Medical and surgical treatment of vascular malformations

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No disclosures
ISSVA Classification

• Tumors
  • Benign
  • Locally aggressive or borderline
  • Malignant

• Vascular malformations
  • Capillary malformations
  • Lymphatic malformations
  • Venous malformations
  • Arteriovenous malformations
Vascular Tumors

• Tumors: benign
  • Infantile hemangioma (IH)

Natural evolution

- Proliferation
- Involution
- Complete resolution

Conservative
Vascular Tumors

• Tumors: benign
  • Infantile hemangioma (IH)

Conservative

Medication

Propranolol\(^1\)
early start
1-2mg/kg/day
Vascular Tumors

• Tumors: benign
  • Infantile hemangioma (IH)

Conservative

Medication

Propranolol\(^1\)
early start
1-2mg/kg/day
Vascular Tumors

• Tumors: benign
  • Infantile hemangioma (IH)

Propranolol: side effects
• Frequent: mild (bronchitis, sleep disorders, diarrhea, ...)
• Rare: bronchospasm, bradycardia, hypotension

Propranolol\(^1\)
early start
1-2mg/kg/day
Vascular Tumors

- Tumors: benign
  - Infantile hemangioma (IH)

Medication

- Propranolol
- Sirolimus$^3$

Conservative

non-responders?
with propranolol?
• Tumors: benign
  • Infantile hemangioma (IH)

Surgical indications:
• non-responders
• strawberry-like
• scalp with alopecia
Vascular Tumors

• Tumors: benign
  • Infantile hemangioma (IH)

Surgical indications:
• non-responders
• strawberry-like
• scalp with alopecia
Vascular Tumors

• Tumors : benign
  • Congenital Hemangioma (CH) : Rapidly Involuting CH
Vascular Tumors

- Tumors: benign
  - Congenital Hemangioma (CH): Partially or Non-involutive CH

Surgery
Vascular Malformations

- Malformations : slow-flow
  - Capillary Malformations (CM)

- Tissue hypertrophy

Conservative
Lazer
Surgery
Vascular Malformations

• Malformations: slow-flow
  • Capillary Malformations (CM)

• Tissue hypertrophy
• Partial resections

Vascular Malformations

• Malformations : slow-flow
  • Lymphatic Malformations (LM)

Sirolimus : VASE trial (EudraCT: 2015-001703-32)
• to treat slow-flow malformations
• 200 patients, 155 with 6 months follow-up, 55 with 2 years follow-up
• 86% efficacy

• Sirolimus\textsuperscript{6}
  • mTOR inhibitor
  • 2mg daily
Vascular Malformations

• Malformations : slow-flow
  • Lymphatic Malformations (LM)

Sirolimus : VASE trial (EudraCT: 2015-001703-32)
  • to treat slow-flow malformations
  • 200 patients, 155 with 6 months follow-up, 55 with 2 years follow-up
  • 86% efficacy

Sirolimus : side effects
  • Very frequent (80-85%): mild (asthenia, mucositis, diarrhea, headache)
  • Grade 3 (15%): mucositis and asthenia
    • dose reduction or temporary stop

• Sirolimus
  • mTOR inhibitor
  • 2mg daily
Vascular Malformations

• Malformations : slow-flow
  • Lymphatic Malformations (LM)

Sirolimus : VASE trial (EudraCT: 2015-001703-32)
  • to treat slow-flow malformations
  • 200 patients, 155 with 6 months follow-up, 55 with 2 years follow-up
  • 86% efficacy

Alpelisib
  • Severe bilateral head and neck LM (1 patient)⁷
  • Efficacy on PIK3CA-related LM in mouse model⁸

• Sirolimus⁶
  • mTOR inhibitor
  • 2mg daily

• Alpelisib ?
  • PIK3CA inhibitor
Vascular Malformations

- Malformations: slow-flow
  - Lymphatic Malformations (LM)

- Surgery
  - complete resection
    - macrocystic
Vascular Malformations

• Malformations : slow-flow
  • Lymphatic Malformations (LM)

Conservative
Sclerotherapy
Medication
Surgery

• complete resection
  • macrocystic
  • cutaneous

• associated with medication
Vascular Malformations

- Malformations: slow-flow
  - Venous Malformations (VM)

Sirolimus: VASE trial (EudraCT: 2015-001703-32)
- to treat slow-flow malformations
- 200 patients, 155 with 6 months follow-up, 55 with 2 years follow-up
- 86% efficacy

