EVEROLIMUS: A CHALLENGING DRUG IN THE TREATMENT OF MULTIFOCAL INOPERABLE CARDIAC RHABDOMYOMA

abstract

Primary cardiac tumors are rare in childhood. The most common of these are rhabdomyomas. Considering that rhabdomyomas often show spontaneous regression, close follow-up may be sufficient in hemodynamically stable cases. However, hemodynamically significant cardiac rhabdomyomas confer a risk of morbidity and mortality. Herein, we report a newborn infant with multifocal cardiac rhabdomyomas treated with everolimus. The optimal dose of the drug was 0.25 mg 2 times per day, 2 days per week. Patients with inoperable cardiac rhabdomyomas and with symptoms may be candidates for everolimus treatment. *Pediatrics* 2012;130:e243–e247

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KEY WORDS
cardiac, heart, rhabdomyoma, newborn, child, everolimus

ABBREVIATIONS
mTOR—mammalian target of rapamycin
PG1—prostaglandin E1
SEGA—subependymal giant cell astrocytoma

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Primary cardiac tumors are rare during childhood and are frequently congenital and benign.\textsuperscript{1,2} The most frequently encountered congenital tumors are rhabdomyomas.\textsuperscript{2} Rhabdomyomas are the most common childhood cardiac tumors, comprising 45% to 75% of primary cardiac tumors.\textsuperscript{1} Studies have demonstrated that the incidence of cardiac rhabdomyoma is 0.002% to 0.25% at autopsy, 0.02% to 0.08% in live-born infants, and 0.12% in prenatal series.\textsuperscript{3–5}

Most patients with cardiac rhabdomyomas are asymptomatic. Others may present with arrhythmias, murmurs, and convulsions related to tuberous sclerosis, intracardiac blood flow obstruction, and problems associated with the respiratory system.\textsuperscript{6–10} Multifocal tumors are associated with tuberous sclerosis in 78% to 95% of rhabdomyoma cases.\textsuperscript{8,11} Spontaneous regression occurs during the first 2 to 4 years in 33% of these cases.\textsuperscript{1}

Tuberous sclerosis is an autosomal dominant neurocutaneous disease characterized by the presence of mass lesions in various organs including the brain, skin, kidney, liver, lung, and heart.\textsuperscript{12} Tuberous sclerosis results from inactivating mutations in either tuberous sclerosis complex 1 (Ch9q34, hamartin) or tuberous sclerosis complex 2 (Ch16p13, tuberin).\textsuperscript{12,13} Mutations in these genes lead to the production of hamartin and tuberin heterodimers that inhibit mammalian target of rapamycin (mTOR), which controls the cell proliferation and growth in normal circumstances.\textsuperscript{12–15} mTOR, a serine-threonine kinase, exerts its effects on cell proliferation, differentiation, growth, and migration via inputs from different pathways. The US Food and Drug Administration has approved 3 mTOR inhibitors: sirolimus, for the prevention of organ rejection in renal transplantation; temsirolimus, for advanced renal cell carcinoma; and everolimus, for pancreatic progressive neuroendocrine tumors, tuberous sclerosis–associated inoperable subependymal giant cell astrocytoma (SEGA), and progressive renal cell carcinoma.

Herein, we report a newborn with multifocal cardiac rhabdomyomas. Because of extensive myocardial involvement, he could not be operated on, but was successfully treated with everolimus.

