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SHORT COMMENTARY

# Lacosamide as add-on in brain tumor-related epilepsy: preliminary report on efficacy and tolerability

**M. Maschio · L. Dinapoli · M. Mingoia · F. Sperati · A. Pace · A. Pompili · C. M. Carapella · A. Vidiri · P. Muti**

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**Abstract** Lacosamide (LCM) is an antiepileptic drug (AED) that has demonstrated a good efficacy in controlling seizures as an add-on in adult epilepsy. To date, there have been no studies on LCM in patients with brain tumor-related epilepsy (BTRE). To evaluate efficacy and tolerability of LCM as an add-on in BTRE, we followed 14 patients suffering from BTRE who had already been treated with other AEDs and who had not experienced adequate seizure control. Eleven patients underwent chemotherapy while being treated with LCM. Mean duration of follow up was 5.4 months (min < 1 max 10 months). Mean seizure number in the last month prior to the introduction of LCM had been 15.4. At last follow-up, the mean seizure number was reduced to 1.9/month. Lacosamide mean dosage was of 332.1 mg/day (min 100 max 400 mg/day). Responder rate was 78.6%. One patient discontinued LCM because of side-effects. There were no other reported side-effects. Preliminary data on the use of LCM in add-on in patients with BTRE indicate that this drug may represent a valid alternative as an add-on in this particular patient population. However, larger samples are necessary in order to draw definitive conclusions.

**Keywords** Antiepileptic drugs · Brain tumor-related epilepsy · Lacosamide

M. Maschio (✉) · L. Dinapoli · M. Mingoia
Center for Tumor-related Epilepsy, Neurology Unit, Department of Neuroscience and Cervical-Facial Pathology, National Institute for Cancer "Regina Elena", Via Elio Chianesi 53, 00144 Rome, Italy
e-mail: maschio@ifo.it

A. Pace
Neurology Unit, Department of Neuroscience and Cervical-Facial Pathology, National Institute for Cancer "Regina Elena", Via Elio Chianesi 53, 00144 Rome, Italy

F. Sperati
Department of Epidemiology, National Institute for Cancer "Regina Elena", Via Elio Chianesi 53, 00144 Rome, Italy

A. Pompili · C. M. Carapella
Division of Neurosurgery, Department of Neuroscience and Cervical-Facial Pathology, National Institute for Cancer "Regina Elena", Via Elio Chianesi 53, 00144 Rome, Italy

A. Vidiri
Department of Radiology, National Institute for Cancer "Regina Elena", Via Elio Chianesi 53, 00144 Rome, Italy

P. Muti
Scientific Direction of National Institute for Cancer "Regina Elena", Via Elio Chianesi 53, 00144 Rome, Italy

## Introduction

Patients with brain tumor-related epilepsy (BTRE) represent a unique patient population that presents difficulties regarding the management of two very different pathologies: epilepsy on the one hand, and brain tumor on the other. Both pathologies require pharmacological treatment and present possible interactions between the various drugs as well as adverse events related to them; all of which can affect physical and cognitive performance and quality of life. Moderating the impact of epilepsy in these patients' lives is therefore an important aim of therapy. Epilepsy, in fact, heavily affects quality of life because it requires one to live with the unpredictability of seizures and the long-term taking of additional medications. In many cases, seizures are drug-resistant, so patients are often forced to take polytherapy. Beside this, polytherapy involves possible side-effects in addition to those already known to systemic treatment [1, 2].

