The Oncologist®

Neuro-Oncology

Seizure Prognosis in Brain Tumors: New Insights and Evidence-Based Management

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Glioma • Glioblastoma • Cancer • Epilepsy • Seizures • Levetiracetam • Valproic acid • Guideline • Review

Abstract

Brain tumor-related epilepsy (BTE) is common in low- and high-grade gliomas. The risk of seizures varies between 60% and 100% among low-grade gliomas and between 40% and 60% in glioblastomas. The presence of seizures in patients with brain tumors implies favorable and unfavorable factors. New-onset seizures represent an early warning sign for the presence of a brain tumor and count as a good prognostic factor for survival. Recurrence or worsening of seizures during the course of disease may signal tumor progression. Each of the modalities for tumor control (i.e., surgery, radiotherapy, chemotherapy) contributes to seizure control. Nevertheless, one third of BTE shows pharmacoresistance to antiepileptic drugs (AEDs) and may severely impair the burden of living with a brain tumor. For symptomatic therapy of BTE, seizure type and individual patient factors determine the appropriate AED. Randomized controlled trials in partial epilepsy in adults to which type BTE belongs and additional studies in gliomas indicate that levetiracetam is the agent of choice, followed by valproic acid (VPA). In the case of recurring seizures, combining these two drugs (polytherapy) seems effective and possibly synergistic. If either one is not effective or not well tolerated, lacosamide, lamotrigine, or zonisamide are additional options. A new and exciting insight is the potential contribution of VPA to prolonged survival, particularly in glioblastomas. A practice guideline on symptomatic medical management including dose schedules of AEDs is supplied. ***The Oncologist*** 2014;19:751–759

Implications for Practice: Seizures are common in low- and high-grade gliomas. New-onset seizures represent an early warning sign and count as a favorable prognostic factor for survival. Each of the modalities for tumor control (i.e., surgery, radiotherapy, chemotherapy) contributes to seizure control. For symptomatic management, levetiracetam followed by valproic acid are the evidence-based antiepileptic agents in low-grade gliomas and other types of brain tumors. In glioblastoma, valproic acid represents the first choice based on its extra effect on survival. With recurring seizures, combining both levetiracetam and valproic acid (polytherapy) seems synergistic. Lacosamide, lamotrigine, or zonisamide are additional options.

Introduction

Seizures are commonly seen in brain tumors, usually in the range of 40% to 60%. They often represent the first clinical sign of a brain tumor and count as a favorable prognostic factor, although reappearance or worsening of seizures may indicate tumor recurrence.

In this review, we focus on seizures in adults with low- and high-grade gliomas. Epidemiology, clinical impact, and the underlying mechanism are discussed, including the significance of isocitrate-dehydrogenase 1 mutations and changes in glutamate and GABA metabolism.

Seizure control can be achieved by both antitumor treatment and antiepileptic drugs (AEDs). Special attention is paid to the appropriate anticonvulsants among the different choices according to evidence-based criteria. This selection not only depends on the type of epilepsy, but also on individual patient characteristics. Pharmacoresistant epilepsy, adverse effects, and potential drug interactions between AEDs and chemotherapeutic drugs often complicate seizure management in brain tumors. A new development is that the use of AEDs may have a beneficial influence on survival. Recently, the activity of valproic acid (VPA) as a histone deacetylase inhibitor (HDACi) has gained attention for its antitumor effects in glioblastoma (GBM), notably in combination with systemic chemotherapy. For practical purposes, a guideline on the medical management of seizure control including dose regimens is supplied.

Literature references were identified through searches of PubMed with the search terms "glioma," "brain tumor," "epilepsy," "seizure," "antiepileptic drugs," and "pharmacoresistance." Articles were identified also through searches of our own files. Only articles in English were reviewed. Studies on children were excluded, as well as articles with fewer than

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10 patients and studies on the traditional enzyme-inducing antiepileptic drugs (i.e., carbamazepine, phenobarbital, and phenytoin).

