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MINI REVIEW

Epilepsy in the cancer patient

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Abstract
Purpose Epileptic seizures in patients with malignancies usually occur as a consequence of brain metastases from systemic cancer or the presence of a primary brain tumor. Other less-frequent causes include metabolic disorders such as electrolyte abnormalities, hypoglycemia, hypoxia and liver failure, paraneoplastic encephalitis, leptomeningeal carcinomatosis, side effects of certain chemotherapeutic agents, central nervous system infections, and pre-existing epilepsy.
Methods We reviewed all published literature in the English language regarding the use of antiepileptic drugs in patients with cancer.
Results In patients with brain metastases or primary brain tumors that had never experienced seizures, prophylactic anticonvulsant treatment is justified only for a period up to 6 months postoperatively after surgical excision of a cerebral tumor, since approximately half of the patients will never develop seizures and the anti-epileptic drugs may cause toxicity and interactions with antineoplastic therapies. For brief prophylaxis, newer antiepileptic drugs such as levetiracetam and oxcarbazepine are superior to older agents like phenytoin. In patients with a malignancy and seizures, certain antiepileptic drugs that express tumor inhibitory properties should be used such as valproic acid and levetiracetam, followed by oxcarbazepine and topiramate that exhibit good tolerance, efficient seizure control and absence of significant interactions with the chemotherapy.
Conclusions Future clinical trials in patients with cancer and epilepsy should focus on combinations of chemotherapeutic interventions with antiepileptic drugs that demonstrate antineoplastic activities.

Keywords Cancer · Antiepileptics, chemotherapy · Valproic acid · Levetiracetam

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Introduction

Epileptic seizures may occur in patients with systemic cancer for a variety of reasons [1]. Primary and metastatic brain tumors are frequently complicated by symptomatic epilepsy, defined as recurrent unprovoked seizures or single isolated seizure episode, both associated with the brain lesion. Brain tumor patients with seizures account for the 4% of epilepsy patients [2]. In some cases, seizures might be the presenting symptom that will lead to the detection of the tumor, whereas alternatively seizures may represent a later manifestation following initial diagnosis or tumor recurrence. Epilepsy accompanies primary intracranial neoplasms in more than 30% of the cases; however, a great variety in frequency exists among different tumor types. Similar incidence rates are reported for brain metastases, ranging from 25 to 40% [3].

In this review, we discuss the various causes of seizures in cancer patients and we briefly discuss the possible

epileptogenic mechanisms. Moreover, we analyze the efficacy of the available antiepileptic pharmaceutical agents and the possible interactions with chemotherapeutic drugs. Finally, we focus on another aspect of antiepileptic treatment, which involves the potential antitumoral effects of certain agents and their potency to enhance current or future cytotoxic therapies.

Incidence and causes of seizures in cancer patients

In patients with cancer, epileptic seizures are mainly triggered by brain metastases or other focal cerebral abnormality and rarely by metabolic disorders such as electrolyte abnormalities, hypoglycemia, hypoxia, and liver failure [4]. Other conditions predisposing to epilepsy include paraneoplastic encephalitis [5] and leptomeningeal carcinomatosis [6]. Chemotherapeutic agents, such as methotrexate, vincristine, ifosfamide, cyclosporine, fludarabine, cytarabine, and cisplatin may also induce an encephalopathy with seizures [7]. Radionecrosis in brain areas and opportunistic central nervous system (CNS) infections are other causes of seizures [3].

Regarding primary brain tumors, epileptic seizures will lead to the initial detection of the intracranial lesion in 30–50% of the patients [8]. In primary brain tumors, epileptogenesis is dependent upon histological type, location, grade, as well as upon the individual's genetic susceptibility. Less aggressive tumor types are proven to be more epileptogenic. It has been suggested that slow growth rates allow for the tumor to gradually infiltrate adjacent areas and induce an epileptic foci by creating abnormal circuits and by preventing normal brain tissue's self-regulation and inhibition locally [9]. In addition, survival rates are higher, resulting in more patients developing seizures at some point of the disease progression, since they are exposed for a longer period to the irritating effects of the lesion. This is particularly evident in gliomas, where 60–85% of the patients with low-grade astrocytomas and oligodendrogliomas suffer from epilepsy, whereas in glioblastoma multiforme the percentage is significantly lower, ranging from 30 to 50% [10]. In a previous study of 119 patients with supratentorial gliomas, half of them presented with seizures, whereas preoperative incidence of epilepsy was 83% in patients with low-grade astrocytoma, 46% in anaplastic astrocytoma, and 36% in glioblastoma [11]. In addition, dysembryoblastic neuroepithelial tumors and gangliogliomas represent the most epileptogenic brain tumors with a seizure incidence of 100% and 80–90%, respectively [12]. Epilepsy is less frequent in meningiomas, ranging from 22 to 60%, although surgical resection may provoke post-treatment seizures in 20% of the patients without such manifestations before surgical intervention [13].

Irrespective of the tumor type and despite the antiepileptic treatment, when seizures are the presenting symptom of a tumor the patient is at increased risk of developing recurrent seizures [14]. Regarding location, tumors developing within the brain cortex are typically more epileptogenic, especially those detected at the frontal, temporal, and parietal lobes. On the other hand, sellar neoplasms and those located in the posterior fossa do not usually cause seizures [15].

