VEGF Targeted Therapies

Daniel J Lenihan, MD
Professor, Division of Cardiovascular Medicine
Director, Cardio-Oncology Center of Excellence
Washington University in St Louis
Presenter Disclosure Information
ACC Cardio-Oncology 1.25.19

• I will not discuss off label use or investigational use in my presentation.

• I have financial relationships to disclose:
  – Consultant (modest): Roche, Pfizer, Takeda, Prothena, BMS, Akcea
Case Presentation
What is so complex about BP control?

- 54 y/o F with stage 3C fallopian tube cancer dx’d 8/2017:
  TAH/BSO, tumor debulking 8/2017
  Carboplatin/taxotere x6 cycles ( -2/2018) with recurrence
  Liposomal doxorubicin/bevicuzumab x3 cycles (7/2018-10/2018) with progression of disease
  Pemetrexed (Alimta) (10/2018)

- PMH:
- LUE DVT on apixaban
- She was recently admitted 11/17-18/2018 with severe headache and BP 190/110; she had no prior history of hypertension. She was started on lisinopril 5mg qD. After discharge, she continued to have elevated BP and was started on HCTZ 25mg.
- Today (11/20/2018), BP 200/115 which improved to 160/90 with 2.5mg IV metoprolol tartrate and 10mg nifedipine IR.
- She had a negative LHC in 2014
- Taxol [Paclitaxel] Anaphylaxis
Case Presentation: Physical Exam/Labs

- BP 160/90 P70 R16 afebrile
- Loud S4, no edema, exam o/w ok
- Hgb 10, plt 151, WBC 4.6, BUN/Cr 19/.8
- CA 125 ag (units/mL, nl<35)- 259 9/2017, as low as 40 3/2018, now 770
- Trop: all normal, NTproBNP 646
- TC 268, HDL 67, LDL 179
Anti-VEGF Therapy can decrease blood flow resulting in cancer control

Willitt, JCO 2006
Therapy for both Oncology and Cardiology are intimately intertwined at the vascular level.

How/why did Cardio-Oncology get started?
Because cardiac safety is a major concern wherever you are.

Drug firm says cancer drug can raise heart risk

Herceptin significantly increases 'cardiotoxicity' in patients, Genentech says

WASHINGTON - An early review of a recent study showed Genentech Inc.'s cancer drug Herceptin can significantly increase the risk of heart problems, the company said in a letter released by U.S. regulators Wednesday.

Meta-Analysis of Randomized Controlled Trials for the Incidence and Risk of Treatment-Related Mortality in Patients With Cancer Treated With Vascular Endothelial Growth Factor Tyrosine Kinase Inhibitors

Fabio A.B. Schutz, Youjin Je, Christopher J. Richards, and Toni K. Choueiri

Abstract

Purpose
Vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors (TKIs) have become the cornerstone in the treatment of several malignancies. These drugs have also been associated with an increase in the risk of potentially life-threatening adverse events, such as arterial thrombotic events, bleeding, congestive heart failure, and others. We performed an up-to-date meta-analysis to determine the risk of fatal adverse events (FAEs) in patients with cancer treated with VEGFR TKIs.

Methods
MEDLINE and PubMed databases were searched for articles published from January 1966 to February 2011. Eligible studies were limited to trials of US Food and Drug Administration-approved VEGFR TKIs ( pazopanib, sunitinib, and sorafenib) that reported patients with cancer with any primary tumor type, randomized design, and adequate safety profile. Statistical analyses were conducted to calculate the summary incidence, relative risk (RR), and 95% CIs by using random-effects or fixed-effects models on the basis of the heterogeneity of included studies.

Results
In all, 4,679 patients from 10 randomized controlled trials (RCTs) were included, with 2,856 from sorafenib, 1,388 from sunitinib, and 435 from pazopanib trials. The incidence of FAEs related to VEGFR TKIs was 1.5% (95% CI, 0.8% to 2.4%) with an RR of 2.23 (95% CI, 1.12 to 4.44; P = .023) compared with control patients. On subgroup analysis, no difference in the rate of FAEs was found between different VEGFR TKIs or tumor types. No evidence of publication bias was observed.

