Review

Epilepsy in Neuro-Oncology: a review with practical management approach

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SUMMARY: *Seizures in oncologic patients represent an important clinical and social complication. Their management needs considering several aspects, among which: (1) seizures recurrence and pharmacoresistance; (2) increased sensitivity to the adverse effects of antiepileptic drugs, (3) changes in clinical response in relation to the progression of the disease, (4) adverse interactions between antiepileptic drugs and chemotherapeutic agents. We can delineate three clinical scenarios in which seizures occur: (1) seizure or epilepsy in patients with a structural "active" neoplastic brain lesion(s) (primary or metastatic), strictly and commonly identified as "brain-tumour associated epilepsy"; (2) seizure or epilepsy in patients without an "active" neoplastic brain lesion, but expression of a structural lesion: peri/post-operative period for any other central nervous system oncologic surgery (e.g. oedema or haemorrhage in pituitary adenoma etc); vascular, paraneoplastic, treatment and infectious complications in systemic cancers; history of a previous central nervous system tumour but not expression of active neoplastic central nervous system disease (e.g. follow-up of meningioma etc); (3) Seizure or epilepsy in other various conditions of any cancer, toxicity of its treatments (mainly acute central nervous system radiotherapy); metabolic and treatment complications in systemic cancers etc. This paper addresses to physicians, in order to choose adequate management and pharmacologic approach in treatment of seizures associated with tumours. The present review refers only to adult patients.*

KEY WORDS: *Anticonvulsants, Brain tumours, Epilepsy, Systemic neoplasms, Treatment guidelines.*

INTRODUCTION

The historical paper of Wroe et al. (1986)[54] describes the differences between neurological and neurosurgical approaches in the management of malignant brain tumour, drawing the conclusion that the neurosurgeon's "interventionist approach was more common, although it did not significantly affect favourably long-term survival". Anyway, surgery in brain tumours is crucial for gaining tumour tissue for histological analysis and relieving symptoms due to neoplastic mass effect and this is much truer as far as the resection of the tumour mass is as extensive as possible.

According to Grisold et al.[16], modern neuro-oncology is a growing new sub-speciality with a strong interdisciplinary character; ranging from internal medicine to radiology, pharmacology and palliative care medicine. Neuro-oncology deals with central (brain and spinal) and peripheral nervous system primary and metastatic tumours and non-metastatic effects of systemic cancers and its treatments. Topics of interest are also drug interferences, neurotoxicity due to cancer treatments, supportive management and neuro-protection, in respect of issues of quality of life. In this context, seizures represent one of the most common clinical features of brain tumour and their

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LIST OF ACRONYMS AND ABBREVIATIONS: **5-FU**= 5-FluoroUracil; **AAN** = American Academy of Neurology; **AANS** = American Association of Neurological Surgeons; **AED** = AntiEpilectic Drugs; **AINO** = Associazione Italiana di Neuro-Oncologia; AP-1 = Alkaline phosphatase 1; **ATLS** = Acute Tumour Lysis Syndrome; **BBB** = Blood-Brain Barrier; **BCNU** = 1,3-Bis(2-Chloroethyl)-1-NitrosoUrea; **BDZ** = BenzoDiaZepine; BID= Bis In Die (Latin: Twice A Day); **BMT** = Bone Marrow Transplant; **CBZ** = CarBamaZepine; CCNU = 1-(2-Chloroethyl)-3-Cyclohexyl-1-NitrosoUrea; **CD4** = cluster of differentiation 4; **CDDP** = Cis-Dichloro-Diamine-Platinum (cisplatinum); **C-Myc** = mRNA Cap Methylation; **CNS** = Central Nervous System; **CT** = ChemoTherapy; **CTD** = ChemoTherapy Drug; **CX** = ConneXins; **DNA** = De-oxyriboNucleic Acid; **DNET** = Dysembryoplastic NeuroEpithelial Tumours; **EEG** = Electroencephalogram; **EIAED** = Enzyme Inducing AntiEpileptic Drugs; **FB**M = FelBaMate; **GABA** = Gamma-AminoButyric Acid; **GBM** = GlioBlastoma Multiforme; **HAT** = Hystone AcetylTransferase; **HDAC** = Hystone De-ACetylase; **HGG** = High Grade Glioma; **HSCT** = Human Stem-Cell Transplant; **IDH** = Isocitrate De-Hydrogenase; **INF** = Interferons; **LCS** = LaCoSamide; **LEAT** = Long-Term Epilepsy-Associated Tumour; **LEV** = LEVetiracetam; **LGG** = Low Grade Glioma; **LGI1** = Leucine-rich Glioma Inactivated 1; **LMT** = LaMoTrigine; **MAB** = Monoclonal AntiBody; **MGMT** = O-6-MethylGuanine-DNA MethylTransferase; **MRP** = Multidrug Resistance Protein; **MTX** = MethoTreXate; **NCSE** = Non-Convulsive Status Epilepticus; **NEIAED**= Non-Enzyme Inducing AntiEpileptic Drugs; **NFKb** = Nuclear Factor Kappa-light-chain-enhancer of activated B cells; **NMDA-AMPA** = N-Methyl-D-Aspartate - α-Amino-3-hydroxy-5-Methyl-4-isoxazolepropionic acid; **OXC** = OXCarbamazepine; **P-21** = P-21 activated kinase; **PB** = PhenoBarbital; **PCNLS** = Primary Central Nervous System Lymphoma; **PCV scheme** = Procarbazine, CCNU and Vincristine scheme; **PHB** = PHenoBarbital; **PHT** = PHenyToin; **PML** = Progressive Multifocal Leukoencephalopathy; **PNS** = Periferic Nervous System; **RANO** = Response Assessment in Neuro-Oncology; **RPLS** = Reversible Posterior Leukoencephalopathy Syndrome; **RT** = RadioTherapy; **SE** = Status Epilepticus; **SIADH** = Syndrome of Inappropriate Antidiuretic Hormone secretion; **TAE** = Tumour Associated Epilepsy; **TMZ** = TeMoZolamide; **TPM** = ToPiraMate; **VPA** = Valproic Acid; **WHO** = World Health Organization.

