Perampanel in Drug-Resistant Epilepsy with Gliomas Seizure Response to Perampanel in Drug-resistant Epilepsy with Gliomas: Early Observations

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Abstract

Background

Drug-resistant epilepsy occurs commonly in gliomas, possibly due to a shared mechanism of AMPA-activation involving both seizure activity and tumor growth. We tested the AMPA-receptor blocker perampanel (PER) in patients with drug-resistant epilepsy (DRE) in low- and high-grade gliomas.

METHODS

Seizure response was defined as 50% drop in seizure frequency or seizure-freedom. Cognitive function was examined by CTCS (Computerized Test on Cognitive Speed), which is sensitive to the type of cognitive dysfunction associated with epilepsy and use of anticonvulsants. Treatment policy included reduction of dose or a discontinuation of one or more concurrent AEDs, once seizure-free response was observed.

RESULTS

Twelve patients were included patients, median age 41 years, 9 men vs 3 women and 6 months median duration of follow-up. An objective seizure response (75 %) was observed in 9 (75 %) out of 12 patients: 50%-seizure response in 3, seizure-freedom in 6, which is plainly more than seen with other types of DRE.

Side-effects occurred in 6 patients. Cognitive function as examined by CTCS improved in 6 out of 8 secondary to lowering of concurrent AEDs. The final median dose of PER was 8 mg (varying between 2-12 mg).

CONCLUSIONS

These results of an objective seizure response in 9 (75%) out of 12 patients treated by PER in DRE may be interpreted as a surrogate-marker of tumor response secondary to AMPA blockade, advancing confirmation by MR imaging. These results warrant further study of PER on tumor activity in gliomas.

Keywords

Drug-Resistant Epilepsy, seizures, glioma, glioblastoma, perampanel, AMPA-receptor, glutamate

Introduction

Drug-resistant epilepsy (DRE) in gliomas occurs in about 30-40 % of low-grade gliomas (LGG) and in about 15-25% of glioblastomas (GBM).[1-4] One of the explanations for the close link between seizures and glioma evolution are elevated extracellular glutamate levels in the peri-glial and -neuronal space with ensuing over-activity of AMPA-receptors in both conditions. [5-7]

The recently introduced non-competitive AMPA inhibitor perampanel (PER) as antiepileptic drug provides the opportunity to apply it not only for seizure control, though also antitumoral agent as illustrated by its non-registered equivalent talampanel. [8] In DRE, besides a recurrence of seizures, the clinical problem is often aggravated by the common association of progression of tumor and cognitive difficulties.[9]

In an attempt to improve on the problem of DRE in gliomas, we applied the use of PER and report here our first experiences in a mixed group of gliomas.

Materials and Methods

Twelve patients with drug-resistant epilepsy were prospectively treated with PER at the Department of Neuro-oncology of the Pitié-Salpêtrière Hospital. Inclusion criteria were: age over 18, seizures associated with glial tumor type, ongoing or recurrent seizure activity at the time of initiating PER, failure on two or more anti-epileptic drugs (AEDs). [10] Seizure response was indicated by a 50% reduction in seizure frequency or by seizure-freedom as compared to baseline. Treatment policy included a reduction of dose or a discontinuation of one or more concurrent AEDs, once seizure-freedom during 4-6 weeks was observed.

As cognitive test, the Computerized Test for Cognitive Speed (CTCS) was applied which measures concentration and reaction time, which are both known to be affected by the epilepsy or the use of anticonvulsants. [11,12] Impairment of cognition is defined as a baseline CSCT score that is </1.5 SD of the lower 95% level of the normal range, corrected for age, sex and education. A difference in score of 0.5 S.D. compared to the individual baseline measurement is considered as deterioration or improvement of baseline cognitive function. [13-16]

Results

Table 1 gives an overview of patient characteristics, including tumor type, type of epilepsy, number of anticonvulsant drugs taken before entry into the study, number of patients showing escalation of Sz. at time of initiating PER and number of patients on concurrent antitumor treatment. Median age was 41 years, and nine out of 12 (75%) patients were men. Tumor types were ganglioglioma 1, low-grade glioma 6, anaplastic glioma 3 and GBM in 2 patients.

