PART I

The role of antiepileptic treatment in relation to clinical and radiological outcome


2

Effect of valproic acid on seizure control and on survival in patients with glioblastoma multiforme

Melissa Kerkhof
Janneke CM Dielemans
Melanie S van Breemen
Hanneke Zwinkels
Robert Walchenbach
Martin JB Taphoorn
Charles J Vecht

Neuro-Oncology 2013,15(7):961-967

Abstract

Background: To examine the efficacy of valproic acid (VPA) given either with or without levetiracetam (LEV) on seizure control and on survival in patients with glioblastoma multiforme (GBM) treated with chemoradiation.

Methods: A retrospective analysis was performed on 291 patients with GBM. The efficacy of VPA and LEV and as polytherapy was analyzed in 181 (62%) patients with seizures with a minimum follow-up of 6 months. Cox-regression survival analysis was performed on 165 patients treated by chemoradiation with both temozolomide and VPA for at least 3 months.

Results: Monotherapy with either VPA or LEV was instituted in 137/143 (95,8%) and in 59/86 (68.6%) on VPA/LEV polytherapy as the next regimen. Initial seizure-freedom was achieved in 41/100 (41%) on VPA, in 16/37 (43.3%) on LEV and in 89/116 (76,7%) on subsequent VPA/LEV polytherapy. At the end of follow-up, seizure-freedom was achieved in 77,8% (28/36) on VPA alone, 25/36 (69,5%) on LEV alone, and in 38/63 (60.3%) on VPA/LEV polytherapy with ongoing seizures on monotherapy. Patients using VPA in combination with temozolomide showed a longer median survival of 69 weeks [95% CI:61.7;67.3] as compared to 61 weeks [95% CI 52.5;69.5] in the group without VPA (HR 0.63 [95% 0.43-0.92] p: 0.016), adjusting for age, extent of resection and MGMT promoter methylation status.

Conclusions: Polytherapy with VPA and LEV strongly contributes to seizure control to either of these as monotherapy. Use of VPA together with chemoradiation by temozolomide results in a 2 months longer survival of patients with GBM.

INTRODUCTION

Glioblastoma multiforme (GBM) is the most frequent primary brain tumor in adults and radiochemotherapy with temozolomide (TMZ) leads to a median survival of 14 months.[1,2] This dismal outlook is often aggravated by the presence of epilepsy, occurring between 40%-60% of cases.[3, 4] One difficulty in the management of seizures associated with brain tumors is the development of treatment-resistance in 20-30 % of patients. Another issue is to avoid the use of enzyme-inducing anticonvulsants like carbamazepine or phenytoin in order not to compromise cotreatment with chemotherapeutic agents.[5] Recently, it has been found that combining valproic acid (VPA) with temozolomide leads to an improved survival of patients with glioblastoma multiforme as well as in children with brain tumors.[6] This could possibly be explained by the chemotherapy-sensitizing properties of VPA, including the inhibition of histone deacetylase leading to improved survival. Here, we report on the use of VPA given either with or without levetiracetam (LEV) on seizure control. In addition, we studied the effect of VPA on survival of patients with GBM.

METHODS

The subjects of this retrospective observational study were patients with a histological diagnosis of GBM according to World Health Organization guidelines following biopsy or surgical resection and treatment in the neuro-oncology clinical at the Medical Center Haaglanden in the period July 1999 - September 2011. Patients were studied for the efficacy of anti epileptic therapy on seizure activity and on survival. Baseline-characteristics of patients were collected in a database, including specific information on the site of the tumor, date and type of surgery, subsequent antitumor therapy, MGMT promoter methylation status (from 2008 onwards) and survival data. Data on seizure characteristics and the use of and duration of anticonvulsant therapy were collected as well. Epilepsy was defined as the incidence of at least one seizure during the course of disease. As a rule, patients received either VPA or LEV as a first line anticonvulsant instituted at a maintenance dose of 1000 mg. In case of ongoing seizures, one of these agents was added to the other rather than raising the dose of the initial agent. In case of ongoing seizures on polytherapy with VPA/LEV, one of these was raised at the time, usually ≤2000 mg for each, and as a rule with the help of therapeutic drug monitoring to estimate the therapeutic window. Rarely were doses higher than 2000 mg given for each agent. Patients referred from elsewhere were occasionally taking other anticonvulsants, whose regimens were left unchanged in cases of seizure control and good tolerability.

