See the corresponding editorial in this issue, pp 1181–1182.

J Neurosurg 118:1183–1187, 2013
©AANS, 2013

Retrospective analysis of the tolerability and activity of lacosamide in patients with brain tumors

Clinical article

Marlon G. Saria, R.N.,[1] Courtney Corle, M.P.H.,[1] Jethro Hu, M.D.,[2] Jeremy D. Rudnick, M.D.,[2] Surasak Phuphanich, M.D.,[2] Maciej M. Mrugala, M.D., Ph.D.,[3,5] Laura K. Crew, N.P.,[4,5] Daniela A. Bota, M.D., Ph.D.,[6–8] Beverly Dan Fu, N.P.,[6] Ryan Y. Kim, B.A.,[1] Tiffany Brown, P.A.,[1] Homira Feely, N.P.,[1,9] Joanne Brechlin, M.B.A., M.P.H.,[1] Bradley D. Brown, B.A.,[1] Jan Drappatz, M.D.,[10,11] Patrick Y. Wen, M.D.,[10,11] Clark C. Chen, M.D., Ph.D.,[9] Bob Carter, M.D., Ph.D.,[9] Jong Woo Lee, M.D., Ph.D.,[10] and Santosh Kesari, M.D., Ph.D.[1]

Departments of [1]Neurosciences and [9]Neurosurgery, Moores Cancer Center, University of California, San Diego, La Jolla; [2]Cochran Brain Tumor Center, Department of Neurology and Neurosurgery, Cedars-Sinai Medical Center, Los Angeles; Departments of [6]Neurology and [7]Neurological Surgery, and [8]Chao Family Comprehensive Cancer Center, School of Medicine, University of California, Irvine, California; Departments of [3]Neurology and [4]Neurological Surgery, and [5]Neuro-Oncology Center, University of Washington School of Medicine, Seattle, Washington; [10]Department of Neurology, Brigham and Women's Hospital; and [11]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts

Object. The object of this study was to determine the tolerability and activity of lacosamide in patients with brain tumors.

Methods. The authors reviewed the medical records at 5 US academic medical centers with tertiary brain tumor programs, seeking all patients in whom a primary brain tumor had been diagnosed and who were taking lacosamide.

Results. The authors identified 70 patients with primary brain tumors and reviewed seizure frequency and toxicities. The majority of the patients had gliomas (96%). Fifty-five (78%) had partial seizures only, and 12 (17%) had generalized seizures. Most of the patients (74%) were started on lacosamide because of recurrent seizures. Forty-six patients (66%) reported a decrease in seizure frequency, and 21 patients (30%) reported stable seizures. Most of the patients (54 [77%]) placed on lacosamide did not report any toxicities.

Conclusions. This retrospective analysis demonstrated that lacosamide was both well tolerated and active as an add-on antiepileptic drug (AED) in patients with brain tumors. Lacosamide's novel mechanism of action will allow for concurrent use with other AEDs, as documented by its activity across many different types of AEDs used in this patient population. Larger prospective studies are warranted.
(http://thejns.org/doi/abs/10.3171/2013.1.JNS12397)

Key Words • **seizure** • **antiepileptic drug** • **primary brain tumor** • **oncology**

As many as 30%–50% of brain tumor patients present with seizures, and many more remain at risk for developing seizures over the disease course.[11] Seizures are considered one of the most incapacitating morbidities in patients with brain tumors in that an isolated event or even the thought of having an event can profoundly impair a patient's quality of life. In many of these patients, the postictal phase is frequently prolonged, increasing seizure-associated morbidity. In addition, it has been established that patients who present with seizures as the first sign of a brain tumor have a higher risk of recurrent seizures.[3]

The management of seizures in these patients is complicated by tumor growth and the numerous adverse effects and drug interactions of traditional AEDs, which are seen more frequently in patients with brain tumors than in the

Abbreviations used in this paper: AED = antiepileptic drug; EIAED = enzyme-inducing AED; NEIAED = nonenzyme-inducing AED.

