Efficacy and Safety of Levetiracetam in Patients With Glioma

A Clinical Prospective Study

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Objective: To evaluate the efficacy and safety of levetiracetam in the management of epilepsy in patients with glioma.

Design: A prospective study in hospitalized patients with a new diagnosis of glioma.

Setting: Department of Neurological Sciences and Visions, Spedali Civili of Brescia.

Patients: From March 1, 2006, until January 1, 2009, 176 consecutive patients (101 men and 75 women) with a first diagnosis of glioma were enrolled in the study. All patients with a diagnosis of epilepsy were treated with levetiracetam.

Main Outcome Measures: Clinical, histological, and magnetic resonance imaging findings were analyzed.

Results: Age at the diagnosis of glioma ranged from 22 to 79 years (mean [SD], 57 [15] years; median, 59 years). Duration of the disease ranged from 27 days to 2½ years (mean [SD], 13.7 [7.8] months; median, 13 months). Eighty-two patients received levetiracetam because of a diagnosis of epilepsy. At the last evaluation (May 1, 2009), 75 of 82 patients (91%) treated with levetiracetam were seizure free; in 2 of these patients, levetiracetam was withdrawn because of intolerable adverse effects. Prompt and long-lasting control of seizures was obtained in 49 of 82 patients (60%) with a dose of levetiracetam that ranged from 1500 to 3000 mg/d, and 9 (11%) of the treated patients needed an increase of levetiracetam dosage to 4000 mg/d to become seizure free. No laboratory abnormalities were observed in patients with concomitant chemotherapy.

Conclusion: The results of this study provide good evidence that levetiracetam is efficacious and safe in patients with epilepsy due to glioma.

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The incidence of epilepsy in adult patients with glioma is approximately 30%, ranging from 20% to 80%, with the highest frequency of epilepsy in low-grade tumors.¹,² Seizures may be the presenting symptom of a brain tumor, or they may occur later during the disease. Only the recurrence of seizures justifies the diagnosis of epilepsy and the use of anticonvulsants.³

The treatment of gliomas often requires systemic chemotherapy and/or glucocorticoids, which are both metabolized by the hepatic cytochrome P-450 system.⁴ Hence, the concomitant use of antiepileptic drugs (AEDs) in patients using chemotherapy or corticosteroids may increase the risk of adverse effects, and it may be responsible for a lesser efficacy because of their detrimental interactions.⁵ Furthermore, almost all AEDs are metabolized by the hepatic cytochrome P-450 system and have inductive or inhibitory effects on 1 or more isoenzymes. One exception to this rule is levetiracetam, which is not metabolized through the P-450 hepatic cytochrome system, does not induce its own metabolism, and has no clinically relevant drug-drug interactions.⁶ For these reasons, levetiracetam may be a particularly useful drug in this group of patients with glioma. Therefore, the present study evaluated the efficacy and safety of levetiracetam in the management of epilepsy in patients with glioma.

Methods

We prospectively enrolled patients with a first diagnosis of glioma and epilepsy who were admitted at the Neurology Clinic or Neurosurgery Department of Spedali Civili of Brescia. Patients were excluded if they had already been diagnosed as having glioma or were taking AEDs at the time of the first observation. Duration of disease was defined for deceased patients as the duration of survival from the first symptom at onset to death; for the patients still alive, duration was measured from the age at onset until
the last visit. Patients were also excluded if they were followed up at another hospital after their first evaluation in our department. All patients underwent an extensive interview in the search of ictoepileptic symptoms suggestive of focal minor seizures. Seizures were categorized based on the Classification and Terminology of the International League Against Epilepsy. Single seizure was defined as a unique episode in the absence of interictal epileptiform abnormalities (IEAs) on the electroencephalogram recording. A cluster of seizures occurring in a 24-hour interval was considered a single episode. The diagnosis of epilepsy was made in the following conditions: (1) recurrent seizures with or without IEAs, (2) single focal or convulsive seizure in the presence of IEAs, (3) single convulsive seizure and history of episodes suggestive of focal seizures with or without IEAs, and (4) seizures occurring for the first time during follow-up with or without IEAs. Only patients with epilepsy were treated with levetiracetam, which was started at a dosage of 500 mg twice daily or 250 mg twice a day in patients older than 70 years. If necessary, the levetiracetam dosage was increased to 3000 or 4000 mg/d. In all patients, the visit interval at follow-up ranged from 1 month, in those who also underwent concomitant chemotherapy, to 3 months. At each follow-up, we rated the recurrence of seizure as daily, weekly, monthly, rare (<1 seizure per month), or no seizures. To better establish treatment choice, the causes of seizure recurrence were categorized as follows: (1) tumor recurrence: seizures associated with radiographic evidence of tumor recurrence after a radiologic response; (2) malignant progression: seizures associated with radiologic or pathological evidence for tumor progression; (3) subtherapeutic anticonvulsant levels: seizures that occurred in the absence of tumor recurrence or other concurrent diseases and stopped after increase of levetiracetam dosage; (4) refractoriness: seizures that occurred despite optimal therapeutic anticonvulsant levels and in the absence of tumor recurrence or other concurrent diseases; and (5) radiotherapy-induced seizures: seizures that occurred during radiotherapy despite optimal therapeutic anticonvulsant levels, absence of tumor recurrence, or other precipitating factors. Seizures that occurred in conditions 1, 2, and 3 were treated by increasing the levetiracetam dosage; those that occurred in condition 4 were treated by adding a second drug, such as oxcarbazepine, topiramate, or valproic acid, based on seizure type, electroencephalogram recording, hematologic abnormalities, and patient age. Furthermore, seizures that occurred during radiotherapy were treated with corticosteroids. Therapeutic levels of levetiracetam were considered dosages with a plasma level within the reference range (15-40 µg/mL) that did not produce adverse effects.

