JPPT | Case Report

Use of Sirolimus in a Premature Neonate With Kaposiform Hemangioedema

Jason Koury, PharmD, BSN; Miel Brown, BS; Suzzette Sturtevant, PharmD; Cody Wiley, MS; and Linda Felton, PhD

Kaposiform hemangioendothelioma (KHE) is a rare, vascular malignancy that is often associated with coagulopathies and thrombocytopenia secondary to platelet trapping. Typically, a person diagnosed with KHE with Kasabach-Merritt phenomenon (KMP) presents with a reddish-purplish lesion, thrombocytopenia, and elevated D-dimer, which can lead to high morbidity and mortality. Sirolimus has been identified as a treatment option for KHE with or without KMP for reduction in lesion size and hematologic parameters. In this case report, a female born at 26.5 weeks was noted at birth to have a purpuric lesion on her right upper back and flank area. She was diagnosed with biopsy-confirmed KHE with KMP. She was started on sirolimus 0.01 mg (0.02 mg/kg; 0.14 mg/m^2) once a day, and because of high trough concentrations treatment was held until concentrations decreased. Sirolimus was then microdiluted to a 0.01 mg/mL concentration in medium-chain triglyceride oil for administration. Prior to discharge from the hospital the commercially available product was dispensed for home use. After 6 months of treatment, she achieved a reduction in lesion size and improvement in hematologic parameters, and treatment was stopped at 9 months.

ABBREVIATIONS AUC, area under the curve; KHE, kaposiform hemangioendothelioma; KMP, Kasabach-Merritt phenomenon; MCT, medium-chain triglyceride

KEYWORDS kaposiform hemangioedema; Kasabach-Merritt phenomenon; newborn; sirolimus; vascular malformation

J Pediatr Pharmacol Ther 2021;26(2):205–209

DOI: 10.5863/1551-6776-26.2.205

Introduction

Kaposiform hemangioendothelioma (KHE) is a rare, vascular malignancy that is often associated with coagulopathies and thrombocytopenia secondary to platelet trapping.[1] Due to the rarity of KHE, it is often difficult to diagnose and can be associated with high morbidity and mortality. The incidence of KHE is estimated to be 0.071 per 100,000 children. Typically, KHE presents as a deep reddish-purple lesion with poorly defined edges and is firm and warm to the touch. About 70% of children with KHE develop Kasabach-Merritt phenomenon (KMP), an enlarging cutaneous lesion with profound thrombocytopenia and coagulation consumption.[1–3] Many children presenting with KHE without KMP have few complications and often do not require treatment, although treatment for KHE with KMP is often required. Complete surgical resection is considered the gold standard for KHE, although it is not always an option and carries a high risk of complications, such as bleeding.[1,3] Treatment with corticosteroids and/or vincristine has often been used to treat KHE; however, the success of these treatments is variable, with response rates of 27% and 72%, respectively.[1,4] From a study of 52 patients (mean age = 10.6 months), sirolimus, a mammalian target of rapamycin inhibitor, has been shown to be effective for symptom relief and tumor size reduction in patients with KHE with or without KMP.[3]

Because of its rarity, a lack of evidence exists relating to treatment of KHE, especially in the neonatal population. To our knowledge, there are no published data on treatment for premature neonates who have a diagnosis of KHE with KMP. Due to the significant pharmacokinetic and dynamic differences in premature neonates compared with term neonates, infants, and children, pharmacologic treatment can be difficult to manage. We present a female born at 26.5 weeks treated with microdiluted sirolimus for biopsy-confirmed KHE with KMP.

Case Summary

A 0.59-kg (0.07-m^2) female, born at 26.5 weeks' gestational age, was shown to have a 3- to 4-cm–diameter, soft, non-protruding, oval-shaped purpuric lesion in the right subscapular region. A biopsy confirmed a diagnosis of KHE with KMP. At presentation, platelets were low, at 57 × 10^3/μL, and the D-dimer was elevated at 2079 ng/mL. The hematology/oncology team consulted a KHE expert from Boston Children's, who recommended sirolimus monotherapy at a starting dose of 0.01 mg (0.02 mg/kg; 0.14 mg/m^2). This is the lowest possible measurable daily dose that enables one to achieve a target serum concentration of 5 to 10 ng/mL. The sirolimus dosing trajectory is provided in the Table. Prior to starting therapy for KHE with KMP,

