EXPERT REVIEWS

Epilepsy in glioblastoma patients: basic mechanisms and current problems in treatment

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Jordi Bruna*[1,3], Júlia Miró[2] and Roser Velasco[1,3]

[1]*Unit of Neuro-Oncology, Hospital Universitari de Bellvitge-ICO Duran i Reynals, Barcelona, Spain*
[2]*Unit of Epilepsy, Department of Neurology, Hospital Universitari de Bellvitge and Cognition and Brain Plasticity Group (IDIBELL), Barcelona, Spain*
[3]*Group of Neuroplasticity and Regeneration, Institute of Neurosciences and Department of Cell Biology, Physiology and Immunology, Universitat Autònoma de Barcelona, Bellaterra, Barcelona, Spain*
**Author for correspondence:*
Tel.: +34 932 607 711
Fax: +34 932 607 882

Glioblastoma-related epilepsy requires paying careful attention to a combination of factors with an integrated approach. Major inter-related issues must be considered in the seizure care of glioblastoma patients. Seizure control frequently requires the administration of antiepileptic drugs simultaneously with other treatments, including surgery, radiotherapy and chemotherapy, with complete seizure relief often being difficult to achieve. The pharmacological interactions between antiepileptic drugs and antineoplastic agents can modify the activity of both treatments, compromising their efficacy and increasing the probability of developing adverse events related to both therapies. This review summarizes the new pathophysiological pathways involved in the epileptogenesis of glioblastoma-related seizures and the interactions between antiepileptic drugs and oncological treatment, paying special attention to its impact on survival and the current evidence of the antiepileptic treatment efficacy, including the potential usefulness of new third-generation compounds.

KEYWORDS: adverse events • antiepileptic drugs • chemotherapy • efficacy • epilepsy • glioblastoma • high-grade glioma • prophylaxis • seizures

Seizures are a common symptom in glioma patients. Approximately 20–40% of the adults with primary brain tumors experience one seizure prior to the tumor diagnosis, and another 20–45% will suffer from seizures during the course of the illness [1]. This incidence rate varies depending on the tumor type, the grade of histological malignization and the tumor location. Subsequently, tumors with a dysplastic neuron composition (e.g., dysembrioplastic neuroepithelial tumors, gangliogliomas), have a very high incidence rate at nearly 100%. Slow-growing glial tumors are more frequently associated with epilepsy than high-grade glioma tumors and intra-axial tumors with cortical involvement are more epileptogenic than extra-axial and deep glial tumors, being insular, frontal and temporal locations more likely to present seizures at presentation or during the course of the disease [2–4]. Specifically, overall incidence of seizures in glioblastoma multiforme (GBM) patients, without considering the location, has been reported between 25 and 50% at presentation and another 20–30% during the course of the disease, although in the large population studies, these figures are restrained to approximately 25% at initiation [2,5–10].

Despite the high frequency of this symptom, retrospective studies have shown suboptimal seizure control in 9–46% of GBM patients, with these treatment refractory patients presenting more than one seizure per month [2,6,7,11]. This fact highlights the importance of adequate integration of epilepsy treatment in the complete therapeutic management of GBM patients.

Brain tumor-related seizures are focal in nature, although secondary generalization is not uncommon and may happen quickly. Moreover, the risk of developing status epilepticus is not negligible; patients with brain tumors comprise 4–12% of the total patients emerging with this epileptic complication [10,12,13].

An appropriate approach to the treatment of tumor-related epilepsy becomes important for many reasons such as to decrease the morbidity associated with seizures [14], to reduce the risk of pharmacoresistent epilepsy [15] and to avoid any impairment in the patients' quality

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of life [16]. Moreover, GBM patients and in general, brain tumor patients, have special considerations, over and above the general non-neoplastic epileptic population, which need to be taken into account in order to not only select the best treatment option for the tumor but also to reduce the therapeutic failures.

Distinctive characteristics of GBM patients with epilepsy

Several specific reasons have been identified that explain the inefficacy and subsequent withdrawal of antiepileptic treatment in GBM patients, which are not shared by other epileptic populations. These factors are mainly related with the pathophysiology of brain tumor-related seizures, the consequences of pharmacokinetic drug interactions, the overexpression of multidrug-transporter proteins in brain tumors, the progressive course of the disease, the oncological treatments and the very often higher rate of adverse events induced by the antiepileptic drugs (AEDs) in this population.

Etiopathogeny of GBM-related seizures

The main mechanism considered to be involved in high-grade glial tumor seizures is the imbalance between the inhibitory and excitatory brain neural networks caused by tissue and neural connectivity damage. Additionally, other mechanisms at the molecular level involving the tumor itself and host factors are emerging, which could explain the different incidence rates between glioma types and histological grades, despite their location.

