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Epilepsy in neuro-oncology: a review

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Summary. Epilepsy associated with neoplastic diseases in any site is a poorly understood manifestation that has important clinical and social implications. This article comprises a review based on a practical approach to three main categories of the population affected: 1) seizure or epilepsy in patients with structural active neoplastic brain lesions (primary or metastatic): strictly and commonly identified as "brain-tumour associated epilepsy (TAE)"; 2) seizure or epilepsy in patients without structural active neoplastic brain lesions: peri/post-operative period for any other CNS oncologic surgery; vascular, paraneoplastic and infectious complications in systemic cancers; and 3) seizure or epilepsy in various other conditions of any cancer: history of a previous CNS tumour (but not expression of active neoplastic CNS disease) or toxicity of its treatments, mainly radiotherapy; metabolic and treatmens complications in systemic cancers, etc. These statements may be shared and spread among neuro-oncologists, general practitioners, medical doctors in emergency rooms and any other specialist involved in the management of such patients.

Key words: brain tumours, systemic neoplasms, epilepsy, anticonvulsants, treatment guidelines

Introduction

In a paper entitled "Seizure Prophylaxis for Brain Tumour Patients. Brief review and guide for family physicians" published in 1993 (1), after describing some illustrative cases in the flow-chart represented on page 1160, the authors conclude that it is appropriate to continue seizure prophylaxis "indefinitely" in the post-surgery period of a supratentorial tumour (excluding meningioma).

There are various main topics which require some explanation:

- the need for a survey of current-practice versus evidence-based patterns of care in neuro-oncology;
- the role of the Neurologist, as Organ Specialist, in a neuro-oncological patient's perspective today;
- the limitation of some issues regarding:
  - clinical trial end-points;
  - medical decompressive therapy;
  - epilepsy in patients with any oncological disease (primary, metastatic or complication of cancer and its treatment);
- the development of guidelines in neuro-oncology;
- the clinical impact and "surrogate" limitations to the use, at least, of "best evidence" (when available).

Seizures are a common presenting symptom of brain tumours and various other oncological conditions and have a significant impact on neuro-behavioural functioning and quality of life (QoL).

This review focuses on a practical approach to three main categories of the population affected:

1. seizure or epilepsy in patients with structural

* This article reflects the author's experience matured at Niguarda Hospital (Milan, Italy) under the guidance of Massimo Collice, Chief of the Neuroscience Department († 2009)

active neoplastic brain lesions (primary or metastatic): strictly and commonly identified as "Brain-Tumour Associated Epilepsy (TAE)";
2. seizure or epilepsy in patients without structural active neoplastic brain lesions: peri/post-operative period for any other CNS oncologic surgery; vascular, paraneoplastic and infectious complications in systemic cancers;
3. seizure or epilepsy in various other conditions of any cancer: history of a previous CNS tumour (but not expression of active neoplastic CNS disease) or treatment toxicity, mainly radiotherapy; metabolic and treatment complications in systemic cancers, etc.

Another possible approach may be to describe the condition at onset of epilepsy and the type of seizure in relation to the pathogenesis and duration of a single/specific oncological disease.

The former approach seems preferable for its greater clinical practicality and also to avoid repetition.

Owing to the heterogeneity of the problem, epilepsy in the neuro-oncological field, it is useful to maintain a distinction between acute symptomatic seizures, unprovoked late seizures and epilepsy, as suggested twenty years ago by the Commission of Epidemiology and Prognosis of the International League Against Epilepsy (2).

The present review is based on our own clinical experience among adult patients.

General Considerations

Referral and management

In 1986 Wroe *et al.* (3) debated the differences between neurological and neurosurgical approaches in the management of malignant brain tumours (mainly regarding the extent of surgery, referral for radiotherapy and seizure prophylaxis), drawing the conclusion that the neurosurgeons' interventionist approach was more common, although it did not significantly or favourably affect long-term survival. More than twenty-five years later, is this widespread heterogeneity of behaviours still justified, and, above all, is it still true that long-term survival is not significantly affected?

As regards epilepsy, this is no longer true: when seizures or status epilepticus are the presenting symptom, they significantly affect the follow up (4).

Moreover, there are geographical (5) and, more obviously, historical-chronological (6) differences in referral and management patterns.