Provoking mechanisms

Several pathophysiological mechanisms are proposed as capable of triggering epileptic seizures in patients with brain tumors. These include the disruption of neuronal connections and inhibition of local network regulation, the impaired glial cell activity, the increased vascular permeability and the abnormal function of the blood brain barrier. In addition, rapidly growing tumors deregulate adjacent areas and result in peritumoral edema and inflammation, necrosis and hemosiderin deposition. These events might initialize abnormal circuits leading to seizure activity in the brain [16, 17].

In low-grade gliomas, partial differentiation of adjacent cortical areas is believed to provoke seizures [18]. Malignant brain tumors demonstrate increased metabolic rates and rapid cell growth leading to hypoxia and acidosis within and around the tumor mass as well as central necrosis, factors that contribute to neuronal excitability [19]. Moreover, adjacent brain cortex tissue is exposed to higher levels of several enzymes, such as lactate, enolase, and adenosine 3′,5′-cyclic monophosphate (cAMP) phosphodiesterase, creating a metabolic imbalance and predisposing to generation of abnormal electrical events [20]. The enhancement of intercellular signaling exchange between neurons is believed to occur as a consequence of the increased expression of the transmembrane gap junction molecules connexins that is frequently observed in epileptogenic brain tumors [21].

Perhaps, the most extensively studied mechanism involves the role of the altered neurotransmitter receptor expression in brain tumors. Gliomas display increased expression of glutamate receptors, enhanced glutamate activity and decreased expression of GABA receptors in the adjacent brain tissue [22]. The up-regulation of molecules such as the kainite and the N-methyl-D-aspartic acid (NMDA) receptors suppresses inhibitory signals and allows for the generation of potent epileptogenic foci [23, 24].

Indications of antiepileptic drug treatment

Therapeutic strategies in patients with cancer and epilepsy must integrate an optimal antiepileptic medication. However, many physicians tend to prescribe antiepileptic agents in newly diagnosed patients with primary or metastatic brain tumors, even in the absence of seizures, based on the fact that epilepsy may occur later during the course of the disease [25]. Two recent meta-analyses failed to provide with sufficient evidence favoring prophylactic anticonvulsant medication in brain tumors. The first study by Glantz et al. [14] analyzed 12 studies with 4 of them providing with level I evidence [14]. The study by Sirven et al. [26] examined five clinical trials that included patients with primary glial tumors, cerebral metastases or meningiomas and no history of seizures. The antiepileptics used were phenobarbital, phenytoin, and valproic acid, and patient evaluation lasted up to 6 months. Lack of antiepileptic prophylactic effect was documented, irrespective of tumor type or pathology [26].

In the study by Rosati et al. [27], patients with brain tumors were considered epileptics and subsequently anticonvulsant treatment was administered if they have had a single convulsive seizure attack with evidence of interictal epileptiform abnormalities in the EEG, had stereotypic symptoms suggestive of focal seizures with or without interictal epileptiform abnormalities, or had experienced a single epileptic seizure episode associated with stereotypic symptoms suggestive of focal seizure with or without interictal epileptiform abnormalities. The authors introduced the term of remote symptomatic seizure in cases of a single seizure and no interictal epileptiform abnormalities or stereotypic symptoms suggestive of focal seizure and distinguished it from symptomatic epilepsy that requires treatment. Among the 35 patients who did not fulfill the criteria to receive antiepileptic treatment, none developed seizures during the follow-up period or until death [27].

A more recent meta-analysis that included all articles from 1966 to 2007 referring to prophylactic treatment with phenytoin, phenobarbital, and valproic sodium found no difference between treated and control groups in terms of the prevention of the first seizure episode in patients with brain tumors. Additionally, the risk of an adverse event was higher for patients on antiepileptic drugs than for controls [28]. Regarding brain metastases, a study by Forsyth et al. [29] including 60 patients found no significant prophylactic benefit from antiepileptic drugs [29]. Similarly, a recent meta-analysis did not support routine prophylactic anticonvulsant treatment in patients without seizures [30].

Questionable remains the efficacy of postoperative administration of antiepileptics after brain tumor resection in patients without epileptic manifestations prior to surgery [31]. However, Franceschetti et al. [32] studied 128 patients with surgically treated brain tumors and reported a significant benefit from short-term antiepileptic drug prophylaxis in patients without preoperative seizures, but again did not observe long-term prophylactic effectiveness [32]. Similarly, Pace et al. [11], by investigating 119 glioma patients that received prophylactic treatment with phenobarbital, carbamazepine, or vigabatrin postoperatively found a high incidence of adverse reactions, 33.8, 14.3, and 12%, respectively, and concluded that long-term prophylactic anticonvulsants are not indicated [11]. On the other hand, a study that evaluated the early postoperative prophylaxis with oxcarbazepine in 150 glioma patients showed significant benefit, since seizure incidence was reduced to 2.7% within the first week [33]. Furthermore, a very recent study reported significant pre- and postoperative prophylaxis, along with minimal toxicity with levetiracetam in patients with primary or metastatic brain tumors. Since 38% had experienced preoperative seizures and 97.5% of all patients remained seizure free at the end of observation, this study clearly favors levetiracetam's use as a prophylactic antiepileptic in surgically treated brain tumors [34].

