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## **Epilepsy meets cancer: when, why, and what to do about it?**

Weller, M ; Stupp, R ; Wick, W

**Abstract:** The lifetime risk of having epileptic seizures is profoundly increased in patients with cancer: about 20% of all patients with systemic cancer may develop brain metastases. These patients and those with primary brain tumours have a lifetime risk of epilepsy of 20-80%. Moreover, exposure to chemotherapy or radiotherapy to the brain, cancer-related metabolic disturbances, stroke, and infection can provoke seizures. The management of epilepsy in patients with cancer includes diagnosis and treatment of the underlying cerebral pathological changes, secondary prophylaxis with antiepileptic drugs, and limiting of the effect of epilepsy and its treatment on the efficacy and tolerability of anticancer treatments, cognitive function, and quality of life. Because of the concern of drug-drug interactions, the pharmacological approach to epilepsy requires a multidisciplinary approach, specifically in a setting of rapidly increasing choices of agents both to treat cancer and cancer-associated epilepsy.

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## **INVITED REVIEW**

### **Epilepsy meets cancer: when, why, and what to do about it?**

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## **Abbreviations**

AED, antiepileptic drugs; CNS, central nervous system; CRMP2, collapsin response mediator protein-2; EEG, electroencephalography; EI-AED, enzyme-inducing AED;

GABA,  $\gamma$ -aminobutyric acid; HDAC, histone deacetylase; MRI, magnetic resonance imaging; SV2A, synaptic vesicle 2A.

### **Contributor statement**

MW prepared the first draft of the manuscript. RS and WW reviewed and revised the manuscript. All authors approved the final version of the manuscript.

### **Search Strategy and Selection Criteria section**

Data for this review were identified by searches of PubMed. References from relevant articles using the search terms „epilepsy, brain tumor, review“, which revealed 881 citations, „epilepsy brain tumor chemotherapy“ (753 citations), „epilepsy, drug interactions, tumor“ (114 citations), „partial epilepsy randomized controlled trial“ (614 citations) and „prognostic factors epilepsy glioma“ (30 citations) were considered.

Articles were also identified through searches of the authors` own files. Only papers in English were reviewed. Data from controlled trials were regarded superior to data from uncontrolled series and the newest article was chosen, if multiple references to a similar topic were available. One abstract was included for novelty reasons. The final reference list was generated on the basis of originality and relevance to the broad scope of this review.

### **SUMMARY**

The lifetime risk of suffering epileptic seizures is profoundly increased in cancer patients: approximately 20% of all patients with systemic cancer may develop brain metastases. These patients as well as patients with primary brain tumors carry a lifetime risk of epilepsy in the range of 20-80%. Moreover, exposure to chemo- or radiotherapy to the brain as well as cancer-related metabolic disturbances, stroke and infection may provoke seizures. The management of epilepsy in cancer patients includes (i) diagnosis and treatment of the underlying cerebral pathology, (ii) secondary prophylaxis using antiepileptic drugs, and (iii) limiting the impact of epilepsy and its treatment on the efficacy and tolerability of anti-cancer treatments, cognitive function and quality of life. Because of the specific concern of drug drug interactions, the pharmacological approach to epilepsy requires a multidisciplinary approach, specifically in a setting of rapidly increasing choices of agents both to treat cancer and cancer-associated epilepsy.

## **Introduction**

Epileptic seizures are a potentially life-threatening symptom of structural or metabolic brain dysfunction. They are among the most common presenting features of patients with primary brain tumors. They are also a frequent complication in patients with disseminated cancer, mostly because of solid brain metastasis or leptomeningeal disease, but may also be caused by exposure to chemotherapy or radiotherapy to the brain, stroke, infection, or general disturbances e.g. of salt or liver metabolism associated with systemic cancer progression. This review focuses on the relevance of epilepsy for clinical oncology with specific consideration of the practical management of epilepsy in cancer patients as well as the increasingly complex interactions between the pharmacological approaches to cancer *versus* cancer-associated epilepsy. For specific aspects related to epilepsy and cancer, the reader is referred to contemporary review articles on epilepsy in primary brain tumor patients,<sup>1,2</sup> drug drug interactions<sup>3,4</sup> and drug-resistant epilepsy.<sup>5</sup>

## **Seizures and epilepsy: their nature and classification**

An *epileptic seizure* is most often a transient event caused by abnormal excessive or synchronous neuronal activity in the brain and can often, but not always, be recognized clinically by symptoms and signs of neurological dysfunction, most commonly altered consciousness and uncontrolled motor activity. As such, seizures can occur in the presence of a transitory precipitating factor, e.g., metabolic disturbance or exposure to a proconvulsive agent, including anti-cancer pharmaceuticals, and are then a symptom of an underlying condition. *Epilepsy*, in contrast, is a disorder of the brain characterized by

an enduring predisposition to generate epileptic seizures in the absence or presence of an underlying structural brain alteration. Accordingly, there are classifications of epileptic seizures as well as classifications of epileptic disorders.<sup>6</sup> The distinction of seizures and epilepsy remains difficult in the context of brain tumors. In general, seizures can, as a symptom, herald the development of any structural brain disease and are then also best conceived as being *symptomatic*, e.g., of a brain tumor. Some patients suffer a single seizure that leads to the diagnosis of a benign tumor that can be resected, and the patient will never suffer a seizure again. In other patients, tumors remain stable with or without specific oncological treatment, but seizure control becomes a life-long therapeutic challenge.

