MEDICAL MANAGEMENT OF VASCULAR ANOMALIES

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INTRODUCTION

• Comprise a heterogeneous group of disorders
• Vast majority of these follow a benign course
• Complicated vascular anomalies can cause disfigurement, chronic pain, and organ dysfunction with significant morbidity and mortality
INTRODUCTION

• Society for the Study of Vascular Anomalies (ISSVA) in 1996, divides these lesions into two broad categories: vascular tumors and vascular malformations

• Vascular malformations are anomalies which occur during the morphological development of the vascular system
INTRODUCTION

• Vascular tumors are broadly divided into hemangiomas and tumors
Vascular Anomalies

Vascular Malformations
- Aterial (AM)
- Capillary (CM)
- Venous (VM)
- Lymphatic (LM)
- Combined (AVM, CLVM, LVM)

Vascular Tumors
- Hemangiomas
  - Congenital
    - Rapidly Involving (RICH)
    - Non-Involving (NICH)
  - Infantile
  - Simple
- Other Tumors
  - Kaposiform Hemangioendotheliomas (KHE)
  - Tufted Angiomas
  - Other
- Due to:
  - Interference with vital structures
  - Liver lesions
  - Genitourinary lesions
  - "Bearded" Airway lesion
  - PHACE syndrome
MANAGEMENT OF VASCULAR ANOMALIES

- Management of vascular malformations is dependent upon the type and location of the malformation as well as its depth.
- Observation and the use of supportive treatments (e.g., compression garments and drug therapy) are sometimes recommended.
- For lesions that are only superficial, laser therapy is commonly used.
- Lesions that are deep may, however, require surgical removal and other therapies. While surgery is complex and was previously associated with the risk of blood loss, advances in technology now enable removal to be more safely performed.
- The management of combined vascular lesions is far more complex, and usually requires evaluation and treatment by a multidisciplinary team.
Sirolimus for the Treatment of Complicated Vascular Anomalies in Children

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**Background.** Vascular anomalies comprise a diverse group of diagnoses. While infantile hemangiomas are common, the majority of these conditions are quite rare and have not been widely studied. Some of these lesions, though benign, can impair vital structures, be deforming, or even become life-threatening. Vascular tumors such as kaposiform hemangioendotheliomas (KHE) and complicated vascular malformations have proven particularly difficult to treat.

**Procedure.** Here we retrospectively evaluate a series of six patients with complicated, life-threatening vascular anomalies who were treated with the mTOR inhibitor sirolimus for compassionate use at two centers after failing multiple other therapies. **Results.** These patients showed significant improvement in clinical status with tolerable side effects. **Conclusions.** Sirolimus appears to be effective and safe in patients with life-threatening vascular anomalies and represents an important tool in treating these diseases. These findings are currently being further evaluated in a Phase II safety and efficacy trial. Pediatr Blood Cancer

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**Key words:** vascular anomalies; vascular malformations; kaposiform hemangioendothelioma; Kasabach–Merritt phenomenon; lymphatic malformation; rapamycin; sirolimus
Sirolimus (Rapamune)

- FDA approved immunosuppressant for solid organ transplant
- Synthetic derivative of Rapamycin; hydrophobic
- 1mg/ml oily suspension or tablets
- Initial dose: 0.8 mg/m$^2$/dose PO BID in children
- Common side effects: mouth sore, nausea, appetite change, headache, acne, cytopenias, transaminitis
- Rare side effects in immunosuppressed: wound healing, lymphoma, renal failure, opportunistic infections
- Pneumocystis prophylaxis recommended.
Sirolimus for Vascular Malformations

- **Likely beneficial**
  - Leaky cutaneous lymphatic vesicles
  - Oral mucosal lymphatic vesicles
  - Recurrent infections
  - Lymphedema associated pain
  - GI bleeding in BRBNS
  - Possibly for bony and lymphatic diseases

- **Unlikely beneficial**
  - Lipomatous
  - Harmartoma
  - AVMs
  - Venous malformations
  - Cappilary malformations
PROCEDURE

• Six patients with complicated, life-threatening vascular anomalies who were treated with the mTOR inhibitor sirolimus for compassionate use at two centers after failing multiple other therapies
The mtor pathway

Receptor Tyrosine Kinases (EGFR, VEGFR)