Table. Sirolimus Dosing Trajectory

DOL	Dosing Weight, kg	Sirolimus Parameters				Comments
		Formulation, mg/mL	Dose, mg (mg/kg)	Dosing Frequency	Serum Concentration, ng/mL	
1	0.6	—	—	—	—	Biopsy performed
6	0.6	1	0.01 (0.02)	Daily	—	Start of therapy
8	0.6	1	0.01 (0.02)	Daily	14.1	Switched to every other day dosing
14	0.6	1	0.01 (0.02)	Every other day	26.4	Dose held
16	—	—	—	—	20.3	Dose held
19	—	—	—	—	16.6	Dose held
22	—	—	—	—	10.1	Dose held
25	—	—	—	—	5.1	Dose held
26	0.8	0.1	0.005 (0.01)	Daily		Microdilution with MCT oil; restarted treatment
32	0.8	0.1	0.005 (0.01)	Daily	2.8	Dose increased
33	1	0.1	0.01 (0.01)	Daily	—	
36	1	0.1	0.01 (0.01)	Daily	3.4	Dose increased
37	1	0.1	0.02 (0.02)	Daily	—	
40	1	0.1	0.02 (0.02)	Daily	4.5	
52	1.5	0.1	0.03(0.02)	Daily	1.6	Duration to twice a day
53	1.5	0.1	0.03(0.02)	Twice a day	—	
80	2.6	1	0.03 (0.01)	Twice a day	—	Transition to standard product
82	2.6	1	0.03 (0.01)	Twice a day	3.0	Dose increased
89	2.6	1	0.04 (0.02)	Twice a day	4.7	

DOL, day of life; MCT, medium-chain triglyceride

hydrocortisone 0.6 mg (1 mg/kg) IV push, twice a day, was administered for prevention of bronchopulmonary disease from birth through day 3 of sirolimus therapy. Generally, sirolimus dosing was administered 1 hour after morning breast milk feeds (61 mL/kg/day). After starting therapy, a trough was drawn prior to the third dose. The trough serum concentration was 14.1 ng/mL, and the sirolimus dosing frequency was changed to 0.01 mg (0.02 mg/kg) by mouth every other day. After 3 doses of the new regimen, a trough of 26.4 ng/mL was obtained, which subsequently led to holding the dose. There were not any drug-drug interactions or renal or hepatic dysfunction that could have contributed to the elevated sirolimus concentrations.

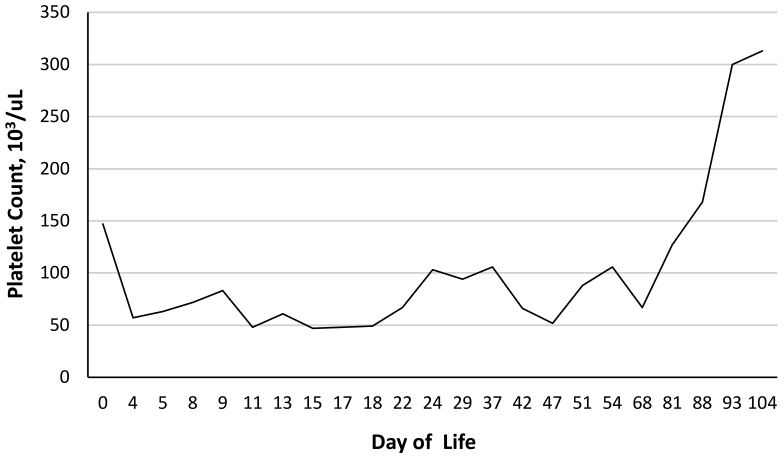
Once the sirolimus serum trough concentration decreased to 5.1 ng/mL the medication was restarted at 0.005 mg (0.01 mg/kg). Because of the previous high trough concentration and the difficulty associated with administering such a small dose, the commercially available 1 mg/mL product was further diluted to 0.01 mg/mL each day before administration. Prior to discharge, the patient was trialed on the 1 mg/mL product, and serum concentrations were monitored to ensure the dosing was not supratherapeutic.

Although target serum concentration goals were not consistently reached, the hematology/oncology team felt the patient had a good clinical response to the sirolimus. The patient was treated with sirolimus for 9 months, resulting in a lesion size reduction and a normalization of platelets and D-dimer (Figures 1 and 2). Per a chart review, other than a drop in her absolute neutrophil count (588/μL) at 9 months, the patient did not experience adverse effects such as nausea, vomiting, infections, or increases in liver function tests or cholesterol values.

Discussion

Sirolimus, a mammalian target of rapamycin inhibitor, works to interfere with an overexpressed signal in the PI3K/AKT pathway that is seen in KHE with KMP, thereby leading to a reduction in tissue overgrowth.[5] Historically, pharmacologic treatment has included corticosteroids or vincristine, both of which have variable positive response rates. Liu et al[4] conducted a

Figure 1. Platelet count.



meta-analysis to assess the effectiveness of treatments, including corticosteroids and vincristine, for the treatment of KHE without KMP. In a cohort with an average age of 6.7 months, corticosteroids had a 27% (95% CI, 0.17–0.36) response, with a mean of 5.25-month treatment duration, and vincristine had a 72% (95%CI, 0.64–0.79) response, with a mean of 6.73-month treatment duration.

