary brain tumors, especially in light of a significant risk of serious adverse events and problematic drug interactions. The incidence of anti-convulsant side effects appears to be higher (20–40%) in brain tumor patients than in general population. This increment is due at least in part to the additive or synergistic effects of concurrently administered drugs (especially chemotherapeutic agents) and to the underlying brain tumors.[24,25] In our study population, there are more people in the AED group who had the drug history of anti-convulsants before GBM diagnosis than in the non-AED group (22.6% versus 18%, *P* 0.078), and these patients had poorer outcome (HR for death 1.211, *P* 0.019). The superiority of our study is that we adjusted for past history of AED use as a potential confounding factor of survival.

There are some disadvantages in our study. First, the genetic alterations of MGMT promoter methylation status and IDH mutations were not available in the NHIRD. Second, other factors associated with OS such as patient performance status, recursive partitioning analysis classes, and clinicopathological parameters (e.g., extent of initial resection, tumor location, and number of lesions) were not analyzed due to the limitation of database. Third, epilepsy anamnesis and seizure frequency, which were associated with physician's choice of AEDs and the aim of treatment, could not be assessed in the database.

In order to overcome these shortcomings, sensitivity analyses were arranged to simulate the distribution of IDH1 mutation and methylation status of MGMT in our cohort. Comprehensive literature review was performed, especially focusing on data in Eastern countries. Approximately, the incidences of IDH1 mutation and MGMT promoter methylation are 15% and 40%. Both of them were favorable prognostic factors, and the HRs of OS were 0.46 and 0.57, respectively.[26-32] We used these assumptions and incorporated status of IDH1 and MGMT promoter into multivariate Cox regression model. These two molecular factors had crucial roles in the survival and tumor behavior of glioma patients and could lead to distinct presentation of epilepsy in those with different tumor subtypes. A study from the Netherlands compared the course of epilepsy in two glioblastoma subtypes. One was histologically lower grade (grades 2 and 3) glioma with glioblastoma-like molecular profile (IDH 1/2 wild type), and the other one was "classical" IDH 1/2 wild-type glioblastoma. The authors disclosed that the former group presented with higher frequency of epilepsy onset before diagnosis, significantly longer median time to diagnosis, and longer median seizure days. Moreover, they also received more often AED polytherapy. Although these two subtypes were both considered glioblastoma IDH 1/2 wild type in the latest WHO 2021 classification, distinct clinical courses were observed.[33] This result showed that molecular factors are of importance and merit further study in the context of epilepsy, AED use, and survival. The 4th edition of WHO classification of central nervous system tumors, published in 2016, incorporated molecular information into the diagnosis of brain tumors for the first time. In the latest 5th edition, the grading and grouping system kept evolving; however, the details of the molecular features were beyond the scope of this study.[34,35]

Sensitivity analysis is a method to determine the robustness of an assessment by examining the extent to which results are affected by changes in methods, models, assumptions, or values of unmeasured variables. It could provide a series of analyses of a dataset to assess whether altering any of the assumptions made leads to different final interpretations or conclusions.[36] Through the above-mentioned statistical efforts, the effects of IDH1 mutation and methylation status of MGMT on our results have been considered, with intention to eliminate the potential bias. Regarding tumor size, surgical treatment codes as surrogates were analyzed. After assessing these factors, the detrimental effects of AED overall and of valproic acid still existed [Table 5]. This advanced statistical method is widely used in scientific reports[37] and could enhance the credibility of our research.

CONCLUSIONS

In summary, improved OS was not observed in patients with AEDs during RT/TMZ in this nationwide population-based study. Adverse dose–dependent relationship on survival added credibility to our research. This topic is highly relevant and merits further study since clinical results were ambiguous. Our real-world data, which would make a contribution to this controversial issue, did not support prophylactic use of AED during CCRT and suggested that the potential effect of a specific drug might be distinct in different patient groups.

List of abbreviations

GBM: glioblastoma multiforme, TMZ: temozolomide, AEDs: anti-epileptic drugs, VPA: valproic acid, CCRT: chemo-radiotherapy, NHIRDs: National Health Insurance Research Databases, LEV: levetiracetam, HDAC: histone deacetylase, MGMT: O6-methylguanine–DNA methyltransferase.

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Conflicts of interest

There are no conflicts of interest.

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