Cancer Therapy Monitoring and Treatment Planning – What Should We Be Doing to Minimize Cardiotoxic Risk?

Joerg Herrmann MD
Professor of Medicine
Department of Cardiology,
Mayo Clinic
DISCLOSURE

Past Relevant Financial Relationship(s)
Takeda (ARIAD) Pharmaceuticals, Advisory Board
Bristol-Myers-Squibb, Advisory Board
Amgen, Advisory Board

Current Relevant Financial Relationship(s)
Amgen, Research Funds
Cancer Therapy Monitoring and Treatment Planning – What Should We Be Doing to Minimize Cardiotoxic Risk?
Cancer Therapy Monitoring and Treatment Planning – What Should We Be Doing to Minimize Cardiotoxic Risk?

Treatment planning

Cancer-Therapy

CV Disease

Pre-existing

Induce

Developing

aggravate

Vascular Disease

Cardiac Disease

Monitoring
Cancer Therapy Monitoring and Treatment Planning – What Should We Be Doing to Minimize Cardiotoxic Risk?
Chemotherapy-induced Vascular Toxicities
Principle Presentations

Chemotherapy-induced vascular toxicity

- Accelerated atherosclerosis
- Acute thrombosis
- Acute vasospasm
Chemotherapy-induced Vascular Toxicities
Principle Presentations

Chemotherapy-induced vascular toxicity

- Accelerated atherosclerosis
- Acute thrombosis
- Acute vasospasm
Case #1

62-Year-Old Female

- dx w/rectal adenocarcinoma

Feb 12
Mar 11
Mar 18
Mar 25
Apr 1
Apr 8
Apr 15

Surgery

5-FU: 750 mg + Leucovorin: 325 ms

BP 204/120 mm Hg, HR 110 BPM, RR 20/min
JVP elevation, bilat pulm. rales, bilat LE edema

Case #1

Biomarker: cTnT 0.82 ng/mL, CKMB 13 IU/L, BNP 1257 pg/mL

TTE
Extensive LV apical akinesis
EF 28%

Sestamibi scan
As above

Apical ballooning syndrome

Case #1

Baseline  Acetylcholine  Acetylcholine + 5-FU

5-FU-induced Vasospasm Mechanism

**Vasoconstrictor stimuli**
- Catecholamines
- Endothelin-1
- Acetylcholine
- Histamine
- Serotonin
- Vasopressin
- Thromboxane A₂
- Thrombin
- Alkalosis

**Smooth muscle cell hyper-reactivity**

**Post-receptor alterations**
- Protein kinase C
- Other:
  - Rho-kinase
  - Ca²⁺ handling
  - G-proteins
  - Ion channels

**CORONARY SPASM**

Modified from Lanza GA et al. Circulation 2001;124:1774-82
5-FU-induced Cardiotoxicity
Presentation and Risk Factors

60% angina, 30% palpitations (VT/Vfib, SCD),
10% cardiac dysfunction (Takotsubo’s)/hypotension (shock)

RR 8.23, p=0.01

IHD = ischemic heart disease

Meyer CC et al. Pharmacotherapy 1997;17:729-36
Chemotherapy-induced Vascular Toxicities
Acute Vasospasm

Chemotherapy-induced vascular toxicity

- Accelerated atherosclerosis
- Acute thrombosis
- Acute vasospasm

Drugs
- 5-fluouracil
- capecitabine
- taxanes
- VEGF inhibitors
Chemotherapy-induced Vascular Toxicities

Acute Vasospasm

Chemotherapy-induced vascular toxicity

- Accelerated atherosclerosis
- Acute thrombosis
- Acute vasospasm

Risk factors
- CAD
- Age >65 years
- Continuous infusion (5-FU)
Chemotherapy-induced Vascular Toxicities

Acute Vasospasm

Chemotherapy-induced vascular toxicity

- Accelerated atherosclerosis
- Acute thrombosis
- Acute vasospasm

Monitoring

- Signs & Symptoms
- Endo-PAT, FMD?
- ECG-ST monitoring
No peeking, mister!
Chemotherapy-induced Vascular Toxicities

Acute Vasospasm

Chemotherapy-induced vascular toxicity

Accelerated atherosclerosis
Acute thrombosis
Acute vasospasm

Prevention

- Prophylactic nitrates, CCB
- testing for CAD, Endoth. dysfct?
Chemotherapy-induced Vascular Toxicities
Principle Presentations