treatment usually follows general rules with some important warnings.

Neurologists should be the coordinators in the diagnosis and treatment process, because they can synthesize and transfer medical evidence inside the multidisciplinary team.

Epilepsy incidence varies according to tumour location and histological type. In 30-50% of patients, a seizure is the first clinical manifestation of brain tumour and up to 30% will later develop seizures. Occurrence of status epilepticus has been reported to be rare, but its course is more severe, although shorter than the one observed in non-tumoural epileptic patients[1].

Low-grade tumours are more epileptogenic than high grade tumours, with DNET displaying a 100% probability to present with seizures, immediately followed by gangliogliomas and LGG whereas GBM onset with seizure accounts for 68%[10,11].

Solid brain metastases seem to cause seizures less frequently than primary brain tumours. New-onset seizures in patients with known brain metastatic lesions may indicate a haemorrhage in the lesion or tumour progression with oedema[51].

Management of seizures may affect directly and deeply the long-term survival in oncologic patients; many papers have shown significant differences in the use of AEDs as well as the importance to consider concomitant treatment in choosing them[35,39].

As shown in Table 1, seizures or status epilepticus are observed as onset symptom or during the course of disease in various oncological conditions[34].

In this setting, it is useful to maintain the distinction between acute symptomatic seizures, unprovoked late seizures and epilepsy, as suggested more than twenty years ago by the Commission of Epidemiology and Prognosis of the International League Against Epilepsy[20].

□ EPILEPTOGENIC MECHANISMS AND EPIGENETIC PHARMACOLOGIC FEATURES

According to You et al.[55], there seem to be two main explanations about the pathogenesis of tumour-related epilepsy: the former relies upon a biochemical theory (excretion of molecules from the tumour, changes in peri-tumoural microenvironment, changes within the tumour cells), and the latter tends to a mechanical explanation (compression of normal tissue surrounding the tumour with subsequent ischemia and hypoxia, which might increase epileptogenesis). Both processes could potentially cause secondary changes, such as changes in neurotransmitters and their receptors, metabolic changes, and inflammatory responses, eventually leading to epileptic seizures.

Many possible mechanisms to explain epileptogenesis in brain-tumour have been singled out, among which: damage of subcortical network (HGG) or partial deafferentation of cortical regions (LGG), inflammatory changes, blood-brain barrier disruption, morphologic changes (inefficient neuronal migration, changes in synaptic vescicles), gap-junctions alterations through aberrant connexins hyperexpression, ionic changes, molecular genetic changes (low or absent

Causes	Incidence	Remarks
Tumour-Related		
- High-grade glioma	~ 30-40%	Further 30% develop in the follow-up
- Low-grade glioma	> 80%	The most common presenting feature
- Meningioma	~ 20-40%	
- Lymphoma (PCNSL)	~ 10-20%	
- Brain mtastases	~ 20-40%	Particularly frequent in hemorrhagic mets (melanoma, etc)
- Meningeal carcinomatosis	~ 10-15%	
Treatment-Related		
- Chemotherapy	< 1% intravenous systemic CT ~ 4% > if INF or 5-FU > 20% intra-arterial or HSCT/BMT	More frequent when the drugs are given intrathecally/arterially or when BBB is disrupted
- Supportive treatments	Rare, but possible and to be kept in mind	Overdose of the same AEDs, certain antibiotics (quinolones, β-lactames, penicillins) triciclic antidepressants, neuroleptics; ciclosporin A; ondansetron, RPLS
- Acute irradiation	Not determined	Difficult to assess because of several confounding factors
- Late-delayed radionecrosis	~ 20-30%	
Myscellany		
- Metabolic causes	Variable (to severity)	Electrolyte abnormalities, hypoglycemia, SIADH, ATLS, etc
- Vascular (acute or sequelae)	> 10%	
- Infectious	> 20%	Incidence increasing in cancer pts
- Limbic encephalitis	> 60%	Paraneoplastic or viral (in immuno-compromised hosts) and difficult to diagnose if NCSE

Table 1. Main causes of epileptic seizures in cancer patients (not only intracranial structural lesions).

expression of tumour-suppressor gene LGI1), genomic and chromosomal instability, peri-tumoural and tumoural microenvironment imbalance (decreased levels of N-acetylaspartate), changes in amino-acids and neurotransmitter receptors.

