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The paediatric oncologist and the evolving medical management of complex vascular anomalies: An institutional experience

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Background: Complex vascular anomalies in children are amenable to medical therapy that can result in complete resolution or improvement in cosmesis and function or serve as a conduit to definitive surgery.

Aim: This study aimed to retrospectively review the management and outcomes of children with complex vascular anomalies.

Setting: The study was conducted at a haematology/oncology unit based out of a paediatric hospital in the Western Cape.

Methods: All patients with biopsy-proven lesions and those diagnosed on magnetic resonance imaging (MRI) from 01 January 2005 to September 2021 were considered eligible for inclusion.

Results: Twenty-five patients presented with a variety of capillary, venous and lymphatic malformations. There were 11 males and 14 females, with a median age of 35 months at presentation (range: 0–156 months). Patients presented with a mass or compartmental enlargement, cutaneous stigmata or bleeding. Hepatic haemangioendotheliomas, kaposiform haemangioendotheliomas and capillary haemangiomas were most common. Kassabach-Merritt syndrome was present in 5/25 (20%) patients. Prednisone, propranolol and vincristine were the most commonly employed first-line medical treatments (15/21; 47.6%). Twelve patients received sirolimus, (11/21; 52%), four as single agent first-line therapy and eight as combination therapy, complicated by transient hyperlipidaemia in only one patient. All but one patient survived: 10 are disease free and 12 are alive with disease. Two patients with Gorham's disease are maintained on long-term low-dose Sirolimus.

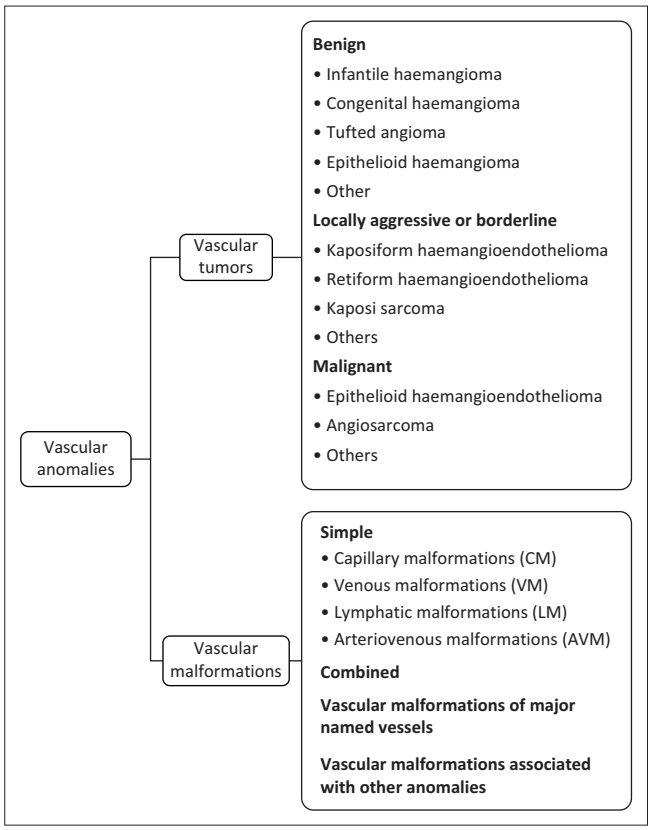
Conclusion: The medical management of complex vascular anomalies yields good results in children. Sirolimus is well tolerated with few manageable side effects with cost being the only prohibitive factor to its broader application.

Keywords: vascular anomalies; vascular tumours; vascular malformations; medical management; sirolimus; mTOR inhibitor; paediatric oncology.

Introduction

Vascular anomalies comprise a spectrum of rare diseases related to disorders of vascular development and remain both diagnostic and therapeutic challenges to treating physicians.[1,2] Vascular anomalies are classified broadly into vascular tumours and malformations.[3] Despite significant morbidity and mortality, there are limited therapeutic options.[1] Their wide variety of presentations, anatomical locations and pathologies dictates whether remediation is best achieved by medical or surgical means or through interventional radiology.

The widely accepted classification system established by the International Society for the Study of Vascular Anomalies (ISSVA) was recently updated in April 2014.[4] Vascular anomalies are classified with respect to histopathological features of increased cell turnover.[2] Vascular tumours are true neoplasms, demonstrating pathologic endothelial cell turnover and abnormal blood vessel proliferation. They are classified into benign, locally aggressive or borderline and malignant tumours. Vascular tumours include haemangiomas and rarer tumours such as tufted angioma (TA) and kaposiform haemangioendothelioma (KHE). Vascular malformations are characterised by morphologically abnormal vascular and lymphatic channels, which form during foetal development, with no demonstrable proliferation.[3,4] Vascular malformations are divided into four groups: simple malformations, combined malformations, malformations of major named vessels and malformations associated with other anomalies. An outline of the classification of vascular tumours and malformations is presented in Figure 1.