Although it is not generally considered first-line treatment for KHE, sirolimus has become a more widely accepted treatment option. Data collected retrospectively by Wang et al[6] corresponded to 26 patients treated for KHE with sirolimus, of which 25 patients also suffered life-threatening KMP. All patients received some form of treatment (e.g., vincristine, corticosteroids, propranolol) prior to the initiation of sirolimus. At the time that KHE was identified, sirolimus was started at a dose of 0.8 mg/m^2 twice a day. The mean age of the patients was 2.9 ± 1.8 months.

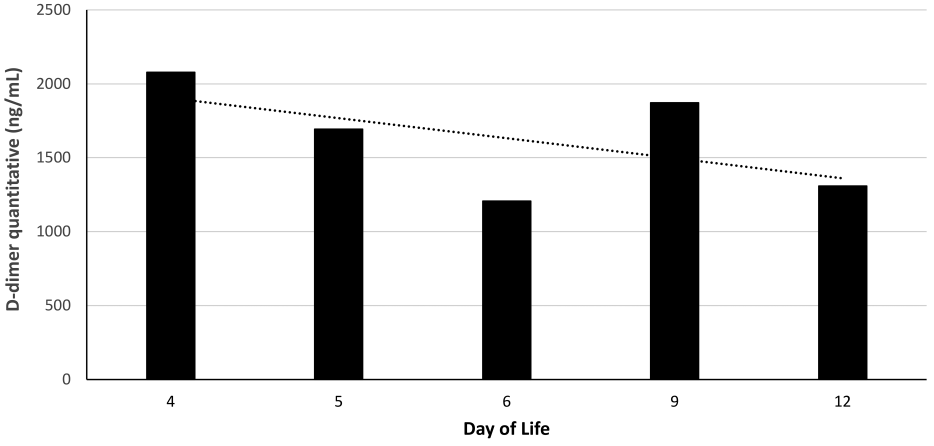
Twenty patients completed treatment in 28.3 ± 12.5 months, with platelet recovery at 3.4 ± 2.7 weeks. In general, it is difficult to determine treatment duration because KHE can persist beyond treatment. We intended to treat the patient describe in this case with sirolimus and concurrent monitoring every 2 months for a period of a year. Because the infant was stable and had clinically improved, the hematology/oncology team made the decision to discontinue sirolimus dosing early.

Ji et al[3] conducted a multicenter, retrospective cohort study in patients with a mean age of 10.6 months (range, 0.5 to 98.0 months) in which 71% of patients also had KMP. Sirolimus was started at 0.8 mg/m^2 twice a day. The authors concluded that sirolimus resulted in a 96% reduction in symptoms, 98% improvement in complications, and 71% of patients showing a ≥75% reduction in tumor size after 12 months. Although all KMP patients had improvement in hematologic laboratory parameters with sirolimus, 6 patients with KMP had to be placed on combination therapy with prednisolone because of progressive tumor enlargement. Two additional studies[7,8] using sirolimus monotherapy reported a reduction of the lesion size and hematologic aspects of KHE with and without KMP.

Pharmacokinetic and dynamic issues arise with sirolimus administration in a premature neonate that make it difficult to appropriately manage therapy. Decreased kidney function and reduced CYP3A4 enzyme concentrations are major developmental considerations in premature neonates, which can affect sirolimus concentration.[9] In addition, the stock solution of 1 mg/mL sirolimus makes it difficult to accurately administer such a small dose. A dose of 0.01 mg (0.01 mL) is equivalent to about 1 drop, and when that drop was administered, trough concentrations were grossly elevated. One hypothesis for the elevated sirolimus concentrations postulated they were the result of a potential administration error of more than a drop, with administration of the medication sitting in the headspace of the syringe. This could have happened if the nurse attempted to administer the full liquid by multiple attempts at pushing the syringe plunger.

Because it was difficult to administer an accurate dose with the stock solution, it was decided to compound a microdilution that would be administered immediately after preparation because of the lack of stability data. Medium-chain triglyceride (MCT) oil was selected over water as the suspending agent because of the lipophilic nature of sirolimus. A total of 0.1 mg (0.1 mL) of sirolimus was mixed with 9.9 mL of MCT oil to obtain a final concentration of 0.01 mg/mL. The dose was then drawn up and delivered to the bedside. Our pharmacy team has collaborated with the University of New Mexico College of Pharmacy to determine the AUC of our solution using high-performance liquid chromatography. Microdiluted sirolimus in MCT oil was stable after 24 hours when analyzed through high-

Figure 2. D-dimer, quantitative.



performance liquid chromatography. Three different 10 mcg/mL samples mixed using the hospital formulation were compared with 3 standard solutions, and all 3 samples demonstrated stability for at least 24 hours after microdiluting. The methods and extended stability data will be presented in a separate article.