It is estimated that approximately 50 million people worldwide suffer from some form of epilepsy, with a lifetime risk of one in 10 individuals to experience at least one seizure. In infants, seizures more often reflect an epileptic disorder without identifiable morphological brain pathology whereas in adults and in particular in the elderly seizures are commonly the first symptom of an underlying structural brain alteration. Cancer patients typically suffer either tonic-clonic generalized seizures that may be secondary to a focal seizure when they have structural brain lesions, which is more common, or not when they are triggered, e.g., by metabolic disturbances or exposure to proconvulsive agents, including anti-cancer pharmaceuticals.

## **Interfaces of epilepsy and cancer**

Cancer patients have a major risk of developing epileptic seizures in the course of their disease whereas patients with epilepsy do probably not exhibit an increased risk of cancer. Yet, it remains controversial whether anti-epileptic drug (AED) treatment may have an impact on the risk of developing cancer. Older AED like phenobarbital or phenytoin have been identified as tumor-promoting agents in animal studies whereas theoretical considerations led to the hypothesis that valproic acid may have tumor-protective properties (see below).<sup>7,8</sup> Eventually, neither hypothesis has been confirmed to be of relevance in human cancer patients. Some rare hereditary diseases, mostly tuberous sclerosis, but also the neurofibromatoses and von Hippel Lindau disease, share epileptic seizures and tumors as disease characteristics. Here, type and location of tumors are likely to modulate the seizure risk. The life-time risk of brain tumor patients to experience epileptic seizures is in the range of 20-80%.<sup>1</sup> It is higher in patients with primary brain tumors than in patients with brain metastasis. Seizures may occur in cancer patients in the absence of CNS involvement. In fact, even in the context of epilepsy in a cancer patient with a brain lesion, it must not be assumed that all epileptic seizures are caused by that lesion although this is *a priori* very likely. Alternative causes provoking or facilitating seizures including medications, metabolic disturbances, stroke or infection, need to be specifically considered, excluded or addressed, too.<sup>9</sup>

### **Management of epilepsy in tumor patients: general principles**

The goals of epilepsy management include understanding its origin, treating its cause where possible, preventing further seizures, and limiting their sequelae. The initial work-up of a suspected seizure requires an assessment of the circumstances of that episode and a thorough consideration of alternative diagnoses, mostly syncope, migraine and



cerebral ischemia. History taking is commonly complemented by electroencephalography (EEG) and cardiological assessments, depending on the circumstances. At presentation of a first epileptic seizure, cerebral magnetic resonance imaging (MRI) is indicated and the preferred imaging method. This may lead to the diagnosis of a hitherto unknown primary brain tumor, metastatic presentation of a previously unknown systemic tumor (most frequently non-small cell lung cancer, but also breast cancer, melanoma or renal cell carcinoma), or spread to the central nervous system (CNS) in a known cancer patient. In general, effective tumor treatment consisting of surgical resection, radiotherapy, pharmacotherapy, or combinations thereof, is likely to contribute to seizure control in brain tumor patients.<sup>10</sup> Brain tumor-associated epilepsy has commonly been considered more difficult to treat than other types of epilepsy, however, this perception is not supported by robust data. If the brain tumor is the accepted cause of epilepsy in brain tumor patients, then it will be difficult to control epilepsy if tumor cannot be controlled. Conversely, it has not been demonstrated that patients with *stable* brain tumors and epilepsy achieve seizure less often than other epilepsy patients, e.g., by pharmacotherapy.

Drug treatment-resistant epilepsy is commonly defined as a failure of adequate trials of two (or more) tolerated and appropriately dosed AED regimens to adequately control seizures.<sup>5,11</sup> Resistance may be related to altered expression or activity of drug transporters at the blood brain barrier, limiting penetration to the tissue of seizure origin, altered expression or activity of the target molecules of AED, or underlying mechanisms of seizure generation that are not covered by the mode of action of currently available AED. Which of these reasons account for resistance to AED in brain tumor-associated epilepsy to what extent, remains controversial. Nevertheless, with the availability of new

classes of AED which are better tolerated, resulting in better treatment compliance, seizures can be controlled with drug therapy either as single agents or in combination in the great majority of patients.

