New Therapies: What are the Cardiovascular Concerns?

Ronald Witteles, MD
February 17, 2017
Stanford University School of Medicine
Outline

How do we assess toxicity?
  – Real-world example
  – How does this get us into trouble?

Specific “New agents”
  – VEGF inhibitors
  – Nilotinib/Ponatinib
  – Proteasome inhibitors
  – BTK inhibitors
  – Checkpoint inhibitors

Final thoughts
Tyrosine Kinase Inhibitors

- Tyrosine kinases: Critically involved in many cellular functions
- Inhibition can have profound effects on tumor growth/survival
  - Examples: Imatinib, sunitinib, sorafenib
- Broader inhibition → broader anti-neoplastic activity
  - Also potential for more off-target side-effects
- Sunitinib
  - Broadly active tyrosine kinase inhibitor – notably inhibits VEGF
  - FDA approved for 3 different tumors
- We can learn a lot from this story…
Sunitinib – First Phase III Trial

- Phase III study for GI stromal tumors (GIST), Lancet 2006
- 312 patients given sunitinib or placebo
- Cardiac monitoring: MUGA at screening, end of each cycle, and treatment end
  - MUGA data not provided in article

Adapted from Demetri et al. Lancet. 2006;368:1329-38.
# Table of Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>Sunitinib (n=202)</th>
<th>Placebo (n=102)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1/2</td>
<td>Grade 3</td>
</tr>
<tr>
<td><strong>Non-haematological</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>58 (29%)</td>
<td>10 (5%)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>52 (26%)</td>
<td>7 (3%)</td>
</tr>
<tr>
<td>Skin discoloration</td>
<td>50 (25%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>47 (23%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>38 (19%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>36 (18%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>30 (15%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>30 (15%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Hand-foot syndrome</td>
<td>19 (9%)</td>
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</tr>
<tr>
<td>Rash</td>
<td>24 (12%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>18 (9%)</td>
<td>6 (3%)</td>
</tr>
<tr>
<td>Mucosal inflammation</td>
<td>24 (12%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>22 (11%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>15 (8%)</td>
<td>6 (3%)</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>14 (7%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Hair-colour changes</td>
<td>14 (7%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>13 (6%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Glossodynia</td>
<td>11 (6%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td><strong>Haematological</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaemia</td>
<td>137 (58%)</td>
<td>7 (4%)</td>
</tr>
<tr>
<td>Leucopaenia</td>
<td>104 (62%)</td>
<td>7 (4%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>86 (43%)</td>
<td>17 (8%)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>80 (40%)</td>
<td>18 (9%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>72 (36%)</td>
<td>8 (4%)</td>
</tr>
</tbody>
</table>

Data are number (%). * Treatment-related. † Anaemia was included in the table, despite a difference of less than 5% between the treatment groups, because of its frequency and clinical relevance in GIST.

Table 2: Adverse events that occurred with a frequency of at least 5% greater on sunitinib than on placebo in per-protocol population.

*Adapted from Demetri et al. Lancet. 2006;368:1329-38.*
Sunitinib (Sutent): Data vs. Label

We noted no evidence of a systematic mean decrease in left ventricular ejection fraction in either treatment group, and no patients were reported to have had clinical evidence of congestive heart failure.

Lancet GIST Study A, October 2006

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In the double-blind treatment phase of GIST Study A, 22/209 patients (11%) on SUTENT and 3/102 patients (3%) on placebo had treatment-emergent LVEF values below the lower limit of normal (LLN). Nine of 22 GIST patients on SUTENT with LVEF changes recovered without intervention. Five patients had documented LVEF recovery following intervention (dose reduction: one patient; addition of antihypertensive or diuretic medications: four patients). Six patients went off study without documented recovery. Additionally, three patients on SUTENT had Grade 3 reductions in left ventricular systolic function to LVEF <40%; two of these patients died without receiving further study drug. No GIST patients on placebo had Grade 3 decreased LVEF.

Sutent Prescribing Information, February 2007

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Sutent Prescribing Information, February 2007

Sunitinib – Second Phase III Study

- 750 patients with untreated metastatic renal-cell CA randomized to receive:
  - Sunitinib
  - Interferon alfa

