Targeting VHL Tumors with RTK Inhibitors

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VHL Gene and Protein

- On chromosome 3p25
- 213 amino acid protein
- Binds to Elongin C/B
- Forms “VBC complex”

Modified from Stebbins and Pavletich, Science, Vol 284, 16 April 1999

VHL Mutation Replicates the Hypoxic State

Transcription of:
VEGF
Other angiogenic factors

VEGF = vascular endothelial growth factor, HIF = hypoxia inducible factor

Relevant Disclosures

Consultant: Peloton, Pfizer, Novartis
Research Funding: Pfizer, Novartis
Loss of VHL Mediated HIF Regulation Drives Angiogenesis

If HIF Regulation is the Main Function of VHL, is Blockade of Downstream Consequences of HIF Upregulation Sufficient to Normalize Phenotype?

VEGF Blocking Agents

Response to Sunitinib

Roma and Zonegel Fam Cancer 2015
One Case Report of Hemangioblastoma Response to Sunitinib

15 Patient Sunitinib Study

<table>
<thead>
<tr>
<th>Lesion site</th>
<th>Number of Lesions</th>
<th>PR (%)</th>
<th>SD (%)</th>
<th>PD (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemangioblastoma*</td>
<td>21</td>
<td>0</td>
<td>19(91)</td>
<td>2(9)</td>
</tr>
<tr>
<td>Renal cell carcinoma*</td>
<td>18</td>
<td>6 (33)</td>
<td>10(67)</td>
<td>2(10)</td>
</tr>
<tr>
<td>Renal cyst</td>
<td>9</td>
<td>0</td>
<td>9(100)</td>
<td>0</td>
</tr>
<tr>
<td>Retinal angiomas</td>
<td>7</td>
<td>0</td>
<td>7(100)</td>
<td>0</td>
</tr>
<tr>
<td>Pancreatic NET</td>
<td>5</td>
<td>0</td>
<td>5(100)</td>
<td>0</td>
</tr>
<tr>
<td>Pancreatic cyst</td>
<td>3</td>
<td>0</td>
<td>3(100)</td>
<td>0</td>
</tr>
</tbody>
</table>

Nine out of 15 patients completed study- most came off study due to poor tolerability

Jonasch and Matin, Annals of Oncology 2011 *(P=0.014)
Pancreatic NETs Responded

06/19/2006 08/17/2006 11/14/2006

07/10/2007 06/19/2008 19/19/2009

Jonasch and Matin, Annals of Oncology 2011

Renal Masses Responded

Baseline 12 Weeks 24 Weeks

Hemangioblastomas Did Not Respond

Comparison of Hemangioblastoma and Renal Cell Carcinoma Tissue Blood Vessels.
VHL Related Tumors

Are Endothelial Cells in RCC and Hemangioblastomas Driven by Same Growth Factors?

Hemangioblastomas

Densely packed, seemingly normal blood vessel channels of varying sizes, separated by stromal cells.

20 Hemangioblastomas
Evaluate Status of Different Receptor Types in Blood Vessels Using Laser Scanning Cytometry
Determine Differences Between Hb and RCC

20 Renal Cell Carcinomas

Jonasch et al Annals of Oncology 2011
<table>
<thead>
<tr>
<th>log(Hb)</th>
<th>log(RCC)</th>
<th>t-test</th>
<th>Wilcoxon’s rank test</th>
</tr>
</thead>
<tbody>
<tr>
<td>N mean</td>
<td>SD</td>
<td>N mean</td>
<td>SD p-value p-value</td>
</tr>
<tr>
<td>pVEGFR in CD31 Cells</td>
<td>20 11.266 0.498</td>
<td>20 11.752 0.378</td>
<td>0.001 0.003</td>
</tr>
<tr>
<td>pVEGFR in CD31 Cells</td>
<td>20 12.977 0.476</td>
<td>20 13.081 0.859</td>
<td>0.639 0.192</td>
</tr>
<tr>
<td>pPDGFR in CD31 Cells</td>
<td>20 10.952 0.654</td>
<td>20 10.805 0.839</td>
<td>0.539 0.82</td>
</tr>
<tr>
<td>VEGFR/ratio</td>
<td>20 0.206 0.122</td>
<td>20 0.372 0.431</td>
<td>0.105 0.043</td>
</tr>
<tr>
<td>PDGFR/ratio</td>
<td>20 0.145 0.067</td>
<td>20 0.157 0.077</td>
<td>0.608 0.602</td>
</tr>
</tbody>
</table>