In addition to the specific treatment of the underlying brain tumor, pharmacotherapy is the mainstay of treating epilepsy in cancer patients (Table 1). The classification of drugs as first, second or third generation AED is inconsistently used in the literature. From a practical oncology perspective, the distinction of enzyme-inducing (EI) AED and non-EI-AED is more relevant (see below). Many considerations support a thoughtful use of AED in patients with primary or metastatic brain tumors, including the possible resistance of the seizure disorder to AED, drug drug interactions, and unwanted effects from AED: rashes, drowsiness and cognitive alterations may severely affect quality of life.<sup>12</sup>

Unwanted effects from AED may also be more common in (brain) cancer patients than in patients with other etiologies of epilepsy.<sup>13</sup> This has most likely multiple reasons, notably comedications such as steroids and chemotherapy, but also exposure to radiotherapy as well as effects of the tumor itself, and psychiatric comorbidity, notably depression. Of note, cognitive side effects from AED have to be weighed against cognitive deterioration induced by seizures, which can be severe and prolonged, too. If AED are indicated following the guidelines below, it is recommended to use non-EI-AED rather than EI-AED and to dose a single agent adequately high, that is to the edge of the recommended dose without unwanted effects, before moving to double or triple AED combinations, which are more difficult to monitor in terms of drug drug interactions, tolerability, safety, and efficacy. There is no evidence that specific AED are more active than others in brain tumor-associated epilepsy. Formal comparative trials of AED specifically in brain tumors have rarely been conducted, and the primary choice of agent

varies among experts. The SANAD trials that had indicated preferential activity of lamotrigine in focal epilepsy and of valproic acid in generalized epilepsy<sup>14,15</sup> cannot be simply extrapolated to patients with brain tumors. In the absence of randomized studies in the brain tumor population of patients with epilepsy, preferred drugs based on tolerability, interactions, and efficacy at present include valproic acid, levetiracetam,<sup>16,17</sup> lamotrigine,<sup>18</sup> and possibly lacosamide.<sup>19</sup> Expression of synaptic vesicle protein 2A (SV2A), the presumed target of levetiracetam, may predict response to the drug.<sup>20</sup> Drug combinations that may be useful in cancer patients with epilepsy include valproic acid *plus* lamotrigine or levetiracetam or levetiracetam *plus* topiramate.<sup>18</sup> The local delivery of AED *via* convection-enhanced delivery is feasible, but plays no role in clinical practice.<sup>21</sup>

### **Are cancer patients at increased risk of epilepsy in the absence of CNS involvement?**

The most common cause of seizures in cancer patients is probably the development of solid brain metastases,<sup>9</sup> but leptomeningeal involvement needs also consideration. Accordingly, the initial work-up of a first seizure in any cancer patient must include neuroimaging, preferably MRI to rule out brain metastases. Neuroimaging, however, may also reveal stroke or infectious complications, which may be more common in systemic cancer patients than in the general population. The work-up may also include a lumbar puncture to analyze the cerebrospinal fluid for malignant cells, microorganisms, lactate and protein. Moreover, various cancer chemotherapy regimens may provoke seizures in a minority of cancer patients, e.g., high-dose chemotherapy with ifosfamide or methotrexate.<sup>9</sup> Chemotherapy-related seizures occurring in the absence of brain metastases usually do not necessitate long-term AED treatment. Rare syndromes of

paraneoplastic disorders with epilepsy have been linked to autoantibodies against ion channels and neurotransmitter receptors, and some of these are tumor-associated, e.g., antibodies to the N-methyl-D-aspartate (NMDA) type of glutamate receptors in patients with teratoma.<sup>22</sup>

### **Epilepsy in systemic cancer patients with CNS involvement**

Solid brain metastases seem to cause seizures less frequently than primary brain tumors, which may be explained by their less infiltrative growth and their inability to biochemically modulate neuronal excitability. New-onset seizures in patients with known brain metastases may indicate hemorrhage into a metastatic lesion, notably in metastatic melanoma patients, or tumor progression with associated edema. Patients undergoing resection of single or multiple brain metastases do not require primary seizure prophylaxis before and after surgery if they have never suffered a seizure.

### **Epilepsy in primary brain tumor patients**

The life-time incidence of epileptic seizures in patients with primary brain tumors varies by diagnosis, age and literature source and is estimated in the range of 20-80%. The incidence is relatively lower in some of the most malignant brain tumors such as glioblastoma and primary central nervous system (CNS) lymphoma, but higher in some more benign, but still infiltrative lesions such as World Health Organization (WHO) grade II diffuse gliomas. The reasons for these differences are multifold, but remain somewhat speculative. Typical features attributed a high seizure risk include location in the temporal lobe and cortical as opposed to white matter involvement. In this regard, oligodendroglial tumors are often located at the interface between cortex and white

