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Response of Subependymal Giant Cell Astrocytoma With Spinal Cord Metastasis to Everolimus

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Abstract

Background—Brain subependymal giant cell astrocytomas (SEGAs) in patients with tuberous sclerosis have been reported to respond to everolimus.

Methods—A 15-year-old male patient with intractable seizures and multiple SEGAs of the brain developed leptomeningeal enhancement and multiple metastatic, histologically confirmed SEGAs of the spinal cord. He received daily everolimus at a dose of 3 mg/m² for 6 weeks, which was then increased to 6 mg/m².

Results—Magnetic resonance image of the brain and spine showed significant reduction in the size of SEGAs after 6 weeks of treatment. The patient has remained free of progression for 24 months. Additional benefits included: excellent seizure control, decrease in the size of cardiac rhabdomyomas, and improved quality of life.

Conclusions—We describe a rare case of metastatic SEGA, which was successfully treated with everolimus.

Keywords

everolimus; SEGA; tuberous sclerosis; spinal cord

Tuberous sclerosis (TS) is an autosomal dominant disorder with variable penetrance that affects multiple organs ranging from mild skin manifestations to severe neurologic manifestations such as seizures, mental retardation, and autism. Brain lesions include tubers, subependymal nodules (SENs), and subependymal giant cell astrocytomas (SEGAs). These

tumors result from abnormal cell migration during embryogenesis. Their location and size are believed to correlate with the severity of neurological manifestations.

SEGAs are slow growing tumors of glioneuronal differentiation arising near the foramen of Monro. They are thought to originate from SENs, which, when enlarged, can cause cerebrospinal fluid obstruction, leading to intracranial hypertension and hydrocephalus. SEGAs arise in up to 20% of TS patients.

Histologically, the presence of a high mitotic rate or necrosis has not been associated with a poor prognosis.¹ However, increasing age has been associated with worse prognosis. Older TS patients are more likely to have large, highly vascular tumors that are not amenable to complete resection. Therefore, SEGAs in these patients are associated with inferior outcomes compared with SEGAs diagnosed in younger patients.²

Complete surgical resection is one of the most important treatments for SEGAs. However, success of resection depends on tumor location and carries important risks and complications. Incomplete resection is associated with a high risk of local recurrence.³ Another treatment modality is gamma knife stereotactic radiosurgery. However, its role remains unclear, especially in patients whose tumor is at risk of malignant degeneration and development of an aggressive glial neoplasm, such as glioblastoma, because of the presence of a mutation in one of the tuberous sclerosis complex (TSC) tumor suppressor genes.⁴

In addition to mortality, SEGAs have significant implications in the quality of life of patients.⁵ Therefore, it is important to understand the molecular pathways that promote tumor proliferation in patients with TS.

Inactivating mutations of the genes TSC1 or TSC2 are found in over 85% of TS patients.⁶ TSC1 and TSC2 proteins form a heterodimer complex that inhibits the mammalian target of rapamycin (mTOR) complex 1 (mTORc1). mTORc1 is a serine-threonine kinase that regulates cell growth and proliferation through interaction with several transcription factors. When TSC1 or TSC2 are deficient, mTORc1 is over-activated, leading to abnormal cell proliferation and growth.⁷ Thus, inhibitors of mTORc1, such as everolimus, may be used as effective treatment modalities for TS-associated tumors.

Preclinical studies of mTOR inhibitors in animal models of TS have demonstrated efficacy in prolonging survival, preventing seizures, and improving learning deficits.^{8,9} Initial reports of efficacy of mTOR inhibitors against SEGAs were published as case series. One of them reported on the response of 3 patients with SEGAs who were treated with single-agent rapamycin. All 3 demonstrated tumor reductions between 50% and 75%, suggesting that singleagent treatment with rapamycin may be a viable alternative to surgical resection.¹⁰ In addition, Lam et al¹¹ reported on the results of 3 TS patients with SEGAs who responded to rapamycin treatment with >50% reduction of tumor size by magnetic resonance imaging (MRI), as well as improvements in other important clinical parameters.

An initial clinical trial of the mTOR inhibitor everolimus included 28 TS patients with progressive SEGAs of the brain who underwent single-agent therapy with everolimus. Seventy-five percent of patients demonstrated a decrease in tumor size of at least 30%.

Thirty-two percent demonstrated a tumor reduction of at least 50% within the initial 3 months of therapy. An additional benefit included decreased seizure activity. No patient required surgery or developed new SEGAs while receiving everolimus. The most common adverse effects included upper respiratory infections and stomatitis. Elevation of total cholesterol, LDL, and triglycerides levels were also reported. Severe adverse effects included bronchitis, leukopenia, or vomiting.¹² On the basis of these encouraging results, everolimus was recently granted accelerated approval by the FDA for treatment of SEGA in patients with TSC who are not surgical candidates.

We present the case of a patient with a SEGA in the right lateral ventricle; leptomeningeal enhancement of the brainstem, medulla, and cranial nerves; and nodular disease along the spinal cord, who demonstrated a significant clinical and radiographic response to treatment with everolimus.