Thus, antiepileptic drug prophylaxis is not indicated in patients with primary or metastatic brain tumors and without a definite history of seizures. However, short-term anticonvulsant prophylaxis after surgical excision of the tumor mass could represent an acceptable clinical practice, since up to 13% of the patients may experience seizures within the first postoperative week, irrespective of the presence of preoperative seizure history or not [35].

Efficacy of antiepileptic medications

The management of symptomatic epilepsy in patients with cancer consists mainly of the selection of the appropriate antiepileptic drug. Several older agents, such as carbamazepine, phenytoin, phenobarbital, valproic acid, and newer ones, like levetiracetam, lamotrigine, gabapentin, and topiramate are included within a list of drugs indicated for epilepsy. Currently, there are no guidelines how to treat patients with secondary, brain tumor-induced epilepsy. Thus, the clinician is expected to select the most appropriate medication, sometimes for each patient individually, by taking into consideration efficacy, tolerability, adverse effects, interactions with co-administrated pharmaceutical agents and perhaps the possible influence on tumor growth and progression.

An important aspect of an optimal antiepileptic drug therapy is its efficacy to control seizures in conjunction with limited adverse effects. Several clinical studies have documented superior effectiveness and/or tolerability of

levetiracetam that exerts its effects through binding to synaptic vesicle protein SV2A [36]. A study of levetiracetam in 18 patients with primary brain tumors and refractory epilepsy showed significant response in all patients, 89% of which remained seizure free with minimal adverse reactions [37]. Similarly, superior results were obtained from the use of levetiracetam compared to phenytoin in a cohort of postcraniotomy glioma patients [38, 39]. Regarding metastatic tumors, levetiracetam reduced seizure frequency to more than 50% in all 13 patients followed, leaving the majority of them seizure free (77%), while the most common complaints included headaches and somnolence [40]. The same authors studied a mixed patient population with primary and metastatic brain tumors treated with levetiracetam—primarily as monotherapy—and observed significant antiepileptic efficacy in 90% of the patients [41]. As add-on therapy, levetiracetam was evaluated in 19 glioma patients suffering from refractory epilepsy. The authors reported a significant response in 14 patients with no remarkable adverse reactions [42]. The most frequent side effects of levetiracetam include psychomotor disturbances, insomnia and somnolence. On the other hand, the drug exerts antiemetic properties of unknown mechanism, which may prove useful in patients receiving chemotherapy [43].

Satisfactory seizure control in brain tumor patients may also be achieved by valproic acid. Van Breemen et al. [44] investigated 99 glioma patients with secondary epilepsy and reported response rates of 79.3% with valproic acid as monotherapy and 81.5% with the combination of valproic acid and levetiracetam, while 52 and 59% remained entirely seizure free [44]. The administration of topiramate was also associated with efficient seizure control in patients with secondary epilepsy due to brain tumors. The response rate was 75.6% and along with the mild side effects offered an adequate antiepileptic intervention [45]. Similar results were obtained from the use of oxcarbazepine, reporting fewer adverse reactions and at least equal with the older medications antiepileptic effect [46].

Based on clinical studies and pharmacological profiles, Vecht and Wilms [47] suggested initializing the anticonvulsant treatment with levetiracetam and in case of inadequate response, the co-administration of valproic acid due to the possible synergistic effects. Topiramate and lamotrigine could be used instead of valproic acid to assist levetiracetam's activity [47]. Another anticonvulsant as add-on medication could be gabapentin, reported to decrease seizure frequency to 50% in a small group of brain tumor patients, leaving half of them seizure free [48]. Van Breemen et al. [3] considered as first-line agents lamotrigine, valproic acid, and topiramate, whereas levetiracetam or gabapentin could be used as add-on agents in refractory cases [3].

In 12 patients with refractory brain tumor epilepsy, tiagabine as add-on therapy was well tolerated and augmented seizure control in 7 of them [49]. Pregabalin, either as monotherapy or in conjunction with other antiepileptics, produced an excellent response in all nine patients applied, but was accompanied by an increased rate of adverse affects [50]. Villanueva et al. [6] argued that hepatic enzyme-inducing antiepileptics and valproic acid should be avoided since these drugs either reduce activity or enhance toxicity of chemotherapy. They recommend the newer antiepileptics like vigabatrin, levetiracetam, gabapentin, and pregabalin followed by lamotrigine, oxacarbazepine, topiramate, and zonisamide, which do not influence the pharmacologic profile of chemotherapeutics [6]. Maschio et al. [51] followed 30 patients with secondary epilepsy due to brain metastatic disease and concluded that levetiracetam, oxcarbazepine, and topiramate may be preferable for this group of patients, since they are well tolerated, have minimal interactions with other drugs and reduce significantly the seizure frequency [51].

