Rationale for Anticoagulation in Pulmonary Hypertension

- High prevalence of microthrombotic lesions histologically (in situ thrombosis) – all etiologies of pulmonary hypertension
- High risk for pulmonary embolism
- Questionable beneficial effect on survival
  - (3 retrospective studies; all using warfarin anticoagulation)
- Consider therapeutic options
- Therapy advised based on individual patient risk/benefit in high PAH patients only

considerations for selecting initial therapy for PAH

- Severity of symptoms/functional class
- Physical examination (right-heart class)
- Rate of progression
- Echocardiogram (RV size and function)
- Cardiopulmonary hemodynamics
- 6-minute walk distance/exercise capacity
- BNP/NT-pro-BNP
- Capability of patient to handle parenteral therapy
  - Parenteral therapy is first choice in very advanced patients
- Other issues
  - Drug-drug interactions, adverse events, comorbid conditions (eg, diabetes), route of administration, dosing intervals, cost

Long-Term Response to Calcium Channel Blocker Therapy in IPAH

- Long-term responders to calcium channel blocker therapy (at least 1 year)
  - Less severe disease at baseline
  - More pronounced decrease in mPAP during acute challenge
  - Long-term responders
    - 54% of acute responders
    - 6.8% (95% CI, 4.7% to 8.9%) of patient sample
  - 5-year survival rate of calcium channel blocker therapy failures: 48%

infusion technology

combination therapy for PAH

- To target multiple disease pathways
  - Endothelin pathway (endothelin receptor antagonists)
  - Nitric oxide pathway (PDE-5 inhibitors)
  - Prostacyclin pathway (prostacyclin analogs)
- Used clinically with little evidence to date
- Used when therapy needs to be augmented because patient response to monotherapy is inadequate
- Must consider the drug interaction potential of agents to be combined
  - Drug interaction between bosentan and sildenafil
  - Drug interaction between bosentan and tadalafil

targets for current therapies in pulmonary arterial hypertension

Management of PAH Therapy

• Up to 100% of PAH patients will report 1 or more adverse effects of PAH therapy
• Most adverse effects should be managed conservatively
• Since there are limited agents and alternatives, patient risk from adverse events need to be judged against reduced efficacy of PAH therapy

Treating Through Side Effects

• Headache
  – Most manageable with pain medications
• Peripheral edema
  – Adjustment in diuretics
• Diarrhea
  – Anti-motility agents (eg, loperamide)
• Flushing
  – Currently un treatable, but mainly cosmetic in nature
• Nasopharyngitis
  – Nasal washing, antihistamines/decongestants
• Jaw pain
  – Behavior modification in eating patterns
• Rash
  – Antihistamines and/or leukotriene modifiers to effect

Monitoring Schedule for Patients with PAH

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline (pretreatment)</th>
<th>Every 3-6 months</th>
<th>3-4 Months after start or change in therapy</th>
<th>If clinical worsening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical assessment WHO functional class HCG</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>6-MWD</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>BNP/NT-proBNP</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Right heart catheterization</td>
<td>X</td>
<td>(X)</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

Case 1-PAH

• Severe PAH, NYHA Functional Class 3b
  – 6-MWD 318m, BDS 5
• Treated with the prostacyclin analog treprostini and PDE5i tadalafil with a good clinical response
• Repeat ECHO, after 6-months demonstrated improvement in RV size and function
  – PAsp now estimated at 72 mmHg
  – 6-MWD – 448m Borg – 3
  – NYHA Functional Class 2

PAH has features of cancer

✓ Self-sufficiency in growth signals
✓ Insensitivity to anti-growth signals
✓ Evading apoptosis
✓ Limitless replicative potential
✓ Sustained angiogenesis
✓ Tissue Invasion - ?
✓ Metastasis - ?
✓ Alteration in cellular metabolism

Cell 2000; 100:57-70

Potential Targets for Treating PH

• Cytokines – IL-6, IL-1β
• Inflamasome
• Tyrosine Kinases
• mTOR
  – Differentiation
  – Migration
  – Metabolism
  – Apoptosis
• Stem Cell Therapy

• Requires new approach to clinical trial design
  – Best outcome measures
• Long term disease modification
  – Duration of trials
  – Long term clinical indices of efficacy

2.5 years of combination therapy

- 6-MWD 465m, BDS 2
- WHO Functional Class – 1
- RVSP – 48, mPA – 33, PCWP – 8, PVR - 3

LV and RV P-V Relationships

- RV is trapezoidal, with poorly defined isovolumic periods
- Similar elastance properties as the LV
  - RV is an energetically efficient pump
  - Efficiency is dependent on the normally low pulmonary hydraulic impedance
  - RV-PV coupling
- Chronic changes lead to progressive change towards an LV pattern of P-V
- Prolonged increase in load, systolic function will decline

AMB - CTA

Echocardiogram

- Marked right ventricular and atrial enlargement
- Normal left ventricular size and function
- Estimated PASP 75 mm Hg
- Displaced interventricular septum
- Saline contrast study did not demonstrate right to left shunting

Targets for Current Therapies in Pulmonary Arterial Hypertension

Infusion Technology
Conclusions

- Patients present with subtle progressive findings
- Cardiac Echo = excellent screening tool
  - May be inaccurate on RVSP
  - May be misleading on RV function
  - Does not provide PVR
- RHC is essential for diagnosis
- Treatment must be individualized to not only severity but to patient preference and lifestyle
- Current treatments are limited and demanding