Median duration of follow-up was 6 months. Seizure response showed unchanged Sz. frequency in two out of 12 (17 %) patients, a 50% Sz. reduction in three out of 12 (25%), seizure-freedom in six out of 12 (50%) and increase in seizure frequency in one out of 12 (8%) patients as shown in Table 2. Seizure response in the six patients not receiving concurrent chemotherapy was unchanged in two, a 50% Sz. reduction in one and Sz.-freedom in three patients. Seizure response in six patients who did receive concurrent chemotherapy was 50% Sz. reduction in two, Sz.-freedom in three and no Sz. response in one patient. The median final dose of perampanel was 8 mg (varying 2 - 12 mg).

Side-effects were seen in six out of 12 (50%) patients, of whom four suffered from dizziness and two from drowsiness. These adverse effects were mainly seen at the time of initiation of therapy, disappearing after the 4-6 weeks. In two out of 12 (17%) patients PER was withdrawn. In one because of severe vertigo at a dose of 2 mg in a patient known with a peripheral vestibular disorder, who also has had difficulties tolerating other anticonvulsants. Because of disappearance of seizures at this low dose, a re-challenge resulted again in severe vertigo. Symptoms disappeared following discontinuation of PER, though the disorder still existed as shown on vestibular testing. Another patient did not respond to PER, neither to subsequent anticonvulsants and unfortunately showed relentless tumor progression.

Cognition as examined by CTCS was applied before start of PER and during follow-up in eight out of 12 patients. Deterioration of cognition was seen in one patient and no change in another, while improvement was observed in six (75 %) out eight patients who had shown seizure-freedom. In two of them dosing of concurrent AEDs could be lowered, in three patients one or two concurrently used AEDs could be discontinued, and in one dosing of concurrent AEDs

remained unaltered. In two patients with objective seizure response, an attempt to discontinue concurrent lacosamide resulted in recurrence of seizures, upon which resuming of lacosamide led again to seizure-freedom without deterioration in cognition.

Discussion

In low-grade gliomas, reappearance of seizures is observed in half the patients as first clinical sign of tumour progression and in two-third of cases in GBM. [17,18] A substantial part will develop DRE, estimated at about 30-40 % in low-grade gliomas and 15-25% in GBM (2, 3). In a series of oligodendrogliomas, 76.5% of 166 patients experienced multiple seizures, of whom slightly more than half (54.3%) had developed DRE. [19]

In our series, a 50% seizure-reduction was observed in 3 out of 12 (25%) patients and seizure-freedom in 6 (50 %) out of 12 patients at a median dose of 8 mg. In placebo-controlled trials of PER in DRE \, seizure-freedom is seen in less than 5 % of cases at doses varying between 8-12 mg. [20,21]

Considering adverse effects, 4 (33%) patients showed dizziness, and two (17%) suffered from drowsiness, often of transient nature seen at the time of initiation of therapy. These observations are similar to figures on side-effects of add-on PER in DRE, including dizziness and vertigo in 32-47 % and somnolence in 11-22%. [22,23]

Cognitive difficulties are common in gliomas due to a combination of prior antitumor therapy, the presence of epilepsy and the taking of AEDs. [24,25] The presence of epilepsy and the use of AEDs mainly affect attention, reaction time and memory [11,12,26,27] The CTCS test is validated to examine these functions. [13-15] This tool provides the advantage of a time-efficient computerized instrument, easily applicable in clinical practice taking less than 2-3 minutes [13-15]. The remarkable improvement of cognitive function we observed is best explained by a reduction in dose or withdrawal of one or more concurrent AEDS, in patients who had achieved seizure-freedom on treatment with PER.

Previous observations indicated that favorable seizure responses in patients with gliomas are often secondary to antitumor-directed effects. As a rule, surgery, radiation therapy and chemotherapy are more effective for seizure control in gliomas than symptomatic therapy with AEDs. [28-31] Although the number of patients in our series are admittedly small, we did not observe differences in seizure response whether patients received systemic chemotherapy along with PER or not.