CASE REPORT

The patient initially presented at 2 months of age with seizures. Genetic testing revealed a de novo germline mutation in the TSC2 gene. Seizures persisted for several years and were refractory to treatment with multiple different anticonvulsant agents and a ketogenic diet. He was followed with MRIs of the brain every other year. At the age of 10 years, MRI demonstrated an interval increase in the size of multiple SENs near the foramen of Monro bilaterally. Additional nodular lesions were observed on the lateral margin of the right ventricle with associated ventricular dilation. The patient underwent initial resection of the largest intraventricular lesion, which was histologically confirmed as a SEGA. At the age of 13 years, MRI demonstrated further progression of the same SEGA, requiring re-resection. The patient also underwent right temporal lobectomy for the treatment of intractable seizures. However, seizures persisted and the patient required treatment with anticonvulsants oxcarbazepine and levetiracetam. One year later, the patient developed severe back pain, worse in the supine position, stopped walking, and became wheelchair bound. MRI of the spine, which had previously been free of disease, showed new enhancement over the surface of the entire cord, extending superiorly into the brainstem, along with new nodular enhancing lesions involving the spine and the cauda equina. Because of concerns for progression to a high-grade glioma, the patient underwent biopsy of the lumbar spine. The biopsy demonstrated small clusters of cells morphologically similar to those from previous resections. Immunohistochemical analysis revealed that the cells were positive for neuron-specific enolase. The MIB-1 reactivity rate was 3% to 4%. Although the cells were negative for EMA, GFAP, S100, and synaptophysin, the biopsy was felt to be most consistent with SEGA (Fig. 1). Clinically, the patient had persistence of seizures and developed extensive renal angiomyolipomas and 2 cardiac rhabdomyomas.

Therapy was initiated with everolimus at a dose of 2.5mg/d (3mg/m²) for 6 weeks. As no toxicity was documented, the dose of everolimus gradually increased to 5mg/d. Serum levels of everolimus consistently measured <2ng/mL, likely related to the use of enzymeinducing anticonvulsant agents, such as oxcarbazepine. After oxcarbazepine was discontinued, the everolimus levels were > 5 ng/mL. Seizures were well controlled with levetiracetam, used as a single agent.

Response

Before starting therapy with everolimus, the patient experienced generalized seizures daily. Within 2 months of beginning therapy with everolimus, seizures decreased significantly. The patient had 3 generalized tonic-clonic seizures over a period of 24 months, likely triggered by a viral illness and febrile episodes, and an occasional asymmetric tonic seizure, each of which lasted for a few seconds. Thus, treatment with everolimus dramatically reduced seizure frequency.

Before treatment with everolimus, the patient experienced severe feeding intolerance, failure to thrive, and severe chronic constipation that required chronic treatment with enemas. At present, the patient has completed 24 months on therapy with everolimus and has gained weight with no episodes of emesis and with spontaneous bowel movements. The patient's lipid profile has remained stable with total cholesterol < 230 mg/dL and triglycerides < 150 mg/dL.

Before everolimus treatment, the patient had lost the ability to sit or move and complained of severe back pain, which was attributed to impingement of SEGAS on the spinal cord. After treatment was started, the patient demonstrated significant improvement of his radiculopathy. He is pain free, more interactive and cooperative with caregivers, assists with transfers in and out of his wheelchair, and is able to stand erect with some assistance.

The main evidence of tumor shrinkage in the patient's brain and spinal cord occurred during the first 6 weeks of therapy. This response has remained stable during 24 months of continuous therapy with everolimus. Volumetric analysis after 24 months of continuous therapy with everolimus demonstrated a > 70% decrease in the size of the lesion near the foramen of Monro and a 45% decrease of the lesion in the right lateral ventricle. The lesions in the upper cervical spine have decreased in size by > 75%, and the lumbar spine lesions have completely resolved (Fig. 2).

There was a decrease in the size of the enhancing SENs and leptomeningeal disease. There were no new brain lesions identified and no evidence of worsening hydrocephalus. Cardiac rhabdomyomas have decreased in size > 80%, since starting the treatment with everolimus. However, extensive kidneys angiomyolipomas have remained unchanged in size.

DISCUSSION

To the best of our knowledge, this is the second report of a SEGA with dissemination to the leptomeningeal space and spinal cord. However, it is the first report of a patient with a SEGA with widely metastatic disease, who was successfully treated with everolimus. Although it is unclear whether these rare sites of disease represent multifocal disease or true dissemination, the key finding is that everolimus treatment was able to produce an objective tumor response in all involved CNS sites. This is important because in similar gliomas like juvenile pilocytic astrocytoma with dissemination, there is often a question of whether this represents multifocal disease or true dissemination. Of interest, in the case of juvenile pilocytic astrocytomas with dissemination, spinal disease often does not respond, whereas disease in the brain does respond to treatment.