- Normal LVEF at baseline & cardiac monitoring performed

Heart Failure: Phase III Study

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sunitinib (N=375)</th>
<th>Interferon Alfa (N=360)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Adverse event</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea‡</td>
<td>53</td>
<td>5</td>
</tr>
<tr>
<td>Fatigue‡</td>
<td>51</td>
<td>7</td>
</tr>
<tr>
<td>Nausea</td>
<td>44</td>
<td>3</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>25</td>
<td>1</td>
</tr>
<tr>
<td>Vomiting‡</td>
<td>24</td>
<td>4</td>
</tr>
<tr>
<td>Hypertension‡</td>
<td>24</td>
<td>8</td>
</tr>
<tr>
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<td>20</td>
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</tr>
<tr>
<td>Asthenia</td>
<td>17</td>
<td>4</td>
</tr>
<tr>
<td>Dry skin</td>
<td>16</td>
<td>1</td>
</tr>
<tr>
<td>Skin discoloration</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>Changes in hair color</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>12</td>
<td>1</td>
</tr>
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<td>Pain in a limb</td>
<td>11</td>
<td>1</td>
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<td>Dry mouth</td>
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<td>10</td>
<td>2</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Chills</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Myalgia</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Influenza-like illness</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Study 2: More Confusion

<table>
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<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Decline in ejection fraction</td>
<td>10 percent</td>
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NEJM metastatic renal cell CA (MRCC) Study, January, 2007

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In the treatment-naïve MRCC study, 78/375 (21%) and 44/360 (12%) patients on SUTENT and IFN-α, respectively, had an LVEF value below the LLN. Thirteen patients on SUTENT (4%) and four on IFN-α (1%) experienced declines in LVEF of >20% from baseline and to below 50%. Left ventricular dysfunction was reported in three patients (1%) and CHF in one patient (<1%) who received SUTENT.

Sutent Prescribing Information (Pfizer), February 2007

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**Sutent Prescribing Information (Pfizer), February 2007**

*NEJM metastatic renal cell CA (MRCC) Study, January, 2007*
Which of *These* is Accurate?

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<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Percent</td>
<td>10</td>
<td>2</td>
</tr>
</tbody>
</table>

**NEJM Treatment-Naïve MRCC Study, January 11, 2007**

In the treatment-naïve MRCC study, 78/375 (21%) and 44/360 (12%) patients on SUTENT and IFN-α, respectively, had an LVEF value below the LLN. Thirteen patients on SUTENT (4%) and four on IFN-α (1%) experienced declines in LVEF of >20% from baseline and to below 50%. Left ventricular dysfunction was reported in three patients (1%) and CHF in one patient (<1%) who received SUTENT.

**Sutent Prescribing Information (Pfizer), February 2007**

In the treatment-naïve RCC study, 103/375 (27%) and 54/360 (15%) patients on SUTENT and IFN-α, respectively, had an LVEF value below the LLN. Twenty-six patients on SUTENT (7%) and seven on IFN-α (2%) experienced declines in LVEF to >20% below baseline and to below 50%. Left ventricular dysfunction was reported in four patients (1%) and CHF in two patients (<1%) who received SUTENT.

**Sutent Prescribing Information (Pfizer), May 2011**

2011: Another Trial, Still Confusion

- 171 patients with pancreatic neuroendocrine tumors (PNET) randomized to receive:
  - Sunitinib
  - Placebo

- No cardiac imaging built in!
  - Note: First patient randomized in June 2007
  - Highlights how this has been thought to be a non-issue or trivial issue based on original Phase III studies
  - Treatment-related heart failure deaths – 2 out of 83 patients!

Continued Inconsistencies: 2011

Five patients who received sunitinib and nine patients who received placebo died during the trial period (from the first study-drug dose until 28 days after the last dose). The deaths were attributed to the disease under study, with the exception of grade 5 cardiac failure (in one patient who received sunitinib) and grade 5 dehydration (in one patient who received placebo), which were both considered to be related to the study drug.

NEJM Phase III PNET Trial, Published February 10, 2011

In the Phase 3 pNET study, cardiac failure leading to death was reported in 2/83 (2%) patients on SUTENT and no patients on placebo.

Sutent Prescribing Information (Pfizer), May 2011

Continued Inconsistencies: 2011

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Sutent Prescribing Information (Pfizer), May 2011

How Can This Happen?
Three Culprit Reasons
Issue 1: CTCAE

- Oncology trial mechanism for grading adverse events
- Far ahead of other fields
- Goal: Have standard definitions for adverse events
- Essentially 100% use/acceptance across Oncology clinical trials
Why the Problems?

Semantics, semantics, semantics

Clinical scenario:
- 50 y.o. man with renal cell CA
- Enrolls in clinical trial of promising new therapy
- Pre-treatment LVEF: 60%
- Post-treatment LVEF: 35%
- Patient is ‘asymptomatic’ from cardiac standpoint

