Novelty Topics

• Management of hypertension in children on new generation chemotherapy
  • Mechanisms of bevacizumab mediate hypertension
  • Implications for models of vascular control
• Blood pressure and cardiovascular risk management with new generation therapy of diabetes mellitus
  • Use of SGLT2 inhibitor medications
• Short tour of a large pheo cohort
Angiogenesis: The Basics

- Effectors:
  - VEGF
  - VEGF-R
  - HIF
  - HO
  - >20 other GFs

- This endothelial cell will generate a new capillary branch.
- Pseudopodial process guides the development of the capillary sprout as it grows into the surrounding connective tissue.
- Capillary sprout hollows out to form tube.
Angiogenesis and Solid Tumors

1971: Proposed as a therapy by Folkman

1999: First therapeutic agent tested in humans

2017: 26 agents on the market
Normal and Disordered Angiogenesis

Normal Angiogenesis
- Growth
- Vessel development
- Wound healing
- Maintenance of capillaries
- Podocyte stability
- ?? Endothelial function

Disrupted angiogenesis
- Non-healing
- Edema
- Nephrosis
- Hypertension
- Pre-eclampsia
Mechanism of Pre-eclampsia

Levine NEJM 2004; 350:672
Mechanism of bevacizumab

- Monoclonal antibody to VEGF to destabilize tumor angiogenesis
- Refractory solid tumors, especially in CNS and metastatic colon
- 94 children received at UAB in 2017
- Estimate >100,000 children currently being treated worldwide
Complications of antiangiogenic therapy

- Hypertension: 60-80%
- Hospitalized for hypertensive emergency: 8-12%
- Proteinuria: 25-40%
- Nephrotic Syndrome 10-15%
Mechanisms of bevacizumab hypertension

- Destabilizes endothelium resulting in impaired endothelium mediated vasodilation
- Blocks induction of eNOS by VEGF worsening endothelial dysfunction
- Induction of ET-1
- Podocyte derived VEGF is an autocrine stabilizer of glomerular capillaries – likely relevant to proteinuria
Mechanism based management of anti-angiogenic hypertension

- Infusion of VEGF or PIGF
  - Counterproductive considering tumor therapy

- Enoxaparin which increases renal clearance of sFLT
  - Might be useful for BP but unclear impact on anti-tumor efficacy or bleeding risk

- Induction of eNOS with arginine
  - Has potential but has not been tested in clinical trials

- CO exposure – induces VEGF through HIF and HO
  - Poor idea in many ways

- ET-1 antagonism (ambrisartan)
  - Likely good approach but drugs not readily available or tested in kids
Experience based therapy

- **Amlodipine (calcium channel blockade)**
  - Recommended 1st line therapy based on use in pre-eclampsia.
  - Sufficient in 50-80%

- **Carvedilol (beta blocker)**
  - Beta blockers shown to blunt maternal sFLT rise in pre-eclampsia literature.
  - Sufficient monotherapy 30-40%, so used as 2nd agent

- **Losartan (Angiotensin receptor blocker)**
  - Many recipients of bevacizumab have pre-existing renal injury and additional renin mediated hypertension or proteinuria
  - Not tested as monotherapy, used 2nd or 3rd agent

- **Lisinopril (Angiotensin Converting Enzyme Inhibitor)**
  - Same issues as ARB
Recommendations

- **Patients receiving anti-angiogenic tumor therapy require close monitoring of BP**
- **Aggressive BP management is required to mitigate morbidity**
- **Therapy**
  - Calcium Channel Blocker (amlodipine)
  - Beta Blocker (carvediolol or atenolol)
  - Angiotensin Receptor Blocker (losartan)
Sweet New Medication?

SGLT2 inhibitors

- Inhibits a Na Glucose transport protein resulting in increased glucosuria
- Used for adjunct therapy for Diabetes Mellitus
- Results in HBA1c improvement of 0.5-1.0% at 12mo
- Concerns regarding polyuria, dehydration and UTIs but not seen in clinical trials

- Initial Large Clinical Trials also showed
  - Improved CV survival
  - Improved BP
  - Decreased CKD Progression
  - Weight loss
SGLT2 Inhibitors - CV Outcomes

Impact of SGLT2i

REDUCED:
- HGBA1c
- Hypertension
- Renin-angiotensin activation
- Serum uric acid
- Vascular remodeling / Inflammation
- Decline of GFR