Sirolimus\(^6\)
- mTOR inhibitor
- 2mg daily
Vascular Malformations

• Malformations: slow-flow
  • Venous Malformations (VM)
  • VASE study\(^6\)

-\(\text{Conservative}\)
-\(\text{Sclerotherapy}\)
-\(\text{Medication}\)

• Sirolimus\(^6\)
  • mTOR inhibitor
  • 2mg daily

• Alpelisib ?
  • PIK3CA mutations found in 20%\(^9\)
Vascular Malformations

- Malformations: slow-flow
  - Venous Malformations (VM)

- Conservative
- Sclerotherapy
- Medication
- Surgery
- Complete resection
  - Well defined
Vascular Malformations

- Malformations : slow-flow
  - Venous Malformations (VM)

- complete resection
  - well defined
  - superficial
Vascular Malformations

• Malformations: slow-flow
  • Venous Malformations (VM)

Conservative
Sclerotherapy
Medication
Surgery

• complete resection
  • well defined
  • superficial
• partial resection

Julien Coulie
Vascular Malformations

• Malformations : slow-flow
  • Venous Malformations (VM)

Conservative
Sclerotherapy
Medication
Surgery

• complete resection$^5$
  • well defined
  • superficial
• partial resection$^5$
• associated with medication
Vascular Malformations

- Malformations: slow-flow
  - Surgery in association with Sirolimus

- Utility of Sirolimus in the perioperative setting
  - no more complications
  - no interruption of Sirolimus

Medication
Surgery
Vascular Malformations

• Malformations: slow-flow
  • Glomuvenous malformation (GVM)
  • Clinic: firm, less compressible, and usually more painful
  • Poor response to medication
  • Surgical resection
Vascular Malformations

• Malformations: slow-flow
  • Fibro-adipose vascular anomaly (FAVA)
  • Imagery: venous malformation associated with adipose tissue
  • Poor response to medication
  • Surgical resection
Vascular Malformations

• Malformations: slow-flow
  • PIK3CA-related overgrowth syndrome (PROS)
  • heterogenous segmental overgrowth phenotypes
  • with or without vascular anomalies
    • CLOVES

Conservative

Surgery

• partial resection
• liposuction
Vascular Malformations

• Malformations : slow-flow
  • PIK3CA-related overgrowth syndrome (PROS)
  • heterogenous segmental overgrowth phenotypes
• with or without vascular anomalies
  • CLOVES
  • Klippel-Trenaunay Syndrome (KTS)
    • persistance of embryonic vein

Conservative

Surgery

• partial resection
Vascular Malformations

• Malformations : slow-flow
  • PIK3CA-related overgrowth syndrome (PROS)
  • heterogenous segmental overgrowth phenotypes
  • with or without vascular anomalies
    • CLOVES
    • Klippel-Trenaunay Syndrome (KTS)

Conservative

Surgery

Medication

• Sirolimus
  • mTOR inhibitor
  • 2mg daily
Vascular Malformations

• Malformations : slow-flow
  • PIK3CA-related overgrowth syndrome (PROS)
  • heterogenous segmental overgrowth phenotypes
  • with or without vascular anomalies
    • CLOVES
    • Klippel-Trenaunay Syndrome (KTS)

Alpelisib : EPIK-P1\textsuperscript{10} study
  • retrospective chart review study
  • 57 patients
  • endpoint : effectiveness of therapy after 24 weeks
  • 37.5% response observed at 24 weeks

  • effect on tissue hypertrophy

Conservative

Surgery

Medication

• Sirolimus\textsuperscript{6}
  • mTOR inhibitor
  • 2mg daily

• Alpelisib\textsuperscript{10}
  • PIK3CA inhibitor
  • 250mg daily
Vascular Malformations

- Malformations: slow-flow
  - PIK3CA-related overgrowth syndrome (PROS)

Alpelisib: EPIK-P1\textsuperscript{10} study
- retrospective chart review study
- 57 patients
- endpoint: effectiveness of therapy after 24 weeks
- 37.5\% response observed at 24 weeks

Alpelisib: side effects
- Frequency?: peripheral insulin resistance\textsuperscript{11}
- Mild: aphthous ulcer\textsuperscript{10}, stomatitis\textsuperscript{10}

Conservative
Surgery
Medication

- Sirolimus\textsuperscript{6}
  - mTOR inhibitor
  - 2mg daily

- Alpelisib\textsuperscript{10}
  - PIK3CA inhibitor
  - 250mg daily
Vascular Malformations