According to Grisold W. *et al.* (7), modern neuro-oncology is a growing new sub-speciality with a strong interdisciplinary character. It has a varied spectrum which extends from primary brain tumours to metastatic and non-metastatic effects of systemic cancers on the central and peripheral nervous system (CNS and PNS) and from drug interference to neurotoxicity due to cancer treatment, from supportive management and neuro-protection to issues affecting quality of life. Neurologists should play a pivotal role in coordination of the diagnosis and treatment process and, in our opinion, in coordination of the summarising and transferring of medical evidence inside the multidisciplinary team and in giving information as to the diagnostic/therapeutic process to patients and their families. In the oncological field it is important to establish how evidence applies to the individual patient in specific settings (8). One clear example of this discrepancy between the neuro-oncological real-world and scientific evidence is the general feasibility of magnetic resonance imaging within 72 hours of surgery for an objective evaluation of the residual tumour: a useful tool in defining influences on regrowth and prognosis, which has been well-known since 1994 (9).

A historical overview with old-AEDs

Old anticonvulsant drugs (old-AEDs) - such as Phenytoin (PHT), Phenobarbital (PB) and Carbamazepine (CBZ) - produce more idiosyncrasies and side effects in these cancer patients than among general epilepsy patients (10). They induce a CYP450-enzyme system and therefore interfere with other commonly used drugs, increasing chemotherapy agent clearance (11, 12), thus contributing to the cumulative haematological toxicity (thrombocytopenia and leukopenia: e.g. respectively from VPA (Valproic Acid) or PHT/CBZ (13-15). Monitoring of drug levels is essential. One third of these patients could be defined as "drug-resistant" and another third only reaches successful sei-

zure control; rash is associated with old-AEDs in 26% and other clinically important toxic side effects are observed in 14%. The hypersensitivity syndrome seems to be much more aggressive and may lead to Stevens-Johnson syndrome and fatal outcome in patients undergoing concomitant cranial irradiation (16, 17).

Practice parameters and behavioural heterogeneity

In May 2000 a Panel of Experts of AAN (18) 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: meta-analysis showed no statistical benefit. Two meta-analyses by Temkin (19) and Sirven (20) show similar conclusions for patients with brain tumours, regardless of neoplastic type, and 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 treatment is currently still characterized by significant behavioural heterogeneity and the literature lacks robust data concerning the efficacy and toxicity of the new recently-marketed AEDs.

Although it is five years since the AAN issued guidelines discouraging the prophylactic use of AEDs in treatment of TAE, they surprisingly still remain the prevailing practice among members of the American Association of Neurological Surgeons (AANS) (21).

The Cochrane Library and "Available Best Evidence"

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

- one (22) on the use of AEDs in the status epilepticus (SE)- two, respectively on the timing (23) and on the rapidity (24) of AED withdrawal. These do not specifically analyse the clinical query as to the oncological population examined and conclude that it is not yet possible to show the best time to withdraw or the rapidity or optimal rate of tapering AEDs. More research is therefore needed on both issues;

- two reviews of outstanding interest: "Antiepileptic drugs for preventing (25) or treating (26) seizures in people/adults with brain tumours". Although the former review substantially shares the conclusion as to the inefficacy of prophylaxis against the onset of seizures in formerly epilepsy-free brain-tumour patients - an inefficacy already expressed by Glantz's, Temkin's and Sirven's meta-analyses - in the discussion it challenges some methodological biases of the AAN Practice Parameters. Thus, this meta-analysis reports how the evidence for seizure prophylaxis with old AEDs is inconclusive, at best. The decision to start using an antiepileptic drug for seizure prophylaxis is ultimately guided by the assessment of individual risk factors and careful discussion with patients.

The second review shows how only one small, open-label, unblinded, randomised trial met the inclusion criteria for evaluation of the safety and feasibility of switching from phenytoin to levetiracetam monotherapy or continuing phenytoin for glioma-related seizure control following craniotomy (27). 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..

Finally, even the most recent review on the use of AEDs as prophylaxis for preventing seizures, following supratentorial craniotomy (28) for either therapeutic or diagnostic reasons in non-traumatic (mainly oncologic) pathology, concludes that no evidence was found to suggest that prophylactic AED treatments are effective in reducing the occurrence of postoperative seizures, death or adverse effects, and that further good quality trials are needed to validate this finding.