It appears then clear that tumors are evolving processes, in which, from an epileptic point of view, different situations can co-exist and contribute to change the seizure frequency as well as condition a different response to the same antiepileptic therapies. The choice of AEDs in neuro-oncology relies on pharmacokinetic characteristics (e.g. enzymatic inducers versus non-enzymatic inducers). Recent studies suggest that, in addition to antiepileptic properties, AEDs have a role as epigenetic modifiers.

Two of the most common forms of epigenetic modification are the acetylation of histones and DNA methylation: the balance between DNA acetylation and deacetylation status is of utmost importance for cell survival and growth. This biochemical process is partially regulated by the activity of hystonedeacetyltransferase and acetyltransferase enzyme. HDACs can modify chromatin structure by removing acetyl groups from histones, resulting in DNA condensation and transcriptional repression.

In tumour cells HDAC activity increases, thus repressing the transcription of genes encoding for antitumour factors, differentiation and cell cycle progression, that is to say, cell growth and proliferation increase, apoptosis reduces.

Glioblastomas meet extensive alterations in methylation of DNA, in addition to alteration of histones acetylation. MGMT is an enzyme that deals with DNA repair: in GBM it undergoes epigenetic modification. The silencing of MGMT via hypermethylation of the promoter represents a positive prognostic factor, be-

cause it promotes the effect of chemotherapeutic alkylating agents by preventing a repair mechanism.
The role of antiepileptic drugs in modulating the acetylation histones state and DNA methylation has also been studied in vitro and in tumour animal cells[7]. Most studies have focused on valproic acid, only a small number were carried out on carbamazepine and levetiracetam.
VPA inhibits HDAC activity in multiple cancer cell lines and animal tumour models. Histone hyperacetilation resulting from VPA exposure appears to be reversible.
VPA shows effects on transcriptions factor such as AP-1 and NFKb, p 21, Cd4, C-Myc as well as on pathways of cell growth and proliferation. VPA has also demonstrated both direct and indirect antiangiogenetic effects inhibiting endothelial cell proliferation in culture and tube formation, in an angiogenesis assay, as well as vascular endothelial growth factor secretion in cultured glioma cells.
In summary, VPA can interfere with the pathways used by tumour cells to escape normal growth restrictions, which would effectively slow the progression of malignancy.
Retrospective studies have shown that adjunct treatment of glioblastoma patients with VPA is associated with an improved survival, in particular in those patients receiving TMZ and radiotherapy[50].
These data have not been confirmed by recent prospective clinical studies, in which valproate use was not associated with improvement of survival[17]. The survival of patients who received VPA did not differ significantly from those with seizure who did not receive VPA. In a multivariate analysis, the association between VPA treatment and survival remained non-significant.
In summary, results of the effective role of VPA on survival in glioblastoma patients are still an open debate. Clinical trials are ongoing on the role of VPA as a HDAC inhibitor.
The epigenetic effect of CBZ and LEV is not yet established, but recent suggestions regarding additional mechanisms of action hold some promises.
For CBZ an inhibitory mechanism on HDAC has been hypothesized, whereas for LEV a modulation of MGMT expression has been speculated. Mechanisms of new AEDs such as lacosamide and perampanel deserve further clinical studies.

☐ ROLE OF HISTOLOGY AND LOCATION OF BRAIN TUMOUR IN SEIZURES

Seizure incidence in brain-tumour patients varies according to tumour location and histology.
Any type of brain tumour can cause epilepsy. The less malignant ones are most involved in the highest rate of seizure recurrence and pharmacoresistance. Smaller tumours and the slow-growing ones are associated with higher rates of seizures than large and rapidly growing neoplasms[10].
The concept of LEAT describes a group of patients affected by low-grade brain tumour and focal chronic epilepsy[11].
Some oncologic subtypes (namely glioneural tumours) are often associated with alterations of cortical development, such as focal cortical dysplasias. In this setting, “dual pathology” (the combination of foreign-tissue lesions, cortical dysgenesias, gliosis or hippocampal sclerosis) represents another strong stimulus contributing to epileptogenesis, particularly in the temporal lobe[11].
The location in cortical areas, obviously, more easily provokes seizures.
HGG causing seizures are mainly located in the temporal lobe, followed by the frontal lobe[23]. LGG are mainly found in the insular, fronto-insular, temporo-insular regions and paralimbic structures[27].
LEAT mainly arises in the temporo-mesial structures (namely limbic lobe) in the site of allo-isocortical transition, where more frequently a neuronal differentiation can be seen.
The incidence of TAE relates to the topographic distribution of brain tumour: previous works suggest that frontal and temporal regions are particularly at risk of seizures or hypothesize that the left hemisphere is more prone to an epileptogenic onset of the disease[19]. Our data taken from a previous study[32,35] do not support this topographic site/side distinction in GBM-patients: in an Epilepsy Onset group there are a right hemisphere-sided prevalence and a slight prevalence of frontal, temporal or carrefour lesions, which however do not reach a statistical significance, but they are worth further studies.
Moreover, the mechanisms of epileptogenesis vary according to the different tumours, because some of them are of intra-axial origin (astrocytoma), whereas others are of extra-axial origin (meningioma).
Epilepsy occurs in > 80% of patients with low-grade glioma and 40-60% of patients with glioblastoma[4,48].