Source: Adapted from Wassef M, Blei F, Adams D, et al. ISSVA board and scientific committee. Vascular anomalies classification: Recommendations from the international society for the study of vascular anomalies. Paediatrics. 2015;136(1):e203–e214. https://doi.org/10.1542/peds.2014-3673[4]

FIGURE 1: Classification of vascular anomalies.

Whilst the majority typically demonstrate a benign course, lesions may be deforming, impair vital structures or, in some cases, become life-threatening. Clinical problems encountered include disfigurement, chronic pain, recurrent infection, coagulopathies such as Kasabach-Merritt syndrome (KMS)[5] and organ dysfunction. These often occur secondary to the growth or expansion of the vascular anomaly.[6,7,8] Symptoms are often progressive and result in worsening quality of life.[8] Despite this, there is a paucity of literature on the evaluation and validation of medical treatment options in the setting of vascular anomalies.

Historically, vascular tumours were treated with corticosteroids and traditional chemotherapeutic agents, either as monotherapy or as adjuncts to a surgical intervention, but the variable efficacy and both short- and long-term side effects sought the trial of alternatives.[9] Noncomplex haemangiomas, such as simple haemangiomas without clinical problems and rapidly involuting congenital haemangiomas, are often conservatively managed with therapeutic abstention owing to their benign, self-limited course. Some vascular tumours such as infantile haemangiomas and KHE, respectively, are now preferentially treated with propranolol or sirolimus, given the proven clinical efficacy, whilst others such as Kaposi's sarcoma still require highly active antiretroviral therapy and sometimes systemic chemotherapy. Histology is, therefore, key in helping to direct appropriate therapy.

Following the discovery of propranolol as a highly effective treatment for infantile haemangiomas in 2008,[10] literature has emerged supporting its use as a first-line treatment supported by two randomised controlled trials demonstrating its clinical efficacy and favourable safety profile.[11,12] Rarer vascular tumours, such as KHE and TA, prove to be therapeutic challenges for clinicians. Often ill-defined and extensive lesions that preclude surgical interventions, treatment is primarily medical, with consensus guidelines suggesting single agent daily steroids. In the past, therapeutic regimens have included combinations of corticosteroids, vincristine, interferon-alpha, aspirin, cyclophosphamide and bevacizumab, with variable results.[9] More recently, sirolimus has gained popularity as monotherapy in the setting of KHE and TA, owing to clinical response and tolerable side effect profile.[1,13]

The mechanisms of action are similar for common agents. Steroids, propranolol and alpha-interferon all inhibit proliferation of endothelial cells in various ways. In mice it has been shown that steroids suppress vascular endothelial growth factor A (VEGF-A) and hence proliferation in infantile haemangioma-derived stem cells,[14] although the exact mechanism is not fully elucidated. Propranolol, a nonselective adrenergic blocker, induces apoptosis of haemangioma-derived endothelial cells in culture,[15] whilst alpha-interferon promotes production of endothelial prostacyclin and is thought to inhibit angiogenesis indirectly through its immunostimulatory effects.[16]

Vascular malformations are a more challenging clinical entity, with past therapies largely limited to supportive and palliative measures for symptomatic relief, typically involving interventional or surgical therapies and adjuvant medical therapy. Owing to the ill-defined and infiltrative nature of the lesions, these procedures are rarely curative, bolstering the call for improved therapeutic modalities.[6] Over the years, several agents or combinations thereof, including corticosteroids, vincristine and interferon and sildenafil, have been employed with variable but often unsatisfactory outcomes.[9] In more recent years, sirolimus has provided great promise in the treatment of complex vascular malformations, demonstrating greater efficacy compared with the less effective historical medical therapies.

Traditionally, dermatologists and surgeons have directed specific medical therapy. However, paediatric oncologists and haematologists have steadily been called on more to direct specific medical therapy for both primary disease and complications, such as consumptive coagulopathy. Similarly, where management requires the use of chemotherapeutics such as vincristine, paediatric oncologists and haematologists are commonly consulted. As sirolimus has assumed an increasingly important role in the management of these lesions, so too has the scope of the paediatric oncologist grown to include monitoring and management of drug complications such as hyperlipidaemias.