These epileptogenic mechanisms comprise of changes in pH, neurotransmitters and ion levels, as well as in the expression of voltage-dependent channels and receptors in tumoral and peritumoral brain tissue [17,18]. Furthermore, observed expression of specific glutamate receptors and glutamate transport impairment in neoplastic glial cells may increase extracellular glutamate resulting in a high excitability [19]. Moreover, the peritumoral tissue has also been demonstrated to present an increased expression of NKCC1 and KCC2 voltage-gated ion channels that cause a perturbation in Cl homeostasis, which leads to a reduction in GABAergic inhibition [20]. Furthermore, macro- or microhemorraging and edema related to the tumor increase the iron and decrease the magnesium and calcium levels respectively, which may change the membrane potential of neurons leading to spontaneous epileptiform discharge [18]. Moreover, changes in the expression of aquaporin-4 found in GBM tumor cells facilitate the appearance of edema and seizures [21]. In addition, pH changes in intra- and extracellular peritumoral tissue have been identified, making the tumoral and peritumoral environment slightly alkaline. It has been postulated that this situation poses a risk of increasing the likelihood of seizures due to its blocking inward-rectifier K^+ conductance [22,23]. Furthermore, studies comprising glioblastoma cell lines have observed enzymatic changes that may impair the synthesis and storage of neurotransmitters leading to alterations in signaling and neuronal excitation [18]. Finally, it has been suggested that the immune response associated to tumor tissue could lead to an upregulation of proinflammatory cytokines that could play a role in epileptogenecity [24].

Considering the mechanism of action of most currently used AEDs, which block the Na^+ and Ca^{2+} channels or enhance inhibitory mechanisms through an increase of GABAergic activity, only a few epileptogenic glioma pathways are involved by AEDs, which might partially explain the failure of treatment in some GBM patients.

Pharmacokinetic considerations

Around 40% of glioma cancer patients present low levels of AEDs at the time of having a seizure [2,25–28]. This finding results, at least partially, from the fact that therapeutic AED levels in cancer patients are difficult to maintain because of pharmacokinetic interactions with concomitant administered medications, including chemotherapy and targeted cancer therapies. This point becomes more relevant in GBM patients as the median age of GBM patients at diagnosis is around 60 years with 25% of the patients being older than 70 years [29], a population segment usually under multiple medications.

Pharmacokinetic interactions can alter the uptake, metabolism, volume of drug distribution (due to competition in protein binding) and the clearance of administrated drugs. These complex pharmacokinetic drug relationships, which are often difficult to predict and control, can be associated with the following two main problems: the reduction of the antineoplastic agents and/or AEDs efficacy and the increase of toxicity related to both treatments. As a result of these drug–drug interactions, the control of tumor-related epilepsy, clinical assessment and patient survival can be compromised.

The activity of the cytochrome P450 system can be either induced or inhibited by AEDs and corticosteroids. Enzyme-inducing AEDs (EIAEDs) accelerate the metabolism of many chemotherapeutic drugs employed against GBM in several trials, such as nitrosureas, irinotecan, taxanes, topotecan, thiotepa, etoposide, vincristine, cyclophosphamide, temserolimus, imatinib, sorafenib, enzastaurin, vatalanib, tipifarnib, gefitinib and erlotinib [30–38]. EIAEDs can lead to a decrease of plasma levels when used with these agents, reducing their exposure and potentially their effectiveness. However, the front-line antineoplastic drug used to treat GBM, temozolomide, is a prodrug that undergoes spontaneous conversion under physiological pH blood conditions into the active alkylating agent, with minor hepatic metabolism [39]. Therefore, no significant interaction should be expected between temozolomide and EIAEDs. Nevertheless, caution must be taken with the prescription of AEDs associated to metabolic acidosis, such as zonisamide and topiramate [40], due to the potential interactions of pH changes with the temozolomide metabolism. Similarly, bevacizumab, another emerging front-line treatment for GBM patients, does not present hepatic nor renal elimination. Therefore, no significant metabolism interactions should be expected with AEDs. Moreover, the *post hoc* analysis of 620 GBM treated patients included in three different prospective trials by the North Central Cancer Treatment Group, with the aim to explore the relationship between EIAEDs and the GBM outcome, disclosed paradoxical results [41]. In this study, the median overall and progression-free survival was significantly

longer in GBM patients who were taking EIAEDs, even after adjusting the multivariate model for known prognostic factors [41]. Previously, and in line with this finding, a Phase II single-arm trial exploring the efficacy of temozolomide and marimastat in high-grade glioma patients showed similar results [42]. Although these results are counterintuitive and the retrospective nature of the analysis together with the lack of information about the AEDs schedule during the chemotherapy treatment can introduce a bias, these studies deserve consideration.

Another relevant interaction with the cytochrome P450 system is the inhibition of the activity of the isoenzyme 2C9 and the glucuronidation by valproic acid and zonisamide [30], increasing the exposure time to the drugs metabolized by these enzymes and therefore, their adverse effects. Valproic acid administration combined with nitrosureas, etoposide and cisplatin increases bone-marrow toxicity [5,43]. Moreover, valproate inhibits the glucoronidation of SN-38 [44], the active metabolite of irinotecan, and can potentially exercise synergistic effects with other histone deacetylase inhibitors, like vorinostat. Nevertheless, valproic acid only decreased temozolomide clearance by 5% [201]. However, valpropic acid in combination with temozolomide has been associated with a higher risk of thrombocytopenia and neutropenia [7,45].

