

Experience of Low Dose Perampanel to Add-on in Glioma Patients with Levetiracetam-uncontrollable Epilepsy

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Abstract

After introduction of levetiracetam (LEV), treatment of seizures in patients with malignant brain tumors has prominently improved. On the other hand, we still experience some cases with LEV-uncontrollable epilepsy. Perampanel (PER) is a noncompetitive α -amino-3-hydroxy-5-methyl-4-isoaxazolepropionate acid receptor antagonist that has recently been approved for treating focal epilepsy as a secondary drug of choice. Available literature reporting PER medication in patients with gliomas is still sparse. Here, we report our initial experience with glioma patients and report efficacy of adding low dose 2–4 mg PER to LEV in patients whose seizure were uncontrollable with LEV monotherapy. Clinical outcome data of 18 consecutive patients were reviewed. This included nine males and nine females aged 24–76 years (median, 48.5 years), treated for glioma between June 2009 to December 2018. We added PER to patients with LEV-uncontrollable epilepsy. Adverse effects, irritability occurred in two patients, but continuous administration was possible in all cases. Though epileptic seizures occurred in four cases receiving 2 mg PER, 17 cases achieved seizure freedom by dose increments; final dose, 2–4 mg PER added to LEV 500–3000 mg. Our study revealed anti-epileptic efficacy of low dose PER 2–4 mg as first add-on therapy to LEV in glioma patients who have failed or intolerable to LEV monotherapy. Low dose PER added on to LEV may have favorable efficacy with tolerable adverse effects in glioma patients with LEV-uncontrollable epilepsy.

Key words: perampanel, levetiracetam, epilepsy, glioma

Introduction

Epileptic seizures are the presenting symptom in 27% of glioma patients.¹⁾ About 51% of the patients suffer seizures during the disease, and 26% become drug-resistant. First-generation anti-epileptic drugs (AEDs) such as phenytoin, carbamazepine, valproic acid, and phenobarbital have been used to treat seizures in patients with glioma.²⁾ These agents are known to cause a higher incidence of side effects in patients with glioma than in other patients with seizures.²⁾ Second-generation AEDs such as levetiracetam (LEV)

have more favorable pharmacokinetics with lesser incidences of side effects than first-generation AEDs.³⁾ After introduction of LEV, treatment of seizures in patients with malignant brain tumors has prominently improved. On the other hand, we still experience some cases with LEV-uncontrollable epilepsy. Here we define LEV-uncontrollable epilepsy as LEV-refractory epilepsy or epileptic seizure in patient intolerable to LEV dose increment.

Perampanel (PER) is a noncompetitive α -amino-3-hydroxy-5-methyl-4-isoaxazolepropionate acid (AMPA) receptor antagonist that has recently been approved for treating focal epilepsy.⁴⁾ AMPA glutamate receptors lack the GluR2 subunit rendering them Ca(2+) permeable and capable of activating the AKT and MAPK pathways.⁵⁾ Altered expression of glutamate transporters increases concentrations of extracellular

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glutamate, which contribute to epileptic discharge, tumor proliferation and peripheral excitotoxicity.⁶⁾ Recently, Vecht et al.⁷⁾ reported the efficacy of PER in glioma patients and reported an objective seizure response in 75% of the patients suffering drug-resistant epilepsy (DRE) with the median dose of 8 mg (varying between 2 and 12 mg). Maintenance dose of PER recommended in drug subscribing information in Japan is 8–12 mg to control epilepsy. It is reported that adverse events of PER increase with increasing dose. Since introduction of PER, available literature reporting PER medication in patients with gliomas is still sparse. We report the efficacy of low dose 2–4 mg PER added to LEV against glioma patients with LEV-uncontrollable epilepsy.

Patients and Methods

Retrospective study

This retrospective study was conducted with the approval of the Ethics Committee of the Tohoku University School of Medicine. All patients were treated at Department of Neurosurgery, Tohoku University School of Medicine.