Among new antiepileptic drugs (AEDs), lacosamide (LCM) is an AED that is used as an adjunctive therapy in patients with partial seizures with or without secondary generalization. Based on recent experimental studies, LCM appears to have a dual mode of action—enhancement of sodium-channel slow inactivation and modulation of collapsing response mediator protein-2 (CRMP-2)—both of which are novel mechanisms for an AED. Without affecting fast inactivation, LCM appears to selectively enhance sodium-channel slow inactivation, which may help normalize activation thresholds and decrease pathophysiological neuronal activity, thus controlling neuronal hyperexcitability [3]. Lacosamide is rapidly and completely absorbed from the gut with a negligible liver first-pass effect and has an oral bioavailability of approximately 100%. It also has low protein binding (<15%). Results from clinical efficacy and safety trials showed that LCM does not affect the plasma levels of carbamazepine, valproic acid, lamotrigine, levetiracetam, oxcarbazepine, or phenytoin to a relevant extent [4, 5]. The peak plasma concentration of LCM occurs approximately 0.5–4 h after administration. The half-life of LCM is about 12–13 h. Lacosamide is eliminated in the urine unchanged (≈40% of the administered dose) and as the *O*-desmethyl metabolite (<30%). The cytochrome P450 (CYP) isoenzyme 2C19 is mainly responsible for the formation of the *O*-desmethyl metabolite. However, there were no clinically relevant differences in the pharmacokinetics of LCM when it was administered to extensive metabolizers (with a functional CYP2C19) versus poor metabolizers (lacking functional CYP2C19) [6]. The most common adverse events (dizziness, headache, and nausea) occur relatively early following exposure to LCM, generally during the titration period. Lacosamide is not associated with an increased risk of rash [7]. This favorable pharmacological and pharmacokinetic profile makes LCM a possible therapeutic choice in patients with BTRE. However, to date, there is only a communication on a retrospective chart review in abstract format on LCM in BTRE [8].

This preliminary report documents experience with LCM in 14 patients with epilepsy related to brain tumor followed at our center from February to September 2010.

## Methods

This is a case series of patients consecutively recruited suffering from BTRE who had already been treated with one or more AEDs (except for lacosamide), whose seizure control had been insufficient, though the AEDs had been at the maximum tolerable dose for the patient. We consecutively recruited patients who had had at least one seizure in the month preceding recruitment. Patients might have been undergoing chemotherapy and/or radiotherapy prior to their first visit at our center, but the stage of their disease and the therapies that they had received prior to arriving at our center, though documented, did not alter our therapeutic approach to seizure control. All patients were treated with the current standard care of patients with brain tumors.

Clinical, epileptological, and demographical characteristics are described in Table 1. At baseline, eligible patients underwent a complete physical and neurological examination. A clinical seizure diary was also given. Epilepsy was diagnosed following the guidelines of the International League Against Epilepsy [9]. Lacosamide was titrated according to the technical file as first to fifth add-on therapy at dosage variable from 200 to 400 mg/day. The dose was divided into two oral intakes. The starting dosage was 100 mg/day with a weekly increase of 100 mg/day. In order to achieve seizure freedom, the dosage of LCM was titrated depending on seizure control and eventual adverse events onset up to the maximum dosage of 400 mg/day. Minimal effective dose was considered to be 200 mg/day [7]. During follow-up, patients had a monthly clinical examination and they were asked to contact us if a seizure occurred. The seizure count was made on the basis of a historical report (for baseline seizure frequency), a seizure diary, and direct contact with the patients and their caregivers during the follow-up. The presence and severity of LCM side-effects was evaluated according to frequency and intensity using the "Common Terminology Criteria for Adverse Events—CTCAE" [10]. Neuro-radiological examination was performed every 3 months. The study was approved by the Institute's Ethical Committee.

We reported continuous data as means and standard deviations and categorical data as frequencies and percentage values. We evaluated the efficacy of LCM in the overall population (ITT; $n$ =14). ITT population (*intent-to-treat*) are patients taking at least one dose of LCM. We used the McNemar test to compare the presence of seizures at baseline and during follow-up. The mean monthly seizures frequencies at baseline and during follow-up were compared using the Wilcoxon signed-rank test.

All statistical analyses were carried out with SPSS statistical software version 18 (SPSS Inc., Chicago IL, USA).