In 2008 a Panel of Experts from the Associazione Italiana Neuro-Oncologia (AINO) proposed some practical management statements: we refer in particular to the chapter on management in the Emergency setting, not discussed in this paper (29). A 2013 revised version is awaiting publication (http://www.neuro-oncologia.eu/news/aggiunti-nuovi-contributi).

Miscellanea

Two further unsolved problems, which create confusion in the conduction of trials, should be taken into consideration:

1] the possible antitumor effect of VPA has been conjectured to be due to an in vitro action on

hystone-deacetylase which induces growth arrest through promotion of apoptosis, reduction of differentiation and suppressed colony-forming efficiency and tumorigenicity (30, 31). In clinical practice a recent paper (32) demonstrated a therapeutic advantage in a local cohort of 236 Glioblastoma patients. Those treated with VPA had significantly longer survival rates than those who had not received any AEDs or who had received other AEDs. On the contrary, steroids may enhance the GABA depressant-inhibitory effects exerting a direct anti-epileptic in addition to the protective antioedema action (33, 34);

2] the drawbacks of generic substitution of branded AEDs with the increase in seizure risk, and health care utilization, especially in brain-tumour patients (35).

Spectrum of epilepsy in neuro-oncology

Causes and remarks of epilepsy in oncology

As shown in Table 1, seizures or status epilepticus are observed as onset symptom or during the course of disease in various primary or metastatic oncological conditions (36).

Tumour-associated epilepsy

The correct identification of seizures as early symptom at the onset of brain tumours is important, because of the different subsequent therapeutic management preferences. Few studies (37, 38) focus on the accounts of symptoms at diagnosis of malignant cerebral gliomas recorded in hospital files versus those elicited at home interviews from patients and relatives: cumulatively these studies show an underestimation of >10% of symptomatic epilepsy.

Tumoral epilepsy is generally referred to as a unique clinical entity in patients with cancers of different histologies, or even in absence of cerebral structural lesions (see below). Viceversa, as we have already pointed out (39), 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); some distort (meningioma), whereas others infiltrate (astrocytoma) and others again destroy (haemorrhagic metastasis) the peritumoral cortex and when epilepsy complicates a therapy (i.e. acute radio-chemotherapy, re-hydrating infusion, antibiotic treatments etc) no focal lesions are observed. The incidence of TAE also relates to the topographic distinction: previous works suggest that frontal and temporal regions are particularly at risk of seizures (40, 41) or hypothesize that the left hemisphere is more prone to an epileptogenic onset of disease (42). Our data taken from a previous study (4) do not support this topographic site/side distinction in GBM-patients: in an Epilepsy Onset group there is a right hemisphere-sided prevalence and a slight prevalence of frontal, temporal or carrefour lesions, that however does not reach a statistical significance, but it is worthy of further studies. Another possibility is the different origin of these newly-diagnosed GBMs arising "secondarily" from the evolution of a previous low-grade glioma, which is a highly epileptogenic lesion.

All the previous considerations suggest that the aetiology of TAE is multifactorial, involving host and tumour factors. As a consequence, even the response to the various AEDs might be different.

Tumor-related seizures are essentially focal, although secondary generalization is common and may occur so quickly that, in certain patients, the focal phase passes unnoticed. The main factor predicting epilepsy is cortical location. Another cause of primary focal epilepsy, specifically seen in cancer patients, is radiation therapy. The epileptogenic effect of acute brain irradiation is difficult to be assessed quantitatively because it is confounded by several factors including residual/relapsing tumour, corticosteroids treatment etc (43, 44).

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 thrombocyto-

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

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 Metastases	~ 20 - 40%	Particularly frequent in hemorrhagic mets (melanoma etc.)
Meningeal Carcinomatosis	~ 10 - 15%	
Treatment-Related		
Chemotherapy (CT)	<1% iv 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 borne in mind	Overdose of the same AEDs, certain antibiotics (quinolones, β-Lactames, penicillin) tricyclic antidepressants, neuroleptics; cyclosporin A; ondansetron, RPLS
Acute Irradiation	? ? ?	Difficult to assess because of several confounding factors
Late-Delayed Radionecrosis	~ 20 - 30%	
Miscellanea		
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

AEDs= anti-epileptic drugs; ATLS= acute tumour lysis syndrome; BBB= blood-brain barrier; BMT= bone marrow transplant; HSCT= human stem-cell transplant; NCSE= non-convulsive status epilepticus; RPLS= reversible posterior leukoencephalopathy syndrome; SIADH= syndrome of inappropriate ADH secretion

penic purpura or sequelae), paraneoplastic (limbic encephalitis) infectious (meningo-encephalitis, abscess, PML etc) and treatment-related (Reversible Posterior Leukoencephalopathy Syndrome -RPLS) complications in systemic cancers (44, 45).

