J Neurooncol (2007) 84:293–296
DOI 10.1007/s11060-007-9373-8

CLINICAL STUDY PATIENT STUDIES

Retrospective analysis of the efficacy and tolerability of levetiracetam in patients with metastatic brain tumors

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Received: 15 February 2007 / Accepted: 7 March 2007 / Published online: 13 April 2007

Abstract Seizures are a common complication of metastatic brain tumors (MBT), affecting approximately 27–50% of all patients during the course of their illness. Treatment of tumor-induced seizures is often inadequate with traditional antiepileptic drugs (AED) due to a variety of factors, including activation of glutamatergic NMDA receptors, alterations of neuronal input pathways, and tumor growth. Levetiracetam (LEV) is a 2nd generation non-enzyme inducing AED with a novel mechanism of action, binding to neuronal synaptic vesicle protein SV2A, that has been previously shown to reduce seizure activity in patients with primary brain tumors. Due to its unique mechanism of action, it has been postulated that LEV may also be effective in controlling seizures from MBT. A retrospective chart review was performed of all Neuro-Oncology Center patients with MBT who had received LEV for seizure control. Thirteen patients were reviewed with a median age of 55.1 years (range: 34–70). Six patients had breast cancer, five had lung cancer, and two had melanoma. LEV was used as an add-on AED in seven patients (54%) and as monotherapy in six patients (46%), with a median dose of 1,000 mg/day (range: 500–3,000). The baseline median seizure frequency was one ictal event every other day. After the addition of LEV, the median seizure frequency was reduced to 0 per week. The seizure frequency was reduced to less than 50% of the pre-LEV baseline in 100% of patients ($P = 0.0002$, Sign test), with 10 patients (77%; confidence interval: 46–95%) noting complete seizure control. The most common adverse event was somnolence and headache, noted in 3 of 13 patients (23%). LEV was very effective and well tolerated in MBT patients with seizures and should be considered for add-on therapy or as a substitute AED for monotherapy.

Keywords Metastatic brain tumors · Seizures · Levetiracetam · Keppra · Antiepileptic drugs

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Introduction

Metastatic brain tumors (MBT) are the most frequent neurologic complication seen in patients with systemic cancer, occurring in 10–40% of patients [1–2]. The systemic cancers most likely to metastasize to the brain include lung, breast, and melanoma, although there are known cases of brain metastases from cancers originating in the colon, rectum, kidney, prostate, testis, and ovary [3]. Seizures occur in 27–50% of patients with MBT during the course of their illness [4, 5]. Primaries with the highest frequencies of seizure activity include melanoma (67%), lung (29%), and gastrointestinal (21%) [4]. Although there is little evidence that patients with MBT should be treated prophylactically with anti-epileptic drugs (AEDs), patients who do develop seizure activity should be placed on an effective AED [6].

Treatment of tumor-induced seizures is often inadequate with conventional AEDs. This inadequacy is due to a

variety of factors, such as activation of glutamatergic NMDA receptors, alterations of neuronal input pathways, and tumor growth. Additionally, the mechanism of action of traditional AEDs may not be effective in treating tumor-induced seizures. Traditional AEDs act through excitatory mechanisms via blockade or inactivation of Na^+ channels (phenytoin, carbamazepine, valproate) and/or Ca^{2+} channels (lamotrigine, topiramate, oxcarbazepine), or through inhibitory mechanisms via stimulation of GABAergic activity (benzodiazepines, phenobarbital, tiagabine, vigabatrin, gabapentin). These mechanisms of action only cover a few of the pathophysiologic mechanisms of tumor-induced seizures known to exist [5]. The majority of traditional AEDs (phenytoin, carbamazepine, phenobarbital, oxcarbazepine) induce the hepatic cytochrome P450 system, which may lead to increased metabolism of corticosteroids and many chemotherapeutic agents that are also metabolized by the hepatic cytochrome P450 system (nitrosurea, paclitaxel, cyclophosphamide, irinotecan, adriamycin, methotrexate) [7–9]. This can lead to inadequate corticosteroid and chemotherapeutic dosing in patients with MBT, which is of significant concern.