Seizures are less common in patients with brain metastases and incidence varies according to primary tumour pathology. In a retrospective study including 470 patients with brain metastases, 24% of patients had experienced tumour related seizures[10]. While seizures occurred in only 16% of individuals with breast cancer and 21% of those with gastrointestinal metastases, seizure incidence was 29% in lung cancer patients and 67% in those with melanoma, maybe due to the more frequent intracranial haemorrhage in this tumour type.
Genetically subtypes of the same hystologic brain neoplasm show different predisposition to develop epilepsy: newly diagnosed GBM but arising as an evolution of a previous LGG (GBM IDH-mutant), are more epileptogenic lesions than wild-type GBM.
All the previous considerations suggest that the aetiology of TAE is multifactorial, involving host and tumour factors. Therefore, even the response to the various AEDs might be different.

□ CLINICAL AND EEG FEATURES OF SEIZURES

In brain tumours, seizures are always focal, with or without alteration of consciousness and/or secondary generalization. Clinical presentation differs according to the lobar involvement and lesion localization (just like non-tumoural epilepsy) but sometimes the correct characterization of seizures might be more difficult due to adjunctive concurrent symptoms secondary to mass growth and swelling, particularly in HGG. In LEAT focal epilepsy is the most common symptom, often the only one, and pharmacoresistance is quite common. Neurological deficits are uncommon in LEAT group, due to the slow growing, whereas in HGG neurological impairment is more common early or during the course. Secondary generalization can always occur, expecially for LEAT located in extra-temporal sites.
EEG characteristics are not specific. Interictal scalp EEG may disclose epileptiform activity (spikes, sharp waves) generally lateralized to tumour site, with or without focal slow activity of lesional origin, this being particularly true for wide mass or after surgery.
Status epilepticus is a well-known condition that can be observed both in epileptic patients and in general population as presenting symptom of epilepsy.
Convulsive SE is defined as tonic-clonic seizures lasting more than 30', even if recent papers have underlined the importance of starting the treatment as soon as possible, within 5' from onset, seen that a convulsive seizure usually lasts no more than 1-2'[13].
Non-Convulsive SE might occur as well, it requires a careful history collection and EEG registering. SE in general population constitutes a neurological emergency, and has significant associated morbidity and mortality.
Globally, patients with TAE are less likely to develop SE than patients with epilepsy in general population[14]. In most cases, TAE presents earlier in the course of the disease, while SE in TAE patients occurs far later in disease course, sometimes to herald tumour progression, as to mean that there is a progressive impairment of the mechanisms which can terminate seizures. In glioma patients also status epilepticus (defined as a continuous seizure for 30 minutes or more) has more severe course and it is associated (as in all brain tumours) with higher mortality and possibly longer duration than in status epilepticus due to other causes[1]. Even when underlying tumour is stable, status epilepticus in glioma and other tumour patients has longer seizure duration, more and longer postictal neurologic deficits and higher rate of long-term neurological deficits[41].
The treatment replies those used in general population, with a care for drugs that can have inducing or non-inducing enzyme properties, especially in patients who follow chemotherapeutic cycles.

□ PATHOGENESIS AND PHARMACORESISTANCE OF TAE

Various causes of drug resistance in TAE have been identified:
- pathophysiology of brain tumour-related seizures
- progressive course of the disease;
- neurosurgical complications (such as meningitis or brain abscess);
- adverse effects of oncological treatment (radio-necrosis, posterior leukoencephalopathy);
- consequences of pharmacokinetic drug interactions
- various and often higher rates of adverse events by AEDs in this population;
- over-expression of multidrug transporter proteins in brain tumour, that cause reduced brain penetration of AEDs ("transporter hypothesis");
- alterations in drug targets that AEDs normally bind in tumour and peritumoural tissue ("target hypothesis");

Drug resistence mechanisms	
Target hypothesis	**Transport hypothesis** (= low level at site of action)
- mismatch AEDs mechanism of action and TAE pathogenesis - tumor relapse/progression	- serum (because of interactions) - MRP1

Table 2. Summary of drug resistance mechanisms in tumor associated epilepsy.

- altered characteristics of blood-brain barrier in brain tumours.

Despite the common view that voltage-gated ion channels controlling cell excitability and synaptic processes responsible for communication among neurons are involved, the specific events leading to TAE are unknown and comprise many changes above mentioned. We can find several reasons for the clinical inefficacy of AED treatment. First, most AEDs act on excitatory mechanisms by blocking and deactivating Na+ channels and/or Ca^{2+} channels, or they enhance inhibitory mechanisms through an increase of GABA-ergic activity. These two important modes of action of AEDs, however, cover only a few of the pathophysiologic mechanisms of TAE[40]. Second, low levels of AEDs have been reported in 60-70% of patients. This is not related to the pathophysiologic mechanisms of TAE, but it is a consequence of the fact that therapeutic AED levels in patients with brain tumours are difficult to maintain because of frequent pharmaco-dynamic and kinetic interactions with concomitant medications, and from changes in plasma protein (especially albumin) levels. Additionally, the multidrug resistance protein-1 may play a role. Recent hypotheses propose that transport of AEDs by drug efflux transporters MRP such as P-glycoprotein to the blood-brain barrier may play a significant role in pharmacoresistance in epilepsy by extruding AEDs from their intended site of action. Over-expression of proteins that belong to the multidrug-resistance pathway can impact at site of action levels of CBZ/OXC, PHT, PHB, LMT, FBM; or it can exert no effect on LEV; no information is available for TPM[26]. Finally, reappearance of seizures during AED treatment may reflect tumour progression-recurrence or a provoked seizure in a particular phase of the disease.