## Results

During treatment with LCM, 11 patients were undergoing chemotherapy, no patient underwent radiotherapy and nine patients died because of neoplastic disease progression (see Table 1). All patients were treated with the current standard care of patients with brain tumors; in that those for

**Table 1** Patients' clinical and vital data

| Patient | Age (years) | Sex | Histology | Surgery | Chemotherapy[a] | Seizure types | Previous AED therapy (mg/day) | Reason for adding LCM | LCM dosage (mg/day) | Side-effects | Number of seizures in the last month before LCM therapy | Mean number of seizures/month during LCM therapy | Duration of LCM therapy (months) | Reasons for LCM withdrawal | Tumoral progression | Death |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 38 | M | AA | PR | BEVACIZUMAB | SP | LEV 3000<br>VPA 1000 | Seizures | 400 | No | 45 | 0 | 3 | – | Yes | Yes |
| 2 | 42 | M | AO | PR | CCNU | SP + SGTC | VPA 1000<br>LTG 300<br>LEV 3000<br>CNZ 1,5 | Hematological toxicity seizures | 400 | No | 1 | 1.8 | 10 | – | No | No |
| 3 | 35 | M | AOA | PR | No | CP + SGTC | LEV 3000<br>LTG 400<br>OXC 1200 | Seizures | 100 | Yes | 30 | 0 | <1 | Blurred vision, dizziness | No | No |
| 4 | 49 | M | GBM | PR | TMZ | CP + SGTC | LEV 3000 | Seizures | 400 | No | 30 | 4.6 | 7 | – | Yes | Yes |
| 5 | 35 | F | AOA | PR | TMZ | SP + SGTC | LEV 3000<br>PGB 300 | Somnolence Seizure | 400 | No | 1 | 0.8 | 9 | – | No | No |
| 6 | 41 | M | GBM | PR | TMZ | CP + SGTC | LEV 3000 | Seizures | 400 | No | 1 | 5.8 | 6 | – | Yes | Yes |
| 7 | 40 | M | LGO | Biopsy | No | SP + SGTC | LEV 3000<br>ZNS 200<br>TPM 100 | Seizures | 400 | No | 30 | 9 | 6 | – | No | No |
| 8 | 47 | F | LGA | PR | TMZ | CP + SGTC | LEV 3000<br>LTG 400<br>TPM 400 | Seizures | 400 | No | 11 | 0 | 10 | – | Yes | Yes |
| 9 | 61 | M | GBM | GTR | TMZ | CP | LEV 3000 | Seizures | 300 | No | 1 | 0.25 | 4 | – | Yes | Yes |
| 10 | 52 | F | AA | PR | TMZ | SP + SGTC | PHT 300<br>CNZ 3 | Seizures; status epilepticus | 400 | No | 30 | 0 | 3 | – | Yes | Yes |
| 11 | 35 | F | LGA | PR | TMZ, BEVACIZUMAB | SP + SGTC | LEV 3000 | Seizures | 200 | No | 30 | 0 | 4 | – | Yes | No |
| 12 | 63 | M | GBM | GTR | FTMU, BEVACIZUMAB | CP + SGTC | OXC 1800 | Somnolence Seizures | 300 | No | 1 | 0 | 2 | – | Yes | Yes |

**Table 1** continued

| Patient | Age (years) | Sex | Histology | Surgery | Chemotherapy[a] | Seizure types | Previous AED therapy (mg/day) | Reason for adding LCM | LCM dosage (mg/day) | Side-effects | Number of seizures in the last month before LCM therapy | Mean number of seizures/month during LCM therapy | Duration of LCM therapy (months) | Reasons for LCM withdrawal | Tumoral progression | Death |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 13 | 48 | F | Gliomatosis cerebri | Biopsy | No | SP + SGTC | LEV 1000 | Itch Seizures | 150 | No | 1 | 2.3 | 3 | – | Yes | Yes |
| 14 | 22 | F | GBM | PR | TMZ BEVACIZUMAB | SP + SGTC | LEV 3000 | Paresthesia Seizures | 400 | No | 3 | 2 | 3 | – | Yes | Yes |

Histological diagnosis: *GBM* glioblastoma multiforme, *AA* anaplastic astrocytoma, *AO* anaplastic oligodendroglioma, *AOA* anaplastic oligoastrocytoma, *LGA* low-grade astrocytoma, *LGO* low-grade oligodendroglioma. Chemotherapy: *TMZ* temozolomide, *FTMU* fotemustine, BEVACIZUMAB, CCNU, lomustine. Surgery: *GTR* gross total resection, *PR* partial resection. Seizures types: *SP* simple partial, *CP* complex partial, *SGTC* secondarily generalized tonic-clonic. AEDs: *CNZ* clonazepam, *LEV* levetiracetam, *LTG* lamotrigina, *OXC* oxcarbazepine, *PHT* phenytoin, *PGB* pregabalin, *TPM* topiramate, *VPA* valproic acid, *ZNS* zonisamide

[a] During follow-up

whom radiotherapy was indicated had received and completed it prior to entering the study.

