Treatment practices and response in Kaposiform hemangioendothelioma: a multi-center cohort study

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Abstract

Background and Objectives: Kaposiform hemangioendothelioma (KHE) and tufted angioma (TA) are rare vascular tumors in children historically associated with significant morbidity and mortality. This study was conducted to determine first line therapy in the absence of available prospective clinical trials. Methods: Patients from 17 institutions diagnosed with KHE/TA between 2005-2020 with $>$ 6 months follow-up were included. Response rates to sirolimus and vincristine were compared at 3 and 6 months. Durability of response and response to other treatment modalities were also evaluated. Results: Of 159 unique KHE/TA subjects, Kasabach-Merritt phenomenon (KMP) was present in 64 (40.3%) and only 2 patients were deceased (1.3%). Over 60% (n=96) demonstrated treatment response at 3 months and >70% (n=114) by 6 months (no significant difference across groups). The vincristine group had higher radiologic response at 3 months compared to sirolimus (72.7% vs 20%, p=0.03) but there was no differences between these groups at 6 months. There were no differences in rates of recurrent or progressive disease between vincristine and sirolimus. Conclusions: In this large, multicenter cohort of 159 patients with KHE/TA, rates of KMP were consistent with historical literature but the mortality rate (1.3%) was much lower. Overall treatment response rates

were high (>70%) and there were no significant difference in treatment response or durability of disease comparing sirolimus to vincristine. Our results support individualized treatment decision plans depending on clinical scenario and patient/physician preferences. Response criteria and response rates reported here will be useful for guiding future treatment protocols for vascular tumors.

Introduction

Kaposiform hemangioendothelioma (KHE) and tufted angioma (TA) are rare vascular tumors that primarily present in young children and are considered locally aggressive or borderline malignant tumors.[1,2] TA and KHE may be a continuum of one disease as they both share histologic features and key to their pathophysiology is disrupted vasculogenesis and abnormal endothelial cell proliferation.[3,4] KHE/TA are uniquely associated with Kasabach Merritt Phenomenon (KMP), which manifests as thrombocytopenia and a consumptive coagulopathy (hypofibrinogenemia and elevated d-Dimer), with variable bleeding[5–7]. KMP is considered a risk factor for severe KHE/TA and has a historical mortality rate of 20-30%[5–8]. Apart from the known risks with KMP, a validated risk stratification in KHE/TA has not been established[3,9].

KHE and TA tumors rarely completely resolve, and full surgical resection is typically not possible given the infiltrative nature of this tumor. More than half of patients experience recurrence of symptoms or KMP after cessation of therapy.[10–14] Front-line medical therapy for KHE/TA is not standardized, but steroids, vincristine, and sirolimus are the most commonly used systemic medications.[4,15] The optimal therapy (ies), schedule, dosing, and duration of treatment are unknown[10,11,16–27]. Experts have proposed either vincristine and steroids or sirolimus as standard treatment[4,28]. A multi-center, prospective, randomized trial (NCT02110069) was recently undertaken to determine optimal front-line therapy (sirolimus vs vincristine) for high risk KHE/TA but closed early due to poor enrollment. Future prospective studies will likely be limited by disease rarity as well as the availability of sirolimus as a highly efficacious oral agent. It is unlikely that prospective data will be generated to establish a standard optimal treatment and to determine durability of response to treatment.

This study was designed and conducted to address these existing gaps in knowledge about treatment for KHE/TA. The primary objective of this multicenter retrospective cohort study was to compare 3-month and 6-month response rates to sirolimus versus vincristine. Secondary objectives included comparison of other treatment regimens and assessment of durability of treatment response.

Methods

Cohort

Members of the American Society of Pediatric Hematology/Oncology (ASPHO) Vascular Anomalies Special Interest Group (VA SIG) were invited to participate by submitting clinical data of patients diagnosed with KHE/TA between January 2005 and January 2020 with at least 6 months of follow-up. Subjects who died within 6 months of diagnosis and met all other eligibility criteria were included. This study was IRB approved at each local institution, and patient clinical and treatment information was collected securely in a REDCap database.[29] Data from each center, excluding protected health information, were adjudicated by Drs. Borst, Jeng, and Adams and sent to the coordinating center for analysis.

Definitions

Clinical: Kasabach-Merritt phenomenon (KMP) was defined strictly as severe thrombocytopenia with a platelet count [?] 50,000/uL at diagnosis or prior to systemic medical therapy. Coagulopathy was defined less strictly and could include hypofibrinogenemia with a fibrinogen < 150mg/dL and/or D-dimer > 2 times the upper limit of normal at diagnosis or prior to systemic medical therapy.