Limitations and complications of antiepileptic medications

Serious side effects of anticonvulsant medications, such as skin reactions, hematological complications, and cognitive impairment, seem to occur more frequently in cancer patients [46, 52, 53]. Concomitant therapeutic interventions could result in increased toxicity by the antiepileptic drugs. Thus, phenytoin may cause erythema multiforme and Steven–Johnson's syndrome when simultaneously administrated with cranial irradiation, a complication reported also by the use of carbamazepine [54–57]. Antiepileptics in conjunction with radiotherapy for low-grade gliomas have been associated with poor performance in various cognitive domains, such as attention and executive function [58]. In addition, valproic acid, as well as carbamazepine, phenobarbital, and phenytoin may cause severe hematological complications, such as platelet and neutrophil depletion and are also associated with a common incidence of encephalopathy [10, 26].

Furthermore, some antiepileptic agents interfere with the activity of enzymes crucial for metabolizing common chemotherapeutic agents resulting in either reduction in chemotherapeutic drug clearance and subsequent increased toxicity or in accelerated clearance and reduced chemotherapeutic efficacy (Table 1). On the other hand, the metabolism of the antiepileptic drug itself is related to the co-administrated chemotherapy, and it could be either enhanced or suppressed. Since antiepileptic drugs exert narrow therapeutic index, their pharmacokinetic profile may be easily altered [59]. Cytochrome P450 (CYP) is a

Table 1 Common interactions between antiepileptic and chemotherapeutic drugs[a, b]

Chemotherapeutic drug	Tumor type[c]	AED accelerating metabolism	AED inhibiting metabolism	Reduce levels of AEDs	Increase levels of AEDs	Others	References[d]
Carboplatin	Recurrent GBM, neuroblastoma, brain metastasis, lung			Phenytoin			62
Cisplatin	Recurrent GBM, neuroblastoma, brain metastasis, lung, lymphoma			Valproic acid, phenytoin, carbamazepine			3, 62
Cyclophosphamide	Neuroblastoma, medulloblastoma, malignant meningioma, brain metastasis, breast, lymphoma	Carbamazepine, phenobarbital, phenytoin, primidone	Valproic acid				6, 59, 60
Dacarbazine	Malignant meningioma, melanoma, lymphoma			Phenytoin			62
Doxorubicin	Neuroblastoma, breast, lung, lymphoma	Carbamazepine, phenobarbital, phenytoin		Valproic acid, phenytoin, carbamazepine			3, 6, 60
Erlotinib	Lung, recurrent GBM, malignant meningioma	Carbamazepine, phenobarbital, phenytoin, primidone					64
Etoposide	Recurrent GBM, neuroblastoma, medulloblastoma, brain metastasis, lung	Carbamazepine, phenobarbital, phenytoin, primidone		Phenytoin			6, 59, 62
Fluorouracil	Brain metastasis, breast, colorectal				Phenytoin		3, 59, 60
Ifosfamide	Malignant meningioma, neuroblastoma, metastatic brain, breast, lymphoma, lung	Carbamazepine, phenobarbital, phenytoin, primidone					6, 59, 62
Imatinib	Recurrent GBM	Carbamazepine, phenobarbital, phenytoin, primidone					63
Irinotecan	Recurrent GBM, colorectal, lung, brain metastasis	Phenytoin, phenobarbital, carbamazepine, primidone					6, 59, 60
Ixabepilone	Breast	Phenytoin, phenobarbital, carbamazepine					60
Methotrexate	Lymphoma	Carbamazepine, phenytoin, phenobarbital		Valproic acid, phenytoin			3, 6, 59, 60, 90
Nitrosoureas (carmustine, lomustine)	Recurrent GBM, medulloblastoma, brain metastasis	Carbamazepine, phenobarbital, phenytoin, primidone		Phenytoin			6, 59, 62
Paclitaxel	Brain metastasis, breast, lung	Carbamazepine, phenobarbital, phenytoin, primidone					6, 59, 60
Procarbazine	Medulloblastoma, lymphoma	Carbamazepine, phenobarbital, phenytoin, primidone				Contraindicated with carbamazepine	59, 60, 62

Table 1 continued

Chemotherapeutic drug	Tumor type[c]	AED accelerating metabolism	AED inhibiting metabolism	Reduce levels of AEDs	Increase levels of AEDs	Others	References[d]
Sunitinib	Renal	Carbamazepine, phenobarbital, phenytoin, primidone					60
Tamoxifen	Breast	Phenobarbital	Valproic acid		Phenytoin		6, 59, 60
Tegafur	Brain metastasis, colorectal				Phenytoin		3, 59
Temozolomide	GBM, low-grade glioma, brain metastasis	–	–				62
Teniposide	Brain metastasis	Carbamazepine, phenobarbital, phenytoin, primidone					6, 59, 62, 90
Thiotepa	Medulloblastoma, metastatic brain, lymphoma, breast	Carbamazepine, phenobarbital, phenytoin, primidone					6, 59, 62
Topotecan	Neuroblastoma, lymphoma, brain metastasis	Carbamazepine, phenobarbital, phenytoin, primidone					6, 59, 62
Vinblastine	Lymphoma, lung, breast	Carbamazepine, phenobarbital, phenytoin, primidone		Phenytoin			6, 59
Vincristine	Recurrent GBM, neuroblastoma, medulloblastoma, malignant meningioma, lymphoma	Carbamazepine, phenobarbital, phenytoin		Phenytoin, carbamazepine			3, 6, 59, 60
Vorinostat	Lymphoma, recurrent GBM					Frequent monitoring with valproic acid	60, 62