On the other hand, many antineoplastic drugs can reduce the activity of some AEDs by way of induction or they can increase the AEDs plasma concentrations, by competitive binding of the cytochrome P450 pathway and by protein displacement, therefore reducing or increasing, respectively, the AED-related side effects. Hence, nitrosureas, carmustine, cisplatin and etoposide reduce the plasmatic levels of phenytoin [30]. Finally, dexamethasone, the main agent used to treat tumor-related edema and a widely used medication in GBM patients, can also induce the CYP2B and CYP2E1 activity and therefore reduce the concentrations of phenytoin and other drugs metabolized by these isoenzymes [30].

Drug resistance

Multidrug resistance proteins, P-glycoprotein (P-gp) and BCRP, the efflux transporter proteins responsible for protecting the body against exogenous substances by reducing drug accumulation in the cells, are all involved in the cellular drug resistance mechanisms [46]. MRP1, MRP3, MRP5, BCRP and P-gp, expressed in glial and endothelial cells of the blood–brain barrier, are also overexpressed in neoplastic glial cells. The overexpression of efflux transporters might limit brain penetration of chemotherapy and of AEDs, therefore compromising their efficacy and increasing the probability of refractoriness to these treatments [47–50]. This fact may play a role in explaining the poor control of tumor-related epilepsy in some GBM patients. However, while experimental studies have provided convincing evidence in favor of the transporter hypothesis, the functional role of overexpressed transporters in the human epileptic brain has only been demonstrated well with regard to P-gp [48]. Thus, it should be advisable to select AEDs that are not a substrate of the P-gp proteins. However, there are no established criteria to define the P-gp substrate status of the different AEDs, and some inconsistencies are emerging when the transport of AEDs by P-gp is studied in different model systems. Moreover, the evidence provided by patient studies are also lacking in this area. Table 1 shows the current evidence about AEDs as substrates of P-gp transporters. Assuming present data, the theoretical best profile in relation with P-gp proteins should be zonisamide, vigabatrin and ethosuximide, with valproate, gabapentin and topiramate showing conflicting evidence [51]. It is noteworthy to highlight the lack of information in new emerging AEDs such as brivaracetam, perampanel, lacosamide and retigabine.

Furthermore, when selecting an AED or a combination of AEDs, it needs to be taken into account that the administration of phenobarbital, phenytoin and carbamazepine induces the expression of P-gp proteins in cell lines. Conversely, levetiracetam, lamotrigine and topiramate do not induce expression of these proteins and with valproate, contradictory results have been published regarding this issue [52–54].

Tumor & oncological treatment considerations

Owing to the nature of the disease, the late onset or the reappearance of seizures during AED treatment does not always imply a treatment failure in GBM patients. Sometimes these seizures may reflect changes in the disease status such as tumor progression, tumor recurrence or spontaneous intratumoral bleeding. In 19% of glioma patients, seizure reappearance has signalled a progression of the disease [6] and in 37% of patients, seizure reappearance occurs at the end-of-life phase [55]. Similarly, other situations not directly related to the tumor must also be evaluated as the potential adverse effects of oncological treatment. The range of symptoms of reversible posterior leucoencephalopathy syndrome also includes seizures and this is an infrequent but reported adverse effect of bevacizumab and tyrosine-kinase inhibitors, both of which are treatments used on GBM patients. Moreover, seizures are a frequent manifestation of radionecrosis in long-term survival patients who had received conventional radiotherapy or radiosurgery rescue treatments. They can also be a manifestation of a neurosurgical complication such as a postoperative brain abscess or meningitis. All these circumstances involve new structural brain lesions and the etiopathogenic cause of the new seizures

Table 1. Summary of the current evidence about antiepileptic drugs as P-glycoprotein substrates.

Type of study evidence	Antiepileptic drugs as P-glycoprotein substrates
Patient studies	Levetiracetam; lamotrigine; oxcarbazepine; carbamazepine
Concordant results in animal and cell-line studies	Phenytoin; phenobarbital; lamotrigine
Divergent results in animal and cell-line studies	Levetiracetam; felbamate
Only performed in cell-line studies	Oxcarbazepine; acetazolamide; eslicarbazepine

differ from the original epileptic focus and may not be covered by the original dosage or the AED used. Therefore, an accurate differential diagnostic and evaluation of the stage of the disease is required when new seizures or uncontrolled epilepsy reappear in GBM patients.

Side effects of AEDs in patients with GBM

Adverse effects of AEDs are more commonly observed in patients with brain tumors than in other types of epilepsy [1]. Therefore, the assessment of a side-effect profile is advisable in the AED selection process as any adverse effects are directly related to patient quality of life perception [56]. This action might also reduce noncompliance and treatment withdrawal. Three of the following main classes of adverse effects emerge with the use of antiepileptics in the GBM population: CNS toxicity, bone marrow toxicity and skin reactions.