Therapy: Treatment groups included: sirolimus (Siro), vincristine (VCR), Siro and VCR together (Siro+VCR), steroids only, and a minimal treatment group that received either beta-blocker, aspirin, or no medical therapy. Treatment groups were determined by the primary agent started within the first 30 days following treatment initiation. Patients in the Siro, VCR, or Siro+VCR categories were allowed to have

also received steroids, but the primary drug therapy must have been initiated less than 30 days after steroids. Patients in the Steroid treatment group did not receive additional therapies. Patients in the Siro+VCR group received both drugs up-front within the 30 days. Patients included in the surgery/interventional radiology (IR) group had either surgical resection or IR embolization as their initial primary mode of treatment, even if they received medical therapy later in their course.

Response: Time to response was determined by number of days since first systemic therapy was initiated. For patients who received no systemic medical therapy, time to response was determined as the time from diagnosis or surgical intervention. Responses were categorized as subjective clinical response (ClinR), radiologic response (RadR), and hematologic response (HemR; in patients with KMP only). ClinR was defined as resolution of symptoms related to tumor, functional deficit, or decrease in size of tumor by visual inspection, even if not a complete response. RadR was defined as any measurable decrease in tumor size on radiographic imaging. If tumor measurements were available, the RECIST criteria for partial response could be used[30]. HemR in patients with KMP was defined as a platelet count > 100,000/μl x 2 consecutive lab measurements without transfusion. Durability of response was determined as time from first response to recurrent disease. Time from diagnosis and treatment initiation to persistent disease or progressive disease were also measured. Progressive disease was defined as any clinically significant increase in volume of tumor by history, exam, or radiologic imaging, worsening or persistence of KMP, or clinically significant worsening of pain or functional status as determined by treatment team. Investigators reported their criteria in determining recurrent, persistent, or progressive disease when applicable.

Statistical analysis

Data were analyzed with the support of two biostatisticians (ZZ and YL) at the Children's Hospital of Philadelphia. Demographic and clinical characteristics were summarized for the overall cohort and by presence or absence of KMP using descriptive statistics. Outcome variables including response rates (e.g., objective hematologic response at 3 months), durability of response (e.g., time to persistent disease from objective hematologic response), and adverse events were summarized overall and by treatment groups. For group (either KMP or treatment groups) comparisons, Wilcoxon rank sum test was used for continuous variables and Fisher's exact test was used for categorical variables. All analyses were performed in R 3.6.3 and a two-sided p-value < 0.05 was considered statistically significant.

Results

Demographic and Clinical Characteristics of Patients with KHE and TA

Investigators from 17 institutions submitted data on 179 patients and 159 met full eligibility criteria after central review (Table 1). Of the 159 patients, 138 (86.8%) carried a diagnosis of KHE, 18 (11.3%) TA, and 3 (1.9%) diagnosed with a combined KHE/TA spectrum. Gender, race, and ethnicity were equivalent across groups. Sixty-four patients (40.3%) had KMP at presentation. Patients with KMP were diagnosed (49.5 versus 293 days, p<0.001) and started treatment (48 versus 300 days, p<0.001) at a younger age than those without KMP. Biopsy for pathologic diagnosis was more common in those without KMP compared to those with KMP (91.6% versus 71.9%, p=0.002). Non-truncal lesions were the most common location in all groups, but more common in those without KMP (65.3% versus 50%, p=0.029). Tumor size was larger in the individuals with KMP, and tumors associated with KMP were more likely to involve more than one anatomic body area. Only 2 patients (1.3%) were described to have multifocal tumors. Some patients without KMP were determined to have coagulopathy (fibrinogen < 150mg/dL and/or D-dimer > 2 times the upper limit of normal) at diagnosis, but this was more common in the those with KMP (79.7% versus 14.7%, p<0.001). Number of hospitalizations, hospital length of stay, and ICU length of stay were all higher for individual with KMP (all p<0.001). Only 2 patients (1.3%) in the cohort were deceased and both had KMP, large tumors ([?] 5cm in size), and had tumor extension across more than one body region. As expected, hematologic parameters were more abnormal in patients with KMP, with lower hemoglobin nadir, lower platelet count nadir, lower fibrinogen nadir, and higher maximum prothrombin time and partial thromboplastin time (all p<0.001, Supplemental Table 1).

Treatment Regimens

The majority of patients (n=136, 85.5%) received systemic medical therapy (Table 2) and systemic therapy was more common in patients with KMP versus those without KMP (95.3% vs. 70%, p=0.05). Siro was the most common treatment (n=51, 32.1%), followed by steroids (n=32, 20.1%), beta-blocker or minimal/none (n=27, 17%), VCR (n=25, 15.7%), surgical/interventional radiology (IR) (n=17, 10.7%), and Siro+VCR (n=7, 4.4%). Time from initial symptoms to treatment initiation (16 vs 169 days, p<0.001) and time from diagnosis to treatment initiation (3 vs. 21 days, p <0.001) were both shorter for patients with KMP compared to those without KMP. Patients with KMP received more blood product transfusions (78.1% vs 6.3%, p<0.001) and more opioid medication use (29.7% vs. 14.7%, p=0.028). Attempts at surgical procedures or IR embolization were equivalent across groups (p=0.2).