Molecular Biological Factors of Seizure Development

A number of molecular biological factors have been recognized in the epileptogenesis of brain tumors. The presence of mutation of codons 132 and 172 of isocitrate-dehydrogenase 1 (*IDH1*) and 2 (*IDH2*) is associated with seizures in low-grade gliomas (LGGs). The more prevalent *IDH1* mutation is present in 70%–88% of LGGs and is located within the cytoplasm; *IDH2* is located within mitochondria [1, 2]. *IDH1* catalyzes isocitrate to α-ketoglutarate as part of the citric acid cycle. If mutated, 2-hydroxyglutarate will be formed instead. This latter product shows structural similarity to glutamate and may activate N-methyl-D-aspartate (NMDA) receptors with ensuing epileptogenesis. In LGGs, the presence of *IDH1* mutations shows a strong association with seizures as the initial clinical symptom, frontal lobe tumor location, and longer survival [3, 4]. The excitatory neurotransmitter glutamate plays an important role in seizure development, in which membrane glutamate transporter proteins are involved. Abnormalities include increased expression of specific glutamate receptor subtypes, low activity of glutamine synthetase, high glutamate concentrations in glioma cells, and almost absent intracellular uptake with excessive extracellular levels. These changes correlate with higher seizure frequency and may affect tumor progression [5, 6]. Disturbances in chloride balance may play a role as well, secondary to changes in chloride cotransporters by reduced potassium chloride cotransporter 2 and increased Na-K-2Cl cotransporter expression, suggesting accompanying changes in GABA metabolism and chloride transport [7, 8]. Glutamergic stimulation of NMDA and AMPA receptors may activate intracellular mTOR, AKT, and MAPK signaling pathways, promoting both cell growth and epileptogenesis [5].

Seizures as a Presenting Sign and Their Relation to Survival

New-onset seizures often represent the first clinical symptom for each type of brain tumor and are often the only clinical sign in neuroglial tumors. More benign gliomas show a higher frequency of seizures than malignant gliomas. Neurogliomas (i.e., dysembryoplastic neuroepithelial tumors [DNETs]) and gangliogliomas have a seizure incidence of 80%–100%, oligodendrogliomas of 70%–90%, diffuse low-grade gliomas of 60%–85%, and glioblastomas (GBMs) of 40%–60% [9, 10, 11]. In GBMs, 40% of patients present with epilepsy, and 20% develop seizures later on [11–13]. Epilepsy as a presenting symptom implies a favorable prognostic factor for duration of survival in both low- and high-grade gliomas [14, 15].

In general, the seizure type in brain tumors is characterized as partial or localization-related epilepsy, and varies between simple partial in 23%–58%, complex partial in 7%–31%, and secondary generalized seizures in 10%–68% [14, 16–18]. Generalized seizures are often seen as the early warning sign of seizures in about half the cases, and partial seizures without loss of consciousness dominate in the case of persisting seizures [16].

In low-grade gliomas, favorable prognostic factors of postoperative seizure control are presence of generalized seizures, surgery within <1 year after presentation, gross tumor resection, and successful preoperative control by AEDs [14, 19, 20]. Approximately 15%–50% of patients with low-grade gliomas demonstrate pharmacoresistant seizures, often associated with insular or temporal tumor location and the presence of simple partial seizures [10, 14, 16, 17, 21, 22]. There is no clear difference in seizure outcome between grade II gliomas or other low-grade pathologies with seizures as the first clinical sign, including pilocytic astrocytomas, DNETs, gangliogliomas, and gangliocytomas. In high-grade gliomas, seizure control is more successful with better performance status and less successful with preoperatively not well-controlled seizures or parietal lobe locations [15].

A recurrence or worsening of seizures following first-line antitumor therapy heralds progression of GBMs in approximately two thirds of patients [12, 14, 15]. In low-grade gliomas, this association is less evident [17, 23].

