Treatment Outcomes of Kasabach-Merritt Syndrome: A Single Hospital Experience

Jassada Buaboonnam, M.D.*, Kleebsabai Sanpakit, M.D.*, Nattee Narkbunnam, M.D.*, Nassawee Vathana, M.D.*, Panjarat Sowithayasakul, M.D., Lillada Anuntarumporn, M.D.*, Rattanavalai Nitiyarom, M.D.***

**Department of Pediatrics, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, **Department of Pediatrics, Faculty of Medicine, Srinakharinwirot University, Bangkok 10110, Thailand.*

ABSTRACT

Objective: Although the outcomes of treatment of Kasabach-Merritt syndrome (KMS) have improved over time, some patients succumb to uncontrollable hemorrhage. Additionally, there is no consensus guideline for the management of KMS. Clinical research on KMS might benefit physicians who treat such patients.
Methods: A retrospective chart review of patients diagnosed as KMS by Siriraj Hospital from 2006 to 2016 was conducted.
Results: Ten patients were diagnosed with KMS. Four patients underwent surgical intervention and obtained pathological results; 3 of them had kaposiform hemangioendothelioma (KHE), while the fourth had infantile hemangioma (IH). The combination of propranolol and prednisolone, with or without vincristine, was the most common first-line regimen, with a complete response of 37.5%. A combination of vincristine, aspirin and ticlopidine (VAT) was prescribed as the second-line therapy for 5 patients, but there were no responses in this cohort. Another 2 patients attained hematological remission with embolization and prednisolone monotherapy. A further 2 patients with KHE who were refractory to other treatments responded well to sirolimus, while the tenth patient died of abdominal hemorrhage.
Conclusion: The combination of propranolol and prednisolone seems to be effective for KMS. Sirolimus may be considered for salvage therapy for those whose disease is recalcitrant to standard treatment, especially in cases of KMS secondary to KHE. However, research on a larger cohort should be conducted to substantiate the efficacy of such treatments.

Keywords: Kaposiform hemangioendothelioma; Kasabach-Merritt syndrome; prednisolone; propranolol; sirolimus
(Siriraj Med J 2017;69: 351-355)

INTRODUCTION

Kasabach-Merritt syndrome (KMS) is a fatal vascular tumor during childhood, complicated by consumptive coagulopathy and thrombocytopenia. The incidence of KMS seems to be very low, accounting for 0.3%-1% of all vascular tumors,[1,2] but the treatment outcomes are dismal, with a mortality rate ranging from 10%-37%.[2] KMS is associated with two types of vascular tumors: kaposiform hemangioendothelioma (KHE) and, to a much lesser extent, tufted angioma (TA).[3-5] Several treatment approaches have been used, such as prednisolone,[6] vincristine,[7] and propranolol,[8] but the optimal treatment remains unclear. Studies on the clinical manifestations, modalities of treatment, and clinical outcomes of such patients may assist physicians in taking care of KMS patients.

MATERIALS AND METHODS

The medical records of patients diagnosed with KMS at the Department of Pediatrics, Siriraj Hospital, Mahidol University, between 2006 and 2016 were retrospectively reviewed. All patients were aged between 0 and 15 years. The clinical criteria of KMS were:

(1) Clinical or radiographical manifestations of

Correspondence to: Rattanavalai Nitiyarom
E-mail: rattanavalai@hotmail.com
Received 4 August 2017 Revised 18 August 2017 Accepted 25 August 2017
doi:10.14456/smj.2017.66

cutaneous or visceral organs indicating a vascular tumor, regardless of size and site; AND

(2) Laboratory results indicating consumptive coagulopathy, i.e., thrombocytopenia and/or an abnormal coagulogram.

The patient data collected included sex, age at diagnosis, initial platelet count and coagulogram, and tumor site. The pathological reports of those who underwent a tissue biopsy or surgical intervention were recorded. Patients treated with propranolol-based therapy were classified by propranolol dosage into 2 groups: 1) standard dose (2 mg/kg/day); and 2) high dose (> 2 mg/kg/day) combined with other medications. The type of supportive care and blood products provided (such as platelet concentrate and cryoprecipitate given to patients to maintain hemostasis which were at the physician's discretion) were also recorded. A hematological response was defined as an increased platelet count of more than 100% of baseline that was sustained for over 4 weeks. A complete hematological remission was defined as a normalization of platelet number (>150,000/mm^3) for more than 4 weeks without a platelet transfusion. A radiographical response was defined as a decrease in the size of the tumor mass of over 50%, relative to the radiographical imaging baseline. The toxicities were classified using Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. This study was approved beforehand by the Ethics Committee, Siriraj Institutional Review Board (Si 452/2016).

