Anticonvulsant therapy in brain-tumor related epilepsy

Walter Fröscher[1], Timo Kirschstein[2,3], Johannes Rösche[2,4]

[1] Lake Constance Epilepsy Centre, Epilepsiezentrum Bodensee,
Centre of Psychiatry, Zentrum für Psychiatrie Südwürttemberg,
Ravensburg-Weissenau, Germany

[2] Klinik und Poliklinik für Neurologie, Universitätsmedizin Rostock,
Germany

[3] Oscar-Langendorff-Institut für Physiologie,
Universitätsmedizin Rostock, Germany

[4] Klinik Lengg, Zürich, Switzerland

Correspondence

Prof. dr. med. Walter Fröscher
Wilhelm-Gindele Str. 9
D–88276 Berg
Phone: (00 49) 751 52225
Fax: (00 49) 751 5573534
E-Mail: w.froescher@arcor.de

SUMMARY

Background. The lifetime risk of patients with brain tumors to have focal epileptic seizures is 10–100%; the risk depends on different histology. Specific guidelines for drug treatment of brain tumor-related seizures have not yet been established.

Aim. This review addresses the special aspects of antiepileptic drug (AED) therapy in brain tumor-related epilepsy.

Methods. We analyzed the literature up to December 2015.

Results. Based on current evidence the management of tumor-related seizures does not differ substantially from that applied to epilepsies from other etiologies. Therefore, the choice of an AED is based, above all, on tolerability and pharmacokinetic interactions with chemotherapeutic drugs. Levetiracetam is recommended by many authors as first-line therapy in brain tumor-related epilepsy. Due to the possibility of interactions, the combination of enzyme-inducing AEDs and chemotherapeutic drugs, is usually not recommended as a first choice. Currently there is no evidence that prophylactic prescription of long-term AEDs in brain tumor-patients who did not present with seizures is justified. Because of the high risk of recurrence, however, AED treatment should be strongly considered after a single brain tumor-related seizure. The decision to withdraw AEDs must carefully consider the risk of seizure recurrence.

Conclusion. At present levetiracetam is the preferred drug in brain tumor-related epilepsy, especially when drug interactions need to be avoided. In the future we hope to acquire more targeted drugs against this disorder by uncovering its pathogenesis.

Key words: brain-tumor • epilepsy • antiepileptic drugs • chemiotherapeutic drugs • pharmacokinetic interactions

BACKGROUND

In the past 15 years, the worldwide incidence of central nervous system tumors was 2.9–5.3 cases per 100,000 person-years for children and adolescents (Lopez, 2015). The lifetime risk of brain tumors is about 0.7%; however, the reported incidence rates vary substantially (Paulus and Hasselblatt, 2012). Epilepsy due to brain tumors constitutes 6–10% of all cases of epilepsy as a whole, and 12% of acquired epilepsy (Maschio and Newton, 2015a). The risk of patients with primary brain tumors or brain metastases to have epileptic

seizures is 10–100% (Fröscher et al., 2014); the frequency of seizures differs widely between different histologies, and, as a consequence, between tumors with different natural histories and growth patterns (Brogna et al., 2008). Patients with low-grade astrocytomas and low-grade oligodendrogliomas are those who develop more often seizures than patients with glioblastomas, brain metastases or meningiomas (Vecht and Wilms, 2010). Most epilepsy-associated tumors have a supratentorial cortical location with a higher incidence of seizures in tumors involving the temporal, frontal or parietal region (Liigant et al., 2001; Hildebrand et al., 2005; Stefan, 2009).

Other risk factors for tumoral epilepsy – besides tumor histology and location – include the size of the tumor, the extent of tumor resection, age at operation older than 40 years, duration of epilepsy before surgery, additional hippocampal sclerosis or cortical dysplasia (dual pathology), postoperative tumor recurrence and brain damage from radiotherapy (Luyken et al., 2003; van Breemen et al., 2007; Prayson, 2011; Paulus and Hasselblatt, 2012).

AIM
This review addresses the special aspects of antiepileptic drug (AED) therapy in brain tumor-related epilepsy.

METHODS
We conducted a literature research for the period from 1980 up to December 2015. The headings used included "brain tumors and epilepsy, interactions between AEDs and chemotherapeutic drugs (CTDs)". The following databases were searched: Medline, Embase, Biosis, EBM Reviews, Psycinfo, Psyndex. Important citations in book chapters and congress abstracts have also been considered.

RESULTS OF THE REVIEW

Seizure classification

Epilepsy in patients with brain tumors is characterized by focal seizures (Kerkhof and Vecht, 2013). According to the revised terminology from 2010 (Berg et al., 2010) these seizures are classified as "focal seizures without impairment of consciousness or awareness, focal seizures with impairment of consciousness or awareness and focal seizures evolving to a bilateral, convulsive seizure". At the onset of the disease, seizure generalization occurs more frequently than during the follow-up after an operation and/or AED therapy (Hildebrand et al., 2005). Seizures may lead to nonconvulsive or convulsive status epilepticus (Maschio, 2012; Swisher et al., 2012).

Tumors and epileptogenesis
Understanding the pathogenic mechanisms that underlie epileptogenesis in brain tumors is essential to identify new treatment targets and to develop effective treatment. Unfortunately, the specific events that occur in a lesion and lead to seizures are only partially known. Epileptogenesis presumably comprises of structural and cellular/molecular changes induced by the tumor that leads to changes in the surrounding tissue and at a further distance, eventually resulting in alterations in functional connections (de Groot et al., 2012).

One of the best known mechanisms that underlie epileptogenesis in gliomas – the most frequent primary brain tumor – is a glutamate-related mechanism. Because gliomas use the neurotransmitter glutamate as a "tumor growth factor" to enhance glioma cell proliferation and invasion, glutamate homeostasis is impaired, with elevated extracellular glutamate concentrations. Such excitatory effects contribute to the generation of epileptic activity in the peritumoral neocortex (Pallud et al., 2013; Liubinas et al., 2014). Substances modulating glutamate receptors like the AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptor may display antiepileptic properties and improve survival in patients with gliomas (Grossman et al., 2009; Pallud et al., 2013). GABAergic signalling is also involved, both in tumor growth and in paradoxical excitatory effects mediated by alterations in neuronal and tumor cell Cl^- homeostasis related to cotransporter changes (Pallud et al., 2013).

A full discussion of tumor-associated epileptogenesis and the pathophysiology of brain tumor-related epilepsy can be found in the very recent overviews of de Curtis et al. (2015) and Salmaggi et al. (2015). Animal models of tumor-associated epilepsy have been recently reviewed by Kirschstein and Köhling (2015).

Seizure treatment in brain tumor patients

General therapeutic considerations
In the treatment of brain tumors, with and without symptomatic epilepsy, it is of prime importance to clarify to which extent the tumor can be removed. A complete resection of the tumor is the best approach for dealing with tumors presenting with epilepsy, and is

often associated with postoperative seizure freedom, especially in benign intracranial tumors. For example, in 69% of 703 patients with supratentorial meningioma and preoperative epilepsy, seizure freedom was achieved after surgery (Englot et al., 2015). Chemotherapy and radiotherapy can also be effective in controlling seizures (Luyken et al., 2003; Seeck, 2003; Brogna et al., 2008; Rudà et al., 2012; Bruna et al., 2013; Tandon and Esquenazi, 2013).

Specific guidelines for treating brain tumor-related seizures are not available (van Breemen et al., 2012; Wallace et al., 2012). Hence, the guidelines for drug treatment of focal seizures can also be applied to tumor-related seizures. In addition to these general guidelines, the following aspects have to be considered in brain tumor-related seizures:

Efficacy of antiepileptic drugs in tumoral epilepsy
Epilepsy associated with brain tumors has commonly be considered to be more difficult to treat than have other types of epilepsy; however, this perception is not supported by robust data (Weller et al., 2012). There is no evidence that the efficacy ranking of currently available AEDs differ for patients with brain tumors compared to patients with focal seizures from other etiologies (Perucca, 2013). A retrospective analysis of 147 consecutive patients with newly diagnosed brain tumors demonstrated no statistical association between tumor type (or tumor location) and success or failure of a particular AED (Lynam et al., 2007). Furthermore, there is no evidence that specific AEDs are more active than others in epilepsy associated with brain tumors (Weller et al., 2012). Therefore, the selection of an AED is based, above all, on tolerability and pharmacokinetic interactions with CTDs.

In many studies and case reports numerous AEDs led to a complete control or a marked reduction of seizures in patients with brain tumor-related epilepsy (brain metastases included). The AEDs used were given alone or in combination. A selection of more recent studies gives the following enumeration of effective AEDs (in alphabetical order): gabapentin (GBP), lacosamide (LCM), lamotrigine (LTG), levetiracetam (LEV), oxcarbazepine (OXC), phenytoin (PHT), pregabalin (PGB), topiramate (TPM), valproic acid (VPA) and zonisamide (ZNS) (Fröscher et al., 2014).