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Effect of Antitumor Therapy on Seizure Control

Surgery

Tumor resection is an essential part of glioma therapy, often showing inherent positive effects on seizure control. In a study of low-grade neuroepithelial tumors, 82% of 207 patients were seizure-free at 1 year following a total or subtotal resection (Table 1) [24]. A large review of 910 neuroglioma patients of whom only 8% were seizure-free before surgery showed that between 68% and 84% of patients with DNETs and between 54% and 94% of those with gangliogliomas became seizure-free following surgery [25–27]. Both a shorter interval until surgery and a gross total versus subtotal resection indicate higher rates of freedom from seizures (87% vs. 54%).

In low-grade gliomas, freedom from seizures was observed in 63%–71% of patients, and a gross total resection produced freedom from seizures in 80% as opposed to 53% by subtotal removal [14, 17, 20, 22]. In high-grade gliomas, mainly glioblastoma, 77% freedom from seizures was seen following primary tumor resection [15].

In epilepsy surgery, the use of intraoperative electrocorticography is applied for determining the location and removal of the excitatory focus. This procedure may also be valid for temporal lobe tumor locations together with performing hippocampectomy or corticectomy [28, 29].

Radio- and Chemotherapy

Radiation therapy contributes to better seizure control in low-grade gliomas and oligodendrogliomas as shown in a randomized European Organisation for Research and Treatment of Cancer phase III trial using external radiotherapy to a total dose of 65 Gy in 30 fractions; 75% of patients became seizure-free [30]. In a series of low- and high-grade gliomas, 76% of patients

Table 1. Effect of antitumor therapy on seizure control

Seizure control by	Tumor type/ no. of patients	Seizure freedom (%)	>50% reduction of seizure frequency (%)	Follow-up	Type of study, duration of follow-up
Surgery					
Luyken et al., 2003 [24]	Pilocytic A/33	73		8 yr	Retrospective study
	A/35	71			12 months after surgery
	OD/15	87			
	GG/82	85			
	DNET/29	86			
Southwell et al., 2012 [27]	Ganglioglioma/66	85		6.9 yr	Retrospective study, 5 yr
Chaichana et al., 2009 [15]	GBM/98	77	12	13.7 months	Retrospective study
	AA/55				Effect primary resection in high-grade gliomas
Martino et al., 2009 [23]	A, AO, OD/19	53		1.1 yr	Retrospective study
					Reoperation in patients with refractory epilepsy
Chang et al., 2008 [14]	LGG/220	67	17	12 months	Retrospective study
					12 months after surgery
Englot et al., 2012 [26]	DNET, GG/910	80		>6 months	
You et al., 2012 [17]	LGG/508	63		32.9 months	Retrospective study
					Effect of primary resection in LGG
Pallud et al., 2014 [22]	LGG/1,509	62		34 months	Retrospective study
					Effect of primary resection in LGG
Radiotherapy					
van den Bent et al., 2005 [30]	A, OA, OD/102	75		12 months	Prospective study
					102 irradiated, 71 not irradiated
					12 months after radiotherapy
Rudà et al., 2013 [18]	A/28	38	76	12 months	Retrospective study
	OD/10				12 months after radiotherapy
	OA/5				
Chemotherapy					
Brada et al., 2003 [32]	A, OD, OA/27	55		3 yr	Prospective study
					Effect of TMZ
Pace et al., 2003 [31]	A, OD, OA/31	13	48	—	Retrospective study
					Effect of TMZ on progressive LGG
Kaloshi et al., 2007 [33]	OD/105		58	30.4 months	Retrospective study
	A, OA/44				TMZ in progressive LGG
Sherman et al., 2011 [34]	A, OD, OA/39		59	39 months	Retrospective study
					TMZ, without additional surgery
Taillandier and Duffau, 2009 [35]	A/5		78	—	Retrospective study
	OA/2				Improved seizure control with first or second line TMZ, PCV, fotemustine, or bevacizumab, with or without surgery
	OD/32				
	Unknown LGG/7				