Sirolimus is currently the most commonly employed medical therapy in the setting of both vascular malformations and

vascular tumours. Hammill et al.[1] retrospectively evaluated the use of sirolimus in six patients with vascular malformations, with the patients showing significant clinical improvement with tolerable side effects. A phase II clinical trial involving 57 evaluable patients, conducted by Adams et al.,[8] found sirolimus, a mammalian target of rapamycin (mTOR) inhibitor that targets angiogenesis and cell growth, to be efficacious and safe for the majority of patients with complicated vascular anomalies. Mammalian target of rapamycin, a serine-threonine kinase regulated by phosphoinositide-3-kinase (PI3K), is involved in several cellular processes, primarily the upregulation of protein synthesis, which results in increased angiogenesis and cellular proliferation. The inhibition of mTOR prevents downstream protein synthesis and subsequent cellular proliferation and angiogenesis.[17] A mixed adult and paediatric prospective phase II study of 19 patients was congruous in its findings, stating sirolimus was both efficacious and well tolerated in patients with vascular malformations that were refractory to conventional treatment.[6] Sirolimus has been consistently cited as successful medical therapy for vascular anomalies.[1,6,18,19]

There are limited reports of vascular anomalies in children in South Africa and Africa. International statistics suggest that the incidence of vascular anomalies ranges from 4.55% to 11.16%, when using the ISSVA classification.[20] Haematology and oncology practitioners in lower- and middle-income settings will increasingly need to develop knowledge and experience in the management of these lesions, as the indications for medical therapy continue to expand and new novel agent pharmacotherapeutics continue to emerge.

The proposed retrospective review will describe the use of varying medical modalities of therapy and their outcomes in children with radiologically confirmed or biopsy proven vascular anomalies in a middle-income setting. The information will be used to generate best practice recommendations, especially in relation to sirolimus, which is a costly drug, so that patient selection for medical and surgical interventions can be tailored to achieve the best outcomes for the largest group of children.

Methods

We undertook a retrospective folder review of all eligible children with biopsy-proven and radiologically confirmed vascular anomalies under the age of 16 years diagnosed and treated at Red Cross War Memorial Children's Hospital from 01 January 2005 until 01 September 2021. The unit sees only the most complex vascular tumours or malformations. Benign, involuting or uncomplicated lesions are largely the remit of the general paediatrician and neonatologist. Patients are selected by virtue of the histology of their lesion because therapy falls within the oncological pharmacopoeia or because there has been clinical difficulty with modes of treatment or disease specific complications, which may include KMS, growth failure or organ dysfunction. We consciously only included vascular tumours that presented clinically and radiologically as malformations, or those that were discovered post-biopsy when conventional therapies failed, to have an intermixed, synchronous malignant component. We specifically did not include patients with Kaposi's sarcoma (or other malignant vascular tumours, which would require chemoradiation as first-line therapy), which falls outside the remit of this review.

Data for all eligible patients were entered in a Microsoft Access© database. All patients were anonymised using a numerical identifier. Each folder was examined for patient characteristics, which included age, sex, anthropometry (weight, height, weight-for-age, height-for-age and weight-for-height), presenting symptoms, the presence or absence of KMS, laboratory markers (including haemoglobin, platelet count, coagulation and liver function tests), histology in those patients where a tissue diagnosis was obtained, imaging modality, treatment interventions (both medical and surgical), treatment complications, the necessity for intensive care unit (ICU) support and outcome. Continuous variables were summarised using mean and standard deviation if normally distributed whilst median and interquartile range was computed for skewed data.

Ethical considerations

Ethical clearance to conduct this study was obtained from the University of Cape Town Faculty of Health Sciences Human Research Ethics Committee (ref. no. 013/2020).

Results

Patient characteristics

A total of 25 patients presented to the haematology oncology service with complex vascular malformations. The majority of these were referred from shared care units further afield, private paediatric practices or other specialist units within the hospital, mainly dermatology and general surgery.

The cohort comprised 11 males and 14 females with a median age of 35 months at presentation (range: 1; 156; interquartile range [IQR]: 51). Four (16%) of the patients in the cohort had abnormal growth parameters. One child with a vascular malformation and infantile fibrosarcoma (IFS) was moderately UWFA and moderately stunted. One with a massive hepatic capillary malformation was moderately wasted. A third with a hepatic haemangioendothelioma was moderately stunted and the last with a long segment intraspinal capillary haemangioma was severely stunted.

