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Subependymal Giant Cell Astrocytoma (SEGA) Treatment Update

Cynthia J. Campen, MD[1] and **Brenda E. Porter, MD, PhD**[*]

[*]The Children's Hospital of Philadelphia, The University of Pennsylvania, 502C Abramson Research Building, 3615 Civic Center Blvd., Philadelphia, PA 19104, USA
porterb@email.chop.edu

[1]Division of Child Neurology, 300 Pasteur Drive, Room A347, Stanford, CA 94305, USA
ccampen@stanford.edu

Opinion statement

Rates of regrowth after resection of subependymal giant cell astrocytoma (SEGA) are low, making surgical resection a successful and permanent therapeutic strategy. In addition to surgical resection of SEGAs, other treatment options now include medications and Gamma Knife™ therapy. Advising patients on medical versus surgical management of SEGAs is currently not easy. SEGAs have been reported to regrow if mTOR inhibitor therapy is stopped, raising the possibility that long-term medication may be required to prevent tumor growth and hydrocephalus. The question of regrowth following medication withdrawal will need to be addressed in more patients to help establish the optimal duration of therapy. The risks of surgery include acute morbidity and the permanent need for ventriculoperitoneal shunting, which must be balanced against the adverse effects of mTOR inhibitors, including immunosuppression (infections, mouth sores), hypercholesterolemia, and the need for chronic drug monitoring. Some additional benefits of mTOR inhibition in patients with tuberous sclerosis complex, however, may include shrinkage of angiofibromas and angiomyolipomas as well as a possible decrease in seizure burden. Recent reports of successful nonsurgical treatment of SEGAs are promising, and it is hoped that further specifics on dosing, duration, and long-term outcome will help patients and physicians to make informed therapeutic choices.

Present treatment recommendations for SEGAs include routine surveillance neuroimaging and close clinical follow-up, paying particular attention to signs and symptoms of acute hydrocephalus. If symptoms arise, or if serial neuroimaging demonstrates tumor growth, neurosurgical intervention is recommended. When gross total resection is impossible, rapamycin and everolimus should be considered, but may not offer a durable response.

Introduction

Inactivation of the tumor suppressor genes hamartin (*TSC1*) or tuberin (*TSC2*) are associated with tuberous sclerosis complex (TSC), a relatively common autosomal dominant genetic disorder affecting up to one out of 6,000 people [1]. The TSC1 and TSC2 proteins act as a heterodimer to suppress mammalian target of rapamycin (mTOR), a serine/threonine protein kinase that regulates cell growth and division. Multiple organs are at risk for developing tumors, including the heart, lungs, skin, and kidneys. The most common findings in the

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brain of TSC patients include tubers in the cortical parenchyma, which are relatively static. Cortical tubers are thought to contribute to the high rate of epilepsy in TSC but do not have a high rate of oncologic growth potential. On MRI imaging, most patients with TSC are found to have subependymal nodules that line the ventricles, with a subset of nodules being completely or partially calcified; some show contrast enhancement [2, 3]. To date, no radiographic features have been identified that will accurately predict which subependymal nodules will grow and require treatment. Reportedly, 5% to 20% of TSC patients develop low-grade CNS lesions known as subependymal giant cell astrocytomas (SEGAs), which arise from the subependymal nodules [3, 4]. Serial neuroimaging demonstrates a continuum from subependymal nodules to SEGAs.

Histopathologically, SEGAs are indistinguishable from subependymal nodules, with loosely cohesive clusters of large cells with round to oval nuclei and no (or minimal) atypia; fine, evenly distributed chromatin; and abundant eosinophilic cytoplasm embedded in abundant thin, hairlike processes [5]. Formed by three types of cells—fibrillated spindle cells, swollen gemistocytic-like cells, and giant pyramidal cells with a ganglioid appearance—SEGAs show both glial and neuronal features. Some authors have demonstrated that all subependymal nodules are clonal and have the capacity to proliferate [6, 7].