Rationale for Therapy

The most common indications for initiating therapy included extent of disease (n=87, 54.7%), coagulopathy (n=65, 40.9%), pain (n=61, 38.4%), and thrombocytopenia (n=59, 37.1%). Reported range for thrombocytopenia for patients starting medical therapy for this indication was 3,000-107,000/uL. Patients with KMP were more likely to have initiated therapy for coagulopathy, anemia, thrombocytopenia, cardiac dysfunction, and airway compression (Table 2). Pain and cosmesis were more likely to prompt therapy initiation for patients without KMP. Other reasons for treatment initiation included avoidance of scarring/contracture, rapid tumor growth, coagulopathy, functional impairment, hypertension (compression of renal vasculature), high output-cardiac failure, airway involvement, proximity to critical structures, and pleural and pericardial effusions.

Treatment Response

Of patients determined to be evaluable for response, 85.7% (96/112) demonstrated a treatment response at 3 months and 89.1% (114/128) by 6 months. The vincristine treatment group had higher RadR at 3 months compared to sirolimus (72.7% vs 20%, p=0.03), but equal at 6 months (76.9% vs 68%, p=0.7). There were no other significant differences in overall response, HemR, or ClinR between the sirolimus and vincristine groups at 3 or 6 months (Table 3). Similarly, there were no significant differences in overall response, RadR, HemR, or ClinR across all treatment groups (Supplemental Table 2) except RadR in the surgical resection group at 3 months only.

Based on previously published data showing improved outcomes in patients with KHE treated with combination of sirolimus and steroids versus sirolimus alone, we also compared these groups in our cohort (Table 4).[31] Small patient numbers precluded statistical comparisons, but 11 of 15 (73.3%) patients who received sirolimus plus steroid had response by 3 months compared to only 1 of 4 (25%) patients who received sirolimus. Treatment responses were not significantly different amongst those who received sirolimus and steroid in comparison to those who received vincristine and steroid.

Treatment Durability

Recurrent and Progressive Disease:

There were no differences in rates of recurrent or progressive disease at 3 and 6 months between the Siro and VCR treatment groups (Table 5). Time to recurrent or progressive disease from start of therapy or from initial treatment response were also equivalent between vincristine and sirolimus. Comparing all treatment groups (Supplemental Table 3), the rate of recurrent disease at 3 months was higher in patients treated with steroids alone (p=0.042), but across all treatment groups, there was no difference in rates of recurrent or progressive disease at 6 months. Although not statistically different from other groups, it was notable that of the 17 patients treated with surgery or IR embolization, 100% had a treatment response by 3 months, but five (29.4%) had recurrent disease within 6 months requiring initiation of systemic medical therapy.

Persistent Disease:

Given the chronic nature of KHE/TA, we also tried to define disease persistence in response to therapy (Supplemental Table 3). We found that rates of persistent disease at 3 months (28.6%, p=0.024) were higher in patients receiving a combination of Siro+VCR compared to those receiving steroids alone (and a significantly higher proportion of patients in the Siro+VCR group required continuation of therapy at 3 months for persistent disease (71.4%, p<0.001). However, by 6 months, rates of persistent disease were equivalent across groups.

When looking at just the VCR and Siro groups (Table 5), a higher proportion of patients in the Siro group were reported to require continuation of therapy at 3 months for persistent disease (27.5% vs. 0%, p=0.003). However, of the VCR group, 22/25 (88%) received adjunctive therapy including 9 (36%) who had Siro added to their regimen and time to initiation of Siro ranged from 29 days to 863 days. Rationale for adding Siro included severity of disease in 5 patients, VCR toxicity in 2 patients (hoarse cry, neutropenia), and loss of central venous access in 2 patients. In the sub-analysis of sirolimus or vincristine treatment with or without steroid use (Table 6), more patients had persistent disease in the two vincristine groups, but small numbers precluded statistical comparison. It was notable that in the VCR + steroid group, 9/19 (47.4%) patients had Siro added to their treatment regimen later.

Adverse Events

Adverse events evaluated in the cohort included multi-organ failure, serious infection, and significant bleeding (Supplemental Table 4). Rates of multi-organ failure and significant bleeding were low across all treatment groups, except combined Siro+VCR treatment group (p=0.002). Infection rates were increased in the vincristine only group compared to sirolimus (24% vs 11.8%, p=0.033). Other adverse events included ptosis secondary to vincristine in 2 patients (one primarily treated with steroids, VCR added later), major airway compromise in 1 patient requiring intubation (Siro+VCR), necrotizing enterocolitis in 1 patient (primary treatment VCR), biliary tract obstruction due to tumor in 1 patient (surgical resection), and severe lymphedema in one Siro patient.