Eight patients presented with a visible mass, four with bleeding (one from thrombocytopaenia, two from gastrointestinal masses and one from an external mass), six with cutaneous stigmata, two with abdominal distention, two with hemihypertrophy and one with flaccid paralysis of the lower limbs; two were detected as an incidental finding on ultrasound screening for an unrelated problem. Histological diagnoses included a variety of both capillary, venous and lymphatic lesions and combinations thereof. Hepatic haemangioendotheliomas (n = 3), KHE (n = 3) and capillary

TABLE 1: Patient characteristics.

No	Diagnosis	KMS	Biopsy proven	Radiologically confirmed	Treatment modalities	Response to therapy	Outcome
1	Infantile hepatic haemangioendothelioma	No	No	MRI	Prednisone × 4 weeks, propranolol × 21 months	Complete resolution	ADF
2	Capillary haemangioma	No	Yes	MRI	Surgical excision (intraspinal mass T8-L3)	Progressive improvement	ADF
3	Epithelioid haemangioendothelioma	No	Yes	MRI	Vincristine × 3 weeks/ dactinomycin × 3 courses, surgical excision, radiotherapy	Complete resolution	ADF
4	Kaposiform haemangioendothelioma (KHE)	Yes Plts 11 Hb 7.5	Yes	MRI	Vincristine × 16 weeks + 10 weeks, propranolol × 8 months + 6 months, prednisone × 4 weeks, sirolimus × 12 months, surgical excision	Complete response	ADF
5	Multiple infantile hepatic haemangioendotheliomas	No	No	MRI	Prednisone (short course). propranolol × 18 months	Clinical response monitored on US, complete resolution by 3 years after initiation of therapy	ADF
6	Diffuse lymphangiomatosis, Gorham's disease spectrum	No	Yes	MRI	Sirolimus × 24 months and continuation on low-dose therapy, probably lifelong	Resolution of cytopaenias because of direct bone marrow invasion.	AWD
7	Diffuse angiomatosis	No	No	CT Angiogram	Propranolol, sirolimus (duration unknown)	No response to propranolol	Lost
8	Benign tufted haemangioma	No	Yes	MRI	No specific therapy	Complete involution	ADF
9	Blue rubber bled nevus syndrome (multiple haemangiomas)	No	Clinical and endoscopy	MRI	Sirolimus × 36 months, discontinued and then restarted 2 years later	Complete resolution of GI bleeds	AWD
10	Klippel-Trenaunay-Weber Syndrome	No	No	MRI	No specific therapy		AWD
11	Kaposiform haemangioendothelioma	Yes Plts 6 Fib 0.7	Yes	MRI	Prednisone × 4 weeks, vincristine × 2 weeks, sirolimus × 24 months	Reduction in size of mass so that it was cosmetically acceptable	AWD
12	Capillary haemangioma (multiple)	Yes Hb 7.3 Plts 20 INR 3.22 aPTT 64.3 Fib 0.2	Yes	Clinical	Vincristine × 12 weeks, prednisone × 4 weeks	Persistent thrombocytopaenia	Lost
13	Lymphatic malformation / Phakomatosis pigmentularis	No	Yes	MRI	Prednisone × 4 weeks, propranolol × 6 months, vincristine × 2 weeks, sirolimus × 4 months	No response on propranolol, changed to sirolimus; mother discontinued therapy for personal reasons	ADF
14	Capillary haemangioma	No	No	MRI	No specific therapy		ADF
15	Venolymphatic malformation infantile fibrosarcoma (IFS)	No	Yes	MRI	Vincristine and dactinomycin × 22 weeks, hind quarter amputation.	Complete resolution	ADF
16	Arteriovenous malformation/infantile fibrosarcoma	Partial Plts 40	Yes	MRI/PET/CT	Bleomycin injections × 2, vincristine and dactinomycin × 24 weeks, surgical excision of residua	Complete response	ADF
17	Massive hepatic capillary vascular malformation	No	Yes	MRI	Vincristine × 5 weeks, prednisone × 4 weeks, sirolimus × 1 week	Clinical deterioration	DD
18	Variant Klippel-Trenaunay-Weber syndrome	No	No	MRI	Propranolol, sirolimus × 24 months	Well with cosmetic and symptomatic improvement	AWD
19	Gorham's disease	Yes Plts 43 aPTT 49/32 Fib 0.3		MRI	Vincristine × 12 weeks, prednisone × 6 weeks, sirolimus × 39 months and 14 months	Complete resolution of KMS and bony destruction; sirolimus long term	AWD
20	Lymphaticovenous malformation	No	No	MRI	Sirolimus × 3 months	Initial increase in size after 2 months but level sub-so dose increased	AWD
21	Kaposiform haemangioendothelioma	No	Yes	MRI	Propranolol × 6 months	Excellent response; stop therapy and watch and wait	AWD
22	Fibroadipose vascular anomaly (FAVA)	No	Yes	MRI	Sirolimus × 15 months	Improvement on interval MRI; same extent but less avidly enhancing; no difference at 15 months on MRI so sirolimus stopped; watch and wait	AWD
23	Hepatic haemangioendothelioma	No	No	CT	Propranolol × 3 months	Good response on imaging after 2 months: 30% smaller. Continue therapy and review in 2 months	AWD
24	Variant Klippel-Trenaunay-Weber Syndrome	No	No	MRI	No therapy indicated; isolated hemihypertrophy	Watch and wait; no definitive therapy yet	AWD
25	Venous malformation	No	Yes	MRI	Sirolimus × 10 months	No response to therapy	AWD