**CASE REPORT**

A term male newborn, the first child of healthy nonconsanguineous parents, was born by normal vaginal delivery. His father had a diagnosis of tuberous sclerosis. Multifocal cardiac rhabdomyomas were diagnosed at 4 months’ gestation. He had cyanosis soon after delivery. His birth weight was 3400 g (75th–90th percentile), and head circumference was 35 cm (75th–90th percentile). His heart rate was 170 beats per minute, blood pressure was 60/40 mm Hg, and oxygen saturation was 85% to 90%. Physical examination revealed mild hepatomegaly. He also had 2 hypopigmented skin lesions on the right lower extremity. A second-degree (II/VI) systolic ejection murmur was heard on the left-sided second intercostal space. The results of electrocardiography were normal. Echocardiography revealed 8 different rhabdomyomas with multiple locations. The sizes of the tumors ranged from 5 mm to 2.5 cm. Two rhabdomyomas were located in the right ventricle, 2 in the mitral papillary muscles, 3 in the interventricular septum, and 1 on the tricuspid valve (Fig 1, top). One was highly mobile and obstructed right ventricle inflow. The 2 largest masses that were located side by side in the interventricular septum had extensive intramural components. Because of the compression by the 2 masses, the interventricular septum was deviated toward the left ventricle. Therefore, it was not possible to measure ejection.

**FIGURE 1**

Echocardiographic images of cardiac rhabdomyomas. Images before (top) and after (bottom) everolimus treatment. The views of the masses are as follows: A, on the tricuspid valve; B, at the interventricular septum; C, D, at right ventricular outflow tract; E, at apical portion of interventricular septum; and F, at the mass at right ventricular inlet portion and beneath the tricuspid valve. Two small masses shown in the top (E and F) disappeared after everolimus therapy. Arrows indicate the location of the masses that disappeared. IVS, interventricular septum; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle; RVOT, right ventricular outflow tract.
fraction by M-mode echocardiography. The left and right ventricular outflow tract velocities were 1.4 m/s and 3.5 m/s, respectively. These values were lower than the expected levels, because it was not possible to place the Doppler ultrasound beams parallel to the ventricular flow tracts because of the location of the masses. The right atrium and right ventricle were dilated. The mass on the tricuspid valve also caused a mild degree tricuspid regurgitation (velocity, 2.4 m/s). The left ventricular smaller masses within anterior and posterior mitral papillary muscles were not associated with any hemodynamic disturbances. A patent foramen ovale with right-to-left shunting and a small patent ductus arteriosus with left-to-right shunting were also detected. Prostaglandin E1 (PGE1; alprostadil, 0.01 μg/kg per minute) was administered to maintain pulmonary blood flow, and furosemide was given for right ventricular heart failure. Cardiac surgeons evaluated the patient, but they deemed the masses ineligible for surgical resection because of extensive intramural myocardial involvement. Instead, we started everolimus treatment, with a dose of 0.25 mg every 6 hours, 2 days per week. We adjusted the dose in accordance with the dose used in a study by Kruger et al.16 We monitored complete blood cell count, hepatic and renal function tests, lipid profile, and lymphocyte subsets (Fig 2). We also monitored serum levels of everolimus and obtained a steady-state serum level of the drug between 5 and 15 ng/mL with a dosing schedule of 0.25 mg 2 times per day, 2 days per week. We also started prophylactic trimethoprim-sulfamethoxazole treatment. After 4 doses of everolimus, the serum level of the drug was very high, and serum triglyceride level reached 398 mg/dL (range, 0–200 mg/dL). After adjustment of everolimus administration and treatment with omega-3 fatty acids, the triglyceride level returned to normal. We adjusted the dose of everolimus to 0.25 mg 2 times per day, 2 days per week, according to serum levels of the drug (Fig 2).

After 2.5 months of everolimus treatment, hemodynamic instability of the patient improved, and he continued to do well clinically. His cardiac rhabdomyomas decreased remarkably in size and echogenicity. Oxygen saturation was 98%, and PGE1 was stopped. Echocardiography revealed 6 masses; 2 small masses in the right ventricle had disappeared. The mass on the tricuspid valve was 10 × 9 mm in size, and the obstructions in the right ventricle inflow and outflow had disappeared. The masses in the interventricular septum became smaller and lost their echogenicity (Fig 1,
The patient and has been symptom-free for 2 months. The patient is now under follow-up prevention of early and late side effects of the drug. We stopped everolimus treatment to promote the restoration of cardiac hemodynamics, which was trivial. After the patient had a high mortality risk and was not eligible for surgical resection.