According to Reif et al. (2012) LEV was the most common AED in patients with tumor-related epilepsy. Numerous authors recommended LEV as the drug of first choice in this situation in children and in adults, independently of the neuropathological classification of the underlying tumor (Lynam et al., 2007; Rosetti and Stupp, 2010; Rudà et al., 2010; Ruggiero et al., 2010; Pruitt, 2011; Wallace et al., 2012; Bruna et al., 2013; Perucca, 2013; Vecht et al., 2014; Piotrowski and Blakely, 2015; Ray et al., 2015). LEV is considered as an attractive option, both as monotherapy and in combination, due to its efficacy, safety, availability of a parenteral formulation, and the pharmacokinetic profile with a lack of interactions with CTDs. According to a 2013 report from the International League against Epilepsy (ILAE) there is level A evidence for LEV (besides carbamazepine (CBZ), PHT and ZNS) as initial monotherapy for adults with partial onset seizures (Glauser et al., 2013). LEV may be titrated very quickly to a clinically effective dose and it is available, both orally and parenterally (Pruitt, 2011; Reif et al., 2012; Rossetti and Stupp, 2010; Rudà et al., 2010; Ruggiero et al., 2010); beyond that, an antitumoral effect of LEV has been postulated (Reif et al., 2012).

Compared to LTG, which has been recommended also as a drug of first choice in focal seizures (Diener et al., 2012), LEV can be uptitrated more rapidly and administered parenterally and it has a lower interaction potential.

In addition to LEV, numerous other AEDs have also been recommended as drugs of first choice in brain tumor-related seizures (in alphabetical order): CBZ, GBP, LCM, LTG, OXC, PGB, TPM, VPA and ZNS (Fröscher et al., 2014).

Several authors (Avila and Graber, 2010; Maschio, 2012; Rudà et al., 2012) recommended the enzyme-inducing AEDs CBZ, PHT, and phenobarbital/primidone (PB/PRM) only as drugs of second or third choice, in spite of their good anticonvulsant efficacy. Maschio and Newton (2015b) concluded that CBZ, PHT and PB/PRM must not be used to treat patients with brain tumor-related epilepsy. This recommendation was largely based on the interactions of CTDs and AEDs (see below). These interactions were discussed as the cause of the shorter survival of those glioblastoma patients who were treated with CTDs and enzyme-inducing AEDs compared with the glioblastoma patients who were treated with the same CTDs and non-enzyme inducing AEDs (Oberndorfer et al., 2005). Even in children with acute lymphoblastic leukaemia, therapy with enzyme-inducing AEDs (PHT, PB, CBZ, or a combination) was significantly related to worse event-free sur-

Table 1. Recommendations of combination therapies after failure of monotherapies

Drug combinations	References
Lamotrigine + Valproic acid	Weller et al., 2012
Levetiracetam + Topiramate	Weller et al., 2012
Levetiracetam + Lacosamide	Schiff et al., 2015
Levetiracetam + Valproic acid	Bruna et al., 2013; van Breemen et al., 2007, 2009; Vecht et al., 2014; Weller et al., 2012

vival, haematological relapse and CNS relapse (Relling et al., 2000).

Because of the possibility of interactions, the combination of enzyme inhibiting AEDs such as VPA and CTDs was not recommended either (Tibussek et al., 2006). Maschio and Newton (2015b) discouraged the use of VPA in the treatment of patients receiving different CTDs due to increased haematological toxicity (see below, *Special aspects of the adverse effects...*).

Monotherapy is preferred; after failure of monotherapy different combinations are recommended (Table 1). These recommendations are based on experience, not on controlled studies.

According to Vecht and Wilms (2010), the combination of LEV and VPA seems synergistic and well tolerated; they prefer VPA as add-on over TPM or LTG, based on its reported antitumor effect – an effect which has been questioned thereafter (see below, Happold et al., 2015). According to the experience of van Breemen et al. (2007), VPA combined with LEV is more active against seizures than either drug alone.

In recent years, a growing list of retrospective analyses has demonstrated that glioma patients exposed to VPA have an improvement of the survival time by several months (Weller et al., 2011; Weller et al., 2013; Guthrie and Aljamel, 2013; Karkhof et al., 2013; Reddy et al., 2015). In the prospective randomized study of Stupp et al. (2005), patients with newly diagnosed glioblastoma were treated with radiotherapy alone or radiotherapy plus temozolomide. Weller et al. (2011) retrospectively analyzed the impact of the interaction between AED use and radiotherapy or chemoradiotherapy on survival in the study of Stupp et al. (2005). Patients treated with VPA alone had a superior survival benefit from temozolomide/radiotherapy compared to patients treated with only an enzyme-inducing AED or patients without any AEDs. In patients who were treated only by radiotherapy (without temozolomide) VPA had no survival benefit. As a cause of the antitumor effect of VPA different mechanisms have been discussed, such as an enhancement of tumor cell radiosensitivity

due to histone deacetylase inhibition or a decrease of the temozolomide clearance by VPA (Weller et al., 2011; Činčárová et al., 2013; Gefroh-Grimes and Gidal, 2015).

An anti-tumor effect is discussed also with other AEDs. The relatively small retrospective study of Reddy et al. (2015) suggested that the use of AEDs (including VPA, PHT, LEV, TPM, PRM, LTG, OXC, CBZ, PGB, GBP and acetazolamide) is associated with improved overall survival in breast cancer patients with brain metastases following whole brain radiotherapy (AEDs were prescribed for either symptom control or seizure prophylaxis, following the diagnosis of brain metastasis). LEV inhibited in vitro glioma cell proliferation and increased glioma cell sensitivity to temozolomide (Bobustuc et al., 2010). In a relatively small, retrospective study, LEV provided a survival benefit in patients with glioblastoma who received temozolomide-based chemotherapy (Kim et al., 2015). There are also data suggesting that CBZ use would be associated with better patient outcomes in glioblastoma; however, these data are rather inconsistent at this time (Gefroh-Grimes and Gidal, 2015). Cell line experiments report anti-tumor effects of TPM (Bauer et al., 2014); in vitro experiments and animal experiments report anti-tumor effects of PHT (Brackenbury et al., 2015). Even in the case of the new AED talampanel (TLP) an anti-tumoral effect has been reported; the underlying mechanism could be an anti-glutamatergic effect (Buckingham et al., 2011; Iwamoto et al., 2010). However, TLP demonstrated this antitumor effect (in newly diagnosed glioblastoma), only, when given as add-on to temozolomide and radiation therapy (Grossman et al., 2009), in patients with recurrent malignant glioma without chemoradiotherapy TLP had no significant antitumor activity (Iwamoto et al., 2010). Because of its anti-glutamatergic effect, an anti-tumor effect is also highlighted for perampanel (Gefroh-Grimes and Gidal, 2015; Rösche et al., 2015).

Unfortunately, a very recent analysis of four contemporary randomized clinical trials in newly diagnosed glioblastoma did not validate an association of VPA or

LEV with improved survival of patients, who were treated with radiotherapy and temozolomide (Happold et al., 2015). A retrospective analysis of patients treated with radiotherapy for glioblastoma also did not confirm the anti-tumor effect of VPA: the use of histone deacetylase inhibitors such as VPA during radiotherapy did not significantly improve outcomes or radiotherapy response (Boehling et al., 2015).

Hitherto, the discussion on the use of enzyme-inducing AEDs with brain tumor-related seizures has not come to a final conclusion (Kerrigan, 2010; Perucca, 2013; Pruitt, 2011). As mentioned above, a retrospective review of patients receiving adjuvant chemotherapy for brain tumors (mostly lomustine = CCNU) revealed a significant decrease in survival with concurrent use of enzyme-inducing AEDs (mostly CBZ) compared to non-enzyme inducing AEDs (mostly VPA; Oberndorfer et al.,2005). However, Jaeckle et al. (2009) found that patients with glioblastoma receiving enzyme-inducing AEDs at baseline had a longer overall survival and progression-free survival and a lower immediate progression frequency than the group of patients who were not receiving enzyme-inducing AEDs.

There are no Class I or Class II studies on which to base recommendations in favor of newer, non-enzyme inducing AEDs in the pharmacotherapy of tumor-related seizures (Pruitt, 2011).

The choice of AEDs in brain-tumor related epilepsy must also take into account practical considerations. The possibility of taking tablets may be interrupted by operations, dysphagia or the occurrence of status epilepticus. Substances such as LEV that can be given parenterally or by the stomach tube, are therefore advantageous. There are currently no guidelines for the treatment of brain tumor patients with status epilepticus (Swisher et al., 2012). Brain tumor-associated status epilepticus appears paradoxically more responsive to simple AED regimes than brain-tumor associated epilepsy or status epilepticus in the general population (Goonawardena et al., 2015).

Pharmacoresistance in patients with brain tumor-related epilepsy

According to many studies, brain tumor-related epilepsy is often drug-resistant (Vecht and van Breemen, 2006; Maschio, 2012; de Groot et al., 2012). However, the therapeutic efficacy show a very wide variation. Overall, using newer AEDs, the rate of response is commonly more than 50%, and the percentage of seizure-free patients ranges between 20 and 91%! (Rudá et al., 2010). In all patients with epilepsy collectively, the pharmacoresistance occurs in 8–40% (Fröscher, 2012) with higher values in patients presenting with focal seizures (van Breemen et al., 2012).

Various causes of a particular drug resistance in brain tumor-related epilepsy are possible (de Groot et al., 2012; Maschio, 2012; Weller et al., 2012; Bruna et al., 2013):

a) pathophysiology of brain tumor-related seizures
b) progressive course of the disease
c) neurosurgical complications such as meningitis or brain abscess
d) adverse effects of the oncological treatment (radionecrosis, posterior leukoencephalopathy)
e) consequences of pharmacokinetic drug interactions
f) very often higher rates of adverse events by the AEDs in this population
g) overexpression of multidrug-transporter proteins in brain tumors (with the consequence of a reduced brain penetration of AEDs; "transporter hypothesis")
h) alterations in drug targets that AEDs normally bind to (possibly altered in tumor and peritumoral tissue; "target hypothesis")
i) altered characteristics of the blood-brain-barrier in metastatic brain tumors.