CNS toxicity

Neurocognitive deficits and behavioral changes are often associated with the use of AEDs in brain tumor patients and may mimic tumor progression, interfering with clinical evaluation. In a study, a cohort of low-grade gliomas compared with healthy subjects, the use of carbamazepine, phenytoin, phenobarbital and valproate was associated to neurocognitive decline in the absence of tumor progression [16]. Conversely, in a recent study of high-grade gliomas, patients treated with phenytoin, valproate and levetiracetam showed no significant cognitive differences than patients without AED treatment. Moreover, levetiracetam- and valproate-treated patients obtained better scores in verbal memory over nontreated patients [57]. However, this was a cross-sectional study just after surgery, without a follow-up of long-term users that did not take into account the seizure burden variable. Phenobarbital and benzodiazepines have the most negative cognitive profile. Other GABAergic AEDs, including gabapentin, pregabalin, vigabatrin and topiramate, are associated with sedative effects and consequently, present a negative impact in cognitive domains. Moreover, topiramate may generate language (word finding) problems. Additionally, other new AEDs have also been related with CNS toxicities. Zonisamide carries an increased risk of developing somnolence and cognitive and psychiatric disturbances [58]. Levetiracetam, often considered safe, is associated to somnolence, fatigue and behavioral changes [59,60]. In addition, a cross-sectional population study found that patients under AED polytherapy, or with phenytoin, presented more cognitive complaints than patients under valproate treatment [59].

Finally, it is important to keep in mind other complications, like tremors related to valproate and other much less frequent central nervous toxicities associated with some AEDs, for example, symptoms due to the hyponatremia induced by carbamazepine and oxcarbazepine, paresthesias associated to topiramate and zonisamide, insomnia due to lamotrigine and very rarely, hyperammonemic encephalopathy or parkinsonian syndrome associated to valproate [61].

Bone marrow toxicity

Hematological toxicity in the general epileptic population, although rare, is a known adverse effect of AEDs. The overall rate of severe neutropenia and thrombocytopenia in a cohort study of 29,357 patients treated with carbamazepine, phenobarbital, phenytoin or valproate was 1.2 and 0.9 per 100,000 prescriptions, respectively. These rates did not present differences among these drugs. Moreover, an age above 60 years had doubled the rate of hematological dyscrasias than younger patients. Nevertheless, bone marrow recovery was observed after the withdrawal of AED treatment [62]. Other prescribed AEDs that are sometimes related with bone marrow suppression are lamotrigine, oxcarbazepine and rarely, topiramate and levetiracetam [7,30]. What is more, this problem can increase in brain cancer patients owing to the pharmacokinetic interaction problems between chemotherapy and AEDs and for the adverse event profile of chemotherapy drugs themselves used in GBM patients, such as temozolomide, nitrosureas and irinotecan. As previously mentioned, the CYP450 isoenzyme inhibitor properties of valproate should be administered with caution when it is combined with chemotherapy. Accordingly, valproate-induced grade 3–4 thrombocytopenia and neutropenia have been reported as a significant adverse events in GBM patients treated with carmustine, fotemustine or the current frontline temozolomide treatment, compared with patients without AEDs or with other EIAED treatments [5,7,43,45]. However, it has to be highlighted that in the majority of these studies, the AED therapy was not updated during chemotherapy treatment and that the patients' survival when treated with valproate and temozolomide, despite the hematological toxicity, were significantly longer than the other patients [5,45,63]. This surprising finding could be explained by a potential antitumoral effect of valproate as a cell differentiation inducer and blocker of tumor cell growth using mechanisms such as deacetylation of histone proteins, diminishing protein kinase C activity, activating the peroxisome proliferator-actived receptors, inhibiting glycogen synthase kinase-3b or regulating the expression of genes implied in the extracellular-regulated kinase-AP1 pathway [64]. Moreover, in a recent GBM cell-line study, a reduction of O6-methylguanine-DNA methyltransferase expression in the cells treated with valproate was observed, which is the main cellular resistance mechanism to alkylating agents [65]. However, although valproate administration and age has been correlated with the total platelet count in temozolomide-treated patients, its administration has not been associated with critical thrombocytopenia (<1,000,000 platelet units) and does not prevent treatment administration or a reduction in the temozolomide dosage [7,45]. Only the accumulated temozolomide dose was found to be the main determining factor associated with thrombocytopenia values below 100,000 units [7].

Skin reactions

The most common adverse event is a skin rash, occurring at frequencies ranging between 2.5 and 6% of patients. Skin adverse events, usually occur within the first 2 months of starting treatment, sometimes can be accompanied by fever, eosinophilia and

lymphadenopathies, which can lead to Stevens–Johnson syndrome and epidermal necrolysis in the worst scenario. Generally, these skin reactions have been associated with phenobarbital, phenytoin, carbamazepine, oxcarbazepine, valproate and lamotrigine. A non-brain tumor-related epilepsy population study showed an incidence of serious skin adverse events of 1.5 for carbamazepine, 3.8 for lamotrigine, 6.9 for phenytoin, 8.2 for phenobarbital and 0.5 for valproate per 10.000 person-years in new users, emphasizing the low risk to valproate users [66]. However, a number of case reports suggest an increase of Stevens–Johnson syndrome in patients under cranial radiotherapy treatment receiving phenobarbital, phenytoin or carbamazepine, although after a review of the literature, the appearance of this dermatological complication remains relatively rare [67].