general epilepsy population.[10,12] Enzyme-inducing AEDs decrease the efficacy of certain chemotherapeutic agents and have been known to reduce corticosteroid efficacy as well.[13] There are no evidence-based treatment guidelines, and optimal antiepileptic therapy in patients with brain tumors remains elusive. First-line treatment using AEDs fails to control seizures in about 60% of patients, and among those who receive second-line monotherapy or polypharmacy, the treatment fails in approximately 60%.[12] Recently, however, second- and third-generation AEDs have been introduced and approved for the treatment of seizures, and the rate of response in brain tumor–induced seizures often exceeds 50%.[9]

Lacosamide (Vimpat, UCB Pharma) is a third-generation AED that has a novel mechanism of action of selectively enhancing slow inactivation of voltage-gated sodium channels. It was approved by the FDA in October 2008 as an adjunctive therapy in the treatment of partial-onset seizures in adults with epilepsy.[1,2,4] Lacosamide has many favorable properties for use in patients with brain tumors. It has a favorable pharmacokinetic profile that includes low protein binding, a 13-hour half-life that permits twice daily administration, rapid and complete oral absorption not affected by food intake, no induction or inhibition of hepatic enzymes, and a very low potential for drug interactions.[1] It is available in the intravenous form with easy 1:1 dose conversion to/from the oral preparation. It has also been reported to be well tolerated, and most adverse events related to the CNS and gastrointestinal events were mild to moderate.[4] In addition, it has been noted that lacosamide is less likely than other AEDs to cause other concerning adverse events such as drug-related rash, weight gain or loss, sedation, or mood dysfunction.[2]

To the best of our knowledge, no published studies have been focused on the tolerability and activity of lacosamide in controlling seizures in patients with brain tumors. Therefore, in this retrospective descriptive analysis, we aimed to determine the tolerability and activity of lacosamide in patients with brain tumors.

Methods

We conducted an institutional review board–approved retrospective chart review of all brain tumor patients who had received lacosamide for seizure management at 5 academic medical centers with tertiary brain tumor programs in the US (Brigham and Women's Hospital, Boston; Cedars-Sinai Medical Center, Los Angeles; University of California, Irvine; University of California, San Diego; and University of Washington, Seattle). Criteria for study eligibility included the diagnosis of a primary brain tumor and placement on lacosamide. Indications for initiating lacosamide therapy included seizure activity that did not respond to prior AEDs, unacceptable adverse effects from previous therapy, or prophylaxis. We collected data on patient demographics, tumor histology, and tumor treatment (Table 1). Seizure type and frequency and use of AEDs were extracted from patient histories and clinic progress notes (Table 2). Seizure frequency data were collected for the time prior to the start of lacosamide therapy. Because of the marked variability in seizure frequency over time, the lack of appropriate objective criteria for evaluating the response to treatment, and the multiple indications for initiating lacosamide, therapeutic activity was defined as any self-reported decrease in seizure frequency.

TABLE 1: Summary of characteristics in 70 patients with brain tumors treated with lacosamide

Variable	No.	Frequency (%)
age in yrs		
mean ± SD	51.2 ± 12.0	
median	51	
sex		
M	40	57.14
F	30	42.86
histology		
glioblastoma	28	40.00
Grade II*	25	35.71
Grade III†	12	17.14
anaplastic/atypical meningioma	3	4.29
anaplastic ependymoma	1	1.43
pleomorphic xanthoastrocytoma	1	1.43
radiation		
yes	57	81.43
no	13	18.57
corticosteroids		
yes	33	47.14
no	33	47.14
unknown	4	5.71
chemotherapy		
yes	59	84.29
no	11	15.71
surgery		
craniotomy	44	62.86
biopsy	16	22.86
both	10	14.29

* Oligodendroglioma, oligoastrocytoma, astrocytoma.
† Anaplastic astrocytoma, anaplastic oligodendroglioma.