Special aspects of the adverse effects of AEDs in brain tumor-related epilepsy

Limited evidence suggests that patients with brain tumors show increased susceptibility to the adverse effects of AEDs (Perucca, 2013), especially with regards to the older, enzyme-inducing drugs (Guerrini et al., 2013). This finding most likely has several reasons, notably co-medications such as steroids and chemotherapy, exposure to radiotherapy, effects of the tumor itself, and psychiatric comorbidity, notably depression (Weller et al., 2012). In two studies, the incidence of skin rashes in patients with primary brain tumors was approximately twice that expected for patients taking AEDs (Moots et al., 1995; Mamon et al., 1999); severe skin reactions, however, were rare (Mamon et al., 1999). Most of the mild drug rashes occurred before the initiation of radiotherapy, suggesting that radiation was not the cause of these reactions. The responsible AEDs were PHT and CBZ, a significant lower incidence of rashes was seen for PB compared with PHT (Mamon et al.,

1999). Even with OXC, skin rashes seem to occur frequently, at least, if OXC is administered during radiotherapy (Maschio et al., 2012).

Increased hematological toxicity with thrombocytopathy, leukopenia and neutropenia has been reported in combined therapy with VPA and chemotherapy (temozolomide, nitrosurea, cisplatin, etoposide e.g.; Bourg et al., 2001; Vecht et al., 2003; Oberndorfer et al., 2005; Weller et al., 2011; Maschio, 2012; Bruna et al., 2013). The increased hematologic toxicity during adjuvant temozolomide or other CTDs with VPA may be related to some extent to the inhibition of the CYP isoenzymes, with the consequence of an increased bioavailability of the CTDs (Vecht et al., 2003; Weller et al., 2011). Even in monotherapy, VPA may induce thrombocytopenia and other coagulopathies which is of some concern for patients who require surgical intervention (Gerstner et al., 2006; Perucca, 2013). Some authors therefore recommend routine discontinuation of VPA prior to surgery, others found no bleeding complications in patients undergoing neurosurgery while receiving VPA; statistically conclusive investigations have not been published (Bauer et al., 2014). A recent study on a cohort of glioblastoma patients receiving radiotherapy and temozolomide did not show any significant difference between VPA and LEV and patients without AED therapy (control group) in terms of neutrophil granulocytes, lymphocytes, and thrombocytes decrease (Tinchon et al., 2015).

Side effects of AEDs are not always negative. Patients with coexisting problems may benefit from some AED side effects, such as decreased nausea with LEV, treatment of neuropathic pain with GBP or PGB, and mood stabilization with VPA and LTG (Avila and Graber, 2010).

Interactions between antiepileptic and chemotherapeutic drugs

There is little information on the occurrence of pharmacodynamic interactions between AEDs and CTDs (Vecht et al., 2003). Pharmacokinetic interactions between AEDs and CTDs can result in the delivery of an unreliable dose of either drug. The consequences of this could be inadequate treatment of the underlying neoplasm, poor seizure control or increased toxicity from elevated concentrations of either drug (Kerrigan, 2010). Of particular importance is the impact of enzyme-inducing AEDs (CBZ, PB/PRM, PHT, less pronounced also OXC, TPM and felbamate (FBM), (Rambeck and May, 2008) with a reduction of the serum level of CTDs and glucocorticoids. The clinical consequences of these interactions are so far inconsistent. As mentioned above, Oberndorfer et al. (2005) found a shorter survival of glioblastoma patients who were treated with CTDs (in most cases lomustine = CCNU) and enzyme-inducing AEDs (in most cases CBZ) compared to the glioblastoma patients who were treated with the same CTDs in combination with non-enzyme inducing AEDs (in most cases VPA). Whether the difference regarding survival between the two groups is due to a decrease of efficacy of CTDs by enzyme-inducing AEDs, or due to increased efficacy of CTDs caused by the enzyme inhibiting properties of VPA remains unresolved (Oberndorfer et al., 2005).

The pharmacokinetic interactions between important CTDs and AEDs are shown in

Table 2 and 3 (further information sources: Baxter and Preston, 2013; Patsalos, 2013). The presented data consider original articles and important reviews. The evidence level and the extent of the presented interactions are variable. Numerous reports are based on animal experiments or single case reports (Vecht et al., 2003; Neher, 2008a; Perucca, 2013). To date there have been no reports that GBP, LCM, PGB, retigabine (RTG), stiripentol (STP), tiagabine (TGB), and vigabatrin (VGB) affect the pharmacokinetics of non-AEDs. Bain et al. (2014) report a possible drug interaction between methotrexate and LEV; coadministration of methotrexate and LEV resulted in delayed elimination of methotrexate (single case). Of the new AEDs LTG, TPM and OXC are associated with most pharmacokinetic interactions with drugs used to treat non-epilepsy disorders (Patsalos et al., 2013).

Initiation of treatment

In patients with a first unprovoked seizure, immediate AED treatment at the time of this first seizure is not well accepted and is debated (Krumholz et al., 2015). The risk of recurrence after a single seizure is considerably higher in patients with structural brain pathology such as brain tumors than in patients with no other risk factors for recurrence, and can be significantly reduced by prescription of a long-term AED treatment (Kim et al., 2006; Perucca, 2013). Therefore, initiation of treatment at the time of first seizure should be strongly considered in patients with brain tumors, both in adults and children (Ruggiero et al., 2010; Perucca, 2013).

Table 2. Outcome of chemotherapeutic drug (CTD)/corticosteroids (CS) – antiepileptic drug (AED) interactions

Affected CTD/CS (in alphabetical order)	CTD/CS serum concentration	Interfering AED	References
9-aminocamptothecin	↓	EIA	Wen et al., 2006
Bevacizumab	-	EIA	Rogers, 2013
Bortezomib	↓	EIA	Weller et al., 2012
Busulfan	↓	PHT	Ruggiero et al., 2010
	- / ↓	CBZ, PB	Ruggiero et al., 2010
Carmustine	↓	EIA	Weller et al., 2012
Cediranib	↓	EIA	Maschio, 2012
Cisplatin	↑	VPA	Ikeda et al., 2005
Cyclophosphamide	↓	EIA	Weller et al., 2012
Cytarabine	-	EIA	Relling et al., 2000
Dexamethasone	↓ / (↑)	PHT	Vecht et al., 2003
	↓	PB	Vecht et al., 2003
Docetaxel	↓	EIA	Weller et al., 2012
Doxorubicin	↓	EIA	Weller et al., 2012
Enzastaurin	↓	EIA	Bruna et al., 2013
Erlotinib	↓	EIA	Weller et al., 2012
Etoposide	↓	EIA	Weller et al., 2012; Motl et al., 2006
	↑	VPA	Vecht et al., 2003
Everolimus	↓	EIA	Perucca, 2013
Fotemustine	↓	EIA	Weller et al., 2012
Gefitinib	↓	EIA	Weller et al., 2012
Ifosfamide	↓	EIA	Weller et al., 2012
Imatinib	↓	EIA	Weller et al., 2012
Irinotecan	↓	EIA, VPA	Weller et al., 2012; Cotterman-Hart, 2015
Lapatinib	↓	CBZ	Cotterman-Hart, 2015
Lomustine (= CCNU)	↓	EIA	Weller et al., 2012
Methotrexate	↓	EIA	Weller et al., 2012
	↑	LEV	Bain et al., 2014
(Methotrexate in CSF)	↑	CBZ, PB	Rogers, 2013
Nimustine	↓	EIA	Weller et al., 2012
Paclitaxel	↓	EIA	Weller et al., 2012
	↑	VPA	Cotterman-Hart, 2015
Pemetrexed	↓	EIA	Weller et al., 2012
Prednisone	↓	PB,PHT	Tibussek et al., 2006
Procarbazine	-	EIA	Rogers, 2013
	↓	CBZ, PB, PHT	Ruggiero et al., 2010; Cotterman-Hart, 2015
SN-38 (active metabolite of Irinotecan)	↑ (glucuronidation of SN-38 inhibited)	VPA	Wen et al., 2006
Sorafenib	↓	EIA	Weller et al., 2012
Tamoxifen	-	CBZ, PHT	Ruggiero et al., 2010
	↓	PB	Ruggiero et al., 2010
Temozolomide	-	CBZ, EIA, PB, PHT	Weller et al., 2012; Rogers, 2013
	(↑) (VPA reduces the clearance by 5%)	VPA	Weller et al., 2012
	↓	CBZ, PHT	Cotterman-Hart, 2015
Temsirolimus	↓	EIA	Weller et al., 2012
Teniposide	↓	CBZ, PB, PHT	Ruggiero et al., 2010

Table 2. Continued

Affected CTD/CS (in alphabetical order)	CTD/CS serum concentration	Interfering AED	References
Thiotepa	↓	EIA	Weller et al., 2012
Tipifarnib	↓	EIA	Wen et al., 2006
Topotecan	↓	EIA	Weller et al., 2012
Valtinib	↓	EIA	Bruna et al., 2013
Vemurafenib	↓	EIA	Weller et al., 2012
Vincristine	↓	EIA	Weller et al., 2012; Villika et al., 1999
Vinorelbine	↓	EIA	Weller et al., 2012