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,
- 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 (HSCT) or Bone Marrow (BMT) Transplant (46, 47).

Main mechanisms of epileptogenesis, late unprovoked or provoked seizures in these patients are described in Table 2.

Definite criteria for labelling seizures as drug-induced are:

1. development of seizures/encephalopathy during or shortly after completion of treatment with the drug (24-48h),
2. exclusion of other metabolic and structural factors,
3. exclusion of seizures produced by other concomitant medications.

In these patients Electroencephalography may disclose:

- a diffuse encephalopathic pattern with focal slow-wave activity,
- electrographic status epilepticus,
- periodic lateralised epileptiform discharges (PLEDs).

Table 2. Main mechanisms of Epileptogenesis, late unprovoked or provoked seizures in oncology.

Suggested Mechanism	Agent
Direct effects on neuronal excitability : altered excitatory NMDA-AMPA or inhibitory GABA pathways	Cyclosporin A, CDDP, MTX
Neurotransmitters: Adenosine, Glutamate etc	MTX, 5-FU
Indirect effects via electrolyte disturbances: hypomagnesemia, hyponatremia, hypocalcemia etc	CDDP, pamidronate
Vasogenic edema: disruption of the BBB	INF-α, 5-FU
Vascular mechanisms: endothelial damage, mineral microangiopathy, nitric oxide reduction, hyperhomocysteine etc.	Cyclosporin A, Tamox, MTX
Structural lesions: subcortical leukoencephalopathy ("U" fibers), Reversible-Posterior-Leukoencephalopathy, Temporo-mesial lobe atrophy etc.	Cyclosporin A, 5-FU, MTX, in cranio-spinal or naso-pharyngeal RTp

Pathogenesis and Pharmacoresistance of TAE

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 in peritumoral brain tissue: local metabolic imbalances, morphological changes in the neuropil, neuronal, glial, perturbation in distribution and function of electrolytes and neurotransmitter disturbances mainly to GABA/Glu balance (48). Several reasons are found for the clinical inefficacy of AE 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 GABAergic activity. These two important modes of action of AEDs, however, cover only a few of the pathophysiologic mechanisms of TAE. Consequently, these mechanisms (such as, morphologic changes, altered receptor and connexin patterns, and changes of cytokine expression) are not influenced by currently used AEDs (49). Second, low levels of AEDs have been reported in 60–70% of patients (18). The latter is mainly unrelated to the pathophysiologic mechanisms of TAE, but results from the fact that therapeutic AED levels in patients with brain tumors are difficult to maintain because of frequent pharmacodynamic and kinetic interactions with concomitant medications, and from changes in plasma protein (especially albumin) levels. Additionally, the multidrug resistance protein-1 (MRP) may play a role. Recent hypotheses propose that transport of AEDs by drug efflux transporters MRP such as P-glycoprotein (Pgp) 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; exerts no effect on LVT; no information is available for TPM (50,51). Finally, reappearance of seizures during AED treatment may reflect tumor progression-recurrence or a provoked seizure in a particular phase of the disease.

Figure 1 synthesizes mechanisms of AEDs resistance.

At the macroscopic level, slow-growing tumors produce an epileptogenic focus by partial deafferentation of cortical regions, thus causing a denervation

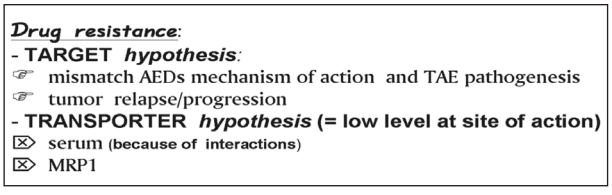

Figure 1. Summary of Drug Resistance Mechanisms in TAE.

hypersensitivity. Recent studies (52, 53), using magnetoencephalograpy, 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 (54). Differently from low-grade gliomas, high-grade tumors, such as GBMs or metastases, induce seizures via abrupt tissue damage due to necrosis, bleeding with subsequent hemosiderin deposition and edema.