Results

Patient Characteristics

The charts for 70 patients with a median age of 51 years and a median follow-up of approximately 6.2 months were reviewed across the 5 sites (Table 1). Glioblastoma accounted for the highest percentage of cases (40%), followed by Grade II gliomas (36%). More than 81% of the cohort had received some form of radiotherapy, and approximately 84% of patients had received some form of chemotherapy. Fifty-five (78%) of the 70 patients suffered from partial seizures, while only 12 (17%) reported having generalized seizures. With the exception of 12 patients (17%), most were taking other AEDs concurrently with

TABLE 2: Summary of seizure information prior to and after the addition of lacosamide

Variable	No.	Frequency (%)
seizure type		
partial	55	78.57
generalized	12	17.14
both	2	2.86
none	1	1.43
reason to start lacosamide		
seizures	52	74.29
toxicity from previous drug	16	22.86
both seizures & toxicity	1	1.43
prophylaxis	1	1.43
lacosamide dose (mg/day)		
200	35	50.00
400	15	21.43
100	10	14.29
300	7	10.00
150	1	1.43
500	1	1.43
600	1	1.43
activity: change in seizure frequency		
decrease	46	65.71
stable	21	30.00
increase	1	1.43
lost to follow-up	2	2.86
toxicity		
none	54	77.14
fatigue	4	5.71
dizziness	2	2.86
confusion	2	2.86
weakness	2	2.86
nausea	2	2.86
blurred vision	1	1.43
tremor	1	1.43
amnesia	1	1.43
irritability	1	1.43
psychosis	1	1.43
rash*	1	1.43
depression	1	1.43
heartburn	1	1.43
suicidal ideation	1	1.43
toxicities by dose		
100 mg daily		
1 side effect	2	12.5
>1 side effect	1	6.25
150 mg daily		
1 side effect	0	0
>1 side effect	1	6.25
toxicities by dose *(continued)*		
200 mg daily		
1 side effect	6	37.5
>1 side effect	2	12.5
400 mg daily		
1 side effect	4	25
>1 side effect	0	0
treatment after lacosamide failure or toxicity		
none	54	77.14
lamotrigine	4	5.71
phenytoin	3	4.29
levetiracetam	3	4.29
clonazepam	3	4.29
pregabalin	2	2.86
topiramate	2	2.86
carbamazepine	1	1.43
zonisamide	1	1.43
vagal nerve stimulator	1	1.43

* Resolved within a few days of discontinuing the drug.

lacosamide (Table 3). A majority of the patients (35 [50%]) were on levetiracetam (Keppra, UCB Pharma) in addition to lacosamide. Eleven patients were taking NEIAEDs concurrently with lacosamide, whereas 12 patients were taking EIAEDs concurrently with lacosamide.

Lacosamide Tolerability

Most of the patients (74%) were started on lacosamide because of recurrent seizures (Table 2). Thirty-five patients (50%) were maintained on a total dose of 200 mg daily. Most patients (54 [77%]) did not report any toxicities. Four patients reported more than one toxicity. The most common toxicity was fatigue (4 cases [6%]), followed by dizziness, nausea, confusion, and weakness (2 cases each). Patients experienced toxicities at several different doses. Of those who did experience toxicities (16 patients), 6 (37.5%) were taking lacosamide as a single agent and 6 (37.5%) were taking lacosamide concurrently with levetiracetam (Table 3).

Lacosamide Activity

Forty-six patients (66%) reported a decrease in seizures, and 38 of these patients (83%) reported a greater than 50% decrease in seizure frequency. Twenty-one patients (30%) reported stable seizures (Table 2). Fifty-four patients (77%) did not require the addition of other AEDs following lacosamide therapy, whereas 16 (23%) required the addition of another AED to manage their seizures. Of those who started lacosamide because they were experiencing seizures (52 patients), 73% had a decrease in seizure frequency. Lacosamide was added on to EIAEDs and NEIAEDs, and the tolerability was similar. Lacos-

TABLE 3: Antiepileptic drug use prior to and concurrent with lacosamide

Variable	No.	Frequency (%)	Clinical Activity (decrease in seizure frequency)	
			No.	Frequency (%)
no. of AEDs used prior to lacosamide*				
1	23	33.33		
2	21	30.43		
3	11	15.94		
0	9	13.04		
≥4	5	7.25		
AEDs used concurrently w/ lacosamide				
levetiracetam	35	50.00	25	71.43
EIAEDs†	12	17.14	10	83.33
NEIAEDs‡	11	15.71	7	63.64
no other AEDs	12	17.14	4	33.33
no. of patients who reported toxicities w/ combination therapy	16			
no other AEDs	6	50.00		
NEIAEDs	2	18.18		
levetiracetam	6	17.14		
EIAEDs	2	16.67		