Abbreviations: A, astrocytoma; AA, anaplastic astrocytoma; AO, anaplastic oligodendroglioma; DNET, dysembryoplastic neuroepithelial tumors; GBM, glioblastoma; GG, ganglioglioma; LGG, low-grade glioma; OA, oligoastrocytoma; OD, oligodendrogliomas; PCV, procarbazine, lomustine, and vincristine; TMZ, temozolomide.

showed >50% seizure reduction and 38% freedom from seizures at 12 months, although no patients could discontinue AEDs [18]. Upfront temozolomide chemotherapy in low-grade gliomas resulted in >50% seizure reduction in 51%–59% of patients and freedom from seizures occurred in 13%–55% [31–34]. Likewise, by using either temozolomide, chemotherapy with procarbazine, lomustine, and vincristine, or with bevacizumab, with or without preceding surgery, >50% seizure reduction was seen in 78% of patients with recurrent low-grade gliomas (Table 1) [35].

Anticonvulsants: Guidelines on Symptomatic Management

Antiepileptic drugs can be initiated after appearance of a single seizure attributable to the presence of a brain tumor. In general, the choice of a specific AED is primarily based on the type of epilepsy. Subsequently, among the approved AEDs for a specific type of epilepsy, the choice of the most appropriate one depends on individual patient factors, particularly age, sex, weight, comorbidity, and cotherapy, including the risk of drug interactions and side effects [36, 37]. Epilepsy in patients with brain tumors belongs to the type of partial epilepsy in adults, either with or without secondary generalized seizures, and is essentially based on focal lesion or brain damage. For this type of seizure, the International League Against Epilepsy (ILAE) has recently updated the most appropriate AED choices based on a meta-analysis of a large number of randomized controlled trials [38]. As such, levetiracetam (LEV), carbamazepine, phenytoin, and zonisamide score as level A anticonvulsants. VPA represents the only level B anticonvulsant. Gabapentin, lamotrigine, oxcarbazepine, phenobarbital, topiramate, and vigabatrin are level C agents [38]. Regarding the issue of individual patient factors, consensus exists in neuro-oncology to avoid enzyme-inducing antiepileptic drugs (EIAEDs), that is, phenobarbital, carbamazepine, and phenytoin, as these accelerate the metabolism and compromise the antitumor effect of many chemotherapeutic agents [39, 40]. For zonisamide, there is as yet hardly any experience in brain tumors [41].

For LEV, numerous studies in brain tumor-related epilepsy (BTE) have been carried out either as monotherapy or add-on therapy, resulting in freedom from seizures between 76% and 91%, a 50% seizure reduction up to 100%, and it counts as one of the best-tolerated AEDs [42–50]. These results are summarized in Table 2. For that reason, together with its designation as a level A agent for partial epilepsy, LEV is the preferred monotherapy choice in patients with brain tumors. LEV may also be effective with seizures in brain metastasis and meningiomas [13, 51, 52]. Nevertheless, one has to realize that these excellent figures probably include the beneficial effects of preceding surgery or other concomitant antitumor therapy.

For VPA monotherapy, the rationale in BTE is based on its designation as a level B agent for partial epilepsy in adults, and is supported by a large experience and efficacy profile in BTE, showing freedom from seizures in 30%–78% of patients with low-grade gliomas or GBMs and good tolerability [11, 12, 16, 17, 50]. VPA may induce or aggravate thrombopenia, particularly in combination with chemotherapy, although multifactorial analysis in GBMs has indicated temozolomide as the only significant factor [53, 54]. For GBMs, we prefer VPA as the anticonvulsant of choice based on its favorable interaction with survival (see Effect of AEDs on Survival section). If seizure control is insufficient with monotherapy of LEV or VPA, polytherapy with both drugs combined is preferred over sequential trials of AED monotherapy [11, 55].

With regard to level C AEDs, there is limited information on gabapentin and lamotrigine in BTE, although both are well tolerated, with lamotrigine showing better efficacy. Topiramate has been studied especially as an add-on therapy, although it may produce considerable cognitive dysfunction [56, 57] (Table 2). Oxcarbazepine as monotherapy in BTE produces freedom from seizures in 40%–62.9% of patients, but it often is not without side effects [58–60]. Lacosamide has been approved as an add-on therapy and has shown 42.9% freedom from seizures in low- and high-grade gliomas (Table 2) [61, 62]. Recently, pregabalin has shown a 49% retention rate as compared with 58% LEV in a randomized comparison [63].