Conclusion
In a meta-analysis of RCTs, the use of VEGFR TKIs was associated with an increased risk of FAEs compared with control patients.
Systemic Effects of Anti-VEGF Therapy

**Tumor Tissues**
(VEGF upregulated)
- Lung cancer (bevacizumab)
  - Inhibition of tumor growth, tumor cavitation
- Hepatocellular carcinoma (sorafenib)
  - Tumor necrosis
- Renal cell carcinoma (sunitinib)
  - Tumor shrinkage, tumor cell necrosis
- Colorectal cancer (bevacizumab)
  - Deceleration of tumor growth
  - Efficient chemotherapy delivery

**Normal Tissues**
(VEGF constitutively expressed)
- Hypertensive remodeling
- Microvascular rarefaction
- Cardiomyopathy (sunitinib and sorafenib)

**Microcirculation**
1. normal arteriole
2. functional rarefaction (endothelial dysfunction, vasoconstriction)
3. anatomic rarefaction

- Thrombotic microangiopathy
- Glomerulopathy/glomerulonephritis
- Proteinuria
- Hypertensive nephropathy

Figure 2. Proposed mechanisms of cardiotoxicity due to VEGF signaling pathway inhibitors sunitinib and sorafenib. A, Sunitinib- and sorafenib-induced cardiotoxicity are secondary to multiple potential mechanisms. B, These effects are attenuated by potential cardioprotective therapies. ACE indicates angiotensin-converting enzyme; AMPK, AMP-activated protein kinase; LV, left ventricle; PDGFR-β, platelet-derived growth factor-β; VEGF, vascular endothelial growth factor.
Stages, Phenotypes and Treatment of HF

At Risk for Heart Failure

STAGE A
At high risk for HF but without structural heart disease or symptoms of HF
- e.g., Patients with:
  - HTN
  - Atherosclerotic disease
  - DM
  - Obesity
  - Metabolic syndrome
- or
- Patients
  - Using cardiotoxic agents
  - With family history of cardiomyopathy

Therapy
- Goals:
  - Heart healthy lifestyle
  - Prevent vascular, coronary disease
  - Prevent LV structural abnormalities
- Drugs
  - ACEI or ARB in appropriate patients for vascular disease or DM
  - Statins as appropriate

STAGE B
Structural heart disease but without signs or symptoms of HF
- e.g., Patients with:
  - Previous MI
  - LV remodeling including LVH and low EF
  - Asymptomatic valvular disease

Therapy
- Goals:
  - Prevent HF symptoms
  - Prevent further cardiac remodeling

STAGE C
Structural heart disease with prior or current symptoms of HF
- e.g., Patients with:
  - Known structural heart disease and HF signs and symptoms

Therapy
- Goals:
  - Control symptoms
  - Improve HRQOL
  - Prevent hospitalization
  - Prevent mortality

Heart Failure

Refactory symptoms of HF at rest, despite GDMT
- e.g., Patients with:
  - Marked HF symptoms at rest
  - Reoccurring hospitalizations despite GDMT

Therapy
- Goals:
  - Control symptoms
  - Improve HRQOL
  - Reduce hospital readmissions
  - Establish patient's end-of-life goals

Options
- Advanced care measures
- Heart transplant
- Chronic intravenous
- Temporary or permanent MCS
- Experimental surgery or drugs
- Palliative care and hospice
- ICD deactivation

Helping Cardiovascular Professionals
Learn, Advance, Heal.

American Heart Association
Sunitinib, a novel oral chemotherapeutic agent with anti-VEGF properties, is associated with hypertension and heart failure.