• Malformations: fast-flow
  • Arterio-venous Malformations (AVM)

### Table 3. Probability of Arteriovenous Malformation Recurrence after Treatment

<table>
<thead>
<tr>
<th>Stage</th>
<th>Embolization Only (254 Treatments in 102 Patients)</th>
<th>Resection with or without Embolization (118 Treatments in 98 Patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Probability (%)</td>
<td>95% CI (%)</td>
</tr>
<tr>
<td>Overall</td>
<td>81</td>
<td>73–87</td>
</tr>
<tr>
<td>Stage I</td>
<td>99</td>
<td>95–100</td>
</tr>
<tr>
<td>Stage II</td>
<td>99</td>
<td>95–100</td>
</tr>
<tr>
<td>Stage III</td>
<td>99</td>
<td>94–100</td>
</tr>
<tr>
<td>Stage IV</td>
<td>100</td>
<td>100–100</td>
</tr>
</tbody>
</table>

• complete resection\textsuperscript{5,12}
• no partial resection
• associated with embolization\textsuperscript{5,12}
Vascular Malformations

• Malformations : fast-flow
  • Arterio-venous Malformations (AVM)

• Thalidomide\textsuperscript{13}
  • Multimodal antiangiogenic effect through VEGF inhibition
  • Anti-inflammatory effect through TNF\(\alpha\) and NO inhibition

• Prospective study, 18 patients
• All responders : reduced pain, ulcerations healed, bleedings stopped.
• 2 apparent complete radiological responses (arteriography)
• Ongoing compassionate use
  • alone or in association of embolization and/or surgery

Medication
• Thalidomide\textsuperscript{13}
  • 50mg daily
Vascular Malformations

• Malformations: fast-flow
  • Arterio-venous Malformations (AVM)

• Thalidomide\textsuperscript{13}

Active surveillance

Embolization

Surgery

Medication

• Thalidomide\textsuperscript{13}
  • 50mg daily
Vascular Malformations

• Malformations : fast-flow
  • Arterio-venous Malformations (AVM)

• Thalidomide\textsuperscript{13}

\begin{itemize}
  \item Thalidomide : side effects\textsuperscript{13}
    \begin{itemize}
      \item Very frequent : fatigue, asthenia
      \item Frequent : peripheral polyneuropathy
        \begin{itemize}
          \item reversible
        \end{itemize}
    \end{itemize}
\end{itemize}

• Thalidomide\textsuperscript{13}
  • 50mg daily
Vascular Malformations

• Malformations: fast-flow
  • Arterio-venous Malformations (AVM)

• Trametinib\textsuperscript{14}
  • Most genetic mutations found in RAS/RAF/ERK/MEK pathway
  • MEK inhibitor

• TRAMAV\textsuperscript{14} study (EudraCT: 2019-003573-26)
  • Prospective study, 10 patients, early results
  • 9 responders: reduced pain, ulcerations healed
  • 2 apparent complete radiological responses (arteriography)

• Thalidomide\textsuperscript{13}
  • 50mg daily

• Trametinib\textsuperscript{14}
  • 1mg daily
Vascular Malformations

• Malformations: fast-flow
  • Arterio-venous Malformations (AVM)

• Trametinib\textsuperscript{14}

Trametinib: side effects\textsuperscript{14}
• Very frequent: acneiform eruptions
• Frequent: bleedings (if AVM involves mucosa)
• Grade 3: 30\% in TRAMAV study

Active surveillance
Embolization
Surgery
Medication

• Thalidomide\textsuperscript{13}
  • 50mg daily
• Trametinib\textsuperscript{14}
  • 1mg daily
Vascular Malformations

• Malformations : fast-flow
  • Arterio-venous Malformations (AVM)

• Thalidomide$^{13}$
• Trametinib$^{14}$
• Other antiangiogenic or targeted therapy ?

Future role as adjuvant or neoadjuvant therapy ?
Conclusions

• Multimodal therapy
  - Sclerotherapy
  - Lazer
  - Embolization
  - Surgery
  - Medication

• Adapted to each clinical and radiological situation

• Theragnostic therapy
  - genetic diagnostic
  - select best responders to each therapeutic strategy
  - use specific available medication


14. Julien Coulie et al. Monocentric Pilot Trial evaluating the safety and efficacy of Trametinib in Arterio-Venous Malformations that are refractory to standard care. Oral presentation at ISSVA 2022 & MS in preparation
Conclusions

Thank you for your attention!