* Median = 2. For 1 patient, data on prior AED use were missing.
† Carbamazepine, phenytoin, oxcarbazepine.
‡ Lamotrigine, pregabalin, valproic acid, topiramate, clonazepam.

amide showed activity regardless of the prior AED class (Table 3). In particular, lacosamide was active in patients on levetiracetam, with 71% reporting a decrease in seizure frequency on combination therapy. Of those who were on lacosamide monotherapy, 33% reported a decrease in seizure frequency. Of those who were on NEIAEDs concurrently with lacosamide, 64% reported a decrease in seizure frequency. Of those who were on EIAEDs concurrently with lacosamide, 83% reported a decrease in seizure frequency. Further subset analysis of other clinical factors was not possible given the limited sample size.

Discussion

It has been suggested that the ideal AED for patients with brain tumors should be prescribed after the first seizure with the goal of complete seizure control while preventing significant adverse effects and pharmacokinetic interactions.[8] Current prescribing practices are guided mainly by the tolerability and toxicity profile of each AED. Between 1989 and 2009, 14 second- and third-generation AEDs were approved for clinical use in both the US and Europe. Of these new AEDs, 5 were not associated with clinically significant pharmacokinetic interactions: gabapentin, lacosamide, levetiracetam, pregabalin, and vigabatrin.[5] Gabapentin has been evaluated in patients with brain tumors and along with levetiracetam has been recommended as an add-on treatment for the control of seizures in patients with brain tumors.[12] Levetiracetam and pregabalin have also been investigated as monotherapy in brain tumor–related seizures.[8] The clinical use of vigabatrin, licensed in 1989, has decreased because of its serious potential adverse effect of visual field defects.[5]

Brain tumor patients with a history of seizures will require long-term treatment with AEDs taken concurrently with other drugs for the management of the tumor and treatment-related adverse effects. However, the risk of drug interactions between anticancer drugs and AEDs is high, particularly when traditional EIAEDs are used.[14] Of the newer AEDs, lacosamide has not been evaluated in a population of patients with brain tumors. Based on the pharmacokinetics and reported interactions with AEDs and other drugs,[14] the use of lacosamide in patients with brain tumors appears to be desirable.

In our population, lacosamide was effective in reducing seizure frequency in 66% of patients. The activity was even greater (73%) in the subset of patients who were placed on lacosamide because of seizures unresponsive to previous therapy. These results compare favorably with those for levetiracetam, for which a significant decrease in seizures has been reported in 47%–82% of patients with epilepsy.[6,7] This finding indicates that lacosamide can be considered as an add-on therapy in patients with brain tumors to reduce seizure frequency. Lacosamide's novel mechanism of action will allow for concurrent use with other AEDs, as documented by its activity across many different types of AEDs in our population.

Lacosamide was also well tolerated in most patients, with 77% reporting no toxicities. The most common adverse events of lacosamide reported in clinical trials are dizziness, headache, fatigue, nausea, and diplopia and were dose related.[1,2,4] These adverse effects were also ob-

served in our sample, but with a lower frequency than reported in the clinical trials (Table 2). Furthermore, neurocognitive deficits associated with the use of AEDs, particularly among patients with brain tumors,[9] were not observed in our sample. And there were no reports of cardiac adverse effects or liver function test abnormalities. In addition, most patients (77%) who were started on lacosamide did not have another add-on agent at a median follow-up of 6.2 months.

Conclusions

We acknowledge the limitations inherent to retrospective medical record reviews, which can only be addressed by conducting a larger prospective study evaluating the efficacy and tolerability of lacosamide in patients with brain tumors. In the meantime, we cautiously conclude that our retrospective analysis has demonstrated that lacosamide was both well tolerated and showed activity as an add-on AED in patients with brain tumors. Furthermore, patients on lacosamide monotherapy (n = 12) also benefitted. The unique safety and tolerability benefits demonstrated, as compared with those for traditional AEDs, make the option of using lacosamide as an add-on treatment viable for patients with brain tumors. While this paper was under review, a report on only 14 patients confirmed our findings on the activity of lacosamide in brain tumor–related epilepsy.[6]