Seizure frequency before the start of anticonvulsant therapy and following each change in type of anti epileptic drug (AED) use was recorded. Efficacy of AED therapy was studied

in patients who had a minimum follow-up period of 6 months; follow-up was censored in April 2012.

Following biopsy or surgical resection, the first-line antitumor treatment was radiation therapy with concomitant and adjuvant TMZ. Before 2005, a total of 34 patients participated in the European Organisation for Research and Treatment of Cancer (EORTC) Brain Tumour and Radiotherapy Group trial on concomitant and adjuvant TMZ, and these patients were also included in the study of Weller et al.[1,2,7] Patients >70 years old or patients with Karnofsky performance score of ≤60 received radiotherapy alone.[1] As antitumor therapy, radiation with TMZ was given if they met the inclusion criteria of the schedule designed by the EORTC Brain Tumour and Radiotherapy Group, and they received this schedule as standard treatment for GBM following publication of this schedule.[1] After 2010, patients without MGMT methylation could participate in trials including temozolomide and temsirolimus. Second-line chemotherapy for recurrent glioblastoma consisted of retreatment with TMZ, chemotherapy with procarbazine/CCNU/ vincristine, or combinations of lomustine, bevacizumab and irinotecan.

For the second analysis on the effect of VPA on survival, we analyzed patients who were treated with concomitant and adjuvant TMZ and received VPA in combination with TMZ. In order to consider the effect meaningful, we required a minimum duration of 3 months of this combination. Other exposure times were analyzed as well. For this part of the study, we compared this group of patients with those patients who had received either none or another anticonvulsant than VPA or had received VPA in combination with TMZ for a period shorter than 3 months. In a subset of our patient group, we reported in 2009 on the efficacy of anticonvulsant therapy in a combined 135 group of patients with low- and high grade gliomas, including 56 patients with GBM.[3] Here we report on patients with GBM only.

Statistics

Descriptive statistics (SPSS v 16.0) were used to define the population and the treatment effect of AEDs on epilepsy frequency. The secondary endpoint was overall survival measured in weeks from diagnosis to death. The minimal follow-up period for survival analysis was 3 months. Patients who were alive at the end of the study were censored at April 2012, or at the day of the last contact. Descriptive statistics were used on defining the population of patients, and statistical evaluation was carried out using both the Chi-square test and Mann-Whitney U-test. Univariate descriptive analysis of overall survival was done with Kaplan-Meier estimates. A log-rank test was used to compare overall survival curves. For multivariate analysis of overall survival, we used Cox proportional hazard models to adjust for confounding factors that may alter the therapeutic effect. We adjusted for known independent prognostic factors: age at tumor diagnosis, extent of resection (complete vs incomplete vs biopsy), and MGMT promoter methylation status. Hazard ratios are presented with 95% confidence intervals (CIs).

RESULTS

In a 12 year period, data were collected on 291 patients who had a newly diagnosed GBM, of whom 181 (62%) had epilepsy. Patients' characteristics are listed in Table 1, showing a slight male preponderance (58.1%) and a median age at tumor diagnosis of 60 years. The median period of follow-up was 9 months (range, 0 - 81). Of 181 patients with epilepsy, 143 had a follow-up of at least 6 months (Fig. 1). The median overall survival was 13 months for the whole study group; 14 months in the group with epilepsy and 8 months in the group without epilepsy (P= .016). At the last follow-up, 18 patients were still alive and 33 were lost to follow-up. During the time of the study, 174 patients had shown progression of tumor.