How should the Oncologist grade this according to CTCAE?
<table>
<thead>
<tr>
<th>CONTENTS</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>3</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>4</td>
</tr>
<tr>
<td>Congenital, familial and genetic disorders</td>
<td>7</td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td>8</td>
</tr>
<tr>
<td>Endocrine disorders</td>
<td>9</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>10</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>12</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>22</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>24</td>
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<tr>
<td>Immune system disorders</td>
<td>26</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>27</td>
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<tr>
<td>Injury, poisoning and procedural complications</td>
<td>34</td>
</tr>
<tr>
<td>Investigations</td>
<td>41</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>44</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>46</td>
</tr>
<tr>
<td>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</td>
<td>50</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>51</td>
</tr>
<tr>
<td>Pregnancy, puerperium and perinatal conditions</td>
<td>56</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>57</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>59</td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td>61</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>65</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>71</td>
</tr>
<tr>
<td>Social circumstances</td>
<td>75</td>
</tr>
<tr>
<td>Surgical and medical procedures</td>
<td>76</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>77</td>
</tr>
</tbody>
</table>
### Cardiac disorders

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left ventricular systolic dysfunction</td>
<td>-</td>
<td>-</td>
<td>Symptomatic due to drop in ejection fraction responsive to intervention</td>
<td>Refractory or poorly controlled heart failure due to drop in ejection fraction, intervention such as ventricular assist device, intravenous vasopressor support, or heart transplant indicated</td>
<td>Death</td>
</tr>
</tbody>
</table>

**Definition:** A disorder characterized by failure of the left ventricle to produce adequate output despite an increase in distending pressure and in end-diastolic volume. Clinical manifestations may include dyspnea, orthopnea, and other signs and symptoms of pulmonary congestion and edema.
## Cardiac disorders

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart failure</td>
<td>Asymptomatic with laboratory (e.g., BNP [B-Natriuretic Peptide]) or cardiac imaging abnormalities</td>
<td>Symptoms with mild to moderate activity or exertion</td>
<td>Severe with symptoms at rest or with minimal activity or exertion, intervention indicated</td>
<td>Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support)</td>
<td>Death</td>
</tr>
</tbody>
</table>

Definition: A disorder characterized by the inability of the heart to pump blood at an adequate volume to meet tissue metabolic requirements, or, the ability to do so only at an elevation in the filling pressure.
## Grade 2 Events

(By Way of Comparison…)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertrichosis</td>
<td>Increase in length, thickness or density of hair that the patient is</td>
<td>Increase in length, thickness or density of hair at least on the usual exposed areas of the body [face (not limited to beard/moustache area) plus/minus arms] that requires frequent shaving or use of destructive means of hair removal to camouflage; associated with psychosocial impact</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Watering eyes</td>
<td>Intervention not indicated</td>
<td>Intervention indicated</td>
<td>Operative intervention indicated</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Flatulence</td>
<td>Mild symptoms; intervention not indicated</td>
<td>Moderate; persistent; psychosocial sequelae</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

**Definition:** A disorder characterized by hair density or length beyond the accepted limits of normal in a particular body region, for a particular age or race.

**Definition:** A disorder of excessive tearing in the eyes; it can be caused by overproduction of tears or impaired drainage of the tear duct.

**Definition:** A disorder characterized by a state of excessive gas in the alimentary canal.
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<td>Vascular disorders</td>
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</table>
**Maybe It’s Grade 3?**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ejection fraction decreased</td>
<td>-</td>
<td>Resting ejection fraction (EF) 50 - 40%; 10 - 15% drop from baseline</td>
<td>Resting ejection fraction (EF) 39 - 20%; &gt;20% drop from baseline</td>
<td>Resting ejection fraction (EF) &lt;20%</td>
<td>-</td>
</tr>
</tbody>
</table>

**Definition:** The percentage computed when the amount of blood ejected during a ventricular contraction of the heart is compared to the amount that was present prior to the contraction.
In the treatment-naïve MRCC study, 78/375 (21%) and 44/360 (12%) patients on SUTENT and IFN-α, respectively, had an LVEF value below the LLN. Thirteen patients on SUTENT (4%) and four on IFN-α (1%) experienced declines in LVEF of >20% from baseline and to below 50%. Left ventricular dysfunction was reported in three patients (1%) and CHF in one patient (<1%) who received SUTENT.
Issue 2: When is an Adverse Event an Adverse Event?

Answer: When it is reported by the local site investigator

When might that make sense?
- Symptom or exam finding in which the subtlety of being the physician taking the history or performing the exam matters

When might that not make sense?
- Objective laboratory or imaging finding
  - Examples: Neutropenia, drop in ejection fraction
Issue 3: Even if an Adverse Event is Reported it May Not Count

Why? It may not be labeled as a “treatment-related” adverse event (TRAE)

Idea: Prevent ‘bad luck’ from affecting trial results
   – Example: Car accident

Why can this be a problem?
   – How do you ever pick up a signal for a previously unknown side-effect?
   – Unexpected side-effects will almost always get missed
TRAEs

Data are number (%). *Treatment-related. †Anaemia was included in the table, despite a difference of less than 5% between the treatment groups, because of its frequency and clinical relevance in GIST.