CBZ – carbamazepine; EIA – enzyme-inducing AED; LEV – levetiracetam; PB – phenobarbital; PHT – phenytoin; VPA – valproic acid; ↑ – increase of serum concentration; ↓ – decrease of serum concentration; - – no change of serum concentration; icon in brackets – influence weak or equivocal

Table 3. Outcome of antiepileptic drug (AED) – chemotherapeutic drug (CTD)/corticosteroids (CS) interactions

Affected AED	AED serum concentration	Interfering CTD/CS	References
Carbamazepine	↓	Cisplatin, Doxorubicin, Methotrexate, Vincristin	Van Breemen et al., 2007; Rudà et al., 2012
Phenytoin	↓	Bleomycin	Neher, 2008a
	↑	Capecitabine	Tanaka et al., 2014
	↓	Carboplatin	Neher, 2008a
	↓	Carmustine	Wen et al., 2006
	↓	Cisplatin	Van Breemen et al., 2007
	↓ / (↑)	Corticosteroids	Vecht et al., 2003
	↓	Dacarbazine	Neher, 2008a
	↓ / ↑	Dexamethasone	Neher, 2008a
	↓	Doxorubicin	Van Breemen et al., 2007
	↑	Erlotinib	Grenader et al., 2007
	↓	Etoposide	Bruna et al., 2013
	↑	Fluorouracil	Vecht et al., 2003
	↓	Methotrexate	Rudà et al., 2012
	↓	Nitrosoureas	Neher, 2008a
	↑	Tamoxifen	Vecht et al., 2003
	↑	Tegafur	Van Breemen et al., 2012
	↓	Vinblastine	Neher, 2008a
	↓	Vincristine	Van Breemen et al., 2007
Valproic acid	↓ / ↑	Cisplatin	Van Breemen et al., 2007, 2012
	↓	Doxorubicin	Van Breemen et al., 2007
	↓	Methotrexate	Van Breemen et al., 2007
	↑	Nitrosoureas	Van Breemen et al., 2012
	↑	Paclitaxel	Cotterman-Hart, 2015

↑ – increase of serum concentration; ↓ – decrease of serum concentration; - – no change of serum concentration; icon in brackets – influence weak or equivocal

Prophylactic AED treatment

Long-term AED prescription before or after surgery in seizure-free brain tumor patients (children and adults) is not recommended based on available evidence. This recommendation applies to both patients with primary brain tumors and patients with metastases (Glantz et al., 2000; Wells et al., 2012; Perucca, 2013; Wu et a., 2013; Sayegh et al., 2014; Kong et al., 2015). The recommendations of the American Academy of Neurology (Glantz et al., 2000) do not advise routine AED prophylaxis because of the lack of efficacy and the potential side effects of AEDs. The same guidelines state: "In patients with brain tumors who have not had a seizure, tapering and discontinuing AEDs after the first postoperative week is appropriate, particularly in those patients who are medically stable and who are experiencing AED-related side effects" (Glantz et al., 2000).

A limitation of the published literature is the predominant use of traditional AEDs (such as PHT, PB), which does not account for contemporary regimens. However, a recent analysis also concludes that prophylactic treatment does not improve seizure control in brain tumor patients (Sayegh et al., 2014). Possibly, selected groups of patients, such as those with cortically based hemorrhagic melanoma metastases, may benefit from prophylactic AED use (Goldlust et al., 2012).

Prognosis in brain tumors and duration of anticonvulsant treatment

The choice of an AED and the decision on the duration of AED treatment must take into account the prognosis of the brain tumor in the individual patient. Patients with benign tumors of WHO grade I such as the typical dysembryoplastic neuroepithelial tumor (DNET) or ganglioglioma have the chance of cure following resection alone; the majority of these patients (adults and children) reach long-term seizure relief (Blümcke, 2012; Lopez, 2015; Louis et al., 2007; Luyken et al., 2003). Patients with WHO grade II tumors typically survive more than 5 years and those with grade III tumors survive 2–3 years; the prognosis of patients with WHO grade IV tumors depends largely upon whether effective treatment regimens are available (Louis et al., 2007). For primary glioblastoms the median survival is 8–18 months (Maschio, 2012; Paulus and Hasselblatt, 2012); epileptic seizures at presentation independently predicted longer survival (Toledo et al., 2015). In the study of Hall et al. (2000) the overall 2-year survival rate for patients with metastatic brain tumors (all tumor types) was 8.1%.

Due to the different prognosis of brain tumors and because of the absence of studies with large, homogeneous groups, the duration of treatment of tumor-related epilepsy cannot be standardized. In case of tumors with a short survival time such as glioblastoma it seems reasonable to maintain the AED treatment through the patient's lifetime (Brogna et al., 2012). In cases of metastases that have been successfully operated on, however, Rossetti and Stupp (2010) recommend a gradual tapering of the AED treatment after at least 3–6 months, as long as the patient has remained seizure-free.

In patients with a good chance of cure by tumor resection, AED discontinuation may be attempted after 2-years of seizure freedom, like in patients without brain tumors (Wells et al., 2012). In the retrospective study of Luyken et al. (2003) on patients with long-term epilepsy-associated tumors [LEAT, "epileptomas" (Japp et al., 2013)] one year after surgery 82% of the patients were seizure free; in 40% of the seizure-free patients the AEDs could be discontinued. In a recent Indian survey, 78 of 105 patients with LEATS (74.2%) were seizure-free and 45 (57.4%) were off medication (Radhakrishnan et al., 2016). In the retrospective study of Jongeling et al. (2015) who analysed 1910 tumor resections in 1640 patients, 28% of patients with low-grade gliomas who became seizure free after tumor resection were able to discontinue AEDs. On the other hand, none of the patients with high-grade gliomas were able to discontinue AEDs after resection.

Children with preoperative seizures, which resolve after complete resection, may be weaned within 3 months of initial surgery, if no postoperative seizures occur and the course is uncomplicated (Wells et al., 2012). Lopez (2015) recommended, however, weaning from medication in the absence of seizures for at the earliest 1 year following surgery. For children who go on to have epilepsy, weaning may be attempted after a 2-year period of seizure freedom, although the risk of recurrence is about 90% in children with symptomatic partial epilepsies compared with an average of 50% in children with other epilepsy syndromes, including idiopathic partial or generalized, cryptogenic partial, and unclassified seizures (Wells et al., 2012). Risk factors for seizure recurrence are an incomplete tumor resection, tumor relapse, more than one tumor resection, whole-brain radiation treatment, and a temporal tumor location (Das et al., 2012; Wells et al., 2012).

Before the reduction of AEDs, tumor progression must be excluded by a differentiated MRI (high-reso-

lution magnetic resonance imaging). On suspicion of tumor progression in a seizure free patient the AEDs should not be reduced.

In case of dose reduction, the electroencephalogram (EEG) is sometimes recommended as a decision criterion. However, the significance of the EEG in this situation is debatable (Krämer, 1999). In the retrospective study of Khan and Onar (2006), slow waves (focal or diffuse) and the presence of sharp waves and spike-wave complexes in the EEG did not correlate with seizure recurrence after AED withdrawal.

Information on the possible speed of AED tapering in seizure free patients is sparse in the literature. In the study of Khan and Onar (2006), in children with brain tumor-related epilepsy, AEDs were withdrawn over a 6–8-week period (median seizure-free period before AED withdrawal was 1.3 years (range, 0.1–11 years)).

The decision to withdraw AEDs should carefully consider the risk of seizure recurrence and especially the chance to regain seizure control. In the study of Khan and Onar (2006) seizures recurred in 27% of patients within a median time of 0.8 years after AED withdrawal. All compliant patients (15 of 17) regained seizure control. The comprehensive review of Schmidt and Löscher (2005) on seizure recurrence after discontinuation of AEDs in seizure-free patients and the seizure outcome of reinstituted treatment in patients with epilepsy – irrespective of the seizure etiology – found worse results. Reinstitution of AEDs after recurrence was not efficacious in approximately 20% of patients.

Impact of brain tumor surgery, radiotherapy, chemotherapy and Tumor Treating Fields (TTF) on tumor-related epilepsy

In assessing the efficacy of an AED in a patient with tumor-related epilepsy, the impact of surgery, radiotherapy, chemotherapy and the recently developed treatment with electric fields (TTF; Stupp et al., 2012) on seizure frequency should also be considered. These methods may control otherwise pharmacoresistant seizures or prolong the duration of seizure freedom (Perucca, 2013; Vecht et al., 2014). Early surgical intervention showed a strong tendency to predict better seizure outcome (Brogna et al., 2008). Overall, excellent outcomes can be accomplished following aggressive initial tumor resection, re-resection in the context of recurrence, and epilepsy style operations in selected patients with a longer history of seizures (Tandon and Esquenazi, 2013).

Conventional cranial radiotherapy contributes to

the reduction of seizure frequency and severity in patients with low-grade and high-grade glioma-related epilepsy, reportedly being effective in decreasing seizure frequency by over 75% (Bruna et al., 2013). Stereotactic interstitial irradiation improves seizure control in 40–100% of unresectable low-grade gliomas; gamma-knife radiosurgery is active in mesiotemporal tumor-related epilepsy and in patients with gelastic or generalized seizures from hypothalamic hamartomas (Rudà et al., 2012). However, seizure frequency increases occasionally after surgery or radiotherapy, secondary to complications such as edema, bleeding or radiation necrosis (Brogna et al., 2008). The onset of seizures was the most common complication (41 (13%) of 316 cases) in patients with metastatic brain tumors treated by stereotactic radiosurgery (Williams et al., 2009).