Discussion

KHE and TA are aggressive vascular tumors that are associated with significant morbidity and are rarely cured. Until the discovery of efficacy of mTOR inhibition with sirolimus in KHE in mid-2000s, vincristine and steroids were the mainstay of medical therapy. The rare nature and widely heterogenous clinical presentation of KHE/TA have made comparison of treatment modalities difficult. This study compares treatment response and durability in the largest cohort of children with KHE/TA to date.

In this cohort, we found similar rates of KMP (40.3%) but a much lower mortality rate (1.3%) compared to historical cohorts. This may be attributed to the introduction of sirolimus for long-term tumor control.[4,12,32,33] Sirolimus was the most common treatment and overall treatment response rates were high (>70% overall by 6 months), and there were no differences in radiologic, hematologic, or clinical response between the VCR and Siro treatment groups at 6 months. Due to chronicity of KHE/TA we also felt it was important to try to evaluate durability of treatment response. We found no significant differences in the rates of progressive or recurrent disease at 3 and 6 months between the VCR and Siro treatment groups. While increased rates of reported persistent disease were noted in the Siro group compared to VCR, we think the lack of a standardized definition of persistent disease across investigators and the frequent addition of sirolimus to patients on VCR regimen precludes confirming this as a valid finding. KHE/TA can be considered a chronic tumor, requiring months to years of therapy with infrequent complete cures, and persistent disease needs to be defined more effectively in future studies.

A recent prospective trial in 73 patients with KHE with KMP showed that upfront sirolimus therapy in combination with steroids improves time to resolution of KMP, durability of platelet response, and overall tumor response at 12 months.[31] In this retrospective cohort, low patient numbers limited comparison of regiments with and without steroids. More patients reported persistent disease in the Siro + steroid group compared to the VCR + steroid treatment group, however again noting that nearly 50% of the patients in the VCR + steroid group added sirolimus to their regimen later.

Different side effect profiles often influence the choice of medical agent. Sirolimus is associated with concerns for delayed wound healing, mucositis, neutropenia, and lymphopenia. Vincristine is associated with constipation, jaw pain, and peripheral neuropathy. Sirolimus may be an agent of choice or an agent of transition for some due to its increased ease of administration, lack of need for central venous access, and demonstrated efficacy. Although there are concerns about immunosuppression secondary to sirolimus, we found a lower rate of infectious complications in the Siro group compared to patients receiving vincristine. However, high adverse event rates in the groups receiving vincristine (VCR and VCR+Siro) could be confounded if these patients had more severe disease leading their physicians to elect treatment with vincristine.

With equivalent treatment response and durability at 6 months, the decision to treat with vincristine or sirolimus, with or without steroids, should account for additional clinical factors, including route of administration, side effects, perceived severity of KMP or urgency to treat, and patient/family preference. While vincristine may bring about more rapid radiologic response and perhaps should be considered for high urgency situations, this is not associated with improved longer-term outcomes in these indolent tumors. Although full surgical resection of KHE is the only curative option, we found that many patients who underwent surgery ultimately ended up needing systemic medical therapy. Fortunately, the high overall treatment response rates and low mortality highlighted in this cohort demonstrate that individual patient factors and family and physician preferences can be encouraged in the management of this rare vascular tumor.

This study represents the largest cohort to date investigating treatment practices and short-term response rates in patients with KHE/TA. Results are limited by the retrospective nature of this study, the clinical heterogeneity of KHE/TA, and variable investigator experience and clinical perspective. Although KHE and TA have overlapping clinical and histopathologic features, their presentation and the urgency for medical therapy can be quite distinct, which may affect assessment of treatment choices and duration in this cohort. Many patients with mild TA are observed only or treated with monotherapy initially, whereas patients who present more acutely with large KHE causing clinical compromise or KMP, multi-modal therapy may be the initial approach. Due to this significant disease heterogeneity, determining baseline response parameters for this population will allow for historical comparison in future treatment protocols. These results augment the ability to make educated decisions for individualized medical management for patients with KHE/TA with and without KMP, particularly when complete surgical excision is not possible or successful. Given the rarity of these tumors, multi-institutional studies are needed to further knowledge of the natural history of KHE/TA and optimal treatment modalities.

Conclusions

In patients diagnosed with KHE/TA, about 40% will exhibit KMP, confirming established rates. Currently, a lower mortality rate (1.3%) exists likely owing to earlier recognition and treatment implementation with improved medical therapy options. Overall treatment response rates are high at $> 70\%$ by 6 months. There was no significant difference in treatment response or durability of disease response comparing sirolimus to vincristine. Our results support individualized treatment decision plans based on disease severity, side effect profile, patient clinical situation, and physician experience. Response criteria and response rates reported here will be useful for guiding future treatment protocols for vascular tumors.

