Perampanel as add-on in patients with brain tumour-related epilepsy: a preliminary report

M Maschio[1], G Pauletto[2], A Zarabla[1], A Maialetti[1], T Ius[2], V Villani[3], A Pace[3], D Giannarelli[4]

[1]Center for Tumor-related Epilepsy, UOSD Neurology, Regina Elena National Cancer Institute, Rome
[2]Neurology Unit, Department of Neurosciences, S. Maria della Misericordia University Hospital, Udine
[3]UOSD Neurology, Regina Elena National Cancer Institute, Rome
[4]Biostatistic Unit, Regina Elena National Cancer Institute, Rome

Introduction:

Epilepsy is one of the most common symptoms of brain tumours. The choice of antiepileptic drug (AED) should be guided by a variety of factors, such as effectiveness of seizure control, tolerability of treatment, and possible pharmacological interactions. Among the most recently marketed drugs, perampanel (PER) is a selective, non-competitive, alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA)-type glutamate receptor antagonist.
To date, PER therapy in patients with brain tumor-related epilepsy (BTRE) has not been studied extensively.
Aim of this study was to evaluate efficacy and tolerability of add-on PER in patients with BTRE and uncontrolled seizures

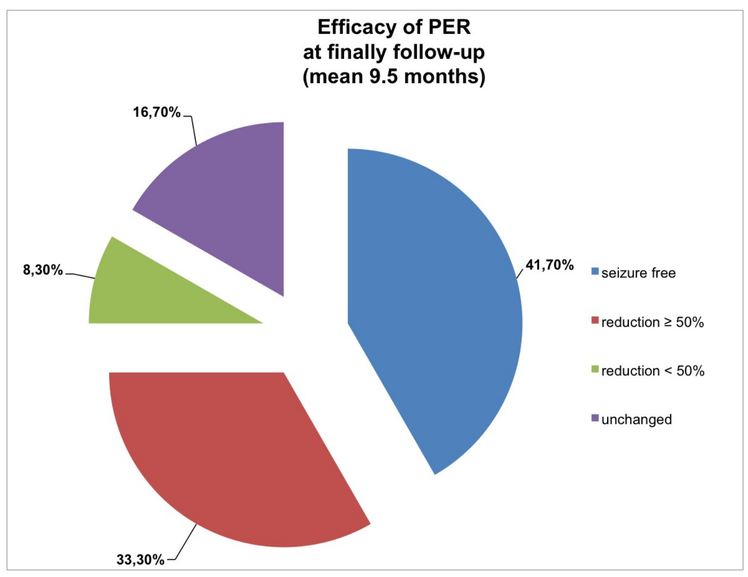
Methods:

This is a retrospective study of 12 patients (10 males, mean age 52.3 years) suffering from BTRE who were consecutively recruited and followed in two Departments in Italy (Rome and Udine) from August 2015 to August 2016 (median period of 9.5 months). All patients attending our Departments usually keep a seizure diary and have monthly clinical examinations.
Baseline data (before PER introduction) included demographic characteristics, Karnofsky performance scale (KPS), brain tumour history (site and histology) and therapy (surgery, chemotherapy, radiotherapy), seizures (type, number) and previous antiepileptic drugs (AEDs), adverse events (AEs) evaluated according to frequency and intensity using the Common Terminology Criteria for Adverse Events (CTCAE), neuro-radiological examinations. PER starting dose and dose titration were based on the SmPC (Summary of Product Characteristics). Seizure count, change in dosage of PER and other AEDs, and AEs were recorded during follow-up.

Results:

At baseline, all patients had partial seizures, with (6 patients, 50%) or without (6 patients, 50%) secondarily tonic-clonic generalization. Prior to PER introduction, 5 (41.7%) and 7 (58.35%) patients were receiving AEDs monotherapy or polytherapy, respectively. Eight of 12 patients were treated with the current standard care of patients with brain tumours (chemotherapy and/or radiotherapy) only before or before and during PER follow-up. Treatment with PER was added due to insufficient seizure control in 11 patients (91.7%) and to AEDs-related adverse effects in 1 (8.3%). The mean (±SD) daily PER dosage was 7.2±1.8 mg (median 7.0 mg).
Efficacy at finally follow-up: The mean number of seizures/month decreased from 12.9±18.1 (median 5.0) at baseline to 3.0±8.5 (median 0.35) at the last follow-up. Five patients (41.7%) were seizure-free and 4 patients (33.3%) had a seizure reduction ≥50%, 1 (8.3%) had a seizure reduction <50% and the seizure frequency was unchanged in 2 patients (16.7%). **Responder rate= 75.0%**
Side effects: Three patients (25%) reported AEs: 1 (agitation) required PER dose reduction, and none discontinued the study.