In our opinion, if either LEV or VPA or its combination is less effective, it is our choice for the present time to use either lacosamide as an add-on AED based on its activity and tolerability in BTE, lamotrigine for its good tolerability and indications of synergistic activity with VPA, or zonisamide considering its efficacy, tolerability, low degree of interactions, and recent designation as a level A agent for the partial epilepsies [38, 61, 62].

Table 3 provides details of the preferred choices of AEDs in tumoral epilepsy, including dosing, titrating, and tapering regimens. These guidelines extend to the perioperative period, even in the absence of preceding seizures. However, ongoing prophylactic use of AEDs in BTE has never indicated clear efficacy, and studies on this issue often have shown methodological shortcomings [40].

Pharmacoresistance

Pharmacoresistant epilepsy is commonly defined as a failure of adequate attempts of two or more appropriately dosed antiepileptic and tolerated drug regimens to control seizures. In LGGs, refractory epilepsy before initial surgery is seen in 50% of patients and is seen following surgery in 15%–35% of cases despite anticonvulsant therapy [17, 66].

One hypothesis to explain treatment resistance is based on alterations in drug targets affecting antiepileptic drug binding. Another one is overexpression of multidrug resistant proteins (MRPs) belonging to the ATP-binding cassette transporter family (i.e., P-glycoprotein, MRP1, MRP5, and breast-cancer resistance protein) [67, 68]. This mechanism results in impaired parenchymal brain access and decreased intracellular drug transport of AEDs that function as substrates of these transporter proteins. This process may likewise contribute to the chemotherapy resistance of gliomas and other cancers [69]. Phenytoin, phenobarbital, carbamazepine, and lamotrigine probably represent substrates for P-glycoprotein, whereas LEV and VPA seem to be less affected [46, 70]. One option to diminish pharmacoresistance is to apply AEDs that are not or are less dependent on multidrug transporter proteins. Nevertheless, our current understanding is limited as it is mainly based on in vitro or animal studies with inconclusive data.

Synergistic Activity of AEDs

Another option to diminish pharmacoresistance is to combine AEDs with synergistic antiepileptic activity. The general approach

Table 2. Efficacy of antiepileptic drugs in low- and high-grade gliomas

	Monotherapy				Add-on			
Antiepileptic drug/study	**Seizure free (%)**	**Reduction >50% (%)**	**Follow-up (months)**	***n***	**Seizure free (%)**	**Reduction >50%**	**Follow-up median (months)**	***n***
LEV	76–91	100	1–13	122	20–77	65–100	1–15	119
Wagner et al., 2003 [42][a]	—	—	—	—	20	65	9.3	26
Maschio et al., 2006 [43]	—	—	—	—	47.4	73	12	19
Maschio et al., 2011 [44][a]	—	—	—	—	72.4	96	12	29
Lim et al., 2009 [45]	87	100	6	15	—	—	—	—
Newton et al., 2006 [46]	—	—	—	—	53	88	1-2	32
Rosati et al., 2010 [47]	91	—	13	82	—	—	—	—
Newton et al., 2007 [51][a,c]	—		—		77	100	15	13
Bähr et al., 2012 [48][b]	76		1	25				
VPA	30.4–77.8	—	9–32.9	467	60.3	—	9	116
You et al., 2012 [17]	30.4	—	32.9	431	—	—	—	—
Kerkhof et al., 2013 [11]	77.8	—	9	36	60.3	—	9	116
TPM					21.4–61	28.8–74	10.3–16.5	68
Maschio et al., 2008 [56]	66.7	15.2	16.5	33	21.4	28.6	16.5	14
Lu et al., 2009 [57][a]	—	—	—	—	61	74	10.3	54
OXC	40–62.9	—	7.1–16.1	60	—	—	—	—
Maschio et al., 2009 [59]	62.9	—	16.1	35	—	—	—	—
Maschio et al., 2012 [60]	40	—	7.1	25	—	—	—	—
LCM	—	—	—	—	42.9	35.7–54.3	5.4–6.2	84
Saria et al., 2013 [62][a]	—	—	—	—	—	54.3	6.2	70
Maschio et al., 2011 [61]	—	—	—	—	42.9	35.7	5.4	14