Conflict of Interest Statement:

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Wassef M, Blei F, Adams D, et al. Vascular Anomalies Classification: Recommendations From the International Society for the Study of Vascular Anomalies. *Pediatrics* . 2015;136(1):e203-214. doi:10.1542/peds.2014-3673

2. ISSVA Classification of Vascular Anomalies ©2018 International Society for the Study of Vascular Anomalies Available at "issva.org/classification" Accessed May 2023. Accessed May 5, 2023. https://www.issva.org/classification

3. Putra J, Gupta A. Kaposiform haemangioendothelioma: a review with emphasis on histological differential diagnosis. *Pathology (Phila)* . 2017;49(4):356-362. doi:10.1016/j.pathol.2017.03.001

4. Ji Y, Chen S, Yang K, Xia C, Li L. Kaposiform hemangioendothelioma: current knowledge and future perspectives.*Orphanet J Rare Dis* . 2020;15(1):39. doi:10.1186/s13023-020-1320-1

5. Kasabach HH, Merritt KK. Capillary Hemangioma With Extensive Purpura: Report of a Case. *Am J Dis Child* . 1940;59(5):1063-1070. doi:10.1001/archpedi.1940.01990160135009

6. Enjolras O, Wassef M, Mazoyer E, et al. Infants with Kasabach-Merritt syndrome do not have "true" hemangiomas. *J Pediatr* . 1997;130(4):631-640. doi:10.1016/s0022-3476(97)70249-x

7. Sarkar M, Mulliken JB, Kozakewich HP, Robertson RL, Burrows PE. Thrombocytopenic coagulopathy (Kasabach-Merritt phenomenon) is associated with Kaposiform hemangioendothelioma and not with common infantile hemangioma. *Plast Reconstr Surg* . 1997;100(6):1377-1386. doi:10.1097/00006534-199711000-00001

8. Gruman A, Liang MG, Mulliken JB, et al. Kaposiform hemangioendothelioma without Kasabach-Merritt phenomenon. *J Am Acad Dermatol* . 2005;52(4):616-622. doi:10.1016/j.jaad.2004.10.880

9. Croteau SE, Gupta D. The clinical spectrum of kaposiform hemangioendothelioma and tufted angioma. *Semin Cutan Med Surg* . 2016;35(3):147-152. doi:10.12788/j.sder.2016.048

10. Adams DM, Trenor CC, Hammill AM, et al. Efficacy and Safety of Sirolimus in the Treatment of Complicated Vascular Anomalies.*PEDIATRICS* . 2016;137(2):e20153257-e20153257. doi:10.1542/peds.2015-3257

11. Drolet BA, Trenor CC, Brandão LR, et al. Consensus-Derived Practice Standards Plan for Complicated Kaposiform Hemangioendothelioma.*J Pediatr* . 2013;163(1):285-291. doi:10.1016/j.jpeds.2013.03.080

12. 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. doi:10.1016/j.jpeds.2012.06.044

13. Sakata N, Suenobu S ichi, Okano M, Ueda S, Kimura M, Takemura T. Impact of sirolimus treatment for refractory kaposiform hemangioendothelioma with exacerbation of the disease 10 years after initial diagnosis. *Rare Tumors* . 2018;10. doi:10.1177/2036361318776185

14. Schaefer BA, Wang D, Merrow AC, Dickie BH, Adams DM. Long-term outcome for kaposiform hemangioendothelioma: A report of two cases.*Pediatr Blood Cancer* . 2017;64(2):284-286. doi:10.1002/pbc.26224

15. Tower R l. Kaposiform haemangioendothelioma: new insights and old problems. *Br J Dermatol* . 2018;179(2):253-254. doi:10.1111/bjd.16834

16. Adams DM, Wentzel MS. The role of the hematologist/oncologist in the care of patients with vascular anomalies. *Pediatr Clin North Am* . 2008;55(2):339-355, viii. doi:10.1016/j.pcl.2008.01.007

17. Ricci KW. Advances in the Medical Management of Vascular Anomalies. *Semin Interv Radiol* . 2017;34(3):239-249. doi:10.1055/s-0037-1604297

18. Adams DM, Ricci KW. Vascular Anomalies: Diagnosis of Complicated Anomalies and New Medical Treatment Options. *Hematol Oncol Clin North Am* . 2019;33(3):455-470. doi:10.1016/j.hoc.2019.01.011

19. Liu XH, Li JY, Qu XH, et al. Treatment of kaposiform hemangioendothelioma and tufted angioma. *Int J Cancer* . 2016;139(7):1658-1666. doi:10.1002/ijc.30216

20. Haisley-Royster C, Enjolras O, Frieden IJ, et al. Kasabach-merritt phenomenon: a retrospective study of treatment with vincristine. *J Pediatr Hematol Oncol* . 2002;24(6):459-462. doi:10.1097/00043426-200208000-00010

21. Barlow CF, Priebe CJ, Mulliken JB, et al. Spastic diplegia as a complication of interferon Alfa-2a treatment of hemangiomas of infancy. *J Pediatr* . 1998;132(3 Pt 1):527-530. doi:10.1016/s0022-3476(98)70034-4

22. Morad AB, McClain KL, Ogden AK. The role of tranexamic acid in the treatment of giant hemangiomas in newborns. *Am J Pediatr Hematol Oncol* . 1993;15(4):383-385.