Cardiac Work reduced

• Preload and afterload reduced
• LVEDP reduced
• Lower cardiac oxygen demand

CV death
HF hospitalization reduced
Empargliflozin lowers BP

- All Type 2 Diabetics, 823 patients randomized to placebo, 10mg, 25mg
- BP endpoint ABPM
- Maximal BP effect seen with lower dose range of SGLT2i
- BP effects do not correlate with HgbA1c
- SBP and DBP reduction observed
- Effect seen in patients on no, 1, or multiple BP medications

Mancia. Hypertension 2016; 68:1355
Empagliflozin effects additive to diuretics and ACEI medications

Mancia. Hypertension 2016; 68:1355
Canagliflozin Reduces Serum Uric Acid in Patients with T2DM
(MJ. Davies, 2015)

- Serum uric acid levels reduced by ~13% in all patients and in a patient subset with hyperuricemia (uric acid ≥ 8 mg/dL)
- Pooled data from 4 Phase 3 trials with CANA (100 or 300 mg) for 26 weeks
- Mechanisms by which SGLT2Is reduce serum uric acid may involve the renal SLC2A9 (GLUT9) transporter (Caulfield 2008) and reduced hyperinsulinemia (Facchini 1991)
SGLT2i in pediatrics

- Nothing to report
- In light of BP data and CKD progression data, pediatric trials are needed
- Currently very expensive
Pheochromocytomas

- Pheochromocytoma = adrenal location
- Paraganglioma = anywhere else
- Tumor of neural crest cell origin
Pheo/Para Cohort

- 1999-2017
  - 34 patients
    - 4 sib pairs
    - 1 with mom
  - 45 episodes of tumors
    - 8 patients with 1 recurrence
    - 1 with 3
  - 59 tumors

- Demographics
  - Male 19 (59%)
  - Age 13.6yr (8mo-18yr)
    - - Relapse 15.2yr
    - + Relapse 10.2yr
  - Race
    - White 17 (53%)
    - Black 8 (25%)
    - Hispanic 5 (16%)
    - Asian 2 (6%)
## Presenting Complaints

<table>
<thead>
<tr>
<th>“Typical Symptoms”</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>90.3%</td>
</tr>
<tr>
<td>Palpitations</td>
<td>25.8%</td>
</tr>
<tr>
<td>Diaphoresis</td>
<td>9.6%</td>
</tr>
<tr>
<td>Flushing</td>
<td>3.2%</td>
</tr>
<tr>
<td><strong>Freq Headache</strong></td>
<td><strong>51.6%</strong></td>
</tr>
<tr>
<td>Anxiety</td>
<td>67.7%</td>
</tr>
<tr>
<td>Weight loss</td>
<td>19.3%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>67.7%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Atypical Symptoms</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Vomiting (exercise)</td>
<td>19.3%</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>22.5%</td>
</tr>
<tr>
<td>Constipation</td>
<td>12.9%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>25.8%</td>
</tr>
<tr>
<td><strong>Chest Pain</strong></td>
<td><strong>35.5%</strong></td>
</tr>
<tr>
<td>Hiccoughs</td>
<td>9.6%</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>12.9%</td>
</tr>
<tr>
<td>Tremor</td>
<td>16.1%</td>
</tr>
<tr>
<td>Weight Gain</td>
<td>12.9%</td>
</tr>
<tr>
<td>Syncope with voiding</td>
<td>6.4%</td>
</tr>
</tbody>
</table>

*Note: All 11 recurrences were asymptomatic, identified on screening*
Presenting Complications

- **Target organ damage**
  - Left Ventricular Hypertrophy 61.2%
  - Retinal lesions 32.2%

- **Comorbid Diagnoses**
  - Migraine 45.2%
  - Cyclic vomiting 12.9%
  - Irritable Bowel Syndrome 32.2%
  - Psychiatric:
    - Anxiety 51.6%
    - Hallucinations 6.4%
    - Depression 25.8%
## Diagnostics: Laboratory Evaluation