In the month prior to the introduction of LCM, patients were in polytherapy with the following drugs: clonazepam, lamotrigine, levetiracetam, oxcarbazepine, phenytoin, pregabalin, topiramate, valproic acid, zonisamide (see Table 1). The mean seizure number had been 15.4 seizures/month. The mean duration of follow-up was 5.4 months (min < 1 max 10 months). Lacosamide mean dosage was 332.1 mg/day (min 100, max 400 mg/day). At last follow-up, mean seizure number was reduced to 1.9/month: six patients were seizure-free (42.9%), five had a seizure reduction ≥50% (35.7), two had a seizure reduction <50% (14.3%), and one had unmodified seizure frequency (7.1%). Therefore, the responder rate was 78.6%. The difference in presence/absence of seizures between baseline and final follow-up was significant ($p < 0.031$). The difference in mean monthly seizure frequency between baseline and follow-up was also significant ($p < 0.022$).

The median percentage seizure reduction was 79.8%.

One patient dropped out due to side-effects (dizziness and blurred vision; grade 2 of CTCAE).

## Discussion

Patients with BTRE are forced to face a host of problems related to both epilepsy and the tumor itself. This presents a complicated therapeutic profile. Indeed, during the course of the disease, while undergoing many treatments (surgical, pharmacological, and radiological), patients experience neurological difficulties due to the tumor and psychological problems related to a probable unfavorable prognosis. In addition, these patients have to deal with epilepsy and the additional pharmacological treatments related to it, the unpredictability of seizures, and the psychological distress caused by this diagnosis. Epilepsy is considered the most important risk factor for long-term disability in brain tumor patients [11]. For these reasons, the choice of the best AED must take into consideration the need to balance efficacy, potential side-effects, and drug-to-drug interactions. In the last year, interest in new AEDs in BTRE is increasing. In fact, recent data is reported in the literature concerning the use of new AEDs, particularly levetiracetam, pregabalin, zonisamide as an add-on, and oxcarbazepine and topiramate as monotherapy [12–16]. Though more studies need to be undertaken with respect to the newer AEDs, they seem to offer promising results with regard to this important balance between efficacy and tolerability.

Together with Newton et al.'s [8] work, which reported that 46% of patients were seizure-free and in 77% of patients with reduced seizure frequency, our data

represents the first paper concerning the use of LCM as an add-on therapy in the BTRE population. Our results are quite similar to those observed by Newton et al. [8] with 42.9% of patients having seizure freedom and with seizure frequency reduced to >50% in 11 patients (78.6%). This effect of LCM on seizure control was also statistically significant.

We observed only one severe side-effect after 1 week of LCM therapy (dizziness and blurred vision). In this patient, LCM administration was discontinued. However, the small sample size and short follow-up does not allow us to explain this side effect. Lacosamide was added at different stages of the oncological disease: this does not allow a consistent assessment of the effectiveness of treatment; nevertheless, our results show that LCM can be a possible therapeutic choice in this patient population. Some studies cited in the literature suggest that oncological therapies could possibly reinforce the efficacy of AEDs regarding seizure control [17, 18]. In the future, we have in mind to evaluate the possible effect of chemotherapy and radiotherapy in this patient population, as we have done before in previous studies [19, 20]. Although this is a small series with a relatively short follow-up in some patients (inherent to the survival of patients with brain tumors), our data show that LCM may be considered as a possible alternative in this patient population. This applies for new studies with a wide and homogeneous sample and a longer follow-up.

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**Conflict of interest** None.

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