23. Hauer J, Graubner U, Konstantopoulos N, Schmidt S, Pfluger T, Schmid I. Effective treatment of kaposiform hemangioendotheliomas associated with Kasabach-Merritt phenomenon using four-drug regimen.*Pediatr Blood Cancer* . 2007;49(6):852-854. doi:10.1002/pbc.20750

24. Blei F, Karp N, Rofsky N, Rosen R, Greco MA. Successful multimodal therapy for kaposiform hemangioendothelioma complicated by Kasabach-Merritt phenomenon: case report and review of the literature.*Pediatr Hematol Oncol* . 1998;15(4):295-305. doi:10.3109/08880019809014013

25. Blatt J, Stavas J, Moats-Staats B, Woosley J, Morrell DS. Treatment of childhood kaposiform hemangioendothelioma with sirolimus.*Pediatr Blood Cancer* . 2010;55(7):1396-1398. doi:10.1002/pbc.22766

26. Hammill AM, Wentzel M, Gupta A, et al. Sirolimus for the treatment of complicated vascular anomalies in children. *Pediatr Blood Cancer* . 2011;57(6):1018-1024. doi:10.1002/pbc.23124

27. Peng S, Yang K, Xu Z, Chen S, Ji Y. Vincristine and sirolimus in the treatment of kaposiform haemangioendothelioma. *J Paediatr Child Health* . 2019;55(9):1119-1124. doi:10.1111/jpc.14370

28. 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. doi:10.1002/ijc.30775

29. Harris PA, Taylor R, Minor BL, et al. The REDCap consortium: Building an international community of software platform partners.*J Biomed Inform* . 2019;95:103208. doi:10.1016/j.jbi.2019.103208

30. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). *Eur J Cancer* . 2009;45(2):228-247. doi:10.1016/j.ejca.2008.10.026

31. Ji Y, Chen S, Zhou J, et al. Sirolimus plus prednisolone vs sirolimus monotherapy for kaposiform hemangioendothelioma: a randomized clinical trial. *Blood* . 2022;139(11):1619-1630. doi:10.1182/blood.2021014027

32. Ji Y, Yang K, Peng S, et al. Kaposiform haemangioendothelioma: clinical features, complications and risk factors for Kasabach-Merritt phenomenon. *Br J Dermatol* . 2018;179(2):457-463. doi:10.1111/bjd.16601

33. Rodriguez V, Lee A, Witman PM, Anderson PA. Kasabach-merritt phenomenon: case series and retrospective review of the mayo clinic experience. *J Pediatr Hematol Oncol* . 2009;31(7):522-526. doi:10.1097/MPH.0b013e3181a71830

TABLE 1 Demographic and Clinical Characteristics of Patients with KHE/TA

	Total (n=159)	Patients with KMP (n=64)	Patients without KMP (n=95)	p-value
Age at diagnosis (days), median [IQR]	154.0 [32.0, 510.5]	49.5 [10.8, 150.8]	293.0 [96.0, 794.0]	<0.001

	Total (n=159)	Patients with KMP (n=64)	Patients without KMP (n=95)	p-value
Age at treatment initiation (days), median [IQR]	159.5 [34.5, 539.8]	48.0 [18.0, 156.0]	300.00[125.0, 1016.0]	<0.001
Female Sex, n (%)	61 (38.4%)	22 (34.4%)	39 (41.1%)	0.4
Diagnosis confirmed by biopsy, n (%)	133 (83.7%)	46 (71.9%)	87 (91.6%)	0.002
Tumor Location, n (%) Truncal Non-truncal Other	46 (28.9%) 94 (59.1%) 19 (12.0%)	26 (40.6%) 32 (50.0%) 6 (9.4%)	20 (21.1%) 62 (65.3%) 13 (13.7%)	0.029
Tumor Size, n (%) < 5cm [?] 5cm Unmeasured/unknown	50 (31.5%) 95 (59.8%) 14 (8.8%)	7 (10.9%) 53 (82.8%) 4 (6.3%)	43 (45.3%) 42 (44.2%) 10 (10.5%)	<0.001
Tumor Extent, n (%) Localized/well-circumscribed or superficial (<3cm) Localized but not well-circumscribed, infiltrative (>3cm) Extensive across 1 body area Extensive, involving more than 1 body area Multifocal Other	21 (13.2%) 66 (41.5%) 40 (25.2%) 28 (17.6%) 2 (1.3%) 2 (1.3%)	0 (0%) 23 (35.9%) 19 (29.7%) 20 (31.3%) 0 (0%) 2 (3.1%)	21 (22.1%) 43 (45.3%) 21 (22.1%) 8 (8.4%) 2 (2.1%) 0 (0%)	<0.001
Presence of Coagulopathy at Diagnosis, n (%)	65 (40.9%)	51 (79.7%)	14 (14.7%)	<0.001
[?] 1 Hospitalizations, n (%)	45 (28.3%)	27 (42.2%)	18 (19.0%)	<0.001
Hospital Length of Stay (days), median [IQR]	2.0 [0.0, 11.0]	13.5 [5.0, 30.5]	0.0 [0.0, 2.0]	<0.001
Length of ICU Stay (days), median [IQR]	0.0 [0.0, 3.0]	4.0 [0.0, 16.0]	0.0 [0.0, 0.0]	<0.001
Deceased, n (%)	2 (1.3%)	2 (3.1%)	0 (0%)	0.2

