ANGIOSARCOMA AND HEMANGIOENDOTHELIOMA

Claudia Mª Valverde
Vall d’Hebrón University Hospital
VASCULAR TUMORS

BENIGN->
- Hemangioma

BORDERLINE
- Hemangioendothelioma

MALIGN->
- Angiosarcoma
- Kaposi
VASCULAR TUMORS

BENIGN->
- Hemangioma

BORDERLINE
- Hemangioendothelioma

MALIGN->
- Angiosarcoma
- Kaposi
HEMANGIOENDOTHELIOMA (HE)

Vascular tumors with a biologic behaviour intermediate between hemangioma and angiosarcoma: Ability to recur locally and some to metastatize but at a far reduced rate compared with angiosarcoma

Subtypes:
- Epithelioid HE
- Kaposiform HE
- Hobnail HE
- Epithelioid sarcoma-like HE
EPITHELIOID EH

Clinical features:
- Rare in childhood
- Both sexes equally
- Usually solitary, slightly painful mass

<table>
<thead>
<tr>
<th></th>
<th>SOFT TISSUE</th>
<th>BONE</th>
<th>LIVER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weiss et al.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local recurrence</td>
<td>13%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metastasis</td>
<td>31%</td>
<td>31%</td>
<td>61%</td>
</tr>
<tr>
<td>Mortality</td>
<td>13%</td>
<td>31%</td>
<td>43%</td>
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</table>

**EPITHELIOID EH**

- **Pathological features**
  - Angiocentric
  - Vascular differentiation more primitive
  - Short strands or solid nests of rounded/slightly spindled endothelial cells.
  - Form small intracellular lumens — "vacuoles"
  - Atypia, >1mit/10HPF, spindling or necrosis -> more aggressive

Weiss et al. Semin Diagn Pathol 1986
Clinical Features:
- Childhood
- Trunk, retroperitoneum.
- Kasabach-Merritt phenomenon
- Ill defined violaceus plaque
- No tendency to regress
- 10% mortality
- Virtually no metastatic.
KAPOSIIFORM HE

- Pathological features:
- Small CD31+ vessels surrounded by actin-positive pericytes-> glomeruloid
- IHQ: vascular (CD31, CD34, FLI1) and lymphatic components (D2-40)
HOBNAIL HE

• Dabska tumor
  - Children
  - Distal Extremities
  - Intraluminal growth of papillary endothelial structures
  - IHQ: CD31, CD34, vWF, VEGF3

• Retiform HE
  - Adults
  - Distal Extremities
  - Local recurrence >.
  - Virtually no metastatic like Dabska. <10% N1
EPITHELIOID SARCOMA-LIKE HE

- Superficial or deep soft tissues of extremities
- Nodules of eosinophilic, cytokeratin + cells
- Atypia mild-moderate with low mitotic activity
- No multicellular vascular channels
- IHQ: CD31, FLI1 +, CD34-

ANGIOSARCOMA

- Malignant tumors that resemble many of the functional and morphological features of normal epithelium.
- Wide morphologic spectrum.
- <1% sarcomas
- Predilection for skin and superficial soft tissue
- At diagnosis, 128 (79.5%) patients had localized disease, whereas 31 (19%) had metastases.

<table>
<thead>
<tr>
<th>Location</th>
<th>N</th>
<th>%</th>
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<tbody>
<tr>
<td>skin</td>
<td>121</td>
<td>33</td>
</tr>
<tr>
<td>soft tissue</td>
<td>89</td>
<td>24</td>
</tr>
<tr>
<td>Breast</td>
<td>30</td>
<td>8</td>
</tr>
<tr>
<td>Liver</td>
<td>31</td>
<td>8</td>
</tr>
<tr>
<td>Bone</td>
<td>20</td>
<td>6</td>
</tr>
<tr>
<td>Spleen</td>
<td>16</td>
<td>4</td>
</tr>
<tr>
<td>Heart &amp; GV</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>Other</td>
<td>49</td>
<td>14</td>
</tr>
<tr>
<td>All</td>
<td>366</td>
<td>100</td>
</tr>
</tbody>
</table>