### Table 2. Nature of Cardiotoxicity, Severity of Heart Failure, and Short Term Outcomes

<table>
<thead>
<tr>
<th>Pt #</th>
<th>BP at baseline</th>
<th>Dose (mg)</th>
<th>Duration of drug (days)</th>
<th>Worst NYHA Class</th>
<th>BNP (pg/ml; normal ≤ 100)</th>
<th>LVEF post-drug</th>
<th>HF Therapy</th>
<th>LVEF post Treatment with HF Therapy</th>
<th>Max BP on Drug</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>150/72</td>
<td>50</td>
<td>44</td>
<td>4</td>
<td>558</td>
<td>25-30%</td>
<td>ACE-I, B-blocker</td>
<td>25-30%</td>
<td>155/85</td>
<td>Expired in 6 months</td>
</tr>
<tr>
<td>2</td>
<td>150/80</td>
<td>50</td>
<td>4</td>
<td>3</td>
<td>3338</td>
<td>30-35%</td>
<td>Nitrate, B-blocker</td>
<td>45-50%</td>
<td>184/110</td>
<td>Expired in 4 months</td>
</tr>
<tr>
<td>3</td>
<td>140/94</td>
<td>25</td>
<td>4</td>
<td>4</td>
<td>2110</td>
<td>25-30%</td>
<td>Increased ACE-I</td>
<td>30%</td>
<td>210/110</td>
<td>Expired in 1 month</td>
</tr>
<tr>
<td>4*</td>
<td>142/67</td>
<td>25</td>
<td>29</td>
<td>2</td>
<td>409</td>
<td>40-45%</td>
<td>Increased ACE-I</td>
<td>60-65%</td>
<td>174/85</td>
<td>LVEF improved then worsened to 35-40% on sunitinib</td>
</tr>
<tr>
<td>5</td>
<td>162/92</td>
<td>50</td>
<td>20</td>
<td>4</td>
<td>409</td>
<td>&lt;20%</td>
<td>Added ACE-I, B-blocker</td>
<td>-</td>
<td>195/97</td>
<td>Expired in 1 month</td>
</tr>
<tr>
<td>6</td>
<td>146/75</td>
<td>50</td>
<td>29</td>
<td>3</td>
<td>356</td>
<td>50-55%</td>
<td>B-blocker</td>
<td>-</td>
<td>160/80</td>
<td>HF symptoms improved after sunitinib was discontinued and sinus rhythm was restored</td>
</tr>
</tbody>
</table>

Khakoo, et al, 2008; 112:2500-8
Incidence of Cardiovascular Toxicity by Type

The incidence of cardiovascular toxicity varied by type of toxicity and by chemotherapy agent received. Many patients received multiple therapies in succession and are included only once in “All Patients.” CV = cardiovascular; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal B-type natriuretic peptide.

Figure Legend:
Incidence (%) and risk (odds ratio, OR) of systemic hypertension* with VEGF signaling pathway inhibitors based on meta-analyses

<table>
<thead>
<tr>
<th>Drug</th>
<th>All grade %</th>
<th>All grade OR</th>
<th>High grade %</th>
<th>High grade OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab</td>
<td>23.6</td>
<td>3.02</td>
<td>7.9</td>
<td>5.28</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>19.1</td>
<td>3.07</td>
<td>4.3</td>
<td>3.31</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>21.6</td>
<td>3.44</td>
<td>6.8</td>
<td>22.72</td>
</tr>
<tr>
<td>Pazopanib</td>
<td>35.9</td>
<td>4.97</td>
<td>6.5</td>
<td>2.87</td>
</tr>
<tr>
<td>Axitinib</td>
<td>40.1</td>
<td>3.00</td>
<td>13.1</td>
<td>1.71</td>
</tr>
<tr>
<td>Regorafenib</td>
<td>44.4</td>
<td>3.76</td>
<td>12.5</td>
<td>8.39</td>
</tr>
<tr>
<td>Vandetanib</td>
<td>24.2</td>
<td>5.1</td>
<td>6.4</td>
<td>8.06</td>
</tr>
<tr>
<td>Cabozantinib</td>
<td>27.8</td>
<td>5.48</td>
<td>12.0</td>
<td>5.09</td>
</tr>
<tr>
<td>Lenvatinib</td>
<td>47.0</td>
<td>12.4</td>
<td>17.7</td>
<td>30.6</td>
</tr>
<tr>
<td>Afiblercept</td>
<td>42.4</td>
<td>4.47</td>
<td>17.4</td>
<td>4.97</td>
</tr>
<tr>
<td>Ramucirumab</td>
<td>20.0</td>
<td>2.77</td>
<td>8.6</td>
<td>3.58</td>
</tr>
</tbody>
</table>
Stages, Phenotypes and Treatment of HF

