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. 

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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...
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,
Informed consent was obtained from the patient’s parents. The patient is now under follow-up for the prevention of early and late side effects of the drug. Due to the improvement in cardiac hemodynamics, we stopped everolimus treatment to prevent long-term side effects of the drug. The patient had a high mortality risk and was no longer responsive to therapy. Therefore, we hoped to prevent the occurrence of regrowth of the masses after discontinuation of the drug. On the follow-up, we found that 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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