Data from AFIP 1966-76. Adapted from Enzinger & Weiss

ANGIOSARCOMA

Etiology/associations:
- Chronic lymphedema
- Radiotherapy
- A-V fistulas
- Foreign material
- Carcinogens: Thorotrast, AsO3 insecticides, Vinyl Chloride
- Other diseases: NF, bilateral Rb, XP
ANGIOSARCOMA

*Poor prognosis:
- Delayed diagnosis
- Margins and multifocal
- Size-> <5 cm 32% 5y OS
  > 5 cm 13% 5y OS
- Localized/ metastatic disease. M1 lung, liver, nodes.
- Primary tumor: visceral/bone vs soft tissue
- ECOG

ANGIOSARCOMA (AS)

Clinical types:
- Cutaneous AS not associated with lymphedema
- Cutaneous AS associated with lymphedema
- Breast AS
- Soft tissue AS
- Radiation induced AS
CUTANEUS AS NOT ASSOCIATED WITH LYMPHEDEMA

- The most common
  AS
- Elderly patients
- Men>Women
- H&N (scalp).
- Margins difficult
- Often multifocal
CUTANEUS AS NOT ASSOCIATED WITH LYMPHEDEMA

- Larger chromatic nuclei
- Papillations
- Irregular vascular channels infiltrating the dermis
- IHQ-> vWF, CD34, CD31.
- Citogenetics-> gains crom 5,8,20 and losses 4,7,22,Y.

CUTANEUS AS ASSOCIATED WITH LYMPHEDEMA

- Steward-Treves Synd.
- Obesity!
- 90% after mastectomy (0.45% mastectomies).
- Latency 10-15y
- 7º decade. (Congenital younger).
- OS 31m
- M1 lung, pleural and chest wall

- Small capillary-sized vessels
- Association with lymphangiomatosis

Woodward AH et al. Cancer 1972
Shon W et al. J Cutan Pathol. 2011
BREAST AS

• Affects breast parenchyma
• Rapidly growing without classic signs of carcinoma
• 3-4º decade
• Early metastasis: lung, skin & bone
• mOS 3-5 y

Vorburger et al. Cancer 2005
BREAST AS

- Ill-defined
- Cellular areas with atypia, mitotic activity and necrosis
SOFT TISSUE/ AS

- All ages
- Extremities or abdominal cavity
- AP-> More epithelioid
- IHQ-> vWF, CD31 and some cytoketatin +.
- 1/3 associated to other diseases: NF
- 50% M1: lung, N1, bone & soft tissue.

RADIOThERAPy INDUCED AS

- 5-10 years latency
- Median 50Gy
- Ecchymosed or thickening of the skin
- Multifocal
- 50% recur and 40% M1

TREATMENT

Angiosarcoma after breast-conserving therapy: long-term outcomes with hyperfractionated radiotherapy.

Progression-free survival rates for the 14 patients at 2 years and 5 years were 71% and 64%, respectively.

The overall and cause-specific survival rates were both 86% at 2 years and 5 years.

TREATMENT: HE

IFN α-2B-> There are several case reports of patients with EHE achieving partial or more complete remission after treatment with interferon α-2B.

Two of these patients had pulmonary involvement as part of more widespread disease.

As part of a more complex treatment strategy including transplantation or resection

Kayler et al. Transplantation 2002;74,128-130
Rosenthal et al. Skeletal Radiol 2001;30,219-222
Vignon-Pennamen et al Ann Dermatol Venereol 1997;124,165-166
Roudier-Pujol et al. Ann Dermatol Venereol 1994;121,898-904
* Complete response to six courses of carboplatin plus etoposide chemotherapy in a patient with pleural EHE is also described, with full remission at 18-month follow-up.

* Complete response after metronomic cyclofosfamide 100mg/12h + prednisone 20mg/d 1w on/1w off


Selective intra-arterial Y-90 microsphere therapy in hemangioendothelioma.