Table 2 synthesizes mechanisms of AEDs resistance.

At the macroscopic level, slow-growing tumours produce an epileptogenic focus by partial deafferentation of cortical regions, thus causing a denervation hypersensitivity. Recent studies[3] using magneto-encephalography to investigate the functional connectivity between brain regions have suggested that low-grade gliomas, through infiltration of white matter and not only infiltration of the cortex, could modify the natural balance and synchronization of normal networks and cause random networks that might have a lower threshold for seizures generating secondary epileptogenesis[30]. Differently from low-grade gliomas, high-grade tumours, such as GBMs or metastases, induce seizures via abrupt tissue damage due to necrosis, bleeding with subsequent hemosiderin deposition and oedema.

The putative mechanism of epilepsy in extrinsic tumours[24], i.e. meningiomas, or seizures/status epilepticus in the immediate post-operative period for a pituitary adenoma or craniopharyngioma, apart from other complications, is likely related to peritumoural oedema, possibly explaining the high frequency of preoperative seizures in supratentorials and the possible regulating role of H2O flux and uptake exerted by Aquaporin-4[9].

□ EPILEPSY IN GENERAL ONCOLOGY

As specified in Table 1 in routine clinical practice, seizures, *with* a radiographic documentation of the epileptogenic lesion, are encountered as an acute manifestation: vascular (such as ischemic or hemorrhagic stroke, sinus thrombosis, thrombotic thrombocytopenic purpuraor sequelae), paraneoplastic (limbic encephalitis) infectious (meningo-encephalitis, abscess, PML, etc.) and treatment-related (RPLS) complications in systemic cancers[15].

In routine clinical practice, seizures, *without* radiographic abnormalities, are encountered also as a manifestation of treatments (CT, MAB) and metabolic complications in systemic cancers:

- electrolyte abnormalities, hypoglycemia, SIADH, lactic acidosis, hyperammonaemia,

Epilepsy in oncology	
Mechanism of epileptogenesis	- Direct effects on neuronal excitability: altered excitatory NMDA-AMPA or inhibitory GABA pathways - Neurotransmitters : adenosine, glutamate, etc. - Indirect effects via electrolyte disturbances: hypomagnesemia, hyponatremia, hypocalcemia, etc. - Vasogenic oedema: disruption of the BBB - Vascular mechanisms: endothelial damage, mineral microangiopathy, nitric oxide reduction, hyperomocisteine, etc. - Structural lesions: subcortical leukoencephalopathy ("U" fibers), reversible-posterior-leukoencephalopathy, iemporo-mesial lobe atrophy, etc.
Agents of late unprovoked or provoked seizures	- Cyclosporin A, CDDP, MTX - MTX, 5-FU - CDDP, pamidronate - INF- α, 5-FU - Cyclosporin A, tamox, MTX - Cyclosporin A, 5-FU, MTX, in RT cranio-spinal or naso-pharyngeal

Table 3. Main mechanisms of epileptogenesis and agents of late unprovoked or provoked seizures in oncology.

- drug toxicity for instance, following accidental overdosage, or in presence of renal or hepatic disorders (when routine dosages of the agents can lead to toxicity),
- a high dose CT schedule or the administration as part of myeloablative treatment in preparation for human stem-cell or bone marrow transplant[33,36].

Main mechanisms of epileptogenesis and agents of late unprovoked or provoked seizures in these patients are described in Table 3.

□ SUGGESTIONS ON MANAGEMENT

In clinical practice, the neurologist should examine the following items:

1. When should we start antiepileptic drug treatment?
2. Should the approach be different in considering the different tumour histotypes?
3. Which factors should be considered in AED selection?
4. Could we stop the antiepileptic therapy in seizure-free patients?

In patients who manifest seizure as clinical onset of glioblastoma have better prognosis than patients without epilepsy at presentation. Berendsen et al.[4] speculates that GBM patients with epilepsy differ in several oncogenic pathways, again supporting the idea that there is a specific tumour related pathophysiology.

All established anti neoplastic treatment modalities for gliomas are associated with improvement of epilepsy:

- resective glioma surgery decreases frequency of seizure and increases a chance of seizure freedom[28]. Even simple "lesionectomy" can increase chances of seizure freedom, but pre or intraoperative localization and resection of epileptogenic brain region obviously increase this chance. Early surgical intervention showed a strong tendency to predict better seizure outcome;
- in a randomized trial radiotherapy for low grade glioma resulted in decrease of seizure[49]. Conventional radiotherapy in patients with low grade glioma related epilepsy contributes to reduce frequency and severity of seizure by over 75%. In unresectable low grade glioma, stereotactic interstitial radiation (or gamma knife) improves seizure control. However, occasionally seizure frequency increases after surgery and radiotherapy secondary to complication as edema bleeding or radiation necrosis. Onset of epilepsy is the most common complication of brain metastasis treated with stereotactic radio-surgery[53];
- chemotherapy reduces seizure in 50-65% of patients and 20-40% become seizure free[35]. Tumour mass reduction is the postulated mechanism for this clinical improvement. Direct anticonvulsant power of chemotherapic drugs is also present: in particular, temozolomide has an important and significant anticonvulsant effect[22]. de Groot et al.[8] pointed out the effect of the combination of procarbazine, CCNU (lomustine) and vincristine (PCV scheme). Dexametasone, the gold standard treat-

ment for oedema, reduces the risk of seizure but individual cases of increased seizure risk have been reported. Rare cases of increase seizure frequency have been described in course of some chemotherapy with 5-fluouracil, cisplatyin and vincristine, methotrexate and cytarabine. These following CTDs can increase seizure risk: ifosfamide, L-asparaginase, etoposide (intra-arterial), interleukin-2, busulfan (high dose), BCNU, carboplatin (intra-arterial), cytosine-arabinoside (high dose, intra-arterial), bevacizuimab, interferon alpha, cyclophosphamide, anthracyclines and nitrosureas.