Chemotherapy reduces seizure frequency in 50–65% of patients with 20–40% becoming seizure free (Rudà et al., 2012). As in the case of radiotherapy, it is also assumed in chemotherapy that the decrease in seizure frequency is caused by reducing tumor size (van Breemen et al., 2012); in addition, an independent anticonvulsant effect of chemotherapy is discussed. Especially, temozolomide had an important (Hu et al., 2011; Koekkoek et al., 2015) or significant (Sherman et al., 2011) anticonvulsant effect. An independent anticonvulsant effect is also discussed in the combination of procarbazine, CCNU (lomustine) and vincristine (PCV scheme; De Groot et al., 2012). The successful treatment of cerebral edema by steroids also reduces the risk of seizures (Reif et al., 2012); however, in individual cases prednisone and prednisolone should be able to increase the risk of seizures (Meyer and Fröscher, 2004).

Some CTDs can increase seizure frequency. Boehmerle et al. (2014) described this adverse event as "rare" (0–5%) with 5-fluorouracil, cisplatin and vincristine and as "occasionally occurring" (5–15%) with methotrexate and cytarabine. The possibility of a seizure rate increasing effect as adverse event has also been associated with the following CTDs: ifosfamide (Boehmerle et al., 2014), L-asparaginase, etoposide (intra-arterial), interleukin-2, busulphan (high-dose), BCNU, carboplatin (intra-arterial), cytosine-arabinoside (high-dose or intra-arterial) (Plotkin and Wen, 2003; Tibussek et al., 2006), bevacizumab, interferon-alpha, cyclophosphamide, anthracyclines, and nitrosureas (Avila and Graber, 2010).

The interim analysis of the treatment with electric fields (NovoTTF-100A system) revealed no change in seizure risk (Stupp et al., 2012, 2014).

DISCUSSION

Specific evidence-based guidelines for the treatment of brain tumor-related seizures are not available (van Breemen et al., 2012; Wallace et al., 2012). Numerous authors recommend LEV as drug of first choice in this situation (Lynam et al., 2007; Rudà et al., 2010; Rossetti and Stupp, 2010; Vecht and Wilms, 2010; Pruitt, 2011; Wallace et al., 2012; Perucca, 2013; Bruna et al., 2013; Vecht et al., 2014; Piotrowski and Blakeley, 2015; Ray et al., 2015); in children one has to consider whether monotherapy is approved. The preference of LEV results from its relatively favourable profile of adverse events combined with a satisfactory anticonvulsant activity. In addition, LEV can be up-titrated rapidly, can be administered parenterally and has no significant interactions (Neher, 2008a, b; Vecht and Wilms, 2012; Weller et al., 2012). The advantage of the lack of interactions is less important if chemotherapy is not required.

Another advantage of LEV might be an antitumoral effect. However, this effect is so far only based on laboratory experiments (Bobustuc et al., 2010; Perucca, 2013). As mentioned above, a pooled analysis of four randomized clinical trials did not validate an association of LEV and, surprisingly, of VPA use with improved survival, challenging the need for a full phase III trial exploring the repurposing of VPA and LEV as add-on to the standard of care treatment of newly diagnosed glioblastoma (Happold et al., 2015). The use of VPA as a preferred drug in patients with brain tumor-related epilepsy is also limited by the risk of an increased haematological toxicity if VPA is combined with different CTDs such as temozolomide, nitrosurea and cisplatin (Bourg et al., 2001; Oberndorfer et al., 2005; Weller et al., 2011).

The position of enzyme-inducing AEDs (especially CBZ, PHT, and PB) in the treatment of tumor-related epilepsy is still under discussion. Monotherapy with CBZ and PHT (besides the enzyme-inhibiting VPA) are recommended even in a recently published book as "initial management approach in most patients" with brain tumor-related epilepsy (Newton and Ray, 2015). However, in another chapter of the very same book, the authors (Maschio and Newton, 2015b) discouraged the use of CBZ, PHT, PB/PRM and (in the case of the concomitant use of several CTDs) VPA. Enzyme-inducing AEDs can reduce the serum concentration of numerous CTDs and thus decrease their efficacy. This could explain the shorter survival of glioblastoma patients receiving enzyme-inducing AEDs compared to patients treated with VPA (Oberndorfer et al., 2005; Weller et al., 2011, 2012). However, Jaeckle et al. (2009) found the opposite result: enzyme-inducing AEDs correlated with superior outcome of patients with glioblastoma. Future prospective randomized studies are needed to explain this contradiction. In this context, one must also take into account that the interaction between enzyme-inducing AEDs and several CTDs does not apply to all of these substances; currently the most important CTD, temozolomide, is not significantly affected, as reported by most authors (Weller et al., 2012; Rogers, 2013). Also, more generally, the problem of pharmacokinetic interactions should not be overestimated. In case of lack of efficacy of a non-enzyme-inducing AED, the use of an eventually effective enzyme-inducing AED is indicated. If pharmacokinetic interactions cannot be avoided, the best dosage can be determined by measuring the serum concentration of AED and CTD.

If neuropsychological side effects of AEDs are suspected, one has to keep in mind other possible causes of psychiatric disturbances in patients with brain tumors before changing the drug regimen. Psychiatric disturbances may be caused by the tumor itself including tumor progression, by chemotherapy and radiotherapy, and of course by the emotional distress (Hemmer, 1956; Pruitt, 2011; Reif et al., 2012; Weller et al., 2012; Spitzer, 2014). The diagnosis of epilepsy in a patient without a brain tumor already implicates an important change in his/her concept of quality of life with negative psychological impact by losing control of one's body and the surrounding environment during seizure activity and by the rejection and marginalization of persons with epilepsy that is still prevalent today. These factors become even heavier to bear in patients who must confront both pathologies: epilepsy and the presence of a brain tumor (Maschio and Newton, 2015b).

No evidence supports AED prophylaxis with older AEDs in patients with brain tumors and no history of seizures, regardless of neoplastic type (Glantz et al., 2000; Sirven et al., 2004; Sayegh et al., 2014). However, prophylactic use of AEDs is still relatively common and this is particularly true for prophylaxis of preoperative seizures (Rossetti and Stupp, 2010; Rudà et al., 2010; de Oliveira et al., 2014; Sayegh et al., 2014). Future prospective studies with contemporary drug regimens are necessary. Perhaps at least high-risk patients can benefit from AED prophylaxis (Sayegh et al., 2014); in the study of Wychowski et al. (2013) AED prophy-

laxis did not reduce tumor-related epilepsy but prevented status epilepticus in patients with glioblastoma.

In patients with brain tumors and a first unequivocal seizure, AED therapy should be initiated; the risk of seizure recurrence in patients with structural brain pathology (Ruggiero et al., 2010; Perucca, 2013) exceeds the risk of adverse events by an AED. The duration of the treatment depends on the prognosis of the underlying brain tumor. In case of cure by tumor resection, AEDs can be withdrawn as in patients without structural brain lesion (Luyken et al., 2003, Wells et al., 2012). No studies have systematically examined yet AED withdrawal in tumor-related epilepsy (Bauer et al., 2014). Unfortunately the risk of recurrence is relatively high (Schmidt and Löscher, 2005; Reif et al., 2012; Wells et al., 2012). If the AED t treatment is well tolerated, we therefore recommend that it should be continued for more than 2–3 years. In case of the foreseeable risk of tumor recurrence or tumor progression, we recommend continuing the AEDs even in seizure free patients; this is particularly true with regard to the fitness to drive. If seizures recur or are pharmacoresistant, one has to consider the possibility of seizure increase by the oncologic therapy next to the question of tumor recurrence.

CONCLUSION

At present, levetiracetam is the preferred drug in brain tumor-related epilepsy; especially when interactions should be avoided. In the future, we hope to get more targeted drugs against this disorder by uncovering its pathogenesis.

ACKNOWLEDGEMENT

CONFLICT OF INTEREST DISCLOSURE

The authors declared no conflict of interests.

REFERENCES

Avila E.K., Graber J.: *Seizures and epilepsy in cancer patients.* Curr. Neurol. Neurosci. Rep., 2010, 10: 60–67.

Bain E., Birhiray R.E., Reeves D.: *Drug-drug interaction between methotrexate and levetiracetam resulting in delayed methotrexate elimination.* Ann. Pharmacother., 2014, 48: 292–296.

Bauer R., Ortler M., Seiz-Rosenhagen M. et al.: *Treatment of epileptic seizures in brain tumors: a critical review.* Neurosurg. Rev., 2014, 37: 381–388.

Baxter K., Preston C.L. (eds): *Stockley's Drug Interactions.* 10th ed., Pharmaceutical Press, London–Chicago 2013.

Berg A.T., Berkovic S.F., Brodie M.J., Buchhalter J., Cross J.H., van Emde Boas W. et al.: *Revised terminology and concepts for organization of seizures and epilepsies: Report of the ILAE commission on classification and terminology, 2005–2009.* Epilepsia, 2010, 51: 676–685.

Blümcke I.: *Epilepsy-associated brain tumors.* In: H. Stefan and W.H. Theodore (eds), *Handbook of clinical neurology. Epilepsy.* part II. 3rd series, Elsevier, Amsterdam 2012, vol. 108: 559–568.