Table 1. Patient characteristics

Number	**291**
Gender, n (%)	
Male	169 (58.1)
Female	122 (41.19)
Median age at tumor diagnosis, y (range)	60 (24-85)
Overall survival (mo)	13.0
Tumor progression, n (%)	174 (59.6)
PFS* median (mo)	8.5
Received chemoradiation with Temozolomide	165 (56.7)
Patients	
Dead	240 (82.2)
Censored†	18 (6.2)
Alive unknown††	33 (11.3)
Epilepsy‡,n (%)	181 (62.0)
Epilepsy as presenting sign, n (%)	123 (42.1)
Seizure classification, n (%)	181
Partial simple	59 (32.6)
Partial complex	9 (5)
Secondary generalized	74 (40.8)
Combination of partial/generalized	26 (14.4)
Missing	13 (7.2)
Status epilepticus, n (%)	21
Partial	10 (47.6)
Generalized	11 (52.4)
MGMT methylation, n (%)	
Unmethylated	82 (28.2)
Methylated	38 (13.1)
Not defined	171 (58.7)

*Progression-free survival based on MRI. † still alive at last date of follow up (April 2012) ††survival unknown, lost of follow-up ‡ patients with at least one seizure

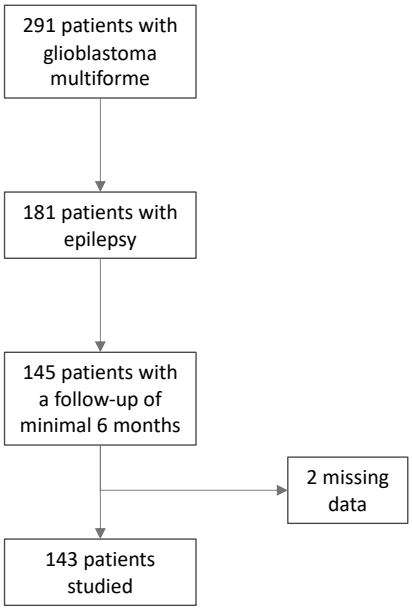

Figure 1. Status of the initial cohort of patients with GBM

Seizure characteristics

A total of 123 of 181 patients (68%) developed epilepsy as presenting sign and 58 (32%) later on (Table 1). Partial seizures occurred in 68 patients (38%), and 74 (40.8%) had partial seizures with secondary generalization. Status epilepticus was observed in 21 patients (11.6%). The most frequently prescribed first AED was VPA in 100; LEV in 37; and another AED in 8 patients (Table 2). During the course of disease, 59 patients (40.7%) needed no alteration in type of AED, excluding adjustments like a lowering or increasing the dose. A change in regimen was performed in the remaining 86 patients (59.3%). In 49 patients LEV was added to VPA because of ongoing seizures (Fig. 2). VPA was discontinued in 10 (10.2%) out of a total of 98 patients due to diverse adverse effects: depression, weight gain, tremor, psychosis, rash, thrombopenia, hepatic function tests abnormalities, or pancreatitis. LEV was given as an alternative in those 10 patients. During the use of LEV, we observed 1 patient with severe fatigue and an allergic reaction, possibly due to interaction with TMZ.

Table 2. Use and effect of AEDs

			Seizure-free, n (%)	Seizure freq < 1 month, n (%)	Seizure freq > 1/month, n (%)
First AED treatment	n (total 145)				
	VPA:	100	41 (41)	33 (33)	26 (26)
	LEV:	37	16 (43.3)	8 (21.6)	13 (35.1)
	Other AED:	8	2 (25)	5 (62.5)	1 (12.5)
	Total		59	46	40
Second AED treatment	n (total 86)				
	LEV + VPA:	59	32 (54.2)	20 (33.9)	7 (11.9)
	LEV mono:	10	7 (70)	2 (20)	1 (10)
	VPA mono:	2	1 (50)	0	1 (50)
	Other combi:	15	7 (46.7)	5 (33.3)	3 (20)
Final AED treatment*	n (total 143)*				
VPA monotherapy	36		28 (77.8)	7 (19.4)	1 (2.8)
LEV monotherapy	36		25 (69.5)	7 (19.4)	4 (11.1)
VPA with LEV ± other AEDs	63		38 (60.3)	16 (25.4)	9 (14.3)
VPA without LEV + other AEDs	2		0	0	2 (100)
LEV without VPA ± other AEDs	4		1 (25)	2 (50)	1 (25)
Other AEDs without VPA/LEV	2		1 (50)	1 (50)	0