Patients

Eighteen glioma patients with LEV-uncontrollable epilepsy were treated with LEV and PER at Tohoku University Hospital from June 2009 to December 2018. The diagnosis was confirmed pathologically in all cases. Patients' characteristics are summarized in Table 1. Postoperatively, all patients with World Health Organization (WHO) grade III or IV tumors received irradiation and chemotherapy using either of nimustine hydrochloride (ACNU), temozolomide, and bevacizumab.⁸⁾ Case 4, WHO grade II diffuse astrocytoma did not receive either irradiation or chemotherapy. Case 8 and 10, WHO grade II oligodendroglioma received only irradiation for residual tumor. Case 13, WHO grade II diffuse astrocytoma received irradiation and temozolomide against recurrent disease. Case 16, WHO grade II oligodendroglioma patient received bevacizumab treatment for recurrent disease after receiving irradiation and temozolomide against initial disease.

All patients had taken 500–3000 mg/day of LEV. PER was initiated when patients developed LEV uncontrollable epileptic seizure. In principle, PER was initiated slowly to avoid side-effects often appearing at introducing the drug, by 2 mg at night for a period of 2–4 weeks, given once daily, and followed by a dose of 4 mg. However, in tumor cases as in this series, rapid titration is necessary in some cases because of the need of seizure control. Only one case, Case 18 had taken 8 mg/day of PER.

Immunohistochemistry

We used routine, previously described immunohistochemical procedures.⁹⁾ Data of immunohistochemical staining against mutated isocitrate dehydrogenase (IDH)-1 was acquired retrospectively.

Results

Patient characteristics

Table 1 gives an overview of patient characteristics, including age/sex, tumor diagnosis, immunohistochemical staining for mutant IDH-1, location of the tumor, existence of residual tumor including gadolinium enhancing region or high intense lesion on T2-weighted MRI, type of epilepsy observed during LEV monotherapy, follow-up period after addition of PER, final dose of LEV, final dose of PER, adverse effect of PER, existence of epileptic attack during the initiation period of PER, seizure frequencies before addition of PER, and time to seizure freedom after addition of PER. The study included 18 patients; age 24–76 years old (median 48.5), nine males and nine females. Tumor diagnoses were seven grade IV glioblastoma, five grade III anaplastic astrocytoma, one grade III anaplastic oligodendroglioma, three grade II oligodendroglioma, and two grade II diffuse astrocytoma. Results for mutant IDH-1 staining were available in 15 cases; 10 cases stained positive whereas five stained negative. The tumor locations were at frontal lobe in 10, at insulo-operculum in three, at front-parietal lobe in one, at temporal lobe in one, multiple lesion or diffuse invasion into more than three lobes in three patients. Presence of residual tumor including gadolinium enhancing region or high intense lesion on T2-weighted MRI was observed in 16 cases. All cases once achieved seizure freedom by dose increments to final dose, 500–3000 mg of LEV. PER was initiated when patients developed LEV uncontrollable epileptic seizure. At the time of PER initiation, Tumor recurrence or progression was noted in 10 patients (Case 1, 3, 5, 6, 11, 13, and 15–18). One developed post-operative seizure (Case 14), and the other seven patients had no change in tumor status (Case 2, 4, 7–10, and 12). The types of epilepsy observed were secondary tonic-clonic in two, simple partial in eight, and complex partial seizures followed by secondary generalization in eight patients.

The duration of follow-up from initiation of PER was 1–21 months (median, 10.6 months). Ten cases died from tumor progression during this observation period (Case 1, 3, 5, 6, 11, 12, and 15–18). There were five cases who have taken a maximum dose of 3000 mg/day of LEV and 13 cases who