[a] Some of the displayed interactions represent the predicted consequences from drug co-administration based on each drug metabolism, rather than experimentally proved ones

[b] These drug interactions are not exclusive neither unique between the co-administrated drugs

[c] Referring to some of the tumors types that each chemotherapeutic agent is used or has been tested

[d] Numbers correspond to references in the reference list of the text

GBM glioblastoma multiforme, *AED* antiepileptic drug

family of enzymes implicated in the metabolism of various endogenous and exogenous molecules. Carbamazepine, phenytoin, phenobarbital, primidone and to a much lesser extent oxcarbazepine, and topiramate are potent inducers of CYP and possibly of glucuronyl transferases and epoxide hydrolase, whereas valproic acid exerts inhibitory effects upon CYP isoenzymes. Levetiracetam, gabapentin, lamotrigine, and vigabatrin do not significantly influence CYP activity. The three isoenzymes CYP3A4, CYP2C9, and CYP2C19 have the greatest affinity for both antiepileptic and anticancer drugs [60, 61]. Examples of antineoplastic drugs that are eliminated rapidly from circulation due to the induction of hepatic enzymes include busulfan, methotrexate, irinotecan, tamoxifen, etoposide, paclitaxel, vincristine, procarbazine, cisplatin, and topotecan [62]. Valproic acid though, by exerting inhibitory enzyme activity, may increase concentrations of nitrosureas, cisplatin, and etoposide leading to subsequent toxicity and imposing the reduction in the antineoplastic agent's dose [61].

Since anticonvulsant medications are frequently introduced in patients with cancer, clinical trials testing novel therapeutic strategies might benefit from taking into account the possible drug interactions. Imatinib mesylate, an agent used to treat certain types of cancer, is primarily metabolized by the CYP3A4 isoenzyme and anticonvulsants up-regulating CYP3A4 result in a 2.9-fold reduction in imatinib's levels [63]. The maximal tolerated dose of erlotinib in patients with recurrent glioblastoma or meningioma is significantly higher when co-administrated with enzyme-inducing antiepileptics [64]. Such interactions are crucial in determining the dosage of anticancer drugs in different groups of patients.

On the other hand, chemotherapeutic agents, such as methotrexate, doxorubicin, and cisplatin, through an enzyme induction mechanism, can decrease efficacy of valproic acid, carbamazepine, and phenytoin [65]. Doxifluridine, fluorouracil, and tamoxifen may reduce the metabolism rate of antiepileptic drugs (phenytoin) and increase susceptibility to toxicity [59]. Moreover, the interactions between anticancer and antiepileptic agents are also determined by their protein-binding capacity. In this way, phenytoin, phenobarbital, and valproic acid compete with cisplatin, etoposide, and teniposide for plasma protein bounding resulting in alterations of the unbound and active proportion of each drug. Furthermore, phenytoin, carbamazepine, and phenobarbital minimize the activity of corticosteroids that are irreplaceable agents in most patients with brain tumors [65].

Overexpression of molecules located on brain endothelial cells that function as modulators of drug transport through the blood brain barrier increase further resistance to antiepileptics. Expression of P-glycoprotein and multidrug resistance proteins 3 and 5 has been found up-regulated in glioma specimens, and since these factors decrease the intracerebral access of antiepileptics such as carbamazepine, phenytoin, phenobarbital, lamotrigine, and felbamate, it is argued that resistance to antiepileptic drug therapy in brain tumors is associated with altered transportation properties through the blood brain barrier [66, 67]. To overcome this limitation, the use of drugs not susceptible to P-glycoptrotein dependence, such as levetiraceram, might prove beneficial to control seizures [62].

Antitumoral effects of antiepileptic drugs

An ideal therapeutic approach against seizures in patients with cancer would include the administration of antiepileptic agents that have antitumor activity. However, among the wide range of anticonvulsants, only valproic acid has been associated with anticancer properties, and representative studies are presented in Table 2. Although in clinical use for decades, it was not until recently that valproic acid was recognized as a histone deacetylase inhibitor (HDACi), capable of inhibiting both class I and II histone deacetylases, resulting in hyperacetylation of histones H3 and H4 [68, 69]. Alterations in the acetylation status of chromatin influence its structure, in a way that it is maintained in a more open conformation, allowing to previously silenced genes to be activated and to previously overexpressed genes to be inhibited. Several molecular pathways have been shown to be affected by valproic acid via gene expression regulation, such as those incorporating ribosomal proteins, oxidative phosphorylation pathways, mitogen-activated protein kinase (MAPK) signaling, focal adhesion pathways, cell cycle regulation, antigen-processing and presentation processes, proteasome and apoptosis pathways, phosphoinositide 3-kinase (PI3 K) and Wnt signaling, calcium and transforming growth factor-beta (TGF-beta) signaling and ubiquitin-mediated proteolysis. For this reason, valproic acid could interfere with crucial cellular processes of carcinogenesis like cell differentiation, proliferation, apoptosis, and migration [70].