PFS 18m

TREATMENT ANGIOSARCOMA

* CHEMO:
- Anthracyclines+ Ifosfamide
- Gemcitabine alone
- Taxanes
- Combinations

* TARGETED THERAPIES
TREATMENT

SARCOMA CHEMO:

- Anthracyclines +/- Ifosfamide
- Gemcitabine alone
- Taxanes
- Combinations
ANTHRACYCLINES

<table>
<thead>
<tr>
<th>Ref</th>
<th>N</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Holloway et al 2005</td>
<td>1</td>
<td>LPD+RT (30 Gy)</td>
<td>PR 4y</td>
</tr>
<tr>
<td>Eiling et al 2002</td>
<td>1</td>
<td>LPD+RT</td>
<td>CR 4m</td>
</tr>
<tr>
<td>Lankester et al. 1999</td>
<td>1</td>
<td>LPD+RT</td>
<td>CR 15m</td>
</tr>
<tr>
<td>Skubitz KM et al 2005</td>
<td>6</td>
<td>LPD</td>
<td>3PR 6, 19, &gt;20 m</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>2 SD 7, 11 m</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1PD</td>
</tr>
<tr>
<td>Italiano A et al 2011</td>
<td>42</td>
<td>Doxo</td>
<td>2 CR (6%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>8PR (23%)</td>
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<td></td>
<td></td>
<td></td>
<td>10 SD (29.5)</td>
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</tbody>
</table>

- Respuestas no dependientes de localización
- PFS 3.7-5.4m
TREATMENT

SARCOMA CHEMO:
- Anthracyclines+- Ifosfamide
- Gemcitabine alone
- Taxanes
- Combinations
GEMCITABINE

- Gem as a single agent (1000 mg/m² i.v. every week for 3 weeks every 4 weeks).
- 8/25 pts radiation induced sarcomas.

<table>
<thead>
<tr>
<th></th>
<th>N</th>
</tr>
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<tbody>
<tr>
<td>Total</td>
<td>25</td>
</tr>
</tbody>
</table>

RR 68%
mPFS 7m
mOS 17m

TREATMENT

SARCOMA CHEMO:
- Anthracyclines+- Ifosfamide
- Gemcitabine alone
- Taxanes
- Combinations
Recent studies present paclitaxel as a single agent with substantial activity against angiosarcoma of the scalp or face, even in patients previously treated with chemotherapy or radiation therapy.
TAXANES

- Case Reports

<table>
<thead>
<tr>
<th>Ref</th>
<th>N</th>
<th>Treatment</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skubitz KM et al. 2005</td>
<td>8</td>
<td>Paclitaxel w</td>
<td>2</td>
<td>3</td>
<td></td>
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<tr>
<td>Vakkalanka B et al. 2010</td>
<td>1</td>
<td>Paclitaxel neo</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Nagano et al. 2007</td>
<td>9</td>
<td>Docetaxel 25mg/m2/w</td>
<td>2</td>
<td>4</td>
<td></td>
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</tbody>
</table>

- Clinical studies/larger series

<table>
<thead>
<tr>
<th>Ref</th>
<th>N</th>
<th>Treatment</th>
<th>RR(CR+PR)</th>
<th>mTTP</th>
<th>mOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schlemmer et al. 2008</td>
<td>32</td>
<td>Paclitaxel w</td>
<td>62% (78% scalp)</td>
<td>7.6m (9.6m scalp)</td>
<td></td>
</tr>
<tr>
<td>Penel N et al. 2008: ANGIOTAX</td>
<td>30</td>
<td>Paclitaxel w</td>
<td>74% (CR+PR+SD) &amp; 2m 42% after 4m</td>
<td>4m</td>
<td>8m</td>
</tr>
<tr>
<td>Italiano A et al 2011</td>
<td>75</td>
<td>Paclitaxel w</td>
<td>53%</td>
<td>4.9</td>
<td>8.5</td>
</tr>
</tbody>
</table>