**Bottom line:**

** Summary**

- Decreased activation state of pVEGFR in hemangioblastoma vs RCC tissue.
- Increased activation state of pFRS2 in hemangioblastomas vs RCC tissue.

**Next Steps:**

1. To explore FGF receptor blockade in patients with hemangioblastomas
2. To further develop the concept of antiangiogenic drugs in VHL patients with RCC and NETs.
Two Trials Moved Ahead

1. Single center pilot study testing dovitinib in VHL patients with hemangioblastomas NCT01266070

2. Multicenter 40 patient pazopanib trial for VHL patients with RCC NCT01436227

Dovitinib

- Oral anti-FGF receptor inhibitor.
- Also blocks VEGFR, c-Kit and Flt3.

Study Design

- 14 patient, single arm study with option to increase sample size if response is seen in hemangioblastomas.
- To be eligible, all patients had hemangioblastomas
- Study stopped after six patients- stable disease, but unacceptable skin toxicity
- Considering other agents with greater FGFR specificity and lower toxicity

Pazopanib in VHL Disease

Kim Jonasch and McCutcheon Targ Oncol 2012
Ongoing Study

- NCT01436227, a Phase II Study of Pazopanib in VHL Patients.
  - Must have at least one measurable lesion.
  - So far 31 out of 40 patients enrolled.

Objectives

Primary
  - Overall response rate in VHL patients with renal tumors

Secondary
  - Safety and tolerability in VHL patients
  - Progression-free survival
  - Effect of ZD6474 on VHL non-renal tumors

Study Design

- Single arm, open label phase 2 study
- ZD6474 oral
- Continuous daily dosing-300mg/day
- Simon optimal two stage design
  - Initial stage: 12 patients
  - If 1 or more of initial 12 respond, maximum of 37 patients will be enrolled
  - Assess response by RECIST q 12 weeks
Eligibility Criteria

- Clinical diagnosis of VHL
- One or more measurable tumors
- Adequate organ function
- ECOG ≤ 2

Demographics

<table>
<thead>
<tr>
<th>Total number of subjects</th>
<th>34</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median, range)</td>
<td>47 20-72</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>16</td>
</tr>
<tr>
<td>Female</td>
<td>18</td>
</tr>
<tr>
<td>Previous renal procedures (median, range)</td>
<td>3 0-8</td>
</tr>
<tr>
<td># of target lesions (median, range)</td>
<td>2 1-6</td>
</tr>
<tr>
<td>Tumor diameter (cm) (mean, range)</td>
<td>2.3 1.2 – 4.0</td>
</tr>
</tbody>
</table>

Response

<table>
<thead>
<tr>
<th>Table 2: Overall Tumor Best Response</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RECIST Response</strong></td>
</tr>
<tr>
<td>Complete Response (CR)</td>
</tr>
<tr>
<td>Partial Response (PR)</td>
</tr>
<tr>
<td>Stable Disease (SD)</td>
</tr>
<tr>
<td>Progressive Disease (PD)</td>
</tr>
</tbody>
</table>