Disclosure

This work was supported in part by NIH Grant No. 3P30CA023100-25S8 (S.K.). Dr. Mrugala is on the speakers' bureau of and is a consultant for UCB Pharma. Dr. Bota serves on the speakers' bureau of Merck, Roche, and Eisai; serves on the clinical advisory board of Epitopoietic Research Corp.; has received research support from the American Cancer Society; and receives institutional support from the University of California, Irvine, for stem cell research. Dr. Kesari is on the speakers' bureau of UCB Pharma, Genentech, and Merck and has received research support from the NIH, Novartis, Merck, and Bristol Meyers Squibb.

Author contributions to the study and manuscript preparation include the following. Conception and design: Kesari, Saria. Acquisition of data: Kesari, Saria, Hu, Rudnick, Phuphanich, Mrugala, Crew, Bota, Fu, Kim, T Brown, Feely, BD Brown, Drappatz, Lee. Analysis and interpretation of data: Kesari, Saria. Drafting the article: Kesari, Saria. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Kesari. Statistical analysis: Kesari, Saria, Corle. Administrative/technical/material support: Kesari, Saria, Brechlin, Wen, Chen, Carter. Study supervision: Kesari.

References

1. Beydoun A, D'Souza J, Hebert D, Doty P: Lacosamide: pharmacology, mechanisms of action and pooled efficacy and safety data in partial-onset seizures. **Expert Rev Neurother 9:**33–42, 2009
2. Chung SS: Lacosamide: new adjunctive treatment option for partial-onset seizures. **Expert Opin Pharmacother 11:**1595–1602, 2010
3. Glantz MJ, Cole BF, Forsyth PA, Recht LD, Wen PY, Chamberlain MC, et al: Practice parameter: anticonvulsant prophylaxis in patients with newly diagnosed brain tumors. **Neurology 54:**1886–1893, 2000
4. Halford JJ, Lapointe M: Clinical perspectives on lacosamide. **Epilepsy Curr 9:**1–9, 2009
5. Johannessen Landmark C, Patsalos PN: Drug interactions involving the new second- and third-generation antiepileptic drugs. **Expert Rev Neurother 10:**119–140, 2010
6. Maschio M, Dinapoli L, Mingoia M, Sperati F, Pace A, Pompili A, et al: Lacosamide as add-on in brain tumor-related epilepsy: preliminary report on efficacy and tolerability. **J Neurol 258:**2100–2104, 2011
7. Rosati A, Buttolo L, Stefini R, Todeschini A, Cenzato M, Padovani A: Efficacy and safety of levetiracetam in patients with glioma: a clinical prospective study. **Arch Neurol 67:**343–346, 2010
8. Rossetti AO, Stupp R: Epilepsy in brain tumor patients. **Curr Opin Neurol 23:**603–609, 2010
9. Rudà R, Trevisan E, Soffietti R: Epilepsy and brain tumors. **Curr Opin Oncol 22:**611–620, 2010
10. Smith KC: The management of seizures in brain tumor patients. **J Neurosci Nurs 42:**28–37, 2010
11. van Breemen MS, Wilms EB, Vecht CJ: Epilepsy in patients with brain tumours: epidemiology, mechanisms, and management. **Lancet Neurol 6:**421–430, 2007
12. Vecht CJ, van Breemen M: Optimizing therapy of seizures in patients with brain tumors. **Neurology 67 (12 Suppl 4):**S10–S13, 2006
13. Villanueva V, Codina M, Elices E: Management of epilepsy in oncological patients. **Neurologist 14 (6 Suppl 1):**S44–S54, 2008
14. Yap KY, Chui WK, Chan A: Drug interactions between chemotherapeutic regimens and antiepileptics. **Clin Ther 30:** 1385–1407, 2008

Manuscript submitted February 27, 2012.
Accepted January 30, 2013.
Please include this information when citing this paper: published online March 1, 2013; DOI: 10.3171/2013.1.JNS12397.

Address correspondence to: Santosh Kesari, M.D., Ph.D., Moores Cancer Center, University of California, San Diego, 3855 Health Sciences Drive, La Jolla, California 92093-0819. email: skesari@ucsd.edu.