Chemotherapy-induced vascular toxicity

- Accelerated atherosclerosis
- Acute thrombosis
- Acute vasospasm
Case #2

62 yo male

- Diagnosis of gastric cancer 8 months ago
- Neo-adjuvant cisplatin, then subtotal gastrectomy
- Subsequent para-aortic lymphadenopathy
- Repeat course of cisplatin
- 5 days after cycle #2, acute onset of chest pain
- ST segment elevation V4-6
Case #2
**Case #3**

41 yo male

- Diagnosed with non-small cell lung CA
- Started on Cisplatin and Gemcitabine
- Acute onset of chest pain 4 days after cycle #1
- ST segment elevation in inferior leads

Ito D et al. Heart Vessels 2012;27:634-8
Case #3

2 days after PCI, finger necrosis

Significance of embolization

Ito D et al. Heart Vessels 2012;27:634-8
Chemotherapy
Cytostatic and Cytotoxic Effects on the Endothelium

Platinum drugs
Taxanes
Cyclophosphamide
Vinca alkaloids
Anthracyclines
Taxanes
VEGF inhibitors
TKIs

Cytotoxic - apoptosis ↑
- necrosis ↑

Cytostatic - proliferation ↓
- migration ↓

Injury ↑ Repair ↓
Thrombotic diathesis
- coagulation
- fibrinolysis

Fibrinolytic pathway
- platelets
- Thrombin

Endothelial activation, increase injury and reduced repair
- cancer
- Thrombotic diathesis
- coagulation
- fibrinolysis

Flow perturbation
- Inner curvature, bifurcation
Increase in Von Willebrand Factor Levels With Cisplatin Chemotherapy

vWF Increase and ATEs With Cisplatin Therapy Correlation with Baseline Risk

High risk fingerprint:
3 or more of the following:
- BMI >25 kg/m²,
- Current smoking
- BP >140/90 mm Hg (or treated)
- Hyperlipidemia (or treated)
- Elevated FPG

<table>
<thead>
<tr>
<th>Risk of arterial events</th>
<th>19% vs. 2%</th>
<th>p&lt;0.05</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline vWF level [%]</td>
<td>114 (51-297) vs. 91 (42-176)</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>Baseline Intima-Media Thickness [um]</td>
<td>660 (550-872) vs. 563 (435-1097)</td>
<td>p&lt;0.05</td>
</tr>
</tbody>
</table>

Von Willebrand Factor Levels In Gastric Cancer Patients

Yang et al. Oncogenesis 2018;7:12
Von Willebrand Factor Production By Gastric Cancers

![Graph showing level of VWF expression and images of poorly differentiated and moderately differentiated gastric cancers.]

Yang et al. Oncogenesis 2018;7:12
Cancer and Clot

Cumulative Incidence of Arterial Thromboembolism

- Patients with Cancer (of any Stage)
- Matched Controls without Cancer

Navi BB et al. J Am Coll Cardiol 2017;70:926-38
Chemotherapy-induced Vascular Toxicities
Acute Vasospasm

Chemotherapy-induced vascular toxicity

- Accelerated atherosclerosis
- Acute thrombosis
- Acute vasospasm

Drugs
- Alkylating agents (cyclophosphamide, platinum compounds)
- Vinca alkaloids
- Bleomycin
- VEGF inhibitors
Chemotherapy-induced Vascular Toxicities
Acute Vasospasm

Chemotherapy-induced vascular toxicity

Accelerated atherosclerosis
Acute thrombosis
Acute vasospasm

Risk factors

- Endothelial dysfunction, plus endothelial injury
- Flow alterations, prior and new (vasospasm)
- Pro-thrombotic stage/platelet-cancer loop
Chemotherapy-induced Vascular Toxicities

Acute Vasospasm

Chemotherapy-induced vascular toxicity

- Accelerated atherosclerosis
- Acute thrombosis
- Acute vasospasm

Monitoring

- Signs & symptoms
- vWF levels?
- Circulating endothelial cells?
- Endothelial progenitor cells?
Chemotherapy-induced Vascular Toxicities

Acute Vasospasm

Chemotherapy-induced vascular toxicity

Accelerated atherosclerosis
Acute thrombosis
Acute vasospasm

Prevention

- Risk stratification:
  - CVRF fingerprint
  - Carotid IMT?
  - vWF levels?
- DAPT?
- Statins?
Chemotherapy-induced Vascular Toxicities
Principle Presentations