Treatment efficacy

The associated increased risk of seizures when a patient presents a brain tumor involves two distinct therapeutic scenarios such as the prophylactic use of AEDs and the treatment of symptomatic seizures.

Treatment prophylaxis

The meta-analysis performed by the American Academy of Neurology in 2000 laid the foundations of the prophylaxis treatment approach [1]. This study concluded that seizure prophylaxis was not effective in preventing first seizures and that the incidence and severity of adverse events were appreciably higher in brain tumor patients than in the general population of patients receiving anticonvulsants. For that reason, the routine use of AED prophylaxis is not recommended. They also provide the recommendation of tapering and discontinuing the AED therapy after the first postoperative week. However, this study leaves a question unanswered. The AEDs used in the studies, included in the meta-analysis, were valproate, phenytoin and phenobarbital, so consequently, the value of other AEDs, particularly the newer ones, remains to be tested. Subsequently, two additional meta-analysis studies have been performed over the past 10 years to address the prophylaxis discussion. These more recent studies point out some methodological flaws of the earlier review but show similar conclusions with some qualifications. One provides no evidence supporting AED prophylaxis for valproate, phenytoin or phenobarbital in patients with brain tumors with no history of epilepsy [68] but the other, although recognizing the unlikely usefulness of these three AEDs, considers the evidence as inconclusive at best. Moreover, this last study noted that the increased risk of adverse events reported in brain tumor patients under AED treatment were provided from data of retrospective studies, making it possible for this to be overestimated [69]. No new randomized prospective trials testing the ability of second and third-generation AEDs in preventing seizures in brain tumor patients have been performed in the last decade.

Another common reason that many brain tumor patients receive anticonvulsant treatment without epilepsy is because they have undergone cranial surgery. However, the evidence of its efficacy provided by prospective trials on brain tumor patients is lacking and up to now suggests that the benefit is little or absent entirely. A meta-analysis of the studies evaluating the AED prophylaxis following craniotomies for any reason found no benefit [70]. More recently, a prospective study involving only patients with supratentorial brain tumors did not find differences in the rate of seizures during the first 7 postoperative days between patients treated with or not treated with phenytoin. However, in this study, nearly all of the patients in both groups were being treated with additional AEDs [71]. Despite this lack of evidence, several retrospective studies involving brain tumor patients have compared the use of levetiracetam and phenytoin as prophylaxis treatment following neurosurgery [72,73]. The results showed a low risk of early postoperative seizures in both treatments (1–4%), although patients treated with levetiracetam developed significantly fewer adverse reactions. However, it is worth noting that in this study, the patients under phenytoin treatment were older and the follow-up was longer than levetiracetam patients [74]. Moreover, another recent meta-analysis including prophylaxis studies for any type of brain injury showed the same results in efficacy for phenytoin and levetiracetam in preventing seizures [75].

Treatment in symptomatic patients

Efficacy of AEDs

Unfortunately, there is a lack of large studies or randomized trials evaluating the efficacy of AEDs in GBM patients with seizures or in patients with any type of brain tumor, or further, comparing the efficacy among different drugs in this population [75]. Only three large prospective unselected population studies with heterogeneous primary brain tumors have attempted to answer this question. The first study, involving 117 patients with high-grade glial tumors, showed that only 13% of the total series (234 patients) became seizure free after the initial treatment, with valproate, carbamazepine, gabapentin, lamotrigine and clobazam being the most commonly administered drugs. Overall, first-line treatment failed in about 60% of the patients and, of this group, a further 60% experienced a second-line failure in monotherapy or polytherapy. However, this study also showed a significant decrease in the risk of seizure generalization [11]. In contrast, a second study of 140 patients, that includes 75 patients with high-grade gliomas, showed better results. Valproate monotherapy achieved a seizure free rate of 52%, increasing this rate to 59% when valproate was combined with levetiracetam. Other treatments, such as levetiracetam in monotherapy or other AED combinations, resulted in complete resolution of the epilepsy in around 30% of the patients. This study also suggests that the combination of valproate with levetiracetam may be a preferable option over sequential trials of AED monotherapy for treatment-resistant epilepsy in brain tumor patients [10]. Finally, in a trial with 82 brain tumor patients, 60 of them with high-grade gliomas, under levetiracetam monotherapy treatment showed a very good response, resulting in 91.5% of the patients being free of seizures [6].

Over the last 10 years, several studies have been reported evaluating the safety and efficacy of second- and third-generation AEDs in brain tumor patients. In general, most of them show a good response and a seizure-free rate with an adequate safety profile.