Bobustuc G.C., Baker C.H., Limaye A., Jenkins W.D., Pearl G., Avgeropoulos N.G. et al.: *Levetiracetam enhances p53-mediated MGMT inhibition and sensitizes glioblastoma cells to temozolomide.* Neuro-Oncol., 2010, 12: 917–927.

Boehling N.S., Sulman E.P.: *Outcomes of patients with glioblastoma receiving concurrent radiation treatment and antiepileptic agents with histone deacetylase inhibitor activity.* Cancer Network (http://www.cancernetwork.com), April 30, 2015.

Boehmerle W., Huehnchen P., Endres M.: *Neurologische Nebenwirkungen von Zytostatika.* Akt. Neurol., 2014, 41: 21–34.

Bourg V., Lebrun C., Chichmanian R.M., Thomas P., Frenay M.: *Nitrosurea-cisplatin based chemotherapy associated with valproate: increase of haematologic toxicity.* Ann. Oncol., 2001, 12: 217–219.

Brackenbury W.J., Nelson M., Yang M., Dowle A.A., Thomas J.R. et al.: *Targeting voltage-gated sodium channels with the antiepileptic drug phenytoin inhibits breast tumor growth and metastasis.* Cancer Res., 2015, 75 (9 Suppl. S), P6-03-10.

Brogna Ch, Robles G., Duffau H.: *Brain tumors and epilepsy.* Expert Rev. Neurother., 2008, 8: 941–955.

Bruna J., Miro J., Roser V.: *Epilepsy in glioblastoma patients: basic mechanisms and current problems in treatment.* Expert Rev. Clin. Pharmacol., 2013, 6: 333–344.

Buckingham S.C., Campbell S.L., Haas B.R., Montana V., Robel St., Ogunrinu T. et al.: *Glutamate release by primary brain tumors induces epileptic activity.* Nat. Med., 2011, 17: 1269–1274.

Činčárová L., Zdráhal Z., Fajkus J.: *New perspectives of valproic acid in clinical practice.* Expert Opin. Investig. Drugs, 2013, 22: 1435–1447.

Cotterman-Hart S.: *Antiepileptic drugs: First generation.* In: H.B. Newton and M. Maschio (eds), *Epilepsy and brain tumors.* Elsevier, Amsterdam 2015, 159–169.

Das R.R., Artsy E., Hurwitz S., Wen P.Y., Black P., Golby A. et al.: *Outcomes after discontinuation of antiepileptic drugs after surgery in patients with low grade brain tumors and meningiomas.* J. Neurooncol., 2012, 107: 565–570.

De Curtis M., Librizzi L., Avanzini G.: *Mechanisms of focal epileptogenesis.* In: H.B. Newton and M. Maschio (eds), *Epilepsy and brain tumors.* Elsevier, Amsterdam 2015, 101–109.

De Groot M., Reijneveld J.C., Aronica E., Heimans J.J.: *Epilepsy in patients with a brain tumor: focal epilepsy requires forced treatment.* Brain, 2012, 135: 1002–1016.

de Oliveira J.A., Santana I.A., Caires I.Q.S., Caires-Lima R., Miranda V.C., Protásio B.M. et al.: *Antiepileptic drug prophylaxis in primary brain tumor patients: is current practice in agreement to the consensus?* J. Neurooncol., 2014, 120: 399–403.

Diener H.C., Weimar C., Berlit P., Deuschl G., Elger C., Gold R. et al. (eds.): *Leitlinien für Diagnostik und Therapie in der Neurologie.* Kap. 76, Gliome. 5. Aufl., Thieme, Stuttgart, 2012, 922–938.

Englot D.J., Magill S.T., Han S.J., Chang E.F., Berger M.S., McDermott M.W.: *Seizures in supratentorial meningioma: a systematic review and meta-analysis.* J. Neurosurg., 2015, 4: 1–10.

Fröscher W.: *Drug resistant epilepsy.* Epileptologia, 2012, 20: 17–23.

Fröscher W., Kirschstein T., Rösche J.: *Antiepileptikabehandlung bei Hirntumor-bedingten epileptischen Anfällen (Anticonvulsant therapy for brain tumor-related epilepsy).* Fortschr. Neurol. Psychiat., 2014, 82: 678–690.

Gefroh-Grimes H.A., Gidal B.E.: *Antiepileptic drugs in patients with malignant brain tumor: beyond seizures and pharmacokinetics.* Acta Neurol. Scand., 2016, 133: 4–16.

Gerstner T., Teich M., Bell N., Longin E., Dempfle C.-E., Brand J. et al.: *Valproate-associated coagulopathies are frequent and variable in children.* Epilepsia, 2006, 47: 1136–1143.

Glantz M.J., Cole B.F., Forsyth P.A., Recht L.D., Wen P.Y., Chamberlain M.C. et al.: *Practice parameter: anticonvulsant prophylaxis in patients with newly diagnosed brain tumors.* Neurology, 2000, 54: 1886–1893.

Glauser T., Ben-Menachem E., Bourgeois B., Caan A.A., Guerreiro C., Kälviäinen R. et al.: *Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes.* Epilepsia, 2013, 54: 551–563.

Goldlust S.A., Hsu M., Lassman A.B., Panageas K.S., Avila E.K.: *Seizure prophylaxis and melanoma brain metastases.* J. Neurooncol., 2012; 108: 109–114.

Goonawardena J., Marshman L.A., Drummond K.J.: *Brain tumor-associated status epilepticus.* J. Clin. Neurosci., 2015, 22: 29–34.

Grenader T., Gipps M., Shavit L., Gabizon A.: *Significant drug interaction: Phenytoin toxicity due to erlotinib.* Lung cancer, 2007, 57: 404–406.

Grossman S.A., Ye X., Chamberlain M., Mikkelsen T., Batch-

elor T., Desideri S. et al.: *Talampanel with standard radiation and temozolomide in patients with newly diagnosed glioblastoma: a multicenter phase II trial.* J. Clin. Oncol., 2009, 27: 4155–4161.

Guerrini R., Rosati A., Giordano F., Genitori L., Barbara C.: *The medical and surgical treatment of tumoral seizures: Current and future perspectives.* Epilepsia, 2013, 54 (Suppl. 9): 84–90.

Guthrie G.D., Eljamel S.: *Impact of particular antiepileptic drugs on the survival of patients with glioblastoma multiforme.* J. Neurosurg., 2013, 118: 859–865.

Hall W.A., Djalilian H.R., Nussbaum E.S., Cho K.H.: *Long-term survival with metastatic cancer to the brain.* Med. Oncol., 2000, 17: 279–286.

Happold C., Gorlia T., Chinot O., Gilbert M., Nabors B., Wick W. et al.: *Does valproic acid improve survival in glioblastoma? A meta-analysis of randomized trials in newly diagnosed glioblastoma.* Neuro-Oncology, 2015, 17: v10–v17. doi:10.1093/neuonc/nov205.10.

Hemmer R.: *Die Verkennung der Hirntumoren infolge psychischer Veränderungen.* Dtsch. Med. Wschr., 1956, 81: 1305–1308.

Hildebrand J., Lecaille C., Perennes J., Delattre J.-Y.: *Epileptic seizures during follow-up of patients treated for primary brain tumors.* Neurology, 2005, 65: 212–215.

Hu A., Xu Z., Kim R.Y., Nguyen A., Lee J.W., Kesari S.: *Seizure control: A secondary benefit of chemotherapeutic temozolomide in brain cancer patients.* Epilepsy Res., 2011, 95: 270–272.

Ikeda H., Murakami T., Takano M., Usui T., Kihira K.: *Pharmacokinetic interaction on valproic acid and recurrence of epileptic seizures during chemotherapy in an epileptic patient.* Br. J. Clin. Pharmacol., 2005, 59: 593–597.

Iwamoto F.M., Kreisl T.N., Kim L., Duic J.P., Butman J.A., Albert P.S. et al.: *Phase 2 trial of talampanel, a glutamate receptor inhibitor, for adults with recurrent malignant gliomas.* Cancer, 2010, 116: 1776–1782.

Jaeckle K.A., Ballman K., Furth A., Buckner J.C.: *Correlation of enzyme-inducing anticonvulsant use with outcome of patients with glioblastoma.* Neurology, 2009, 73: 1207–1213.

Japp A., Gielen G.H., Becker A.J.: *Recent aspects of classification and epidemiology of epilepsy-associated tumors.* Epilepsia, 2013, 54 (Suppl. 9): 5–11.

Jongeling A.C., Canoll P.D., Schevon C., Srinivasan S.: *Seizure outcomes after glioma resection.* Epilepsy Currents. Conference: 68th Annual Meeting of the American Epilepsy Society, AES 2014 Seattle, WA United States. Conference Publication: 15 (pp 503–504), 2015.

Kerkhof M., Dielemans J.C., van Breemen M.S., Zwinkels H., Walchenbach R., Taphoorn M. et al.: *Effect of valproic acid on seizure control and on survival in patients with glioblastoma multiforme.* Neuro-Oncol., 2013, 15: 961–967.

Kerkhof M. and Vecht Ch.J.: *Seizure characteristics and prognostic factors of gliomas.* Epilepsia, 2013, 54 (Suppl. 9): 12–17.

Kerrigan S.: *Drug treatment of epilepsy in people with brain tumors.* Eur. J. Oncol., 2010, 4: 9–10.