**Table 2:** Adverse events that occurred with a frequency of at least 5% greater on sunitinib than on placebo in per-protocol population

Lancet GIST study, October, 2007

* Listed are all treatment-related adverse events of interest and those occurring in at least 10% of patients in the sunitinib group. All severity was graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.

NEJM Renal Cell CA study, January, 2007

*Adapted from Motzer et al. NEJM. 2007;356:115-24 and Demetri et al. Lancet. 2006;1329-38*
How Big of a Problem is This?

- Probably bigger than any of us think…
- While the problems with CTCAE are unique to cardiac monitoring in cancer trials, the other issues can apply to most clinical trial adverse event monitoring
- Note: These studies appeared in NEJM (x2) and Lancet
Does This Matter?
It Matters: Subsequent Sunitinib Data

It Matters: Meta-Analysis of Sunitinib: Relative Risk of HF (P<0.001)

Initiated in late 2007 in Stanford GU Oncology clinics for all patients receiving targeted therapy:

- VEGF TKIs (Sunitinib, sorafenib, pazopanib, bevacizumab)
- mTOR inhibitors: Everolimus, temsirolimus

Included:

- EKG (baseline)
- TTE (baseline & q 3 months)
- NT-BNP & troponin I (baseline & q3 months)
- BP assessment (monthly)
- Note: Extra TTE/biomarker assessment at 1 month when logistically possible

Adapted from Hall et al. J Am Coll Cardiol HF. 2013;1:72-78.
Assessment of Toxicity

Performed using CTCAE v4.0
- Problems with CTCAE? Yes, but...
- Universal system for grading toxicities

Toxicities assessed:
- Heart failure
- Ejection fraction decreased
- Cardiac troponin I increased
- Hypertension
<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>Prehypertension (systolic BP 120 - 139 mm Hg or diastolic BP 80 - 89 mm Hg)</td>
<td>Stage 1 hypertension (systolic BP 140 - 159 mm Hg or diastolic BP 90 - 99 mm Hg); medical intervention indicated; recurrent or persistent (&gt;=24 hrs); symptomatic increase by &gt;20 mm Hg (diastolic) or to &gt;140/90 mm Hg if previously WNL; monotherapy indicated Pediatric: recurrent or persistent (&gt;=24 hrs) BP &gt;ULN; monotherapy indicated</td>
<td>Stage 2 hypertension (systolic BP &gt;=160 mm Hg or diastolic BP &gt;=100 mm Hg); medical intervention indicated; more than one drug or more intensive therapy than previously used indicated Pediatric: Same as adult</td>
<td>Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated Pediatric: Same as adult</td>
<td>Death</td>
</tr>
</tbody>
</table>

"Hypertension"
**“Hypertension”**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>Prehypertension (systolic BP 120 - 139 mm Hg or diastolic BP 80 - 89 mm Hg)</td>
<td>Stage 1 hypertension (systolic BP 140 - 159 mm Hg or diastolic BP 90 - 99 mm Hg); medical intervention indicated; recurrent or persistent ((\geq24) hrs); symptomatic increase by &gt;20 mm Hg (diastolic) or to &gt;140/90 mm Hg if previously WNL; monotherapy indicated Pediatric: recurrent or persistent ((\geq24) hrs) BP &gt;ULN; monotherapy indicated</td>
<td>Stage 2 hypertension (systolic BP (\geq160) mm Hg or diastolic BP (\geq100) mm Hg); medical intervention indicated; more than one drug or more intensive therapy than previously used indicated Pediatric: Same as adult</td>
<td>Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated Pediatric: Same as adult</td>
<td>Death</td>
</tr>
</tbody>
</table>
Any Cardiovascular Toxicity

Adapted from Hall et al. J Am Coll Cardiol HF. 2013;1:72-78.
Hypertension (Grade 2+)

Adapted from Hall et al. J Am Coll Cardiol HF. 2013;1:72-78.
Non-Hypertension Toxicity

Adapted from Hall et al. J Am Coll Cardiol HF. 2013;1:72-78.
Elevated NT-pro-BNP

Adapted from Hall et al. J Am Coll Cardiol HF. 2013;1:72-78.
Decreased LVEF (Grade 2-4)

Adapted from Hall et al. J Am Coll Cardiol HF. 2013;1:72-78.
Hypertension

- Preexisting HTN: 47%
- Treatment with anti-hypertensive agents during therapy:
  - At least 1 agent: 85% of patients
  - At least 2 agents: 52% of patients

Table 4: Cardiac Medications Before/During Cancer Therapy

<table>
<thead>
<tr>
<th></th>
<th>Beta-blockers</th>
<th>ACEI/ARB</th>
<th>CCB</th>
<th>Diuretics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-treatment</td>
<td>22%</td>
<td>26%</td>
<td>14%</td>
<td>19%</td>
</tr>
<tr>
<td>Initiation or dose increase with treatment</td>
<td>24%</td>
<td>25%</td>
<td>47%</td>
<td>14%</td>
</tr>
</tbody>
</table>