SEGAs typically arise from subependymal nodules in the area of the foramen of Monro, and can be unilateral or bilateral. SEGAs are slow-growing tumors and typically have no symptoms until obstructive hydrocephalus develops [2, 3]. They are distinguished from subependymal nodules by increasing size on serial neuroimaging, or by signs and symptoms of obstructive hydrocephalus. Without intervention, SEGAs typically continue to grow slowly over weeks to months, with only sparse evidence of regression or growth stabilization. Rarely, SEGAs can exhibit more aggressive behavior, associated with parenchymal invasion or extensive peritu-moral edema, or they can occur in an atypical location such as the pineal or hypothalamic regions. They typically project into the ventricle and can produce acute or chronic hydrocephalus.

Typically, serial neuroimaging every 1 to 3 years is recommended for pediatric patients with TSC, even in the absence of symptoms [8]. If a subependymal nodule has grown over the interval of routine imaging, more frequent follow-up imaging is appropriate. Symptoms can be subtle in the early presentation of a SEGA. Complaints in patients with TSC that warrant urgent imaging include positional headache (worse in a dependent position), sudden worsening of seizures, or progression to include nausea, vomiting, diplopia, and lethargy.

Clinical series suggest a male predominance, with a mean age at surgery of 11 years [3, 4]. In a series of 14 surgical patients, SEGA was identified at a mean of 90 months of age, and surgical intervention occurred at a mean of 38 months after identification. Surgery was performed for evidence of hydrocephalus in nine of 12 patients, and for evidence of tumor growth in five of 12 [9]. In one series, ten of 21 patients with SEGA died, six as a direct result of tumor growth (acute obstructive hydrocephalus in five, and intratu-moral hemorrhage in 1). In this series, death from brain tumor was most common at ages 10 to 19 years [10]. In patients followed by a neurologist experienced in caring for patients with TSC, deaths from SEGAs are rare, but morbidity including vision loss, chronic ventriculoperitoneal shunting, and headache are still seen.

Treatment

Pharmacologic treatment

- The goal of pharmacologic therapy is shrinkage or stabilization of the SEGA.

- Rapamycin (sirolimus) and everolimus have been shown to have efficacy in stabilizing and in some cases shrinking SEGAs [11••, Class III; 12, Class IV].

Rapamycin (sirolimus)

Rapamycin (Rapamune; Pfizer, New York, NY) initially showed efficacy against renal angiomyolipomas, but subsequent investigations in SEGAs demonstrated similar efficacy [13]. In a report of five cases of SEGA in patients with TSC treated with rapamycin, all tumors were reduced significantly in size. An average of 65% reduction of astrocytoma volume was observed. Surgery was avoided in all five patients, and only mild adverse effects were observed. Clinical response may not be durable, however, as in most cases, the SEGA regrew when rapamycin was stopped, [12, Class IV].

Standard dosage—1.5 mg/m^2 per day, though 24-h trough levels are followed and adjusted to achieve a level of 10 to 15 ng/mL. Not all patients tolerate this level, and 5 ng/mL was used with success in one patient [12, Class IV].

Contraindications—SEGAs causing significant hydrocephalus and impending herniation should undergo surgical resection for acute management. Severe infections are a contraindication for rapamycin therapy, as rapamycin decreases immune function.

Main drug interactions—Sirolimus is known to be a substrate for both cytochrome P-450 3A4 (CYP3A4) and p-glycoprotein (P-gp). Inducers of CYP3A4 and P-gp may decrease sirolimus concentrations, whereas inhibitors of CYP3A4 and P-gp may increase sirolimus concentrations. Because epilepsy is a common problem in patients with TSC, and some antiepilepsy drugs utilize CYP3A4 and the P-gp transporter, sirolimus may have complex interactions with antiseizure medications. Known inducers of the CYP3A4 include phenytoin, carbamazepine, phenobarbital, oxcarbazepine, and rufinamide.

Main side effects—Aphthous ulcers, hypercholesterolemia, thrombocytopenia, acneiform rash, immunosuppression, and impaired wound healing.

Cost—1 mg/mL (60): $613.45; 1 mg (30): $318.86; 2 mg (100): $2081.47.