RESULTS

Patient characteristics

Ten patients were diagnosed with KMS (5 females and 5 males). The median age at diagnosis was 2 months (range: 1 day to 3 years), and 3 patients were aged less than 1 month. Four patients underwent surgical intervention and obtained pathological results; 3 patients had KHE, and the fourth had infantile hemangioma (IH). Cutaneous involvement was observed in 9 patients, while visceral organ (retroperitoneum and spleen) involvement without cutaneous lesion was observed in 1 patient. At diagnosis, thrombocytopenia presented in all patients, and hypofibrinogenemia presented in 5 patients, but all patients had normal coagulogram (Table 1).

Treatment modalities and clinical outcomes

First-line treatment

Of the 10 patients, 8 were treated initially with propranolol-based therapy; the ninth and tenth patients were treated initially with vincristine monotherapy and prednisolone monotherapy, respectively. Four patients (40%) responded hematologically to their initial treatments and subsequently attained complete hematological remission. Three out of the 8 patients (37.5%) who were treated with the propranolol-based therapy, responded. One responder was treated with prednisolone monotherapy (Table 2).

TABLE 1. Clinical characteristics of KMS patients.

Clinical characteristics	N	Median (min, max)
Sex		
Female	5 (50%)	
Male	5 (50%)	
Age at diagnosis (months)		2 (1 day, 36 months)
Abnormality of hemostatic laboratories		
Thrombocytopenia	10 (100%)	10,000 (5,000/mm^3, 48,000/mm^3)
Hypofibrinogenemia	5 (50%)	75 (50 mg/dl, 148 mg/dl)
Co-morbidity		
Pre mature infant	3 (30%)	
Pathological diagnosis	4 (30%)	
Kaposiform hemangioendothelioma	3 (20%)	
Infantile hemangioma	1 (10%)	

TABLE 2. Clinical data of 10 KMS Patients.

Patient number	Age of onset	Pathological study	Site	Treatment (chronological order)	Outcomes	Time to hematological response (days)
1	3 mo	KHE	Left clavicle	1) H+P 2) VAT 3) Embolization	CHR Alive	25
2	1 mo	ND	Neck and chest	H+P	CHR Alive	56
3	36 mo	KHE	Retroperitoneum and spleen	1) V 2) Partial splenectomy 3) Si	CHR Alive	28
4	0 d	IH	Left thigh	H+P	CHR Alive	28
5	4 d	KHE	Left arm and neck	1) H+P 2) VAT 3) Si	CHR Alive	15
6	0 d	ND	Abdomen	1) S+P 2) VAT	Dead	N/A
7	5 mo	ND	Right leg	1) H+P 2) VAT	Lost to follow-up	N/A
8	8 mo	ND	Chest wall	1) H+P 2) VAT	Lost to follow-up	N/A
9	6 mo	ND	Chest wall	S+P+ V	CHR Alive	45
10	1 mo	ND	Left thigh	P	CHR Alive	38

Abbreviations: CHR, complete hematological response; d, day; H, high dose propranolol; IH, infantile hemangioma; KHE, kaposiform hemangioendothelioma; mo, month; ND, biopsy not done; N/A, not applicable; P, prednisolone; S, standard dose propranolol; Si,sirolimus; V, vincristine; VAT, vincristine + aspirin +ticlopidine

Second-line treatment

Six patients who failed their first-line treatment were given second-line treatment. Five patients were provided with a combination of vincristine, aspirin and ticlopidine (VAT), but the sixth patient underwent a partial splenectomy. Of the 5 patients treated with VAT, 2 patients were lost to follow-up; 1 patient died of severe intra-abdominal hemorrhage 3 days after receiving treatment; and 2 patients did not respond to treatment and were subsequently treated with other modalities (Table 2).