Adapted from Hall et al. J Am Coll Cardiol HF. 2013;1:72-78.
Outcomes of Those with LVEF Drops

- 23 patients with LVEF drops
  - 19 received standard HF therapy with BB & ACE-I or ARB
    - Improved LVEF: 9 patients
    - No change in LVEF: 6 patients
    - No further LVEF assessments: 4 patients
  - 4 did not receive standard HF therapy
    - 2 improved LVEF with cessation of cancer therapy alone
    - 2 had no further LVEF assessments due to entering hospice for end-stage malignancy

Adapted from Hall et al. J Am Coll Cardiol HF. 2013;1:72-78.
Proposed Screening Algorithm

Baseline assessment of LVEF and NT-proBNP
BP control prior to treatment

BP at every clinic visit and weekly home monitoring

LVEF assessment + NT-proBNP at 1 month and every 3 months on treatment

Screening for heart failure at every clinic visit

SBP>140 or DBP>90?

10% Fall in LVEF, elevated NT-proBNP, or 100% increase in previously elevated NT-proBNP?

Prompt initiation of antihypertensive therapy

Symptoms of heart failure?

Referral to Heart Failure Specialist

Adapted from Hall et al. J Am Coll Cardiol HF. 2013;1:72-78.
Pazopanib vs. Sunitinib

- Trial of 1110 patients published in NEJM 2013
- Front-line therapy for RCC
- TTE or MUGA obtained every 3 cycles
  - “Cardiac dysfunction” = 13% Pazopanib, 11% Sunitinib

Bevacizumab:
Relative Risk for Grade 3+ ‘CHF’ –

<table>
<thead>
<tr>
<th>Study</th>
<th>Bevacizumab</th>
<th>Control</th>
<th>RR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miles et al, 2010</td>
<td>3/497</td>
<td>0/233</td>
<td>3.29 (0.17 to 63.42)</td>
<td>.43</td>
</tr>
<tr>
<td>Brufsky et al, 2009</td>
<td>4/458</td>
<td>0/221</td>
<td>4.35 (0.24 to 80.50)</td>
<td>.32</td>
</tr>
<tr>
<td>Robert et al, 2009</td>
<td>14/817</td>
<td>1/403</td>
<td>6.91 (0.91 to 52.33)</td>
<td>.06</td>
</tr>
<tr>
<td>Miller et al, 2007</td>
<td>8/365</td>
<td>1/346</td>
<td>7.58 (0.95 to 60.32)</td>
<td>.06</td>
</tr>
<tr>
<td>Miller et al, 2005</td>
<td>7/229</td>
<td>2/215</td>
<td>3.29 (0.69 to 15.64)</td>
<td>.14</td>
</tr>
<tr>
<td>Overall</td>
<td>36/2,366</td>
<td>4/1,418</td>
<td>4.74 (1.84 to 12.19)</td>
<td>.001</td>
</tr>
</tbody>
</table>

Test for heterogeneity: Q = 0.60; P = .963; I² = 0%
Other TKIs – More Trouble…

- Trastuzumab (its own talk…)

- ‘Multitargeted’ TKIs
  - Imatinib (largely case-report level)
  - Dasatinib: Pulmonary hypertension, pleural effusions
  - Nilotinib/ponatinib: Vascular thrombosis (High rates!)

The Ponatinib Story...

- **Ponatinib**: Potent oral TKI
  - Active against BCR-ABL mutation including form resistant to other TKIs
- **Phase 2 open-label trial** of 449 CML/ALL patients x 15 months who had failed dasatinib/nilotinib
- **Manuscript** doesn’t report specific cardiac monitoring other than usual CTCAE
- **Per manuscript**...
  - Cites arterial thrombotic events “possibly” treatment related = 4.5%
  - If ignore treatment relation → 15.6% (!)

---

*Adapted from Cortes et al, New Engl J Med. 2013; 369:1783-1796*
Later Analysis... Uh-Oh

2012 – FDA Approval

After Subsequent Analysis...