Data were collected with regard to the age at diagnosis, sex, seizure type at onset, time of appearance of seizures, location of the lesion, histological grade, type of surgery, postoperative radiation, or chemotherapy. Histological classification was determined using the histological classification of brain tumors approved by the World Health Organization. Imaging analysis includes conventional T1- and T2-weighted magnetic resonance images, before and after gadolinium injection, and magnetic resonance spectroscopy. The purpose of neurosurgery was mainly driven by the removal of the tumor without any major attempt to delineate or remove the epileptogenic cortex. All patients operated on underwent a contrast computed tomography examination within 3 to 6 hours after surgery; on the basis of the neurosurgeon report and the postsurgical contrast computed tomogram, tumor removal was defined as partial (<50% of residual tumor), subtotal (50%-80%), and total (absence of residual tumor). Patients with glioblastoma multiforme received systemic chemotherapy according to the protocols of Stupp et al in which temozolomide was given concomitant or adjuvant to radiotherapy.

Statistical analysis was performed to assess possible correlations between drug resistance and several other variables, including patient age, Karnofsky Performance Status Scale score, tumor location and extension, tumor grade, type of treatment, and type of surgery. Statistical analysis was performed by the t test, cross-tabulation test, and Fisher exact test using SPSS statistical software (SPSS Inc, Chicago, Illinois), with P < .05 considered statistically significant.

RESULTS

Demographic data of the patients are reported in Table 1. From March 1, 2006, until January 1, 2009, 176 consecutive patients (101 men and 75 women) were enrolled in the study. Age at the diagnosis of glioma ranged from 22 to 79 years (mean [SD], 57 [15] years; median, 59 years). Duration of the disease ranged from 27 days to 2½ years (mean [SD], 13.7 [7.8] months; median, 13 months). During the study, 132 patients had a recurrence of glioma, and at the last evaluation, 45 of 176 patients (26%) were still alive. The histological features of
Glioma are reported in Table 2. At the last evaluation, 13 of the 176 patients (7%) had only a single seizure that never recurred until death in all of them. No patients in the group without epilepsy, including those with single seizure, received an antiseizure medication outside the study.

Eighty-two of the 176 patients (47%) had been diagnosed as having epilepsy. Duration of epilepsy ranged between 13 months and 4.2 years (mean ± SD, 17.2 [5] months). In 75 of 82 patients (91%), epilepsy was the presenting symptom of the disease. In 7 of 82 patients (9%) who presented with other neurologic symptoms at the onset of glioma, focal seizures with (3 patients) or without (4 patients) secondary generalization first appeared during the follow-up. All of these patients had a high-grade glioma, and the seizure appearance was related to the tumor recurrence (4 patients), malignant progression (2 patients), or radiotherapy (1 patient). The most common type of seizure at onset was partial, and in 19 of 82 patients (23%), a previous history of unrecognized focal seizures was also depicted. The efficacy of levetiracetam with regard to seizure type and histological features is reported in Table 3. At the last evaluation, 75 of 82 patients (91%) were seizure free with a monotherapy of levetiracetam (73 patients), topiramate (1 patient), and valproic acid (1 patient). The mean follow-up in these patients was 13.1 months (range, 10 months to 2.9 years). Only 2 of these 75 patients were included after a single seizure because they had a partial motor epileptic status or recurring sensory-motor seizures. Forty-nine of 82 patients (60%) had prompt and long-lasting control of seizures with the initial dosage of levetiracetam, ranging from 1500 to 3000 mg/d, and only 9 of 82 (11%) needed an increase in levetiracetam dosage to 4000 mg/d to become seizure free. In 14 of 75 patients (19%) whose seizures were present at tumor onset, the reappearance of seizures at follow-up was due to clinical and radiologic evidence of tumor recurrence (8 patients) or malignant progression (6 patients). In all of them, the increase of levetiracetam dosage led to the full control of seizures, and all 14 patients became seizure free. In the 2 patients who were receiving monotherapy with topiramate (300 mg/d) and valproic acid (1500 mg/d), levetiracetam therapy had been stopped because of intolerable diarrhea or visual hallucinations with psychotic thoughts.