In conclusion, as suggested by Avila et al.[2] in a recent review from RANO working group, seizure outcome is an important response criterion of outcome in glioma treatment.

The following suggestions on the management of epilepsy in oncology are the logical and deductive conclusions rising from the analysis of the above-mentioned literature.

Statements are outlined without any strict and intrusive indication of specific drugs.

In our experience[32,35], this particular population of epileptics has to cope with some additional problems:

- peak doses of AED should be reached as quickly as possible after diagnosis;
- the availability of an intravenous formulation which makes the drug likely to be used even in the peri-operative and emergency period;
- a shift to an intramuscular or subcutaneous administrable AED should be provided for in the terminal phase of the disease when the patient is generally unable to swallow;
- sensitisation reactions to AEDs, or seizures, may appear abruptly and dramatically when the steroid is interrupted (e.g. after surgery or awaiting the beginning of radiotherapy) also considering that steroids enhance the GABA inhibitory effect and therefore should protect from epilepsy;
- although phenytoin, carbamazepine, phenobarbital and divalproex are still the most commonly prescribed AEDs for brain tumour patients, the possible leukopenia or thrombocytopenia is a drawback in a patient who will receive cytotoxic chemotherapy;
- every AED shows a specific profile of CNS toxicity, thus complicating the cognitive, behavioural, physical symptoms;
- within the group of malignant neoplastic diseases, epilepsy associated with brain metastases seems to be more easily controllable than TAE in high-grade gliomas.

☐ ANTICONVULSANT PROPHYLASIS

In May 2000, a Panel of Experts of AAN[12] examined twelve studies (four randomized controlled trials and eight cohort studies) to establish the ability of prophylactic anticonvulsants to prevent first seizures in patients with brain tumours: the meta-analysis showed no statistical benefit. Temkin[46] concludes that for patients with brain tumours, regardless of neoplastic type, and with no prior history of seizures:

1. prophylactic therapy with old-AEDs (PHT, VPA, PB, CBZ) is ineffective;
2. tapering and discontinuing anticonvulsants after the first post-operative week is appropriate.

Besides these two well-known recommendations, TAE prophylaxis is currently still characterized by significant behavioural heterogeneity and the literature lacks robust data concerning efficacy and toxicity of new, recently marketed AEDs.

The prophylactic use of AEDs still remains the prevailing practice pattern among members of the AANS[43].

☐ THE COCHRANE LIBRARY AND "AVAILABLE BEST EVIDENCE"

In the Cochrane Library there are 6 reviews on the subject:

- one[31] on the use of AEDs in the SE and two on the timing and on the rapidity[44] of AEDs withdrawal. These do not specifically analyse the clinical query for the oncological population examined and conclude that it is not yet possible to show the best time to withdraw or the rapidity of the optimal rate of tapering of AEDs. More research is therefore needed for both issues;
- two reviews of outstanding interest: "Antiepileptic drugs for preventing[47] or treating[21] seizures in people/adults with brain tumours". Although the former review substantially shares the conclusion of prophylactic inefficacy on the onset of seizures in formerly epilepsy-free brain-tumour patients, inefficacy already expressed by Glantz's, Temkin's and Sirven's meta-analyses, in the discussion it challenges some methodological biases of AAN Practice Parameters. Therefore, this meta-analysis reports how the evidence for seizure prophylaxis with old AEDs is inconclusive, at best. The decision to start an antiepileptic drug for seizure prophylaxis is ultimately guided by the assessment of

individual risk factors and careful discussion with patients.

The latter review shows how only one small, open-label, unblinded, randomised trial met the inclusion criteria for the evaluation of the safety and feasibility of switching from phenytoin to levetiracetam monotherapy or continuing phenytoin for glioma-related seizure control following craniotomy[25]. Levetiracetam appears to have been at least as well tolerated and as effective as phenytoin for the treatment of seizures in people with brain tumours.

In 2008, a panel of experts of the AINO proposed some practical management statements; we refer in particular to the chapter on management in the Emergency setting, not discussed in this present paper[6]. A 2013 revised version is awaiting publication (http://www.neuro-oncologia.eu/news/aggiunti-nuovi-contributi).

In conclusion, if a long-term antiepileptic prophylaxis is not justified in seizure-free patients, the risk of recurrence after a single seizure is considerably higher in patients with structural brain lesion(s) and initiation of treatment should be considered in these patients[35,45].

❒ **A. Seizure or epilepsy in patients with a structural active neoplastic brain lesion(s)**

As stated before, TAE generally refers to seizure or epilepsy in patients with structural active neoplastic brain lesion(s), primary or metastatic.