Cell Membrane

PI3K

Ras

Raf

PTEN

Akt/PKB

TSC2

TSC1

mTOR

S6 → ↑ protein synthesis → eIF-4E

↓ cell growth & proliferation

↑ angiogenesis
RESULTS

• Summary of first 6 patients treated with sirolimus
<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Gender</th>
<th>Diagnosis</th>
<th>Affected Locations</th>
<th>Previous Treatment(s)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10 months</td>
<td>Female</td>
<td>KHE + KMP</td>
<td>Abdomen, Back, Chest, Left leg, Pelvis, Retroperitoneum</td>
<td>Steroids, Vincristine, Cyclophosphamide, Interferon, Bevacizumab, Embolization</td>
<td>Resolution of KMP, Resolution of high-output cardiac failure, Improvement in size and color of lesion</td>
</tr>
<tr>
<td>2</td>
<td>6 years</td>
<td>Male</td>
<td>LM</td>
<td>Pleural effusion, Mediastinum, Paraspinal, Bone lesions, Cutaneous (chest/back/shoulder)</td>
<td>Interferon, Celecoxib, Thoracoscopic decortication, Pleurodesis, Chest tubes</td>
<td>Resolution of pleural effusions, Decrease in size/discholoration of lesion, Stabilization of bony lesions, Improvement in pain scale score</td>
</tr>
<tr>
<td>3</td>
<td>6 years</td>
<td>Male</td>
<td>CLVM</td>
<td>Lung, Liver, Left lower extremity, Pelvis, buttocks, Retroperitoneum</td>
<td>LMWH, Interferon, Ibuprofen, Surgical debulking, Sclerotherapy</td>
<td>Decreased blebbing, leaking, Drain removal, Decreased leg circumference</td>
</tr>
<tr>
<td>4</td>
<td>14 years</td>
<td>Female</td>
<td>LM</td>
<td>Chylous pleural effusion, Mediastinum, Spleen, Bone lesions</td>
<td>Chest Tube, Pleurodesis, Ligation of the thoracic duct, Celecoxib</td>
<td>Resolution of pleural effusion, Stabilization of bony lesions</td>
</tr>
<tr>
<td>5</td>
<td>14 years</td>
<td>Female</td>
<td>LM</td>
<td>Bilateral pleural effusions, Pericardial effusion, Bone lesions</td>
<td>Chest Tube, Pleurodesis, Ligation of the thoracic duct, Celecoxib</td>
<td>Resolution of effusions, Stabilization of bony lesions</td>
</tr>
<tr>
<td>6</td>
<td>7 months</td>
<td>Male</td>
<td>LM</td>
<td>Bilateral chylous pleural effusions, Bone lesions, T11-L4, Liver, Intraabdominal Spleen</td>
<td>VATS x2, Pleurodesis, Ligation of thoracic duct, Pericardial window, Chest tubes</td>
<td>Resolution of pleural effusions and respiratory failure, Near-complete resolution of abdominal lesions, Normalization of PT, PTT, fibrinogen, Improvement in bony lesions, Improvement in gross motor skills</td>
</tr>
</tbody>
</table>
RESULTS

• Summary of first 6 patients treated with sirolimus
  – Demographics Gender: 3 male, 3 female
  – Age: 7 months to 14.75 years (mean 7.25 years)
  – Diagnoses: 1 KHE with KMP, 1 CLVM, 4 lymphatic malformations
  – Heavily pretreated (3 to 6 prior interventions)

• Results
  • All had improvement in symptoms
  • None had exacerbation of disease while on sirolimus
  • Side effects were tolerable
RESULTS

• Patient 6: Bony Lesions

Before sirolimus therapy

16 months on sirolimus therapy
RESULTS

- Patient 2
RESULTS

• Average length of initial treatment: 21 months (range 2-31 months)
• Average length of follow up: 43 months (range 28 -59 months)
• Five of six patients have required additional treatment: 4 are currently on low-dose sirolimus (once daily) and one of these is starting to taper
CONCLUSIONS

- Sirolimus is an effective medication for life-threatening vascular anomalies with good responses and limited side effects.
- Patients have had no long term or developmental issues observed to date.
- Patients with symptoms of recurrence elected to be restart sirolimus for improvement in quality of life.
- Sirolimus shows particular promise in the treatment of KHE and can stabilize other diagnoses, but is not a cure.
CONCLUSIONS

• Further studies are needed to identify mechanisms and to determine optimal length of therapy, as well as to continue to monitor for long-term side effects.

• These findings are currently being further evaluated in a Phase II safety and efficacy trial.
Phase II Clinical Trial

- FDA funded, drug supplied by Pfizer, two institution study
- Children and young adults with complicated vascular anomalies (0-31 years)
- Primary Aims:
  - Determine Efficacy
  - Demonstrate Safety
- Secondary Aim: Biomarker Analysis
  - Blood: VEGF-A, C, D, II-8, Pleiotrophin, IGF-1, Endothelin-1, Thrombospondin and Angiopoietin-1/2
  - Tissue: Phosphorylated Akt, phosphorylated ERK-1/2, mTOR, and phosphorylated S6 kinase
- Accrual: 60 patients (currently 39 enrolled)
- Oral sirolimus therapy: initial dosing 0.8mg/m²/dose BID; target 10-15 ng/mL

Eligible Diagnoses:
- KHE +/- KMP
- Tufted Angioma +/- KMP
- Capillary Lymphaticovenous Malformation (CLVM)
- Lymphaticovenous Malformation (LVM)
- Microcystic Lymphatic Malformation
- Capillary Lymphatic Arterial Venous Malformations
- PTEN Overgrowth syndrome + vascular anomaly
- Lymphangiectasia Syndromes

Qualifying Complications:
- Coagulopathy
- Chronic pain
- Recurrent cellulitis (>3/year)
- Ulceration
- Visceral and or bone involvement
- Cardiac dysfunction

Clinicaltrials.gov
REFERENCES

1. *Sirolimus for the Treatment of Complicated Vascular Anomalies in Children* - Adrienne M. Hammill, MD, PhD, MarySue Wentzel, RN, Anita Gupta, MD, Stephen Nelson, MD, Anne Lucky, MD, Ravi Elluru, MD, PhD, Roshni Dasgupta, MD, Richard G. Azizkhan, MD, and Denise M. Adams, MD

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THANK YOU