matter and cause seizures frequently whereas primary CNS lymphomas are more commonly growing in the white matter and are usually not diagnosed because of an epileptic seizure. In some types of brain tumors such as dysembryoplastic neuroepithelial tumors, the natural course of the tumor is very benign, but the severity of epilepsy dictates the necessity for surgical intervention.<sup>23</sup> In such instances, surgery should be performed at centers specialized in epilepsy surgery. In low-grade gliomas, complete resection, shorter seizure history < 1 year, seizures other than focal seizures, and previous seizure response to pharmacotherapy were associated with better seizure control after surgery.<sup>24</sup> In general, surgical tumor resection may greatly contribute to the reduction of seizure frequency and severity in patients with brain tumor-associated epilepsy. Beyond surgical resection,<sup>25,26</sup> other anti-tumor treatments such as radiotherapy and chemotherapy may improve seizure control e.g. in patients with low-grade gliomas.<sup>27</sup> Some patients treated with temozolomide chemotherapy report improvement of seizure frequency well before any objective tumor regression is demonstrated by neuroimaging. Another compelling example of a nonsurgical anti-tumor treatment that helped to improve epilepsy in more than half of patients was recently provided by the introduction of the mTOR inhibitor, everolimus, as an experimental agent to inhibit the growth of subependymal giant cell astrocytomas in patients with tuberous sclerosis.<sup>28</sup> The rationale for everolimus is enhanced mTOR activity resulting from lack of upstream control exerted by the tuberin/harmartin complex.

The proximate causes of why brain tumor patients suffer seizures at all and whether seizures in these patients have a different cause compared with other structural neurological brain disease such as multiple sclerosis or stroke have remained obscure. Little research has been done to specifically address this issue, as reviewed in depth

recently.<sup>2</sup> Tumor location in proximity to cortical structures likely plays a role because neurons are considered the source of seizures. Ischemia of surrounding brain induced by tumor-associated changes in perfusion and the blood vessel network may contribute to seizure activity. Certain histological subtypes of primary brain tumors take up or release neurotransmitters and may thereby modulate neuronal excitability. Notably excessive glutamate levels have been proposed to mediate neuronal receptor-dependent excitation triggering seizure activity. Accordingly, it has been proposed that glioblastoma patients suffering seizures have lower glutamine synthase levels than seizure-free patients.<sup>29</sup> Glutamine synthase consumes ammonia and glutamate to generate glutamine. Moreover, tumor cells may also express ion channels and neurotransmitter receptors and the controversial discussion on the cellular origin of primary brain tumors with the possible link to neural progenitor cells have supported the hypothesis that some tumor cells themselves may generate electrical activity promoting seizures.<sup>30-32</sup> Conversely, not only the tumor, but also the type of host response including inflammatory changes may determine the likelihood of developing symptomatic epilepsy.<sup>33</sup> More recently, indoleamine 2,3-dioxygenase is a cytokine-inducible enzyme that participates in tryptophan and serotonin metabolism has been associated with seizure activity in inflammation.<sup>34</sup> Due to its intimate role in different tumors including brain tumors,<sup>35</sup> indoleamine 2,3-dioxygenase-mediated tryptophan catabolism may also be involved in seizures in brain tumor patients. Whether it is protective or promoting seizure activity remains to be shown, but would allow for an innovative treatment approach.

**Do AED exhibit intrinsic anti-tumor properties?**

Intrinsic antitumor activity of certain AED and synergy with chemotherapy or radiotherapy have been suggested in some, but not all studies. For instance, phenytoin has been attributed anti-mitotic and anti-invasive properties, and valproic acid has been suggested to induce cell differentiation, growth arrest, apoptosis, autophagy, and these effects were proposed to be mediated by histone deacetylase (HDAC) inhibitory properties.<sup>36-40</sup> These issues were most often addressed in the context of gliomas, given the high need for AED treatment in this patient population. We did not observe cytotoxic or antiproliferative effects of either carbamazepine, phenytoin or valproic acid in cultured glioma cells at concentrations likely to be achieved *in vivo*.<sup>41</sup> Yet, valproic acid alone delayed growth in medulloblastoma xenograft models in severe combined immunodeficiency mice in the apparent absence of relevant systemic toxicity,<sup>37</sup> but because of differences in valproic acid metabolism of valproic acid in mouse and man, these interesting observations in mice are difficult to extrapolate to human patients. Moreover, valproic acid when combined with the DNA (cytosine-5) methyltransferase inhibitor 5-aza-2'-deoxycytidine reduced the incidence of medulloblastomas and rhabdomyosarcomas in heterozygous Patched 1 knockout mice.<sup>38</sup> The same combination induced expression of the candidate tumor antigen NY-ESO-1 in cultured glioma cells.<sup>39</sup> If AED act *via* HDAC inhibition only to potentially inhibit tumor growth when administered alone, their antitumor activity can be predicted to be low, given that much more powerful HDAC inhibitors have shown rather limited single agent activity in human cancer patients.<sup>42</sup>