Despite the well-known fact that TAE differs from other forms of epilepsy for the underlying mechanism, clinical manifestation and response to treatment, epilepsy treatment protocols mostly do not contain specific guidelines for glioma patients.

Gliomas are progressive in nature therefore type and severity of seizures may evolve over time in relation to underlying tumour. A spontaneous worsening of epilepsy can predict a progression of the glioma

In glioma-associated epilepsy, the percentage of patients who become seizure free varies between 23 and 87% depending on subpopulation and study type[18].

In this "chapter A" group we refer (Table 4) to glioma (WHO grade II-IV) patients, brain or dural metastases, atypical and malignant (WHO grade II-III) meningioma, supratentorial anaplastic (WHO grade III) ependimoma etc., in short, all the lesions which require a further radio-chemotherapy program after surgery:

1. seizure-free patients at onset require only peri-operative (± 7 days before and after surgery) profilaxis with the following limitations, after careful discussion in cases selected according to histology or site risk:
   - the extension of AE profilaxis till the end of radiotherapy,
   - a "prudential long-term profilaxis" because of the patient's will, singularity, physical job risk etc.
2. patients with epilepsy at onset require a long-term profilaxis, established as soon as possible.

As far as drug choice is concerned (Table 5):

- in general, new-AEDs (LEV, chronoVPA, TPM, LCS, OXC in order of our preference) present a more favourable profile both in terms of haematological and cognitive efficacy/toxicity and in terms of pharmaco-kinetic and dynamic interactions with the other treatments[37] (in spite of the above-mentioned adverse effects);
- LEV-VPA-LCS-PHB are available also in parenteral formulations particularly useful in fast titration, status epilepticus, general anaesthesia and terminal phase of disease;
- average dosages are similar to what currently indicated in general epileptic population;
- the titration of the most suitable AED (feasible with the cited drugs) should be performed in the pre-operative period;
- in patients without indications for a long-term prophylaxis or with another in range AED, in case of the neuro-anaesthetist's decision of starting PHT in operating room, PHT should be suspended within two weeks and in any case possibly within RT, because of the high risk of sensitisation of this association;
- low-levels, poor compliance and generic substitution are frequent causes of recrudescence;
- in cases of a "certain" acute symptomatic seizures (e.g.: starting of radio-chemotherapy, febrile intercurrent disease, proved low-level of AED in use, etc.) a short treatment (7-10 days, awaiting resolution/removal of the trigger) with a BDZ in monotherapy or in add-on is advisable: clobazam 10-20 or clonazepam 2-4 mg bid (if at the RT starting, adjunct of dexametasone is useful);
- in cases of proved insufficiency of the current AED the add-on of a second AED (inside the above-mentioned list) with different mechanism of action is preferred to a substitution, because of the pharmaco-resistance;

"Best choice" AEDs	
Ideal drug	- Fast titration - Linear kinetic - Intravenous formulation - High absorption - Low protein bound - Reduced interactions (kinetic and dinamic) - Plasma long half-life - Renal escretion - No epatic enzyme induction - No plasma levels monitoring
Ideal management	• *Clinician-related* - Neutral evidences: therefore only "prudential prophylaxis" in absence of seizure because of: - patient's will (singleness, dangerous job) - site ± histology (temporo-mesial or fronto-rolandic site, hemorragic mets) • *Drug-related* - new AEDs = NEIAED (+ os/iv): LVT, VPAch, LCM, BDZ; or TMP, OxCBZ, etc. - major anti-epileptic efficacy - less toxicity - hematologic - neurologic - absence of interaction - poor sensitivity • Timing and/or Host-related - other AEDs (os/ev/im: TPM, OxCBZ, PHT, PB, BDZ, etc.)

Table 4. Criteria for the "best choice" of antiepilectic drugs.

- in cases of convulsive or non-convulsive status epilepticus, see the specific guidelines cited.

❒ **B: Seizure or epilepsy in patients without any active neoplastic brain lesion but due to a structural change**

This group includes patients:

1. with acute symptomatic seizures in the peri/post-operative period for any other CNS oncologic surgery (pituitary adenoma, craniopharyngioma, etc.) because of brain oedema, haemorrhage or any other complication to be treated in add-on or in monotherapy (in absence of a previous prophylaxis) with a fast acting drug such as BDZs;
2. who may develop chronic epilepsy due to treatment (RT), vascular, paraneoplastic or infectious lesions as complications in a systemic cancer (including RPLS) to be treated as indicated in chapter A.

❒ **C: Seizure or epilepsy in other various conditions of any cancer**

This group includes:

1. patients with a history of a previous CNS tumour or during their follow-up (but not expression of active/relapsing neoplastic CNS disease: meningioma etc.) who may develop an unprovoked late seizure (either a brief simply partial seizure, or a prolonged generalized one) which requires a careful diagnostic and treatment evaluation for the risk of repetition;
2. patients with treatments and metabolic complications in systemic cancer without a radiographic presence of epileptogenic lesion. In the other patients, since most seizures are

Table 5. Current available AEDs: peculiar characteristics in neuro-oncologic patients[35]. *Legenda*: AED = AntiEpileptic Drug; BZD = Benzodiazepines; Ca = Calcium channel; CYP = Cytochrome P-450; GABA = γ-AminoButyric Acid; GBP = Gabapentin; inhib. =enzyme inhibition; iv = intravenous; K = Kidney; L = liver; LCM = Lacosamide, LTG = Lamotrigine; LVT = Levetiracetam; Na = sodium channel; NMDA = N-Mehyl-D-Aspartate; OXC = Oxcarbazepine; PGB = Pregabalin; PHB = Phenobarbital (and primidone); PHT = Phenytoin; RUF = Rufinamide; SIADH = Syndrome of Inappropriate Antidiuretic Hormone Secretion; SV = Synaptic Vesicle; TPM = Topiramate; VPA = Valproic Acid; ZNS = Zonisamide.