*2 missing cases

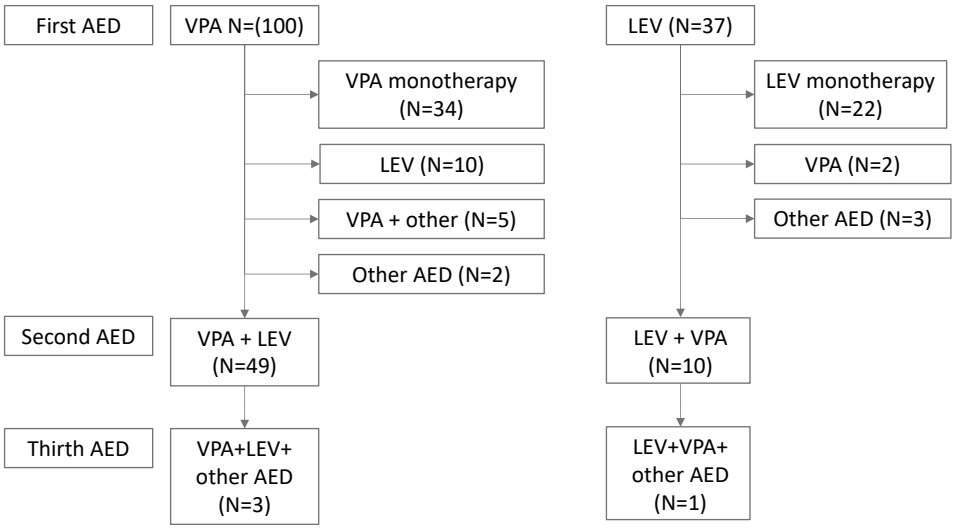

Figure 2. Flowchart. Use of LEV and VPA during the study

Seizure control

The treatment efficacies of different AEDs are summarized in Table 2. Monotherapy with either VPA or LEV was instituted in 95,8% (137/143) of patients with GBM. Seizure-freedom was observed in 41/100 (41%) on initial VPA and in 16/37 (43.3%) on initial LEV monotherapy. A total of 59 out of 86 patients (68.6%) received VPA/LEV polytherapy as next regimen because of ongoing seizure activity, of whom 32/59 (54.2%) became seizure-free. In total, receiving a first and second AED treatment with either VPA or LEV and if necessary subsequent polytherapy, 76.7% of patients (89/116) became seizure free. At the end of the follow-up period, seizure-freedom was observed in 77.8% of patients (28/36) on VPA alone, 25/36 (69.5%) on LEV alone, and 38/63 (60.3%) on VPA/LEV polytherapy.

Of patients who still had ongoing seizure activity at the end of the follow-up period, 7 (16.7%) received VPA alone, 9 (23.1%) LEV alone, and 17 (26.6%) combined VPA/LEV polytherapy. A total of 22 patients (14.9%) received a third AED regimen because of ongoing seizure activity of 2 or more seizures/month. Of these, 18 patients used a combination of VPA/LEV with or without another AED, of whom 7 patients became seizure free, 7 had a seizure frequency of < 1 /month, and 4 had a seizure frequency of > 1 per month.

Survival analysis and determinants

Of the total group of patients with GBM, 165 received radiation with concomitant and adjuvant TMZ for a minimum period of 3 months. Eight patients in this group showed early progression and died in 3 months. In this group we analyzed whether the use of VPA in combination with TMZ had an effect on survival. One hundred eight patients used VPA in combination with TMZ compared to 57 patients in the group not receiving VPA (ie, no or another anticonvulsant) or treatment with VPA during a shorter period than 3 months (Table 3). There were no statistical significant differences between the patient characteristics of these 2 groups, including MGMT promotor methylation status. The median survival of the whole group was 68 weeks. The group using VPA in combination with TMZ during at least 3 months had a significantly longer median survival of 69 weeks [95% CI:61.7-67.3], compared to 61 weeks [95% CI 52.5-69.5] in the group not using VPA (hazard ratio 0.63; 95% CI 0.43-0.92]; P= .016 (Fig. 3), adjusting for age at diagnosis, resection, and MGMT promoter methylation status. The occurrence of early progressive death in any of the 3 groups (receiving TMZ and VPA for 3 months or more; receiving TMZ and VPA for < 3 months; or receiving no AEDs (no seizures)) did not influence the observed differences in survival. As there were only 7 patients who used an enzyme-inducing AED in combination with TMZ, this group was too small to be included for analysis. For progression-free survival, we observed a borderline significant effect with a minimum period of 3 months coexposure of VPA and TMZ (P= .06).