FAVA, Fibroadipose Vascular Anomaly; KMS, Kasabach-Merrit Syndrome; KHE, Kaposiform haemangioendothelioma; MRI, magnetic resonance imaging; Hb, haemoglobin; Plts, platelets; INR, international normalised ratio; aPTT, activated partial thromboplastin time; Fib, fibrinogen; ADF, alive, disease-free; AWD, alive with disease; DD, died of disease.

haemangiomas (n = 3) were amongst the most common with a range of others (Table 1). One child had a biopsy proven intermediate-grade epithelioid haemangioendothelioma requiring surgery and chemoradiation. Two others had biopsy proven IFS arising in their malformations requiring surgery and chemotherapy. The first patient had neo-adjuvant chemotherapy and underwent surgery after successful cytoreduction. The second who had a semi-emergent

hindquarter resection for escalating systemic compromise from the vascular component of the mass, received adjuvant chemotherapy for suspected residua on postoperative imaging once histology unexpectedly revealed the presence of an IFS.

Five patients had concomitant KMS at presentation, four complete and one partial, only one of which had clinical bleeding at presentation. All patients normalised their full blood counts and clotting profiles within a week of the initiation of steroid therapy. Only one child with significant bleeding required blood product support with repeated units of cryoprecipitate, fresh frozen plasma and platelets. Other than that, blood support was rarely necessary. One patient was HIV-positive and presented with a pulmonary haemorrhage related to a *Pneumocystis jirovicii* infection requiring ventilatory support. His occipital mass, which was an incidental finding, was found to be a benign tufted haemangioma on tissue biopsy and was felt to be completely unrelated to his bleeding. Two other patients were HIV exposed but received antenatal prophylaxis and were subsequently proven to be HIV-negative.

Treatment interventions

Owing to the complexity of vascular anomalies, patients received a combination of medical and surgical interventions during the course of their disease. One of the patients with a vascular malformation and an occult IFS received local bleomycin injections prior to the discovery of the IFS, one underwent surgery only, two had both medical and surgical interventions and three required no definitive therapy; latterly, a watch and wait approach was adopted.

Five patients received various combinations of first-line medical management only which included prednisone, propranolol and vincristine. The treatment durations lasted from 1 to 21 months (Table 1). Eight patients in total received oral prednisone (1 mg/kg – 2 mg/kg in divided doses), given either as a short course for one week (1/8) or for 4–6 weeks with gastric prophylaxis with steroids weaned to stop over a week (mean: 3.9 weeks, median: four weeks). Eight patients in total received oral propranolol (0.6 mg/kg – 1.7 mg/kg in divided doses depending on age) with dose adjustment at each visit dependent on weight and blood pressure measurement (mean: 13 months: median: 14 months). One patient had their propranolol discontinued because he developed bronchospasm and was later diagnosed with asthma. Nine patients in total received intravenous vincristine, which was given once weekly (1.5 mg/m^2 intravenous [IV]) to facilitate involution of a mass and to promote resolution of KMS (mean 10.8 weeks; median 12 weeks). Three (3/9) of those for whom chemotherapy was indicated received vincristine according to a recognised treatment regimen, two with an IFS within a vascular malformation and one with an intermediate-grade epithelioid haemangioendothelioma who also received adjuvant radiotherapy. One patient with a KHE received a second course of vincristine and propranolol after initial therapy with prednisone, propranolol, vincristine and sirolimus because his mass started to enlarge, and he developed KMS (platelets 11 × 10^9/L) after sirolimus had been stopped. He went on to have excision of his mass in addition to a second course of medical therapy.

