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Quality of life, mood and seizure control in patients with brain tumor related epilepsy treated with lacosamide as add-on therapy: A prospective explorative study with a historical control group

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ABSTRACT

Objective: Brain tumor-related epilepsy (BTRE) is often drug resistant and patients can be forced to take polytherapy that can adversely affect their quality of life (QoL). Lacosamide (LCM) is a new antiepileptic drug (AED) used as adjunctive therapy in patients with partial seizures with or without secondary generalization, with a favorable pharmacokinetic profile that seems to be effective and well tolerated.
Therefore it represents a possible therapeutic choice for patients with BTRE. We propose a prospective study with a historical control group to evaluate the effect of LCM as add-on therapy on seizure control and quality of life in patients with BTRE. This study has been designed to test the superiority of Lacosamide over Levetiracetam as an add-on. We compared a prospective cohort of 25 patients treated with Lacosamide with a historical control group ($n = 19$) treated with Levetiracetam as an add-on.
Methods: We recruited 25 adult patients (M 18, F 7; mean age 41.9) affected by BTRE with uncontrolled partial-onset seizures treated with AED polytherapy. We added LCM as an add-on. Patients were evaluated at baseline, after 3 months and at 6 months.
This population has been compared with a historical control group of 19 BTRE adult patients (M 13, F 6; median age 48.0, range: 28–70) with uncontrolled partial-onset seizures treated with LEV as add-on.
The patients underwent QoL, mood and adverse events tests (Adverse Event Profile-AEP) and evaluation of seizure frequency.
Results: Twelve patients had high grade gliomas, and thirteen had low grade gliomas. During follow-up, thirteen patients underwent chemotherapy, three radiotherapy and five patients had disease progression. Nine patients had simple partial seizures, eight had complex partial seizures, and eight had secondary generalized seizures. Fifteen patients were in monotherapy and ten in polytherapy with AEDs. **LCM** was added up to reach the maximum dosage of 400 mg/die (mean final dose 300 mg/die). Four patients dropped out due to poor compliance and 1 for inefficacy.
In the historical control group treated with LEV (mean final dose 2000 mg/die) 12 patients had high-grade gliomas, and 7 had low grade gliomas. Thirteen patients were in monotherapy and 6 in polytherapy with AEDs.
In the 22 patients evaluable of 25 patients treated with LCM, we observed at final follow-up 7 patients seizure free, 12 with a significant reduction of seizures ≥ 50%, 2 stable and 1 patient with number of seizures increased.
Mean seizure frequency at baseline compared with baseline period: the mean number of seizures significantly decreased from baseline (9.4) to final follow-up (1.2) ($P = 0.005$). The Responder Rate was 86.4%.
Comparing responder rate of 22 evaluable patients with LCM with responder rate of 19 patients with LEV we didn't observe significant differences ($p = 0.31$).
In our patients treated with LCM we didn't observe significant difference at 3 and 6 months in QoL tests results; we observe a significant reduction in the mean score of Karnofsky Performance Status (KPS) and Barthel Index (BI) between baseline and 6 months of follow-up (KPS $p = 0.003$; BI $p = 0.007$).
No clinical side effects were observed.
Conclusion: Comparing the LCM with the historical group treated with LEV in add-on, we observed that LCM seems to have a higher clinical efficacy than LEV.

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In our patients, we did not observe any significant changes in QoL tests, indicating stability in all quality of life domains explored, despite the objective worsening in their functional status. Although this is a small series with a relatively short follow-up, our data indicates that LCM in add-on in patients with BTRE appears to be as effective as LEV in add-on, without impact on mood and quality of life.

1. Introduction

Symptomatic seizures are the first symptom in 20–40% of patients suffering from brain tumors (BT). During the evolution of disease an additional 20–45% of patients will develop symptomatic seizures. In these patients the maintenance of a good quality of life (QoL) is critical because patients undergo numerous treatments (surgery, chemotherapy and/or radiotherapy) and confront an often-dismal prognosis [1]. The progress of oncological therapy permits an improvement in life expectancy of cancer patients, but may have an impact on quality of life, in term of physical and psychosocial function. Moderating the impact of epilepsy in their lives is therefore an important aim of therapy. Patients with brain tumor-related epilepsy (BTRE) receive treatment with antitumoral drugs, corticosteroids and antiepileptic drugs (AEDs) that often come with important side effects [2,3]. Although seizure frequency in patients with BTRE can effectively be reduced using AEDs, these drugs can interact with the metabolism of corticosteroids, can reduce the efficacy of a variety of chemotherapeutic agents (CT), and can induce side effects more frequently compared with non-tumoral epileptic patients [2,3]. These side effects (cognitive impairment, myelosuppression, liver dysfunction and dermatological reaction) occur during therapy with traditional enzyme-inducing AEDs (carbamazepine, phenobarbital, phenytoin) [4]. To date, there have been few studies evaluating newer AEDs and the role they may play in reducing many of the negative effects of the typical enzyme-inducing AEDs in the treatment of patients with BT [5–7].