[a]Mixed monotherapy and add-on therapy, especially add-on therapy.
[b]Prospective evaluation during 1 month postoperatively. Studies included a minimum of 10 patients. Carbamazepine and phenytoin are not included because they are enzyme inducers; vigabatrin is not included because it induces visual defects.
[c]Study on brain metastasis.
Abbreviations: LCM, lacosamide; LEV, levetiracetam; TPM, topiramate; OXC, oxcarbazepine; VPA, valproic acid.

in epilepsy therapy is to use at least two subsequential monotherapies trials of anticonvulsant therapy before two AEDs are combined. However, recently there has been a tendency toward earlier antiepileptic polytherapy because of potential synergisms [64, 65]. One such combination is the addition of lamotrigine to VPA, although its drawback is the need to slowly uptitrate the dose of lamotrigine because of enzyme inhibition by VPA of UDP-glucuronosyltransferase glucuronidation of lamotrigine [71, 72]. In addition, the use of LEV in combination with a range of AEDs including VPA and lacosamide may produce enhanced antiepileptic activity [55, 62]. In GBMs, we found indications that combined LEV/VPA produces better seizure control [11]. These effects of LEV seem particularly apparent if combined with AEDs that enhance GABAergic activity or reduce glutaminergic neurotransmitter activity, such as VPA or benzodiazepines [73–76]. A major advantage of synergism is that lower dosages of AEDs would be sufficient for similar or better antiseizure effects. This implies smaller cumulative doses and thus reduced risks of drug toxicity given that antiepileptic therapy in BTE is prone to neurotoxicity [77].

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Effect of AEDs on Survival

The use of VPA in patients with GBMs has recently drawn attention because of its potential beneficial antitumor activity. First indications were observations that cotherapy with VPA produced a 3-month longer survival as compared with carbamazepine in patients with GBMs [78]. Several studies have appeared on the effect of VPA on survival in both children

Table 3. Symptomatic management of seizures in brain tumors

Low-grade glioma (and other types of primary brain tumors or brain metastasis, except GBM)
First-line AED: LEV
Medication schedule: 500 mg b.i.d. (first week 250 mg b.i.d.); if necessary, up to 750–1,500 mg b.i.d. (therapeutic window 5–25 mg/L)
Be alert to irritability or ill temper
If seizures continue, add VPA 500–1,000 mg b.i.d. (20 mg/kg); if necessary, up to 1,500 mg b.i.d. (therapeutic window 50–100 mg/L)
Glioblastoma
First-line AED (preferably during first-line chemotherapy including temozolomide): VPA
Medication schedule: 500–1,000 mg b.i.d. (20 mg/kg); if necessary, up to 1,500 mg b.i.d. (therapeutic window 50–100 mg/L)
Be alert to thrombopenia, particularly in association with chemotherapy
If seizures continue, add LEV 500 mg b.i.d. (first week 250 mg b.i.d.); if necessary, up to 750–1,500 mg b.i.d. (therapeutic window 5–25 mg/L)
Low-grade glioma and GBM if combined LEV/VPA is insufficient[a]
Add either LCM, LTG, or ZNS (to replace VPA or LEV)
LCM medication schedule: start 50 mg b.i.d. for 1 week, and then 100 mg b.i.d.; if necessary, increase weekly by 50 mg b.i.d., up to 200 mg b.i.d. or start at 200 mg s.i.d. in a single loading dose and continue after 12 hours on a maintenance of 100 mg b.i.d. (therapeutic window 10–20 mg/L)
LTG medication schedule:
With VPA cotherapy: start 25 mg every other day for 2 weeks, and then 25 mg per day for 2 weeks; thereafter, increase weekly by 25–50 mg per day until 50–100 b.i.d.
Without VPA cotherapy: start 25 mg s.i.d. for 2 weeks, and then 50 mg per day for 2 weeks; thereafter, increase the dose (bi)weekly by 50–100 mg s.i.d. until 100 mg b.i.d. is achieved; if necessary, up to 500 mg per day (therapeutic window 5–15 mg/L)
ZNS medication schedule: start 25 mg b.i.d.; after 1 week, increase to 50 mg b.i.d.; thereafter, if necessary, increase the dose weekly by100 mg per day up to 150–250 mg b.i.d. (therapeutic window 10–40 mg/L)