Everolimus

Everolimus (Afinitor; Novartis, East Hanover, NJ) was approved for the treatment of SEGA by the US Food and Drug Administration (FDA) in October, 2010. Everolimus is very similar to rapamycin in chemical composition: a 2-hydroxyethyl group has been introduced in position 40 of rapamycin. This change results in a slight increase in bioavailability and a shorter half-life. The adverse-effect profiles of the two drugs appear very similar.

A study of 28 patients (age ≥3 years) who were treated with everolimus reported a significant reduction in SEGA size in 75% of patients [11••, Class III]. The patients also had a mild improvement in seizure burden; whether this change was due to decreased intracranial pressure or a direct effect of mTOR inhibition on the seizure focus is not clear. Perhaps longer follow-up of this patient population will help determine the duration of therapy needed to prevent regrowth of SEGAs in this high-risk population.

Standard dosage—Trough levels should be followed, with levels of 5 to 10 ng/mL being the target range. Dosing is based on body surface area:

0.5 m^2 to 1.2 m^2: 2.5 mg once daily

1.3 m^2 to 2.1 m^2: 5 mg once daily

>2.2 m^2: 7.5 mg once daily

Contraindications—SEGAs causing significant hydrocephalus and impending herniation should undergo surgical resection for acute management. Severe acute infections are a contraindication, as everolimus decreases immune function.

Main drug interactions—Everolimus is known to be a substrate for both cytochrome P-450 3A4 (CYP3A4) and p-glycoprotein (P-gp). Inducers of CYP3A4 and P-gp may decrease everolimus concentrations, whereas inhibitors of CYP3A4 and P-gp may increase everolimus concentrations. Because epilepsy is a common problem in patients with TSC, and many antiepilepsy drugs utilize CYP3A4 and the P-gp transporter, everolimus may have complex interactions with antiepilepsy drugs. Known inducers of CYP3A4 include phenytoin, carbamazepine, phenobarbital, oxcarbazepine, and rufinamide.

Main side effects—Aphthous ulcers, hypercholesterolemia, thrombocytopenia, acneiform rash, immunosuppression, and impaired wound healing.

Cost—Wholesale acquisition cost of approximately $5,700 to $6,200 for a 28-day supply.

Surgery

- Standard therapy for SEGAs traditionally has been operative resection [4, 14, 15•]. Gross total resection is curative. If tumor remains, it frequently will continue to grow. Historically, surgery was performed for one of three indications: acute hydrocephalus, worsened seizure burden, or significant interval growth on serial neuroimaging. More recently, some authors have argued for earlier surgical intervention to avoid the sequelae of hydrocephalus [3, 16].
- Complications of intraventricular surgery are numerous, including transient memory impairment, hemiparesis, infection, and shunting. Permanent sequelae include chronic ventriculoperitoneal shunt placement and rare cases of stroke with resultant hemiparesis. Death has occurred [4, 15•].

Gamma knife therapy

- A sustained reduction in SEGA size and no regrowth over at least a 2-year follow-up period have been reported in small case series of 2 to 6 patients treated with Gamma Knife™ therapy [14, 17•, Class IV].
- One study investigating stereotactic radiosurgery in SEGA reported a total of six patients, three with TSC. Of these, all had Gamma Knife™ surgery (GKS) as a primary treatment for the SEGA. The pre-GKS tumor volumes were 5.9, 3.4, and 2.1 cm^3, and the patients received 13, 15, and 11 Gy. Progression occurred in one patient, with a progression-free interval of 2 and 4 3/4 years in the other two; the mean follow-up was 5.8 years [17•, Class IV]. For Gamma Knife™ therapy to become a standard of care, a study looking at short-term and long-term outcomes is needed to assess efficacy and safety.

Main side effects

Of special concern in TSC patients who already lack one copy of a tumor suppressor gene is the potential increased risk of a radiation-induced secondary tumor. A glioblastoma multiforme has been reported 8 years after SEGA radiation in a patient with TSC [18]. As surgical resection and mTOR inhibitors do not pose this theoretical risk, it seems prudent to

reserve Gamma Knife™ therapy for patients with contraindications to the more standard treatment regimens or those in whom these regimens have failed.

Contraindications

The reduction in SEGA size is not immediate, so Gamma Knife™ therapy is not appropriate for large tumors producing significant hydrocephalus.

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