Chemotherapy-induced vascular toxicity

- Accelerated atherosclerosis
- Acute thrombosis
- Acute vasospasm
Case #4

63 yo male
- arterial hypertension, smoker, started on Nilotinib 400 mg BID in October 2006
- development of bilat. claudication in Sept. 2007
- intervention with stents 2 months later
Case #5

70 yo female
- CML, on nilotinib since 2004
- Diagnosed with PAD and CAD, presenting with acute ischemic stroke

Cardiovascular Events With Nilotinib
Incidence and Prediction

Hadzijusufovic E et al: Leukemia 2017; 31:2388
ARCH Mutations and AOD in CML Patients

≥1 ARCH mutations 64.7%

p<0.05

Hadzijusufovic E et al: Leukemia 2017; 31:2388
Clonal Hematopoiesis of Indeterminate Potential (CHIP)

TET2 deficiency increases pro-IL-1β expression (via epigenetic mechanisms) and pro-IL-1β processing (via NLRP3 inflammasome expression and activity)
Interleukin-1β Production in Plaques
Correlation with Plaque Stability and Hypercholesterolemia

Jiang X. et al., under review

Jiang et al., submitted, under revision
Bcr-Abl TKIs

Dose-Dependent Toxicity to Endothelial Cells

- 0.11 μM or 0.17 μM ponatinib corresponding to 30mg and 45 mg
- 5.3 μM imatinib corresponding to 400 mg
- 4.3 μM nilotinib corresponding to 400mg

Clinically relevant dose spectrum

Cardiovascular Events in CML Patients

Nilotinib vs. Ponatinib

More than one third with a CV event!
Risk may persist even after discontinuation!

Nicolini FE et al. Blood 2013:122:4020
Vascular Monitoring with Bcr-Abl TKIs
Provisional Recommendations

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Imatinib</th>
<th>Nilotinib</th>
<th>Dasatinib</th>
<th>Bosutinib</th>
<th>Ponatinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>REC</td>
<td>REC</td>
<td>REC</td>
<td>REC</td>
<td>REC</td>
</tr>
<tr>
<td>Clinical cardiovascular assessment, including blood pressure</td>
<td>REC</td>
<td>REC</td>
<td>REC</td>
<td>REC</td>
<td>REC</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>REC</td>
<td>ACI</td>
<td>ACI</td>
<td>ACI</td>
<td>ACI</td>
</tr>
<tr>
<td>Fasting lipid panel</td>
<td>ACI*</td>
<td>ACI</td>
<td>ACI</td>
<td>ACI</td>
<td>ACI</td>
</tr>
<tr>
<td>Echocardiogram</td>
<td>ACI*</td>
<td>REC</td>
<td>ACI</td>
<td>ACI</td>
<td>ACI</td>
</tr>
<tr>
<td>ECG</td>
<td>ACI</td>
<td>ACI</td>
<td>ACI</td>
<td>ACI</td>
<td>ACI</td>
</tr>
<tr>
<td>Ankle-brachial index</td>
<td>REC</td>
<td>ACI</td>
<td>ACI</td>
<td>REC</td>
<td>REC</td>
</tr>
</tbody>
</table>

1-month follow-up

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Imatinib</th>
<th>Nilotinib</th>
<th>Dasatinib</th>
<th>Bosutinib</th>
<th>Ponatinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical cardiovascular assessment</td>
<td>REC</td>
<td>REC</td>
<td>ACI</td>
<td>REC</td>
<td>REC</td>
</tr>
<tr>
<td>Blood pressure check</td>
<td>ACI</td>
<td>ACI</td>
<td>ACI</td>
<td>ACI</td>
<td>ACI</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3- to 6-month follow-up

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Imatinib</th>
<th>Nilotinib</th>
<th>Dasatinib</th>
<th>Bosutinib</th>
<th>Ponatinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical cardiovascular assessment</td>
<td>REC</td>
<td>REC</td>
<td>REC</td>
<td>REC</td>
<td>REC</td>
</tr>
<tr>
<td>Blood pressure check</td>
<td>REC</td>
<td>ACI</td>
<td>ACI</td>
<td>ACI</td>
<td>ACI</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>REC</td>
<td>ACI</td>
<td>ACI</td>
<td>ACI</td>
<td>ACI</td>
</tr>
<tr>
<td>Fasting lipid panel</td>
<td>REC</td>
<td>ACI</td>
<td>ACI</td>
<td>ACI</td>
<td>ACI</td>
</tr>
<tr>
<td>Echocardiogram</td>
<td>ACI*</td>
<td>ACI*</td>
<td>ACI</td>
<td>ACI</td>
<td>ACI</td>
</tr>
<tr>
<td>ECG</td>
<td>ACI*</td>
<td>ACI*</td>
<td>ACI</td>
<td>ACI</td>
<td>ACI</td>
</tr>
<tr>
<td>Ankle-brachial index</td>
<td>REC</td>
<td>ACI</td>
<td>ACI</td>
<td>REC</td>
<td>REC</td>
</tr>
</tbody>
</table>