In only 7 of the 82 patients (9%) (1 with oligodendroglioma grade II, 3 with oligodendroglioma grade III, 2 with anaplastic astrocytoma, and 1 with glialblastoma multiforme), seizures were refractory despite antiepileptic polytherapy. The add-on of other AEDs included oxcarbazepine (3 patients), topiramate (2 patients), or oxcarbazepine plus valproic acid (2 patients). In these patients, seizure frequency at the last evaluation was daily in 1 patient, monthly in 1 patient, weekly in 3 patients, and rare in 2 patients. In 6 patients, the localization of the glioma was frontal with motor seizures. A transitory somnolence was the only mild adverse effect, and it was observed in 4 patients. No correlation was found between drug resistance and several variables, including patient age, Karnofsky Performance Status score, tumor location and extension, tumor grade, type of treatment, and type of surgery.

### Table 2. Histological Grades of the Glioma in Patients With and Without Epilepsy

<table>
<thead>
<tr>
<th>Histological Grades</th>
<th>Patients With Epilepsy (n=82)</th>
<th>Patients Without Epilepsy (n=94)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I-II (n=22)</td>
<td>1/22 (5)</td>
<td>0/94 (0)</td>
</tr>
<tr>
<td>Pilocytic astrocytoma</td>
<td>1/22 (5)</td>
<td>0/94 (0)</td>
</tr>
<tr>
<td>Astrocytoma II</td>
<td>3/22 (14)</td>
<td>3/94 (4)</td>
</tr>
<tr>
<td>Oligodendroglioma II</td>
<td>8/22 (37)</td>
<td>5/94 (5)</td>
</tr>
<tr>
<td>Fibrillary astrocytoma</td>
<td>1/22 (5)</td>
<td>1/94 (1)</td>
</tr>
<tr>
<td>Total</td>
<td>13/82 (16)</td>
<td>9/94 (10)</td>
</tr>
<tr>
<td>Grade III (n=36)</td>
<td>4/36 (11)</td>
<td>3/36 (9)</td>
</tr>
<tr>
<td>Anaplastic oligodendroglioma</td>
<td>4/36 (11)</td>
<td>3/36 (9)</td>
</tr>
<tr>
<td>Anaplastic oligoastrocytoma</td>
<td>2/36 (6)</td>
<td>4/36 (11)</td>
</tr>
<tr>
<td>Anaplastic astrocytoma</td>
<td>9/36 (25)</td>
<td>14/36 (39)</td>
</tr>
<tr>
<td>Total</td>
<td>15/36 (41)</td>
<td>21/36 (58)</td>
</tr>
<tr>
<td>Grade IV (n=118)</td>
<td>51/118 (44)</td>
<td>64/118 (55)</td>
</tr>
<tr>
<td>Glioblastoma multiforme</td>
<td>51/118 (44)</td>
<td>64/118 (55)</td>
</tr>
<tr>
<td>Gliosarcoma</td>
<td>3/118 (3)</td>
<td>0/118 (0)</td>
</tr>
<tr>
<td>Total</td>
<td>54/118 (46)</td>
<td>64/118 (55)</td>
</tr>
</tbody>
</table>

### Table 3. Seizure Types and Histological Grades in 82 Patients With Primary Brain Tumor and Epilepsy

<table>
<thead>
<tr>
<th>Seizure Type</th>
<th>Seizure Free</th>
<th>Drug Resistant</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complex partial</td>
<td>28/28 (100)</td>
<td>0/28 (0)</td>
<td>28/82 (34)</td>
</tr>
<tr>
<td>Simple partial motor</td>
<td>14/20 (70)</td>
<td>6/20 (30)</td>
<td>20/82 (25)</td>
</tr>
<tr>
<td>Simple partial sensory</td>
<td>9/10 (90)</td>
<td>1/10 (10)</td>
<td>10/82 (12)</td>
</tr>
<tr>
<td>Secondary generalization</td>
<td>24/24 (100)</td>
<td>0/24 (0)</td>
<td>24/82 (29)</td>
</tr>
<tr>
<td>Histological grade I-II</td>
<td>22/22 (100)</td>
<td>0/22 (0)</td>
<td>22/82 (27)</td>
</tr>
<tr>
<td>III</td>
<td>32/36 (89)</td>
<td>4/36 (11)</td>
<td>36/82 (44)</td>
</tr>
<tr>
<td>IV</td>
<td>21/24 (88)</td>
<td>3/24 (13)</td>
<td>24/82 (29)</td>
</tr>
</tbody>
</table>