Khan R.B. and Omar A.: *Seizure recurrence and risk factors after antiepileptic drug withdrawal in children with brain tumors.* Epilepsia, 2006, 47: 375–379.

Kim L.G., Johnson T.L., Marson A.G., Chadwick D.W.: *Prediction of risk of seizure recurrence after a single seizure and early epilepsy: further results from the MESS trial.* Lancet Neurol., 2006, 5: 317–322.

Kim Y.H., Kim T., Joo J.D., Han J.H., Kim Y.J., Yun C.H. et al.: *Survival benefit of levetiracetam in patients treated with concomitant chemoradiotherapy and adjuvant chemotherapy with temozolomide for glioblastoma multiforme.* Cancer, 2015, 121: 2926–2932.

Kirschstein T., Köhling R.: *Animal models of tumor-associated epilepsy.* J. Neurosci. Methods, 2015, Jun 16. pii: S0165-0270(15)00225-3. doi: 10.1016/j.jneumeth.2015.06.008. [Epub ahead of print].

Koekkoek J.A.F., Dirven L., Heimans J.J., Postma T.J., Vos M.J., Reijneveld J.C. et al.: *Seizure reduction in a low-grade glioma: More than a beneficial side effect of temozolomide.* J. Neurol. Neurosurg. Psychiatry, 2015, 6: 366–373.

Kong X., Guan J., Yang Y., Li Y., Ma W., Wang R.: *A meta-analysis: Do prophylactic antiepileptic drugs in patients with brain tumors decrease the incidence of seizures?* Clin. Neurol. Neurosurg., 2015, 134: 98–103.

Krämer G.: *Tumorbedingte epileptische Anfälle bei Erwachsenen.* Epilepsieblätter, 1999, 12: 2–6.

Krumholz A., Wiebe S., Gronseth, G.S., Gloss D.S., Sanchez A.M., Kabir A.A. et al.: *Evidence-based guideline: Management of an unprovoked first seizure in adults.* Neurology, 2015, 84: 1705–1713.

Liigant A., Haldre S., Öun A., Linnamägi Ü., Saar A., Asser T. et al.: *Seizure disorders in patients with brain tumors.* Europ. Neurol., 2001, 45: 46–51.

Liubinas S.V., O'Brien T.J., Moffat B.M., Drummond K.J., Morokoff A.P., Kaye A.H.: *Tumor associated epilepsy and glutamate excitotoxicity in patients with gliomas.* J. Clin. Neurosci., 2014, 21: 899–908.

Lopez J.: *Brain-tumor-related epilepsy in children.* In: H.B. Newton and M. Maschio (eds.), *Epilepsy and brain tumors.* Elsevier, Amsterdam 2015, 65–99.

Louis D.N., Ohgaki H., Wiestler O.D., Cavenee W.K., Burger P.C., Jouvet A. et al.: *The 2007 WHO classification of tumors of the central nervous system.* Acta Neuropathol., 2007, 114: 97–109.

Luyken C., Blümcke I., Fimmers R. Urbach H., Elger C.E.,

Wiestler O.D. et al.: *The spectrum of long-term epilepsy-associated tumors: long-term seizure and tumor outcome and neurosurgical aspects.* Epilepsia, 2003, 44: 822–830.

Lynam L.M., Lyons M.K., Drazkowski J.F., Sirven J.I., Noe K.H., Zimmerman R.S. et al.: *Frequency of seizures in patients with newly diagnosed brain tumors: a retrospective review.* Clin. Neurol. Neurosurg., 2007, 109: 634–638.

Mamon H.J., Wen P.Y., Burns A.C., Loeffler J.S.: *Allergic skin reactions to anticonvulsant medications in patients receiving cranial radiation therapy.* Epilepsia, 1999, 40: 341–344.

Maschio M.: *Brain tumor-related epilepsy.* Curr. Neuropharmacol., 2012, 10: 124–133.

Maschio M., Dinapoli L., Sperati F., Fabi A., Pace A., Vidiri A. et al.: *Oxcarbazepine monotherapy in patients with brain tumor-related epilepsy. Open-label pilot study for assessing the efficacy, tolerability and impact on quality of life.* J. Neuro-Oncol., 2012, 106: 651–656.

Maschio M., Newton H.B.: *Brain tumor-related epilepsy: Introduction and overview.* In: H.B. Newton and M. Maschio (eds.), *Epilepsy and brain tumors.* Elsevier, Amsterdam 2015a, 1–9.

Maschio M., Newton H.B.: *Clinical approach to brain tumor-related epilepsy.* In: H.B. Newton and M. Maschio (eds.), *Epilepsy and brain tumors.* Elsevier, Amsterdam etc., 2015b, 207–223.

Meyer A., Fröscher W.: *Anfallssteigernde Medikamente und Drogen.* In: W. Fröscher, F. Vassella, A. Hufnagel (eds.), *Die Epilepsien.* 2. Aufl., Schattauer, Stuttgart–New York 2004, 523–541.

Moots P., Marciunas R., Eisert D., Parker R.A., Laporte K., Abou-Khalil B.: *The course of seizure disorders in patients with malignant gliomas.* Arch. Neurol., 1995, 52: 717–724.

Motl S., Zhuang Y., Waters Ch. M., Clinton St.: *Pharmacokinetic considerations on the treatment of CNS tumors.* Clin. Pharmacokinet., 2006, 45: 871–903.

Neher K.-D.: *Interaktionen: Beeinflussung der Serumkonzentration von Antiepileptika durch andere Medikamente.* In: Fröscher W., Blankenhorn V., May Th. W., Neher K.-D., Rambeck B., Steinhoff B.J.: *Pharmakotherapie der Epilepsien.* 4. Aufl., Schattauer, Stuttgart–New York, 2008a, 135–177.

Neher K.-D. Interaktionen: *Beeinflussung der Serumkonzentration von Nicht-Antiepileptika durch Antiepileptika.* In: W. Fröscher, V. Blankenhorn, Th.W. May, K.-D. Neher, B. Rambeck, B.J. Steinhoff: *Pharmakotherapie der Epilepsien.* 4. Aufl., Schattauer, Stuttgart–New York, 2008b, 178–196.

Newton H.B., Ray L.: *Supportive care of brain tumor patients.* In: H.B. Newton and M. Maschio (eds), *Epilepsy and brain tumors.* Elsevier, Amsterdam 2015, 45–63.

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, 72: 255–260.

Pallud J., Capelle L., Haberfeld G.: *Tumoral epileptogenicity: how does it happen?* Epilepsia, 2013, 54 (Suppl. 9): 30–34.

Patsalos P.N.: *Drug interactions with the newer antiepileptic drugs (AEDs) – Part 2: Pharmacokinetic and pharmacodynamic interactions between AEDs and drugs used to treat non-epilepsy disorders.* Clin. Pharmacokinet., 2013, 52: 1045–1061.

Paulus W., Hasselblatt M.: *Tumoren.* In: G. Klöppel, H.H. Kreipe, W. Remmele (eds.), *Pathologie*, Bd. Neuropathologie. 3. Aufl. Springer, Berlin–Heidelberg, 2012, 481–549.

Perucca E.: *Optimizing antiepileptic drug treatment in tumoral epilepsy.* Epilepsia, 2013, 54 (Suppl. 9): 97–104.

Piotrowski A.F., Blakeley J.: *Clinical management of seizures in patients with low-grade glioma.* Semin. Radiat. Oncol., 2015, 25: 219–224.

Plotkin S.R., Wen P.Y.: *Neurologic complications of cancer therapy.* Neurol. Clin., 2003, 21: 279–318.

Prayson R.A.: *Brain tumors in adults with medically intractable epilepsy.* Am. J. Clin. Pathol., 2011, 136: 557–563.

Pruitt A.A.: *Medical management of patients with brain tumors.* Curr. Treat. Options Neurol., 2011, 13: 413–426.

Radhakrishnan A., Abraham M., Vilanilam G., Menon R., Menon D., Kumar H. et al.: *Surgery for "Long-term epilepsy associated tumors (LEATs)": Seizure outcome and its predictors.* Clin. Neurol. Neurosurg., 2016, 141: 98–105

Rambeck B. and May Th.W.: *Enzyminduktion in der Leber durch Antiepileptika.* In: W. Fröscher, V. Blankenhorn, Th.W. May, K.-D. Neher, B. Rambeck, B.J. Steinhoff: *Pharmakotherapie der Epilepsien.* 4. Aufl., Schattauer, Stuttgart–New York 2008, 128–130.

Ray L., Maschio M., Newton H.B.: *Antiepileptic drugs and brain tumor patients.* In: H.B. Newton and M. Maschio (eds), *Epilepsy and brain tumors.* Elsevier, Amsterdam 2015, 195–205.

Reddy J.P., Dawood S., Mitchell M., Debeb B.G., Bloom E., Gonzales-Anqulo A.M. et al.: *Antiepileptic drug use improves overall survival in breast cancer patients with brain metastases in the setting of whole brain radiotherapy.* Radiother. Oncol., 2015, 117: 308–314.

Reif P.S., Strik H., Rosenow F.: *Therapeutisches Management bei Patienten mit tumorassoziierter Epilepsie – Pharmakotherapie.* Z. Epileptol., 2012, 25: 104–113.

Relling M.V., Pui C.-H., Sandlund J.T., Rivera G.K., Hancock M.L., Boyett J.M. et al.: *Adverse effect of anticonvulsants on efficacy of chemotherapy for acute lymphoblastic leukaemia.* Lancet, 2000, 356: 285–290.