Age at diagnosis was an independent prognostic factor for overall survival (P= .001), while extent of resection and MGMT promoter methylation status were not significant in a multivariate Cox' analysis (Table 4).

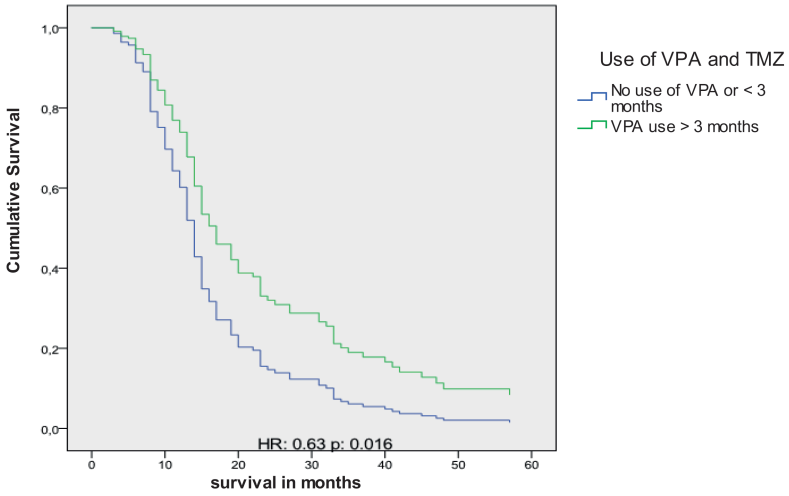

Figure 3. Kaplan-Meier curve of patients treated with chemoradiation with and without VPA for a minimum of 3 months. HR, hazard ratio

Table 3. Characteristics of patients receiving chemoradiation with TMZ

	VPA during 3 months n = 108	No VPA or < 3 months n= 57	P - value
Age at tumor diagnosis,y	58	58	0.97
Extent of surgery			0.08
Total	86	47	
Partial	13	10	
Biopsy	8	0	
MGMT methylation status			0.32
Methylated	16	7	
Unmethylated	31	23	
Missing/inconclusive	61	27	

Table 4. Independent prognostic factors for survival with VPA on multivariate Cox regression analysis

	Hazard ratio (95% CI)	P - value
Overall survival		
VPA during 3 mo	0.63 (0.43-0.92)	0.016
Age, y, at diagnosis	1.03 (1.01-1.05)	0.001
Complete resection vs incomplete vs biopsy	1.36 (0.96-1.93)	0.084
MGMT	1.04 (0.84-1.29)	0.695

DISCUSSION

This study focused on the efficacy of VPA on seizure control and on survival in patients with GBM. Age (median 60 y), sex distribution (58% males), and survival (median 13 mo) corresponded well with recent data of patients with GBM receiving chemoradiation with TMZ.[1,2, 8, 9] The total frequency of seizures we observed was in 62% of patients, which is somewhat higher than reported in 2 earlier, smaller series of patients with GBM, varying between 36 and 60%.[3, 4] Status epilepticus was observed in 21 (11.6%).