[a]When satisfactory seizure control is achieved with either LCM, LTG, or ZNS in combination with LEV/VPA, consider tapering VPA or LEV after 1 or 2 months, as the use of three AEDs can easily lead to cumulative neurotoxicity (less alertness, sleepiness, memory loss, vertigo, imbalance). When adding LTG, it is better to maintain the use of VPA. When adding LCM or ZNS, it is better to maintain LEV. Withdrawal of VPA or LEV can be carried out over 2 to 4 weeks up to a 3-month period.

Abbreviations: AEDs, antiepileptic drugs; GBM, glioblastoma; LCM, lacosamide; LEV, levetiracetam; LTG, lamotrigine; VPA, valproic acid; ZNS, zonisamide.

Table 4. Effect of valproic acid on survival in glioblastoma

Study	VPA/other AEDs (*n*)	Survival with VPA (months)	Survival without VPA (months)	Hazard ratio
Weller et al., 2011 [53]	49/113	17.4	14.4	0.41
Kerkhof et al., 2013 [11]	108/57	15.9	14.0	0.63
Guthrie et al., 2013 [79]	24/98	13.7	11.6	0.56
Barker et al., 2013 [80][a]	29/374	23.9	15.2	
Felix et al., 2013 [81][b]	47/10	34	24	

[a]VPA and radiotherapy.

[b]Study carried out in high-grade glioma, medulloblastoma, and ependymoma in children.

Abbreviations: AEDs, antiepileptic drugs; VPA, valproic acid.

and adults [11, 53, 79–81]. A post hoc analysis of the pivotal European Organisation for Research and Treatment of Cancer/National Cancer Institute of Canada study on temozolomide chemoradiation in GBMs, in which 97 patients received VPA, showed a 3-month longer survival [53]. Another study of GBMs in 108 patients on VPA using the same combination produced similar results (Table 4) [11].

The mechanism as an HDACi of VPA probably explains these observations. By virtue of this activity, VPA or other HDACis may stimulate histone protein acetylation together with demethylation of parts of the DNA genome, leading to at least partially restored expression of upregulated oncogene or downregulated tumor suppressor genes with ensuing normalization of cell cycle control function. This would affect cell growth, angiogenesis, and tumor invasion, as well as apoptosis and autophagy [82, 83]. Although other HDACis such as trichostatin, vorinostat, and sodium butyrate have shown antitumor effects [84, 85], randomized and phase II studies in a number of hematological and solid cancers have indicated efficacy of VPA given in combination with chemotherapeutic agents [86–88]. An important aspect of these observations is that administration of HDACis together with chemotherapeutic or DNA-demethylating agents such as 5-azacytidine seems to act synergistically. This may be explained by the epigenetic modulation by HDACis, which would lead to better accessibility of chemotherapy secondary

to lesser condensation of chromatin by acetylation of histone proteins. In this way, greater accessibility of chemotherapy to unfolded parts of DNA would facilitate the efficacy of restored cell functions such as apoptosis and autophagy [83, 89–91]. It is uncertain whether other anticonvulsants may also affect tumor growth. LEV may inhibit transcription of the O-6 methylguanine-DNA methyltransferase repair protein gene and may interact with temozolomide [92]. Some EIAEDs, notably carbamazepine, might prolong survival in GBM, although the numbers studied are small [79, 93].