Pat.	Age (years)	Sex	KPS	Histology	Site of tumour	Surgery	Chemotherapy	Conformational RT	Seizure type	No. of seizures in themonth before entering the study	Baseline AED therapy (mg/day)	PER dose assigned (mg/day)	Duration of follow-up with PER	Mean seizures number during PER follow-up	Adverse effects with PER	Disease progression during PER follow-up
1	37	M	100	AOA	Frontal	Gross total resection	No	°	SP	1.0	CBZ-LEV 1000-1500	6	8 months	0.0	No	No
2	56	F	70	AA	Frontal	Gross total resection	No	°	SP+SGTC	8.0	LEV 2000	8	8 months	0.2	Anxiety increased	Yes
3	51	M	60	GBM	Temporal	Partial resection	Fotemustine *	°	SP+SGTC	3.0	LEV 1000	10	9 months	0.0	No	Yes
4	76	M	100	LGA	Insular	Gross total resection	No	No	CP+SGTC	1.0	LEV 2000	6	12 months	1.0	No	No
5	31	M	90	LGA	Temporal	Gross total resection	No	No	CP	30.0	LCM-ZNS 300-200	10	13 months	30.0	Agitation (dose reduction)	No
6	75	M	100	GBM	Frontal	Gross total resection	Other °	No	SP	5.0	LCM-LEV 300-3000	6	15 months	1.0	No	Yes
7	48	M	90	GBM	Frontal	Gross total resection	Bevacizumab °	No	SP+SGTC	7.0	LCM-LEV 400-3000	6	10 months	0.0	No	Yes
8	46	M	100	AOA	Multilobular	Biopsy	Temozolomide °	No	SP+SGTC	30.0	VPA-LEV-LTG 1500-3000-200	6	12 months	0.5	No	No
9	40	F	100	LGA	Frontal	Partial resection	No	No	SP+SGTC	2.0	LTG 400	4	10 months	0.9	No	No
10	33	M	100	MET	Multicentric	No	No	No	SP	5.0	LEV-CBZ 3000-1200	8	8 months	2.6	Vertigo	No
11	60	M	90	LGA	Temporal	Partial resection	Temozolomide °	No	SP	60.0	LCM-LEV 400-3000	8	6 months	0.0	No	No
12	74	M	100	AA	Frontal	Partial resection	Temozolomide °	No	SP	3.0	PB 100	8	6 months	0.0	No	No



Legend
KPS = Karnofski performance index; RT = radiotherapy; AED = antiepileptic drug; PER = perampanel; M = males; F = females; SP = simple partial seizures; SGTC = secondarily generalized tonic-clonic; CP = partial complex; CBZ = carbamazepine; LEV = levetiracetam; LCM = lacosamide; ZNS = zonisamide; VPA = valproic acid; LTG = lamotrigine; PB = phenobarbital; AOA= anaplastic oligoastrocytoma; AA= anaplastic astrocytoma; GBM= glioblastoma multiforme; LGA= low-grade astrocytoma; MET= brain metastases.
*= before PER follow-up; °= before and during PER follow-up

Conclusions:

To date there are very few published data on the effects of PER on seizures control in brain tumour patients.
In our patients PER as add-on was effective in seizure control and quite well tolerated.
Our results (responder rate 75%) are consistent with the findings of Vecht C. (Vecht C., et al, 2017) on 12 patients with BTRE in which PER for 6 months (median daily dose of 8 mg) was associated with a high seizure response rate (75%).
Despite the limitation of our study due to the small sample and short follow-up, our data confirm the efficacy and a good tollerability of PER in add-on in BTRE patients. Prospective controlled studies are needed to confirm these preliminary findings.

References
•Maschio M. Brain tumor-related epilepsy. Curr Neuropharmacol 2012;10(2):124-33
•Krauss GL, Serratosa JM, Villanueva V et al. Randomized phase III study 306: adjunctive perampanel for refractory partial-onset seizures. Neurology 2012;78:1408-15
•Rösche J, Piek J, Hildebrandt G, Grossmann A, Kirschstein T, Benecke R. Perampanel in the treatment of a patient with glioblastoma multiforme without IDH1 mutation and without MGMT promotor methylation. Fortschr. Neurol. Psychiatr. 2015;83(5):286-289
•Vecht C, Duran-Pena A, Houillier C, durant T, Capelle L and Huberfeld G. Seizure response to perampanel in drug-resistant epilepsy with gliomas: early observations. J Neurooncol 2017 DOI 10.1007/ s11060-017-2473-1

Sin
XLVIII CONGRESSO NAZIONALE
14-17 OTTOBRE 2017 – NAPOLI
WebPoster
http://congress.wooky.it/NEURO2017/