KHE = Kaposiform hemangioendothelioma, TA = tufted angioma, KMP = Kasabach-Merritt phenomenon, IQR = interquartile range

*p-value denotes comparison between the "Patients with KMP" and "Patients without KMP" groups. Fisher's exact tested used for comparison of categorical variables and Wilcoxon rank sum test for continuous variables.

Other Tumor Location: included abdominal wall, tongue, mons pubis, back, mesenteric, iliacus muscle, cheek, and axilla, sacroiliac, intraspinal, mandible, and liver/bile duct

Other Tumor Extent: included a tumor that was > 16cm in size but confined to axilla and a 3cm tumor that was localized but intra-connected to multiple visceral organs (pancreas, liver, bile duct)

TABLE 2 Treatment Information

Systemic Therapy Given, n (%)
Primary Treatment Category, n (%) Sirolimus Vincristine Siro+VCR Steroids Minimal Surgery/IR
Time Between Initial Symptoms and Treatment Initiation (days), median [IQR]
Time Between Diagnosis and Treatment Initiation (days), median [IQR]
Received Blood Product Transfusions, n (%)
Received Opioid Medication, n (%)
Interventional Radiology Procedure Attempted, n (%)
Surgical Resection Attempted, n (%)
Reason for Treatment Initiation, n (%) Coagulopathy Thrombocytopenia Anemia Pain Recurrent cellulitis Visceral or bone

Siro = sirolimus, VCR = vincristine

*p-value denotes comparison between the "Patients with KMP" and "Patients without KMP" groups. Fisher's exact tested used for comparison of categorical variables and Wilcoxon rank sum test for continuous variables.

TABLE 3 Short and Long-Term Treatment Response with Sirolimus vs Vincristine

	Treatment Group	Treatment Group	Treatment Group	Treatment Group
Treatment Response	Total (N=76) n (%)	Sirolimus (N=51) n (%)	Vincristine (N=25) n (%)	p-value
Any response at 3 months	53/63 (84.1%)	30/39 (76.9%)	23/24 (95.8%)	0.074
HemR at 3 months	26/27 (96.3%)	11/12 (91.7%)	15/15 (100%)	0.4
RadR at 3 months	10/21 (47.6%)	2/10 (20%)	8/11 (72.7%)	0.030
ClinR at 3 months	50/57 (87.7%)	28/34 (82.4%)	22/23 (95.7%)	0.2
Any response at 6 months	61/70 (87.1%)	38/46 (82.6%)	23/24 (95.8%)	0.2
HemR at 6 months	30/31 (96.8%)	15/16 (93.8%)	15/15 (100%)	>0.9
RadR at 6 months	27/38 (71.1%)	17/25 (68%)	10/13 (76.9%)	0.7
ClinR at 6 months	59/66 (89.4%)	36/42 (85.7%)	23/24 (95.8%)	0.4

*p-value denotes comparison between the "Sirolimus" and "Vincristine" groups, Fisher's exact test

TABLE 4 Comparison of Steroid vs. No Steroid Groups – Treatment Response

	Treatment Group	Treatment Group	Treatment Group	Treatment Group	
Treatment Response	Sirolimus only (N=4) n (%)	Siro + Steroids (N=15) n (%)	VCR only (N=5) n (%)	VCR + Steroids (N=19) n (%)	p-value* (steroid groups only)
Any response at 3 months?	1/2 (50%)	11/12 (91.7%)	4/5 (80%)	17/17 (100%)	0.4
HemR at 3 months?	0	7/8 (87.5%)	3/3 (100%)	12/12 (100%)	0.4
RadR at 3 months?	0	2/3 (66.7%)	1/1 (100%)	5/7 (71.4%)	>0.9
ClinR at 3 months?	1/2 (50%)	9/10 (90%)	3/4 (75%)	16/16 (100%)	0.4
Any response at 6 months	2/3 (66.7%)	13/14 (92.9%)	4/5 (80%)	17/17 (100%)	0.5
HemR at 6 months?	0	10/11 (90.9%)	3/3 (100%)	12/12 (100%)	0.5
RadR at 6 months?	1/2 (50%)	6/7 (85.7%)	3/3 (100%)	6/8 (75%)	>0.9
ClinR at 6 months?	2/3 (66.7%)	12/13 (92.3%)	4/5 (80%)	16/16 (100%)	0.4