TS is a potentially devastating disease because of the involvement of different organ systems. Limited evidence is available with regard to the prediction of aggressive behavior in SEGA. Histologic features have failed to show any correlation with clinical course or survival.¹³ Furthermore, studies have not identified a relationship between the proliferation index and tumor growth.¹⁴

Before the availability of mTOR inhibitors, the clinical management of patients with SEGAs was based on monitoring with imaging and management of symptoms to control local disease. Patients with SEGA metastasis are extremely rare and, until recently, very unlikely to survive their disease. There is one report in the literature of a patient with SEGA metastatic to the spinal cord who was treated with temozolomide but whose condition rapidly deteriorated and died.¹⁵ Reports of extraventricular SEGAs are uncommon and include description of a 7-year-old with the disease.¹⁶ However, most reports of extraventricular SEGA are during the neonatal period.^{16,17}

The mechanism underlying the rare, aggressive behavior of some SEGAs is unknown. In the present case, metastases could have developed spontaneously or could have resulted from seeding of the cerebrospinal fluid during the preceding incomplete resection. In the other reported case with spinal metastases, the spinal lesions were evident at the time of initial presentation.¹⁵

With the recent FDA approval of everolimus for treatment of SEGAs in patients with TSC, physicians can now offer a targeted treatment alternative to TS patients who are not candidates for surgical resection. Different mTOR inhibitors have been tried in this population; however, the agent with the most available clinical information in patients with TS is everolimus. In addition, it has been shown that everolimus has increased CNS penetration compared with rapamycin.¹⁸

Because of significant advances in the understanding of TS biology, preclinical data that support the use of mTOR inhibitors in this setting, and results of a recent phase III trial,¹⁹ the management of patients with TSC has changed dramatically. Patients now have the option of medical therapy for the control of SEGAs, as well as for the control of other systemic manifestations of TS.

Multiple clinical trials of mTOR inhibitors, such as everolimus, for TSC patients with angiomyolipomas, SEGA, and epilepsy are ongoing (<http://www.clinicaltrials.gov>). A recently completed phase III trial reported results from a study in which 117 TS patients were randomized to receive either placebo or everolimus. Twenty-seven of 78 TS patients in the everolimus group had at least a 50% reduction in the size of SEGAs. No similar (> 50%) reduction was observed in any of the 39 patients in the placebo group. The most commonly reported toxicities in the treatment group were stomatitis, mouth ulceration, pyrexia, bronchitis, vomiting, or upper respiratory infection.¹⁹

Questions remain with regard to optimum dosing and duration of therapy with everolimus. It has been shown that patients can experience tumor recurrence shortly after stopping the treatment with everolimus.¹² However, it is not clear whether patients who continue to receive treatment with prolonged courses of everolimus can develop resistance to the drug.

To date, there are no published reports of SEGA progression in patients on active therapy with everolimus. However, research is ongoing to better understand why patients with SEGA and mutation of TSC2 have lower response rates to everolimus than patients with mutation of TSC1.¹⁹ Further, it is also unclear why some patients exhibit an excellent response to everolimus in some organs but not in others. This was the case in our patient who demonstrated dramatic response to everolimus treatment in SEGAs and cardiac rhabdomyomas but no response in renal angiomyolipomas. Moreover, the effect of everolimus on prolongation of life for patients with TS is also unclear. A very interesting question is whether everolimus can prevent neurological deterioration in symptomatic TS patients. This is a question that will need to be addressed in future clinical trials.

In summary, the use of mTOR inhibitors has created a new and exciting alternative, or adjunct, to surgery for the treatment of patients with SEGA and TS. We have described a patient with SEGA, with evidence of disease dissemination to the leptomeninges and spinal cord. Our patient exhibited significant improvement of symptoms and measureable disease regression within 6 weeks of therapy with everolimus. This suggests that targeted therapy with everolimus offers promise in the treatment of SEGAs and other TS-related complications.

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Figure 1.

A, Hematoxylin & eosin (H&E) staining of a representative section from a primary subependymal giant cell astrocytomas (SEGA) from the lateral ventricle of our patient (H&E, $\times 400$). B, Representative section from a SEGA lesion metastatic to the spinal cord (H&E, $\times 400$). C, MIB-1 immunohistochemical analysis of the spinal cord lesion, showing a low rate of proliferation ($\times 200$). D, Diffuse reactivity for neuron-specific enolase, supporting the diagnosis of SEGA ($\times 400$).

Figure 2.

A–D, Before treatment with everolimus. A, Coronal FLAIR, postcontrast image of a large subependymal giant cell astrocytoma (SEGA) in the right ventricle. B, Coronal FLAIR, postcontrast image of a SEGA near the foramen of Monro. C, Sagittal T1 postcontrast image of an upper cervical spine SEGA. D, Sagittal T1 postcontrast image of SEGAs in the lower spine. E–H, Twenty months after everolimus therapy. E, Coronal FLAIR, postcontrast image demonstrating a 45% reduction in size of the SEGA versus in (A). F, Coronal FLAIR, postcontrast image demonstrating >75% reduction in size compared with (B). G, Sagittal T1 postcontrast image demonstrating >75% reduction in size compared with (C). H, Sagittal T1 postcontrast image demonstrating complete resolution of SEGAs compared with (D).