Third-line treatment

Three patients were administered third-line therapy; 2 were treated with sirolimus, and the other underwent radiological embolization. All three achieved complete hematological remission (Table 2).

The hematological response could be evaluated in 7 patients (Table 2). The median times to the hematological responses for the propranolol-based therapy and sirolimus were 45 and 21.5 days, respectively. A radiographical response could be evaluated in 1 patient (patient no.3), and the time to that response was 180 days (Fig 1). Six patients were treated with high-dose propranolol-

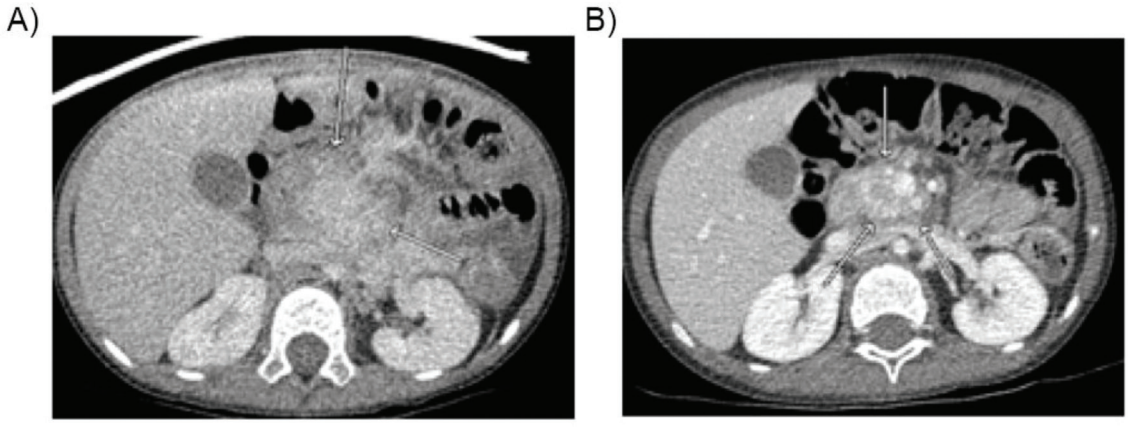

Fig 1. Radiographical change of kaposiform hemangioendothelioma after being treated with sirolimus (arrows indicate boundary of tumor). A) before treatment with sirolimus B) 180 days after treatment with sirolimus.

containing therapy, and two patients (33.3%) responded. Two other patients were treated with standard-dose, propranolol-containing therapy, and only one (50%) responded. One patient developed vincristine-induced peripheral neuropathy grade 2, and one patient developed transaminitis grade 2 due to sirolimus, which gradually improved without dose adjustment. No patients in this study demonstrated side effects from propranolol.

DISCUSSION

Albeit rare, KMS can cause severe visceral hemorrhage leading to death in a few patients. KHE is commonly associated with KMS, and it is characterized by a lobulated, spindle-shaped endothelium with microthrombi. TA, a rare vascular tumor marked by small, tufted vessels with aggregations of dilated capillaries, is also associated with KMS.[7] In our study, 3 patients had KHE associated with KMS, but none had TA-associated KMS.

Prednisolone is used as the first-line therapy for KMS,[9] and the dosage varies from 3-5 mg/kg/day.[9,10] The major disadvantages of prednisolone include recrudescence after the discontinuation of treatment, and adverse effects such as growth retardation.[11] The use of prednisolone monotherapy in KMS has gradually declined in our institute since recent studies demonstrated the efficacy of propranolol in infantile hemangioma (IH) and KMS.[12] Several antineoplastic agents, such as vincristine and cyclophosphamide, exert therapeutic efficacy in the treatment of vascular tumors.[13,14] Vincristine is usually prescribed for KMS therapy because of its safety profile, efficacy and cost effectiveness. Patients with KMS who are treated with a combination of vincristine and the anti-platelet agents, aspirin and ticlopidine, had a good response, particularly in terms of normalization of their platelet numbers. The rationale for the use of anti-platelet agents is based on the mitigating role of disseminated intravascular coagulopathy (DIC), thereby inhibiting the platelet-endothelium interaction.[15] All 11 patients in a previous study achieved a hematological response.[15] However, patients in this cohort did not attain normalization of their platelet numbers after treatment with the VAT regimen.