The putative mechanism of epilepsy in extrinsic tumors (55, 56), such as meningiomas, or for example seizures/status epilepticus in the immediate post-operative period for a pituitary adenoma or craniopharyngioma, apart from other complications, is more likely related to peritumoral edema, possibly explaining the high frequency of preoperative seizures in supratentorial tumors and the possible regulating role of H_2O flux and uptake exerted by Aquaporin-4 (57).

New AEDs

For the above-mentioned reasons, the problem of the proper selection of medications and their potential side effects in these patient populations is of great importance.

Each AED has unique characteristics (summarized in Table 3), including mechanism of action, spectrum of activity, pharmacokinetic and pharmacodynamic properties, likelihood for dose-related side effects, and risk of serious health problems, such as idiosyncratic reactions and finally direct and indirect costs.

Regarding the clinical efficacy of AEDs, studies with the old-AEDs, as summarized, are few and offer conflicting data. As for the new-AEDs, the literature shows a 63% of seizure-free patients with OXC monotherapy; 56% with topiramate monotherapy; a responder rate from 28 to 100% with gabapentin, lacosamide, pregabalin, tiagabine, and zonisamide in add-on; 47-87% of seizure-free patients with levetiracetam both in mono-therapy or as add-on (58-73). These AEDs, although with many important differences among them, share a lot of similarities, including pharmacodynamic actions on ion-channels and cognitive side-effects, with levetiracetam as a notable exception. For this reason the following description of single drugs takes into consideration only some peculiar aspects (74-80).

Levetiracetam

Levetiracetam (LVT), probably the most studied among newAEDs, has a putative unique mechanism of action related to its binding to synaptic vesicles, and favorable pharmacokinetic properties, lacking hepatic metabolization. It is available in oral and intravenous formulations, and it may be titrated quickly, achieving therapeutic efficacy within hours. Being able to give this drug intravenously is an extremely attractive trait which makes treatment in emergency or perioperative situations a possibility. LVT has not been shown to cause any induction or inhibition of the cytochrome P450 enzymes including uridine diphosphate-glucuronyl-transferase or epoxide hydroxylase. Therefore it exhibits low clinically relevant pharmacokinetics both with other AEDs and with drugs that could possibly be used to treat neuro-oncologic patients. Furthermore, its bioavailability of 100%, following both oral and intravenous administration, may last longer, in the cerebrospinal fluid, than the plasmatic half-life.

Oxcarbazepine

Oxcarbazepine (OXCBZ) has been studied retrospectively to assess its efficacy and tolerability versus old-AEDs (mostly phenobarbital and carbamazepine) in patients with primary and metastatic brain tumors. The results show similar efficacy but significantly fewer side effects with oxcarbazepine. However, the group of patients on old-AEDs had more primary brain tumors, were more prone to suffer from side effects of AEDs, than the oxcarbazepine group. However, OXCBZ is loaded by hematologic toxicity on 3 series, HypoNa, hypersensitivity syndrome, mainly during concomitant Rt, enzymatic induction.

Gabapentin

A study of gabapentin (GBP) as add-on therapy in 14 patients with primary (10 patients) and metastatic brain tumors (4 patients) produced seizure reso-

Table 3. Currently available AEDs: peculiar characteristics in neuro-oncologic patients.

AED	*Parenteral Form*	*Site of action*	*CYP-inducer / Metabolism*	*PB %*	*AED (↓ activity) effect on Chemotp*	*Chemotp (↓ 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, Doxorubicin,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 (inhibitor 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 calc, parestestesias
ZNS	No	Na, Ca	(Inhib. 2E1) / L	50	-	-	Drowsiness, headache, renal calc
LTG	No	Na	No / L	50	Methotrexate	-	Rash, ↓ cognitive, drowsiness, folate reductase inhib, 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