### **Interactions of cancer therapy and AED: tolerability**

Pharmacokinetic as opposed to pharmacodynamic interactions of AED and various anti-cancer drugs are the most important area to consider for the general oncologist at the interface between cancer care and epilepsy.<sup>3,4</sup> Although many AED are metabolized in the liver, only certain agents like phenytoin, carbamazepine and derivatives, and phenobarbital, induce CYP450-dependent hepatic enzymes and thus increase their own metabolism and more importantly, the metabolism and degradation of many commonly used cytotoxic agents (Table 2). Most new AED are neutral in this regard whereas valproic acid may inhibit metabolism and consequently augment half-life and toxicity of concomitant medications. For the design of clinical trials, also outside neurooncology, this calls for groups separated for the use of EI-AED or non-EI-AED, since maximal tolerated doses as well as effective doses may be relevantly different. Alternatively, many new trials *per se* exclude patients on EI-AED. The spectrum of AED as well as the spectrum of anti-cancer agents is steadily increasing. There are various websites beyond Pubmed or Medline where information on such interactions can be retrieved. These require regular up-dating. Importantly, the risk of using such EI-AED does not only include the risk of delivering expensive, but necessarily ineffective medical cancer therapy, but also a sudden increase in toxicity and loss of tolerability when such EI-AED are withdrawn and replaced by non-EI-AED. Thus, special attention to drug drug interactions is required not only when implementing, but also when tapering AED. Conversely, the enzyme-inhibiting effect of valproic acid appears clinically of lesser importance, although increased myelosuppression may develop in patients receiving nitrosoureas or cisplatinum-based chemotherapy or temozolomide concomitantly with valproic acid.<sup>43,44</sup> There are also safety concerns regarding the choice of AED in cancer patients beyond drug-drug interactions. Various neurosurgeons fear an increased risk of



peri-operative bleeding complications in valproic acid-treated brain tumor patients, although this is not supported by the literature.<sup>45,46</sup> The risk of severe skin toxicity is increased when patients are treated with phenytoin or carbamazepine or oxcarbazepine not only in combination with procarbazine, but also with radiotherapy.<sup>47</sup> Finally, EI-AED decrease the bioavailability of steroids, necessitating careful clinical monitoring when EI-AED are newly introduced in steroid-dependent brain tumor patients. Conversely, when EI-AED are replaced by non-EI-AED, it should be assessed whether steroid doses can be lowered. Based on these considerations and the unfavorable safety profile of these drugs regarding cognitive function, we propose to select *a priori* newer AED, which are devoid of such interactions.

### **Interactions of cancer therapy and AED: efficacy and survival**

Because of the enzyme-inducing activity described above, older AED such as phenytoin, phenobarbital or carbamazepine may enhance the metabolism of many commonly administered chemotherapy agents and thus decrease their efficacy (Table 2). Accordingly, there is now a trend to favor non-EI-AED for cancer patients, in order to allow effectively the administration of chemotherapy and targeted agents that often show increased hepatic metabolism in EI-AED-treated patients. Conversely, it has not been demonstrated that the enzyme inhibitory activity of valproic acid results in clinically relevant increases in anti-cancer drug levels and that this increases their activity through a pharmacokinetic mechanism.

Intrinsic anti-tumor activities (see above) or pharmacodynamic potentiation of radiotherapy or chemotherapy have been proposed to be mediated by some AED.

However, there is only limited data from *in vitro* studies indicating additive or synergistic

activity of AED with cancer therapeutics. For instance, we did not observe a modulation of the cytotoxic or antiproliferative effects of several anti-cancer drugs, including vincristine, cytarabine, doxorubicin, cisplatin, 3-bis-(2-chloroethyl)-1-nitrosourea (BCNU) and teniposide (VM26), by either carbamazepine, phenytoin or valproic acid in cultured glioma cells at concentrations likely to be achieved *in vivo*.<sup>41</sup> More recently, levetiracetam has been proposed to sensitize glioblastoma cells to temozolomide *via* suppression of O<sup>6</sup>-methylguanine-DNA-methyltransferase expression,<sup>48</sup> thus targeting one of the major resistance pathways of alkylating agent chemotherapy.<sup>49</sup>

Since the life-time risks of glioblastoma patients to experience epileptic seizures as well as AED-associated toxicity are considerable, and since these patients are now commonly exposed to chemotherapy, there has traditionally been significant interest in the choice of AED in glioblastoma. A retrospective analysis of three trials performed by the North Central Cancer Treatment Group indicated a possible association of EI-AED use, but not of seizure history, with a favorable outcome in glioblastoma patients.<sup>50</sup> Yet, the implications of this observation remain unclear in that the chemotherapy regimens used in these trials are not considered active.<sup>51</sup> Accordingly, we retrospectively assessed a potential predictive association with outcome of AED use within the pivotal trial of radiotherapy alone *versus* radiotherapy plus concomitant and adjuvant temozolomide for newly diagnosed glioblastoma that was conducted by the European Organization for Research and Treatment of Cancer and the National Cancer Institute of Canada Clinical Trials Group.<sup>52</sup> We identified 387 patients (68% of all patients) who received any AED; 110 patients (28% of those receiving AED) were prescribed exclusively non-EI-AED, mostly valproic acid, while the others received at least one EI-AED, either phenytoin, carbamazepine, oxcarbazepine, or phenobarbital. We specifically