What is the expected timeline and pace of progression?
### Vascular Monitoring with Bcr-Abl TKIs
#### Provisional Recommendations

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Imatinib</th>
<th>Nilotinib</th>
<th>Dasatinib</th>
<th>Bosutinib</th>
<th>Ponatinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical cardiovascular assessment, including blood pressure</td>
<td>Follow good clinical practice</td>
<td>REC</td>
<td>REC</td>
<td>REC</td>
<td>REC</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>REC</td>
<td>ACI</td>
<td>ACI</td>
<td>ACI</td>
<td>ACI</td>
</tr>
<tr>
<td>Fasting lipid panel</td>
<td>ACI</td>
<td>ACI*</td>
<td>ACI</td>
<td>ACI</td>
<td>ACI</td>
</tr>
<tr>
<td>Echocardiogram</td>
<td>ACI</td>
<td>ACI*</td>
<td>ACI</td>
<td>ACI</td>
<td>ACI</td>
</tr>
<tr>
<td>ECG</td>
<td>REC</td>
<td>ACI</td>
<td>ACI</td>
<td>ACI</td>
<td>ACI</td>
</tr>
<tr>
<td>Ankle-brachial index</td>
<td>REC</td>
<td>ACI</td>
<td>ACI</td>
<td>ACI</td>
<td>ACI</td>
</tr>
</tbody>
</table>

**Timeline to detection:** every 3, 6, or 12 mo., every TKI, every patient?
## Vascular Monitoring with Bcr-Abl TKIs
### Provisional Recommendations

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Imatinib</th>
<th>Nilotinib</th>
<th>Dasatinib</th>
<th>Bosutinib</th>
<th>Ponatinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical cardiovascular assessment, including blood pressure</td>
<td>REC</td>
<td>REC</td>
<td>REC</td>
<td>REC</td>
<td>REC</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>REC</td>
<td>ACI</td>
<td>ACI</td>
<td>ACI</td>
<td>REC</td>
</tr>
<tr>
<td>Fasting lipid panel</td>
<td>ACI</td>
<td>ACI*</td>
<td>ACI</td>
<td>ACI</td>
<td>ACI</td>
</tr>
<tr>
<td>ECG</td>
<td>ACI*</td>
<td>ACI</td>
<td>ACI</td>
<td>ACI</td>
<td>ACI</td>
</tr>
<tr>
<td>Ankle-brachial index</td>
<td>REC</td>
<td>ACI</td>
<td>ACI</td>
<td>ACI</td>
<td>REC</td>
</tr>
<tr>
<td>1-month follow-up</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical cardiovascular assessment</td>
<td>REC</td>
<td>REC</td>
<td>ACI</td>
<td>REC</td>
<td>REC</td>
</tr>
<tr>
<td>Blood pressure check</td>
<td>ACI</td>
<td>ACI</td>
<td>ACI</td>
<td>ACI</td>
<td>REC</td>
</tr>
<tr>
<td>3- to 6-month follow-up</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical cardiovascular assessment</td>
<td>REC</td>
<td>REC</td>
<td>REC</td>
<td>REC</td>
<td>REC</td>
</tr>
<tr>
<td>Blood pressure check</td>
<td>REC</td>
<td>ACI</td>
<td>ACI</td>
<td>ACI</td>
<td>REC</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>REC</td>
<td>ACI</td>
<td>ACI</td>
<td>ACI</td>
<td>ACI</td>
</tr>
<tr>
<td>Fasting lipid panel</td>
<td>REC</td>
<td>ACI</td>
<td>ACI</td>
<td>ACI</td>
<td>REC</td>
</tr>
<tr>
<td>Echocardiogram</td>
<td>ACI</td>
<td>ACI*</td>
<td>ACI</td>
<td>ACI</td>
<td>ACI</td>
</tr>
<tr>
<td>ECG</td>
<td>ACI*</td>
<td>ACI</td>
<td>ACI</td>
<td>ACI</td>
<td>ACI</td>
</tr>
<tr>
<td><strong>Ankle-brachial index</strong></td>
<td>REC</td>
<td>ACI</td>
<td>ACI</td>
<td>REC</td>
<td></td>
</tr>
</tbody>
</table>