However, all the series share important limitations, such as a small number of patients, a retrospective nature, heterogeneity regarding tumor histologies, antineoplastic treatments, and the status of the disease (progression vs stable) and most importantly, no control groups with first-generation AEDs. Only a small randomized controlled trial comparing the safety and feasibility of switching from phenytoin to levetiracetam monotherapy in patients with glioma and seizures following craniotomy has been identified. However, this study does not provide statistical comparisons, is very small (20 and nine patients in levetiracetam and phenytoin arms, respectively) and the group of patients treated with levetiracetam had a higher proportion of gross total resections. Although both treatments had a good seizure-response ratio, 57% of the phenytoin-treated patients reported coordination problems compared with no patients from the levetiracetam group. Conversely, the levetiracetam subgroup reported behavioral problems of up to 13% with 0% in the phenytoin subgroup [76]. Table 2 summarizes the main studies on this issue. Furthermore, only one small study shows data concerning the quality of life before and after starting levetiracetam treatment. This study found a statistical improvement in some domains using specific epilepsy quality-of-life questionnaires (seizure worry, fatigue, medication effects, social function and distress seizure worry). Nevertheless, this impact was not reflected into the commonly employed cancer quality-of-life EORTC questionnaires and the patients presented a significant cognitive decline evaluated by means of a Mini Mental State test. Authors attributed this cognitive potential adverse event to tumor progression, although this variable was not adequately controlled and analyzed [77].

Impact of oncological treatment on GBM-related epilepsy

Management of epilepsy in GBM patients mainly relies on AEDs. However, evidence in brain tumor patients, usually with low-grade gliomas, supports the additional role of the oncologic treatment to control seizures related to brain tumors.

Surgery

The need for surgical intervention in a high-grade glioma patient is not usually based on the epilepsy criteria. However, several studies involving low-grade glioma demonstrate that surgical brain-tumor removal yields a high rate of reduction in seizure frequency [15,78], with many patients even becoming seizure free after oncological surgery, mainly when gross total resection is achieved [15]. The best seizure control is usually associated with the proximity between the resected lesion and the epileptogenic focus [79]. However, in up to a third of patients, the epileptogenic focus is beyond the tumor borders [80].

Radiotherapy

Conventional cranial radiotherapy contributes to the reduction of seizure frequency and severity in patients with low-grade and high-grade glioma-related epilepsy [81,82], reportedly being effective in decreasing seizure frequency by over 75% [81]. Interestingly, a Phase III EORTC study comparing adjuvant radiotherapy versus

Table 2. Summary of the main studies about the efficacy of antiepileptic drugs in high-grade glioma patients.

Study (year)	Drugs	Study type	n	Histology	Serious AE‡ (%)	Response ratio	Seizure freedom	Ref.
Perry (1996)	Gabapentin	Prospective	14 (add-on)	Mixed (8 HGG)	7.1	100	57	[98]
Striano (2002)	Tiagabine	Prospective	11 (add-on)	Mixed (1 HGG)	0	63.6	27.2	[99]
Maschio (2008)	Topiramate	Prospective	47 (33 add-on)	Mixed (28 HGG)	8.5	72	54.4	[100]
Lu (2009)		Prospective	227 (108 tumors)	Mixed (0 HGG)†	5.3	74†	61†	[101]
Novy (2009)	Pregabalin	Retrospective	9 (6 add-on)	Mixed (6 HGG)	22	100	55.6	[102]
Maschio (2012)		Prospective	25 (add-on)	Mixed	8	76		[103]
Maschio (2009)	Zonisamide	Prospective	6 (add-on)	Mixed (4 HGG)	33.3	66.7	0	[104]
Maschio (2009)	Oxcarbazepine	Retrospective	35	Mixed (25 HGG)	8.6	NR	62.9	[105]
Maschio (2011)	Lacosamide	Prospective	14 (add-on)	Mixed (12 HGG)	7.1	78.6	42.9	[106]
Wagner (2003)	Levetiracetam	Prospective	26 (add-on)	Mixed (18 HGG)	5.6	65	20	[107]
Newton (2006)		Retrospective	41 (33 add-on)	Mixed (25 HGG)	2.4	90	58.5	[108]
Maschio (2006)		Prospective	19 (add-on)	Mixed (12 HGG)	0	73.6	47.4	[109]
Lim (2009)		Prospective; randomized	20	Mixed (11 HGG)	0	NR	87	[72]
Rosati (2010)		Prospective	82	Mixed (60 HGG)	0	91.5	91.5	[6]
Maschio (2011)		Prospective	29	Mixed (19 HGG)	3.5	100	72.4	[77]
Bähr (2012)		Prospective	27	Mixed (17 HGG)	0	NR	61.9	[110]

†Data from subpopulation of tumors.
‡Serious AE leading to the withdrawal of medication.
HGG: High-grade tumor; NR: Not reported..

observation in low-grade glioma showed a lower rate of seizures in the irradiated group (25 vs 41%), which indirectly supports the potential role of this therapy in epilepsy-related brain tumors [83]. Furthermore, some evidence in seizure control improvement with sterotactic radiosurgery in glioma patients has also been reported [84].

Chemotherapy

Antineoplastic agents can also be effective in controlling seizures, although evidence in GBM populations is lacking. Studies involving low-grade glioma patients have reported a reduction in seizure frequency with temozolomide [85,86] and nitrosurea-based chemotherapy [87], with seizure response ratios of 51–100%.