Propranolol has been widedly used as a frontline treatment for IH with dramatic responses.[12,16] Mechanistic studies have revealed the role of the interference of endothelium proliferation and angiogenesis, the restriction of vascular tone, and the induction of apoptosis. The decrease in the release of nitric oxide from the endothelium resulting in vasocontriction is an early effect. By comparison, the inhibition of the growth factors and cytokines involved in vascular proliferation, and the induction of apoptosis of the proliferating endothelium, are intermediate and late effects, respectively.[17] However, the response rate for the treatment of KHE, TA and KMS with propranolol was not as good as that of IH, at 36%.[8] Our study also demonstrated similar results, i.e., 37.5% of those treated with the propranolol-based regimen responded. Recent studies have shown that patients treated with a higher dose (3 mg/kg/day) responded better than those treated with the conventional dose (2 mg/kg/day). A reduction in the bioavailability of propranolol, which can be overcome by dose increment, may contribute to the poor response.[18,19] However, our study, however, did not demonstrate a difference in the response rates of a high dosage and a conventional dosage of propranolol.

The combination of propranolol and prednisolone is also effective in IH. Another advantage of the combination is that it has fewer adverse effects than a monotherapy of either propranolol or prednisolone. It has been hypothesized that both agents mitigate the adverse effects of each other, i.e., prednisolone has a hyperglycemic effect, which is potentially abrogated by propranolol, and the hypotensive

effect of propranolol is rescued by the salt-retention effect of prednisolone.[20] Likewise, all of our patients who were treated with a combination of propranolol and prednisolone never experienced hypoglycemia or hypotension.

Sirolimus appears to have been effective in the treatment of several vascular tumors, inhibiting the mechanistic target of rapamycin (mTOR) pathway, which regulates the phosphatidylinositol 3-kinase (PI3K)/AKT signaling pathway, ultimately involving the switching process of cell growth and angiogenesis.[21] In our cohort, 1 patient with KHE had a rapid hematological response within 2 weeks, but the radiographical change was gradual, and this result was concordant with other studies.[21,22] Hematological and gastrointestinal adverse events have been common in large cohort studies,[22] but patients in our study were not affected.

Patients with KHE seemed to respond poorly to conventional medications (e.g., prednisolone, propranolol and vincristine), but they dramatically responded to sirolimus. This finding might benefit physicians when selecting a treatment for those with KHE responding poorly to standard treatment.

The small number of patients and the heterogeneity of the treatment modalities are limitations of this study. A further cohort study should be conducted collaboratively with other institutes in order to enroll more patients and therefore elucidate the patterns of response and the toxicities of the various treatment modalities.

In conclusion, the combination therapy of propranolol and prednisolone appears to have been a safe treatment option in several cases of KMS. Sirolimus may be considered for those who do not respond, especially in cases of KMS secondary to KHE.