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma MN+NME</td>
<td>95%</td>
<td>99%</td>
</tr>
<tr>
<td>Plasma NE+Epi</td>
<td>91%</td>
<td>62%</td>
</tr>
<tr>
<td>Plasma VMA+HMA</td>
<td>58%</td>
<td>62%</td>
</tr>
<tr>
<td>Urine MN+NMN</td>
<td>98%</td>
<td>95%</td>
</tr>
<tr>
<td>Urine NE+Epi</td>
<td>97%</td>
<td>84%</td>
</tr>
<tr>
<td>Urine VMA+HMA</td>
<td>41%</td>
<td>29%</td>
</tr>
<tr>
<td>Chromagranin A</td>
<td>89%</td>
<td>96%</td>
</tr>
</tbody>
</table>

Havekes et al. Pediatr Nephrol 2009; 24:943
Diagnoses: Imaging

- US: poor sensitivity in small tumors
- MRI thought to be more sensitive for small tumors than CT – both may miss small multiples
- $^{123}$I-MIBG 83-95% sensitive, risk of false negative for small, extra-adrenal
- Fusion imaging

Functional PETs
- $^{18}$F-FDA: risk of false positive because of strong adrenal uptake. + in DA secretors missed by MIBG
- $^{18}$F-FDG: superior for metastatic and SDHb but higher risk of false positive than MIBG
Tumor Locations: 45 cases, 59 tumors

<table>
<thead>
<tr>
<th>Location</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenal</td>
<td>33</td>
</tr>
<tr>
<td>Right Adrenal</td>
<td>12</td>
</tr>
<tr>
<td>Left Adrenal</td>
<td>19</td>
</tr>
<tr>
<td>Bilateral</td>
<td>2</td>
</tr>
<tr>
<td>Para-aortic</td>
<td>17</td>
</tr>
<tr>
<td>Mesentary</td>
<td>4</td>
</tr>
<tr>
<td>Bladder Wall</td>
<td>2</td>
</tr>
<tr>
<td>Bowel Wall</td>
<td>1</td>
</tr>
<tr>
<td>Chest wall</td>
<td>1</td>
</tr>
<tr>
<td>Lung (mets)</td>
<td>1</td>
</tr>
<tr>
<td><strong>Cases with multiple tumors</strong></td>
<td><strong>7 (15.5%)</strong></td>
</tr>
<tr>
<td>Gene</td>
<td>Published Prevalence</td>
</tr>
<tr>
<td>--------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>SDHa</td>
<td>rare</td>
</tr>
<tr>
<td>SDHb</td>
<td>8-45%</td>
</tr>
<tr>
<td>SDHc</td>
<td>0-9%</td>
</tr>
<tr>
<td>SDHd</td>
<td>6-29%</td>
</tr>
<tr>
<td>VHL</td>
<td>0-52%</td>
</tr>
<tr>
<td>RET (MEN2)</td>
<td>4-32%</td>
</tr>
<tr>
<td>NF-1</td>
<td>0-10%</td>
</tr>
<tr>
<td>Other: SDHAF2, TMEM127, MAX, HIF2A, KIF1B, PHD1, PHD2, FH, HRAS, BAP1, MEN1</td>
<td>0-8%</td>
</tr>
<tr>
<td>Unknown</td>
<td>10-70%</td>
</tr>
</tbody>
</table>
Blockade

- **Our protocol**
  - Phenoxybenzamine escalating does x2 wks
  - Addition of Metyrosine for second week
  - Propranolol if needed for tachycardia
  - Volume expansion with Na/water intake

- **Other protocols**
  - Amlodipine
  - Phenoxybenzamine alone
  - Phenoxybenzamine then Propranolol
Pre-Op Targets

- Resting BP consistently <50th %ile
- Mild to moderate orthostatic symptoms
- Moderate to severe nasal congestion
- Moderate to severe fatigue
- Volume expansion: >10% weight gain
- Admit 1-2 days pre-op for final medication titration and IVF
Blockade Results

- Protocols complications
  - Amlodipine 2/2
  - Phenoxy alone 2/3
  - Phenoxy/Propranolol 3/6
  - Phenoxy/Metyr 0/34

- Post Op
  - Significant risk of hypotension
  - Mitigated by volume expansion
  - May need Vasopressin infusion
  - Short acting medications
  - Polyuria is common
  - Hyponatremia is common
  - Screen for adrenal insufficiency
Conclusions

- Hopefully this met the definition of “Novel”
- Anti-angiogenic cancer chemotherapy will be providing us a lot of patients in the near future
- SGLT2i inhibitors hold promise in diabetics with hypertension but must to studied in children
- Pheos aren’t so difficult