Levetiracetam (LEV) is a 2nd generation non-cytochrome P450 inducing AED with a novel mechanism of action [7, 10, 11]. LEV binds with high-affinity to the synaptic vesicle protein SV2A, which is enriched in synaptic vesicles and is believed to be involved in synaptic vesicle exocytosis and presynaptic neurotransmitter release [12, 13]. In an audiogenic mouse model of epilepsy, there is a strong correlation between the affinity of a compound for SV2A and its anti-epileptic effect [13]. LEV also induces a reduction of Ca^{2+} current through neuron-specific, high voltage activated n-type Ca^{2+} channels [14, 15]. Additionally, LEV reduces the effect of Zn^{2+} and the beta-carbolines on GABA and glycine, the main inhibitory receptors of the central nervous system [16]. Multiple studies have shown that LEV exerts neuroprotective effects via stimulation of neurotrophic factors that reduce the amount of inflammation and neuronal death that occurs with seizures [17, 18].

Due to the unique mechanism of action of LEV, its lack of significant drug–drug interactions, and its lack of interaction with the hepatic cytochrome P450 system, it has been suggested as the best choice of AED in patients with brain tumors [7, 19]. Many studies have shown that LEV as add-on or monotherapy reduces the seizure activity in patients with primary brain tumors [19–21]. Some of these studies have included patients with MBT, but none of them have isolated these patients and their results of epilepsy treatment with LEV. To test the effectiveness of LEV in the treatment of tumor-induced epilepsy in patients with MBT, we have performed a retrospective analysis of the efficacy and tolerability of LEV in a cohort of patients that have received the drug while being followed at the Dardinger Neuro-Oncology Center.

Materials and methods

A retrospective chart review was conducted of all patients with MBTs that had received LEV for seizure control at the Dardinger Neuro-Oncology Center. Criteria for eligibility in the study included the diagnosis of MBT, placement on LEV, and at least one follow-up visit after beginning treatment with LEV. Indications to initiate LEV therapy included: seizure activity that persisted after maximal therapy with traditional AEDs, potential drug interactions with chemotherapeutic agents or corticosteroids, and unacceptable adverse side effects of other AEDs. Patients with concomitant epileptic conditions were excluded. Data regarding seizure frequency was obtained from patient histories, hospital charts, and clinic notes. For each patient, seizure frequency data was collected for a minimum interval of 4 weeks after the initiation of LEV, with additional data being collected at each scheduled follow-up visit after the initial 4 week visit. Significant improvement in seizure frequency was defined as a greater than 50% reduction in seizure activity as compared to the pre-LEV baseline. Additional data collected about each patient included age, gender, primary tumor site, and treatment modalities.

Results

A total of 13 patients were reviewed with a median age of 55.1 years (range: 34–70). Of the total cohort, six patients had breast cancer, five had lung cancer, and two had melanoma. Eleven of the 13 patients (85%) suffered from partial seizures, while 2/13 (15%) suffered from generalized seizures. The majority of patients had already received some form of irradiation (whole-brain radiation, gamma knife) and many had received or were currently receiving chemotherapy (e.g. tamoxifen, paclitaxel, herceptin). Most of the patients remained clinically and radiologically stable during the study, without significant change in tumor size by MRI imaging. Each patient had their post-LEV seizure frequency evaluated after 1 month of treatment with LEV, and at each subsequent scheduled visit. The mean length of time each patient's seizure frequency was followed after the initiation of LEV was 15 months (range: 1 month–4 years). For patients in which LEV was used as add-on therapy for inadequate seizure control by other AEDs, the initial AED (phenytoin, carbamazepine, valproate, oxcarbazepine) had already been titrated to adequate

therapeutic levels. LEV was used as an add-on AED in seven patients (54%) and as monotherapy in six patients (46%), with a median dose of 1,000 mg/day (range: 500–3,000). The interval of evaluation of seizure frequency during LEV treatment was 4 weeks for all patients. Prior to initiating LEV therapy, the median seizure frequency was one ictal event every other day (range: 2 every day–1 every month). After the initiation of LEV, the median seizure frequency was reduced to 0 per week (range: 0–2 every month). All patients (100%) had their seizure frequency reduced to less than 50% of their pre-LEV baseline ($P = 0.0002$, Sign test), with 10 patients (77%) noting complete seizure control (confidence interval: 46–95%). If analyzed by primary tumor site of origin, complete seizure control was noted in 5/6 (83%) patients with breast cancer, 3/5 (60%) patients with lung cancer, and 2/2 (100%) patients with melanoma. There were no correlations noted between the use of irradiation or chemotherapy and clinical response to LEV.

A total of 6/13 (46%) patients experienced adverse side effects from LEV. The most common side effects were somnolence and headache, each experienced by 3/13 (23%) patients. Blurry vision was experienced by 2/13 (15%) patients and 1/13 (8%) patients experienced nausea and vomiting while on LEV. The clinical response to LEV did not appear to correlate with dosage or the presence of side effects (Table 1).