REFERENCES

1. Shim WK. Hemangiomas of infancy complicated by thrombocytopenia. Am J Surg. 1968;116(6):896-906.
2. Kwok-Williams M, Perez Z, Squire R, Glaser A, Bew S, Taylor R. Radiotherapy for life-threatening mediastinal hemangioma with Kasabach-Merritt syndrome. Pediatr Blood Cancer. 2007;49(5):739-44.
3. Malhotra Y, Yang CS, McNamara J, Antaya RJ. Congenital kaposiform hemangioendothelioma with Kasabach-Merritt phenomenon successfully treated with low-dose radiation therapy. Pediatr Dermatol. 2014;31(5):595-8.
4. Zukerberg LR, Nickoloff BJ, Weiss SW. Kaposiform hemangioendothelioma of infancy and childhood. An aggressive neoplasm associated with Kasabach-Merritt syndrome and lymphangiomatosis. Am J Surg Pathol. 1993;17(4):321-8.
5. Seo SK, Suh JC, Na GY, Kim IS, Sohn KR. Kasabach-Merritt syndrome: identification of platelet trapping in a tufted angioma by immunohistochemistry technique using monoclonal antibody to CD61. Pediatr Dermatol. 1999;16(5):392-4.
6. Kim T, Roh MR, Cho S, Chung KY. Kasabach-merritt syndrome arising from tufted angioma successfully treated with systemic corticosteroid. Ann Dermatol. 2010;22(4):426-30.
7. Enjolras O, Mulliken JB, Wassef M, Frieden IJ, Rieu PN, Burrows PE, et al. Residual lesions after Kasabach-Merritt phenomenon in 41 patients. J Am Acad Dermatol. 2000;42(2 Pt 1):225-35.
8. Chiu YE, Drolet BA, Blei F, Carcao M, Fangusaro J, Kelly ME, et al. Variable response to propranolol treatment of kaposiform hemangioendothelioma, tufted angioma, and Kasabach-Merritt phenomenon. Pediatr Blood Cancer. 2012;59(5):934-8.
9. Wananukul S, Nuchprayoon I, Seksarn P. Treatment of Kasabach-Merritt syndrome: a stepwise regimen of prednisolone, dipyridamole, and interferon. Int J Dermatol. 2003;42(9):741-8.
10. Ozsoylu S. High-dose intravenous methylprednisolone for Kasabach-Merritt syndrome. Am J Hematol. 1989;31(3):219-20.
11. Hall GW. Kasabach-Merritt syndrome: pathogenesis and management. Br J Haematol. 2001;112(4):851-62.
12. Leaute-Labreze C, Dumas de la Roque E, Hubiche T, Boralevi F, Thambo JB, Taieb A. Propranolol for severe hemangiomas of infancy. N Engl J Med. 2008;358(24):2649-51.
13. Wang Z, Li K, Yao W, Dong K, Xiao X, Zheng S. Steroid-resistant kaposiform hemangioendothelioma: a retrospective study of 37 patients treated with vincristine and long-term follow-up. Pediatr Blood Cancer. 2015;62(4):577-80.
14. Fukushima H, Kudo T, Fuskushima T, Takahashi-Igari M, Shiigai M, Mori K, et al. An infant with life-threatening hemangioma successfully treated with low-dose cyclophosphamide. Pediatr Int. 2011;53(6):1073-5.
15. Fernandez-Pineda I, Lopez-Gutierrez JC, Chocarro G, Bernabeu-Wittel J, Ramirez-Villar GL. Long-term outcome of vincristine-aspirin-ticlopidine (VAT) therapy for vascular tumors associated with Kasabach-Merritt phenomenon. Pediatr Blood Cancer. 2013;60(9):1478-81.
16. Drolet BA, Frommelt PC, Chamlin SL, Haggstrom A, Bauman NM, Chiu YE, et al. Initiation and use of propranolol for infantile hemangioma: report of a consensus conference. Pediatrics. 2013;131(1):128-40.
17. Storch CH, Hoeger PH. Propranolol for infantile haemangiomas: insights into the molecular mechanisms of action. Br J Dermatol. 2010;163(2):269-74.
18. Hermans DJ, van Beynum IM, van der Vijver RJ, Kool LJ, de Blaauw I, van der Vleuten CJ. Kaposiform hemangioendothelioma with Kasabach-Merritt syndrome: a new indication for propranolol treatment. J Pediatr Hematol Oncol. 2011;33(4):e171-3.
19. Filippi L, Tamburini A, Berti E, Perrone A, Defilippi C, Favre C, et al. Successful Propranolol Treatment of a Kaposiform Hemangioendothelioma Apparently Resistant to Propranolol. Pediatr Blood Cancer. 2016;63(7):1290-2.
20. Koay AC, Choo MM, Nathan AM, Omar A, Lim CT. Combined low-dose oral propranolol and oral prednisolone as first-line treatment in periocular infantile hemangiomas. J Ocul Pharmacol Ther. 2011;27(3):309-11.
21. Hammill AM, Wentzel M, Gupta A, Nelson S, Lucky A, Elluru R, et al. Sirolimus for the treatment of complicated vascular anomalies in children. Pediatr Blood Cancer. 2011;57(6):1018-24.
22. Lackner H, Karastaneva A, Schwinger W, Benesch M, Sovinz P, Seidel M, et al. Sirolimus for the treatment of children with various complicated vascular anomalies. Eur J Pediatr. 2015;174(12):1579-84.