In principle, the treatment of seizures in patients with brain tumor does not differ essentially from that of other types of partial epilepsy of adult onset provided that enzyme-inducing AEDs are avoided because of possible interactions with chemotherapy.[5] It was our approach to start with either VPA or LEV monotherapy in low maintenance dose followed by early polytherapy with both anticonvulsants in case of ongoing seizure activity. In brain tumor patients, VPA has been observed to contribute to seizure control[3,4,10] and LEV is known for its absence of drug interactions and its good efficacy and tolerability.[11-14] Possibly, the initial relatively low percentages of seizure freedom on monotherapy are explained by a policy of early polytherapy rather than escalating of the dose of the initial anticonvulsant. At the end of the follow-up period, we observed seizure freedom in 77.8% of patients on VPA alone and 69.5% on LEV alone, corresponding to previous studies in patients with brain tumors.[11-14]

A final percentage of seizure-freedom in 76.7 % of patients compares favorably with other observations of achieving seizure freedom in patients with partial types of epilepsy. Prospective studies on the effect of sequential trials of anticonvulsant indicate that first-line anticonvulsant therapy results in seizure freedom in 47%-63 of patients and another 13%-26% on second line regimen, usually subsequent monotherapy, and that 29%-40% of patients continue to have seizures despite successive treatment attempts.[15-18] Our approach of initial therapy with either VPA or LEV alone and subsequent VPA/LEV polytherapy may seem to compare favorably with other studies on achieving seizure freedom by applying subsequent monotherapy trials with anticonvulsants.[16-18] A number of factors may account for this. In most trials on partial epilepsies, at least 2 seizures

are required for inclusion, while in our study a single seizure was sufficient. All patients underwent active antitumor treatment, which is known to contribute strongly to seizure control. Although epilepsy in brain tumors is known for its treatment resistance, this holds true mainly for low-grade gliomas, particularly with tumors of the medial temporal lobe, including dysembryoblastic tumors and gangliogliomas of childhood.[19]

Nevertheless, our study not only showed the efficacy of anticonvulsants of VPA and LEV as monotherapy, but also showed that combining them resulted in ongoing seizure activity in only 14.9% of the total group of patients with seizures. These observations on the efficacy of anticonvulsant polytherapy may be explained by experimental studies on a synergistic activity of LEV, possibly related to cell-membrane or ion-channel changes associated with the SV2a protein.[20] This seems to be particularly apparent if LEV is combined with AEDs that enhance the gamma-aminobutyric acid-ergic activity or reducing glutamergic neurotransmitter activity, like VPA or benzodiazepines.[21, 22] One advantage of synergistic cotherapy is that lower total dosages of AEDs are sufficient for a similar or better antiseizure effect. Smaller cumulative doses also imply that the risk of drug toxicity will be reduced, including lesser risk on cognitive dysfunction. In patients with brain tumors, the presence of seizures and anticonvulsant therapy are each more unfavorably independent factors for neurocognitive functioning than having had previous surgery or radiation therapy.[23] Our study was retrospective and neither took into account the dosages needed to attain these results nor included a formal analysis of cognitive function. We have observed before that by combining VPA and LEV in a relatively low dose of both, good effects on seizure control can be achieved in combination with maintained cognitive function.[13] Earlier reports on LEV have established its good tolerability with respect to cognitive function, including studies in patients with brain tumors.[24,25] Nevertheless, these impressions need to be substantiated by proper prospective studies.

The use of VPA in patients with GBM has recently drawn attention because of its potential antitumor activity. Based on a post-hoc analysis of data from a prospective trial on the efficacy of chemoradiation in patients with GBM, it appears that the use of VPA in combination with TMZ produces a median gain of 3 months survival compared with use of enzyme-inducing AEDs, the omission of any AED, or use of TMZ alone.[7] In our analysis, we adjusted for age at diagnosis, extent of surgical resection, and MGMT promoter methylation status. We were able to confirm the findings of Weller et al[7] and established a significant median gain of 2 months when both VPA and TMZ were combined for a minimum of 3 months. Possibly, the somewhat shorter survival in our series is explained by the relatively low doses of VPA prescribed. The observed effects of VPA on survival of GBM patients may be explained by the histone deacetylase-inhibiting properties of VPA leading to a stronger acetylation of histone proteins together with less methylation activity on promoter sites of many individual genes, including tumor-suppressor genes with ensuing apoptosis and autophagy of cancer cells, particularly if given together with chemotherapeutic agents.[26,27] The absence of MGMT expression as a predictive factor is

in line with recent findings that enhanced antitumor effects in GBM are associated with valproate-mediated reduced expression of MGMT in TMZ-resistant malignant glioma cell lines.[32] Nevertheless, our results must be interpreted with caution, since it is a selective and retrospective analysis.