**DISCUSSION**

Cardiac tumors have been reported in <0.32% of patients of all ages. The most common cardiac tumor in the pediatric population is the rhabdomyoma. Approximately half of all rhabdomyomas are associated with tuberous sclerosis. However, multifocal cardiac rhabdomyomas are associated with tuberous sclerosis in 70% of cases, and this was also true for our case.

An important characteristic of cardiac rhabdomyomas is spontaneous regression, and this occurs in ~50% of all cases. The main treatment of symptomatic cardiac tumors is surgical resection. This is indicated in patients with inflow and outflow obstruction, which leads to hemodynamic instability, valvular dysfunction, and dysrhythmias, because of the risk of sudden death. However, patients with giant tumor masses compressing or infiltrating the heart frequently cannot undergo complete resection. For these patients, restoration/preservation of sufficient heart function is the primary goal. Because of extensive intramural myocardial involvement, our patient had a high mortality risk and was not eligible for surgical resection.

Surgery is not usually recommended in patients with normal hemodynamics because of the possibility of spontaneous regression of rhabdomyomas. However, 1 study reported that, of 103 benign tumors that caused sudden death, 9 (8.7%) were rhabdomyomas. The present case exhibited obstruction of both ventricular outflow tracts, so continuous intravenous PGE1 infusion was given to establish pulmonary blood flow and hemodynamic stability. Moreover, cardiac masses were multifocal, with extensive intramural involvement, and surgical resection was not possible. Tiberio et al reported a near-resolution of a left ventricular rhabdomyoma in a patient at the end of 13 months of everolimus treatment, originally administered for the treatment of SEG. We began everolimus treatment in our patient after learning about the results of Tiberio et al.

Everolimus is an mTOR inhibitor that has been reported to be effective against SEG in tuberous sclerosis, renal cell carcinoma, and neuroendocrine tumors. After the report of near-total regression of a cardiac rhabdomyoma, the present case is the first case in which everolimus was used to treat inoperable multifocal cardiac rhabdomyoma. Because the masses became markedly smaller after everolimus therapy, pulmonary blood flow increased and the patient no longer required PGE1 infusion. Cyanosis disappeared, and his weight has become appropriate for his age.

This is the first report of a newborn infant with cardiac rhabdomyoma treated with everolimus. We monitored the serum levels and side effects to define the optimal dose and schedule of the drug. We documented some side effects, including omega-3-responsive transient hypertriglyceridemia, self-limited diarrhea, decreased CD/CD8 ratio, and decreased lymphocyte percentages. We aimed to restore hemodynamic stability in the patient with a serum level of 5 to 15 ng/mL everolimus. In this way, we hoped to prevent long-term side effects of the drug. Side effects did develop, and the serum level of the drug reached as high as 83.5 ng/mL during the first 4 doses of 0.25 mg. However, we then found an optimal dose and schedule for the drug: 0.25 mg 2 times per day, 2 days per week.

We also monitored the patient for regrowth of the masses after discontinuation of the drug. On the follow-up, we found that only the echogenicity of the residual mass in the interventricular septum was slightly increased. Everolimus treatment was not restarted.

In conclusion, primary cardiac tumors in childhood are rare, but rhabdomyoma is the most common type. Considering the fact that rhabdomyomas often show spontaneous regression, close follow-up may be sufficient in hemodynamically stable cases. However, inoperable multifocal cardiac rhabdomyomas causing symptoms may be candidates for everolimus treatment. The duration of everolimus treatment should be decided according to the resolution of symptoms and findings on echocardiography. The optimal dose of the drug may be 0.25 mg 2 times per day for 2 days per week. However, additional studies should be performed to confirm the effectiveness of everolimus in the treatment of cardiac rhabdomyomas.

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