Recently, one has observed that an early seizure response in low-grade gliomas is often a surrogate marker of an objective imaging response, usually appearing at six months or later after the initiation of tumor-directed therapy. [30,32] The AMPA-blocking analogous agent talampanel has demonstrated prolonged survival in a randomized phase II trial in de novo GBM, though was not registered for reason of side-effects.

PER is a highly protein-bound agent, metabolized in the liver mainly by the 3A4 co-enzyme to inactive metabolites. It has no strong enzyme-inducing or -inhibiting effects, though as enzyme-substrate it is susceptible to 3A4 agents. Carbamazepine and phenytoine enhance its clearance by a factor 1.5- 2, necessitating dose-adaptation of PER. [33,34] For the same reason, in cancer, the 3A4 inducers CCNU, vincristine and cisplatin can accelerate the metabolism of PER with a factor 1,2-2.3. [33]

Apart from direct antiepileptic effects of PER, its AMPA-receptor blocking activity may also contribute to tumor control resulting in early seizure control. [5,8] Overexpression of the AMPA-receptor in GBM facilitates migration and proliferation of GBM cells. [35] High-grade glioma samples overexpress GluA1 proteins and the inhibition of GluA1 blocks AMPA-receptor mediated activation of the MAPK pathway resulting in reduction of glioma cell proliferation.[36-38] These data indicate that GluR-antagonists talampanel or perampanel may impair tumor activity both in gliomas as in systemic cancer. [37]

In conclusion, we observed a higher seizure response than to be expected, a similar rate of adverse effects and a better cognitive function. The improvement in attention and reaction time seems best explained by a reduction in dose or by withdrawal of one or more concurrent AEDs in patients who achieved seizure-freedom upon treatment with PER. Apart from direct anti-seizure effects, these preliminary results may also secondary to its AMPA-blocking effects on glioma cells. Early seizure responses following antitumor-directed therapy in gliomas can be considered as a surrogate-marker of early tumor responses, advancing confirmation by MR imaging by 6 months or more.

These favorable results of PER certainly need confirmation in larger studies focusing on seizure control and on the antitumor effects of PER. In low-grade and anaplastic gliomas, PER warrants study as antitumor agent at the time of concurrent seizure recurrence and tumor progression; in *de novo* glioblastoma as an adjuvant to standard chemoradiation to examine time to progression and survival.

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Table 1
Patient Characteristics

No of Patients	12
M / F	9 / 3
Median Age (range)	41 yr (31-65 yr)
Type of Tumor	
Ganglioglioma	1
Low-grade Astro- or Oligo(astro)dendroglioma	6
Anaplastic Astro- or Oligo(astro)dendroglioma	3
Glioblastoma	2
Sz. as Presenting Sign of Tumor	9
Type of Epilepsy [1]	
Simple Partial Seizures	7
Complex Partial Seizures	4
Generalized Seizures	1
Partial Status Epilepticus	2
Total Number of AEDs taken before entry	
2	4
3	4
4	1
5 or more	2
Escalation of Sz. at Time of Initiating Perampanel	9/12
On Concurrent Antitumor Treatment	6/12

[1] Two patients had more than one type of Sz.

Table 2

Summary of Results

Median Duration of Follow-up		6 months	
Efficacy			
	Unchanged	2	17 %
	50% Sz. response	3	25 %
	Seizure-freedom	6	50 %
	Increase in Sz. frequency	1	8 %

Initial Number of Concurrent AEDs		Final Number of Concurrent AEDs
	No of Pts	No of Pts
1 AED	1	4
2 AEDs	4	5
3 AEDs	5	3
4 AEDs	2	0

Side-effects[1]	6/12
Dizziness/vertigo	4
Drowsiness	2
Withdrawal	2/12
Due to Side-effects	1
Due to Lack of Efficacy	1
Cognitive Change [2]	
Unchanged	1
Improved	6
Deteriorated	1
Not tested	4
Final Dose of Perampanel	
2 mg	1
4	2
6	3
8	3
10	1
12	2

[1] Side-effects of dizziness were often short-lived up to 1-2 hrs after taking perampanel

[2] As assessed by CTCS