Even though data exist using sirolimus in neonates and infants, to our knowledge, there are no data specific to how to use sirolimus in a premature neonate. With a confirmed biopsy diagnosis, treatment was started at an earlier age than has been seen in previous studies. Dosing was started at the lowest possible measurable dose, recommended by a KHE expert consult from Boston Children's, which was different that the starting dose taken from the existing literature. It is important to note that our patient differed from others in that KHE was identified earlier in a premature neonate, which made it difficult to extrapolate a dose based on previous studies. Even the lowest measure dose of the commercial product proved to be too much, as was evident based on the elevated serum sirolimus concentrations.

Conclusions

There are limited data relating to the optimal treatment of KHE with KMP; therefore, treatment decisions can be difficult. Based on expert opinion from a KHE expert from Boston Children's, sirolimus at the lowest measurable starting dose of 0.01 mg (0.02 mg/kg) was chosen over various other treatments, such as vincristine or corticosteroids. For a difficult situation, given a narrow therapeutic index and lack of dosing information in premature neonates, it was especially crucial to ensure consistent and accurate dosing. While the patient was an inpatient, we monitored sirolimus concentrations every few days, and then we monitored every 2 months while the patient was an outpatient, which provided safe care to our patient, as seen by the limited adverse effects she experienced. It is important to note that we potentially saw fewer adverse effects because we accepted lower limits of sirolimus concentrations. Our microdilution provides a solution with which to measure an accurate treatment dose for symptom and lesion management, providing that meticulous sirolimus concentration monitoring is available. It is our hope that this article will provide data to support premature neonates born with KHE with or without KMP.

Article Information

Affiliations. Department of Inpatient Pharmacy (JK, MB, SS), University of New Mexico Hospitals, Albuquerque, NM; University of New Mexico College of Pharmacy (CW, LF), University of New Mexico, Albuquerque, NM

Correspondence. Jason Koury, PharmD, BSN; jaskoury@salud.unm.edu

Disclosures. The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria. The authors had full access to all patient information in this report and take responsibility for the integrity and accuracy of the report.

Ethical Approval and Informed Consent. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation. The institutional review board of our institution determined that the study was "not human research"; hence, it was exempt from review. Informed consent was not required.

Submitted. April 3, 2020

Accepted. June 22, 2020

References

1. Drolet BA, Trenor CC III, Brandão LR, et al. Consensus-derived practice standards plan for complicated kaposiform hemangioendothelioma. *J Pediatr.* 2013;163(1):285–291.
2. Croteau SE, Liang MG, Kozakewich HP, et al. Kaposiform hemangioendothelioma: atypical features and risks of Kasabach-Merritt phenomenon in 107 referrals. *J Pediatr.* 2013;162(1):142–147.
3. Ji Y, Chen S, Xiang B, et al. Sirolimus for the treatment of progressive kaposiform hemangioendothelioma: a multicenter retrospective study. *Int J Cancer.* 2017;141(4):848–855.
4. Liu XH, Li JY, Qu XH, et al. Treatment of kaposiform hemangioendothelioma and tufted angioma. *Int J Cancer.* 2016;139(7):1658–1666.
5. Adams DM, Trenor CC III, Hammill AM, et al. Efficacy and safety of sirolimus in the treatment of complicated vascular anomalies. *Pediatrics.* 2016;137(2):e20153257. doi:10.1542/peds.2015-3257.
6. Wang Z, Yao W, Sun H, et al. Sirolimus therapy for kaposiform hemangioendothelioma with long-term follow-up. *J Dermatol.* 2019;46(11):956–961.
7. Nadal M, Giraudeau B, Tavernier E, et al. Efficacy and safety of mammalian target of rapamycin inhibitors in vascular anomalies: a systematic review. *Acta Derm Venereol.* 2016;96(4):448–452.
8. Tasani M, Ancliff P, Glover M. Sirolimus therapy for children with problematic kaposiform haemangioendothelioma and tufted angioma. *Br J Dermatol.* 2017;177(6):e344–e346.
9. Kearns GL, Abdel-Rahman SM, Alander SW, et al. Developmental pharmacology—drug disposition, action, and therapy in infants and children. *N Engl J Med.* 2003;349(12):1157–1167.