Proteasome Inhibitors – Another Case Example
The Carfilzomib Story – Instructive

Proteasome inhibitors: Disrupts ubiquitin-proteasome pathway → cellular apoptosis

Ubiquitin-proteasome system: Involved in normal cardiomyocyte function → theoretical risk for cardiotoxicity from proteasome inhibition

Bortezomib/Carfilzomib: Proteasome inhibitors, approved for treatment of myleoma
  – Carfilzomib: Irreversibly binds to proteasome → sustained effect

Cardiac events in this population: Causality can be difficult to determine (particularly if no control!)
  – Symptoms/events can be due to:
    - Treatment toxicity
    - Non-cardiac symptoms (e.g. fatigue/dyspnea)
    - Bone-marrow shunting/high-output heart failure
    - Fluid-retention due to IVF and/or steroids
    - Amyloidosis (often unrecognized)
Bortezomib Data

- Original trial in NEJM (2005)
  - Bortezomib vs. High-dose dexamethasone
  - No prospective cardiac monitoring reported

- Out of 663 patients randomized/received drug...
  - Cardiac deaths possibly related to study drug:
    - Bortezomib: 3
    - Dexamethasone: 1 (sudden death)
  - “The incidence of cardiac disorders during treatment with bortezomib and dexamethasone was 15% and 13%, respectively… 7 patients receiving bortezomib (2%) and 8 receiving dexamethasone (2%) had CHF during the study.”

- Adverse event table only lists adverse events reported by ≥ 15% (!) of patients

Bortezomib Meta-Analysis

- 2014 Meta-Analysis of 25 clinical trials with 5718 patients
- Included prospective Phase 2/3 trials which reported incidence of cardiotoxicity
  - Included LVEF decline, “CHF”, cardiomyopathy, cardiac arrest, and cardiac arrhythmia
- Overall incidence: 3.8%
  - High-grade toxicity: 2.3%
- Not significantly increased vs. control groups
- My (admittedly anecdotal) take: Bortezomib cardiotoxicity is not a significant clinical problem

2012: Carfilzomib Signals?

June 2012: FDA publishes briefing document for Oncologic Drugs Advisory Committee (ODAC)

Points out there were 9 deaths due to cardiac issues during Phase 2 trials involving 526 myeloma patients
  - 23% experienced cardiac side-effects of any degree of severity, including CHF, cardiac arrest, or arrhythmia
  - Onyx pharmaceuticals only cited 4 deaths; FDA identified 5 more

Notes it is “very concerned” about “severe toxicities, including deaths” observed w/carfilzomib use

July 20, 2012: Carfilzomib approved
  - Original approval based on 266 patient Phase-2 study of patients who had relapsed myeloma after receiving bortezomib-based & thalidomide-based regimens
5 WARNINGS AND PRECAUTIONS

5.1 Cardiac Arrest, Congestive Heart Failure, Myocardial Ischemia

Death due to cardiac arrest has occurred within a day of KYPROLIS administration. New onset or worsening of pre-existing congestive heart failure with decreased left ventricular function or myocardial ischemia have occurred following administration of KYPROLIS. Cardiac failure events (e.g., cardiac failure congestive, pulmonary edema, ejection fraction decreased) were reported in 7% of patients. Monitor for cardiac complications and manage promptly. Withhold KYPROLIS for Grade 3 or 4 cardiac events until recovery and consider whether to restart KYPROLIS based on a benefit/risk assessment [see Dosage and Administration (2.4)]. Patients with New York Heart Association Class III and IV heart failure, myocardial infarction in the preceding 6 months, and conduction abnormalities uncontrolled by medications were not eligible for the clinical trials. These patients may be at greater risk for cardiac complications.
Analysis of 526 Patients in Phase 2 Carfilzomib Studies

- Dose-reduction due to cardiac AE: 6 patients (1.1%)
- Treatment discontinuation due to cardiac AE: 23 patients (4.4%)
  - CHF (1.5%)
  - Cardiac arrest (1.0%)
  - Myocardial ischemia (0.6%)
- AE occurring within 1 day of dosing: 62 patients (11.8%)
- No control arms so unclear causality vs. disease itself
- Notes that per sponsor, 5 cardiac AE deaths, 3 patients died from disease progression but with associated cardiac component – all felt “possibly related to carfilzomib”

<table>
<thead>
<tr>
<th>Grouped adverse event, n, (%)</th>
<th>Any AE</th>
<th>≥Grade3</th>
<th>SAE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any cardiac</td>
<td>116 (22.1)</td>
<td>50 (9.5)</td>
<td>41 (7.8)</td>
</tr>
<tr>
<td>Cardiac arrhythmia</td>
<td>70 (13.3)</td>
<td>12 (2.3)</td>
<td>11 (2.1)</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>38 (7.2)</td>
<td>30 (5.7)</td>
<td>26 (4.9)</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>18 (3.4)</td>
<td>7 (1.3)</td>
<td>5 (1.0)</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>9 (1.7)</td>
<td>3 (0.6)</td>
<td>2 (0.4)</td>
</tr>
</tbody>
</table>

ASPIRE Study

- Carfilzomib/lenalidomide/dexamethasone vs. lenalidomide/dexamethasone for relapsed myeloma
  - 792 patients, randomly assigned
  - 24-month survival: 73.3% vs. 65.0% (favoring carfilzomib)

Adverse events (all grades/grade 3 or higher):
- Dyspnea: 19.4%/2.8% vs. 14.9%/1.8%
- Cardiac failure: 6.4%/3.8% vs. 4.1%/1.8%

“Cardiac failure” included (in decreasing order of frequency): Cardiac failure, congestive cardiac failure, pulmonary edema, hepatic congestion, cardiopulmonary failure, acute pulmonary edema, acute cardiac failure, and right ventricular failure.