Corticosteroids

The antiepileptic activity of corticosteroids has not been properly assessed in tumor-related epilepsy. However, steroids could enhance the GABA-depressant effect, as shown by some corticosteroids compounds [88]. Conversely, corticosteroids are susceptible to agents affecting the isoenzyme CYP3A4. Thus, EIAED can enhance the clearance of dexamethasone. Therefore, the combination of corticosteroids and EIAED presents unpredictable interactions. For this reason, a close monitorization of AED plasmatic levels should be recommended, particularly during the withdrawal or increasing doses of dexamethasone [30]. On the other hand, it has not been reported in the studies focused on pharmacokinetic interactions between corticosteroids and valproate or with temozolomide. However, valproate is a substrate of the isoenzymes CYP2E1, CYP2C9 and CYP2C19 [30]. Hence, it also should be advisable to monitor the plasma valproic acid concentration during the introduction of corticosteroids treatment. Finally, one of the consequences of bevacizumab therapy is a steroid-sparing effect in a significant proportion of GBM patients, reducing the potential interactions between AED and corticosteroids [89].

Expert commentary

To date, the knowledge on optimal antiepileptic therapy in patients with brain tumors is limited and there are no firm evidence-based guidelines regarding the management of seizures in these patients. Moreover, the nature of GBM seizures is also not well known, as is reflected in population observational studies that have shown disparate ratios of refractory glioma-related epilepsy (9–46%) [2,6,7,10,11]. Probably this fact is the result of the heterogeneity of the glioma type involved, the lack of control of surgery extension performed and complementary oncological treatments administered. The incomplete data about the natural history of seizures and the lack of randomized trials when it is known that placebo interventions in epilepsy improve the seizures ratio by up to 15% [90] prevent comparisons of efficacy between single-arm treatment studies. This highlights the need to increase the authors knowledge in this neuro-oncological field.

However, the authors can take into account some practical considerations when selecting a first-line AED for GBM patients who suffer from seizures. First, the selection of a drug with an available intravenous presentation can prove very useful as these patients will need surgical intervention if the presentation symptom of their GBM is a seizure. They also have a risk of status epilepticus (4–12%). Moreover, dysphagia is a frequent symptom in the end-of-life stages of these patients making intravenous administration a practical option. Second, the AED selected has to have a quick titration and drugs like lamotrigine, whose initiation requires a long time period of dosage increments before therapeutic ranges are reached, should be avoided. Other considerations, based on current evidence are more controversial. Second-generation AEDs, in the general epileptic population, have not proven better efficacy than older AEDs [91] and although they provide superior tolerability, the evidence provided is insufficient [61,92]. Therefore, knowing the increased ratio of adverse events due to the AED in the glioma population, the supposed better tolerability in non-brain cancer patients is not enough to give a recommendation in favor of newer AED in GBM patients. Additionally, the best pharmacokinetic profile of almost all newer compounds makes these AEDs the theoretical drugs of choice to treat GBM-related epilepsy. However, the metabolism of front-line chemotherapy used in GBM treatment is not significantly interfered with in the first-generation of AEDs. The hematological toxicity related to the interaction between these cytostatics and older AEDs does not diminish the number of cycles or the total dose of chemotherapy administered to the patients [7,45]. The impact of pharmacological interactions on survival presents unexpected results in favor of first-generation drugs according to the only available retrospective studies [41,45,63]. Moreover, the efficacy of old and newer AEDs on GBM-related seizures has not been adequately tested providing no good quality evidence. One conclusion that has emerged analyzing the studies of second-generation compounds is the different ratio of seizure freedom between patients treated with an add-on or in first monotherapy (Table 2); the latter showing better ratios of response, which is a consequence of selection population bias. Of these new AEDs, only levetiracetam was used in both types of studies. Despite impressive results of the recent study using levetiracetam as first-line therapy [6], the drug used as an add-on therapy showed similar efficacy results as other new compounds. However, again, the sample size, the heterogeneous glioma types involved, the lack of a control group, the uncontrolled role or missing data of the surgery extension and complementary oncological treatments prevent us from drawing valid conclusions about the efficacy of new and older AEDs.

Taking into account these suboptimal data, two drugs emerge as potential first election compounds in treating GBM-related seizures, valproic acid and levetiracetam. The advantages of valproate provide a favorable additional impact on the survival rate of patients treated with temozolomide. It has been widely used in GBM patients, has a good tolerability profile and has the advantage of not being a substrate or inducer of P-gp proteins. As an alternative, levetiracetam treatment has also been widely used in treating glioma-related epilepsy in recent years, showing very good efficacy and tolerability.

The authors would recommend the use of valproate in moderate doses (1000–2000 mg/day) as a first-line agent in patients treated with temozolomide, evaluating a switch to levetiracetam

after completing oncological treatment and according to the tolerance presented by the patients. If the seizure control is insufficient, adjunctive therapy with levetiracetam, rather than sequential trials of AED monotherapy, should be recommended. In patients treated only with radiotherapy, supportive palliative treatment or second-line chemotherapy treatments, both options are equally recommended. Finally, in cases of refractory epilepsy when using these two drugs, it is advisable to plan oncological rescue treatment if the disease remains rather than adding a third compound. In cases with no measurable disease, the addition of oxcarbazepine or lacosamide is recommended. When valproate is administered, it should be advisable to monitor the plasma level of valproate if increasing doses of dexamethasone are necessary.