**Comment**

Brain tumors account for approximately 4% to 5% of all causes of epilepsy in patients who present with seizure disorders. Seizures may represent the symptom that leads to the diagnosis, but they may also appear later during the disease. For this reason, it is current practice to use AEDs in patients with brain tumors even in the absence of seizures despite the increasing evidence that AEDs do not prevent epileptogenesis and that most of them may reduce antitumoral drug levels and efficacy of chemotherapy. Furthermore, previous studies that dealt with the efficacy of AEDs in tumoral epilepsy had a smaller number of patients and were usually retrospective.

Regarding the usefulness of levetiracetam in patients with glioma, we previously illustrated the better efficacy of levetiracetam compared with the oldest AEDs in a small series of patients with glioma. The results of the present study further reinforce the belief that levetiracetam is efficacious and safe in treating symptomatic epilepsy due to brain tumor. At the last evaluation, 75 of 82 patients (91%) were seizure free with a monotherapy of levetiracetam (73 patients), topiramate (1 pa-
tient), and valproic acid (1 patient). Forty-nine patients (60%) had prompt and long-lasting control of seizures with the initial dosage of levetiracetam, ranging from 1500 to 3000 mg/d. In the last 23 patients (31.5%), an increase of levetiracetam dosage to 3000 to 4000 mg/d was necessary because of subtherapeutic drug levels (9 patients), tumor recurrence (8 patients), and malignant progression (6 patients). No relevant laboratory abnormalities were encountered in patients taking both levetiracetam and chemotherapy agents (temozolomide in 45 patients and fotemustine in 3 patients). We have only observed the occasional occurrence of somnolence, especially at the beginning of levetiracetam therapy. A slower drug titration probably reduces the risk of its occurrence. In our study, the persistence of seizures was observed in only 7 patients (9%). In such patients, seizures persisted despite the add-on of other AEDs, including oxcarbazepine (3 patients), topiramate (2 patients), or oxcarbazepine plus valproic acid (2 patients). We failed to find any relationship between refractoriness and several variables, including patient age, Karnofsky Performance Status Scale score, tumor location and extension, tumor grade, type of treatment, and type of surgery.

Previous studies1,3,4,16,20,24 reported higher percentages of refractoriness, which ranged between 25% and 80%, in patients with primary brain tumors. The demographic features of these series were similar to those reported in the present study, which is representative of unselected adults with supratentorial glioma. The only relevant difference is that the administered AEDs in these previous studies1,3,4,16,20,24 were valproic acid, carbamazepine, phenytoin, and gabapentin either in mono- or combination. Other studies20,22,23 showed that the add-on of levetiracetam led to some patients being seizure free or having seizure reduction. Considering all these results, including those of the present study, it is tempting to speculate that a stronger antiepileptic effect of levetiracetam in epilepsy due to glioma, a disease involving the astrocytes, might be at least in part related to its peculiar antiepileptic properties and especially to its ability to prevent impairment of astroglial regulatory properties under inflammatory conditions.26

In conclusion, the results of this study have provided good evidence that levetiracetam is efficacious and safe in patients with epilepsy due to glioma. Therefore, levetiracetam might be considered a first-line therapy for epileptic seizures due to brain tumors.

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REFERENCES

2. Hauser WA, Ammengol JD, Kurland LT. Incidence of epilepsy and unprovoked sei-
5. Ammengol JD, Hauser WA, Lee JR, Rocca W. Incidence of acute symptomatic sei-
11. Stupp R, Mason WP, van den Bent MJ, et al; European Organisation for Re-
search and Treatment of Cancer Brain Tumor and Radiotherapy Groups; Na-
tional Cancer Institute of Canada Clinical Trials Group. Radiotherapy plus con-
12. Siomin V, Angelov L, Li L, Vogelbaum MA. Results of a survey of neurosurgical practice patterns regarding the prophylactic use of anti-epilepsy drugs in pa-
mittee of the American Academy of Neurology. Practice parameter: anticonvul-
17. Pace A, Bow E, Innocenti P, et al. Epilepsy and gliomas: incidence and treat-
20. Sartori HB, Goldlust SA, petrol D. Retrospective analysis of the efficacy and tol-
25. Hildebrand J, Lecaiile C, Perennes J, Delattre JY. Epileptic seizures during fol-