compared three groups of patients, those without AED, those treated with valproic acid alone, and those treated with EI-AED only. After controlling for potentially confounding factors, we still observed a significant increase in overall survival of patients treated with valproic acid in the experimental arm, but not in the radiotherapy arm, suggesting a specific interaction between valproic acid and temozolomide chemotherapy. This association remains after adjusting for potentially confounding factors and imbalances. Moreover, hematological toxicity in patients treated with chemoradiotherapy and valproic acid was increased.<sup>44</sup> Nevertheless, our analysis has some limitations and should be interpreted with caution. The data were generated from an unplanned and insufficiently powered retrospective analysis with limited statistical power. AED use for the purpose of this analysis refers only to baseline use, that is, at study entry when patients were treated with radiotherapy with or without temozolomide chemotherapy, but no detailed data on further AED treatment were collected during the course of the study. The reason for the prescription of AED was not recorded, thus, patients may have been receiving AED because of a seizure at disease presentation or as primary prophylaxis during the peri- and postoperative phase. We assume that only a minority of patients was maintained on valproic acid throughout the planned six cycles of adjuvant temozolomide, raising the possibility that any sensitization to chemoradiotherapy by valproic acid might have been underestimated here. At least two mechanisms for this improved efficacy of temozolomide chemotherapy conferred by comedication with valproic acid may be considered. Temozolomide is a prodrug converted to 3-methyl-(triazen-1-yl)imidazole-4-carboxamide which is either hydrolyzed or unchanged prior to excretion. No effect of phenytoin, carbamazepine, or phenobarbital on temozolomide clearance has been observed whereas valproic acid decreased its clearance by 5%

(<http://www.temodar.com> ). To some extent, the increased hematological toxicity during adjuvant temozolomide chemotherapy with valproic acid may thus be related to an increased bioavailability of temozolomide. Yet, thrombocytopenia is not an uncommon side effect in patients treated with valproic acid alone. Moreover, the negative result for temozolomide dose intensification in the Radiation Therapy Oncology Group 0525 trial<sup>53</sup> strongly argues against the hypothesis that valproic acid simply increases the biologically active dose of temozolomide. Increased hematological toxicity has previously been observed when glioma patients were co-treated with valproic acid and nitrosourea-based chemotherapy, but survival data by AED use were not reported.<sup>43</sup> Alternatively, our observation may lend support to the notion that HDAC inhibitory properties of valproic acid sensitize glioma cells for temozolomide. The EC<sub>50</sub> for valproic acid-induced HDAC inhibition is 500  $\mu$ M,<sup>36</sup> which probably exceeds the clinically achieved plasma concentrations. Yet, some glioblastoma patients reoperated after exposure to valproic acid exhibit evidence of HDAC inhibition.<sup>54</sup> A prolonged survival of 14 months versus 11 months was observed in glioblastoma patients treated with adjuvant CCNU who received a non-EI-AED, mainly valproic acid, compared with patients on EI-AED, mainly carbamazepine.<sup>55</sup> A phase I dose escalation trial of valproic acid combined with 5-fluorouracil, epirubicin, and cyclophosphamide confirmed that HDAC inhibition could be achieved *in vivo*.<sup>56</sup> Yet, a phase I trial exploring valproic acid *plus* dacarbazine/interferon- $\alpha$  chemoimmunotherapy in metastatic melanoma showed only moderate tolerability, but no indication of enhanced activity.<sup>57</sup> Exploratory trials using HDAC inhibitors more potent than valproic acid such as vorinostat in combination with temozolomide radiochemotherapy may provide further support for this hypothesis.

Selective HDAC inhibitors might also have a preferred tolerability profile compared with valproic acid, which induces weight gain, alopecia and tremor in some patients (Table 1). In any case, this analysis from a randomized phase III trial supports the view that the choice of AED in brain tumor patients may affect survival.<sup>44</sup>

### **Frequently asked questions (FAQ) regarding epilepsy and cancer**

The interface between cancer and epilepsy currently provides an area of many interesting observations, active clinical and laboratory research, and opportunities to improve quality of life and outcome in cancer patients. Yet, there are at the same time many questions that arise in daily clinical practice and for many of which there are no answers that could be based on several or even one adequate clinical trial.

Table 3 summarizes some of these classical questions (and answers). Improved cancer therapy, as well as early and regular prenatal care, allow normal pregnancies and pregnant women with cancer to deliver healthy babies. Here it may be important to attempt decreasing pharmacotherapy to monotherapy and to taper doses of AED to the lowest possible level. There is no anticonvulsant of choice; however, the best safety data are available for lamotrigine.<sup>58</sup> In women who have not had a seizure for 2-5 years, an attempt at complete AED withdrawal is warranted. Patients should be offered preconceptual genetic counseling.