Twelve patients received sirolimus orally at a standard dose of 0.8 mg/m^2/dose 12 hourly (mean 17.2 months; median 15 months). Doses were adjusted to maintain an ideal target drug level between 5 ng/mL and 15 ng/mL according to serum sirolimus level testing and titrated against treatment response and drug tolerance. Three patients received sirolimus as first-line therapy, whilst eight patients received it as second-line therapy singly or in combination with a first line agent because of a poor or inadequate response to first-line therapy and the severity and potentially poor prognosis of their disease, as was the case of the child with Gorham's disease, where long-term disease control is known to be complex. The exact duration of drug administration was unknown in a single patient who was lost. One patient, who was suspected to be nonadherent after 10 months and ran persistently subtherapeutic drug levels (< 5 ng/mL), showed no response to therapy and sirolimus was stopped. Out of the 12 patients, 10 (83%) showed objective responses by clinical examination, objective radiological assessment or normalisation of laboratory parameters. One patient who received sirolimus died, but this was likely because of the fact that the drug was commenced too late in a child with rapidly progressing disease who was already requiring ventilatory support. Other than that adverse event, the drug was well tolerated in all patients. Only one of the 12 patients experienced elevated cholesterol and triglyceride levels whilst on sirolimus therapy but did not require any statin therapy, and her lipogram was normalised once sirolimus therapy was completed. None of the patients on sirolimus experienced any significant abnormal elevations in their liver function tests and none required concomitant anti-emetic therapy. All the patients still receiving sirolimus, both those on therapeutic doses and long-term low-dose maintenance therapy (two patients with Gorham's [spectrum] disease) are well without any biochemical derangements.

All but one infant, with a massive hepatic capillary malformation, have survived. Ten are alive and disease-free whilst 12 are alive with disease; two of those were on long-term maintenance sirolimus therapy. Two patients have been lost to follow-up but are presumed alive.

Discussion

Vascular anomalies comprise a heterogeneous group of disorders of vascular development exemplified by the range of pathological and radiological diagnoses in our cohort. The current classification system divides vascular anomalies into two broad categories: vascular tumours, which arise secondary to endothelial hyperplasia and vascular malformations, lesions that arise secondary to vascular dysmorphogenesis and exhibit normal endothelial turnover.[3] Complex vascular anomalies are rare and present to a variety of specialists, both medical and surgical, as was the case in

the large majority of our patients. The complex nature of vascular anomalies, with their variable natural history, saw several combinations of medical treatments as well as surgical interventions.

In this study setting, prednisone, propranolol and vincristine were employed as standard first-line agents, given their cost-effectiveness, availability and predictable and manageable side effect profiles. They were employed primarily to reduce the size of masses, making them amenable to surgical resection, to manage medical complications, such as KMS, and to render improved cosmetic and functional results. Both prednisone and propranolol have long formed the cornerstone of medical management in the setting of vascular anomalies, predominantly infantile haemangiomas. Propranolol emerged as a promising new therapeutic option for vascular anomalies after serendipitously demonstrating efficacy in infantile haemangiomas. First described by Leaute-Labreze and colleagues,[10] successful treatment of infantile haemangiomas using propranolol has been reported in a number of case reports and subsequent studies. A case report by Filippi et al.[21] reported propranolol's efficacy in treatment of a KHE in a 7-year-old child whose lesion was unresponsive to first-line treatment with vincristine and prednisone. Similarly, in a case series (n = 30) by Manunza et al.,[22] in children with complicated infantile haemangiomas, propranolol demonstrated clinical efficacy by regression of facial lesions. In a larger retrospective review conducted at a tertiary vascular anomalies centre, Buckmiller et al.[23] observed clinical improvement of haemangiomas in 97% of the 41 patients during propranolol therapy. Two randomised controlled trials have since been published wherein they estimate the agent to have an estimated treatment failure rate of only 1% – 2%.[11,12] Furthermore, propranolol demonstrated efficacy in the management of lymphatic malformations and diffuse lymphangiomatosis, with variable improvements documented in clinical status.[24,25]

Prior to propranolol, corticosteroids had been frequently employed as first-line therapy. Sadan and Wolach[26] concluded that high-dose oral corticosteroids provided a safe and efficacious therapeutic option in treatment of infantile haemangiomas. In a systemic review and meta-analysis on the use of corticosteroids in infantile haemangiomas, Izadpanah et al.[27] reported an overall efficacy of 69.1%, with similar responses reported in other studies.[28,29] The administration of systemic corticosteroids, however, is associated with a number of side effects, prompting a trial of alternatives.