**Cutoff for detection: 0.02 at 6 months?**
Chemotherapy-induced Vascular Toxicities

Principle Presentations

- Accelerated atherosclerosis
- Acute thrombosis
- Acute vasospasm
Chemotherapy-induced Vascular Toxicities
Acute Vasospasm

Chemotherapy-induced vascular toxicity

- Accelerated atherosclerosis
- Acute thrombosis
- Acute vasospasm

**Drugs**
- Nilotinib
- Ponatinib
- Cisplatin?
- VEGF inhibitors?
Chemotherapy-induced Vascular Toxicities
Acute Vasospasm

Risk factors
- persistent endothelial dysfunction
- unrepaired endothelial injury
- CV risk factors, esp. uncontrolled
- Genetic predisposition
Chemotherapy-induced Vascular Toxicities

Acute Vasospasm

Chemotherapy-induced vascular toxicity

- Accelerated atherosclerosis
- Acute thrombosis
- Acute vasospasm

Monitoring

- Signs & symptoms
- ABI?
- Carotid IMT?
- CCTA?
- Stress test?
Chemotherapy-induced Vascular Toxicities

Acute Vasospasm

Chemotherapy-induced vascular toxicity

- Accelerated atherosclerosis
- Acute thrombosis
- Acute vasospasm

Prevention

- Strict CVRF control, esp. lipids (anti-IL-1β), blood pressure, nicotine abstinence
- ASA, statins, other?
- Pre-therapy testing?
Chemotherapy-induced Vascular Toxicities

Chemotherapy-induced vascular toxicity

**Accelerated atherosclerosis**
- Nilotinib
- Ponatinib
- Cisplatin?
- VEGF inhibitors?

**Acute thrombosis**
- Cyclophosphamide, platinum compounds
- Vinca alkaloids
- Bleomycin
- VEGF inhibitors

**Acute vasospasm**
- 5-fluorouracil
- Capecitabine
- Taxanes
- VEGF inhibitors

**Drugs**

**Screening**
- Signs & Symptoms (ABI, stress test, CCTA?)
- Signs & Symptoms (vWF, CEC, EPC?)
- Signs & Symptoms Vasoreactivity studies ECG-ST monitoring

**Prevention**
- Strict RF control, esp. lipids (anti-IL-1β)
- ASA, statins, other?
- Risk stratification: CVRFs, FMD, vWF? DAPT, statins?
- Prophylactic Nitrates, CCB (testing for CAD, ED?)

**Signs & Symptoms**
- Accelerated atherosclerosis
- Acute thrombosis
- Acute vasospasm
Cancer Therapy Monitoring and Treatment Planning – What Should We Be Doing to Minimize Cardiotoxic Risk?
Cancer Therapy Monitoring and Treatment Planning – What Should We Be Doing to Minimize Cardiotoxic Risk?

Treatment planning

Cancer-Therapy

CV Disease

Pre-existing

aggravate

induce

Developing

Vascular Disease

Cardiac Disease

Monitoring
Earlier with ponatinib?

**Average Time to Clinical Recognition**

*Peripheral Arterial Disease with Nilotinib*

- Female, <60 years old
  - No cardiovascular risk factor: 49.4 months
  - ≥1 cardiovascular risk factor: 36.9 months
- Female, ≥60 years old
  - No cardiovascular risk factor: 39.7 months
  - ≥1 cardiovascular risk factor: 22.2 months
- Male, ≥60 years old
  - No cardiovascular risk factor: 28.2 months
  - ≥1 cardiovascular risk factor: 15.7 months
- Male, <60 years old
  - No cardiovascular risk factor: 12 months
  - ≥1 cardiovascular risk factor: 12 months

*Time between nilotinib initiation and PAOD onset, (months, * means)*

Spectrum ABI Decline
Cardiovascular Health Study (men and women ≥ 65 years)

0.15 cutoff for significant progression

Incident PAD (N=218)
Non-Cases (N=2071)

9.3% incidence

Spectrum ABI Decline
Cardiovascular Health Study (men and women ≥ 65 years)

0.03 cutoff for significant progression at 1 year?
Spectrum ABI Decline
Cardiovascular Health Study (men and women ≥ 65 years)

0.015 cutoff for significant progression at 6 mo.? 