Need for Future Studies

In general, it is desirable that once an AED is accepted for partial epilepsy in adults, additional good-quality studies on efficacy and tolerability are carried out in BTE to further assess its appropriateness. Ideally, this again would be based on randomized prospective studies, although once a drug has been registered, it is doubtful that such studies will be performed considering time and costs involved. Rather, analysis of collected data from studies carried out in well-defined subgroups and application of pharmacotherapeutical characteristics in relation to individual patient factors will provide sufficient and reliable information. One example of such an approach is a consensus paper of the ILAE on preferred AED drug choices in HIV-positive patients, based on pharmacotherapeutic understanding of antiretroviral agents and AEDs, including potential drug-drug interactions and the outcome of studies on plasma concentrations (therapeutic drug monitoring) with both agents combined [94]. Therefore, phase II studies or postapproval studies on AEDs that have recently been registered, such as zonisamide monotherapy or add-on lacosamide, are necessary before general acceptance in the clinical practice of BTE [95, 96]. Ongoing randomized trials and registration studies in partial epilepsy in adults may well enlarge the number of AEDs that qualify for application in BTE.

Conclusion

In recent years, considerable gains in knowledge have been achieved in the field of tumor-related epilepsy. The great advantage of the introduction of second- and third-generation antiepileptic drug therapy has been its overall good tolerability and absence or weak tendency of interactions. AED application in BTE is primarily based on the outcome of randomized trials designed for the common type of partial or localization-dependent epilepsy in adults to which BTE belongs. Subsequently, the particular choice for an approved or registered AED in clinical practice depends on its pharmacotherapeutical properties in relation to individual patient features including cotherapy and comorbidity. For that reason, it is better to avoid EIAEDs in BTE because they compromise concurrent chemotherapy. The recent designation of a number of AEDs that qualify as level A or B agents for partial epilepsy in adults together with pharmacotherapeutical understanding indicate the use of LEV followed by VPA as the AED monotherapy of choice in BTE. In case either one is insufficiently active as a single agent or—as a next therapeutic step—in combination, as in the case of untoward effects, subsequent AEDs that represent justifiable choices are lacosamide, lamotrigine, and zonisamide, based on their therapeutic profile.

Despite these options, the occurrence of pharmacoresistance is not rare and is seen in 10%–35% of BTE. Indications that LEV works synergistically with other anticonvulsants including VPA seems one approach to tackle pharmacoresistance. In addition, as BTE seems prone for a high incidence of side effects of AEDs, a great advantage of synergistic activity would be that smaller doses of AEDs are sufficient to achieve similar results, implying fewer risks of neurotoxicity. Synergistic activity of AEDs in neuro-oncology with the aim of improving both pharmacoresistance and cognitive functioning warrants attention and study.

Another reason for the reappearance or worsening of seizures following a long period of seizure control is progression of low-grade glioma or GBM. This necessitates another round of symptomatic management by AEDs and re-evaluation of the tumor status. In that case, it is relevant to realize that surgical resection, radiotherapy, and chemotherapy contribute to seizure control in BTE. These observations probably extend to recurrent tumor and deserve further investigation.

Although VPA belongs to the group of classical AEDs in use for decades, it is only recently that there have been strong indications that this broad-spectrum AED may improve survival in cancer. This action is most probably based on its activity as an HDACi influencing the epigenetic mechanisms that determine the status of acetylation of histone proteins and of demethylation of DNA. In this way, a cascade of transcription processes is triggered that control cell cycle pathways. An intriguing aspect of these observations includes the efficacy of valproate in combination with chemotherapeutic agents including temozolomide, resulting in improved survival of GBM. Together, these observations on valproate as well as of other HDACis open new and exciting avenues for phase II and III studies in combination with different types of chemoradiation. It is unclear to what extent other AEDs may offer similar advantages.

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Disclosures

Charles J. Vecht: UCB Pharma (H). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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