Table 1 Patient characteristics

Case	Age/ Sex	Diagnosis	mIDH-1 staining of tumor	Location of the tumor	Existence of residual tumor	Type of epilepsy	Follow-up (months)	Dose of LEV (mg)	Dose of PER (mg)	Adverse effect of PER	Epileptic attack during 2 mg PER	Seizure frequencies before addition of PER	Time to seizure freedom after addition of PER
1	72/M	GBM	(-)	Rt. frontal	(+)	Simple partial	7	1000	2	No	No	Occasionally	0
2	47/M	AA	(+)	Rt. insulo- operculum	(+)	Simple partial	13	2000	2	No	No	1/month	0
3	38/F	AA	(+)	Blt. Frontal/ Lt. parietal	(+)	Complex partial followed by secondary generalization	2	2000	4	No	Yes	Occasionally	1 month
4	49/F	DA	N/A	Rt. frontal	(+)	Complex partial followed by secondary generalization	18	500	4	No	No	2/month	0
5	50/F	AO	(+)	Lt. frontal	(+)	Complex partial followed by secondary generalization	5	1000	4	No	No	2/month	1 month
6	73/M	GBM	(-)	Rt. temporal	(+)	Simple partial	1	1000	4	No	Yes	2/week	3 days
7	30/F	GBM	(+)	Lt. frontal	(-)	Complex partial followed by secondary generalization	17	1000	4	No	No	2/month	0
8	26/M	OL	(+)	Rt. insulo- operculum	(+)	Simple partial	10	1000	4	No	No	2/day	0
9	24/F	GBM	N/A	Rt. frontal	(+)	Secondary tonic-clonic	21	1500	4	Irritability	No	Occasionally	0
10	38/F	OL	(+)	Lt. frontal	(+)	Complex partial followed by secondary generalization	18	1500	4	Irritability	No	1/3 months	0

(Continued)

Table 1 (Continued)

Case	Age/ Sex	Diagnosis	mIDH-1 staining of tumor	Location of the tumor	Existence of residual tumor	Type of epilepsy	Follow-up (months)	Dose of LEV (mg)	Dose of PER (mg)	Adverse effect of PER	Epileptic attack during 2 mg PER	Seizure frequencies before addition of PER	Time to seizure freedom after addition of PER
11	67/M	GBM	(+)	Rt. front- parietal	(+)	Complex partial followed by secondary generalization	6	2000	4	No	Yes	1/day	11 days
12	76/M	GBM	(-)	Lt. frontal	(-)	Complex partial followed by secondary generalization	15	2000	4	No	No	1/month	0
13	38/M	DA	(+)	Lt. insulo- operculum	(+)	Simple partial	13	2000	4	No	Yes	1-2/day	11 days
14	29/F	AA	(+)	Rt. frontal	(+)	Simple partial	16	3000	4	No	Yes	2/day	5 days
15	55/M	GBM	(-)	Multiple lesion	(+)	Complex partial followed by secondary generalization	5	3000	4	No	Yes	1/week	2 months
16	48/M	OL	(+)	Rt. frontal	(+)	Simple partial	12	3000	4	No	Yes	1/week	4 days
17	74/F	AA	N/A	Lt. frontal	(+)	Simple partial	7	3000	4	No	Yes	3-4/day	1 month
18	68/F	AA	(-)	Diffuse lt. hemisphere	(+)	Secondary tonic-clonic	4	3000	8	No	No	continuous	Not achieved

AA: anaplastic astrocytoma, AO: anaplastic oligodendroglioma, DA: diffuse astrocytoma, F: female, GBM: glioblastoma, lt: left, LEV: levetiracetam, M: male, mIDH-1: mutant IDH-1, N/A: not analyzed, OL: oligodendroglioma, PER: perampanel, rt: right.

have intolerance of LEV dose escalation because of adverse effect, mainly somnolence. We added PER in addition to LEV. As PER usually requires about 20 days to achieve constant serum concentration, the gradual dose increment is proposed to avoid side effects. However, in tumor cases as in this series, rapid titration is necessary in some cases because of the need of seizure control. In this series, 2 mg PER was given for 2–4 weeks at the initiation of PER, then increased to 4 mg. Adverse effects, irritability occurred in two patients. These adverse effects were mainly seen at the time of initiation of therapy, disappearing after 4–6 weeks with continuous use of PER. Epileptic seizures occurred in four cases during administration of 2 mg PER in initiation therapy. The seizure frequencies before addition of PER were occasionally in four, 1–2 a month in five, 1–2 a week in three, 1–4 a day in five patients, and continuous in one patient. All but one case achieved seizure freedom by dose increments to final dose, 2–4 mg PER. The duration of time to seizure freedom after addition on PER was 0–2 months (median, about 11 days) except one case. In another one patient (Case 18), seizure freedom was achieved with 8 mg PER. PER was well tolerated and did not increase the toxicity of radiation therapy and chemotherapy; ACNU, temozolomide, bevacizumab in these patients.