Rösche J., Piek J., Hildebrandt G., Grossmann A., Kirschstein T., Benecke R.: *Perampanel in the treatment of a patient with glioblastoma multiforme without IDH 1 mutation and without MGMT promotor methylation.* Fortschr. Neurol. Psychiat., 2015, 83: 286–289.

Rogers L.R.: *Chemotherapy and immunotherapy of brain tumors: What the epileptologist must know.* Epilepsia, 2013, 54 (Suppl. 9): 105–108.

Rossetti A.O., Stupp R.: *Epilepsy in brain tumor patients.* Curr. Opin. Neurol., 2010, 23: 603–609.

Rudà R., Bello L., Duffau H., Soffietti R.: *Seizures in low-grade gliomas: natural history, pathogenesis, and outcome after treatments.* Neuro-Oncol., 2012, 14: 55–64.

Rudà R., Trevisan E., Sofietti R.: *Epilepsy and brain tumors.* Curr. Opin. Oncol., 2010, 22: 611–620.

Ruggiero A., Rizzo D., Mastrangelo St., Battaglia D., Attinà G., Riccardi R. et al.: *Interactions between antiepileptic and chemotherapeutic drugs in children with brain tumors: Is it time to change treatment?* Pediatr. Blood Cancer, 2010, 54: 193–198.

Salmaggi A., Granata T., Rigamonti A.: *Pathophysiology of brain tumor-related epilepsy.* In: H.B. Newton and M. Maschio (eds.), *Epilepsy and brain tumors.* Elsevier, Amsterdam 2015, 111–118.

Sayegh E.T., Fakurnejad S., Oh T., Bloch O., Parsa A.T.: *Anticonvulsant prophylaxis for brain tumor surgery: determining the current best available evidence.* J. Neurosurg., 2014, 121: 1139–1147.

Schiff D., Lee E.Q., Nayak L., Norden A.D., Reardon D.A., Wen P.: *Medical management of brain tumors and the sequelae of treatment.* Neuro-Oncol., 2015, 17: 488–504.

Schmidt D., Löscher W.: *Uncontrolled epilepsy following discontinuation of antiepileptic drugs in seizure-free patients: a review of current clinical experience.* Acta Neurol. Scand., 2005, 111: 291–300.

Seeck M.: *Surgical treatment of tumoral temporal-lobe epilepsy.* Lancet Neurol., 2003, 2: 722–723.

Sherman J.H., Moldovan K., Yeoh H.K., Starke R.M., Pouratian N., Shaffrey M.E. et al.: *Impact of temozolomide chemotherapy on seizure frequency in patients with low-grade gliomas.* J. Neurosurg., 2011, 114: 1617–1621.

Sirven J.I., Wingerchuk D.M., Drazkowski J.F., Lyons M.K., Zimmerman R.S.: *Seizure prophylaxis in patients with brain tumors: A meta-analysis.* Mayo Clin. Proc., 2004, 79: 1489–1494.

Spitzer M.: *Chemo-Gehirn – Nebenwirkungen von Chemotherapie in Erleben, Denken, Fühlen und Handeln.* Nervenheilkunde, 2014, 33: 319–324.

Stefan H.: *Hirntumoren und Epilepsien.* Z. Epileptol., 2009, 22: 65–71.

Stupp R., Mason, W.P., van den Bent M.J., Weller M., Fisher B., Taphoorn M.J. et al.: *Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma.* N. Engl. J. Med., 2005, 352: 987–996.

Stupp R., Wong E.T., Kanner A.A., Steinberg D., Engelhard

H., Heidecke V. et al.: *NovoTTF-100A versus physician's choice chemotherapy in recurrent glioblastoma: A randomised phase III trial of a novel treatment modality*. Eur. J. Cancer., 2012, 48: 2192–2202.

Stupp R., Wong E., Scott Ch., Taillibert S., Kanner A., Kesari S. et al.: *Interim analysis of the EF-14 trial: A prospective, multi-center trial of NovoTTF-100A together with temozolomide compared to temozolomide alone in patients with newly diagnosed GBM*. Neuro-Oncol., 2014, 16 (Suppl. 5): v1. Doi: 10.1093/neuronc/nou265.40.

Swisher Ch.B., Doreswamy M., Gingrich K.J., Vredenburgh J.J., Kolls B.J.: *Phenytoin, levetiracetam, and pregabalin in the acute management of refractory status epilepticus in patients with brain tumors*. Neurocrit. Care, 2012, 16: 109–113.

Tanaka H., Jotoku H., Takasaki M., Ibayashi Y., Watanabe K., Takahashi M.: *Effect of capecitabine therapy on the blood levels of antiepileptic drugs – report of two cases*. Gan To Kagaku Ryoho., 2014, 41: 527–530.

Tandon N. and Esquenazi Y.: *Resection strategies in tumoral epilepsy: Is a lesionectomy enough?* Epilepsia, 2013, 54 (Suppl. 9): 72–78.

Tibussek D., Distelmaier F., Schönberger S., Göbel U., Mayatepek E.: *Antiepileptic treatment in paediatric oncology – an interdisciplinary challenge*. Klin. Pädiatr., 2006, 218: 340–349.

Tinchon A., Oberndorfer S., Marosi C., Gleiss A., Geroldinger A., Sax C.: *Haematological toxicity of valproic acid compared to levetiracetam in patients with glioblastoma multiforme undergoing concomitant radiochemotherapy: a retrospective cohort study*. J. Neurol., 2015, 262: 179–186.

Toledo M., Sarria-Estrada S., Quintana M., Maldonado X., Martinez-Ricarte F., Rodon J. et al.: *Prognostic implications of epilepsy in glioblastomas*. Clin. Neurol. Neurosurg., 2015, 139: 166–171.

Van Breemen M.S.M., Wilms E.B., Vecht Ch. J.: *Epilepsy in patients with brain tumors: epidemiology, mechanism and management*. Lancet Neurol., 2007, 6: 421–430.

Van Breemen M.S.M., Wilms E.B., Vecht C.J.: *Seizure control in brain tumors*. In: W. Grisold and R. Soffietti (eds.), *Handbook of clinical neurology. Neuro-oncology.* Elsevier, Amsterdam 2012, vol. 104 (3rd series), 381–389.

Van Breemen M.S.M., Rijsman R.M., Taphoorn M.J.B., Walchenbach R., Zwinkels H., Vecht J.C.: *Efficacy of anti-epileptic drugs in patients with gliomas and seizures*. J. Neurol., 2009, 256: 1519–1526.

Vecht C.J., Kerkhof M., Duran-Pena A.: *Seizure prognosis in brain tumors: new insights and evidence-based management*. Oncologist, 2014, 19: 751–759.

Vecht Ch.J., and van Breemen M.: *Optimizing therapy of seizures in patients with brain tumors*. Neurology, 2006, 67 (Suppl. 4): S10–S13.

Vecht C.J., Wagner G.L., Wilms E.B.: *Interactions between antiepileptic and chemotherapeutic drugs*. Lancet Neurol., 2003, 2: 404–409.

Vecht Ch.J. and Wilms E.B.: *Seizures in low- and high-grade gliomas: current management and future outlook*. Expert Rev. Anticancer Ther., 2010, 10: 663–669.

Villikka K., Kivistö K.T., Mäenpää H., Joensuu H., Neuvonen P.J.: *Cytochrome P450-inducing antiepileptics increase the clearance of vincristine in patients with brain tumors*. Clin. Pharmacol. Ther., 1999, 66: 589–593.

Wallace E.M., O'Reilly M., Twomey M.: *A review of the use of antiepileptic drugs in high-grade central nervous system tumors*. Am. J. Hosp. Palliat. Care, 2012, 29: 618–621.

Weller M., Gorlia T., Cairncross J.G., van den Bent M.J., Mason W., Belanger K. et al.: *Prolonged survival with valproic acid use in the EORTC/NCIC temozolomide trial for glioblastoma*. Neurology, 2011, 77: 1156–1164.

Weller M., Stupp R., Wick W.: *Epilepsy meets cancer: when, why, and what to do about it?* Lancet Oncol., 2012, 13: e375–e382.

Wells E.M., Gaillard W.D., Packer R.J.: *Pediatric brain tumors and epilepsy*. Semin. Pediatr. Neurol., 2012, 19: 3–8.

Wen P.Y., Schiff D., Kesari S., Drappatz J., Gigas D.C., Doherty L. et al.: *Medical management of patients with brain tumors*. J. Neurooncol., 2006, 80: 313–332.

Williams B.J., Suki D., Fox B.D., Pelloski C.E., Maldaun M.V., Sawaya R.E. et al.: *Stereotactic radiosurgery for metastatic brain tumors: a comprehensive review of complications*. J. Neurosurg., 2009, 111: 439–448.

Wu A.S., Trinh V.T., Suki D., Graham S., Forman A., Weinberg J.S. et al.: *A prospective randomized trial of perioperative seizure prophylaxis in patients with intraparenchymal brain tumors*. J. Neurosurg., 2013, 118: 873–883.

Wychowski T., Wang H., Buniak L., Henry J.C., Mohile N. et al.: *Considerations in prophylaxis for tumor-associated epilepsy: prevention of status epilepticus and tolerability of newer generation AEDs*. Clin. Neurol. Neurosurg., 2013, 115: 2365–2369.