These results on effective seizure control and improved survival in patients with GBM seem to provide an extra argument of applying VPA as a first-line anticonvulsant in patients not only in patients with high-grade gliomas but also in those with low-grade gliomas, particularly when one expects that they may be treated with systemic chemotherapy, particularly TMZ. Nevertheless, VPA should be used with caution given its risk for worsening of thrombocytopenia and other bone marrow toxicities associated with chemotherapy, which can be enhanced by the enzyme-inhibiting properties of VPA.[7, 28] In terms of seizure control, a good alternative AED is the use of LEV, based on efficacy, tolerability, and absence of drug-drug interactions.[12, 29] As seizures in brain tumor patients are known to be often treatment resistant for medical therapy with AEDs, synergistic activity by anticonvulsant combination therapy including LEV may provide an important tool to achieve better seizure control and less risk for neurotoxicity and deserves more study.[20, 30, 31]

Recent observations of longer survival for patients with GBM and children with brain tumors receiving both VPA and TMZ are supported by the findings of this analysis.[6, 7] The strength of our study lies in the large number of patients with epilepsy and GBM receiving fairly homogeneous both antiseizure and antitumor therapy. Although these results seem promising, they need further testing in a preferably randomized future study.

REFERENCES

1. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 2005 Mar 10;352:987-996.
2. Stupp R, Hegi ME, Mason WP, et al. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. Lancet Oncol 2009 May;10:459-466.
3. van Breemen MS, Rijsman RM, Taphoorn MJ, Walchenbach R, Zwinkels H, Vecht CJ. Efficacy of anti-epileptic drugs in patients with gliomas and seizures. J Neurol 2009 Sep;256:1519-1526.
4. Wick W, Menn O, Meisner C, et al. Pharmacotherapy of epileptic seizures in glioma patients: who, when, why and how long? Onkologie 2005 Aug;28:391-396.
5. Glantz MJ, Cole BF, Forsyth PA, et al. Practice parameter: anticonvulsant prophylaxis in patients with newly diagnosed brain tumors. Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2000.May 23;54:1886-1893.
6. Felix FH, Trompieri NM, de Araujo OL, da Trindade KM, Fontenele JB. Potential role for valproate in the treatment of high--risk brain tumors of childhood-results from a retrospective observational cohort study. Pediatr Hematol Oncol 2011 Oct;28:556570.
7. Weller M, Gorlia T, Cairncross JG, et al. Prolonged survival with valproic acid use in the EORTC/NCIC temozolomide trial for glioblastoma. Neurology 2011 Sep 20;77:1156-1164.
8. Chaichana KL, Halthore AN, Parker SL, et al. Factors involved in maintaining prolonged functional independence following supratentorial glioblastoma resection. Clinical article. J Neurosurg 2011 Mar;114:604-612.
9. Helseth R, Helseth E, Johannesen TB, et al. Overall survival, prognostic factors, and repeated surgery in a consecutive series of 516 patients with glioblastoma multiforme. Acta Neurol Scand 2010 Sep;122:159-167.
10. Oberndorfer S, Piribauer M, Marosi C, Lahrmann H, Hitzenberger P, Grisold W. P450 enzyme inducing and non-enzyme inducing antiepileptics in glioblastoma patients treated with standard chemotherapy. J Neurooncol 2005 May;72:255-260.
11. Maschio M, Albani F, Baruzzi A, et al. Levetiracetam therapy in patients with brain tumour and epilepsy. J Neurooncol 2006 Oct;80:97-100.
12. Rosati A, Buttolo L, Stefini R, Todeschini A, Cenzato M, Padovani A. Efficacy and safety of levetiracetam in patients with glioma: a clinical prospective study. Arch Neurol 2010 Mar;67:343-346.
13. Wagner GL, Wilms EB, Van Donselaar CA, Vecht C. Levetiracetam: preliminary experience in patients with primary brain tumours. Seizure 2003 Dec;12:585-586.
14. Lim DA, Tarapore P, Chang E, et al. Safety and feasibility of switching from phenytoin to levetiracetam monotherapy for glioma-related seizure control following craniotomy: a randomized phase II pilot study. J Neurooncol 2009 Jul;93:349-354.
15. Brodie MJ, Perucca E, Ryvlin P, Ben-Menachem E, Meencke HJ. Comparison of levetiracetam and controlled-release carbamazepine in newly diagnosed epilepsy. Neurology 2007 Feb 6;68:402-408.
16. Brodie MJ, Barry SJ, Bamagous GA, Norrie JD, Kwan P. Patterns of treatment response in newly diagnosed epilepsy. Neurology 2012 May 15;78:1548-1554.