ENDEAVOR Study

ENDEAVOR Study:
- Carfilzomib/dex vs. bortezomib/dex
- 929 patients randomized, median f/u 12 months
- Median progression-free survival: 18.7 months vs. 9.4 months (favoring carfilzomib)
- SAE: 48% in carfilzomib group, 36% bortezomib
  - HTN: 9% vs. 3%

Deaths:
- Carfilzomib: 22 (5%) – 5 due to cardiac events
- Bortezomib: 21 (5%) – 6 due to cardiac events

Stopped due to dyspnea: 1 patient (carfilzomib), 5 patients (bortezomib)

ENDEAVOR Study

- Cardiac failure SAE ≥ Grade 3:
  - Carfilzomib: 8 subjects (1.7%)
  - Bortezomib: 3 subjects (0.7%)

- Atrial fibrillation SAE ≥ Grade 3:
  - Carfilzomib: 5 subjects (1.1%)
  - Bortezomib: 4 subjects (0.9%)

- Dyspnea SAE ≥ Grade 3:
  - Carfilzomib: 8 subjects (1.7%)
  - Bortezomib: 0 subjects (0%)

- Cardiac failure AE (any grade, not necessarily SAE):
  - Included in decreasing order of frequency, “cardiac failure, EF decreased, pulmonary edema, acute cardiac failure, congestive cardiac failure, acute pulmonary edema, RV failure, acute LV failure, chronic cardiac failure, cardiopulmonary failure, hepatogular reflex (!!!), and LV failure”
  - Carfilzomib: 38 subjects (8.2%)
  - Bortezomib: 13 subjects (2.9%)

ENDEAVOR Echo Substudy

- Preplanned substudy of 151 patients:
  - TTE at baseline, every 3 months, and end of treatment, analyzed centrally
  - Endpoint: Significant LVEF reduction (≥10% reduction if started with LVEF≤55% or to <45% if started >55%) at 24 weeks from baseline

- Only one patient with LVEF reduction during 24 weeks (in bortezomib arm)

- Three more patients had LVEF reduction at any time during the study (2 carfilzomib, 1 bortezomib)

Ibrutinib – Atrial Fibrillation

- Bruton tyrosine kinase (BTK) inhibitor in the B-cell receptor signaling pathway
- Effective in CLL, SLL, mantle cell lymphoma, Waldenstrom’s macroglobulinemia
- Randomized trials → apparent increase in risk of atrial fibrillation
  - Possible mechanism: BTK-related kinases present in human heart, interact with PI3K-Akt pathway → important in stress response
  - Mice with less PI3K-Akt activity → much more AF
- 2016: Meta-analysis published of 20 manuscripts, including 4 randomized trials
- Relative risk in full meta-analysis (20 studies): 3.5
- Randomized trials → most important data, as those without control arm raise question of new diagnoses because of increased surveillance

Ibrutinib – Atrial Fibrillation

Total AF among 759 ibrutinib patients & 759 control (placebo or other chemotherapy) patients:

– Ibrutinib: 40 patients (5.3%)
– Control: 10 patients (1.3%)

Note: Real rates likely higher because:
– Regular rhythm monitoring not built into trials
– Highest risk patients may have been excluded

Checkpoint Inhibitors

- Major recent advance in cancer therapies → enormous development
- Basic mechanism: Unleash ‘checkpoints’ on the immune system → attack tumors
  - Prototypes:
    - Anti-CTLA-4 antibody (e.g. ipilimumab),
    - Anti-programmed death-1 (PD-1) antibody (e.g. nivolumab, pembrolizumab)
  - Problem: Toxicity from unleashed immune action on normal tissues → GI, skin, endocrine, hepatic, pulmonary toxicity

- Obvious next question...
  - Could they cause myocarditis?

- Answer:
  - Yes, and it can be very bad/fatal
  - Fortunately, seems fairly uncommon…

- In clinical trials, no routine testing for myocarditis by biochemical analysis or cardiac imaging...
Reported on 2 fatal cases of patients treated with nivolumab/ipilimumab who developed fulminant myocarditis clinical picture
- Both with severe electrical instability

Postmortem autopsies & sequencing of cell types in myocardial infiltrates

Findings:
- Both with T-cell & macrophage infiltrates
- Selective clonal T-cell populations infiltrating the myocardium were identical to those present in tumors & skeletal muscles
- PDL-1 highly expressed on myocardial tissue

Interrogated Bristol-Meyers Squibb corporate safety databases
- 18/20594 patients (0.09%) with drug-related SAEs of myocarditis were reported
- More common with combination Rx than with nivolumab alone (0.27% vs. 0.06%)

# Dizzying Array of Toxicities – Need for Cardio-Oncology Specialists!

Adapted from Witteles et al. Circulation. 2015;132:1835-1845.