Lacosamide (LCM) is a new AED used as adjunctive therapy in patients with partial seizures with or without secondary generalization [8]. Lacosamide is rapidly and completely absorbed from the gut with a negligible liver first-pass effect and has an oral bioavailability of approximately 100% and does not affect the plasma concentrations of carbamazepine, phenytoin, levetiracetam, lamotrigine, topiramate or valproic acid [9]. The peak plasma concentration of LCM occurs approximately 0.5–4 h after administration. The half-life of LCM is about 12–13 h. The drug is less than 15% protein bound [10]. 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 lacosamide when it was administered to extensive metabolizers (with a functional CYP2C19) versus poor metabolizers (lacking functional CYP2C19) [11]. Therefore it represents a possible therapeutic choice for patients with BTRE. However, LCM has not been systematically evaluated in patients with BTRE. Therefore, we conducted a prospective study with a historical control group to evaluate the effect of LCM as add-on therapy on seizure control and quality of life in patients with BTRE.

This study has been designed to test the superiority of lacosamide over levetiracetam in add-on [12]. We compared a prospective cohort of 25 patients treated with lacosamide with a historical control group (n = 19) treated with levetiracetam in add-on. The study was approved by the Institute's Ethical Committee and each participant signed informed consent.

2. Materials and methods

Primary aim:

To compare efficacy on seizure control of LCM as add-on versus LEV as add-on.

Secondary aims:

To evaluate the impact on QoL, on mood and on functional status at 3 and 6 months as compared with baseline.

To evaluate the occurrence of adverse events during therapy with LCM using Adverse Events Profile (AEP).

To evaluate the effect of LCM treatment on seizure control as add-on in patients with brain tumor-related epilepsy, after 6 months period of treatment.

2.1. Patients population

2.1.1. Patients with brain tumor-related epilepsy

Patients who receive standard AED therapy and have uncontrolled seizure activity despite adequate AEDs dosages, were recruited. LCM was added as first or second add-on to these specific drugs: carbamazepine, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, topiramate or valproate. Gabapentin, pregabalin, zonisamide can be only used as add on drugs to the monotherapy drug mentioned above. Patients were followed for 6 months and they systematically underwent neurological examination, evaluation of seizure frequency and administration of QoL tests.

All patients that had uncontrolled seizures during the treatment period at LCM maximum tolerated doses and needed another AED added were considered as treatment failures and analyzed as such (Last Observation Carried Forward "LOCF") to give seizure frequency at AED change.

2.1.2. Inclusion criteria

Patients Age ≥ 18 years ≤ 75 (both sexes) with primary BT (astrocytoma II and III WHO, oligodendroglioma II and III WHO and multiform glioblastoma), cerebral lymphoma, with previous surgical resection or biopsy. Informed consent signature. Patients in a stable phase of disease (evidenced by unchanged neuroradiological examinations), with symptomatic epilepsy characterized by partial seizures with or without secondary generalization and with ≥2 seizure in the last month, despite treatment with the maximum tolerated stable dose of 1–2 AED. Seizure retrospective count at least in the last 28 days. Patients could be also in treatment with CT, radiotherapy (RT) and corticosteroids started before LCM introduction. Patients treated for the oncological disease following international oncological guidelines.

2.1.3. Exclusion criteria

Patients Age ≤ 18 years ≥ 75 (both sexes) with primary BT; Karnofsky Performance Status < 60; Patients with previous epilepsy before tumor onset; Patients with other chronic neurological and psychiatric diseases; Patients with brain metastases; Patients childbearing or breast feeding; Allergy or intolerance to soya, peanuts, lacosamide, lacosamide tablet excipients; Patients with known preexisting second or third degree AV block.

2.2. Drug

LCM as first or second add-on therapy at dosage variable from 200 to 400 mg/die. Dose was taken orally, twice daily. The investigational product was provided by the participating center to patients as part of the study, delivered as tablets. The starting dosage was 100 mg/die,