Outline

1. TKI-induced hypertension: Monitoring and Treatment
2. Proteinuria induced by TKIs
3. Considerations for trial design
Hypertension on Sutent


Normotensive patients

HTN: Rapid, Can be Severe

HTN:
26% to 87%

Robinson, Humphreys, CJASN 2010
VEGF mediates NO-dependent hypotension

anti-VEGF agents reduce urinary NO and increase ET-1

Humphreys 2010, 2012
Model

- VEGF
- VEGFR-2
- eNOS
- NO
- VSMC constriction
- ET-1
- EC dysfunction
- NO → sGC → cGMP

→ VSMC constriction
→ afterload
→ Hypertension
Initial Cardiovascular Health Assessment

1. History: CVD, DM, previously documented LVH or carotid wall thickness, age, smoking, family history of early CVD
2. Physical exam: BP and waist circumference
3. Labs: SCr, 24-hr protein excretion or ACR, FBG and lipid profile

SBP < 140mmHg and/or DBP < 90mmHg

- Antiangiogenic therapy
  - BP monitoring- weekly during first cycle, then every 2-3 wks.
  - Consider daily BP home monitor if ≥ 2 risk factors.*

SBP > 140mmHg and/or DBP > 90mmHg

- Confirm diagnosis

HTN

- Controlled
- Uncontrolled

Treat HTN

Do not start, decrease dose, or discontinue antiangiogenic drug

*de Jesus-Gonzalez N et al. 2012
Recurrent Proteinuria on anti-Angiogenic Therapies

Urine Protein:Creatinine (gm/g)

Weeks since starting protocol

- Sunitinib
- Sorafenib
- Retaspimycin, erlotinib, nilotinib
- Imatinib
- SBP>200
- Fatal MI
- Recurrent Proteinuria on anti-Angiogenic Therapies
Is Proteinuria Rare?

✓ 46 consecutive women enrolled in a Phase II trial of Cediranib for ovarian cancer
✓ Age 41 – 77 years
✓ 25% had baseline HTN
✓ BP recorded twice daily, UA every two weeks

Schopick ...Humphreys, CJASN 2010
New Proteinuria in 30% within 6 Weeks

Proteinuria = UA > 1+

Schopick et al, CJASN 2010
Normal glomerular capillary loop cross section
Thickened endothelial cell cytoplasm with new rim of Bsmt membrane that it is secreting

The capillary lumen is very narrowed
Hypothetical Model of Disruption of VEGF Signaling in Renal Thrombotic Microangiopathy

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<th>Normal</th>
<th>Bevacizumab administration</th>
<th>VEGF KO</th>
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<tr>
<td>Podocyte</td>
<td>Glomerular basement membrane</td>
<td>sFlt-1 receptor</td>
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<tr>
<td>VEGF</td>
<td>VEGFR-2</td>
<td>Endothelial injury</td>
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<td>Capillary</td>
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<td>Bevacizumab</td>
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Are On-Target Toxicities Desirable If They Can Be Managed?

On target toxicity vs. Off target toxicity
Apatanib-treated breast CA

PFS = 5.5 vs. 2.7 mo (P = 0.011)

HTN = SBP > 140 or DBP > 90

OS = 14.8 vs. 5.3 mo (P = 0.002)

Fan et al., Breast Cancer Res Treat (2014)
On-target toxicities as a pharmacodynamic biomarker: Neuroendocrine CA

Berutti et al., BMC Cancer, 2015
Managing anti-VEGF renal toxicities

Control BP, use ACE/ARB first, followed by diuretics and CCB

Monitor urine protein and kidney function monthly

If sub-nephrotic proteinuria, may continue therapy with aggressive BP and ACE/ARB

If renal failure, nephrotic proteinuria or hypertensive emergency occurs, need dose reduction, washout or discontinuation (in consultation with oncology)
Considerations for future trial design

Example: Apatanib for refractory gastric CA

- Blinded RCT, 800 pts, “positive” results:
  - PFS 2.6 vs. 1.8 mo, OS 6.5 vs. 4.7 mo
  - Objective response in only 1.7%

Biomarker needed to enrich study population!

- Most common gr ³⅓ AEs: HTN, Proteinuria, hand-foot in 2-8%

- Analyze outcomes based on AEs, those that correlate study biology for candidate predictive biomarkers pre-Rx
Thank You