- 40% 2-3rd line
- RR pretreated= naive
- >RR in scalp
- After adjustment to the performance status and compared with exclusive palliative care, the following treatments significantly improve the outcome: doxorubicin-based regimen as first-line chemotherapy (HR = 0.38, P = 0.0165), weekly paclitaxel as first-line regimen (HR = 0.36, P = 0.0146) and metastasectomy (HR = 0.09, P = 0.0221).
Angiosarcoma: a study of 98 cases with immunohistochemical evaluation of TLE3, a recently described marker of potential taxane responsiveness.

98 total cases; 37 cutaneous, 48 soft tissue/visceral and 13 post-irradiation

The median time to death was 2.1 years.
TLE3 reactivity was observed in 0/37 (0%) cutaneous angiosarcomas, in 28/48 (58%) cases from soft tissue/viscera and in 4/13 (31%) post-irradiation angiosarcomas. (p = <0.0001).
Improved 5-year survival was seen in vasoformative angiosarcomas (p = 0.03).

TLE3 expression was not associated with taxane response

TREATMENT

SARCOMA CHEMO:
- Anthracyclines+- Ifosfamide
- Gemcitabine alone
- Taxanes.
- Combinations
Angiosarcoma of the scalp with complete response to a biweekly gemcitabine and docetaxel (GEMDOC) chemotherapy regimen.

Gemcitabine (1,500 mg/m²) and docetaxel (50 mg/m²) administered biweekly. The patient was free of disease at the 15-month follow-up.

A case of advanced scalp angiosarcoma successfully treated with combination chemotherapy of adriamycin, cisplatin and ifosfamide.

Adriamycin, cisplatin, ifosfamide and paclitaxel combination as front-line chemotherapy for locally advanced and metastatic angiosarcoma. Analysis of three case reports and review of the literature.

Adriamycin 40 mg/m2 day 1, ifosfamide 3 g/m2 day 1-2, cisplatin 35 mg/m2 day 1-2 and paclitaxel 175 mg/m2 day 3

Shkoukani MA et al. Ear Nose Throat J. 2011
TREATMENT ANGIOSARCOMA

* CHEMO:
- Anthracyclines+- Ifosfamide
- Gemcitabine alone
- Taxanes.
- Combinations

• TARGETED THERAPIES:
- Antiangiogenics
- Other
In an immunohistochemical study of 49 angiosarcomas, more than half of the tumors were positive for all three markers: D2-40 (53%), VEGFR3 (57%) and Prox-1 (76%)
Sporadic cutaneous angiosarcomas generally lack hypoxia-inducible factor 1alpha: a histologic and immunohistochemical study of 45 cases. Accordingly, the hypoxic response pathway is not thought to be a documentable common mechanism of angiogenesis in this entity.

Abedalthagafi M et al. Ann Diagn Pathol. 2010
Consistent MYC and FLT4 gene amplification in radiation-induced angiosarcoma but not in other radiation-associated atypical angiosarcoma or other radiation-associated atypical vascular lesions.

High-level MYC amplification was found in 100% of secondary AS, but in none of the AVL or other radiation-associated sarcomas.

Guo T et al. Genes Chromosomes Cancer. 2011
Koshiji M et al. The EMBO J. 2004
Coamplification of FLT4 (encoding VEGFR3) was identified in 25% of secondary AS, but not in other types.

3/6 patients with both MYC and FLT4 amplification, were treated with sorafenib with complete response in one patient (26 m on treatment) and a partial response in the remaining two.
KDR activating mutations in human angiosarcomas are sensitive to specific kinase inhibitors.

Expression profiling->AS up-regulation of vascular-specific receptor tyrosine kinases, including TIE1, KDR, SNRK, TEK, and FLT1.

Full sequencing of these five candidate genes identified 10% of patients harboring KDR mutations.

A KDR-positive genotype was associated with strong KDR protein expression and was restricted to the breast anatomic site with or without prior exposure to radiation.

