Tumor and Angiogenesis: Targeting the targets.

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Goals of discussion -
- Discuss angiogenesis
- Discuss anti-angiogenesis strategies
- Discuss metronomic chemotherapy
- The use of metronomic chemotherapy and tyrosine kinase inhibitors in veterinary medicine
- Discuss side effects of these agents and their management

Angiogenesis

- Formation of new vessels from existing
- Multiple step process
- Several methods
- Key triggers:
  - Hypoxia
  - Glucose deprivation
  - Cellular acidosis
Angiogenesis and tumor

- Needed for tumor progression, survival and metastatic disease.
- Without vascular supply - tumor proliferation and apoptosis are balanced
- Angiogenic switch - multiple factors
- Balance from anti-angiogenic shifts to pro-angiogenic

ANTI-ANGIOGENIC
- Angiostatin
- Endostatin
- Thrombospondin-1/2
- Vascostatin
- Platelet-associated platelet factor-4
- Osteopontin
- Tissue inhibitor metalloproteinases (TIMP)
- Interleukin -12

ANGIOGENIC
- Vascular endothelial growth factor (VEGF)
- Platelet-derived growth factor (PDGF)
- Angiopoietins
- Acidic and basic growth factors
- Transforming growth factor-a/b
- Tumor necrosis factor-a
- Epidermal growth factor
- Cyclooxygenase-2
- Interleukin-6/8

4 tumor strategies
- 1. Angiogenesis
  - Sprouting and non-sprouting
- 2. Vascular co-option
  - Tumor grows along blood vessels
- 3. Vasculogenesis
  - Bone marrow driven
- 4. Vasculogenic mimicry
  - Multistep, multi-strategy
Tyrosine Kinase

- Protein tyrosine kinase - TK's
  - Kinases have ability to phosphorylate other proteins
  - Cell surface, cytoplasm and intracellular
  - Stimulation leads to ordered sequence of events:
    - Gene activation/inhibition
    - Proliferation
    - Survival
    - Migration
- Split kinase family
- "split" by kinase insert
**RTK dysregulation - Human cancer**

<table>
<thead>
<tr>
<th>Receptor Tyrosine Kinase (RTK)</th>
<th>Tumor Type</th>
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<tbody>
<tr>
<td>EGFR family</td>
<td>Breast, ovarian, lung, colon, stomach, glioblastoma</td>
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<tr>
<td>IGF family</td>
<td>Sarcomas - cervical, kidney</td>
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<tr>
<td>PDGFR family</td>
<td>Glioblastoma, ovarian, CML</td>
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<tr>
<td>KIT AML</td>
<td>AML, GIST, lung, seminoma, MCT</td>
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<tr>
<td>VEGF family</td>
<td>HSA, Kaposi's sarcoma, melanoma, angiogenesis</td>
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<tr>
<td>FLT3 AML</td>
<td>AML</td>
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<tr>
<td>NGRF family</td>
<td>Papillary thyroid, FSA, AML</td>
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<tr>
<td>MET AML</td>
<td>Papillary thyroid, osteosarcoma, liver, colon, kidney</td>
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<tr>
<td>AXL AML</td>
<td>AML</td>
</tr>
<tr>
<td>Tie family</td>
<td>Stomach, hemangioblastoma, angiogenesis</td>
</tr>
<tr>
<td>RET family</td>
<td>Thyroid, MEN</td>
</tr>
<tr>
<td>ALK non-Hodgkin's lymphoma</td>
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**Receptor tyrosine kinase and angiogenesis**
- Tumor needs adequate blood supply
- Multistep process
- Recruitment of endothelial precursors to site and stimulated to grow to vessel with receptor activation
- Key factors
  - VEGF
  - PDGF
  - FGF

**Tyrosine kinase inhibitors**
- Small molecule inhibitors
- Target specific protein - often an ATP binding site
- Block protein function - blocks downstream signal
- Often orally administered
Tyrosine kinase inhibitors (TKI’s) in veterinary medicine

- Gleevec™ (Imatinib mesylate)
- Palladia™ (Toceranib phosphate)
- Kinavet-CA1™ (Masitinib mesylate)
Palladia™
Small molecule inhibitor
Tyrosine kinase inhibitor
SU11654

Palladia
Approved for Grade II and III mast cell tumor
With or without regional lymph node involvement
Blocks C-KIT
Blocks other tyrosine kinase receptors:
VEGFR 1/2/3
PDGFR α/β
FLT3
RET
CSF-1

Proangiogenesis: Mediated by VEGF Family of Growth Factors and Receptor Tyrosine Kinases (RTKs)
Initial phase I trial for Palladia

- Mast cell tumor responses
- Other tumors: carcinoma, sarcoma, MM, melanoma
- Inhibition of VEGF, PDGF and KIT

Suninitib
- Activity in other tumor types
- Renal cell carcinoma, GIST, pancreatic NET

Preliminary evidence for biologic activity of toceranib phosphate (Palladia®) in solid tumors

- Administration of Palladia to dogs with other tumor types
- Biological activity
  - Anal gland carcinoma
  - Metastatic OSA
  - Thyroid
  - Head and neck carcinoma
  - Nasal
- Single agent or in combination
- VCO 2012

Low dose chemotherapy or metronomic therapy
- Continuous therapy with low dose anti-cancer drugs
- Goal: affect tumor microenvironment
- Tumor vasculature, stroma, circulating endothelial precursors (CEPs)
- VEGF inhibitors with low dose cytotoxic chemotherapy
- Immunomodulatory effects
- Time

Chemotherapy types
- Cytotoxic
- Targeted
Palladia and metronomic chemotherapy
- Initial dose 3.25 mg/kg PO EOD
- 2.0 – 2.75mg/kg PO EOD v. MWF
- Often used with cyclophosphamide or chlorambucil
- NSAID therapy
- Concurrent chemotherapy

Combination therapy - 3 drugs
- Palladia
- Cyclophosphamide or chlorambucil
- NSAID
- Tumors:
  - All types
  - Increased consideration for hematopoietic malignancies

Side effects
- Range of toxicities noted
- Likely influenced by:
  - Stage of disease
  - Concurrent disease
  - Other medications
  - Type of malignancy
- Dose
Side effects - clinical signs

- Gastrointestinal
  - Diarrhea
  - Anorexia
  - Vomiting
  - Weight loss
  - Nausea
  - Lameness

Laboratory changes

- Hematologic
  - Neutropenia
  - Thrombocytopenia
  - Anemia
- Biochemical
  - Increase ALT
  - Hypoalbuminemia
  - Hyperbilirubinemia
  - Elevated creatinine

- Hepatic
  - Elevated LE’s, failure
- Renal
  - PLE, failure
  - Pancreatitis
  - Hypertension
  - Other
Management

Gastrointestinal:
- Drug holiday
- Concurrent medications:
  - Prednisone
  - Gastric protectants
  - Anti-emetics
  - Anti-diarrheal

Hematological
- Neutropenia
- Thrombocytopenia
- Monitor

Renal
- ACE inhibitors
- Monitor

Hepatic
- Hepatic protectants
- Dose
Guidelines for use
2.5 - 2.75 mg/kg EOD v. MWF
Baseline:
Weight, CBC, Chemistry, UA, UPC, BP
Rechecks:
Weekly vs. every other week, then monthly
Monthly - PC, CBC, quarterly - full labs
Case based:
DVM education
Use with caution
Client education:
MONITOR, MONITOR, MONITOR