Several studies have documented the efficacy of both agents, with propranolol now preferred owing to a more favourable side effect profile.[11,12,27] All first line agents were well tolerated in our patients. Those receiving longer courses (4–6 weeks) of steroid therapy received standard gastric prophylaxis with proton pump inhibitors. Those receiving propranolol had regular blood pressure monitoring and in all but one patient with an established contraindication (bronchospasm), therapy proceeded without incident. Similarly, vincristine has been employed as primary or adjunctive agents in the patients with complex vascular malformations. Several investigators have reported successful use of vincristine in severe cases of vascular tumours that were refractory to initial steroid therapy.[30,31,32] Five of the eight patients (62.5%) in our cohort who received first-line medical therapy alone (propranolol, prednisone, vincristine), demonstrated satisfactory responses and did not require additional medical therapy.

Sirolimus, by contrast, has historically been reserved as second-line therapy in our setting until more recently, where histology has helped to identify patients who would benefit most in the context of a multidisciplinary discussion. Given the cost of the drug and our resource limitations, patients only received it after rigorous discussion about the potential benefits and risks. Since its emergence as a newer, targeted agent, sirolimus has demonstrated its clinical efficacy in patients with vascular anomalies and especially in those with refractory disease.[1,6,8,33] This is mirrored in our findings, where patients who received sirolimus, often following prior multimodal treatment, experienced no disease progression and often clinical improvement. In our experience, drug tolerance was acceptable, with minimal biochemical derangements, none of which required specific pharmacological interventions. Similar findings with regard to the side effect profile have been demonstrated in other studies, with liver enzyme derangement and hyperlipidaemias reported.[1,33]

Our experience has revealed that sirolimus is both efficacious and safe when used in patients with a robust indication. Initially, these were limited to patients with limb or life-threatening malformations,[1] but over time, patients with less aggressive lesions who may also derive benefit from earlier therapy have gained access to sirolimus. Despite this trend in high-income environments, the cost of the drug locally remains prohibitive, and in patients who have shown no clinical benefit or where adherence cannot be guaranteed, the drug has been discontinued in an attempt to make it available for others who may benefit, particularly for those patients without medical aid support. In an effort to facilitate appropriate decision-making and just access to care, especially for poorer patients, two important changes have emerged at our institution. The first is the development of a standard operating procedure (Box 1),[1,34,35] which has created uniformity by standardising practice in a setting-appropriate fashion. The second is the formation of a vascular multidisciplinary meeting initiated by our paediatric surgical team for discussion of complex cases from within and outside of our institution, which has allowed us to draw on a larger pool of available experts in an effort to broaden our knowledge and experience.

We concede that the interpretation of clinical data in a small cohort of patients can be made onerous by combination therapy, although in most patients, therapies were employed sequentially. Combinations were more common in children on first-line regimens. In some patients managed in a shared care environment, drug and biochemical monitoring was not always standardised, and this may have impacted our

BOX 1: Standard operating procedure for patients under consideration for commencement of sirolimus therapy.