Transient transfection of KDR mutants into COS-7 cells showed ligand-independent activation of the kinase

<table>
<thead>
<tr>
<th>KDR&lt;sup&gt;A1065T&lt;/sup&gt;</th>
<th>KDR&lt;sup&gt;D717V&lt;/sup&gt;</th>
<th>KDR&lt;sup&gt;WT&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>

- Serum
- VEGF
- P-VEGFR2
- T-VEGFR2
- Actin

Which was inhibited by specific KDR inhibitors

<table>
<thead>
<tr>
<th></th>
<th>KDR&lt;sup&gt;A1065T&lt;/sup&gt;</th>
<th></th>
<th>KDR&lt;sup&gt;D717V&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorafenib (µM)</td>
<td>1.0</td>
<td>Sunitinib (µM)</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>0.5</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(-)</td>
<td>(-)</td>
<td></td>
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</tbody>
</table>

These data provide a basis for the activity of vascular endothelial growth factor receptor-directed therapy in the treatment of primary and radiation-induced AS.
Angiosarcoma of the retroperitoneum: report on a patient treated with sunitinib.

The hepatic mass tumors had VDT values of 16 days on paclitaxel, 66 days on doxorubicin, and 145 days on sunitinib.
Scalp Angiosarcoma Remission with Bevacizumab and Radiotherapy without Surgery: A Case Report and Review of the Literature.

<table>
<thead>
<tr>
<th>Ref</th>
<th>N</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Koontz et al.2008</td>
<td>2</td>
<td>Bvz+RT</td>
<td>2 CR 8.5&amp;26m</td>
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<tr>
<td>Gkalpakiotis et al.2008</td>
<td>1</td>
<td>RT</td>
<td>1CR 5y</td>
</tr>
<tr>
<td>De Yao et al.2011</td>
<td>1</td>
<td>Bvz+RT</td>
<td>1CR 7m</td>
</tr>
</tbody>
</table>

De Yao JT et al. Sarcoma. 2011
Antiangiogenetic therapy with pioglitazone, rofecoxib, and metronomic trofosfamide in patients with advanced malignant vascular tumors.

Patients: 5 angiosarcomas and 1 hemangioendothelioma

Treatment: pioglitazone (45 mg per day orally) plus rofecoxib (25 mg per day orally) and, after 14 days, trofosfamide (3 x 50 mg per day orally).

Outcome: 2 CR, 1 PR and 3 SD. PFS 7.7 months

<table>
<thead>
<tr>
<th>Ref</th>
<th>Phase</th>
<th>Treatment</th>
<th>N</th>
<th>RR</th>
<th>SD</th>
<th>mPFS</th>
<th>PFS 24w</th>
<th>mOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maki RB et al</td>
<td>II</td>
<td>Sorafenib 400 bid</td>
<td>37(VS)</td>
<td>14%</td>
<td>21%</td>
<td>3.8m</td>
<td></td>
<td>14.3</td>
</tr>
<tr>
<td>George S et al</td>
<td>II</td>
<td>Sunitinib 37.5mg</td>
<td>2</td>
<td>0%</td>
<td>0%</td>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Von Mehren M et al</td>
<td>II</td>
<td>Sorafenib 400 bid</td>
<td>8/37 (VS)</td>
<td>0%</td>
<td>75%</td>
<td>5m</td>
<td>38%</td>
<td>23m</td>
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<tr>
<td>Sleijfer S et al</td>
<td>II</td>
<td>Pazopanib 800mg</td>
<td>5/44(VS)</td>
<td>?</td>
<td>?</td>
<td>3m</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&quot;others&quot;</td>
<td></td>
</tr>
<tr>
<td>Agulnik M et al</td>
<td>II</td>
<td>Bevacizumab 15mg/kg/3w</td>
<td>26</td>
<td>12%</td>
<td>62%</td>
<td>?</td>
<td></td>
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</tbody>
</table>

TREATMENT ANGIOSARCOMA

* CHEMO:
- Anthracyclines+- Ifosfamide
- Gemcitabine alone
- Taxanes.
- Combinations

• TARGETED THERAPIES:
- Antiangiogenics
- Other
Clinicopathologic assessment of postradiation sarcomas: KIT as a potential treatment target.