Abbreviations and Notes common to Text, Tables and Figures
5FU 5-fluorouracil, 9AC 9-aminocampothecin, AED antiepileptic drug, BDZ benzodiazepines, Ble bleomycin, Bus busulfan, Ca calcium channel, Car carboplatin, CBZ carbamazepine, chemo chemotherapy, Cis cisplatin, cog cognitive/behavioral, Cpc capecitabine, CYP cytochrome P-450, Dac dacarbazine, Dex dexamethasone, Dox doxorubicin, Eto etoposide, GABA γ-aminobutyric acid, GBP gabapentin, h/a headache, Ifo ifosfamide, inhib. enzyme inhibition, Iri irinotecan, IV intravenous, K kidney, L liver, LCM lacosamide, LTG lamotrigine, LVT levetiracetam, Mtx methotrexate, Na sodium channel, Nit nitrosurea, NMDA N-methyl-D-aspartate, n/v nausea and vomiting, OXC oxcarbazepine, Pac paclitaxel, PB protein binding, PGB pregabalin, PHB phenobarbital (and primidone), PHT phenytoin, Prd prednisone, Pro procarbazine, RUF rufinamide, SIADH syndrome of inappropriate antidiuretic hormone secretion, Srl sirolimus (and temsirolimus), SV synaptic vesicle, Tam tamoxifen, Ten teniposide, Thi thiotepa, Tmz temozolomide, Top topotecan, TPM topiramate, Vbl vinblastine, Vnc vincristine, VPA valproic acid, ZNS zonisamide.

lution in half the patients, a reduction of more than half in seizure frequency in all patients, and severe somnolence in only one patient.

Pregabalin

In a study of pregabalin (PGB) in nine patients with primary brain tumors, 100% of the patients had a greater than 50% reduction in seizure frequency and 66% became seizure-free. However, 45% experienced side effects (mainly fatigue), leading to discontinuation of the drug in 25%.

Topiramate

In a retrospective study of 47 patients with brain tumors (45 primary tumors) taking topiramate (TPM) as adjunctive therapy or monotherapy (mean dosage, 240 mg/d), 76% of the patients had seizure reduction of greater than 50% and 56% became seizure-free; 8% of the patients experienced side effects, leading to discontinuation of the drug in 6%. Neuropsychological and cognitive cumulative damage and nephrolithiasis are among the commonest adverse effects.

Valproate

As for Valproate (VPA), an AED still commonly used in Chrono formulation, see above. Hepatic enzymatic inhibition and toxicity, thrombocytopenia, plasma level monitoring are of special consideration in neuro-oncologic patients.

Phenobarbital

As for Phenobarbital (PB), another old-AEDs commonly used and referred to in previous meta-analyses, it is a drug whose hypnotic, sedative, anti-epileptic and anti-spastic properties have been well-known as well as its hepatic enzyme induction and cognitive toxicities. We point out the possibility of intra-muscular or subcutaneous administration route useful in this

particular population of patients at the terminal phase of the disease.

Lacosamide

Lacosamide is a new-AED with a novel mechanism of action involving selective enhancement of slow inactivation of voltage-gated sodium channels and results in stabilization of hyper-excitable neuronal membranes. Because of this different mechanism of action, LMT may be suitable for concurrent use with other AEDs, as documented by its activity across many different types of AEDs administered in this patient population. Published (81-83) clinical trials of retrospective analysis in small populations as add-on (monotherapy in 2 patients of ref 84) with a median dose of 100 mg/day (range 50-225 mg/day) demonstrated that lacosamide was both well tolerated and active as an add-on antiepileptic drug in patients with brain tumours with seizure freedom or frequency reduction from 42% to 78%.

Lamotrigine

The large randomized and controlled, but not double-blind, standard and new antiepileptic drugs (SANAD) trial (84) reported lamotrigine to be more effective than carbamazepine, oxcarbazepine, topiramate and gabapentin in patients with focal seizures. A comparison with this literature on patients with a brain tumour is difficult since research reports on antiepileptic drug treatment in the general epilepsy population are often restricted to populations with specific seizure types or epilepsy syndromes, while patients with a brain tumour should not be stratified according to seizure type (always partial) for study purposes, but according to the general neuro-oncologic context.

On the other hand, in our personal experience (85) of a prospective phase II study of efficacy and tolerability in a sequence of consecutive randomization for assigned monotherapy with new-AEDs, in 200 adult patients with histologically proved primary or metastatic supratentorial brain tumours, LTG, at a dosage of 300-450 mg/d , in 41 pts, with a median age of 59y, in 6 months of median follow-up showed greater toxicity (even severe: i.e. 10% of toxic epidermal necrolysis) and less efficacy compared to other AEDs (TPM, OxCBZ and ChVPA) which caused its interruption.