Table 4: Adverse Events (as defined by CTCAE version 4.0)*

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>No. with &gt; Grade 2 or (%)</th>
<th>No. with &gt; Grade 3 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiographic abnormality</td>
<td>24 (19.7%)</td>
<td>6 (40.0%)</td>
</tr>
<tr>
<td>Prolonged QTc interval</td>
<td>3 (2.5%)</td>
<td>-</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>9 (7.4%)</td>
<td>-</td>
</tr>
<tr>
<td>Mood disturbance (anxiety/depression)</td>
<td>9 (7.4%)</td>
<td>-</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>8 (6.4%)</td>
<td>1 (10.0%)</td>
</tr>
<tr>
<td>Elevated serum creatinine</td>
<td>7 (5.7%)</td>
<td>-</td>
</tr>
<tr>
<td>Hypertension</td>
<td>7 (5.7%)</td>
<td>2 (10.0%)</td>
</tr>
<tr>
<td>Elevated ALT/AST</td>
<td>6 (4.9%)</td>
<td>1 (10.0%)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>4 (3.3%)</td>
<td>-</td>
</tr>
<tr>
<td>Lactose</td>
<td>4 (3.3%)</td>
<td>-</td>
</tr>
<tr>
<td>Micronutrient Deficiency</td>
<td>3 (2.5%)</td>
<td>-</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>3 (2.5%)</td>
<td>-</td>
</tr>
<tr>
<td>Diuretics</td>
<td>3 (2.5%)</td>
<td>-</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3 (2.5%)</td>
<td>-</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>2 (1.6%)</td>
<td>1 (10.0%)</td>
</tr>
<tr>
<td>Elevated CPK</td>
<td>2 (1.6%)</td>
<td>-</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>2 (1.6%)</td>
<td>-</td>
</tr>
<tr>
<td>TOTAL*</td>
<td>122</td>
<td>10</td>
</tr>
</tbody>
</table>

* Only those events with > 1% incidence are listed
* Total includes all adverse events, including those with less than 1% incidence
VHL- A Regulatory Hub

Antiangiogenic Agents Summary

- Response in RCC and in NETs.
- Long-term tolerability an issue.
- Less successful in hemangioblastomas- reason unclear at moment.
  - Require additional study to identify vulnerabilities in Hb
  - Consider more potent FGFR inhibitors.

HAF Differentially Regulates HIF1a and HIF2a, and is Potentially Targetable

Koh and Powis TIBS 2012
HIF2α Inhibitor

- Peloton pharmaceuticals
- HIF2α inhibitor in clinical trials.
- May be a good agent to test in patients with VHL disease.

Point Mutations Destabilize VHL But May Retain Functionality

Over One Third of Mutations are Missense (Hereditary and Sporadic)

Can we rescue these mutant proteins?

Raising Level of “Rescuable” Mutant R167Q VHL Isoform Abrogated Tumor Growth

Researchers have long noticed a second band below VHL30, which seems to vary from blot to blot. We observed that proteasome inhibition enhanced this band.

Proteasome inhibition enhances lower band in a time-dependent manner.

...and is dependent on protein synthesis.
A CK2 inhibitor, CX4945 (silmitasertib) markedly reduced accumulation of the lower band after proteasome inhibition.

Alanine substitution of the CK2 phosphorylation sites (aa 33, 38 and 43) ablated presence of lower band.

A chymotrypsin inhibitor, AEBSF, markedly reduced accumulation of the lower band after proteasome inhibition.

CK2 blockade enhances R82P mutant’s ability to regulate H12α levels in RCC cell lines.
CK2 effect is VHL dependent.

Therapeutic Opportunities
**Silmitasertib**

- AKA CX4945
- Highly specific CK2 inhibitor
- In clinical trials for other diseases
- Relatively well tolerated

- Trial design in discussion with Senhwa Biosciences

**Summary**

- Antiangiogenic RTK therapy can round off the edges of VHL phenotype.
- We need to perform additional detailed analysis of VHL disease related endothelial biology to refine RTK approach.
- Future efforts should focus on upstream stabilization of VHL defect.