At Risk for Heart Failure

**STAGE A**
- At high risk for HF but without structural heart disease or symptoms of HF
  - e.g., Patients with:
    - HTN
    - Atherosclerotic disease
    - DM
    - Obesity
    - Metabolic syndrome
    - Or
    - Patients using cardiotoxins
    - With family history of cardiomyopathy

**THERAPY**
- Goals
  - Heart healthy lifestyle
  - Prevent vascular, coronary disease
  - Prevent LV structural abnormalities
- Drugs
  - ACEI or ARB as appropriate for vascular disease or DM
  - Statins as appropriate

**STAGE B**
- Structural heart disease but without signs or symptoms of HF
  - e.g., Patients with:
    - Previous MI
    - LV remodeling including LVH and low EF
    - Asymptomatic valvular disease

**THERAPY**
- Goals
  - Prevent HF symptoms
  - Prevent further cardiac remodeling
- Drugs
  - ACEI or ARB as appropriate
  - Beta blockers as appropriate
  - In selected patients
    - ICD
    - Revascularization or valvular surgery as appropriate

**STAGE C**
- Structural heart disease with prior or current symptoms of HF
  - e.g., Patients with:
    - Known structural heart disease and HF signs and symptoms

**THERAPY**
- Goals
  - Control symptoms
  - Improve HRQOL
  - Prevent hospitalization
  - Prevent mortality
- Strategies
  - Identification of comorbidities
- Treatment
  - Diuresis to relieve symptoms of congestion
  - Follow guideline driven indications for comorbidities, e.g., HTN, AF, CAD, DM
  - Revascularization or valvular surgery as appropriate

**Heart Failure**

**STAGE D**
- Refractory HF
  - e.g., Patients with:
    - Marked HF symptoms at rest
    - Recurrent hospitalizations despite GDMT

**THERAPY**
- Goals
  - Control symptoms
  - Improve HRQOL
  - Reduce hospital readmissions
  - Establish patient’s end-of-life goals
- Options
  - Advanced care measures
  - Heart transplant
  - Chronic inotropes
  - Temporary or permanent MCS
  - Experimental surgery or drugs
  - Palliative care and hospice
  - ICD deactivation

HFpEF
- Goals
  - Control symptoms
  - Prevent hospitalization
  - Prevent mortality
- Drugs for routine use
  - Diuretics for fluid retention
  - ACEI or ARB
  - Beta blockers
  - Aldosterone antagonists
- Drugs for use in selected patients
  - Hydralazine/isosorbide dinitrate
  - ACEI and ARB
  - Digoxin
  - In selected patients
    - CRT
    - ICD
    - Revascularization or valvular surgery as appropriate