Tested in C6 glioma cells, valproic acid induces neuronal differentiation, along with growth arrest and suppression of cell migration [71]. Similar effects were observed in malignant neuroblastoma cells, where morphological changes compatible with neuronal differentiation were accompanied by down-regulation of N-myc, induction of bcl-2 and neural cell adhesion molecule, and up-regulation of the excreted antiangiogenic factors thrombospondin-1 and activin A. Moreover, valproic acid was shown to act in a synergistic manner toward these antitumoral effects with interferon-alpha [72]. In combination with interferon-gamma, valproic acid increased caspase-8 promoter activity in medulloblastoma cells,

Table 2 Indicative preclinical studies of valproic acid's anticancer effect

Tumor type	Effect	Reference
C6 glioma cell in vitro	Inhibition of proliferation, migration; neuronal-like differentiation	Benítez et al. [71]
Malignant glioma cell lines in vitro	Inhibition of proliferation of 86HG39, A172, 85HG66 cell lines; inhibition of migration in T98G and 85HG66 cell lines	Knüpfer et al. [74]
Human glioma cell lines in vitro	Enhancement of radiosensitivity; accumulation in G(2)-M cell cycle phase	Chinnaiyan et al. [84]
Malignant glioma cell lines in vitro and in vivo	Enhancement of radiosensitivity; in vivo tumor growth delay	Camphausen et al. [83]
Malignant glioma cell lines in vitro	G(1) or G(2) phase accumulation; induction of p21/WAF1, topoisomerase-II and GFAP; enhancement of etoposide cytotoxicity	Das et al. [75]
Glioma cell lines in vitro and in vivo	Induction of autophagy; synergistic effect with rapamycin, Ly294002 and temozolomide	Fu et al. [82]
Human glioma cell lines in vitro	Synergistic effect with nitrosureas; inhibition of cell proliferation	Ciusani et al. [80]
Human glioblastoma, melanoma and SKNMC tumor cell lines, in vitro	Growth inhibition; apoptosis; down-regulation of MMP-2 and MMP-9; increase in TIMP1; inhibition of migration	Papi et al. [78]
Medulloblastoma cell lines in vitro and in vivo	Together with interferon-gamma restore caspase-8 expression and sensitize to TRAIL-induced cell death	Häcker et al. [73]
Medulloblastoma cell lines in vivo	Prolongation of survival; inhibition of proliferation and angiogenesis; apoptosis; differentiation	Shu et al. [79]
Medulloblastoma cell lines in vitro and in vivo	Cell cycle arrest; apoptosis; senescence; differentiation; activation of p21; suppression of TP53, CDK4 and C-myc; inhibition of tumor growth in vivo	Li et al. [76]
Pancreatic and colon cell lines in vitro	Up-regulation of GRP78; inhibition of APP; inhibition of cell proliferation	Venkataramani et al. [77]
Neuroblastoma model	Synergistic effect with interferon-alpha; inhibition of cell growth; neuronal differentiation; down-regulation of N-myc, up-regulation of bcl-2 and neuronal adhesion molecule; up-regulation of thrombospondin-1 and activin A	Cinatl et al. [72]
Human breast cancer cell lines in vitro	Up-regulation of MT1 receptor; inhibition of proliferation with melatonin	Jawed et al. [81]

GFAP glial fibrillary acidic protein, *MMP* matrix metalloproteinases, *TIMP* tissue inhibitor of matrix metalloproteinases, *TRAIL* tumor necrosis factor-related apoptosis-inducing ligand, *CDK* cyclin-dependent kinase, *TP53* tumor protein 53, *GRP78* glucose regulate protein 78, *APP* beta-amyloid precursor protein, *MT1* melatonin

rendering them vulnerable to tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)-mediated apoptosis and suppressed tumor growth in vivo [73]. Regarding cell growth, most studies with valproic acid report reduced proliferation rates and/or apoptosis in different malignant cell types [74]. Valproic acid treatment resulted in up-regulation of p21/WAF1, suppression of CDK4 and cell cycle arrest [75–77].

Besides causing growth arrest and apoptosis, valproic acid may also interfere with other fundamental processes of carcinogenesis. For instance, valproic acid decreased the invasive capacity of neural crest-derived human tumor cell lines via inhibition of matrix metalloproteinase-2 and matrix metalloproteinase-9 (MMPs) and induction of tissue inhibitor of metalloproteinases-1 [78]. In addition, in vivo medulloblastoma models treated with valproic acid display decreased growth rates and angiogenesis [79].

Several studies aimed to introduce simultaneous anticancer and antiepileptic therapeutic interventions by taking advantage of valproic acid's gene-modulating properties. In this way, valproic acid enhanced the cytotoxicity of nitrosoureas and etoposide in glioma cells and synergized with interferon-alpha and gamma to suppress neuroblastoma and medulloblastoma growth, respectively [72, 73, 75, 80]. Valproic acid up-regulated melatonin MT1 receptor expression in C6 glioma and breast cancer cells and in combination with melatonin-inhibited cell proliferation [81]. In association with rapamycin, LY294002 and temozolomide, valproic acid triggered autophagic death in glioma cells [82]. Since valproic acid's anticancer activity has been documented in a number of solid tumors, including some that frequently invade the brain, its potent antitumoral effect against brain metastases remains to be clarified [70].