17. Kwan P, Brodie MJ. Early identification of refractory epilepsy. N Engl J Med 2000 Feb 3;342:314-319.
18. Stephen LJ, Kwan P, Brodie MJ. Does the cause of localisation-related epilepsy influence the response to antiepileptic drug treatment? Epilepsia 2001 Mar;42:357362.
19. Schramm J, Aliashkevich AF. Surgery for temporal mediobasal tumors: experience based on a series of 235 patients. Neurosurgery 2007 Feb;60:285-294.
20. Surges R, Volynski KE, Walker MC. Is levetiracetam different from other antiepileptic drugs? Levetiracetam and its cellular mechanism of action in epilepsy revisited. Ther Adv Neurol Disord 2008 Jul;1:13-24.
21. Kaminski RM, Matagne A, Patsalos PN, Klitgaard H. Benefit of combination therapy in epilepsy: a review of the preclinical evidence with levetiracetam. Epilepsia 2009 Mar;50:387-397.
22. Leppik I, De RK, Edrich P, Perucca E. Measurement of seizure freedom in adjunctive therapy studies in refractory partial epilepsy: the levetiracetam experience. Epileptic Disord 2006 Jun;8:118-130.
23. Taphoorn MJ, Klein M. Cognitive deficits in adult patients with brain tumours. Lancet Neurol 2004 Mar;3:159-168.
24. Milligan TA, Hurwitz S, Bromfield EB. Efficacy and tolerability of levetiracetam versus phenytoin after supratentorial neurosurgery. Neurology 2008 Aug 26;71:665669.
25. Zachenhofer I, Donat M, Oberndorfer S, Roessler K. Perioperative levetiracetam for prevention of seizures in supratentorial brain tumor surgery. J Neurooncol 2011 Jan;101:101-106.
26. Batty N, Malouf GG, Issa JP. Histone deacetylase inhibitors as anti-neoplastic agents. Cancer Lett 2009 Aug 8;280:192-200.
27. Tan J, Cang S, Ma Y, Petrillo RL, Liu D. Novel histone deacetylase inhibitors in clinical trials as anti-cancer agents. J Hematol Oncol 2010;3:5.
28. Bourg V, Lebrun C, Chichmanian RM, Thomas P, Frenay M. Nitroso-urea-cisplatinbased chemotherapy associated with valproate: increase of haematologic toxicity. Ann Oncol 2001 Feb;12:217-219.
29. Perucca E, Johannessen SI. The ideal pharmacokinetic properties of an antiepileptic drug: how close does levetiracetam come? Epileptic Disord 2003 May;5 Suppl 1:S17S26.
30. Brodie MJ, Sills GJ. Combining antiepileptic drugs--rational polytherapy? Seizure 2011 Jun;20:369-375.
31. Kaminski RM, Matagne A, Leclercq K, et al. SV2A protein is a broad-spectrum anticonvulsant target: functional correlation between protein binding and seizure protection in models of both partial and generalized epilepsy. Neuropharmacology 2008 Mar;54:715-720.
32. Ryu CH, Yoon WS, Park KY, Kim SM, Lim JY, Woo JS, Jeong CH, Hou Y, Jeun SS. Valproic acid downregulates the expression of MGMT and sensitizes temozolomideresistant glioma cells. J Biomed Biotechnol. 2012:987495