Representative cases

Here we present three representative cases in whom adverse event of irritability was observed (Case 9), in whom drug resistant epilepsy due to tumor progression was controlled (Case 11), and in whom peri-surgical epilepsy was controlled (Case 14).

Case 9 A 24-year-old woman was admitted with severe headache and nausea. T1-weighted MRI with gadolinium detected cystic mass lesion in the right insular lobe (Fig. 1A). Tumor removal was performed and histological examination revealed WHO grade IV glioblastoma (Fig. 1B). After the surgery, she suffered symptomatic epilepsy and monotherapy of LEV 1500 mg was given resulting in seizure freedom. A 60-Gy extended local brain radiation and chemotherapy with temozolomide were performed. Two years after the initial surgery, seizure developed again. Because of the somnolence, she rejected the dose increment of LEV. Then, we added 4 mg PER to LEV and achieved seizure freedom. Adverse effect, irritability was seen at the time of initiation of therapy, but disappeared after 4 weeks with continuous use of PER.

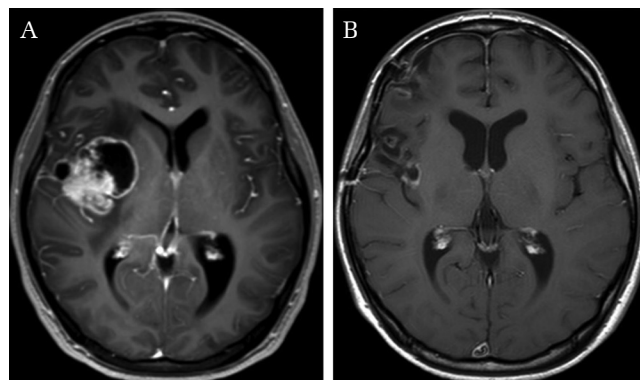


Fig. 1 Representative case; Case 9. A 24-year-old woman in whom adverse effect of perampanel was observed. T1-weighted MRI with contrast enhancement detected cystic mass lesion in the right insular lobe (A). Tumor removal was performed and histological examination revealed WHO grade IV glioblastoma (B).

Case 11 A 67-year-old man was admitted with complex partial seizure with secondary generalization. T1-weighted MRI with gadolinium detected cystic mass lesion in the right front-parietal lobe (Fig. 2A). Biopsy was performed and histological examination revealed WHO grade IV glioblastoma. A 60-Gy extended local brain radiation and chemotherapy with TMZ and bevacizumab were given (Fig. 2B). Monotherapy of LEV was performed and seizure freedom was achieved. During the maintenance chemotherapy with TMZ and bevacizumab, 14 months after initial biopsy, T1-weighted MRI with contrast enhancement demonstrated hyperintense lesion in the right frontal lobe (Fig. 2C) and epileptic seizures recurred. Then, we added 4 mg PER to LEV and achieved seizure freedom.

Case 14 A 29-year-old woman was admitted with partial seizure. T2-weighted MRI demonstrated hyperintense lesion in the right frontal lobe (Fig. 3A). Tumor removal was performed and histological examination revealed WHO grade II oligodendroglioma (Fig. 3B). Monotherapy of LEV was started and seizure freedom was achieved. Three years after the initial surgery, T2-weighted MRI demonstrated hyperintense lesion in the right frontal lobe which located on the right frontal lobe involving the primary motor cortex, suggesting tumor progression (Fig. 3C). Then, tumor removal was performed using direct cortical stimulation monitoring. Two days after the surgery, partial seizure recurred. This seizure lasted for a week though 2 mg PER was added to LEV. Interictal EEG obtained during this period revealed slow wave at right central indicating functional disturbance. Afterward, 4 mg PER was added to LEV and seizure freedom was achieved. The histological examination