Table 3 Summary of important findings from clinical trials analyzed in the manuscript

Study	No. of patients	Diagnosis	Anticonvulsant agent	Conclusions	Reference
Meta-analysis of 4 randomized clinical trials and 8 cohort studies to assess efficacy of prophylactic anticonvulsant medication in cancer patients	1,017	Brain metastasis, glioma, meningioma, sellar tumor	Phenytoin, valproic acid, phenobarbital, others	Prophylactic administration of AEDs is not indicated, AED-associated side effects are especially common and occasionally life-threatening	Glantz et al. [14]
Meta-analysis of five prospective randomized controlled trials to assess efficacy of prophylactic anticonvulsant medication in brain tumors	403	Brain metastasis, glioma, meningioma	Phenytoin, valproic acid, phenobarbital	No evidence for AED prophylaxis in patients with brain tumors and no history of seizures	Sirven et al. [26]
Prospective study about seizure incidence and role of prophylactic anticonvulsants	64	Glioma	Phenytoin, levetiracetam	Prophylactic AED treatment is not justified	Rosati et al. [27]
Prospective randomized study on the efficacy of prophylactic AEDs in brain tumor patients	100	Metastatic and primary brain tumors	Phenytoin, phenobarbital	Prophylactic AED therapy is not justified	Forsyth et al. [29]
Prospective study on the efficacy of prophylactic AEDs in surgically treated supratentorial neoplasms	128	Supratentorial neoplasms	Phenytoin, phenobarbital	Benefit of a short-term preventive treatment with AEDs after surgery	Franceschetti et al. [32]
Retrospective analysis of the efficacy and tolerability of levetiracetam as perioperative seizure prophylaxis in supratentorial brain tumors	78	Glioma, meningioma, primary CNS lymphoma, brain metastasis, radiation necrosis	Levetiracetam	Low (2.5%) seizure frequency in the early postoperative period with levetiracetam; drug well tolerated	Zachenhofer et al. [34]
Retrospective analysis of the effectiveness of levetiracetam in brain tumors	41	Glioma, primary CNS lymphoma, brain metastasis	Levetiracetam	Levetiracetam proved very effective in brain tumor patients with seizures	Newton et al. [41]
Observational study on the efficacy of AEDs in patients with brain tumors and seizures	99	Glioma, ependymoma, meningioma, brain metastasis	Valproic acid, levetiracetam, carbamazepin, lamotrigine	The combination of valproic acid and levetiracetam proved the most efficient	van Breemen et al. [44]
Retrospective analysis of the efficacy, safety and impact on life expectancy of levetiracetam, oxcarbazepine and topiramate monotherapy in patients with seizures and brain metastases	70	Brain metastases	Levetiracetam, oxcarbazepine, topiramate	Significantly reduce seizure frequency, produce few side effects and appear not to affect life expectancy	Maschio et al. [51]
Retrospective analysis evaluating the effects of enzyme-inducing and non-enzyme-inducing AEDs in patients with GBM treated with standard chemotherapeutic agents on survival and hematotoxicity	168	GBM	Carbamazepine, phenytoin, valproic acid	Significantly increased survival with non-enzyme-inducing AEDs compared to enzyme-inducing AEDs; increased hematotoxicity with valproic acid	Oberndorfer et al. [88]
Correlative analysis of enzyme-inducing anticonvulsants use with outcome	620	GBM	Enzyme and non-enzyme-inducing AEDs	Paradoxically, enzyme-inducing AEDs correlated with better outcome of patients with glioblastoma	Jaeckle et al. [89]
Retrospective analysis in children to determine whether AEDs compromise the efficacy of cancer chemotherapy	716	Acute lymphoblastic leukemia	Phenytoin, phenobarbital, carbamazepine	Enzyme-inducing AEDs increases the systemic clearance of several antileukemic agents and lower efficacy of chemotherapy	Relling et al. [90]

CNS central nervous system, *AED* antiepileptic drug, *GBM* glioblastoma multiforme