Siro = sirolimus, VCR = vincristine

*p-value denotes comparison of Siro + Steroids to VCR + steroids only, Fisher's exact test

HemR = hematologic response, in patients with KMP only (platelet count > 100,000/μl x 2 consecutive lab measurements without transfusion)

RadR = radiologic response (any measurable decrease in tumor size on radiographic imaging, if tumor measurements were available, the RECIST criteria for partial response was used)

ClinR = clinical response (resolution of symptoms, functional deficit, or decrease in size of tumor by visual inspection, even if not a complete response), radiologic response

TABLE 5 Durability of Response at 3 months and 6 months (Vincristine vs. Sirolimus)

	Treatment Group	Treatment Group
Durability of Response	Total (N=76)	Sirolimus (N=51)
Persistent disease 3 months from start of therapy, n (%)	2/76 (2.6%)	2/51 (3.9%)
Persistent disease 6 months from start of therapy, n (%)	5/76 (6.6%)	5/51 (9.8%)
Time to persistent disease from start of systemic therapy (days), median [IQR]	566 [365.9-1493]	414 [352-1148]
Persistent disease requiring change in treatment agent, n (%)	9/76 (11.8%)	7/51 (13.7%)
Persistent disease requiring continuation of current therapy, n (%)	14/76 (18.4%)	14/51 (27.5%)
Recurrent disease 3 months from start of therapy, n (%)	2/76 (2.6%)	1/51 (2%)
Recurrent disease 6 months from start of therapy, n (%)	1/76 (1.3%)	0/51 (0%)
Time to recurrent disease from start of systemic therapy (days), median [IQR]	825.5 [372.3-1273.5]	1024 [583-1318]
Recurrent disease requiring change in treatment agent, n (%)	8/76 (10.5%)	5/51 (9.8%)
Recurrent disease requiring re-initiation of prior therapy, n (%)	13/76 (17.1%)	11/51 (21.6%)
Progressive disease 3 months from start of therapy, n (%)	1/76 (1.3%)	1/51 (2%)
Progressive disease 6 months from start of therapy, n (%)	1/76 (1.3%)	1/51 (2%)
Time to progressive disease from start of systemic therapy (days), median [IQR]	730 [395-885]	730 [562.5-1215]
Progressive disease requiring change in treatment agent, n (%)	3/76 (3.9%)	2/51 (3.9%)

	Treatment Group	Treatment Group
Progressive disease requiring re-initiation of prior therapy, n (%)	3/76 (3.9%)	2/51 (3.9%)

*p-value denotes comparison between the Vincristine and Sirolimus groups, Fisher's exact test

TABLE 6 Comparison of Steroid vs. No Steroid Groups Durability of Response

	Treatment Group	Treatment Group
Durability of Response	Sirolimus only (N=4)	Siro + Steroids (N=15)
Persistent disease 3 months from start of therapy, n (%)	0 (0%)	2 (13.3%)
Persistent disease 6 months from start of therapy, n (%)	0 (0%)	3 (20%)
Time to persistent disease from start of therapy (days), median [IQR]	1631.5 [977.3, 2285.8)	257.5 [123.3, 551]
Persistent disease requiring change in treatment agent, n (%)	1 (25%)	3 (20%)
Persistent disease requiring continuation of current therapy, n (%)	2 (50%)	4 (26.7%)
Recurrent disease 3 months from start of therapy, n (%)	0 (0%)	1 (6.7%)
Recurrent disease 6 months from start of therapy, n (%)	0 (0%)	1 (6.7%)
Time to recurrent disease from start of therapy (days), median [IQR]	1915.5 [1509.8, 2321.3]	430.5 [268.5,637.8]
Recurrent disease requiring change in treatment agent, n (%)	1 (25%)	3 (20%)
Recurrent disease requiring re-initiation of prior therapy, n (%)	1 (25%)	4 (26.7%)
Progressive disease 3 months from start of therapy, n (%)	0 (0%)	1 (6.7%)
Progressive disease 6 months from start of therapy, n (%)	0 (0%)	1 (6.7%)
Time to progressive disease from start of therapy (days), median [IQR]	730 [730, 730]	1700 [1700, 1700]
Progressive disease requiring change in treatment agent, n (%)	0 (0%)	1 (6.7%)
Progressive disease requiring re-initiation of prior therapy, n (%)	1 (25%)	0 (0%)

Siro = sirolimus, VCR = vincristine

*p-value denotes comparison of Siro + Steroids to VCR + steroids only, Fisher's exact test