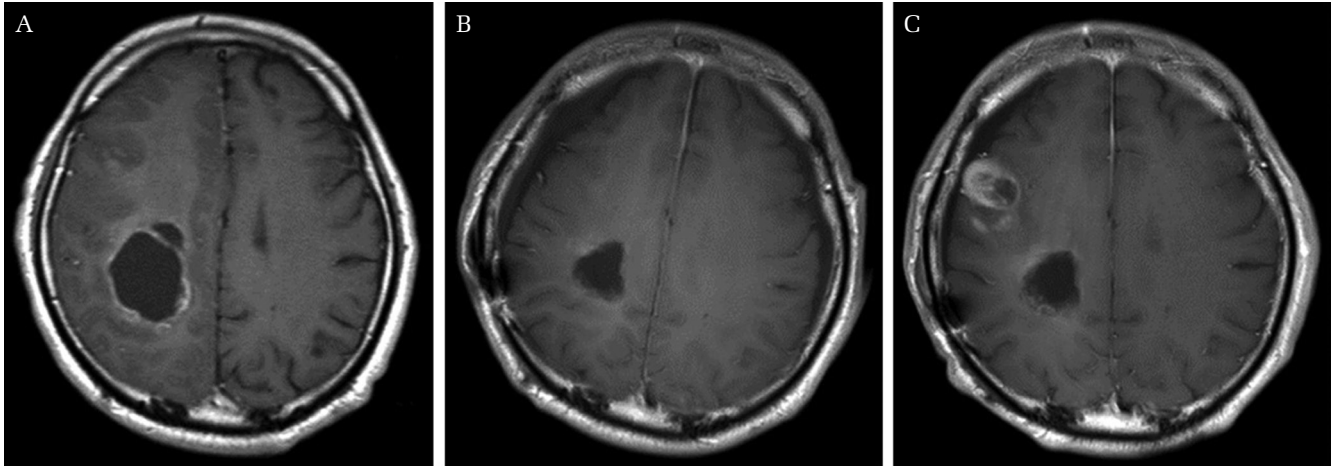


Fig. 2 Representative case; Case 11. A 67-year-old man suffered with glioblastoma. T1-weighted MRI with contrast enhancement obtained at initial presentation (A), and obtained after 60 Gy extended local radiation and chemotherapy with TMZ and bevacizumab (B). T1-weighted MRI with contrast enhancement obtained 14 months after initial biopsy demonstrated additional hyper-intense lesion in the right frontal lobe (C).