Suggestions on management

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, referring the reader to other articles on the subject (29, 74-80).

In our experience, 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;
- sensitization reactions to AEDs, or seizures, may appear abruptly and dramatically when the steroid is interrupted (e.g. after surgery or at 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 tumor 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.

Chapter A: seizure or epilepsy in patients with a structural active neoplastic brain lesion(s)

We refer (Figure 2) to glioma (WHO grade II-IV), 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 perioperative (±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.

As for the drug choice:

- in general, new-AEDs (LVT, chronoVPA, TPM, LCM, OXCBZ in order of our preference) present a more favourable profile both in terms of hematologic and cognitive efficacy/toxicity and in terms of pharmaco-kinetic and dynamic interactions with the other treatments (in spite of the above-mentioned adverse effects);
- LVT-VPA-LCM-PHB are available also in parenteral formulations particularly useful in fast titration, status epilepticus, general anestesia 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 dintoin in operating room, PHT should be suspended within two weeks and in any case possibly within RT, because of the high risk of sensitization 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 BDZ in monotherapy or in add-on is advisable: clobazam 10-20 or clonazepam 2-4mg 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) a different mechanism of action is preferred to a substitution, because of the pharmacoresistance;
- in cases of convulsive or non-convulsive status epilepticus (SE), see the specific guidelines cited.

Chapter B: seizure or epilepsy in patients without a structural active neoplastic brain lesion(s)

This group includes:

1. patients with acute symptomatic seizures in the peri/post-operative period for any other CNS

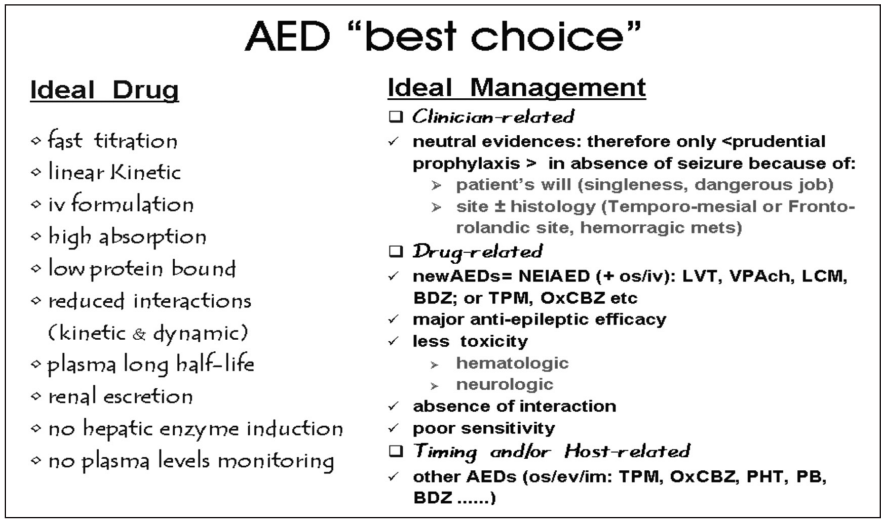

Figure 2. AED "Best Choice".

oncologic surgery (pituitary adenoma, craniopharyngioma etc) because of brain edema 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 BDZ;
2. patients who may develop chronic epilepsy due to vascular, paraneoplastic and infectious lesions as complications in a systemic cancer to be treated as indicated in chapter A.

Chapter 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 brief simply partial, or a prolonged generalized seizure) which require a careful diagnostic and treatment evaluation for the risk of repetition;
2. patients with treatments and metabolic complications in systemic cancer with (RPLS) or without (all the others) a radiographic documentation of the epileptogenic lesion. Patients with RPLS should be considered as in B2 (see above). In the other patients, since most crises are 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 action. Furthemore BDZ 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 appreciation of 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, or -on the contrary- when epilepsy is the major clinical problem (and the only "measurable" clinical event of treatments, Ct and RT, 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 (non AEDs) or receiving NON-Enzyme Inducing AEDs (NEIAEDs) versus receiving Enzyme Inducing AEDs (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 (86); or whether the VPA may exert an antitumour effect (87,88). Up to now, these questions have still remained 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 multi-disciplinary 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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