Anti-epileptic drug	Parental form	Site of action	CYP-inducer / Metabolism	Protein binding (%)	AED (↓ activity) effect on chemotherapy	Chemotherapy (↓ activity) effect on AED	Adverse effects to consider
PHB	iv + im	GABA	1A2, 2A6, 2B6, 2C9, 2C19, 3A4 / L, K	50	Nitrosurea, Prednisone, Methotrexate, 9-aminocampothecin, Thiotepa, Ifosfamide, Doxorubicina, Tamoxifen, Teniposide, Etoposide, Paclitaxel, Procarbazine, Vincristine	Temozolomide	Drowsiness, Stevens-Johnson, shoulder-hand syndrome, cognitive
PHT	iv	Na	1A2, 2B6, 2C9, 2C19, 3A4 / L, K	90	Dexamethasone, Busulfan, Vinblastine, Vincristine, 9-aminocampothecin, Teniposide, Irinotecan, Methotrexate, Paclitaxel, Procarbazine, Sirolimus, Teniposide, 5-fluorouracil	Nitrosurea, Doxorubicin, Carboplatin, Cisplatin, Temozolomide, Vinblastine, 5-fluorouracil, Dexamethasone, Tamoxifen, Teniposide, Doxorubicin, Procarbazine, Bleomycin, Capecitabine	Rash, Stevens-Johnson, incoordination
CBZ	No	Na	1A2, 2B6, 2C9, 2C19, 3A4 / L	75	Methotrexate, Paclitaxel, Vinblastine, Vincristine, 9-aminocampothecin, Sirolimus Procarbazine	Temozolomide	Stevens-Johnson, anemia, SIADH, ↓ cognitive, leukopenia, diplopia
OXC	No	Na	3A4 / L	40	-	Temozolomide	Rash, diplopia, hyponatremia
BDZ	iv/im + rectal/nasal	GABA agonist	= / L	80	-	-	Sonnolence, drowsiness, ↓ cognitive
VPA	iv	Na, GABA	2A6 (inibitor of 2C9, 2C19, 3A4) / L	90	-	Methotrexate, Doxorubicin, Cisplatin	Thrombocytopenia, neutropenia, tremor, pancreatitis, hair loss
TPM	No	Na, NMDA, GABA	3A4 / L, K	30	-	Temozolomide	↓ cognitive, renal calculi, parestestesias
ZNS	No	Na, Ca	(Inhib. 2E1) / L	50	-	-	Drowsiness, headache, renal calculi
LTG	No	Na	No /L	50	Methotrexate	-	Rash, ↓ cognitive, drowsiness, folate reductase enzyme inhibition, very slow titration
GBP	No	GABA, Ca	No /K	< 5	-	-	Drowsiness, ataxia, weight gain
PGB	No	GABA, Ca	No /K	< 5	-	-	Thrombocytopenia, drowsiness, ↓ pain, splenic edema
LVT	iv	SV	No /K	< 5	-	-	Agitation, psychosis, drowsiness
LCM	iv	Na	No /K	< 5	-	-	Drowsiness
RUF	iv	Stab Na channels (?)	No /K	< 5	-	-	Rash, fatigue, drowsiness

acute-symptomatic, the use of a fast acting AED such as clonazepam, clobazam or lorazepam prior to, and until 24 hours (up to 4-7 days) after chemotherapy administration, may be appropriate both in emergency management and as prophylaxis in the follow-up. Lorazepam is used most often and offers the advantages of both lack of any drug interaction and an antiemetic effect. Furthemore BDZs exert an ansiolitic action, particularly useful in these patients. In case of a long-term prophylaxis, new-AEDs are an attractive alternative.

□ CONCLUSIONS

In conclusion, only in recent years have we seen new interest in problems related to anticonvulsant medications in neoplastic disorders mainly for drug interactions, timing of titrations, choice in relation to short survival in patients with glioblastoma or brain metastases. On the other hand, in some settings epilepsy is the major clinical problem (and the only clinical "measurable" efficacy outcome of treatments response), like in patients with low-grade gliomas and in long survivors with high-grade gliomas. This new interest raises the following problems: whether the status of not-receiving AEDs or receiving NEIAEDs versus receiving EIAEDs can affect survival and therefore must be considered a prognostic factor which can influence the outcome and the endpoints, thus justifying the introduction of a further stratification variable in future prospective clinical trials or whether the VPA or LEV may exert an antitumour effect. Up to now, these questions are still unsolved.

In neuro-oncology, a specialized and well-organized team, with the organ specific neurologist as a reference guide, seems to be the best response to the needs of patients with CNS tumours and other neoplastic conditions, who now frequently have to receive care in more than one location. The multidisciplinary approach allows an optimization of the care process, the standardization of treatments, and therefore the collection of conclusive clinical data, the improvement of patients' quality of life and, finally, a cut in social costs.

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