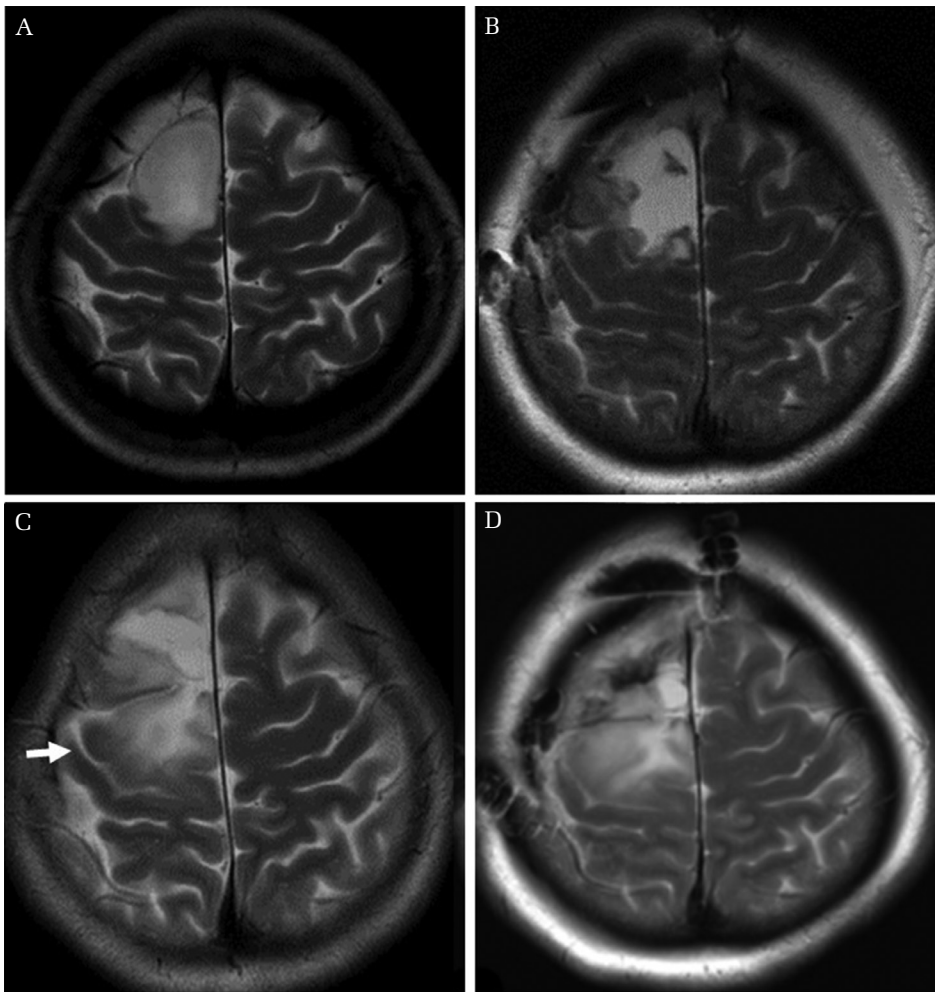


Fig. 3 Representative case; Case 14. A 29-year-old woman initially admitted with partial seizure. T2-weighted MRI obtained at initial presentation (A) and after surgery (B). Tumor removal was performed and histological examination revealed WHO grade II oligodendroglioma. T2-weighted MRI obtained at recurrence; 3 years after initial surgery (C) and after second surgery (D). Partial removal was performed using direct cortical stimulation. *White arrow* indicates the central sulcus.

revealed WHO grade III anaplastic astrocytoma. Then, 60 Gy extended local brain radiation, and chemotherapy with ACNU were given.

Discussion

After introduction of LEV, treatment of seizures in patients with malignant brain tumors has prominently improved.^{2,10)} LEV monotherapy once resulted in seizure freedom also in our series. On the other hand, we still experience some cases with LEV-uncontrollable epilepsy. Especially in tumor cases, LEV-uncontrollable epilepsy often accompanies tumor recurrence or occurs in cases that have progressive tumor.^{11,12)} Dose escalation of LEV is one strategy we often take in the case of epilepsy resistant to LEV. However, the adverse effect, mainly somnolence, hinder the dose escalation in some cases.

Perampanel is a noncompetitive AMPA receptor antagonist that has recently been approved for treating focal epilepsy.⁴⁾ In placebo controlled trials of PER in DRE of patients who had a diagnosis of simple or complex partial seizures and failed at least two AEDs in the previous 2 years, increasing PER dose from 8 to 12 mg could produce additional benefits in seizure control.¹³⁾ Liguori et al.¹⁴⁾ reported the efficacy and tolerability of PER and LEV used as first add-on therapy in patients with epilepsy affected by secondarily generalized seizures. They reported the similar efficacy of PER and LEV in reducing the frequency of secondarily generalized seizures. Moreover, fewer patients treated with PER showed adverse effects than patients treated with LEV.

In glioma patients with DRE, Vecht et al.⁷⁾ reported that PER at the final median dose of 8 mg (varying between 2 and 12 mg) resulted in objective seizure response in nine (75%) out of 12 patients. Though, in our series, anti-epileptic efficacy was observed with low dose PER 2–4 mg when used in addition to LEV in glioma patients who have failed LEV monotherapy. The discrepancy between our observation and Vecht's observation may due to the severity of drug resistance as in Vecht's study all recruited patients already received more than two anti-epileptic drugs while in our study PER was used as second in line. In addition, Kanemura et al.¹⁵⁾ reported the usefulness of PER with LEV for patients with DRE. They reported that PER appeared significantly more effective in patients with LEV than in those without LEV. Seizure-free status was significantly more frequent among patients with LEV than among those without LEV.