## Table 1. Incidence of Cardiotoxicity in Selected Chemotherapeutic Agents

<table>
<thead>
<tr>
<th>Class/Drug</th>
<th>Selected Indication</th>
<th>HF</th>
<th>Hypertension</th>
<th>Myocardial Ischemia</th>
<th>Thromboembolism</th>
</tr>
</thead>
</table>
| Anthracyclines | Doxorubicin | Breast, lymphoma | Very common | ... | ... | ...
|      | Daunorubicin | Leukemia | Very common | ... | ... | ...
|      | Epirubicin | Breast, gastric | Very common | ... | ... | ...
|      | Idarubicin | Leukemia | Very common | ... | ... | ...
|      | Mitoxantrone | Leukemia | Common | Rare | Rare | ...
| Alkylating agents | Cyclophosphamide | Hematologic | ... | Very rare | ...
|      | Carboplatin | Bladder, lung, ovarian | Very common | Very rare | Common | Very rare |...
|      | Ifosfamide | Cervical, sarcoma | Very common | ... | ...
| Antimicrotubule agents | Paclitaxel | Breast, lung | Very rare | Rare | ... | ...
|      | Docetaxel | Breast, lung | Rare | Rare | Rare | ...
| Antimetabolites | 5-Fluorouracil | Colorectal | Very rare | Very common | ...
|      | Capecitabine | Colorectal, breast | Very rare | Common | Rare |
| Hormone therapies | Tamoxifen | Breast | Very common | Very rare | Very rare | Very rare |
|      | Anastrozole | Breast | Very common | Rare | Rare | Very rare |
| Monoclonal antibody-based targeted therapies | Trastuzumab | Breast, gastric | Very common | Rare | ... | Very rare |
|      | Bevacizumab | Colorectal | Very common | Rare | Very common | Very common |
| Small molecule-targeted therapies | Imatinib | Leukemia, GIST | Rare | ... | Rare | Very rare |
|      | Dasatinib | Leukemia, GIST | Rare | Rare | Rare | Rare |
|      | Sorafenib | RCC, HCC | Common | Very common | Rare | Very common |
|      | Sunitinib | GIST, RCC | Very common | Very common | Rare | Very common |
|      | Lapatinib | Breast | Rare | ... | ... | ...
|      | Nilotinib | Leukemia | Rare | Rare | Very common | Very common |
|      | Ponatinib | Leukemia | Rare | Rare | Very common | Very common |
|      | Bortezomib | Multiple myeloma | Rare | Very rare | Very rare | Very rare |
| Other | Everolimus | RCC | Common | Very common | ...
|      | Temsirolimus | RCC | Common | Very common | Very common | Very rare |
|      | Thalidomide | Multiple myeloma | Rare | Common | Very common | Very common |
|      | Lenalidomide | Multiple myeloma | Rare | Common | Very common | Very common |

GIST indicates gastrointestinal stromal tumor; RCC, hepatocellular carcinoma; HF, heart failure; RCC, renal cell carcinoma; ..., not well-established complication of unknown; very rare, <1%; rare, 1% to 5%; common, 6% to 10%; and very common, >10%.
Remember: Real World ≠ Clinical Trials

Incidence of CHF in 47,806 real-world breast cancer patients from SEER database

Adapted from Du et al. Med Oncol. 2011;28:S80-S90.
Conclusions: My Take on the ‘New Agents’

For most new therapies, true risk of cardiac toxicity is hard to know
- Lack of routine monitoring
- Confusing/misleading adverse event reporting
- Lack of data transparency

Risks of overstating & understating event rates

My best assessment as of now:
- TKIs (Sunitinib, Sorafenib, etc.):
  - Hypertension risk = Certain/common
  - Cardiomyopathy risk = Present/less common – likely varies based on breadth of “kinome” inhibition
- Ponatinib/Nilotinib – Thrombosis!
- Proteasome inhibitors (Bortezomib, Carfilzomib)
  - Bortezomib toxicity: Not clear it even exists
  - Carfilzomib toxicity: Probably exists, ? Risk overestimated
- BTK inhibitors (Ibrutinib)
  - Atrial fibrillation risk: Very real, fairly common
- Checkpoint inhibitors
  - Clearly exists, but not common
  - When it occurs – at least without prospective screening – it appears to be often severe/life-threatening
Final Thoughts: Be Careful!

“Data is like garbage. You better know what you are going to do with it before you collect it.”

-Mark Twain