Almost a quarter of people diagnosed with epilepsy are >60 years of age. Underlying factors are discovered in a greater proportion than in younger patients, including cerebrovascular disease, dementia, trauma and tumors. Treatment should be kept at the lowest effective dose since there is an increased risk of side effects and idiosyncratic reactions.<sup>59</sup> There is an increased risk of pharmacological interactions due to

polypharmacy. The likelihood and severity of adverse reactions is increased. Since long-term AED treatment is considered an independent risk factor for osteoporosis, calcium and vitamin D supplements should be considered with AED treatment in the elderly. Further, epilepsy is associated with an increased risk of mental health disorders, such as anxiety, depression and suicidal thoughts.<sup>60</sup>

## **Conclusions**

Recognition and secondary prophylaxis of seizures and epilepsy in cancer patients are a major challenge that commonly requires a multidisciplinary approach. The major goals, freedom from seizures, achieving seizure control with an acceptable safety and tolerability of AED, and achieving seizure control without interfering with the efficacy of cancer treatment, can often be achieved, however, careful monitoring and thoughtful clinical decision making are required.

## **Conflicts of Interest**

MW has received honoraria for lectures or advisory board participation from Antisense Pharma, Magforce, Merck & Co, Merck Serono, and Roche, as well as research support from Merck & Co. and Merck Serono.

RS has received honoraria for lectures or consultancy or both from Merck & Co, Roche, and Celgene. RS is a principal investigator on a Merck-Serono/EORTC-sponsored clinical trial investigating cilengitide in glioblastoma, and has served as an uncompensated advisor to Novocure Ltd.

WW has received honoraria for lectures or advisory board participation from Magforce, Merck & Co, Merck Serono, and Roche, as well as research support from Apogenix, Boehringer Ingelheim, Eli Lilly, and Merck & Co.

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**Table 1. AED profiles.**

	<b>Mode of action</b>	<b>Daily dose (mg)</b>	<b>Therapeutic serum level (µg/ml)</b>	<b>Unwanted effects</b>	<b>Drug int</b>
<b>Phenobarbital</b>	GABAergic, prolonging chloride channel opening	50-300	10-40	Sedation, cognition↓, allergy	Enzyme (P450)
<b>Primidone</b>	GABAergic, prolonging chloride channel opening	500-1500	5-15	Sedation, cognition↓	Enzyme (P450)
<b>Clobazam</b>	GABAergic, facilitating chloride channel opening	10-30	0.1-0.4	Sedation	Sedative medication
<b>Clonazepam</b>	GABAergic, facilitating chloride channel opening	0.5-4	0.02-0.08	Sedation, cognition↓	Sedative medication
<b>Phenytoin</b>	Sodium channel blocker (fast inactivation)	200-350	10-20	Dizziness, allergy, hepatotoxicity, gingival hyperplasia, cerebellar atrophy, skin toxicity	Enzyme (P450), in requirement
<b>Carbamazepine</b>	Sodium channel blocker (fast inactivation)	600-2000	4-8	Dizziness, nausea, ataxia, hyponatremia, leukopenia, hepatotoxicity, skin toxicity	Enzyme (P450), in requirement



<b>Oxcarbazepine</b>	Sodium channel blocker (fast inactivation)	900-2400	10-35	Hyponatremia, leukopenia, skin toxicity	Enzyme (P450), le
<b>Valproate</b>	Unclear, inhibition of ion channels (?), promotion of GABA signaling (?)	1200-2400	50-100	Tremor, weight↑, coagulation disorders, thrombocytopenia, teratogenicity	Multiple glucuron hydrolas → increa chemoth
<b>Lamotrigine</b>	Sodium channel blocker (fast inactivation)	100-300	2-15	Skin toxicity, tremor, sedation (rare)	Carbama phenoba reduce la whereas lamotrigi
<b>Gabapentin</b>	Calcium channel blocker (high voltage), GABA agonist (?)	900-3000	2-20	Sedation, weight gain	Limits bi and may morphine
<b>Pregabalin</b>	Calcium channel blocker (high voltage)	150-600	2-5	Sedation, weight gain	No relev
<b>Topiramate</b>	Multiple: sodium channel blocker, GABA agonist, NMDA receptor antagonist	50-200	2-20	Sedation, fatigue, inappetence, weight loss, psychosis	May red contrace
<b>Levetiracetam</b>	SV2A receptor binding	1000-3000	3-30	Sedation (rare), psychiatric side effects	No relev
<b>Lacosamide</b>	Sodium	100-400	10-20	Dizziness, nausea,	No relev

	channel blocker (slow inactivation), CRMP2 binding			headache, cognition↓, skin toxicity	
<b>Zonisamide</b>	Multiple	300-500	20-30	Dizziness, ataxia, anorexia	No or mi cytochro may red
<b>Tiagabine</b>	GABAergic, blocks synaptic GABA uptake	15-70	0.02-0.08	Dizziness, fatigue	Levels a cotreatm
<b>Vigabatrin</b>	GABAergic, inhibits GABA transaminase	200-300	0.8-36	Visual field defects, fatigue, sedation	Reduces 25%