In the present study, though the half-life of PER is long as 105 h, time to seizure freedom was relatively short in many patients as demonstrated in Table 1; immediately after addition of PER in eight, 2–5 days

in three, 11 days in two patients. This observation is very important especially for high-grade glioma patients. LEV-uncontrollable seizure often take place with the tumor recurrence or progression. In patients suffering recurrent or progressive high-grade glioma and developed LEV-uncontrollable epilepsy, rapid re-induction of seizure freedom is the most importance since durative seizure may result in prolonged hospital stay. It may be pointed out that the median follow-up time from initiation of PER in our study was relatively short as median follow-up at 10.6 months. Moreover, observation periods of two patients still are just 1 and 2 months, rendering it difficult to determine the efficacy of PER as anti-epileptic drugs. Although this is the limitation of this retrospective study, this also is a result of the fact that LEV-resistant seizure often take place with the tumor recurrence or progression as 10 patients (Case 1, 3, 5, 6, 11, 12, and 15–18) already passed away in this observation period. Even considering all these limitations, we believe that it is clinically meaningful to report the efficacy of PER added onto LEV in brain tumor patients suffering LEV-uncontrollable epilepsy because this enable patients to stay at home for the rest of their prognosis.

Adverse events of PER include dizziness, somnolence, headache, fatigue, irritability, nausea, and fall. These occur in $\geq 5\%$ of PER-treated patients.¹³⁾ Among these common adverse events, the onset of dizziness, irritability, and fall were reported to increase during incrementing the dose.¹³⁾ In our cases, adverse event, irritability occurred in two patients. These adverse effects disappeared after 4–6 weeks with continuous administration. It is recommended to slowly increase the dose with a month interval to avoid side effects associated with dose escalation. In two cases who developed irritability, dose escalations were performed with 2 weeks interval. However, on the other hand, epileptic seizures occurred in eight (44.4%) cases during the administration of 2 mg PER in our series. Therefore, dose escalation with a month interval may be difficult in tumor cases. Our observations suggest that dose escalation with shorter interval may still be tolerable and reasonable for the early seizure control.

Presenting with seizure as first symptom is reported to be significantly associated with IDH-1 mutation in lower grade glioma.¹¹⁾ Mutation of IDH-1 in low-grade gliomas causes production of D-2-hydroxyglutarate (D2HG), a steric analogue of glutamate.⁶⁾ D2HG is structurally similar to glutamate and increases the electrical activity of neurons which cause epilepsy.¹²⁾ Since, PER is a noncompetitive AMPA receptor antagonist, it is suspected that the efficacy of PER differs between tumors with or without IDH mutations. In our series of 18 patients, 10 cases revealed to

have IDH-1 mutant tumors whereas five to have IDH-1 wild type tumors. No difference was observed between the IDH-1 gene status and efficacy of PER.

We reported our initial experience with LEV plus PER against LEV-uncontrollable epilepsy in tumor patients. Combination of drugs with different mechanisms of action may have achieved the control of tumor associated epilepsy. In addition, Ca²⁺-permeable AMPA receptors is reported to regulate growth of human glioblastoma.¹⁶⁾ Ishiuchi et al.¹⁷⁾ reported that blockage of Ca²⁺-permeable AMPA receptors suppressed migration and induced apoptosis in human glioblastoma cells. Izumoto et al.¹⁸⁾ also reported the efficacy of PER in glioma patients with uncontrollable epilepsy. Seizure control was obtained in all patients. They also revealed that tumor volume reduction was detected in eight ninths of these patients on MRI. Considering the fact that recurrence of epileptic seizure often accompanies tumor progression, use of PER might be a reasonable strategy.

Conclusion

Low dose PER added on to LEV may have favorable efficacy with tolerable adverse effects in glioma patients with LEV-uncontrollable epilepsy. When choosing an AED for the treatment of seizures in patients with malignant brain tumors, the efficacy and the tolerability of the AED should be taken into account. These results warrant further study of PER on tumor activity in gliomas.

Conflicts of Interest Disclosure

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