On the other hand, the recommendation in the end-of-life phase of GBM patients with previous history of epilepsy should be the maintenance of the AED treatment, despite the problems with swallowing or the impaired level of consciousness, due to the higher risk of reappearing seizures in the advanced stage of the illness. Hence, drugs with intravenous presentation are useful in patients admitted to hospitals or a switch to intramuscular drugs like phenobarbital should be advisable and it has been proved as a reasonable option in patients who will die at home or in hospices [55].

Finally, the only well-established evidence found is not to use valproate, phenobarbital or phenytoin as prophylactic treatment in patients with brain tumors, leaving the question open regarding new AEDs.

Five-year view

There are several recently approved third-generation AEDs and numerous new compounds undergoing Phase II and Phase III clinical evaluation that have attractive mechanisms of action for glioma patients who suffer seizures [88]; therefore, it is mandatory that in the next few years, the authors clarify the question of which is the best first-line treatment for GBM patients, ensuring that there are adequate clinical trials, paying special attention to CNS toxicities.

Brivaracetam is a high-affinity SV2A and also displays inhibitory activity at neuronal voltage-dependent sodium channels with an expecting potency and efficacy superior to levetiracetam. Moreover, brivaracetam has intravenous presentation and Phase III studies have shown a favorable safety and tolerability profile emerging as a potential drug in treating GBM-related seizures [88]. Another recently available new compound, perampanel, is potentially useful in GBM patients due to its novel mechanism of action, reducing the ability of glutamate to activate the AMPA receptors via noncompetitive and highly selective binding [93]. However, Phase III studies have reported some adverse events such as somnolence, dizziness, fatigue and headache more frequently than placebo and a discontinuation rate of 7.1–10.3% [94–96]. When this drug is to be tested in glioma patients, the adverse events of perampanel will need to be monitored carefully. However, eslicarbazepine, a new derivate of carbamazepine and oxcarbazepine, does offer the advantage of a single daily dose.

Other interesting drugs under development that possess actions useful in treating the specific pathophysiological mechanisms involved in GBM-related seizures are NAX 810-2, a GalR2-preferring galanin agonist that inhibits glutamate release and possesses anti-inflammatory effects [88]; tonabersat, a benzoylamino-benzopyran class of compound that inhibits acute and chronic inflammation-induced expression of connexins and suppresses neuron–glia communication via gap junctions

Key issues

- Seizures are a common symptom of glioblastoma at presentation and during the course of the disease. Moreover, between 10 and 40% of patients will present refractory glioblastoma-related epilepsy.
- Glioblastoma epileptogenic mechanisms are comprised of changes in pH, cytokines, neurotransmitter (mainly glutamate) and ion levels, as well as the expression of potassium voltage-dependent channels and receptors in tumoral and peritumoral brain tissue. However, most of the currently used antiepileptic drugs do not focus specifically on these mechanisms of action.
- Pharmacokinetic interactions between antiepileptic drugs and antineoplastic agents have to be taken into account in order to prevent adverse events. However, these interactions have not demonstrated a negative impact on patient's survival.
- Neurocognitive deficits and behavioral changes are often associated with the use of antiepileptic drugs in brain tumor patients, which may mimic tumor progression, interfering with clinical evaluation and impairing the quality of life.
- No evidence supports the antiepileptic prophylaxis of phenytoin, valproate or phenobarbital. However, the usefulness of new antiepileptic compounds in prophylaxis treatment has not yet been tested.
- Patients treated with valproate and temozolomide, despite the increased risk of hematological toxicity, have a significantly longer overall survival than other glioblastoma patients not treated with valproate.
- Combination of valproate with levetiracetam may be a preferable option over sequential trials of antiepileptic drug monotherapy for the treatment of resistant epilepsy in glioblastoma patients.
- Among the second-generation antiepileptic drugs, levetiracetam has been widely used in treating glioma-related epilepsy, showing a good efficacy and tolerability.
- There is a lack of large studies or randomized trials evaluating the efficacy of antiepileptic drugs in glioblastoma patients with seizures or in patients with any type of brain tumor, or further, comparing the efficacy among different drugs in this population.
- To date, the knowledge on optimal antiepileptic therapy in patients with glioblastoma is limited and there are no firm evidence-based guidelines regarding the management of seizures in these patients.

[88]; valnoctamide, a valproic acid second-generation derivate that possesses a novel mechanism of action inhibiting the myo-inositol phosphate synthase [88] and VX-765, which has anti-inflamatory properties due to it being a selective and reversible inhibitor of interleukin-converting enzyme [97]. Another novel compound, ganaxolone, is a neurosteroid analog of a progesterone metabolite with GABAergic activity, effects on neuronal and glial differentiation and anti-inflammatory properties. Although it is not believed to have nuclear hormone activity and cannot be biotransformed to metabolites with such activity, the safety profile of this compound has to be tested carefully in brain tumor patients [88].

Finally, the efficacy and safety of second- or third-generation AEDs needs to be tested in the prophylaxis of GBM seizures. Thus, a prospective randomized trial using lacosamide is currently ongoing [202].

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