Discussion

The incidence of seizures in patients with MBT ranges from 27 to 50% [4, 5]. The overall incidence of seizure activity appears to be highest in patients with melanoma as the primary tumor (67%), followed by lung as the primary (29%), and gastrointestinal as the primary (21%) [4]. Patients with MBT and seizure activity that is poorly controlled despite adequate doses of conventional AEDs are in need of further treatment with an add-on AED. LEV as an add-on AED has been shown to be efficacious in many patients with primary brain tumors and seizures [19–21]. The results of this study suggest that LEV is a good choice for an add-on AED in patients with MBT, because 54% of our cohort received LEV for this reason and all patients showed benefit. There was significant improvement in seizure frequency in 100% of patients after the initiation of LEV, with 71% noting complete seizure control. LEV also seemed to be effective when used as monotherapy, which occurred in 46% of our cohort. LEV as monotherapy caused significant improvement in seizure frequency in 100% of patients, with 83% noting complete seizure control. Recent studies in adult patients with various forms of partial and generalized epilepsy suggest that LEV is active and well tolerated when used as monotherapy [22–24]. One study even showed that LEV as first-line monotherapy was as effective as carbamazepine in treating newly diagnosed epilepsy [24]. The American Academy of Neurology has concluded that there is insufficient evidence at this time to recommend the use of LEV as monotherapy for newly diagnosed epilepsy patients or in those with refractory partial seizures [25–27]. Further clinical trials with LEV (i.e. prospective randomized placebo controlled) are needed before the AAN will recommend LEV as first-line monotherapy for the treatment of epilepsy.

Table 1 Efficacy and incidence of side effects of LEV in patients with MBT

	Metastatic breast	Metastatic lung	Metastatic melanoma
Total patients	6	5	2
Sz free	5	3	2
<50% sz	1	2	0
No effect	0	0	0
Side effects	3	2	1
LEV mono Tx	2	4	0
LEV add-on Tx	4	1	2

Abbreviations: Sz-seizure, Mono-monotherapy, Tx-treatment

The results of this study confirm that LEV is well tolerated and can improve seizure control in patients with MBT. However, due to the relatively small size of our cohort and the limitations of retrospective analyses from confounding variables, including tumor status, treatment status, and clinical status at the start of LEV treatment, our data is not able to serve as an official endorsement of efficacy in this patient population.

Tumor-induced seizures need to be considered separately from traditional epilepsy when selecting appropriate AED therapy. The severity of AED side effects in patients with brain tumors appears to be 20–40% higher than in the general population requiring AEDs, largely due to the presence of drug-drug interactions [3]. The most commonly cited AED side effects noted in patients with brain tumors are myelosuppression, thrombocytopenia, rash, changes in behavior or cognition, ataxia, and elevated liver enzymes [28]. These side effects are even more worrisome in patients who are immunocompromised secondary to chemotherapy or radiation therapy. The side effects experienced by patients with brain tumors and MBTs taking LEV seem to be milder than with traditional AEDs. Less than 50% of patients in this study experienced adverse effects while on LEV, and the adverse effects that were experienced were mild, including somnolence, headache, blurry vision, nausea, and vomiting. Another study also noted mild side effects from LEV, including somnolence,

headache, dizziness, and paresthesia [20]. Many traditional AEDs (phenytoin, carbamazepine, phenobarbital, oxcarbazepine), corticosteroids, and chemotherapeutic agents commonly given to patients with brain tumors (nitrosurea, paclitaxel, cyclophosphamide, irinotecan, adriamycin, methotrexate) are known to induce the hepatic cytochrome P450 system [7–9]. These interactions can cause inadequate serum levels of AEDs, corticosteroids, and chemotherapeutic agents in patients with brain tumors, resulting in inadequate seizure control and inadequate treatment of the malignancy. Valproate is a known inhibitor of the hepatic cytochrome P450 system, and can cause increased and sometimes toxic serum levels of chemotherapeutic agents [29, 30]. In contrast, LEV does not interact with the hepatic cytochrome P450 system, so there is less opportunity for negative drug-drug interactions, making it a better choice of AED in many patients with brain tumors and seizure activity [7, 11, 19].

In conclusion, this retrospective cohort study has demonstrated that LEV was both effective and well tolerated in patients with MBT and persistent seizure activity. Based on its unique mechanism of action, relative lack of drug–drug interactions, and mild side effect profile, LEV is a good choice for add-on AED treatment for patients with MBT. LEV may also be effective as monotherapy in selective patients.

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