Institutional guidelines for the referral, management and assessment of patients requiring sirolimus
Sirolimus (Rapamycin™) was initially isolated as an antibiotic and antifungal agent, but has subsequently shown to be an effective cytostatic, antiproliferative and immunosuppressive agent. It inhibits vascular endothelial growth factor, a key regulator in lymphangiogenesis and angiogenesis. The goal of treatment is to maintain functionality, control associated symptoms and preserve aesthetic integrity. The use of sirolimus in lymphatic malformation is not well established.
Cost is a major limitation – patients need to be selected carefully.
Workup:
• Appropriate imaging, preferably with MRI (ultrasound often does not adequately gauge the true extent of the lesion)
• Tissue to ascertain histology as a routine is mandatory.
In selected cases a biopsy may not be indicated, for example, where the radiological features of a microcystic/macrocystic lymphatic malformation are clear cut and there are no features to suggest possible malignancy, especially in cosmetically sensitive areas; these cases need to be discussed and agreed upon at the Tumour Board Meeting.
The following tissue diagnoses qualify:
▪ Kaposiform hemangioendotheliomas with/without Kasabach-Merritt phenomenon
▪ Tufted angioma with/without Kasabach-Merritt phenomenon
▪ Capillary lymphaticovenous malformation (CLVM)
▪ Venous lymphatic malformation (VLM)
▪ Microcystic lymphatic malformation (MLM)
▪ Multifocal lymphangiomatosis and thrombocytopenia (MLT)/cutaneovisceral angiomatosis and thrombocytopenia (CAT)
▪ Capillary lymphatic arterial venous malformations (CLAVM)
▪ Phosphatase and tensin homolog (PTEN) overgrowth syndrome with vascular anomaly (hamartoma tumour syndrome)
▪ Lymphangiectasia syndromes
• Discussion at Tumour Board (if referred by Paediatric Surgery, please forward summary to Haem/Oncology for inclusion at next available Tumour Board discussion)
Indications:
• Airway compromise
• Limb or life-threatening complications (e.g. massive intrathoracic or intra-abdominal lesions)
• Significant functional compromise because of the lesion, where conventional therapy (compression therapy, sclerotherapy or surgical excision) is inadequate
• Where surgery would cause significant disfigurement (e.g. where a lesion involves the face)
• Alternative management has been tried but failed (e.g. sclerotherapy or compression bandages)
• Intractable pain (e.g. invading bone)
Side effects (most common):
• Hypertriglyceridemia
• Hypertension
• Abdominal pain and diarrhoea
• Anaemia, thrombocytopenia and leucopenia
Follow-up:
• Full blood count (FBC), liver function, renal function, triglyceride and cholesterol levels should be checked prior to initiating sirolimus.
• Sirolimus trough level should be checked 2 weeks after starting and then monthly. Target drug level – 5 ng/mL – 15 ng/mL (however, patients may show clinical response on a lower drug level).
• If the drug level is persistently below 2 ng/mL and adherence is poor despite adequate counselling, sirolimus should be stopped.
• A trial of 6 months is given to assess response to treatment – either by objective clinical assessment (e.g., serial measurement of affected area) or radiological imaging. If no response despite adequate drug levels – stop sirolimus.

Source: Please see the full reference list of the article, Hammill A, Wentzel M, Gupta A, et al. Sirolimus for the treatment of complicated vascular anomalies in children. Pediatr Blood Cancer. 2011;57(6):1018–1024. https://doi.org/10.1002/pbc.23124, for more information

ability to draw substantiative conclusions about treatment response. In addition, we did not consider any quality-of-life (QOL) assessments, which focused specifically on psychological, scholastic and functional improvements and may have limited our appreciation of potential benefit from medical therapy.

Conclusion

Children with complex vascular anomalies benefit from decision-making based in comprehensive multidisciplinary care environments, particularly where resource limitations may impact access to care. Our experience has been positive, albeit boutique, and although first-line medical management yields predictable and favourable results, there exists a small group of children who may benefit from the addition of sirolimus therapy to a standard regimen or alternatively where sirolimus may be used as a first-line intervention. Good clinical decision-making is also supported by developing a set of evidence-based criteria to determine who is most likely to derive benefit, especially when the agent is expensive.

Despite our still small but evolving experience, we can report that sirolimus is a safe and efficacious agent for treating complex vascular anomalies in children, with cost remaining the major prohibitive factor. It is ideally delivered in a structured setting with rigorous cost-benefit assessment. Access to sophisticated imaging with ultrasound and magnetic resonance imaging (MRI), as well as access to diagnostic pathology services, provides a distinct advantage. Imaging continues to provide accurate assessments of response to therapy, without the subjectivity of interindividual clinical assessment, particularly where those improvements may be subtle and incremental. Standardised clinical follow-up, drug level and biochemical monitoring is important and a more defined QOL assessment, both psychosocial and functional, is something to aspire to and presents an exciting opportunity, both for improved clinical practice and research in the future.

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Competing interests

The authors declare that they have no financial or personal relationships that may have inappropriately influenced them in writing this article.

Authors' contributions

M.M. is the primary author and participated in the writing, editing and referencing of the document; H.d.Q. reviewed and edited the document and validated data; A.D. reviewed and edited the document; and M.H. supervised the overall writing and composition of the manuscript, including sections as indicated here.

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Data availability

Access to data is restricted, but reasonable requests will be considered by the corresponding (M.M.) author and only with the expressed consent of the head of the Clinical Unit of Red Cross War Memorial Children's Hospital.

Disclaimer

The views and opinions expressed in this article are those of the authors and do not necessarily reflect the official policy or position of any affiliated agency of the authors.

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