CRMP2, collapsin response mediator protein-2; GABA,  $\gamma$ -aminobutyric acid; NMDA, N-methyl-D-aspartate; SV2A, synaptic vesicle 2A;

**Table 2. Commonly used anti-cancer drugs negatively affected by EI-AED comedication.**

<b>Alkylating agents</b>	Nitrosoureas: carmustine (BCNU), lomustine (CCNU), nimustine (ACNU), fotemustine; thiotepa; cyclophosphamide; ifosfamide
<b>Mitotic inhibitors</b>	Vinca-alcaloids: vincristine, vinorelbine; paclitaxel, docetaxel
<b>Topoisomerase inhibitors / DNA-damaging agents</b>	irinotecan, topotecan, etoposide, adriamycin
<b>Antimetabolites</b>	Methotrexate, pemetrexate
<b>Signal transduction inhibitors</b>	Imatinib, erlotinib, gefinitib, sorafenib, temsirolimus, everolimus, vemurafenib
<b>Proteasome inhibitors</b>	Bortezomib

**Table 3. Frequently asked questions (FAQ) in the context of epilepsy and cancer.**

<p><i>Should all brain tumor patients receive AED?</i></p>	<p>There is no evidence that primary prophylaxis with AED decreases ever seizure in brain tumor patients.<sup>13,61,62</sup> This statement is based on examining phenobarbital, phenytoin, or valproic acid and may not be extrapolated to other AED.</p>
<p><i>Should all brain tumor patients who undergo a craniotomy receive AED?</i></p>	<p>No, there is also no evidence that primary prophylaxis with AED decreases the risk of a first-ever seizure in brain tumor patients undergoing craniotomy.</p>
<p><i>Should I take my patient off AED if these were instituted without good reason?</i></p>	<p>Yes, but slowly not to provoke seizures, and specific attention to the pharmacokinetics of co-medications is warranted when EI-AED are discontinued.</p>
<p><i>Should all brain tumor patients receive AED after the first seizure?</i></p>	<p>Yes, because epilepsy is highly likely to be symptomatic and requires further seizures until the tumor has been adequately treated.</p>
<p><i>How long should brain tumor patients with a presenting seizure, who remain seizure-free after surgery, receive AED?</i></p>	<p>In the absence of randomized trial data, tapering and discontinuation of AED over 4–6 weeks is recommended, depending on histology and tumor control. Recurrent seizures in this patient population is strongly associated with tumor progression.</p>
<p><i>How long should brain tumor patients, who experience seizures after surgery, be maintained on anticonvulsants?</i></p> <p><i>How long should brain tumor patients, who experience seizures and never had surgery, be maintained on anticonvulsants?</i></p>	<p>The occurrence of seizures later than 48–72 h after surgery, or within 24 h after surgery, in brain tumor patients with no other predisposing factor usually indicates the need for long-term AED treatment. Often patients will never become seizure-free and experience only a reduction in seizure frequency and severity. The decision to start and eventually discontinue AED requires the consideration of various factors, notably tumor control. The risks of recurrent seizures, e.g. bony metastases or anticoagulation, need to be weighed against the benefits of receiving AED. In a general population of patients with (largely) idiopathic epilepsy free from seizures for 2 years, the rate of relapse within the first 2 years of withdrawal is in the range of 50%,<sup>63</sup> and is probably higher in brain tumor patients with symptomatic epilepsy. The social implications of seizure recurrence, e.g. driving, work, and leisure activities, need to be considered, too.</p>
<p><i>Which AED is best for cancer patients with epilepsy?</i></p>	<p>EI-AED should be avoided with few exceptions. Valproic acid and phenytoin can be dosed quickly and intravenously.<sup>16,17</sup> Lamotrigine needs to be started slowly, mainly due to the allergic potential but has otherwise favourable toxicity profile and efficacy.</p>
<p><i>What is the role of serum level monitoring in cancer patients on AED?</i></p>	<p>Routine monitoring of serum levels of AED is not required and also not available for all agents described in Table 2. Rationales include (i) to assess patients' compliance, (ii) to assess whether physical or mental symptoms may represent AED toxicity and (iii) to assess whether appropriate dosing is being achieved.</p>

	achieved in AED-unresponsive patients who continue to experience seizures.
<i>Which of my cancer patients require monitoring by EEG?</i>	Monitoring by EEG is not required for the majority of cancer patients. EEG monitoring is of value in the initial work-up of suspected seizures and if there is concern about continuous seizure activity in the course of disease. The EEG has an important role in the management of patients with biologically benign brain tumors where epilepsy is the major burden of the disease.
<i>Which of my cancer patients should be allowed to drive?</i>	Country-specific regulations need to be considered. Seizure control and cognitive control are required. However, it is important to recognize that tumor-related neurological deficits other than seizures, such as hemianopia or motor deficits, may interfere with the competence to drive. We recommend not to permit driving for an interval following brain surgery or when there is overt brain tumor progression, irrespective of a positive or negative seizure history. Further, driving should not be permitted during tapering and withdrawing AED.