HF/LF
- Goals
  - Control symptoms
  - Prevent hospitalization
  - Prevent mortality
- Drugs for routine use
  - Diuretics for fluid retention
  - ACEI or ARB
  - Beta blockers
  - Aldosterone antagonists
- Drugs for use in selected patients
  - Hydralazine/isosorbide dinitrate
  - ACEI and ARB
  - Digoxin
  - In selected patients
    - CRT
    - ICD
    - Revascularization or valvular surgery as appropriate
<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Prehypertension (SBP 120 to 139 mmHg or DBP 80 to 89 mmHg)</th>
<th>Normal SBP &lt;120 mmHg and DBP &lt;80 mmHg</th>
<th>Normal SBP &lt;120 mmHg and DBP &lt;80 mmHg</th>
<th>Optimal SBP&lt;120 mmHg and DBP &lt;80 mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 2</td>
<td>Stage 1 hypertension (SBP 140 to 159 mmHg or DBP 90 to 99 mmHg); recurrent or persistent (≥24 hours); symptomatic DBP increase by &gt;20 mmHg; monotherapy indicated</td>
<td>Prehypertension SBP 120-139 mmHg or DBP 80-89 mmHg</td>
<td>Elevated SBP 120-129 mmHg and/or DBP &lt;80 mmHg</td>
<td>Normal SBP 120-129 and/or DBP 80-84</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Stage 2 hypertension (SBP ≥160 mmHg or DBP ≥100 mmHg); more than one drug or more intensive therapy than previously used indicated</td>
<td>Stage 1 SBP 140-159 mmHg or DBP 90-99 mmHg BP drugs targeting &lt;140/90 if &lt;60 years, CKD, DM, &lt;150/90 for all other</td>
<td>Stage 1 SBP 130-139 mmHg and/or DBP 80-89 mmHg Initiate pharmacologic therapy if atherosclerotic cardiovascular disease (ASCVD) is present or 10 year ASCVD risk ≥10%</td>
<td>High normal SBP 130-139 and/or DBP 85-89 BP drug treatment may be considered if the CV risk is very high, or established CVD, especially CAD.</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention needed</td>
<td>Stage 2 SBP ≥160 mmHg or DBP ≥100 mmHg BP drugs targeting &lt;140/90 if &lt;60 years, CKD, DM, &lt;150/90 for all other patients, can consider two drug therapy</td>
<td>Stage 2 SBP ≥140 mmHg and/or DBP ≥90 BP drugs targeting &lt;130/80mmHg</td>
<td>Grade I SBP 140-159 and/or DBP 90-99 BP drugs target &lt;140/90 as 1st objective, if well tolerated further target is &lt;130/80 but not &lt;120 SBP In older&gt;65 y, target SBP 130-140, and DBP&lt;80, Initiate with two-drug combination</td>
</tr>
</tbody>
</table>
Which of the following therapies is not associated with hypertension as the predominant adverse event?

1. Sunitinib
2. Vandetinib
3. Pazopanib
4. Imatinib
5. Cabozantinib
The Stanford Monitoring Algorithm for Targeted Therapies

Cardiovascular monitoring algorithm for patients with renal cell carcinoma receiving targeted chemotherapy. BP = blood pressure; DBP = diastolic blood pressure; SBP = systolic blood pressure; other abbreviations as in Figure 1.
In screening for cardiac dysfunction, LVEF is not very helpful

Narayan, V et al; Clin Cancer Research 2017; p 3601-9
Increased resistance and LV afterload appears clinically with anti VEGF therapy

Catino, A et al
Circ:HF 2018: e004408

Figure 3. Longitudinal trajectories in vascular function and echocardiography parameters across all visits. Longitudinal trends in vascular function, echocardiographic parameters, and cardiac biomarker BNP (B-type natriuretic peptide) using piecewise linear regression with confidence intervals estimated using robust (Huber–White) sandwich-based SEs^{10-32} to illustrate the mean trend in vascular function measures across visits. Figures grouped according to echocardiographic parameters and BNP (A), blood pressure (B), large artery stiffness (C), resistive load (Continued)
In Renal Cell Cancer, renin-angiotensin inhibitors are critical therapies.

Definition of a “Kinase Inhibitor”:

- A drug that interferes with cell communication and growth and is sometimes used to treat cancer
There are several proposed mechanisms responsible for the significant hypertensive response noted with VEGF inhibitors. Which of the mechanisms below is most likely to be related to the hypertension caused by this class of therapies?