Fourteen of 16 tumor samples were KIT-positive (88%).

Five of 23 (22%) spontaneous soft tissue sarcomas of comparable histological types, including 2 angiosarcomas, were KIT-positive.

No mutations in exon 11 of the c-kit gene were found.
Dramatic and durable efficacy of imatinib in an advanced angiosarcoma without detectable KIT and PDGFRA mutations.

Phase I evaluation of a fully human anti-αv integrin monoclonal antibody (CNTO 95) in patients with advanced solid tumors.

A fully human monoclonal antibody to anti–αv integrins (CNTO 95) has been shown to inhibit angiogenesis and tumor growth in preclinical studies.

Of the six patients who received extended dosing, one patient (10.0 mg/kg), with cutaneous angiosarcoma, had a 9-month partial response.

Cancer-specific mutations in PIK3CA are oncogenic in vivo.

They induce tumors in the chorioallantoic membrane of the chicken embryo and cause hemangiosarcomas in the animal. These tumors are marked by increased angiogenesis and an activation of the Akt pathway.

The H1047R induced tumors classify as hemangiosarcomas; tumors caused by the helical domain mutations E542K and E545K were diagnosed as either hemangiomas or hemangiosarcomas.

Inhibition of H1047R-induced tumor growth by RAD001 therapy (10mg/kg/d)

INMUNOTHERAPY:
Complete remission in a patient with angiosarcoma by the combination of OK-432, rhIL-2, and radiotherapy.
Recombinant human interleukin-2 (rhIL-2) has been used for the treatment of angiosarcoma because it has a direct effect on tumor cells and also activates natural killer (NK) cells, and lymphokine-activated killer (LAK) cells.

OK-432, a penicillin- and heat-inactivated lyophilized powder of a Streptococcus pyogenes A3 sub strain. Toll-like receptor 4 (TLR4) on dendritic cells (DCs) recognize OK-432 polysaccharide antigen->signaling pathway->expression of inflammatory genes and stimulates dendritic cells.

OK-432 for 6 days followed by rhIL-2 for 30 days. The levels of NK cell and LAK cell activity were up-regulated after combination therapy.

INMUNOTHERAPY:

Liposome-encapsulated muramyl tripeptide phosphatidylethanolamine adjuvant immunotherapy for splenic hemangiosarcoma in the dog: a randomized multi-institutional clinical trial.

Thirty-two dogs with HSA and without gross evidence of metastases were treated with splenectomy, stratified by clinical stage, and randomized to receive doxorubicin/cyclophosphamide chemotherapy and either L-MTP-PE immunotherapy or lipid equivalent (placebo liposomes).

Dogs receiving L-MTP-PE had significantly prolonged disease-free survival ($P = 0.037$) and overall survival ($P = 0.029$).

Dogs receiving L-MTP-PE had significantly greater serum tumor necrosis factor-alpha ($P < 0.001$) and interleukin 6 ($P = 0.007$) activities.

Galectin-3 as a potential therapeutic target in tumors arising from malignant endothelia.

Galectin-3 (Gal-3), a beta-galactoside-binding lectin implicated in tumor progression and metastasis, endothelial cell biology and angiogenesis, and regulation of apoptosis and neoplastic cell response to cytotoxic drugs

CONCLUSIONS

Rare: <1% sarcomas and heterogeneous group.

* Poor prognosis
* Surgery remains mainstay of treatment +/- RT as in other sarcomas
* Histotype tailored chemotherapy-> Taxanes & anthracyclines
* Novel approaches:
  - Antiangiogenics: TKIs, Mabs, ..
  - Immunotherapy
  - Others: PI3K, Gal3, integrins

Need for specific trials and international collaboration!
Thank you!