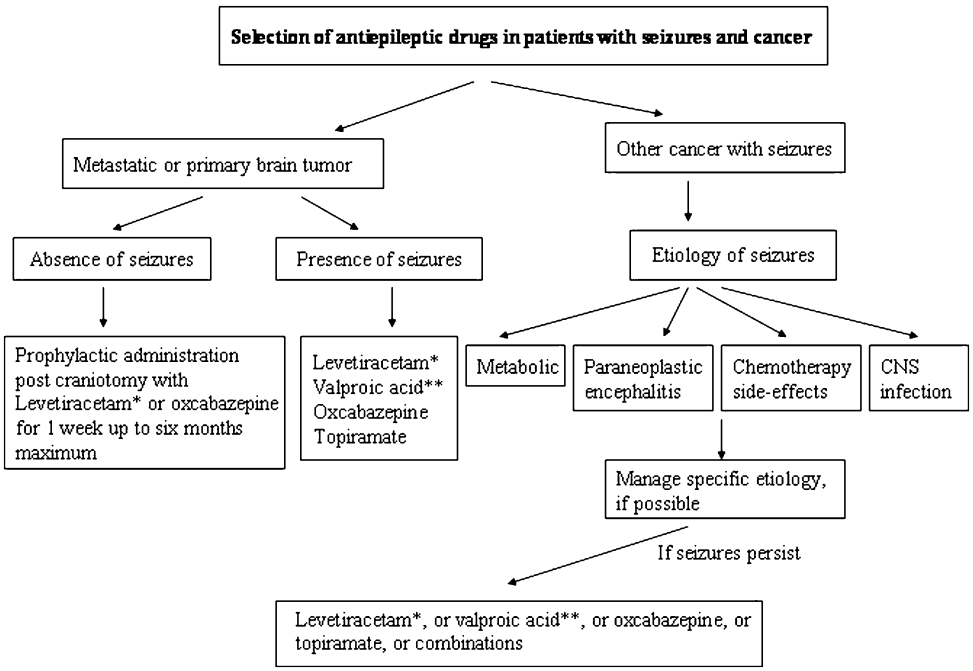

Fig. 1 Algorithm for antiepileptic drug selection in patients with epilepsy and cancer. *Levetiracetam is especially recommended when the primary tumor is treated with alkylating agents. **Valproic acid has anticancer activities. Frequent serum levels, complete blood count and liver function tests should be monitored

Interestingly, the valproic acid-induced hyperacetylation of histones may contribute to the enhancement of radiotoxicity in tumor cells. Thus, the growth of brain tumor xenografts in mice was further inhibited when irradiation was combined with valproic acid administration [83]. Similarly, Chinnaiyan et al. [84] reported that radiosensitization of glioma cells by valproic acid was sustained up to 24 h and involved the modulation of DNA repair processes associated with the histone gammaH2AX [84].

Recently, Bobustuc et al. [85] evaluated the effect of antiepileptics on O(6)-methylguanine-DNA methyltransferase (MGMT) expression in gliomas [85]. MGMT is a DNA repair enzyme that has been recognized to play a pivotal role in enhancing resistance to alkylating drugs, such as temozolomide. MGMT is frequently up-regulated in gliomas, rendering alkylating treatment insufficient [86]. In a clinical study, endogenous methylation and subsequent silencing of MGMT promoter proved to be an independent favorable prognostic factor in patients with glioblastoma. Moreover, only patients with tumors harboring a methylated MGMT promoter benefited from temozolomide treatment [87]. In the study by Bobustuc et al. [85], it was shown that levetiracetam is a potent inhibitor of MGMT that augments p53 binding on the MGMT promoter by recruiting the mSin3A/histone deacetylase 1 (HDAC1) corepressor complex. Subsequently, levetiracetam sensitized glioma cells to temozolomide. Thus, it was suggested that in glioblastoma cases with MGMT over-expression, levetiracetam may enhance the cytotoxic effect of chemotherapy [85].

Limited data in the literature is available regarding the influence of antiepileptic drugs on survival of patients with brain tumors. Non-enzyme inducers and particularly valproic acid that exerts tumor inhibitory effects are shown to prolong survival of glioblastoma patients receiving CCNU chemotherapy compared to enzyme inducers (carbamazepine) [88]. On the contrary, a more recent study reported enhanced overall survival of glioblastoma patients receiving enzyme-inducing anticonvulsants, without proposing an explanation for the mechanism other than the possible increased toxicity by non-enzyme inducers [89]. The application of enzyme-inducing antiepileptics in pediatric patients with acute lymphoblastic leukemia, receiving concomitant chemotherapy, was associated with increased hematological and CNS relapse as well as worse event-free survival. The authors documented accelerated clearance of teniposide and methotrexate but not of cytarabine and linked the unfavorable outcome to the lower efficacy of chemotherapy due to the up-regulation of catabolic enzymes [90].

Table 3 summarizes the results from some important clinical studies analyzed in this review. Large scale clinical studies are needed to investigate the possible antitumoral contribution of certain antiepileptics in humans with primary or metastatic brain tumors. There is preclinical evidence that molecular targeted combination of these agents with the available therapeutic interventions might offer survival benefit in patients with cancer. Although recent clinical studies evaluating seizure control reported conflicting results regarding overall survival by the use of

valproic acid in patients receiving anticancer treatment, these studies were not designed to take advantage of the possible antitumoral and synergistic mechanisms of action of valproic acid according to preclinical data [44, 88, 89].

Conclusion

The management of cancer-related epilepsy is often challenging but also very substantial for the patients, the majority of which are associated with an unfavorable survival outcome. An algorithm for the proper selection of an antiepileptic drug in patients with cancer and epilepsy is depicted in Fig. 1. Although patients with primary or metastatic brain tumors are susceptible to epileptic seizures, prophylactic anticonvulsant treatment is not indicated, since many patients may never develop seizures and in addition it can increase unnecessary toxicity. However, the prophylactic use of anticonvulsants could be an acceptable decision postoperatively, after surgical excision of the tumor mass and for a limited time period, less than 6 months, provided that the patient has remained seizure free after surgery. For such antiepileptic prophylaxis newer agents, such as levetiracetam and oxcarbazepine are superior to older ones like phenytoin. In patients with brain tumor-induced epilepsy, certain antiepileptics, such as levetiracetam and valproic acid, are beneficial. Alternative antiepileptic drugs include oxcarbazepine and topiramate because of their tolerance, efficient seizure control and absence of significant interactions with anticancer drugs. Controlling the epileptic seizures and contributing to tumor suppression simultaneously would represent an attractive therapeutic approach against primary or metastatic brain tumors.

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