1. A functional increase in the nitric oxide production with VEGF inhibition
2. An increase in the capillary density as that seen in anatomic rarefaction
3. A substantial increase in vascular resistance and left ventricular afterload
4. A reduction in endothelin-1 activity
**BP at baseline**

- **Normal BP values**
  - Other CV risk factors?
    - NO
    - YES
      - Start therapy preferring CCB and ACEi/ARBs
  - It may be reasonable to start cardio-protective therapy (Bb, ACEi/ARBs)

- **High-normal BP (130-140/85-90 mmHg)**
  - Well controlled BP?
    - NO
    - YES
      - Reinforce therapy, CCB and ACEi/ARBs if not yet used (even for normal-high BP)

- **Newly diagnosed HTN (>140/90 mmHg)**

- **Known HTN on treatment**

**Start anti VEGF therapy**

**Hypertensive crisis**

- Consider to hold anti VEGF therapy for several weeks until adequate BP control is achieved

**HYPERTENSION**

1. Start therapy with ACEi/ARBs or CCB (if not already used)
2. Add the other drug. In selected cases, it may be reasonable to start with combination therapy
3. Titrate drugs to maximum doses
4. Add a second generation-beta blocker or a diuretic

**BP still elevated**
Statins are helpful in renal cell cancer especially with anti-VEGF directed therapy.

Fig. 1. Kaplan-Meier estimates of OS for (A) the overall cohort, (B) patients receiving VEGF-targeted therapy, (C) patients receiving mTOR-targeted therapy and (D) patients receiving IFN-a therapy stratified by statin users versus non-users.
In a survey of oncologists in France, the responses are revealing.

What about the chemotherapy decision regarding cardiac safety?

Fig. 2. Approach to the onset of left ventricular dysfunction in relation to its severity and the type of cancer therapy used. Results are expressed as percentage and 95% confidence interval. HF, heart failure; LVEF, left ventricular ejection fraction; VSP, vascular endothelium growth factor signal pathway.
Case study: 61 y/o F, who presented originally with metastatic renal cell cancer with a pathologic fracture in her femur, was recently started on sunitinib as front line therapy for her cancer. She was treated for 4 weeks on and then 2 weeks off. During the 3rd week of therapy her BP was noted to be 210/115 on several occasions and she was instructed to take clonidine whenever the BP was that high. She now comes to see you a few days before she is to restart her therapy. Her current medical regimen for BP control is amlodipine 5mg daily and metoprolol tartrate 25 mg bid. Her exam is notable for a BP of 158/96, P 98/min, 1 cm JVD, clear lungs, RRR with a loud S4, and mild ankle edema. Her labs are remarkable for a Cr 1.7 mg/dl, Hgb of 11.5 and a K+ of 4.1 meq/l.

What is the target BP goal for her ongoing therapy and what components of the medical regimen should you emphasize?

1. goal <160/90 mm Hg, continue with intermittent clonidine for any values higher than the goal and use loop diuretics for edema.
2. goal <140/90 mm Hg, focus on vasodilators and combined adrenergic blockers as well as angiotensin system inhibitors
3. goal <150/90 mm Hg, maximize the single class of anti-hypertensive therapy strategy over the next several months
4. goal <130/80 mm Hg, increase exercise, lose weight, eat beets at least twice a day, and check an Echo every 4 months.
Our new definition of cardiotoxicity must include:

- **Electrical**
  - Arrhythmias
  - Conduction Disease

- **Metabolic**
  - Hyperlipidemia
  - Hyperglycemia

- **Myocardial**
  - Decline in LVEF
  - Congestive Heart Failure
  - Restrictive Cardiomyopathy
  - Myocarditis
  - Infiltration

- **Vascular**
  - Atherosclerosis
  - Hypertension
  - Arterial Thrombosis
  - Venous Thrombosis
  - Proteinuria
  - Pulmonary Hypertension

- **Structural**
  - Valvular Heart Disease
  - Pericarditis
  - Pericardial Effusion
  - Pericardial Constriction
  - Tumor
Dr. Daniel Lenihan, Director, Cardio-Oncology

Dr. Ronald Krone – Founder of Cardio-Oncology at Washington University

Dr. Andrew Kates
Dr. Katie Zhang
Dr. Joshua Mitchell
Dr. Andy Kates
Dr. John Gorcsan, III
Dr. Justin Vader
Holly WieseHan, NP
Ann Mahoney, RN
Kaitlin Moore, RC
Madison Alexander RC
Kate Coates RC
Caroline Foster, RN
Kim Gal, Program Coordinator